Diploma thesis

The impact of Sarcopenia on patients with colorectal liver metastasis undergoing partial hepatectomy.

Submitted by

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Affidavit:

I sincerely declare that I have written the following diploma thesis, on my own, without any help from third parties.

Moreover, I declare that I have not used sources other than those I have quoted.

Graz, 14.02.2022 Florian Faschinger eh.

Acknowledges:

This thesis and my degree in medicine would not have been possible without the guidance, trust, and help from various people in my life.

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List of abbreviations

APC ..... *Adenomatous-polyposis-coli*

KRAS ..... *Kirsten rat sarcoma*

TP53..... *Tumor Protein 53*

DNA ..... *Deoxyribonucleic acid*

TNM..... *Tumor-node-metastasis*

UICC..... *Union internationale contre le cancer*

G ..... *Grading*

R..... *Residual tumor*

R0..... *No residual tumor*

R1..... *Microscopic residual tumor*

R2..... *Macroskopic residual tumor*

EGFR ..... *Epidermal Growth Factor Receptor*

VEGF ..... *Vascular Endothelial Growth Factor*

CT..... *Computer tomography*

MRI ..... *Magnetic Resonance Imaging*

PET CT..... *Positron emission tomography*

AST..... *Aspartate Transaminase*

ALT..... *Alanine Aminotransferase*

CEA ..... *carcinoembryonic antigen*

CA 19-9 ..... *Carbohydrate antigen 19-9*

CSHA ..... *Canadian Study of Health and Aging*

DXA..... *Dual X-Ray Absorptiometry*

EWGSOP2 ..... *European Working Group on Sarcopenia in Older People 2*

WHO ..... *World health organization*

BMI ..... *Body Mass Index*

KAGES..... *Steiermärkische Krankenanstaltengesellschaft*

ASA ..... *American Society of Anesthesiologists*

ECOG..... *Eastern Cooperative Oncology Group Score*

DICOM ..... *Digital Imaging and Communications in Medicine*

L3 ..... *height of the third lumbar vertebra*

TPA ..... *Total psoas area*

HU ..... *Hounsfield unit*

IQR ..... *Interquartile range*

OR ..... *Odds ratio*

CI ..... *Confidence interval*

HR ..... *Hazard ratio*

SMI ..... *Skeletal Muscle Index*

SPSS ..... *Statistical Product and Service Solutions*

OP ..... *Operation*

SO ..... *Sarcopenic Obesity*

FUP ..... *Follow up*

LOS ..... *Length of stay*

Charlson C.I. ..... *Charlson Comorbidity Index*

CRLM ..... *Colorectal liver metastasis*

CRC ..... *Colorectal Carcinoma*

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Abstract:

Introduction: Sarcopenia is described as generalized, age-related, progressive loss of muscle mass, muscle function, and, moreover, a surrogate parameter for the Frailty syndrome. It is associated with significantly higher morbidity and mortality. In most cases, Sarcopenia remains undiagnosed, although the social and economic damages plus the burden on our healthcare system can be estimated as remarkable.

Methods: For our retrospective study, we used data from 342 patients undergoing partial hepatic resection due to colorectal, hepatic metastasis between 2005 and 2019. We compared non-sarcopenic with sarcopenic and sarcopenic obese patients. By measuring the preoperative muscle mass of patients at the height L3 with OSIRIX DICOM viewer using CT scans and calculating the Skeletal muscle Index (SMI), the presence of sarcopenia could be estimated.

Results: 342 patients were included. Preoperative CT scans were available in 251 patients. We incorporated multiple parameters, especially turning our attention to overall survival.

Overall survival in months between non-sarcopenic (63,6) and sarcopenic (49,5) patients differed significantly (p-value 0,01). However, after a Kaplan Meier analysis, a log-rank test was insignificant. (p-value 0,06)

After another Kaplan Meier analysis, a further log-rank test comparing non-sarcopenic with sarcopenic obese patients in terms of postoperative survival in months showed a statistical significance (p-value 0,011).

Generally, patients suffering from Sarcopenia or sarcopenic obesity died more frequently of disease during the observation period than non-sarcopenic patients.

Discussion: Given the progressing obsolesce of the western population, the relevance of sarcopenia and its impact on health, economy, and our social system will rise rapidly. Our study showed a significant impact on the patient's mortality and long-term survival apart from a few unclear parameters. The data matches the current literature and shows that measures to treat and prevent this condition must be taken as soon as possible.

Zusammenfassung:

Einleitung: Sarkopenie wird als generalisierte, altersbedingte, fortschreitende Verlust von Muskelmasse, Muskelfunktion und außerdem als Surrogatparameter für das Frailty-Syndrom beschrieben. Sie ist mit höherer Morbidität und Mortalität der Patient/innen verbunden. Sarkopenie bleibt in den meisten Fällen unerkannt, obwohl die sozialen und wirtschaftlichen Schäden sowie die Belastung unseres Gesundheitssystems als beachtlich einzuschätzen sind.

Methodik: Für unsere retrospektive Studie verwendeten wir Daten von 342 Patient/innen, die sich zwischen 2005 und 2019 einer Leberteilresektion aufgrund von colorektalen Lebermetastasen unterzogen. Wir verglichen nicht-sarkopene mit sarkopenen und sarkopen-adipösen Patient/innen. Durch Messung der präoperativen Muskelmasse in Höhe L3 mit dem OSIRIX DICOM-Viewer unter Verwendung von CT-Scans, und anschließender Berechnung des Skeletal Muscle Index (SMI) konnte das Vorhandensein von Sarkopenie abgeschätzt werden.

Ergebnisse: 342 Patient/innen wurden eingeschlossen. Präoperative CT-Scans waren bei 251 Patient/innen verfügbar. Wir prüften mehrere Parameter, wobei wir uns insbesondere auf das Gesamtüberleben konzentrierten.

Das Gesamtüberleben in Monaten zwischen nicht-sarkopenen (63,6) und sarkopenen (49,5) Patient/innen unterschied sich signifikant (p-Wert 0,01). Nach einer Kaplan-Meier-Analyse und einem anschließenden Log-Rank-Test, konnte dies nicht bestätigt werden (p-Wert 0,06)

Nach einer weiteren Kaplan-Meier-Analyse zeigte ein weiterer Log-Rank-Test, zwischen nicht-sarkopenen und sarkopen-adipösen Patient/innen hinsichtlich des postoperativen Überlebens in Monaten, eine statistische Signifikanz (p-Wert 0,011). Im Allgemeinen verstarben Patient/innen, die an Sarkopenie oder sarkopener Adipositas litten, während des Beobachtungszeitraums häufiger an ihrer Grunderkrankung als nicht-sarkopene Patient/innen.

Diskussion: Angesichts der fortschreitenden Überalterung der westlichen Bevölkerung wird die Relevanz der Sarkopenie und ihre Auswirkungen auf Gesundheit, Wirtschaft und unser Sozialsystem rapide zunehmen. Unsere Studie zeigte abgesehen von einigen unklaren Parametern einen signifikanten Einfluss auf die Mortalität und das Langzeitüberleben der Patient/innen. Die Daten stimmen mit

der aktuellen Literatur überein und zeigen, dass Maßnahmen zur Behandlung und Vorbeugung dieser Erkrankung so schnell wie möglich ergriffen werden müssen.

1 Introduction

1.1.1 Liver anatomy

The liver, which is the largest gland in the human body and the largest intestinal organ, weighs about 1500 grams. Its location is in the right upper quadrant of the abdominal cavity.

The liver is separated into two main surfaces. First, we have the convex diaphragmatic surface. As the name says, this surface is located directly beneath the diaphragm, which separates the thoracic cavity from the abdominal cavity.

The concave visceral surface is in tight contact with abdominal organs and with essential blood vessels. Lateral, we have the right kidney and the right colic flexure.

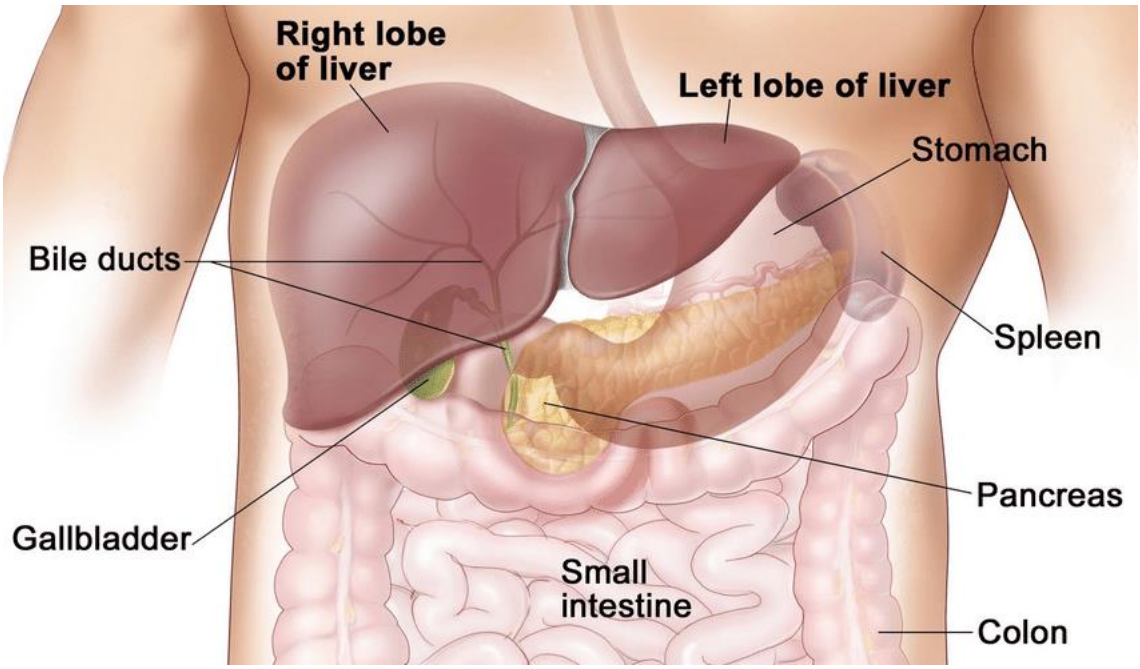


Figure 1: Anatomy of the liver and location in the abdominal cavity.

The liver's central hilum contains the hepatic artery, the portal vein, and the bile duct. Right underneath, the gall bladder is located. Cranially to the gall bladder, the hilum, and the inferior vena cava have their place. There is also close contact with the stomach on the left side.

Anatomically, on the diaphragmatic surface, this organ is divided by the falciform ligament into a more prominent right lobe, and a smaller left lobe. On the visceral surface, there are, additionally, the caudate and the quadrat lobe. However, the

functional liver border between the two main lobes is an imaginary line between the inferior vena cava and the gall bladder, corresponding to the main blood vessels' distribution pattern.

These four lobes, in total, are subdivided into eight liver segments.

This segmentation is based on its blood supply from a hepatic artery branch and a portal vein branch.

The first liver segment is the caudate lobe. It is situated on the visceral surface, left of the inferior vena cava, and above the liver hilum. It receives blood from both the portal vein's main branches and has its own venous drain, flowing directly into the inferior vena cava. Based on the caudate lobe, segments II to VIII are organized clockwise and from dorsal to ventral.

The superior segment II and the inferior segment III locate medial of the falciform ligament.

Segment IV, which matches with the quadrat lobe, is placed lateral of the falciform ligament. It is subdivided into a superior segment IVa and an inferior segment IVb.

Segment V and VIII are located laterally of the hilum. VIII is the superior, and V is the inferior unit.

The remaining segments are segments VI and VII. Segment VI's position is lateral to segment V, and segment VII's position is lateral to segment VIII.

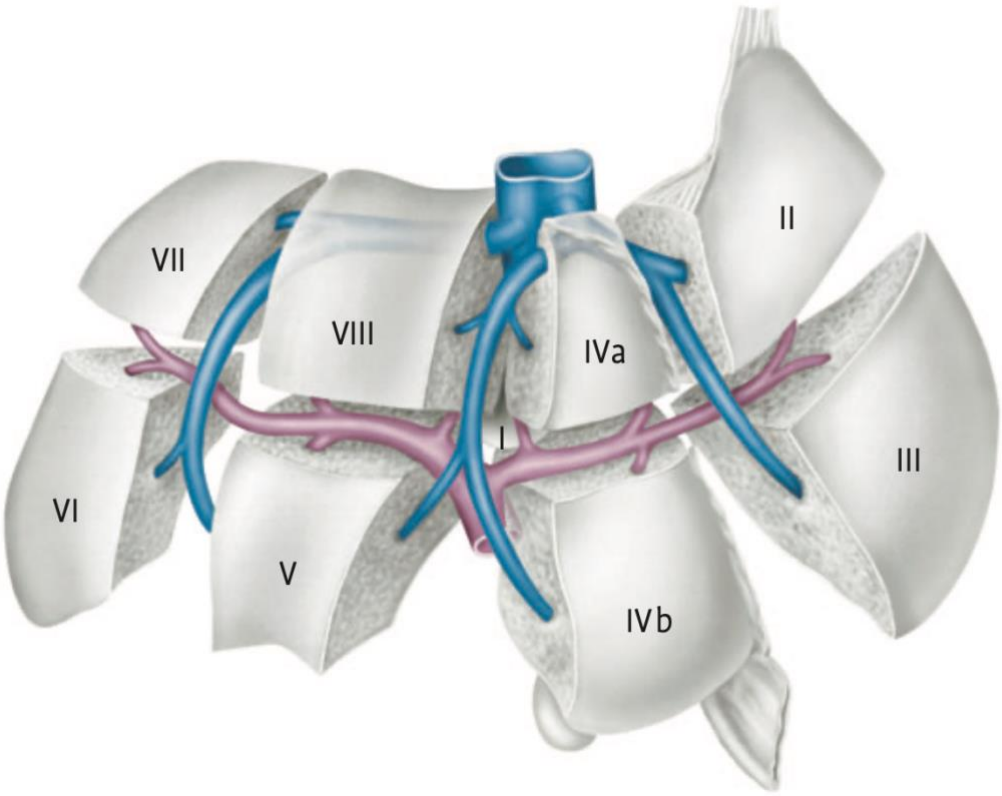


Figure 2: Segmentation of the liver

Out of the eight liver segments, the bile is drained into the left and right hepatic duct, which is united to form the common bile duct. The common bile duct forms, together with the cystic duct, coming from the gall bladder, the main bile duct.
The bile duct unites right before the hepatopancreatic ampulla with the pancreatic duct and leads into the duodenum(1) (2).

1.1.2 Liver physiology

The liver is a metabolic, highly active organ. Its functions go from sharing substrates and sharing energy between different metabolic systems to synthesizing substances distributed to other body parts.
Processing, storing, and releasing nutrients, such as carbohydrates, fats, proteins, and vitamins, is a central function.
Besides, the liver is in charge of storing iron, producing many blood substances required for coagulation and metabolizing hormones. It also removes toxic substances from the body. Bilirubin, a waste product of the degradation of red blood

cells, is one of them. Furthermore, the liver metabolizes various medications, drugs, and alcohol.

Another main function of the liver is the production of bile. The hepatocytes synthesize 800 to 1000 milliliters of this fluid per day. It can flow directly through the bile duct into the duodenum or drains through the cystic duct into the gall bladder, where it stays until it is needed.

Bile plays two important roles. First, it is essential for digesting and reabsorbing fats. It emulsifies the large fat particles into smaller, more digestible particles, which then can be exploited by the pancreatic lipase, and it also aids in absorbing the digested fat end products through the mucosal membrane.

Second, bile acts as a transport medium for several waste products like bilirubin or excesses of cholesterol.

Due to increased blood levels of bilirubin, obstruction of the intrahepatic and extrahepatic bile ducts can lead to jaundice, hinting at hepatic, biliary, or pancreatic pathologies(3).

1.2.1 Large intestine's anatomy

The passage between the small and the large intestine is the so-called ileocecal valve. It marks the beginning of the approximately 1,5-meter-long large intestine and its first part, the caecum. It is located in the right iliac fossa inferior with its appendix, an intestinal diverticulum extending from the inferior part.

The subsequent structure is the colon.

It divides itself into four parts. The ascending colon passes from the caecum to the right colic flexure, which stands in contact with the right hepatic lobe. On the other side, the left colic flexure locates anterior to the left kidney. Between these two, there is the transverse colon.

The descending colon passes from the left flexure to the left iliac fossa and opens into the sigmoid colon. This S-shaped structure ends at the third sacral segment and goes into the twelve- to the fifteen-centimeter-long rectum, which follows the sacral and coccyx bone shape, creating the sacral flexure. Finally, the anal canal, which begins at the approximately 80-degree anorectal flexure, marks the end.

The large intestine is characterized by its three tenias, reinforcing the large intestine's muscle layer and its typical bulges, called haustra. The epiploic appendices are characteristic attachments of fat tissue fixed on the colon's surface.

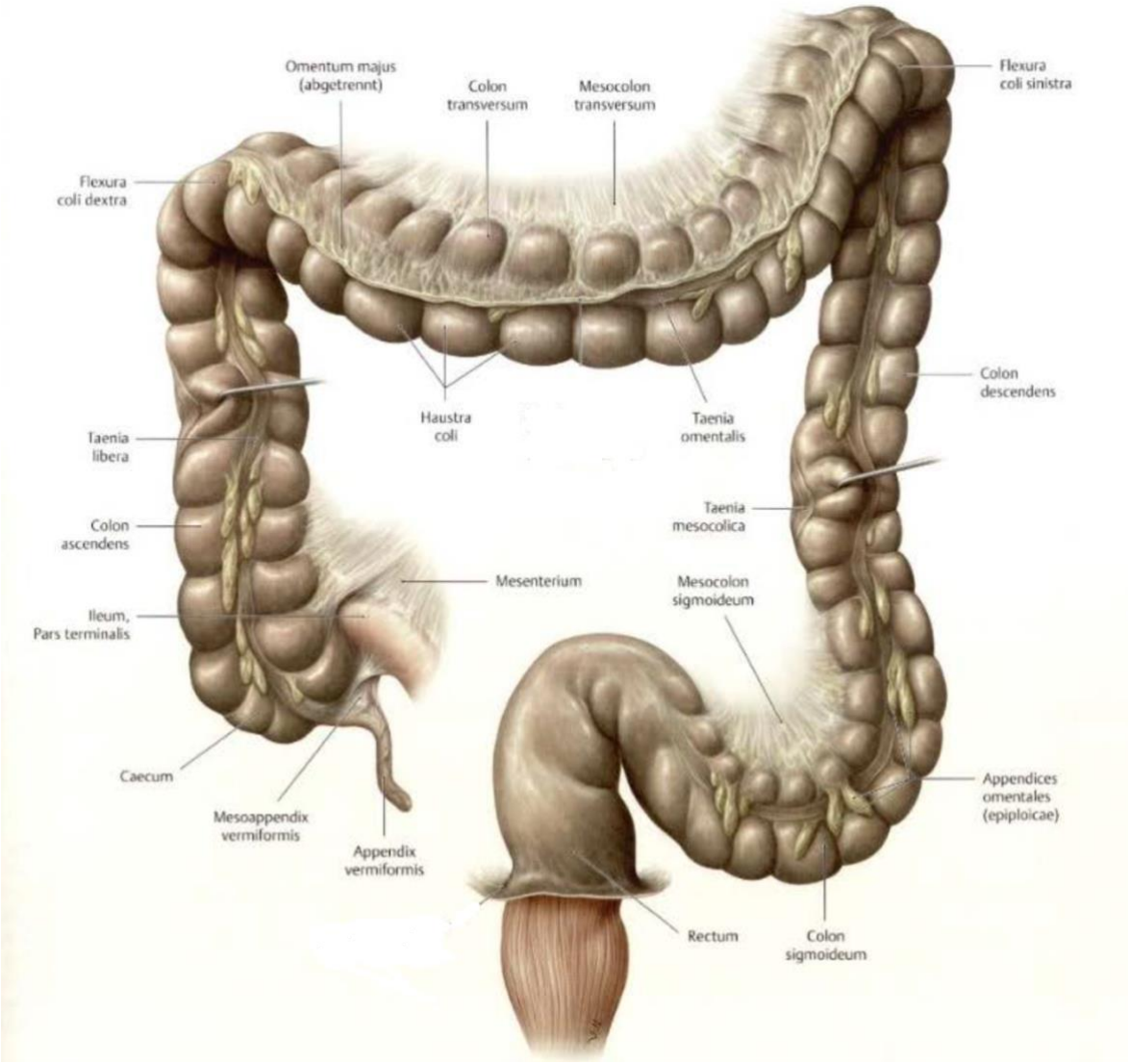


Figure 3: Large intestine's anatomy

The large intestine's vascularization assures blood flow through the superior and inferior mesenteric artery and its correspondent veins. Branches of the superior mesenteric artery supply the caecum, the ascending colon, and the transverse colon's main parts. Except for the middle and inferior rectum supplied by branches of the iliac arteries, the remaining parts are supplied by the inferior mesenteric artery branches(4).

1.2.2 Large intestine's physiology

The large intestine can efficiently absorb electrolytes, such as sodium or chloride. Due to the osmotic gradient, water follows.

About 1500 milliliters of chyme daily flow into the large intestine. After absorbing water and electrolytes, about 100 milliliters of fluid or less will be excreted in the feces. This process occurs mainly in the large intestine's proximal half, which gives it the name “absorbing colon.”

The intestinal flora consists mainly of bacteria, especially coliform bacteria. It digests small amounts of cellulose and incomplete digested lactose, leading to methane or carbon dioxide. Forming substances like vitamin b 12, thiamin, and vitamin k is another essential function. (3) The distal half of the large intestine, also called the storage colon, acts as feces storage. A stretch attraction in the rectum, induced by the feces, provokes the rectal temenos, which leads to defecation.

The large intestine is not essential for survival. Large parts can be resected due to several diseases, for example, colorectal carcinomas or chronic inflammatory bowel diseases(5).

1.3 Colorectal carcinoma

Colorectal carcinoma is a malignant neoplasia of the large intestine.

It is the third most common carcinosis in men and women. In Austria, eleven percent of cancer-related deaths occurred due to colorectal carcinoma in 2017. The five years survival rate is about 62 percent (6).

60-70-year-old patients have the highest possibility to sicken from colorectal carcinoma. Less than 20 percent of the cases occur at 50 years or less. It affects slightly more men than women.

This disease is most prevalent in highly developed countries such as the United States of America, the United Kingdom, or Austria.

The most common risk factors are a diet low in fiber and high in red meat, smoking, and advanced age. Furthermore, chronic inflammatory bowel diseases and familial syndromes like familial adenomatous polyposis or hereditary nonpolyposis cancer increase disease likelihood.

In ninety percent of all cases, colorectal adenocarcinoma is the histologically most frequent form. The mucinous adenocarcinoma, the signet ring cell carcinoma, or the small cell carcinoma are rare subtypes.
Usually, colorectal carcinoma emerges from a pre-stage, called adenoma.
The adenoma-carcinoma pathway explains the evolvement from regular mucosa to invasive adenocarcinoma.

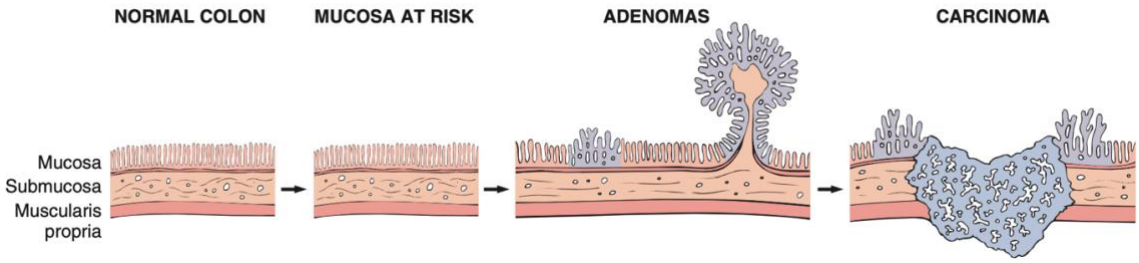


Figure 4: Colorectal carcinoma pathogenesis

Mutation in the tumor suppressor gene APC can lead to early adenoma. Mutation in protooncogene KRAS leads to late-stage adenoma, and changes in other tumor suppressor genes like TP53 result in invasive colorectal adenocarcinoma.
75 % of colorectal adenocarcinomas have their origin in this molecular pathway.

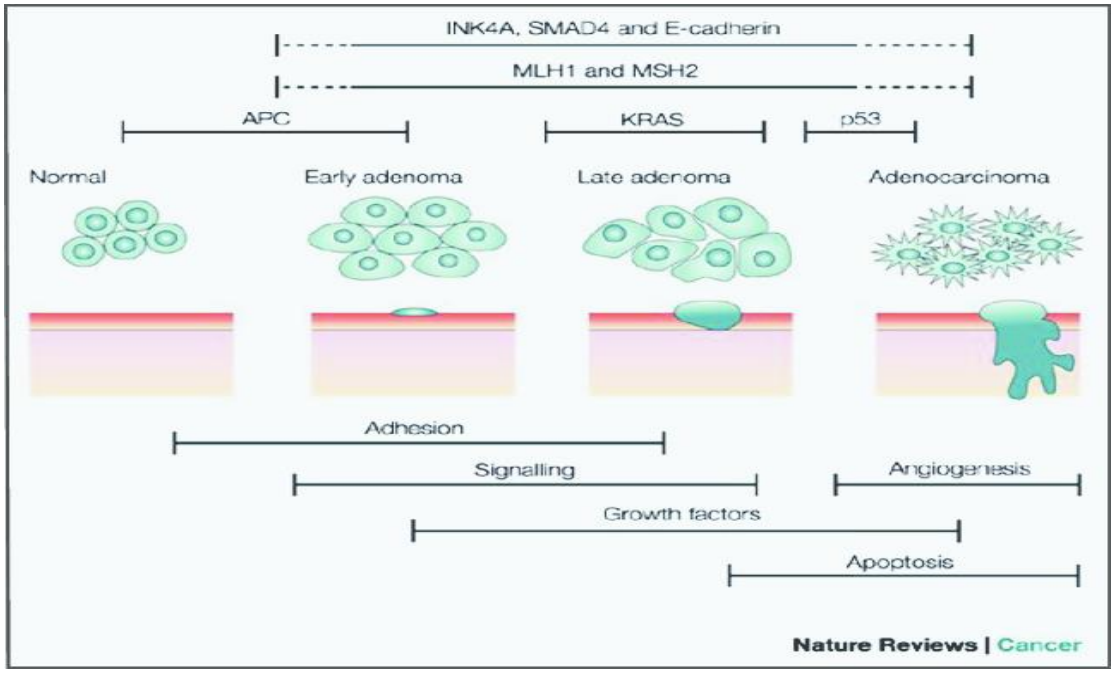


Figure 5: Adenoma-carcinoma sequence

Another essential molecular pathway is the microsatellite instability pathway. Loss of DNA mismatch repair genes in microsatellite sequences located in coding or promoter regions of genes involved in cell growth regulation leads to colorectal neoplasia. It is associated with patients who suffer from familial syndromes like hereditary nonpolyposis cancer.

Unfortunately, colorectal carcinoma and its pre-stages remain asymptomatic in the early phase. However, the detection rate of pre or early-stage neoplasia has improved significantly due to endoscopic screening.

Colorectal carcinoma can occur in every part of the large intestine. About ten percent appear in the caecum and the ascending colon. This percentage also applies to the transverse and the descending colon. Thirty percent occur in the sigmoid colon, and the rectum is affected in fifty percent of cases. Depending on the location, symptoms of advanced disease can be different. Right-sided colorectal carcinoma may include fatigue and weakness due to iron deficiency anemia. Therefore, iron deficiency anemia in older men and postmenopausal women should be treated as colorectal cancer until the contrary is proven. Left-sided colorectal cancer often expresses itself in occult bleeding, cramping, or changes in bowel habits. Furthermore, typical b symptoms like weight loss, fever, or night sweat are common in advanced stages.

Significant prognostic factors happen to be the depth of infiltration and the presence of metastasis. Common lymphatogenous metastasis routes are to paracolic and paraaortic lymph nodes as well as lymph nodes along the feeding arteries and the marginal arteries. In 75 percent of cases, distant metastases travel via portal vein to the liver. Pulmonary metastases occur in fifteen percent and bone metastasis in five percent of cases.

The TNM (tumor-node-metastasis) staging system and the UICC classification are the most common staging classifications.

UICC stage	Definition	TNM stage
0	Carcinoma in situ	Tis, N0, M0
IA	Infiltration as far as the submucosa	T1, N0, M0
IB	Infiltration as far as the muscularis propria	T2, N0, M0
IIA	Infiltration of all wall layers	T3, N0, M0
IIB	Extension beyond the organ	T4, N0, M0
IIIA	Regional lymph node metastases	T1/2, N1, M0
IIIB	N1: 1–3 lymph nodes	T3/4, N1, M0
IIIC	N2: >3 lymph nodes	Tx, N2, M0
IV	Distant metastases	Tx, Nx, M1

Figure 6: Staging of colorectal cancer

Another important prognostic factor is the histological grading of the tumor. Dependent on the grade of cell dysplasia, the grading varies from G1 (low-grade dysplasia) to G4 (high-grade dysplasia) (7).

Tumor staging is also essential to apply proper treatment.

The therapy is highly dependent on the progression of the disease.

Nearly all patients benefit from surgical intervention. The goal is an R0 resection of the tumor and regional lymphadenectomy.

In the early stages, like T1, a local excision may be sufficient. In later stages, a radical procedure is necessary.

Dependent on the tumor's localization, different colon parts are removed.

Tumors in the coecum and ascending colon require right hemicolectomy,

including radical excision of the coecum, the ascending colon, the right part of the transverse colon, the ileocolic and colic artery, plus lymphadenectomy. If neoplasia locates in the right flexure or the proximal transverse colon, this requires an extended right hemicolectomy with additional excision of the distal transverse colon and the middle colic artery.

Tumors located in the middle of the transverse colon can be resected with transverse colectomy.

Left-sided colorectal carcinoma in the descending or proximal sigmoid colon requires excision of the distal transverse colon, the left colic flexure, the descending colon, as well as the proximal sigmoid colon, and ligature of the inferior mesenteric artery.

If the carcinoma's location is in the left flexure of the transverse's colon distal part, extended left hemicolectomy with additional resection of the proximal transverse colon is inevitable.

Neoplasia in the middle or distal sigmoid colon indicates the sigmoid colectomy and ligature of the inferior mesenteric artery, distal of the left colic artery's origin.

The most common localization of colorectal carcinoma is, as mentioned before, the rectum.

Total mesorectal excision, which includes the sigmoid colon and the rectum until below the inferior transverse fold of the anal canal, is necessary if a rectumcarcinoma is in the middle of the lower third of the rectum.

Tumor in the upper third requires partial mesorectal excision, which ends above the inferior transverse fold.

In most cases, continence is likely due to the artificial creation of an anastomosis between the left intestinal loops or pouches.

In case of progressed anal cancer, a radical perianal amputation of the rectum, which leads to colostomy, is necessary (8).

From colon carcinoma in UICC stadium II, after R0 resection, there is a relative indication for adjuvant chemotherapy. From UICC stadium III onwards, there is an absolute indication.

In most cases, a combination of several chemotherapeutics, such as the Folfox schema, which includes oxaliplatin, folinic acid, and fluorouracil, is used.

In the case of rectum carcinoma, from stadium UICC II, there is a recommendation for neoadjuvant radiation and chemotherapy, including chemotherapeutics like Capecitabine or fluorouracil. After neoadjuvant radiochemotherapy and surgical intervention, there is no evidence that adjuvant chemotherapy has any benefit.

Despite distant metastases to the lung or liver, there can still be a curative approach if the metastases are resectable.

If there are non-resectable metastases or distant metastases beyond the lung or liver, or the patient is, due to other conditions, a non-surgical candidate, this indicates palliative treatment (9).
Depending on the patient's condition, it includes palliative chemotherapy combined with biological therapy, like EGFR or VEGF inhibitors. In some cases, surgical intervention due to obstruction or similar may be necessary (10).

1.4 Hepatic metastases:

Hepatic metastases are the most common hepatic neoplasia. One-third of all malign neoplasia leads to liver metastases, predominantly gastrointestinal tract cancer, breast cancer, lung cancer, or malign Melanoma.
Macroscopic, it can manifest in solitary or multiple nodes, but also a complete overtake of the liver parenchyma is possible (11).
The most common source of hepatic metastases is the colorectal carcinoma. About 20 percent of patients have visible hepatic metastases at diagnosis. Nearly 50 percent develop liver metastases after colorectal resection (12). They can remain mainly asymptomatic in the beginning. However, symptoms like nausea, loss of appetite, jaundice, abdominal pain, or ascites are possible in advanced stages of the disease.
Imaging tests are an efficient tool to detect liver metastases. The most common tool to evaluate disease is the abdominal CT scan. In particular cases, the MRI is a valuable alternative. The Pet CT scan is a highly sensitive and specific method to rule out further extrahepatic metastases. For observing the size and the liver's texture, the ultrasound is a non-invasive and safe option.
A needle biopsy of the lesions may be necessary if the imaging test results do not give 100 percent certainty or in case no primum is detected.
Blood tests can be a helpful tool, as well. Raised liver enzymes like AST or ALT point out the damage to the liver parenchyma. Elevation of tumor marker levels such as the so-called carcinoembryonic antigen (CEA) or CA 19-9 after treatment can point to hepatic metastases (13).

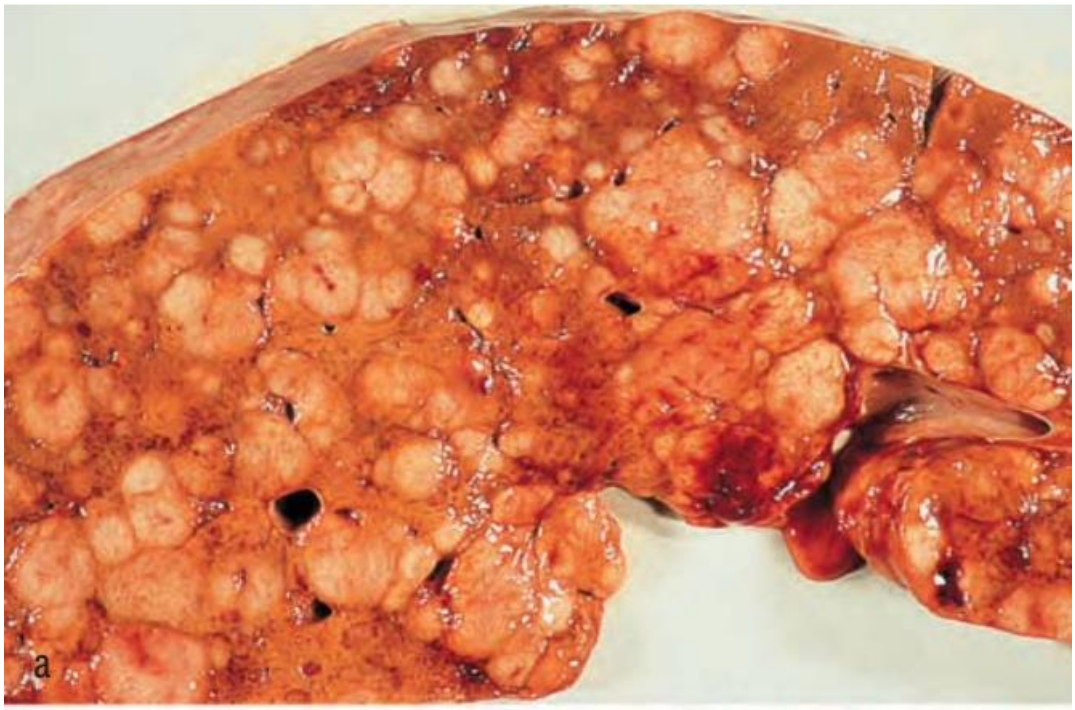


Figure 7: Hepatic metastases

1.5 Treatment of non-resectable hepatic metastases.

Unfortunately, 80 percent of patients present with non-resectable disease. For the majority of these patients, chemotherapy is the only option. Data shows that median survival can be extended significantly. In the best-case scenario, chemotherapy can transform a non-resectable candidate into a surgical candidate. Additional use of monoclonal antibody therapy, such as Bevacizumab, has been shown to improve the prognosis as well (14).

Another way of treating unresectable hepatic metastases is local ablative options. Radiofrequency ablation, microwave ablation, and cryotherapy are safe and effective ways to treat liver neoplasia.

All three use thermic effects to induce tumor necrosis. The selection of the method depends on several circumstances, like the lesions' size and location (15).

One more local therapy option is hepatic arterial infusion. Hepatic metastases derive their blood supply mainly through the hepatic arteries. Because the regular liver parenchyma receives blood mainly from the portal vein system, targeted therapy through local chemotherapy through the hepatic vein is promising.

Data shows significantly higher overall survival and lower side effects than regular systemic chemotherapy (16).

1.6 Partial hepatectomy

Surgical intervention on the liver differs from surgical intervention on other organs due to its ability for regeneration. Residual non-cirrhotic liver parenchyma regenerates step by step after surgery.

Liver resections have a long history. The first partial hepatic resections were conducted at the end of the nineteenth century.

Generally, there are two main categories of surgical procedures. On the one hand, there are anatomical resections and, on the other hand, non-anatomical resections. Anatomical resections orientate at the liver's segmental composition, defined by its blood vessels and biliary ducts.

Non-anatomical procedures do not follow this system. Usually, they are used to treat small, mostly benign lesions, with no need for extended hepatic resection and debridement after liver injury (17). Furthermore, due to the larger amount of preserved liver parenchyma after a non-anatomical resection, it can be an option in case of hepatic comorbidities, such as liver cirrhosis, where additional loss of liver parenchyma could lead to liver insufficiency.

Dependent on the lesions' localizations and sizes, various possible surgical procedures can be used.

A resection of segments V, VI, VII, VIII defines a right hemihepatectomy. If it includes segment IV as well, we speak of an extended right hemihepatectomy.

Resecting segments II, III, and IV results in a left hemihepatectomy. Adding segments V and VI lead to an extended left hemihepatectomy. Central liver resection is defined as a resection of segments IV, V, and VIII.

A segmentectomy stands for resection of a single liver segment. If necessary, segmentectomies can also be combined to preserve more healthy liver parenchyma.

Besides, resectioning major blood vessels like the hepatic arteries, the portal vein, or the inferior vena cava with subsequent reanostomisis or reconstruction is possible. The same applies to the biliary tract.

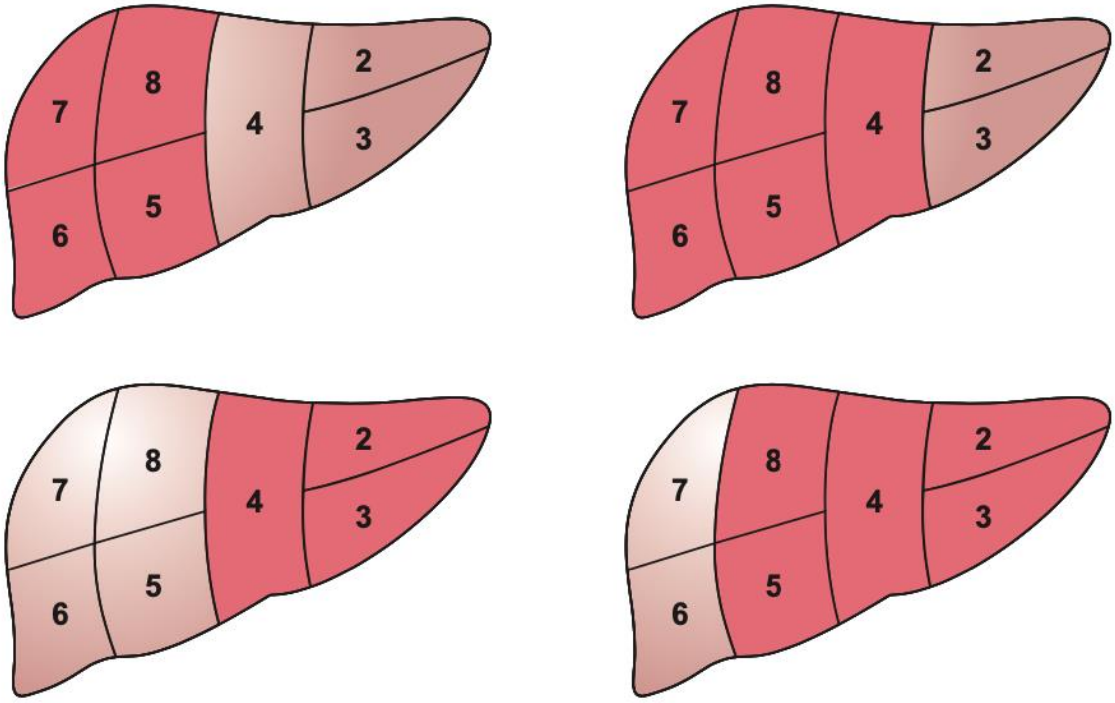


Figure 8: (Extended) right and left hemihepatectomy visualized

The anatomical resection's advantages are less blood loss, less postoperative necrotic tissue, and fewer biliomas, which is an accumulation of bile inside the abdominal cavity.

A combination of anatomical and non-anatomical resection is also possible (18).

Hepatic resections mostly have neoplastic causes. On the one hand, these lesions can be benign. The most common ones are liver hemangioma and focal nodular hyperplasia. On the other hand, primary and secondary malign neoplasia is an absolute indication for surgical intervention. The most frequent primary liver cancers are hepatocellular carcinoma and cholangiocellular carcinoma. Secondary neoplasia is another term for hepatic metastases, mainly from the gastrointestinal tract but also from the breast, lung, or skin.

Apart from neoplasia, other causes like liver abscesses can be an indication. Generally, every circumscribed liver lesion may be a potential cause for hepatic resection (19).

1.7 Requirements for surgical intervention and common comorbidities

Surgical intervention is the gold standard for treating colorectal liver metastases.

The patient's eligibility for surgery depends on several circumstances and is crucial. Additional extrahepatic metastases have to be ruled out. A healthy liver would tolerate a reduction down to twenty percent. According to the comorbidity's severity, more liver parenchyma must be preserved if the patient already has a hepatic disease (20).

Less than three hepatic veins and seven liver segments should be involved, and the patient must not suffer from severe hepatic insufficiency or severe accompanying diseases.

The essential requirement is the possibility of an R0 resection of the hepatic metastases.

For evaluation of resectability, every patient with colorectal liver metastases should be presented to a hepatobiliary surgeon.

Neoadjuvant chemotherapy may be an option to improve the resectability of primary unresectable patients (21).

An interesting method is the so-called portal vein embolization. Due to occlusion of the portal vein's blood flow to the liver segments that will be resected, atrophy of the same liver segments and compensating hypertrophy of the non-affected liver segments follows. This results in more healthy liver parenchyma, which is essential for the patient's operability (22).

In most cases, people who receive hepatic resection due to hepatic colorectal metastases are of advanced age. It follows that these patients usually suffer from several comorbidities, which should be taken into account. Common comorbidities in the elderly include diabetes, cerebrovascular disease, or chronic pulmonary disease. A proper tool is the so-called Charleston Comorbidity index to predict the patient's comorbidities. This system, developed in the late '80s, assigns a specific score to a specific comorbidity based on its severity. Furthermore, one point is added for each decade over forty years. We can predict the patient's one-year mortality and express it in a certain percentage by adding these scores (23).

Comorbidity	Score
Prior myocardial infarction	1
Congestive heart failure	1
Peripheral vascular disease	1
Cerebrovascular disease	1
Dementia	1
Chronic pulmonary disease	1
Rheumatologic disease	1
Peptic ulcer disease	1
Mild liver disease	1
Diabetes	1
Cerebrovascular (hemiplegia) event	2
Moderate-to-severe renal disease	2
Diabetes with chronic complications	2
Cancer without metastases	2
Leukemia	2
Lymphoma	2
Moderate or severe liver disease	3
Metastatic solid tumor	6
Acquired immuno-deficiency syndrome (AIDS)	6

Figure 9: Charleston Comorbidity Index

Another frequent and significant comorbidity in the elderly that the Charleston Comorbidity Index does not cover is the Frailty syndrome.

1.8 Frailty Syndrome

The Frailty syndrome is a complex geriatric constellation. It describes a state of high vulnerability, decreased resistance to stressors, and low functional reserve. Frailty is tightly associated with Sarcopenia, defined as a loss of skeletal muscle mass and function.

Approximately five percent of the elderly are presumed to suffer from Frailty syndrome (24) (25).

The following five criteria, specified by Fried et al. in a cohort study of more than 5300 men and women over 65 years old, define the Frailty phenotype as a geriatric syndrome.

These are:

- Slow walking speed
- Unintentional weight loss (More than ten pounds in the last year)

- Exhaustion (self-reported)
- General weakness
- Low level of activity

If three or more of these five criteria correlate with the patient's clinical picture, we speak of the Frailty syndrome. Pre-Frailty defines a stage where the likelihood of progression to Frailty is elevated. In case of suffering from one or two criteria after Fried, we call it a pre-Frailty stage.

Frailty induces dysregulation in several physiological regulatory circuits, such as the endocrinologic system, and disturbs the ability to maintain homeostasis.

Nutritional disturbance, muscle loss, or cognitive deficits are expected consequences. Along with further diseases, psychosocial conditions like depressive state or social withdrawal are also associated with Frailty and can be a potential cause or a potential consequence (25).

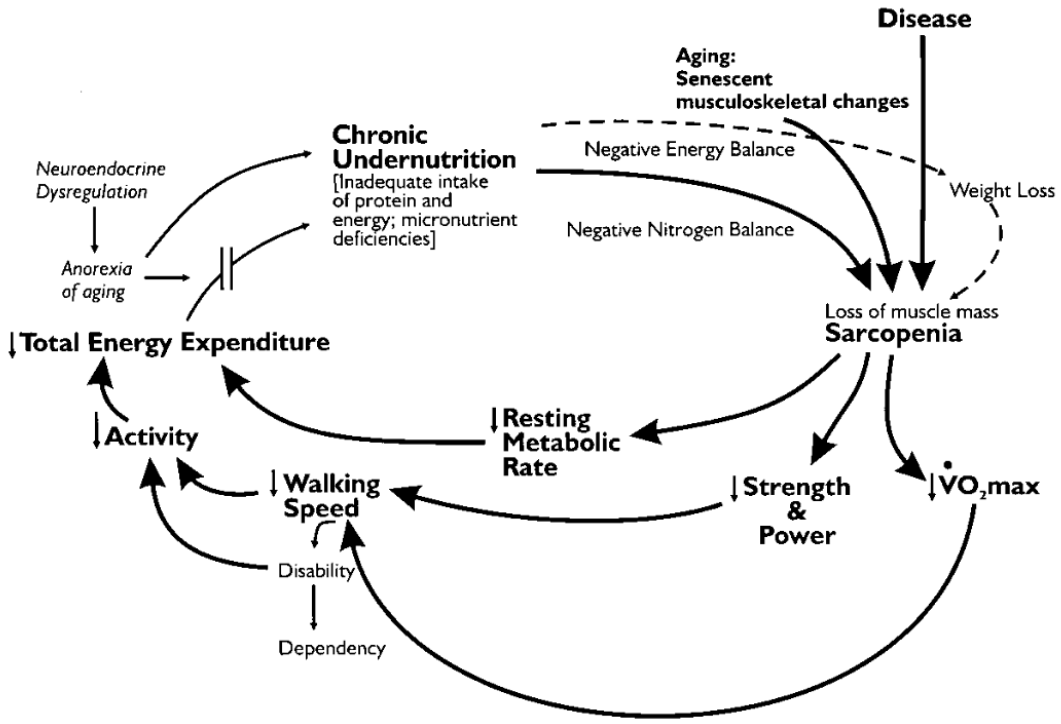


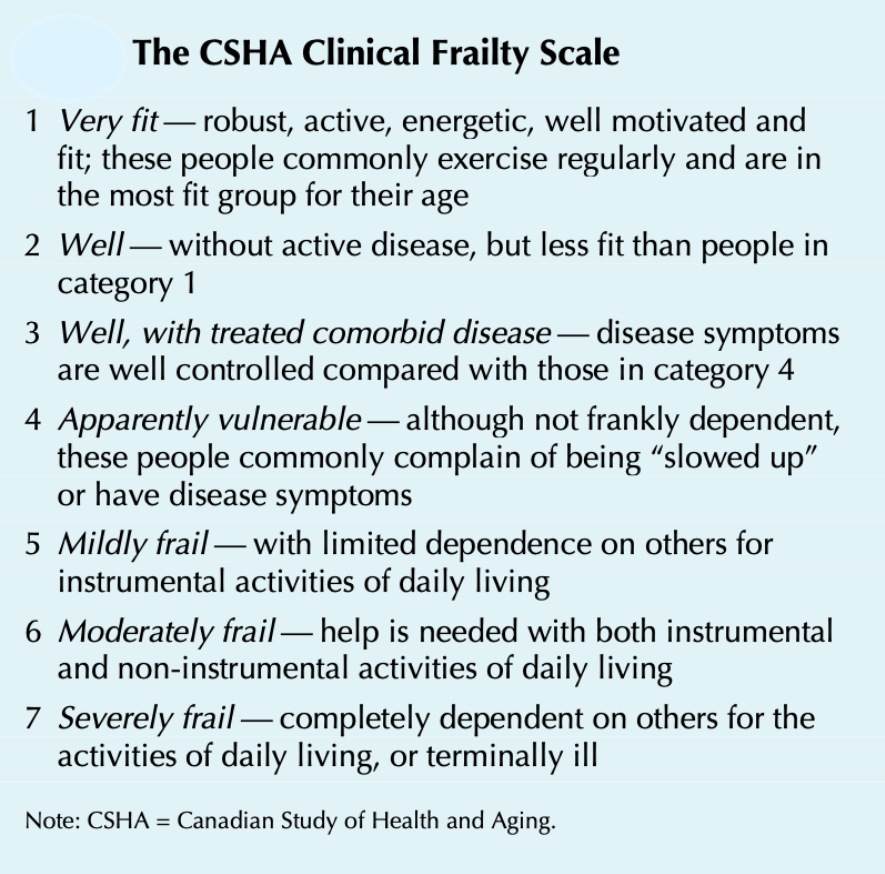
Figure 10: Cycle of Frailty

The CSHA Frailty Index is a tool to estimate the degree of Frailty. It incorporates and adds 70 clinical deficits, including the presence and severity of current conditions, psychosocial risk factors, neurological deficits, and ability in daily living activities.

Unlike the Frailty phenotype, further conditions besides physical disabilities are included. Therefore, it enables a comprehensive assessment.

To provide an easier but effective way for predicting the patient's Frailty level, Rockwood et al. defined the CSHA Frailty Scale.

The CSHA Frailty Scale is a simple possibility for the examiner to assign the patient to a particular grade of Frailty. This seven-step scale goes from very fit to severely frail and can be used by trained medical staff to estimate the patient's Frailty grade in a clinical setting (26).



The CSHA Clinical Frailty Scale

1 *Very fit* — robust, active, energetic, well motivated and fit; these people commonly exercise regularly and are in the most fit group for their age

2 *Well* — without active disease, but less fit than people in category 1

3 *Well, with treated comorbid disease* — disease symptoms are well controlled compared with those in category 4

4 *Apparently vulnerable* — although not frankly dependent, these people commonly complain of being "slowed up" or have disease symptoms

5 *Mildly frail* — with limited dependence on others for instrumental activities of daily living

6 *Moderately frail* — help is needed with both instrumental and non-instrumental activities of daily living

7 *Severely frail* — completely dependent on others for the activities of daily living, or terminally ill

Note: CSHA = Canadian Study of Health and Aging.

Figure 11: CSHA Clinical Frailty Scale

The etiology and pathogenesis of Frailty is a complex topic and includes multiple elements.

The aging process is one of the most critical risk factors, but also genetics, lifestyle, which includes malnutrition, and other medical conditions, have a considerable impact.

Chronic inflammation and immunologic processes seem to play an essential role in the course of the disease.

The health outcomes of Frailty can be severe. Due to increased risk of falling, disability, social isolation, just to name a few potential consequences, it leads to overall higher morbidity and mortality of patients (27).

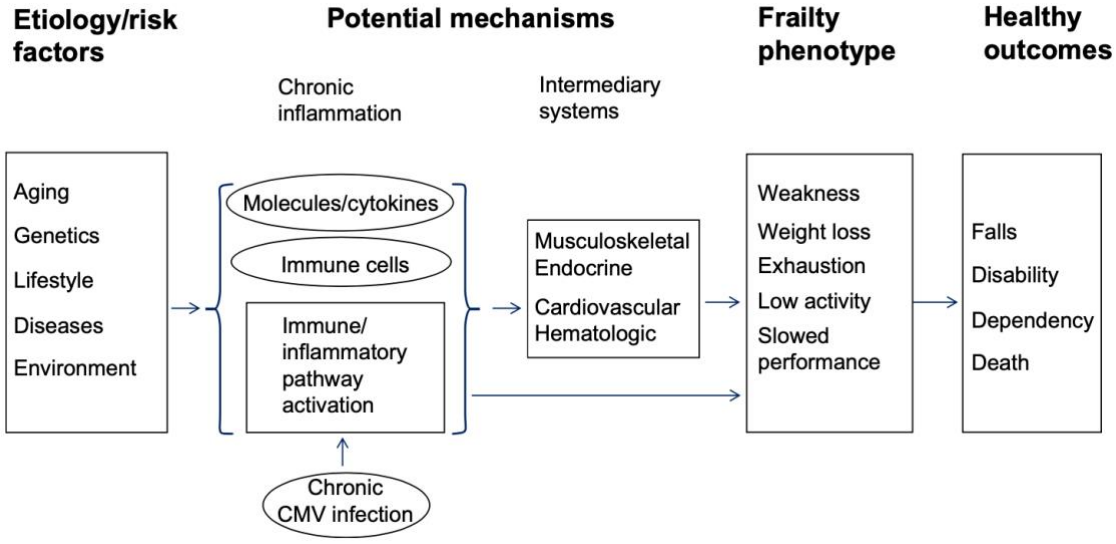


Figure 12: Pathogenesis of Frailty

To reduce the degree of Frailty, an individual tailored multifactorial treatment of a multidisciplinary team including geriatricians, physiotherapists, nurses, dieticians, and rehabilitation physicians would be an optimal setting.

Due to Frailty's multifactorial etiology, a combined therapy containing nutritional supplementation, physical activity, and cognitive training showed promising results. To prevent Frailty development, a regular geriatric assessment and monitoring of the patient's physiological reserve is an efficient way to identify pre-frail stages and enables early intervention. Furthermore, well-balanced nutrition, physical exercise, and mental health reduce the risk significantly (28).

1.9 Sarcopenia

Sarcopenia is a generalized, age-related, and progressive muscle disorder that leads to loss of muscle tissue and muscle function.

As we already know, Sarcopenia is tightly associated with Frailty syndrome and therefore increases adverse health events, such as falls, functional decline, and in the end, mortality, significantly. The prevalence of Sarcopenia progresses with the

advanced age of the population. Studies have shown a prevalence between four and forty percent, depending on population and diagnosis criteria.

Most cases of Sarcopenia remain undiagnosed, although it can be detected with simple tools.

Symptoms such as falling, weakness, muscle wasting, weight loss, and difficulties accomplishing everyday tasks hint at Sarcopenia.

Measuring the patient's grip strength or conducting the so-called chair stand test can give a picture of his or her muscle function.

The next diagnostical step would be a measurement of muscle mass.

Dual X-Ray Absorptiometry (DXA) is the most effective way to estimate lean muscle mass in a clinical setting.

CT and MRI can also be used but play a more critical role in research, particularly in oncologic patients' follow-up scans (29). Muscle quantity can be measured as total skeletal muscle mass, as Appendicular Skeletal Muscle Mass, which stands for the muscle mass of the extremities, or as muscle mass of a specific body area, such as the psoas area.

When Sarcopenia is diagnosed, we can estimate the severity by pursuing tests like quantifying the patient's gait speed and many others.

The following table gives an overview of cut-off points, defined by the European Working Group on Sarcopenia in Older People (EWGSOP2).

Test	Cut-off points for men	Cut-off points for women
EWGSOP2 sarcopenia cut-off points for low strength by chair stand and grip strength		
Grip strength	**<27 kg**	**<16 kg**
Chair stand	**>15 s for five rises**	
EWGSOP2 sarcopenia cut-off points for low muscle quantity		
ASM	**<20 kg**	**<15 kg**
ASM/height^2	**<7.0 kg/m^2**	**<5.5 kg/m^2**
EWGSOP2 sarcopenia cut-off points for low performance		
Gait speed	**≤0.8 m/s**	
SPPB	**≤8 point score**	
TUG	**≥20 s**	
400 m walk test	**Non-completion or ≥6 min for completion**	

Figure 13: Sarcopenia Cut-Off Points

The development of so-called primary Sarcopenia is highly associated with age. Furthermore, genetic and lifestyle factors seem to play a role without a specific cause.

Other or additional factors than age cause secondary Sarcopenia, for instance, inflammatory, endocrinologic, or oncologic conditions.

In lockstep with bone mineral density, the human muscle strength and function peak are in young adulthood. Afterward, it starts constantly decreasing, with higher progression in advanced age. There is also an association between birth weight and muscle strength over a lifetime.

Therefore, an individual reaching their maximum muscle mass and muscle strength in young adulthood would decrease the likelihood of Sarcopenia. Further intervention, such as physical exercise or adjusted nutrition, slows down or stops the progression.

In conclusion, we must recognize that Sarcopenia is a highly prevalent and relevant condition that needs to be considered.

Many questions have been answered in recent years, but more research is necessary for patients' goods due to the social and economic damage caused by this condition and its adverse health events (30).

1.9.1 Sarcopenic obesity

Sarcopenic obesity defines a state of coexistence between Sarcopenia and obesity. As already mentioned, Sarcopenia includes the presence of low muscle mass and low physical performance.

Unfortunately, there are no universally valid parameters or cut-off points to define Sarcopenic obesity right now. In addition to the existence of Sarcopenia, a high amount of body fat is the most obvious parameter.

The WHO considers persons with a Body Mass Index over 25kg/m ^{2} overweight and over 30 kg/m ^{2} obese.

Therefore, a reasonable way to detect the presence of sarcopenic obesity is a measurement of low muscle mass and high body fat with diagnostic imaging in combination with an elevated BMI (31).

Statistically, the most frequent cohort suffering from high body fat is 60 to 75 years.

The etiology of obesity is multifactorial and includes low physical activity, malnutrition, and age-related changes in body composition.

Since obesity is associated with various other conditions, such as musculoskeletal conditions, that contribute to low physical activity and changes in the endocrinologic system, obesity and insulin resistance often occur together. Since insulin is a highly active anabolic hormone, insulin resistance may reinforce muscle catabolism.

Furthermore, high body fat is associated with pro-inflammatory cytokines, linked to a decline in muscle mass and strength. Moreover, obese patients with low muscle strength showed elevated inflammatory values such as C-reactive protein and Interleukin 6 (32).

The consequences of sarcopenic obesity can be severe. An elevated risk of disability, cardiovascular disease, diabetes, poor outcomes in oncologic disease, reduced psychological health, and overall higher mortality has been shown.

The difficulty in the treatment of sarcopenic obesity is in finding the right balance between weight loss and increasing muscle mass. A special diet combined with physical activity is the best course of action. Pharmacotherapeutic intervention requires further investigation, especially in the endocrinologic system (33).

In conclusion, the impact of sarcopenic obesity on the patient's morbidity and mortality is most likely significant, potentially even more than in sarcopenic patients, which must be confirmed with further data.

1.9.2 Impact of Sarcopenia in surgical oncology

Regarding the development of Frailty and the many adverse health outcomes, Sarcopenia is associated with a significant impact on peri and postoperative complications. Furthermore, a legitimate question is the impact on the overall survival of patients undergoing oncologic surgery.

In a review of S. Joklekar et al., which includes several studies with over 3000 patients in total, postoperative complications, and long-term survival, was analyzed. The patients suffered from solid tumors, like colorectal carcinoma, colorectal hepatic metastasis, esophageal carcinoma, hepatocellular carcinoma, pancreatic cancer, Melanoma, and bladder carcinoma.

With this quantity of cancer types comes various surgical interventions, such as partial hepatectomy, esophagectomy, or pancreatectomy, just to name a few.

The Clavien Dindo grading system, used in most studies, is a simple and effective tool to categorize the severity of peri and postoperative complications.

	Definitions
I	Any deviation from the normal postoperative course without the need for pharmacological treatment other than the "**allowed therapeutic regimens**", or surgical, endoscopic and radiological interventions
II	Requiring **pharmacological** treatment with drugs beyond those allowed for grade I complications. Blood transfusions and total parenteral nutrition are also included.
III	Requiring **surgical, endoscopic or radiological intervention.**
IV	**Life-threatening complication** requiring critical care management; CNS complications including brain haemorrhage and ischemic stroke (excluding TIA), sub-arrachnoidal bleeding.
V	**Death** of a patient

Figure 14: Clavien Dindo Classification

Several studies showed a significant increase in postoperative complications (Clavien Dindo ≥1) and severe postoperative complications (Clavien Dindo ≥ 3) in sarcopenic patients, such as infectious, gastrointestinal, or cardiopulmonary complications., compared to non-sarcopenic patients.

Furthermore, Sarcopenia was also associated with the length of postoperative stay in an intensive care unit.

Not only muscle mass but also muscle quality was a predictor of complications.

A study by Sabel et al. referred to complications after therapeutic lymph node dissection in stage three Melanoma, and an over eight percent increase of complications for every ten Hounsfield unit decrease in muscle density was detected.

Another study by Wan et al. analyzing postoperative morbidity after radical cystectomy due to bladder cancer showed similar results (34).

A review by M. Cornet et al., referring to several studies which analyzed the impact of Sarcopenia on patients undergoing hepatic resection due to primary or secondary malign liver neoplasm, also suggests an impact on postoperative minor and

significant complication as well as an increase in the postoperative hospital stay. However, not every study showed a statistically significant difference.
An overall increased postoperative mortality could not be proven due to the lack of studies and relatively small sample sizes.
Some studies have shown a statistically significant influence in terms of long-term survival, but others have not (35).
A recent Italian study published in September 2020 by G. Berardi et al., including 234 patients undergoing hepatic resection due to malign liver neoplasm, showed the following results. Depending on muscle mass and strength, measured with CT scans and the grip strength of patients, the sample was divided into the following four cohorts. Group A (normal muscle mass/muscle strength), Group B (reduced muscle strength), Group C (reduced muscle mass), Group D (reduced muscle mass/strength).
Analogous to previous studies, the postoperative morbidity was significantly increased in group D (3,92 times higher) compared to the group without sarcopenic patients. Similarly, the length of the hospital stays and the readmission rate raised (36).
In conclusion, Sarcopenia has a significant impact on postoperative morbidity. The influence on postoperative mortality and long-term survival must be verified with additional data.

1.9.3 Obsolescence of the western population

If we speak of Frailty or Sarcopenia, the tight association with advanced age is the most significant factor. If we look at the expected obsolescence of the population, mainly in more developed countries, we cannot negate the enormous impact of Sarcopenia on the population's physical and mental health.
In Austria, the percentage of the population with an age of 65 years or higher amounts to approximately 19 percent. In 2050 the estimated fraction of people this age will be 28 percent (37).

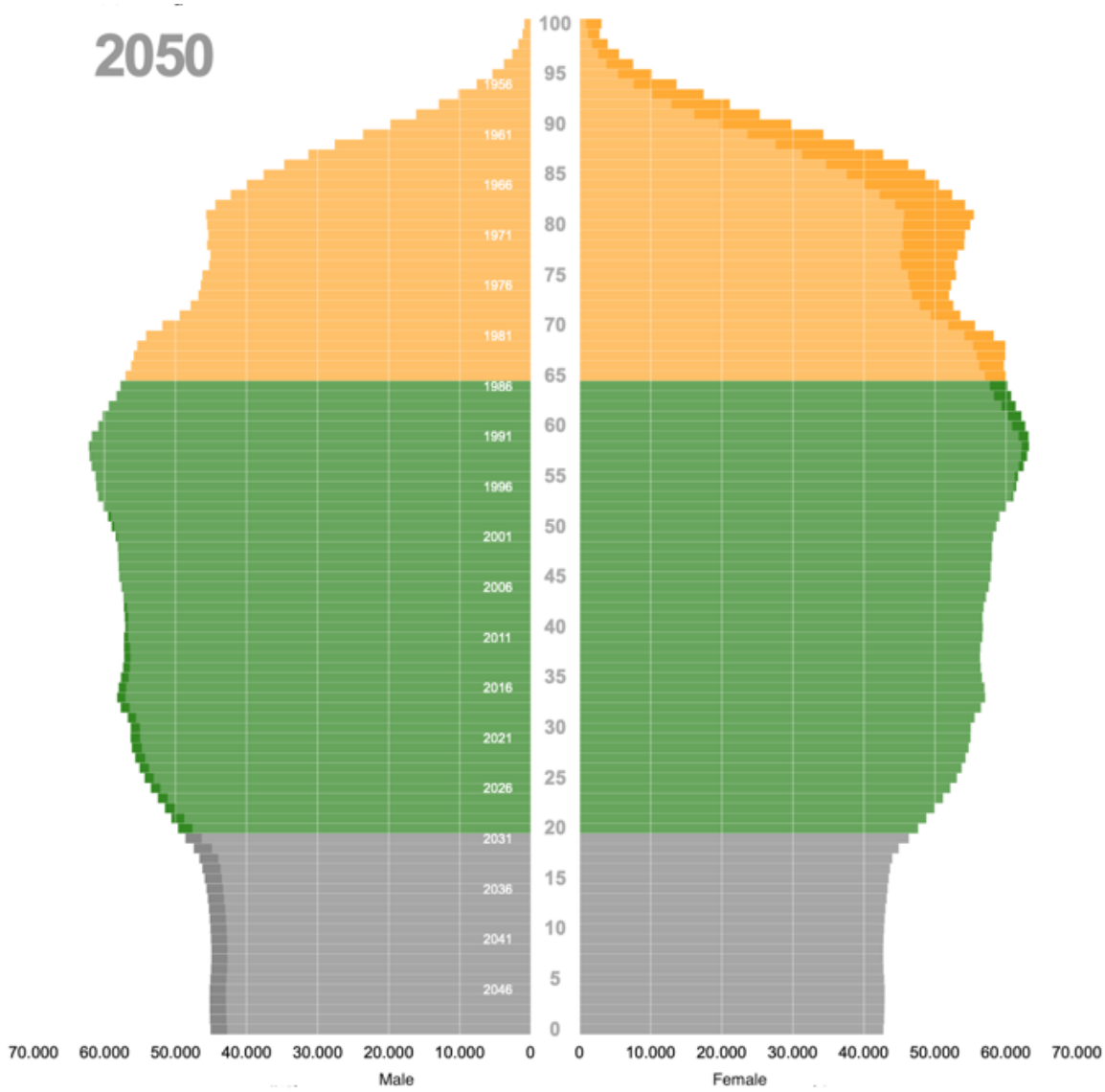


Figure 15: Estimated population pyramid of Austria in 2050

Another question is the financial viability of the social security system to treat the adverse health outcomes of Sarcopenia and the availability of enough medical staff to treat this enormous number of patients in the future.

In the case of western European countries, predictions show that this problem cannot be solved solely with youth immigration from other countries (38).

This problem is unavoidable, and the importance of research and prevention of Sarcopenia is undeniable because of these circumstances.

2.0 Methods

2.1 Data acquisition

The data used in the statistical analysis was realized by research associates of the Medical University of Graz's department of general and visceral surgery.

I collected data from March to October 2020 and accumulated data from patients undergoing partial hepatectomy in 2019.

The clinical data processing program Open Medocs, the standard software of all hospitals of KAGES (hospital association of Styria), was the data source.

Finally, the data was transferred into the so-called "Liver Database" of the general and visceral surgery department, a Microsoft Excel document, including the data of approximately 1200 patients who received partial hepatectomy between the years 2005 and 2019.

The Liver Database includes a large variety of parameters, from the primary disease, the date of surgery, and the survival time after surgery, over blood test results to tumor histology and non-surgical treatment.

Parameters, which point out the patient's general condition, also play an essential role.

The ASA scheme is the most common way of predicting the patient's perioperative risk. Evaluating the ASA score is a standard measure in every anesthesiologic preoperative assessment. It goes from ASA I to ASA VI (39).

ASA Physical Status Classification System	
I.	A normal healthy patient
II.	A patient with mild systemic disease
III.	A patient with severe systemic disease
IV.	A patient with severe systemic disease that is a constant threat to life
V.	A moribund patient who is not expected to survive without surgical procedure
VI.	A declared brain-dead patient whose organs are being removed for donor purposes The addition of 'E' indicates emergency surgery.

Figure 16: ASA Classification system

To describe oncologic patients' physical state and limitations, a common way is to utilize a classification developed by the ECOG score

- ECOG 0: Self-sustaining, fully active without limitation
- ECOG 1: Limited in physical activity, ambulant treatable, able to execute light work.
- ECOG 2: Capability of self-care, Unable to do regular work or activity
- ECOG 3: Confined to bed more than 50 percent of waking hours, not capable of total self-care
- ECOG 4: Completely in need of care, bed-ridden (40)

These two score-systems and the already mentioned Charleston Comorbidity Index are the main instruments used in the database used to estimate the overall physical condition of study participants.

2.2 CT Imaging and the identification of Sarcopenia

Diagnostic imaging is essential in every preoperative assessment, especially in large and complex operations like a partial hepatectomy. Preoperative CT images were used to detect the presence of Sarcopenia.

Measuring the muscle quantity on the one hand and the actual muscle quality, on the other hand, was our approach.

We used the OSIRIX MD DICOM viewer, an image processing software, to present and handle radiologic images, such as X-Ray, CT, MRI, and PET CT scans.

All measurements were conducted at the Height of L3. An excellent way to identify the Height of L3 in CT imaging is to scroll through the patient's CT scan until recognizing the iliac crest's highest points.

Then we measured the left and right psoas muscle's surface in the unity cm^2, which adds up to the total psoas area (TPA).

Muscle density is a surrogate parameter for muscle quality. Therefore, the evaluation of muscle density in CT imaging is essential.

The Hounsfield unit (HU) describes the attenuation of x-ray radiation in different types of tissue in computer tomography.

It can go from -1000 (air) to more than 2000 (dense bones) or 3000 units (metal).

These numbers can be reconstructed in grayscales to produce a CT image. Therefore, dense tissue with a high number of Hounsfield units that absorb more radiation appears brighter, and less dense tissue appears darker (41).
The possible range of Hounsfield units in skeletal muscle tissue is between -190 HU and +150 HU, with a protrusive peak at +50 HU (42).
Consequently, we can act on the assumption that a higher number of Hounsfield units means a higher muscle quality. So, we also quantified the Hounsfield units of the two psoas muscles with Osirix and added the results to the Liver database.
Furthermore, the surface of the paraspinal muscles (Musculus erector spinae, Musculus quadratus lumborum), the musculus transversus, obliquus externus et obliquus internus abdominis, and the musculus rectus abdominis were measured.
The sum of all these muscles areas, including the psoas muscles, results in the total skeletal muscle mass at the Height of L3.
To identify the presence of Sarcopenia, we used the so-called “Skeletal muscle index (cm^2/m^2) at height L3.” The Skeletal muscle index is the quotient between the skeletal muscle mass at a certain height and the body surface area. It is a valuable option to predict the patient’s muscle mass.
The following figures show the procedure of Measurement.

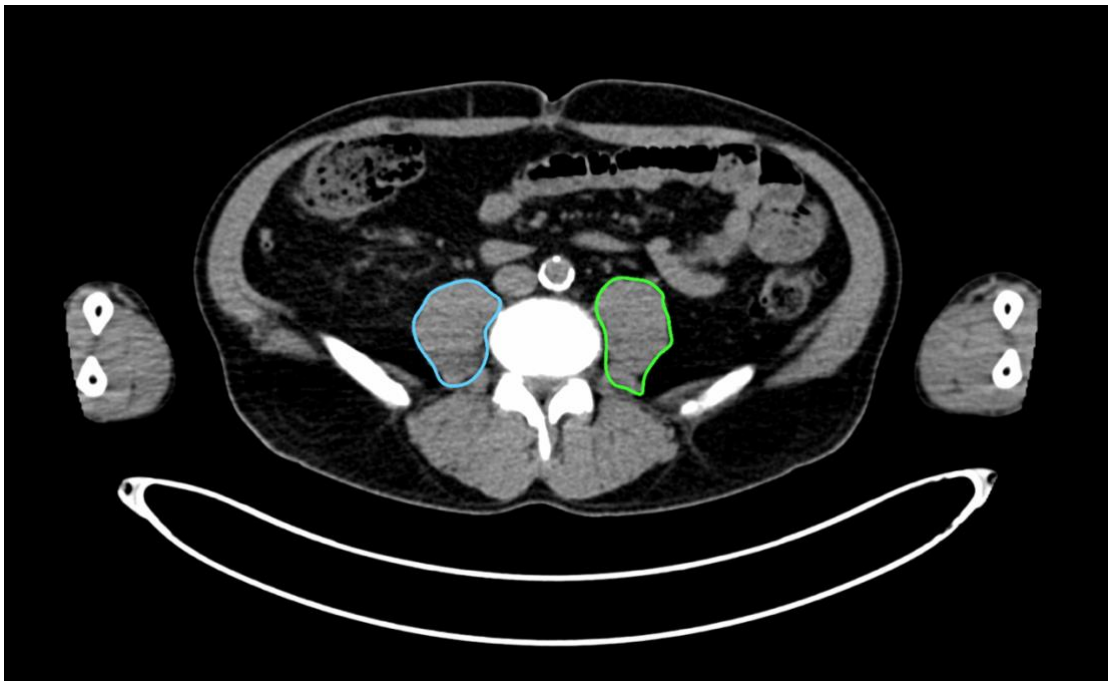


Figure 17: Measurement of the psoas muscles at Height L3

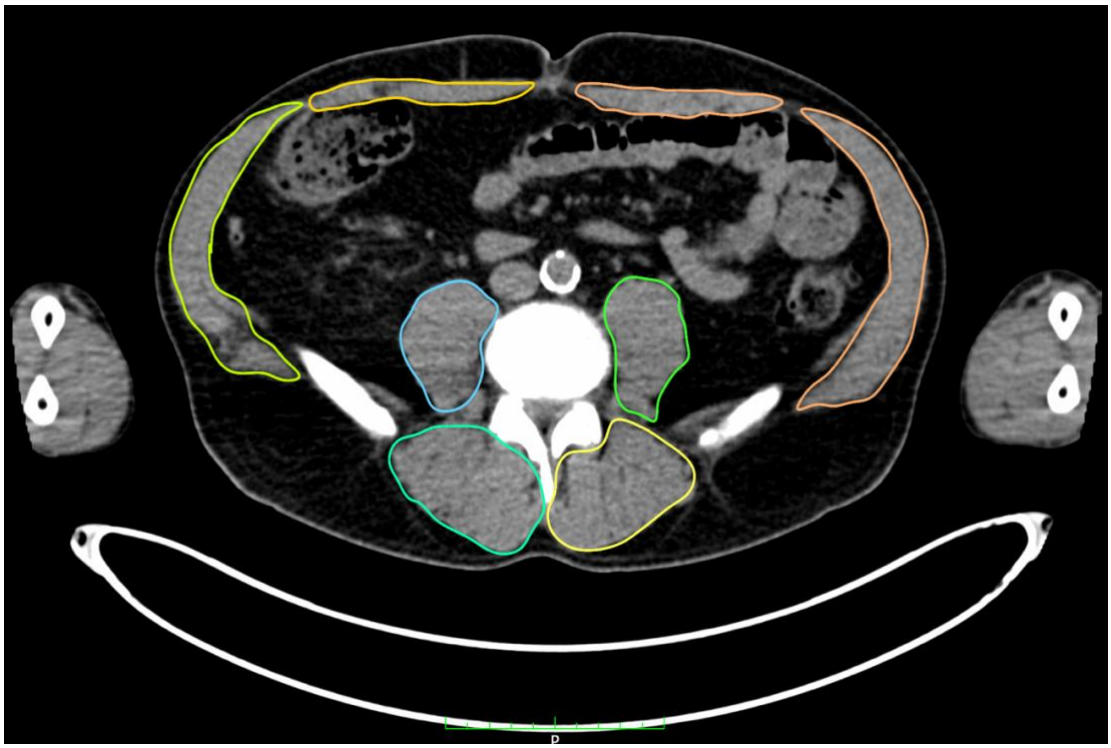


Figure 18: Measurement of the psoas, lower back, and abdominal muscles at height L3

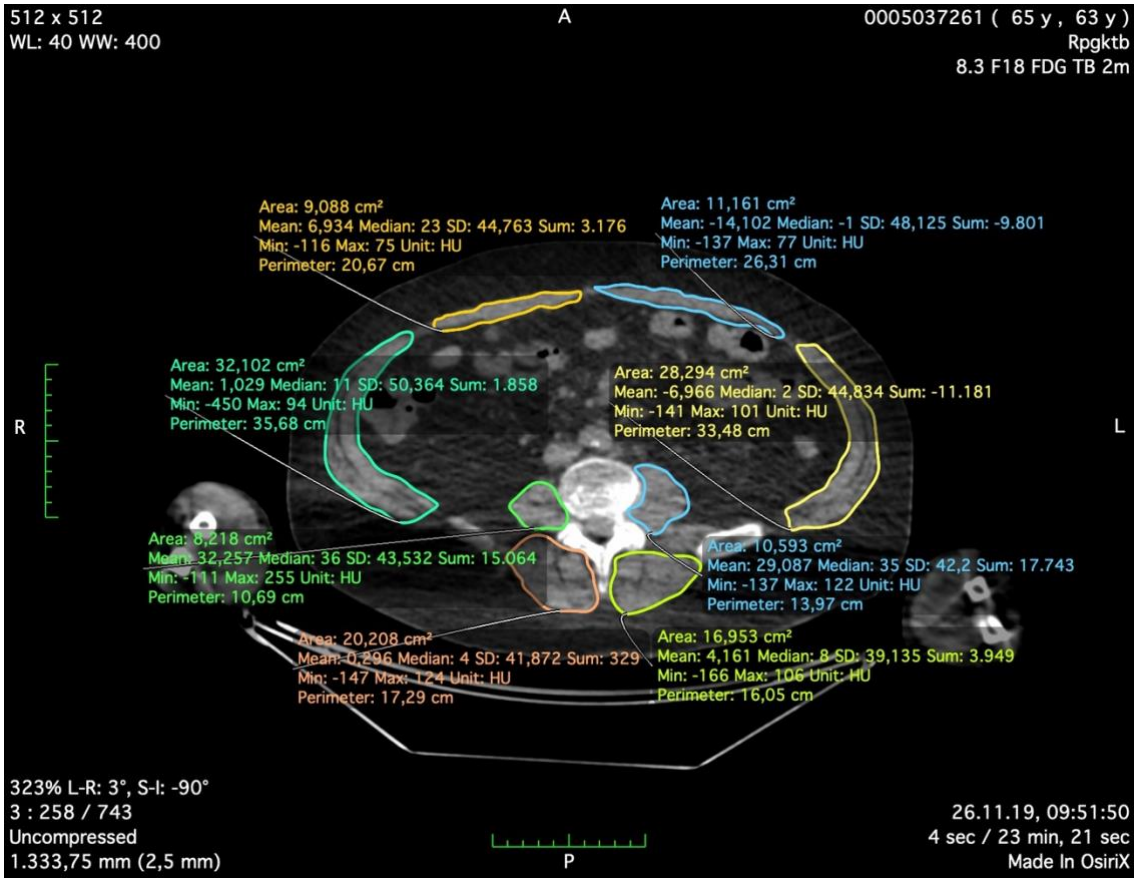


Figure 19: Measurements, picturing the results

2.3 Statistical analysis

Continuous and categorical variables were reported as medians with interquartile ranges (IQR) and as whole numbers and percentages, respectively. The distributions of categorical and numerical variables between independent groups were compared using Fisher exact test and a Mann-Whitney U test. Statistically significant variables in the univariate analysis were subjected to a multivariable logistic regression model with backward elimination method (likelihood-ratio test). Odds ratio (OR) and 95% confidence interval (CI) were calculated to determine the probability of tumor location and sarcopenia. Overall survival was analyzed using the Kaplan-Meier method, and differences in survival were evaluated with the log-rank test. The association of relevant clinicopathological variables with postoperative mortality was computed using Cox proportional hazards models; backward stepwise selection was used to identify variables for the multivariable Cox proportional hazards model. Results were reported as hazard ratios (HR), where appropriate, with 95 % confidence intervals (95 % CI). The impact of low skeletal muscle mass was evaluated both as a continuous and a categorical variable. As previously reported and validated, to obtain the specific sex categorical cut-off value for low skeletal muscle mass, optimum stratification was assessed through a series of sensitivity analyses, and low skeletal muscle mass was defined in categorical analyses as the lowest quartile. The SMI cut-offs to define low skeletal muscle mass were 33,25 cm^2/m^2 in females and 34,94 cm^2/m^2 in males. SMI entered univariate and multivariate analysis as described above. A P value of less than 0.05 was considered to be statistically significant. For statistical analysis, SPSS 26.0 (IBM, Chicago) was used, images were generated using SciStat (www.scistat.com, MedCalc, Ostend, Belgium).

3.0 Results

In total, 342 patients suffering from hepatic metastases of colorectal carcinomas were included in the study. To evaluate their pre-peri and postoperative physical condition, multiple parameters were included. The number on the right column represents the median in all following columns.

	All patients
Age OP	68 (60-75)
Follow up (months)	28 (13-61)
Length of hospital stay (days)	15 (11-18)
BMI	25 (23-29)
Charlson Comorbidity Index	7 (6-8)
Primary tumor size (in cm)	4 (3-5,5)
Size largest metastasis (in cm)	2 (1,2-3,7)
Neutrophile granulocytes (G/l)	3,7 (2,7-4,8)
Thrombocytes (G/l)	212 (173-264)
Lymphocytes (G/l)	1,4 (1,1-1,9)
Albumin (g/dL)	4,2 (4,0-4,5)

Table 1: All patients

Preoperative abdominal CT scans were available from 251 patients. Sixty-three of these patients are sarcopenic, defined by the skeletal muscle index (SMI). One hundred eighty-eight patients are considered non-sarcopenic. Due to a lack of data or CT scans, the rest of the patients could not be included in further analysis.
So, from here on, all analyses presented are analysis of these 251 patients' images were available. Figure 20 displays the relation between sarcopenic and non-sarcopenic patients. Nearly a quarter of patients was sarcopenic.

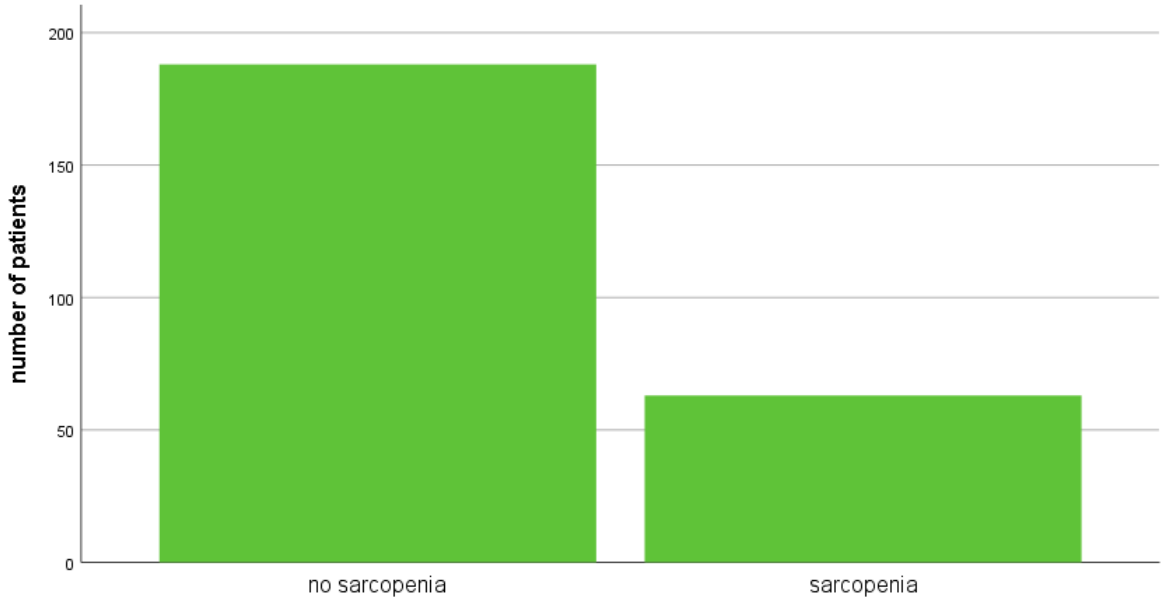


Figure 20: Number of patients (Non-Sarcopenic/Sarcopenic)

The following table shows multiple parameters of non-sarcopenic patients compared to parameters of sarcopenic patients.

	No Sarcopenia	Sarcopenia	p-value
Number of patients	188	63	-
Age OP	67 (60-74)	70 (63-78)	0,05
Follow up (months)	27 (14-63)	17 (9-45)	0,03
Length of hospital stay (days)	15 (11-19)	14 (11-19)	0,3
BMI	26 (24-29)	24 (22-27)	0,05
Charlson Comorbidity Index	7 (6-8)	7 (6-8)	0,9
Primary tumor size (in cm)	4 (3-5)	4 (3-6)	0,9
Size largest metastasis (in cm)	2 (1,1-3,5)	2,4 (1,7-4,0)	0,03
Neutrophile granulocytes (G/l)	3,7 (2,7-4,8)	3,8 (2,9-5,8)	0,08
Thrombocytes (G/l)	206 (166-259)	229 (193-272)	0,03
Lymphocytes (G/l)	1,4 (1,0-2,0)	1,45 (1,08-1,83)	0,9
Albumin (g/dL)	4,25 (4,0-4,5)	4,2 (3,88-4,33)	0,9

Table 2: Non-Sarcopenic/Sarcopenic patients

Comparing the postoperative course of patients, sarcopenic patients were significantly older than non-sarcopenic patients and showed a lower follow up, resembling higher overall mortality (Figure 21), larger metastases, and a lower BMI. These patients were comparable in other parameters like the Charlson Comorbidity Index or the preoperative ASA scores. Therefore, these routine clinical parameters fail to display the actual patient's condition. Furthermore, preoperative Serum Albumin did not show any difference, nor did the patients Lymphocytes. Significance is highlighted in the table.

	No Sarcopenia	Sarcopenia	p-value
Overall survival in months	63,6 (56,3-71)	49,5 (36,7-62,2)	0,01

Table 3: Survival Non-sarcopenic/sarcopenic patients

Overall survival in months did differ significantly between patients with and without Sarcopenia (p=0.01). However, a Log Rank Test after a Kaplan Meier Analysis did not confirm this high significance and remained below significant level (p=0,06), Fig 21)

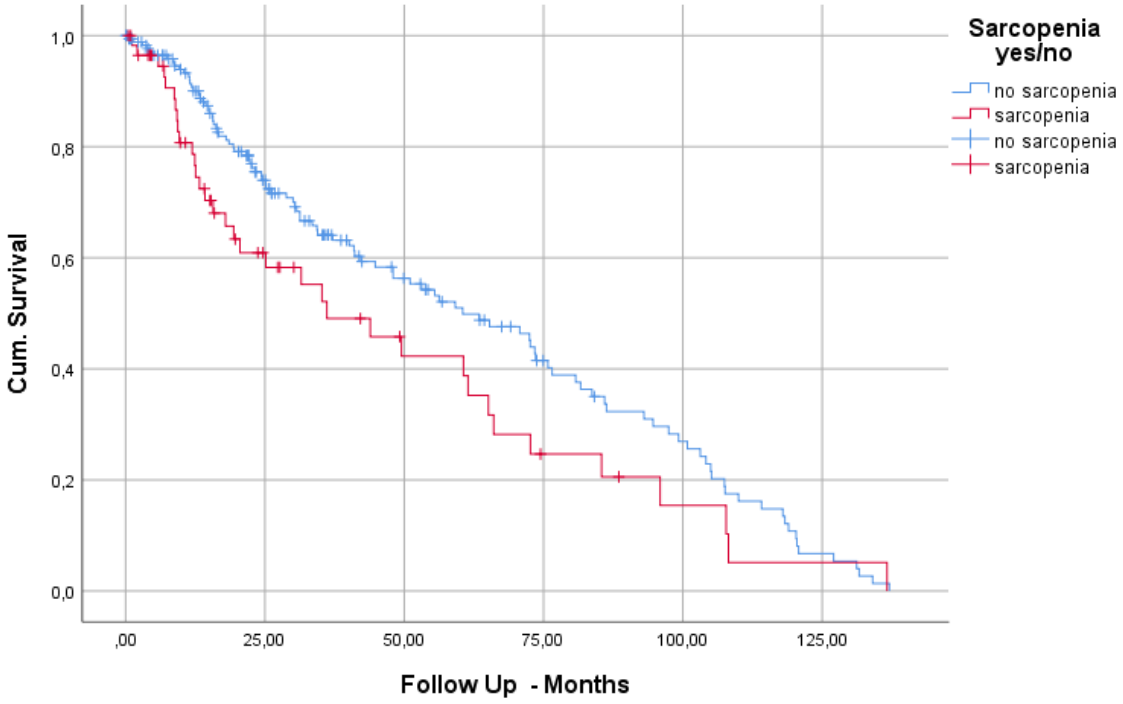


Figure 21: Survival sarcopenic/non-sarcopenic patients, Kaplan Meier Diagram

In addition, 26 patients with diagnosed Sarcopenia also showed sarcopenic obesity. A subsequent analysis on this particular patient cohort was performed for different suggestions regarding postoperative outcomes in the literature (43).
Sarcopenic obesity was defined as patients having Sarcopenia and a BMI > 25 kg/m^2.

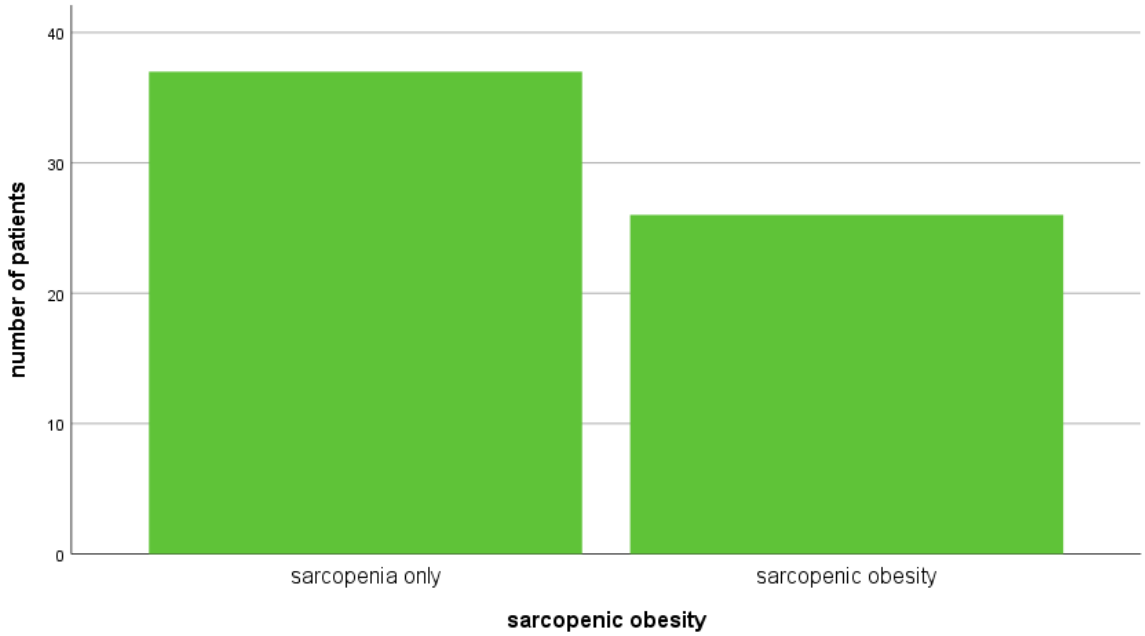


Figure 22: Number of patients: Sarcopenia only/sarcopenic obesity

Nearly one-third of patients were diagnosed with sarcopenic obesity.
The following table compares multiple parameters from all patients to sarcopenic patients and patients suffering from sarcopenic obesity.

	All patients	Sarcopenia	SO	p-value
Number	221	63	26	
Male	158 (71,5%)	34 (54%)	6 (23,1%)	0,01
Female	63 (28,5%)	29 (46%)	20 (76,9%)	0,001
Age op	67 (60-74)	70 (63-78)	73 (66-78)	0,05
FUP (months)	27 (14-63)	17 (9-45)	17 (7-42)	0,03
LOS (days)	15 (11-19)	14 (11-19)	15 (11-17)	0,8
BMI	25 (23-29)	24 (22-27)	27 (26-30)	0,07

Charlson C.I.	7 (6-8)	7 (6-8)	8 (6-8)	0,9
Prim. size cm	4 (3-5,5)	4 (3-6)	3,5 (3-5)	0,9
Size met larg.	2 (1,2-3,6)	2,4 (1,7-4,0)	2,8 (1,5-5)	0,06
Neutro. abs.	3,7 (2,7-4,8)	3,8 (2,9-5,8)	3,7 (3,18-5,58)	0,9
Thrombocytes	210 (168-263)	229 (193-272)	241 (199-310)	0,05
Lymphocytes	1,4 (1,0-2,0)	1,45 (1,08-1,83)	1,45 (1,18-1,9)	0,9
Albumin	4,2 (4,0-4,5)	4,2 (3,88-4,33)	4,2 (3,8-4,5)	0,9

Table 4: All patients/sarcopenic patients/sarcopenic obese patients

Patients who had sarcopenic obesity were significantly older (p=0,05) and had larger metastases compared to sarcopenic patients and non-sarcopenic individuals. The proportion of female patients was significantly higher among patients with sarcopenic obesity. However, sarcopenic obesity did not significantly impact overall survival or the patient's follow-up.

Status follow up:

1 = Alive with disease

2 = Alive without evidence of disease

3 = Dead of disease

4 = Dead of other causes

	All		Sarcop.		SO	
	Number	Percent	Number	Percent	Number	Percent
In total	217		63		26	
1	86	39,6	22	34,9	11	42,3
2	44	20,3	12	19	7	26,9
3	71	32,7	22	34,9	8	30,8
4	16	7,4	3	0,5	0	0

Table 5: Status follow up All patients/sarcopenic patients/sarcopenic obese patients

Patients with Sarcopenia and sarcopenic obesity showed a higher percentage of recurrence and a higher percentage of patient deaths during the observation period than non-sarcopenic patients.

Patients with sarcopenic obesity had higher odds for worse postoperative survival (in months) compared to non-sarcopenic patients (Log Rank: p=0.011), as seen in the Kaplan Meier analysis.

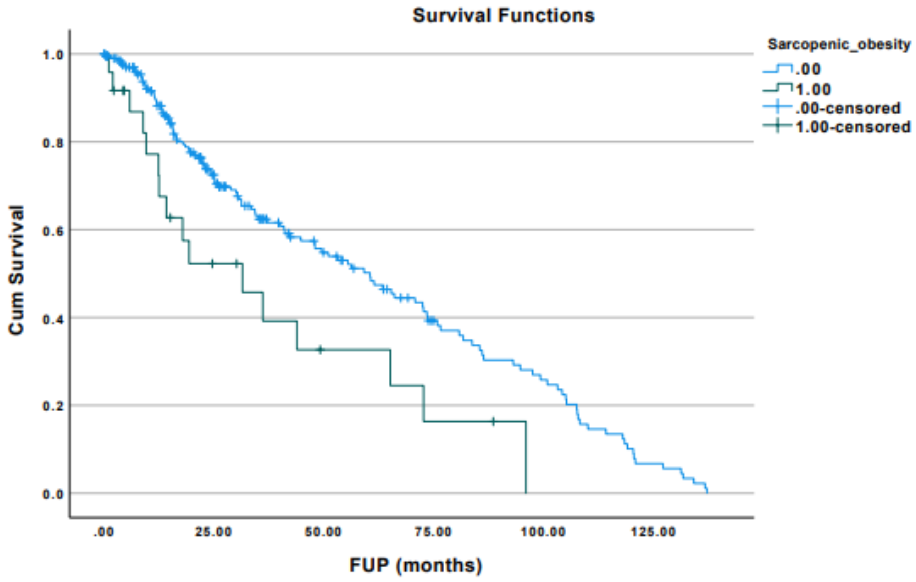


Figure 23: Survival sarcopenic obese patients/non-sarcopenic patients, Kaplan Meier Diagram

Oddly, in our patients' complications, according to Clavien Dindo, those without Sarcopenia experienced more complications than patients with Sarcopenia or sarcopenic obesity. Even though this difference was not significant, it is still not in accordance with the current literature. Table 6 shows that patients with Sarcopenia had a complication rate of 10%, with Clavien Dindo grading above three, whereas patients without Sarcopenia had 11,3% with Clavien Dindo grading three or higher. Patients with sarcopenic obesity showed higher rates of mild complications than patients with Sarcopenia (Clavien Dindo grading one) but did not show any higher rates in the other Clavien Dindo gradings.

Clavien Dindo Classification:

	All		Sarcop.		SO		p-val.
	Number	Percent	Number	Percent	Number	Percent	
In total	220		60		26		
0	50	22,7	17	28,3	9	34,6	0,5
1	136	61,8	33	55	16	61,5	0,05
2	9	4,1	4	6,6	1	3,8	0,8
3	14	6,4	5	8,3	0	0	0,07
4	7	3,2	1	1,6	0	0	0,09
5	4	1,8	0	0	0	0	0,07

Table 6: Clavien Dindo; All patients/sarcopenic patients/sarcopenic obese patients

Patients with Sarcopenia and sarcopenic-obesity did not show higher percentages of T3 and T4 primaries in their medical history compared to non-sarcopenic patients.

T Score Primary tumor:

	All		Sarcop.		SO		p-val.
	Number	Percent	Number	Percent	Number	Percent	
In total	201		56		23		
T0	1	0,5	0		0	0	
T1	6	3,0	4	7,1	1	4,3	0,8
T2	35	17,4	10	5,6	4	17,4	0,09
T3	119	59,2	31	55,4	13	56,5	0,5
T4	40	19,9	11	19,6	5	21,7	0,3

Table 7: T Score Primary Tumor; All patients/ sarcopenic patients/sarcopenic obese patients

Neither patients with sarcopenic obesity nor sarcopenic patients had a higher percentage of KRAS mutations in their primaries, as shown in table 8.

KRAS Mutation (Yes/No):

	All		Sarcop.		SO		p-val.
	Number	Percent	Number	Percent	Number	Percent	
In total	201		54		23		
Yes	60	29,9	17	31,5	8	34,8	0,8
No	141	70,1	37	68,5	15	65,2	0,7

Table 8: Kras Mutation; All patients/sarcopenic patients/sarcopenic obese patients

Rates of neoadjuvant chemotherapy or adjuvant chemotherapy did not differ between patients with Sarcopenia or those with sarcopenic obesity. See tables 9 and 10.

Adjuvant Chemotherapy (Yes/No):

	All		Sarcop.		SO		p-val.
	Number	Percent	Number	Percent	Number	Percent	
In total	211		56		25		
Yes	162	76,8	41	73,2	19	76	0,8
No	49	23,2	15	26,7	6	24	0,5

Table 9: Adjuvant Chemo; All patients/sarcopenic patients/sarcopenic obese patients

Neoadjuvant chemotherapy for primary tumor (Yes/No):

	All		Sarcop.		SO		p-val.
	Number	Percent	Number	Percent	Number	Percent	
In total	211		57		24		
Yes	78	37	20	35,1	9	37,5	0,5
No	133	63	37	64,9	15	62,5	0,6

Table 10: Neoadjuvant Chemo; All patients/Sarcopenic/sarcopenic obese patients

4.0 Discussion

The human physiognomy compiles over 600 skeletal muscles. We can only stand straight, keep balance, walk, run, bend over, scratch your knee, get dressed, go shopping because of our skeletal muscles.

Muscle functionality and muscle decrease are only realized by us when they begin to fail; their muscle mass starts to decrease. This leads to difficulties in performing activities of daily living and, as a result, a decrease in quality of life. Patients' autonomy decreases, and the necessity for care and dependency increases subsequently (44).

According to the WHO, over one-third of the world's population will be above 65 years when we reach 2035. As age is one significant risk factor for cancer development, our future treatment would target this population (45).

We carried out a study on patients who underwent liver resection for metastases after colorectal carcinoma. Looking at the patient's age, we saw that patients who suffer from Sarcopenia are older than patients without Sarcopenia. In these patients, age proved to be one of the major risk factors for worse outcomes. These findings confirm the existing literature (46) (47) (48) (49).

Older adults with difficulties in performing activities of daily living are eligible to receive home care or may qualify for housing in a residential living facility. However, due to governmental regulation, residential living facilities will dissolve soon, and older adults will be more and more empowered to live independently as long as possible (also called 'aging in place'). Nevertheless, this also corresponds to most older adults' wish, who prefer to stay at home. By that, older adults can keep their familiar environment.

Aging in place is also thought to reduce the burden of costs that strain Western health care systems. The financial viability of the social security system to treat the adverse health outcomes of Sarcopenia and the availability of enough medical staff to treat this enormous number of patients in the future is at stake when it comes to this problem.

In the case of western European countries, immigration from younger populations is the only way to save this upcoming age gap and the financial gap we are prone to face (38).

Insight into the prevalence of Sarcopenia, its characteristics, health, and economic consequences are of utmost importance to know who is at risk for Sarcopenia, and secondly to assess what can be discovered to help overcome Sarcopenia- or at least prevent and treat it to form a sustainable, affordable health care system.

Previous studies described Sarcopenia as an independent prognostic factor in patients following hepatectomy and a risk factor for postoperative complications. Unfortunately, only a minority of patients present with resectable disease. In the presented study, low skeletal muscle density was identified in patients with malignant diseases prone to an increased mortality rate in the long term and an increased morbidity rate in the short term.

In this population-based retrospective analysis, we found that those with existing Sarcopenia have a worse outcome after liver resection for CRLM than patients with no Sarcopenia. This worse outcome was especially prominent for patients' overall survival.

As already mentioned, Sarcopenia itself has been recognized as a predictive factor for higher mortality and morbidity rates and has been underlined in the literature several times as a negative predictive value (50) (51) (52). Our findings align with the literature and underline the importance of the determination of Sarcopenia preoperatively.

Sarcopenic obesity is relatively new to the scientific community regarding surgical research. Sarcopenic obesity can be even more predictive for adverse outcomes. In addition, it was also underlined in our study that the overall survival rate was even worse in patients who had sarcopenic obesity with a subsequent lower-scoring follow-up.

Recently our group investigated the localization of primary CRC and found a higher prevalence of Sarcopenia for right-sided colorectal primaries. This was also observed in the presented analysis (53).

Sarcopenia has been found to worsen the postoperative outcome, as well as the functional impairment and disability after colorectal surgery by affecting mobilization, impairing breathing, and decreasing physical performance in these

patients. So, it might be interesting to see if Sarcopenia existed before the colon resection. This could be researched in further studies.

Sarcopenia itself is caused by a multifactorial mechanism. This mechanism can alter endocrine function, systemic inflammatory response, and insulin resistance. The change in these mechanisms seems to determine the worse prognosis for sarcopenic patients. By identifying these mechanisms and knowing which patient is prone to a worse prognosis, we would also alter patient outcomes by applying concepts of pre-habilitation (54).

Generally, the concept of pre-habilitation is discussed to better the postoperative outcome or post-hospital outcome of patients with and without Sarcopenia who undergo surgeries. We know that by altering the mechanisms, Sarcopenia can be reversed to a certain stage and thus benefit from pre-habilitation. We have already shown that Sarcopenia can be ameliorated after liver resection for patients undergoing various resections. Another step is to investigate this in further analysis for different entities.

However, this study has some limitations. Images were not obtainable of all patients, the time between CRC - CRLM resection was variable, and not all patients had received chemotherapy prior to colon resection. An influence of KRAS status or other mutations respectively was not observed by Sarcopenia.

Several conclusions can be drawn from this evaluation of the effect of preoperative Sarcopenia in CRLM patients. Patients with Sarcopenia had significantly lower survival. Therefore, CT assessed Sarcopenia seems to hold the potential to predict postoperative morbidities and needs to be assessed. Thorough diagnosis of patients scheduled for hepatic resection, or surgeries of all kinds, it is mandatory to distinguish patients prone not to benefit at all.

5.0 Conclusion

As a predictor of overall morbidity and mortality, Sarcopenia has, most likely, a negative impact on the individual oncologic patient undergoing hepatic surgery but also on the whole population in terms of social and economic damage.

We also showed that the quite-recently-identified clinical picture of sarcopenic obesity has the potential to exacerbate this problem.

The estimated prognosis of obsolesce in the western world will multiply the numbers of sarcopenic and oncologic patients.

Considering these facts, reasonable strategies for preventing and treating Sarcopenia must be elaborated immediately, and more research has to be done.

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