Diploma Thesis

The influence of gender on frailty syndrome in surgical patients undergoing major hepatic resection

Submitted by

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Affidavit

Herewith I, Andrea Tomberger, declare that I have written the present diploma thesis fully on my own and without any assistance from third parties.

Furthermore, I confirm that no sources have been used in the preparation of the thesis, other those indicated in the thesis itself.

Graz, 25.05.2018 Andrea Tomberger

Acknowledgments

This thesis would not have been possible without the guidance and the help of several individuals, who in one way or another contributes and extended their valuable assistance in the preparation and completion of this study.

First of all, I would like to thank my supervisor, Priv.-Doz.^{in} Dr.^{in} Doris Wagner whose encouragement, guidance and support from the initial to the final level enabled me to develop an understanding of the subject of this thesis.

Last, but not least, I owe my deepest gratitude to my family, my husband Thomas and son Paul, who supported me during my undergraduate studies and helped me to be strong to finish it.

Abstract

Introduction: Sarcopenia is widely used as a surrogate for the frailty syndrome. The prevalence of frailty among surgical patients is one of the most limiting factors for their postoperative outcome. No study on the progression or reversal of frailty after surgery exists until now. We aimed to depict the course of muscle mass as surrogate for frailty in a cohort of patients undergoing major hepatic resections.

Methods: Records of patients who underwent hepatic resection in our institution in between 2006-2016 were reviewed and frailty was defined as sarcopenia using the skeletal muscle index (SMI) preoperatively, 6 months and 12 months after operation. Threshold values for sarcopenia were SMI less than 41 cm^2/m^2 for women, SMI less than 43 cm^2/m^2 for men with BMI less than 25 kg/m^2, and SMI less than 53 cm^2/m^2 for men with BMI of 25 kg/m^2 or greater.

Results: 966 patients (female: 51.4%, male: 48.6%) were included, pre and postoperative CT scans were available from 920 patients (95.2%). Median age was 66 years (35-87), 62% had major hepatectomies. The SMI differed significantly between men and women and decreased significantly throughout the follow up (preoperative SMI: 23.55± 19.15 cm^2/m^2, 6 months: 18.31±7.3 cm^2/m^2, 12 months: 13.23±18.41 cm^2/m^2 p=0.001). This decrease was more pronounced in men as compared to women (men: preoperative SMI: 25.54± 17.31 cm^2/m^2, 6 months: 20.17± 13.45 cm^2/m^2, 12 months: 14.36± 12.23 cm^2/m^2; women: preoperative SMI: 21.71± 13.25 cm^2/m^2, 6 months: 16.58± 11.32 cm^2/m^2, 12 months: 12.18± 14.76 cm^2/m^2, p=0.0001). Postoperative complications did not differ between male and female patients neither did the length of stay, ICU stay or preoperative comorbidities, age and disease severity (all p>0.5).

Discussion: Although women had lower preoperative sceletal muscle mass, they seem to recover better as compared to men. The increase in frailty syndrome overall in the patients requires close further investigations and monitoring.

Zusammenfassung

Einleitung: Sarkopenie, also der Schwund der Skelettmuskulatur wird häufig als Surrogatparameter für das Frailty-Syndrom verwendet. Das Vorliegen von Frailty wirkt sich deutlich negativ auf das postoperative Outcome bei chirurgischen Patienten aus. Bis heute gibt es Studien zur Entwicklung und Progression von Frailty nach Operationen. Unser Ziel war es, den Verlauf der Muskelmasse als Ersatz für die Gebrechlichkeit in einer Kohorte von Patienten darzustellen, die sich einer Leberresektion unterziehen mussten.

Methoden: Bei allen Patienten die zwischen 2006 und 2016 an der Medizinischen Universität Graz eine Leberresektion durchgeführt wurde, wurden klinische Parameter gesammelt und die Skelettmuskelmasse gemessen. Frailty wurde als Sarkopenie mit dem Skelettmuskelindex (SMI) präoperativ, 6 Monate und 12 Monate nach der Operation definiert. Schwellenwerte für Sarkopenie waren SMI weniger als 41 cm2 / m2 für Frauen, SMI weniger als 43 cm2 / m2 für Männer mit einem BMI von weniger als 25 kg / m2 und SMI weniger als 53 cm2 / m2 für Männer mit einem BMI von 25 kg / m2 oder größer.

Ergebnisse: 966 Patienten (weiblich: 51,4%, männlich: 48,6%) wurden eingeschlossen, prä- und postoperative CT-Scans von 920 Patienten (95,2%) waren vorhanden. Das mittlere Alter betrug 66 Jahre (35-87), 62% hatten eine grossen Lebereingriff (Leberresektion über 2 Segmente). Der SMI unterschied sich signifikant zwischen Männern und Frauen und nahm signifikant während des Follow-up ab (präoperative SMI: 23,55 ± 19,15 cm2 / m2, 6 Monate: 18,31 ± 7,3 cm2 / m2, 12 Monate: 13,23 ± 18,41 cm2 / m2 p = 0,001). Dieser Rückgang war bei Männern im Vergleich zu Frauen ausgeprägter (Männer: präoperative SMI: 25,54 ± 17,31 cm2 / m2, 6 Monate: 20,17 ± 13,45 cm2 / m2, 12 Monate: 14,36 ± 12,23 cm2 / m2; Frauen: präoperative SMI: 21,71 ± 13,25 cm^2 / m^2, 6 Monate: 16,58 ± 11,32 cm^2 / m^2, 12 Monate: 12,18 ± 14,76 cm^2 / m^2, p = 0,0001). Die postoperativen Komplikationen unterschieden sich nicht zwischen männlichen und weiblichen Patienten, weder die Aufenthaltsdauer, der Aufenthalt auf der Intensivstation oder präoperative Komorbiditäten, Alter und Schwere der Erkrankung (alle p> 0,5).

Diskussion: Obwohl Frauen eine geringere präoperative Skelettmuskelmasse aufwiesen, scheinen sie sich im Vergleich zu Männern besser zu erholen. Der Anstieg des Frailty-Syndroms insgesamt bei den Patienten erfordert eine genaue Untersuchung und Überwachung.

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1 Introduction

1.1 Liver Anatomy and Function

1.1.1 Liver Anatomy

The liver represents the largest inner organ of the human body and can weigh up to 1.5 kg. Located in the right upper quadrant of the abdomen, below the rips and beneath the diaphragm, it is divided into 2 parts- the right and the left liver lobe by the fossae for the gallbladder and the inferior vena cava.

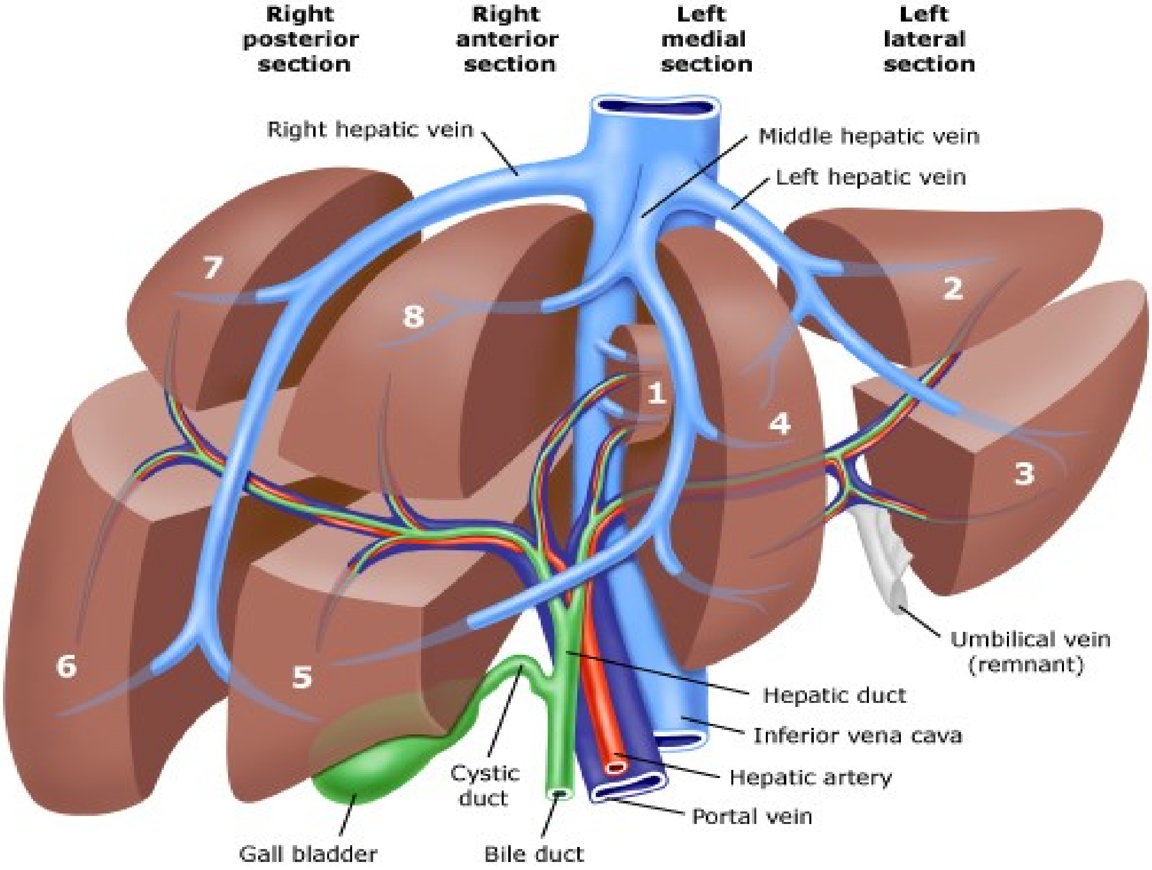

Fig. 1: Segments of liver (by Couinad)

Each segment has its own vascular inflow, outflow and biliary drainage. A branch of the portal vein, hepatic artery and bile duct is in every centre of each segment. Each segment has its own vascular outflow through the hepatic veins.(1)

The classification system uses the vascular supply in the liver to separate the functional units (numbered I to VIII):

Unit I is the caudate lobe and is situated posterior I and it receives its supply from both the right and the left branches of portal vein. It contains one or more hepatic veins which drain directly into the IVC.

The remainder of the units (II to VIII) are numbered in a clockwise fashion:

units II and III lie medial to the falciform ligament with II superior to the portal venous supply and III inferior

unit IV lies lateral to the falciform ligament and is subdivided into IVa (superior) and IVb (inferior)

Units V to VIII make up the right part of the liver:

unit V is the most medial and inferior

unit VI is located more posteriorly

unit VII is located above unit VI

unit VIII sits above unit V in the superior-medial position

The liver is considered to be the largest glandular organ of the human body and performs multiple metabolic and secretory functions to keep the body pure of toxins and harmful substances. Also, the organ does regulate the blood volume together with the spleen and bone marrow the liver destroys worn out red blood cells.

The liver secretes 800 to 1.000 ml of bile each day which is concentrated and stored in the gallbladder. Bile consists of many different substances, as bile salt, cholesterol and bilirubin and contributes to the digestion as well as the absorption of fat.

1.1.2 Liver Function

The liver regulates the composition of blood, including the amounts of sugar (glucose), protein, and fat that enter the bloodstream. It removes bilirubin, ammonia, and other toxins from the blood. Bilirubin is a by-product of the breakdown of hemoglobin from red blood cells. The liver processes most of the nutrients absorbed by the intestines during digestion and converts these nutrients into forms that can be used by the body.

Vitamin A, iron, and other minerals can be stored by the liver. Cholesterol and certain important proteins, such as albumin are produced by the liver. The liver also produces clotting factors, these chemicals needed to help blood clot. Alcohol and many drugs are metabolized by the liver.

1.2 Liver Neoplasm

Primary neoplasms of the liver are consisting of cells that resemble the normal constituent cells of the liver. Several distinct types of tumours can develop in the liver because the liver is made up of various cell types. These growths can be benign or malignant.

1.2.1 Malignant neoplasm

Malignant neoplasm includes primary malignant tumor the hepatocellular carcinoma (HCC) as well as the cholangiocarcinoma (CCA) and secondary malignant neoplasm as metastases.

1.2.1.1 Hepatocellular carcinoma (HCC)

Hepatocellular carcinoma (HCC) is the sixth most common primary liver malignancy and is a leading cause of cancer-related death worldwide. HCC is more prevalent in males as compared to female patients (2.4:1), with a higher incidence in Eastern and Southern Asia, Middle and Western Africa, Melanesia, and Micronesia/Polynesia.(2) Regardless of geographic location, chronic viral hepatitis, alcoholism and smoking are main factors for tumour genesis while cirrhotic remodelling of the liver still is the greatest risk factor. Other risk agents like Aflatoxine (Aspergillus flavus), steroids or several metabolic diseases can also be a factor to cause HCC. Microscopically, there are four architectural and cytological types of hepatocellular carcinoma: fibrolamellar, pseudoglandular, pleomorphic and clear cell. The grading depends on the tumours histologic pattern. Typical places for metastasis are the lung, the bone, skin and abdominal lymph nodes.

Fig. 2.: Hepatocellular Carcinoma in a non-cirrhotic liver

This image shows a unifocal, yellow-tan, well-circumscribed tumor in the background of a normal liver. Of hepatocellular carcinoma (HCC), 10-30% arise in noncirrhotic liver.

1.2.1.2 Cholangiocarcinoma (CCA)

Cholangiocarcinoma (CCA) is an epithelial cancer originating from the bile ducts with features of cholangiocyte differentiation. CCA is the second most common primary hepatic malignancy, and epidemiologic studies suggest its incidence is increasing in Western countries.(3) CCA is classified into extrahepatic and intrahepatic forms of the disease. Signs and symptoms of cholangiocarcinoma include: Jaundice which is a yellowish tinge to the skin and the whites of the eyes. This is caused when the bile ducts become blocked and bile produced by the liver flows back into the bloodstream. Jaundice may also cause dark-coloured urine, pale-coloured stools and itchy skin, fatigue, abdominal pain, unintended weight loss

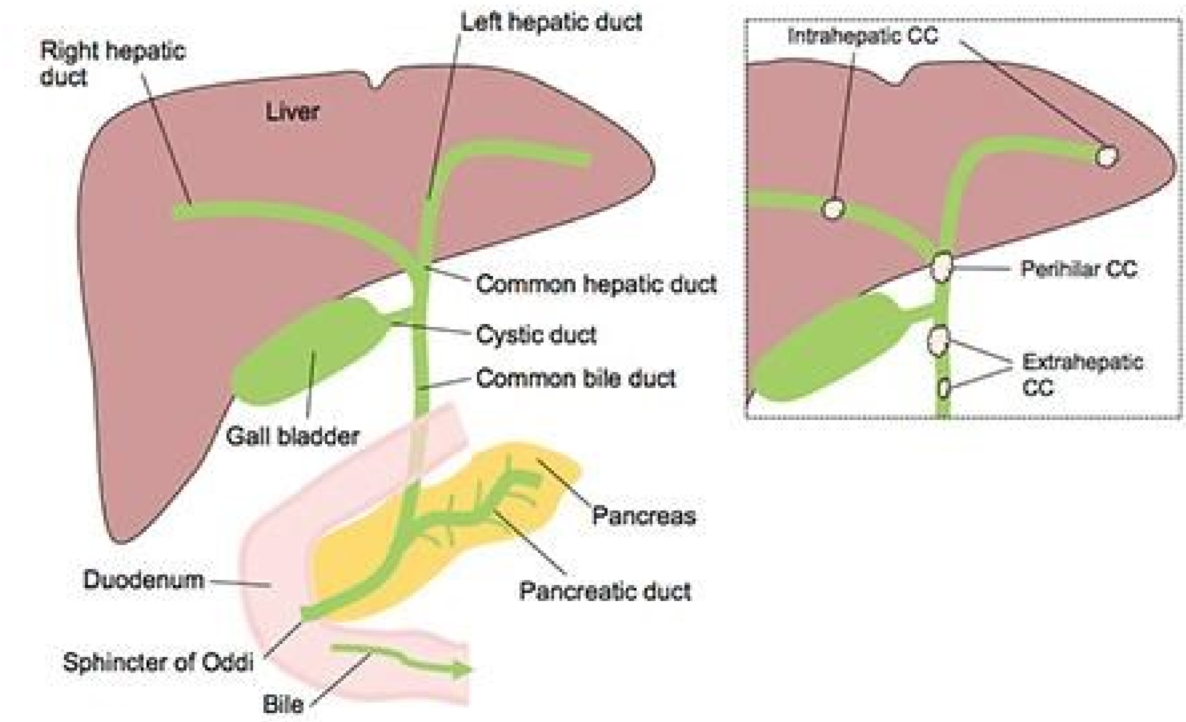

Fig. 3: Localisation of CCA

CCA is classified into intrahepatic, perihilar, and distal/extrahepatic subtypes. 5-10 % of CCA are located intrahepatic, 60-70% are located at the bifurcation of the biliary system - perihilar (Klatskin tumor) and 20-30% are located extrahepatic. For the perihilar Type there is a own classification called Bismuth-Corlette classification.

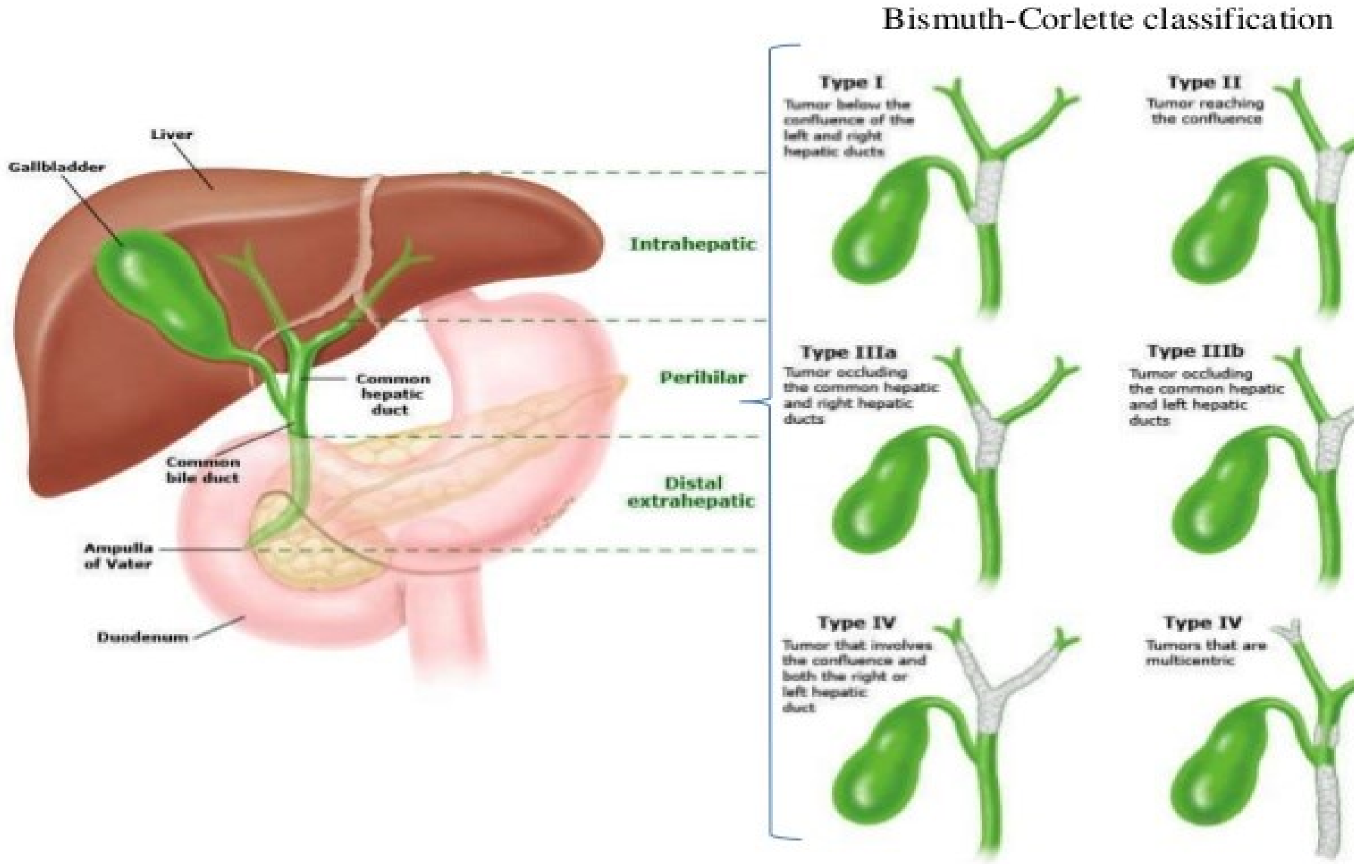

Fig 4: Bismuth Corlette classification

The Bismuth–Corlette classification system provides an anatomic description of the tumour location and longitudinal extension in the biliary tree (Fig 3, Fig 4). It is limited due to its failure to characterize the radial extension of the cancerous lesion. However, it provides a practical manner for surgical oncologists to describe the lesion and in turn, the anticipated extent of liver that may need to be resected to achieve complete extirpation of the malignancy. Type I lesions involve the common hepatic duct (CHD) immediately below the confluence; type II tumors involve the CHD and extend to the confluence but not beyond; type IIIa masses involve the CHD to the confluence and extend into the main right hepatic duct; type IIIb lesions involve the CHD to the confluence and extend into the main left hepatic duct and type IV tumours involve the CHD and extend past the confluence involving both the right and left hepatic ducts.(4)(5)

1.2.1.3 *Secondary malignant neoplasms – metastases*

The most common liver metastases derive from colorectal carcinomas, other origins are breast, lung, stomach and pancreatic.

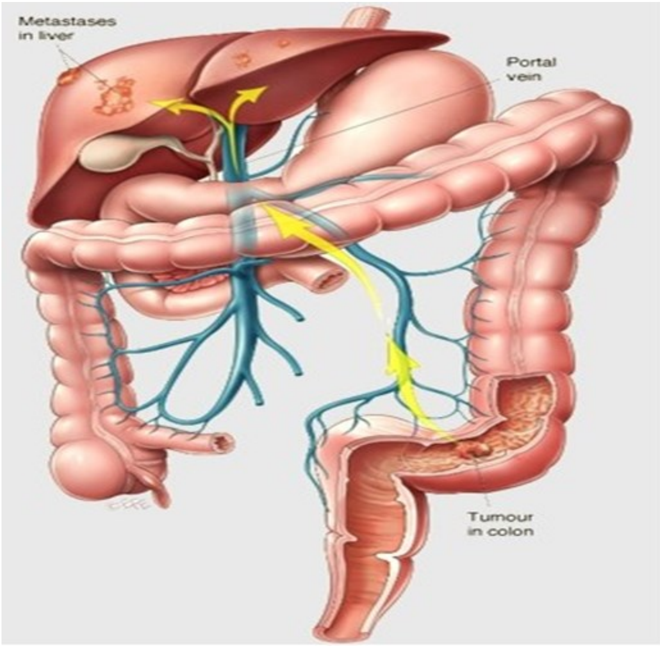

Fig. 5: Blood from the bowel flows directly to the liver. This means the liver is a common place for colorectal cancer to spread to.

About 50-60% of patients with colorectal carcinoma develop liver metastases during their lifespan. Colon cancer risk factors are environmental and genetic factors, familial polyposis coli, personal and family history of cancer, inflammatory bowel disease, alcohol, obesity, smoking and the change in protective factors such as physical activity.(6) Often secondary liver cancer does not cause any symptoms for a long period of time. If symptoms do occur, they may include: weight loss, loss of appetite, high temperature, nausea, lethargy (extreme tiredness) and enlarged spleen. Liver metastases may also cause discomfort in the upper, right part of the abdomen because of an enlarged liver. This enlargement may cause pain in the right shoulder because nerves beneath the diaphragm are connected to nerves in the right shoulder. The enlarged liver stimulates the nerves in the diaphragm and causes shoulder discomfort.(7) Imaging tests are an important part of diagnosing liver metastases. It is common for patients to have one or more imaging tests when the cancer may have spread to the liver. The imaging tests used to diagnose liver metastases include the following. Computed tomography (CT) scan is a common imaging test to check for liver metastases. It can also check for metastases in organs and tissues around the liver. The CT scan is usually done with contrast medium to show areas more clearly. Ultrasound is used to check for an enlarged liver or changes in its shape or texture. It is also used to guide a biopsy needle or laparoscope to a specific area of the liver. Magnetic resonance imaging (MRI) is used to find small metastatic tumors in the liver. Positron emission tomography (PET) scan is used to check for metastases in organs and tissues around the liver.

Blood tests: The most common blood tests used to help diagnose liver metastases are liver function tests. Other blood tests that may be abnormal include a complete blood count (CBC), blood glucose (sugar) and blood clotting tests.

Sometimes tumor marker tests are done if you have had cancer before. These tests measure the amount of a specific protein in the body. For example, carcinoembryonic antigen (CEA) is a tumor marker measured in the blood. It is usually checked during follow-up after treatment for colorectal cancer. An increase in CEA levels over time could mean the cancer has come back and it may have spread to the liver.

Biopsy: A biopsy is the removal of cells or tissues so they can be examined under a microscope. It may be needed to diagnose liver metastases. It is done when there is liver metastasis based on imaging tests or if there is no history of cancer. A biopsy may also be done to check tumor markers that help guide treatment. A percutaneous needle biopsy or endoscopic biopsy during laparoscopy may be used.

Other tests: If liver metastases are found before the primary cancer is diagnosed, to find the primary location. CT scan of the chest to check for lung cancer, colonoscopy to check for colorectal cancer, laparoscopy to examine organs in the abdomen and pelvis

1.2.2 Benign liver tumors

Benign liver tumours are relatively common but usually subclinical. Most are detected incidentally by ultrasound or other scanning techniques. Others are discovered because of hepatomegaly, right upper quadrant pain, or intraperitoneal hemorrhage. Liver function tests are usually normal. The most important benign liver tumors are cavernous hemangioma, focal nodular hyperplasia (FNH) and hepatocellular adenoma (liver cell adenoma – LCA)

1.2.2.1 Cavernous hemangioma

These tumors consist of cavernous, blood- filled vascular spaces of variable size lined by a single epithelial layer. It is the most common benign liver tumor typically presenting in adults. These benign tumors are thought to be congenital malformations that enlarge by ectasia, not hyperplasia or hypertrophy. Hemangiomas may occur singly or in multiples and are well-circumscribed masses of spongy consistency, typically measuring less than 4 cm in width. Statistically, hemangiomas are more likely to develop between the ages of 30 and 50. Women are more likely to develop liver hemangiomas than men. Women who have been pregnant are more likely to develop the syndrome than women who have not been pregnant. Also, hormone replacement therapy for complications of menopause or other medical reasons increases the likelihood of developing hemangiomas. This suggests that female reproductive hormones, especially estrogen, which is found in greater amounts in women and whose production increases during pregnancy and which is a component of hormone replacement therapy, may play a role in the growth of liver hemangiomas.(8) However, the exact mechanism by which this happens is unknown.

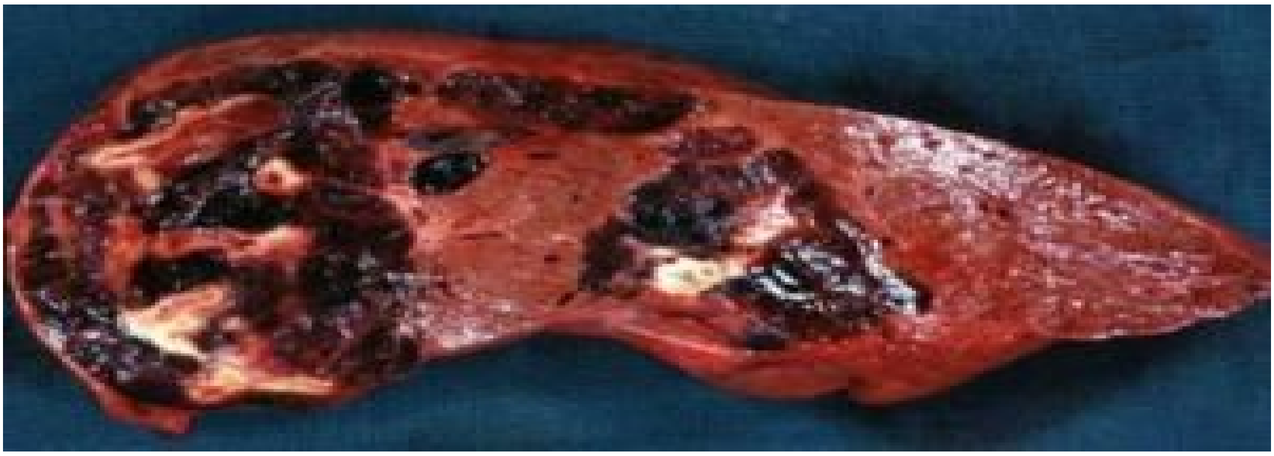

Fig. 6: liver hemangioma

1.2.2.2 Focal nodular hyperplasia (FNH)

The FNH is the second most common tumor of the liver. It is non-malignant and not of vascular origin. FNH is seen in both sexes and throughout the age spectrum, although it is found predominantly in women (ratio f:m – 8:1) between the ages of 20 and 50 years. (9)

FNH is divided into two types (10): typical: 80% atypical: 20%

Typical FNH lesions demonstrate a mass which is often quite large with well-circumscribed margins but poorly encapsulated. A prominent central scar with radiating fibrous septae is characteristic, but this is present in less than 50% of cases.

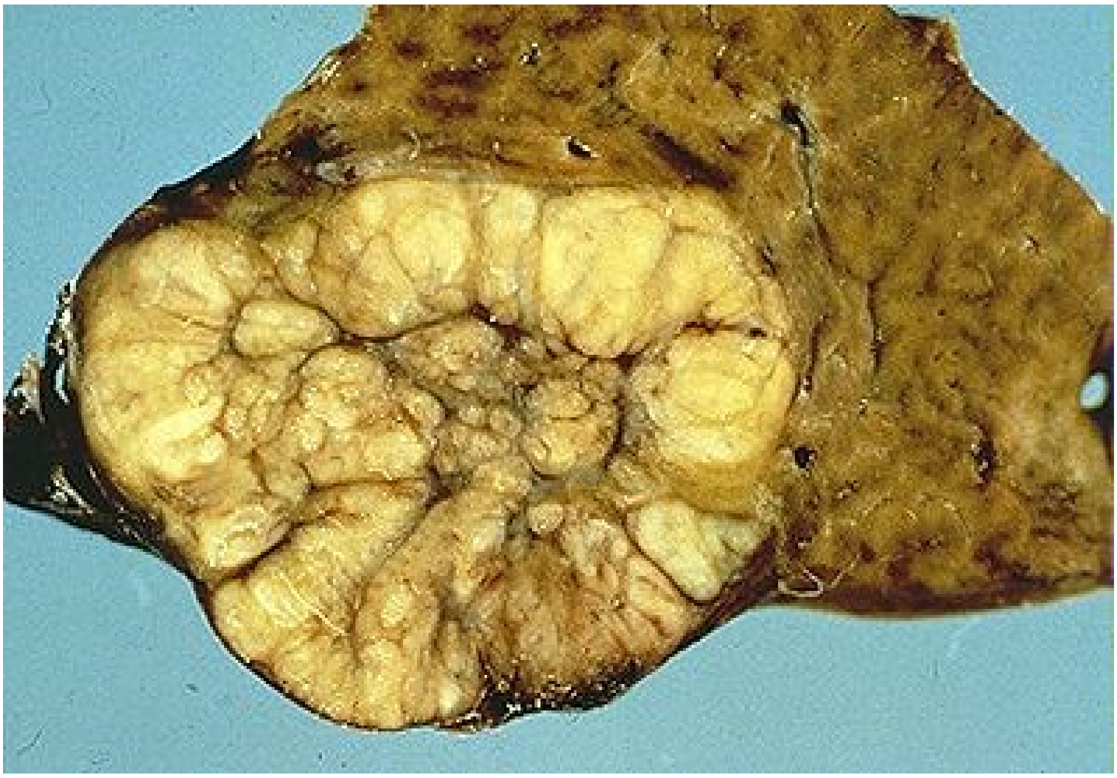

Fig. 7: Surgical specimen showing a mass lesion within a noncirrhotic liver. Note the central stellate scar. Courtesy of Frank A Mitros, MD.

Histologically the lesion is composed of abnormal nodular architecture, mal-formed vessels, and cholangiolar proliferation(10).

Atypical FNH refers to a lesion which lacks the central scar and central artery, thus harder to distinguish from other lesions on gross inspection and imaging, or abnormal nodular architecture but with abnormal cholangiolar proliferation. Atypical features also include pseudocapsule, lesion heterogeneity, non-enhancement of the central scar and intralesional fat. Nodules can grow and disappear, and new nodules can appear even after resection(10).

1.2.2.3 Hepatocellular adenoma

Hepatocellular adenoma (also known as hepatic adenoma or hepadenoma) is a rare, benign liver tumor. It most commonly occurs in people with elevated systemic levels of estrogen, classically in women taking estrogen-containing oral contraceptive medication.(11) Other medications which also alter circulating hormone levels, such as anabolic or androgenic steroids, Barbiturates, clomifene, have also been implicated as risk factors.(12) The tumors are usually solitary, have a predilection for haemorrhage, and must be differentiated from other focal liver lesions.

Hepatic adenomas are, typically, well-circumscribed nodules that consist of sheets of hepatocytes with a bubbly vacuolated cytoplasm. The hepatocytes are on a regular reticulin scaffold and less or equal to three cell thick.

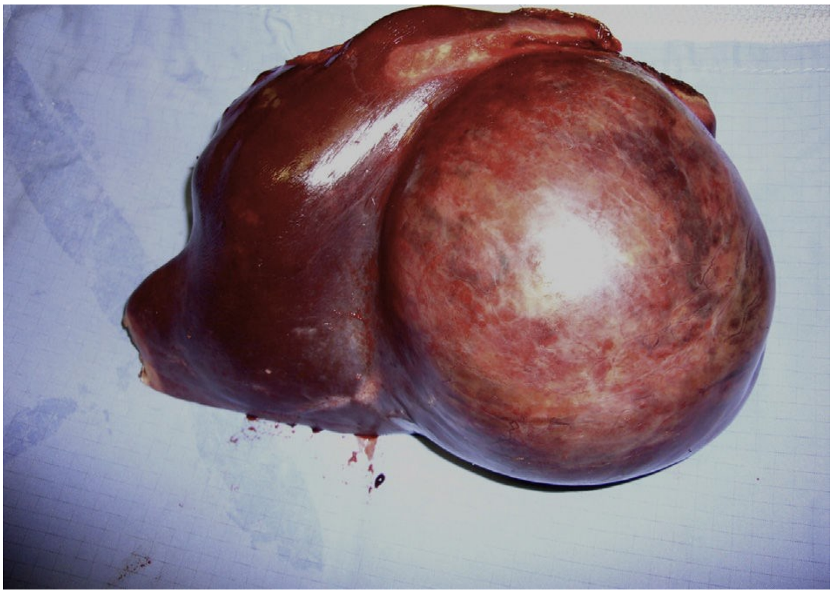

Fig. 8: 11cm hepatic adenoma

1.3 Liver Resection

1.3.1 Indications for liver surgery

Most of the hepatectomies are performed for the treatment of hepatic neoplasm, benign or malignant.

Hepatectomy may also be the procedure of choice to treat intrahepatic gallstones and cysts of the liver.

1.3.2 Types of liver surgery

To resect the liver means to surgically remove a part or the whole organ and is also called hepatectomy fully or partial. A hepatectomy is considered a major surgery done under general anesthesia. Access is accomplished by laparotomy, typically by a bilateral subcostal incision, possibly with midline extension. An anterior approach is made simpler by the liver hanging maneuver. Hepatectomies may be anatomic, i.e. the lines of resection match the limits of one or more functional segments of the liver as defined by the Couinaud classification. There are also other technics as irregular (atypic, not related to lead compounds) or "wedge" (partial) hepatectomies. Anatomic resections are generally preferred because of the smaller risk of bleeding and biliary fistula. The Pringle manoeuvre is usually performed during a hepatectomy to minimize blood loss - this can lead to reperfusion injury in the liver due to Ischemia. The Pringle maneuver is a surgical maneuver used during abdominal operations. A large atraumatic haemostat is used to clamp the hepatoduodenal ligament interrupting the flow of blood through the hepatic artery and the portal vein for helping to control bleeding from the liver(13).

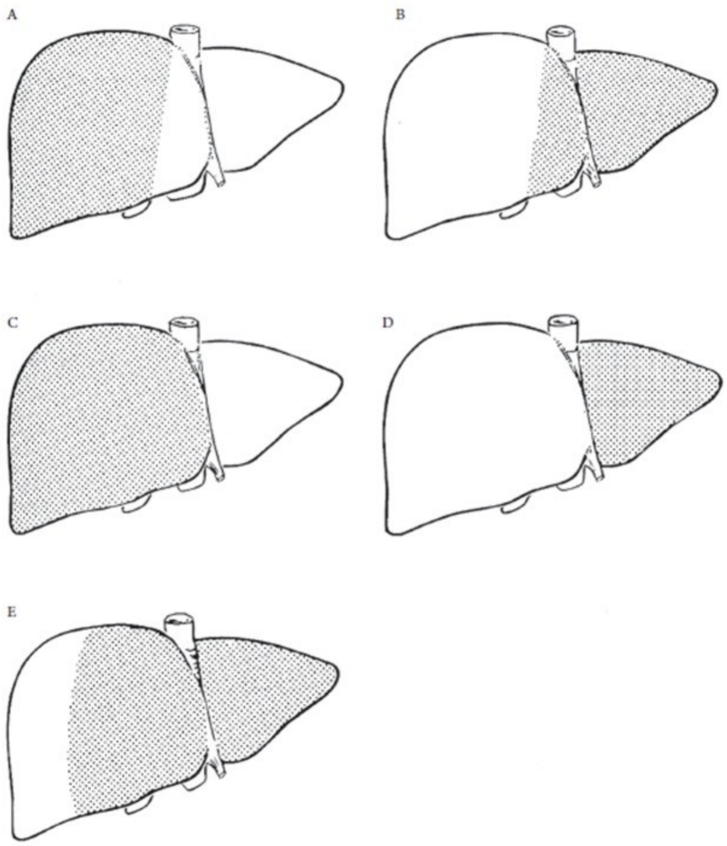

Fig. 9: Commonly performed hepatic resections shown in the shaded areas. A. Right hepatectomy. B. Left hepatectomy. C. Extended right hepatectomy (right trisegmentectomy, or right lobectomy). D. Left lobectomy. E. Extended left hepatectomy (left trisegmentectomy). Blumgart LH, Belghiti J. Surgery of the liver, biliary tract, and pancreas. 4th ed. Philadelphia, PA: Saunders Elsevier, 2007).

Depending on the part of the liver to be removed liver resection is further divided into different sub types:(7)

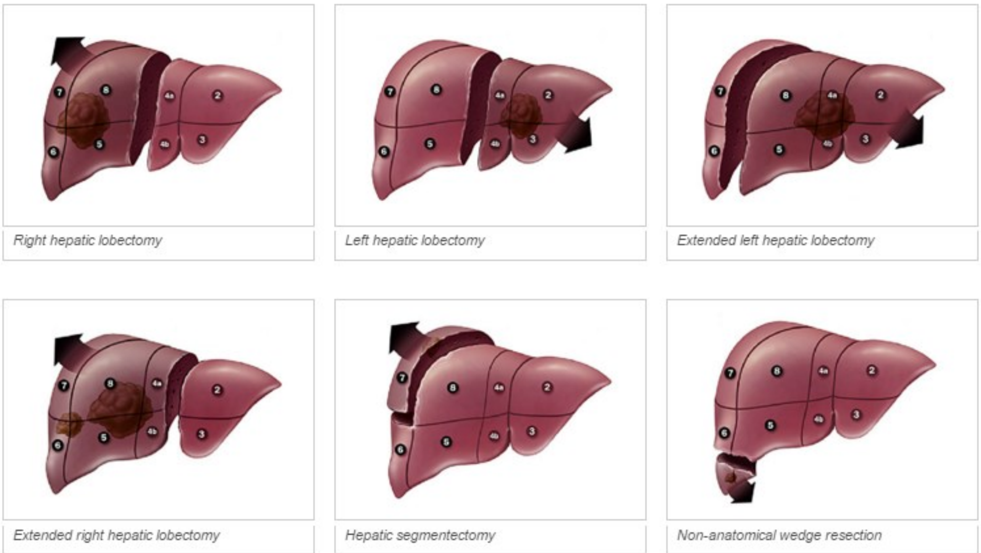

Fig. 10: Liverresection according to segments

Right Hepatic Lobectomy: right hepatectomy (or hemihepatectomy) involves resection of segments V-VIII

Left Hepatic Lobectomy: left hepatectomy involves resection of segments (II-IV)

Extended Left Hepatic Lobectomy: also known as left trisegmentectomy includes resection of all liver medial to the umbilical fissure and a portion of the right liver (segments II-IV and segments V and VIII)

Extended Right Hepatic Lobectomy: also known as right lobectomy or right trisegmentectomy involves resection of all segments lateral to the umbilical fissure (IV-VIII, and sometimes I)

Hepatic Segmentectomy: also known as left lateral segmentectomy involves resection of all liver medial to the umbilical fissure only (segments II and III)

Non Anatomical Wedge Resection: Wedge resection is a surgical procedure to remove a triangle-shaped slice of tissue. It is used to remove a tumour or some other type of tissue that requires removal and typically includes a small amount of normal tissue around.(14)

2 Preoperative Conditions and relevance in Surgery

The risk of perioperative complications is higher in older patients, not only as far as so-called “conventional” complications leading to morbidity and mortality are concerned but also complications specifically resulting in loss of autonomy. As a result, the question is often asked during the preoperative evaluation of such patients as to whether the patient is “too old for surgery?”

There are two factors to be considered in such a question: first, the ageing process is never identical in any two patients and, secondly, the indicators of perioperative risk in an elderly patient are not the same as those in younger patients. Currently the number of elderly patients undergoing surgery worldwide is increasing steadily, thus making the above question all the more relevant in the current and future practice of perioperative medicine, not only for the quality of the administered care but also for its financial cost-effectiveness.(15)

Frailty represents one of the most critical issues facing health care due to its inherent relationship with poor health care outcomes. Frailty is present in 10% to 20% of individuals 65 years and older and increases with advancing age.(16)

Austrians population is growing!

By the year 2030, the country will grow to nine million inhabitants.

In 2012, 1.51 million (18 percent) of the population were 65 and over. By 2020, the 1.01 million populations will be 13 percent larger than in 2012. By 2030, this number will increase to 2.16 million (up 43 percent) and to 2.70 million by 2060 (up 79 percent) Percent. This corresponds to a long-term increase of nearly four-fifths of the current starting level.(17)

3 Frailty Syndrom

Frailty is a common condition in older adults. It is defined as: clinically recognizable state of increased vulnerability resulting from aging-associated decline in reserve and functions across multiple physiologic systems such that the ability to cope with every day or acute stressors is comprised. Sarcopenia is widely used as surrogate for frailty. It is a condition characterized by loss of skeletal muscle mass and function. (18)

In the absence of a gold standard, frailty has been operationally defined by Fried et al. as meeting three out of five phenotypic criteria.(19) There are 5 components do define the frailty syndrome: low grip strength, low energy, slowed waking speed, low physical activity, and/or unintentional weight loss. There are also a number of risk factors to develop the frailty syndrome, e.g. age, gender, chronic diseases such as cardiovascular diseases, diabetes, anemia, autonomic dysfunction, obesity and level of physical activity.

There is also a pre-frail stage, in which one or two criteria are present, identifies a subset at high risk of progressing to frailty

The overall concept of Frailty goes over the purely somatic level and includes also mental and social dimensions.

Lifestyle factors such as nutrition and the risks of under- and over-nutrition, physical activity and smoking behaviour, but also physical, psychological and socioeconomic factors play an important role in the development of frailty. Often the Frailty circle is so called a vicious circle of undernutrition, Sarcopenia, progress of aging and disease. The negative feedback and the mutually reinforcing interactions of the individual influencing factors lead to the development of Frailty, which in turn favours the development of other diseases. This leads to a decrease in muscle strength, endurance and resilience, which leads to a reduction in walking speed with a subsequent risk for functional impairment, dependency and care needs. The decrease in physical activity results in a decrease in the overall energy balance, which leads to a reduced calorie requirement, poor appetite and thus to chronic malnutrition. This in turn promotes the development of sarcopenia and at the end of this cycle there is an increased danger of falling, hospitalization and often death.(19)

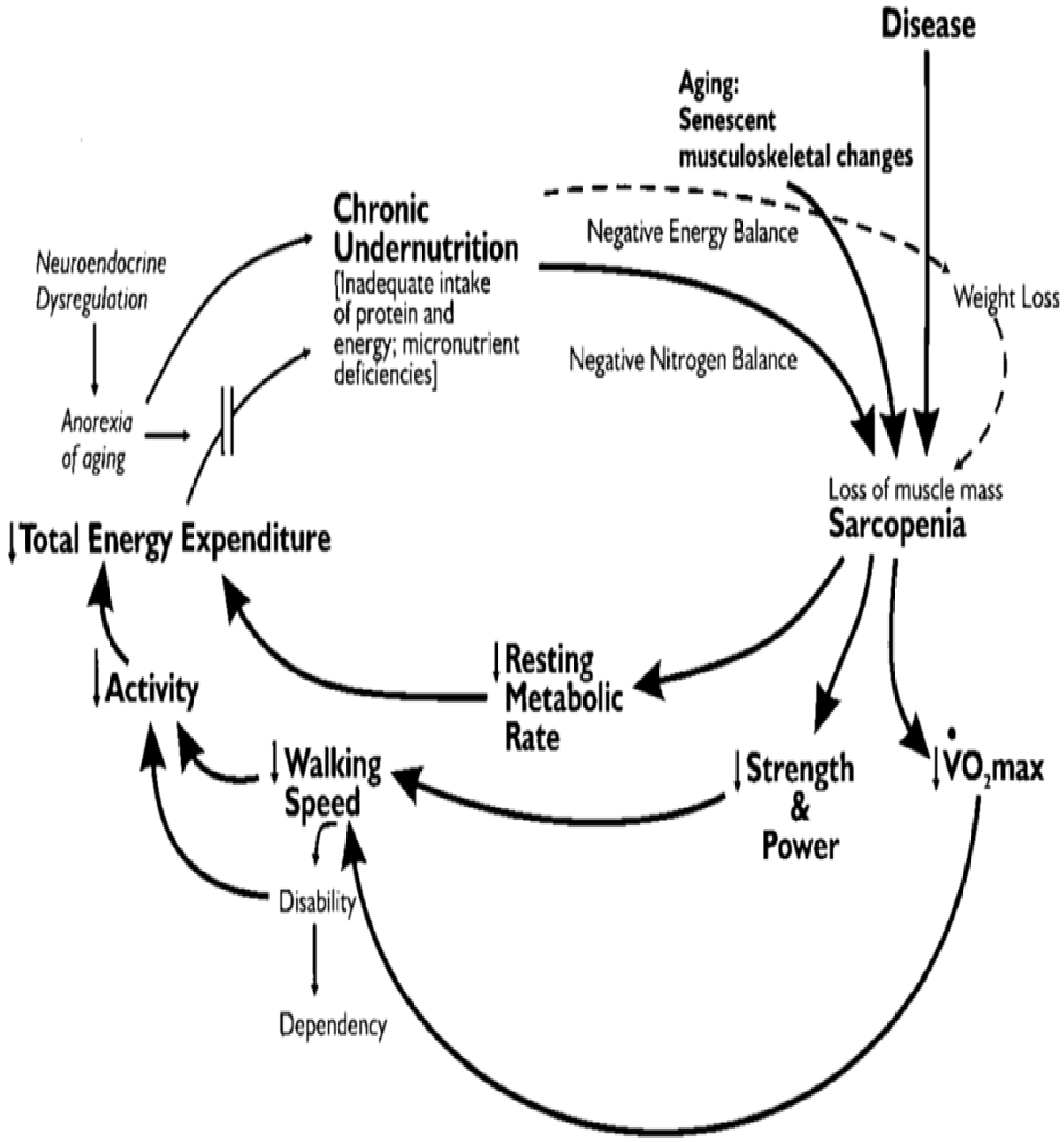

Fig. 11: Linda P. Fried et al. Frailty in Older Adults: Evidence for a Phenotype. Journal of Gerontology: MEDICAL SCIENCES 2001, Vol. 56A, No. 3, M146–M156

The Frailty circle of Fried shows the linking of the individual factors, like loss of appetite and immobility. Frailty can be initiated at any point of the circle and be a progress of the disease.

3.1 Frailty phenotype and the Frailty Index

Physical Frailty Phenotype (19)(PFP)

1. Unintentional weight loss, of more than 10 pounds in prior year or, at follow-up, of 5% of body weight loss in prior year
2. Weakness: grip strength in the lowest 20% at baseline, adjusted for gender and body mass index.
3. Poor endurance and energy: as indicated by self-report of exhaustion.
4. Slowness: The slowest 20% of the population was defined at baseline, based on time to walk 15 feet, adjusting for gender and standing height.
5. Low physical activity level: A weighted score of kilocalories expended per week was calculated at baseline, based on each participant's report. The lowest quintile of physical activity was identified for each gender.

Main characteristic of Frailty phenotype and the Frailty Index

Frailty phenotype	Frailty Index (FI)
Signs, symptoms	Diseases, activities of daily living, results of a clinical evaluation
Possible before a clinical assessment	Doable only after a comprehensive clinical assessment
Categorical variable	Continuous variable
Pre-defined set of criteria	Unspecified set of criteria
Frailty as a pre-disability syndrome	Frailty as an accumulation of deficits
Meaningful results potentially restricted to non-disabled older persons	Meaningful results in every individual, independently of functional status or age

3.2 The CSHA Clinical Frailty Scale

The CSHA (Canadian Study of Health and Aging) is a representative 5-year prospective cohort study. They also developed CSHA scales for function and overall clinical frailty, with the goal of creating tools that could stratify elderly patients as to their relative degree of vulnerability (i.e., their risks of death and of entry into an institutional facility) with simple clinical descriptors.

Rooted in their theoretical model of fitness and frailty and the importance of function (which we reported in earlier investigations)(20), our Clinical Frailty Scale (Fig.8) ranges from 1 (robust health) to 7 (complete functional dependence on others).(21)

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

Fig. 12: Clinical frailty scale by CSHA

3.3 Groningen Frailty Index (GFI)

The GFI is a validated, 15-item questionnaire with a score range from zero to fifteen that assesses the physical, cognitive, social, and psychological domains. A GFI score of four or greater is considered the cut-off point for frailty.(22)

4 Impact in surgery

Preoperative Assesment

A preoperative assessment tool such as the American Society of Anaesthesiology (ASA) score is routinely used prior to surgical procedures. The ASA score is known for its simplicity and suitability for estimation of operative risk, but it considers only organ-specific diseases and is effective only in determining postoperative survival irrespective of the patient preoperative conditions. Most conventional scoring systems fail to incorporate the cumulative effect of all of the deficits in an aging individual's health and also do not take into account the functional reserve of an aging individual. The FI incorporates all the facets of an individual's health that are currently recognized as contributing to postoperative morbidity and mortality. It takes into account the individual's chronologic age, nutritional status, comorbidities, activities of daily living, functional status, and physiologic health.(23)

The number of older people undergoing a planned operation has risen sharply in recent decades. Technically, most interventions are also possible on very elderly patients. But yet frailty-related data are not fully integrated into the perioperative treatment process. For medical decisions in the context of for example patient anaesthesia as well as for adequate monitoring, intensive care physicians need a comprehensive picture of the status of the patient and their individual risks. Frailty in surgical patients is consistently associated with a greater risk of surgical complications, seen in lengths of hospital stay, and discharge to a rehabilitation facility. It can even lead to a cascade of events resulting in disability, loss of independence, diminished quality of life, high health care costs, and mortality. In addition, frail patients are at a higher risk for readmission, suffer from lower quality of life following surgery, and their postoperative care tends to be more cost intense. In these elderly patients, there is greater heterogeneity in the physical constitution than in younger patients, which makes a geriatric assessment indispensable.(24) One of these components of a geriatric assessment is the evaluation of frailty.

In the study by Makary et al. frailty is shown to be a predictor of the surgical outcome of old patients. The incidence of postoperative complications is higher in patients with Frailty (11.4%) than in patients without Frailty (3.9%). Furthermore, a longer hospital stay in frail patients is shown.(25) The decision as to whether a patient can tolerate surgery is often subjective and can misjudge a patient's true physiologic state. The concept of frailty is an important assessment tool in the geriatric medical population, but has only recently gained attention in surgical patients.(26)

5 Sarcopenia

The term is from Greek σάρξ sarx, "flesh" and πενία penia, "poverty". In 1989, Irwin Rosenberg proposed the term ‘sarcopenia’ to describe this age-related decrease of muscle mass.(27)

Age-related muscle loss begins at about 25-30 years. Sarcopenia is the degenerative loss of skeletal muscle mass (0.5–1% loss per year after the age of 50), quality, and strength associated with aging.(28) From the age of 70, the muscle power is reduced by about 3 percent annually; especially the speed of power is lost.

The cause of sarcopenia is multifactorial, with environmental causes, disease triggers, inflammatory pathway activation, mitochondrial abnormalities, loss of neuromuscular junctions, reduced satellite cell numbers, and hormonal changes all thought to contribute.

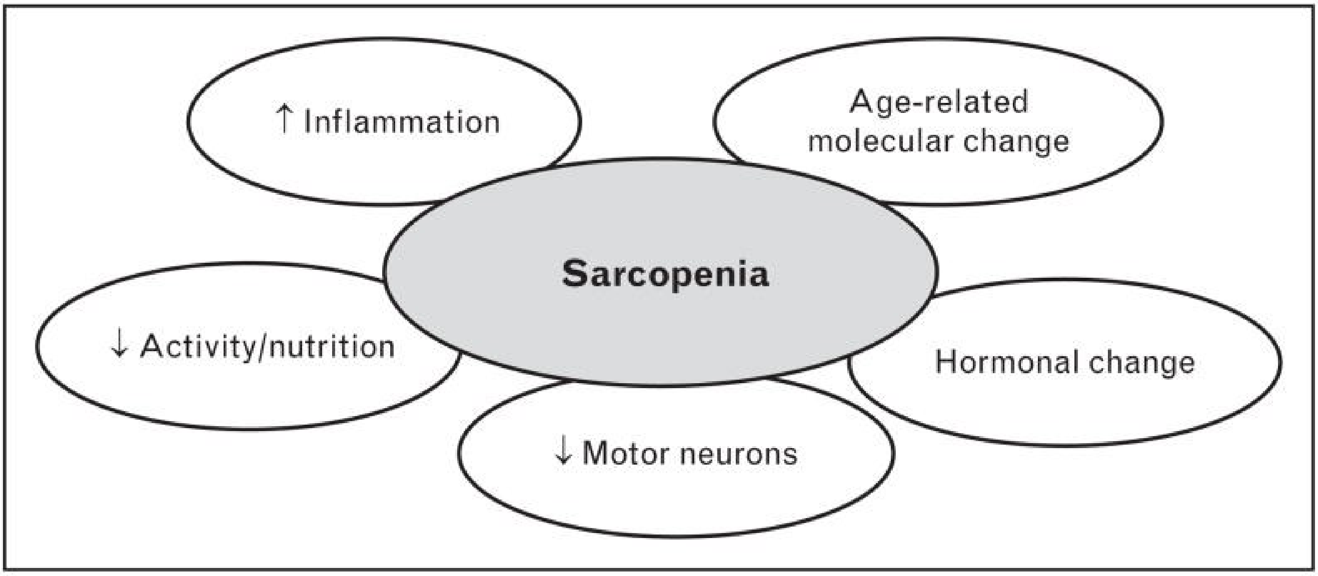

Fig. 13: Multifactorial cause of sarcopenia. The ovals represent domains known to influence the maintenance of skeletal muscle strength and mass in aging organisms.(29)

Sarcopenia is a component of the frailty syndrome and can be seen by measuring the muscle mass on abdominal CT.

Since the beginning sarcopenia and frailty have been studied in parallel. Being organ-specific, sarcopenia was more frequently object of research in basic science, whereas the concept of frailty tended to be more easily applied in the clinical setting. Determining whether frailty is due to sarcopenia, or sarcopenia is a clinical manifestation of frailty is consuming considerable efforts, and (from a very practical viewpoint) rather resembles the problem of “the egg and the chicken.”.(30)

6 Population development

During the last years frailty became a more and more important part in geriatric patient care. During the last 10 years the number of patients over 65 years of age doubled in surgery.(24) Overall, the age of the European / Austrian population is rising constantly and will be during the upcoming years. In 2017, 18.6% of the Austrian population is over 65 years old. According to Statistics Austria's forecasts, in the year 2050, 27.3% of Austrians will be over 65 years old. That means more than one in four Austrians will be living in working age.

Vorausberechnete Bevölkerungsstruktur für Österreich 2015-2100 laut Hauptszenario

Jahr	Bevölkerungsstruktur						
	Insgesamt	Unter 20 Jahre	20 bis unter 65 Jahre	65 und mehr Jahre	Unter 20 Jahre	20 bis unter 65 Jahre	65 und mehr Jahre
	absolut				in %		
2015	8.629.519	1.692.442	5.342.640	1.594.437	19,6	61,9	18,5
2016	8.739.130	1.711.427	5.412.970	1.614.733	19,6	61,9	18,5
2017	8.813.858	1.716.704	5.461.088	1.636.066	19,5	62,0	18,6
2018	8.883.827	1.724.447	5.500.004	1.659.376	19,4	61,9	18,7
2019	8.949.503	1.734.369	5.531.186	1.683.948	19,4	61,8	18,8
2020	9.010.815	1.745.431	5.553.706	1.711.678	19,4	61,6	19,0
2021	9.067.850	1.757.679	5.565.479	1.744.692	19,4	61,4	19,2
2022	9.120.539	1.769.832	5.569.342	1.781.365	19,4	61,1	19,5
2023	9.169.773	1.781.423	5.569.233	1.819.117	19,4	60,7	19,8
2024	9.215.952	1.792.655	5.563.846	1.859.451	19,5	60,4	20,2
2025	9.258.903	1.803.005	5.552.654	1.903.244	19,5	60,0	20,6
2030	9.432.086	1.847.458	5.430.362	2.154.266	19,6	57,6	22,8
2040	9.646.812	1.850.641	5.289.431	2.506.740	19,2	54,8	26,0
2050	9.771.160	1.825.455	5.275.328	2.670.377	18,7	54,0	27,3
2060	9.825.196	1.853.361	5.183.545	2.788.290	18,9	52,8	28,4
2070	9.907.212	1.875.122	5.174.676	2.857.414	18,9	52,2	28,8
2080	10.010.938	1.877.493	5.211.608	2.921.837	18,8	52,1	29,2
2090	10.059.279	1.888.332	5.217.855	2.953.092	18,8	51,9	29,4
2100	10.096.328	1.900.525	5.226.922	2.968.881	18,8	51,8	29,4

Q: STATISTIK AUSTRIA - Bevölkerungsprognose 2016. Erstellt am 11.11.2016.

Fig. 14: Predicted population structure for Austria 2015-2100 according to the main scenario

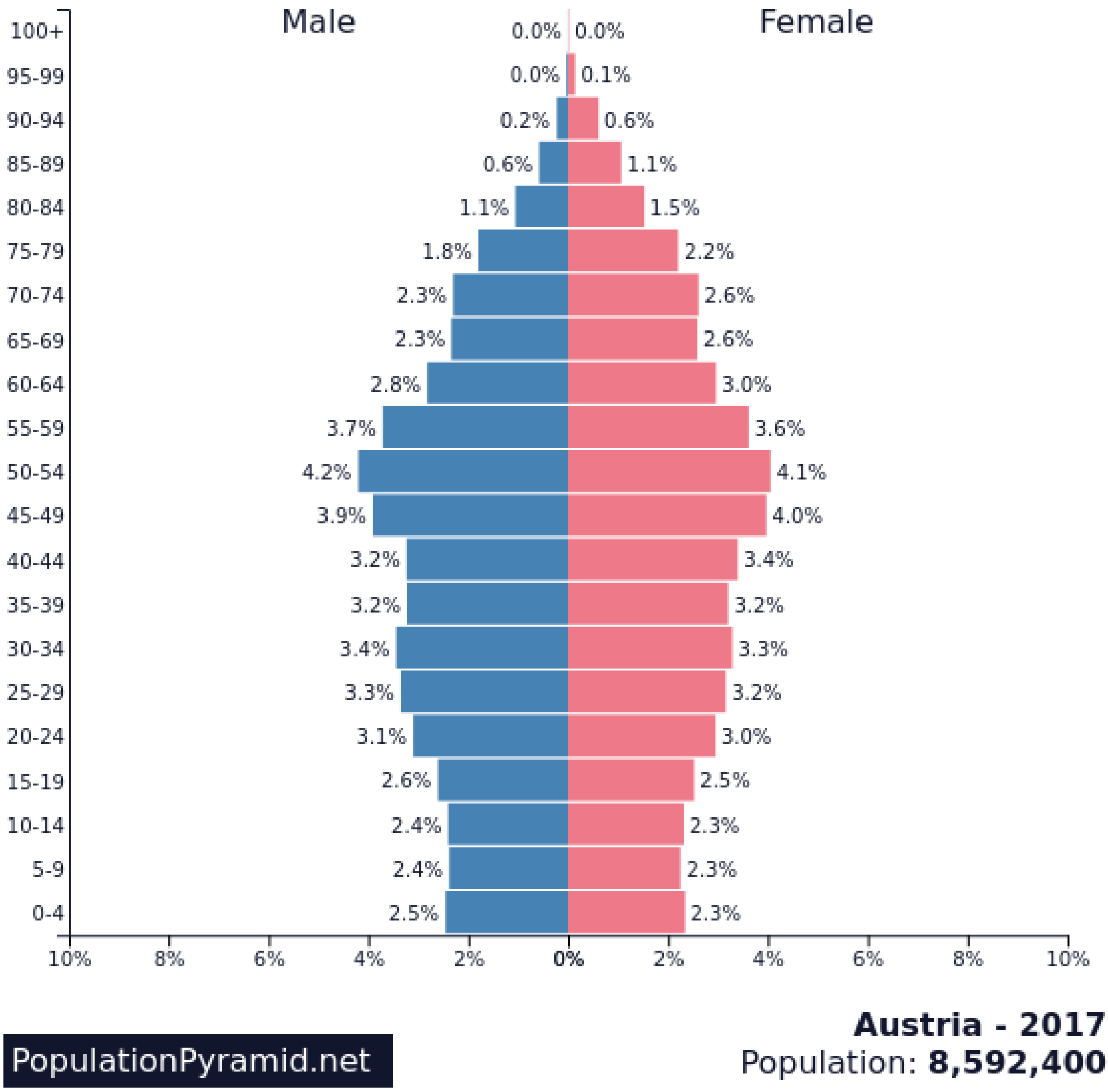

Fig. 15: aging pyramid Austria

Increasing age leads to increasing numbers of aged and therefore increasing numbers of geriatric patients.(24)

Therefore, it is necessary to use an easily measurable and objective surrogate parameter for Frailty. In comparison to cachexia, which occurs mainly in chemotherapy or in generalized tumors, sarcopenia is a better surrogate parameter. The weight mainly represents the nutritional status, the sarcopenia or the loss of muscle mass, however, is a better indication of frailty / Frailty.(25)

Patients with Frailty syndrome have been shown to have smaller muscle density and lower muscle mass(31). Thus, Frailty can be associated with sarcopenia. In the work of Mijnarends et al. it is found that old frail people suffer significantly more sarcopenia. Similarly, sarcopenia increases with age in older people who do not have Frailty syndrome(32).

7 Gender and diseases

In health, more than in other social sectors, sex (biological) and gender (behavioral and social) variables are acknowledged useful parameters for research and action because biological differences between the sexes determine male-specific and female-specific diseases and because behavioral differences between the genders assign a critical role to women in relation to family health.(33)

Gender medicine must consider the needs of both sexes. This might require giving greater attention to women where specific data on women are lacking and greater attention to men where specific data on men are lacking. For example, more data on men are needed in regard to osteoporosis and depression, whilst more data on women are urgently needed in the cardiovascular area.(34)

It is more and more clear that we have to look at our patients in two different ways, men and women. Women do have different symptoms, outcomes and ways to recover.

Medical research and diagnostic methods are often exclusively for men and therefore also for men as long as clinical studies are performed exclusively on men. The researchers fear that women could jeopardize the success of a study or falsify the results through a possible pregnancy or hormonal fluctuations. Also, therapies and medications are therefore geared towards male bodies. Whether the drugs - in the appropriate dosages - for women may be less helpful or even harmful, remains undetected. In order for diseases to be better researched and treated in the future, data must be collected in an increasingly gender-differentiated manner. Gender mainstreaming here means strengthening the consideration of possible gender differences as a quality feature of research.(35)

Self-perception: body awareness and the handling of health burdens are also a result of gender-specific socialization. This leads to a different willingness to avail of prevention services such as cancer screening. Gender-differentiated analyzes make it possible to identify relevant deficits in medical provision and to take measures to compensate them.

It has been proven that certain diseases are different in women than in men. Particularly striking differences in sex are found in rheumatism or cardiovascular diseases.

According to WHO chronic diseases, such as heart disease, cancer, diabetes, chronic respiratory diseases and stroke, are by far the leading cause of mortality in the world, representing 60% of all deaths. (36)

8 Methods

This retrospective study includes 966 patients (female: 51,4%, male: 48,6%) over a time of 10 years (2006-2016) who underwent liver resection at the Department of General Surgery at the Medical University of Graz, Austria.

8.1 Image/CT Analyse

Osirix MD (DICOM Viewer, Pixmeo, Bernex, CH) was used to analyse the patients CT scan. Each patient's record was reviewed for CT images taken prior to surgery, 6 month after and a year after.

Muscle mass was measured of electronically stored CT images, which had been taken for diagnostic purpose.

In order to assess sarcopenia, the muscle areas of the left (LPA - Left Psoas Area) and right Psoas muscle are measured and added to the total Psoas area (TPA - Total Psoas Area). This measurement is performed at the level of the third lumbar vertebra (L3). The correct setting can be found by scrolling from cranial to caudal, where the left and right iliac crests are clearly recognizable. Furthermore, the skeletal muscle mass (sceletal muscle mass L3) is measured in this setting. In addition, the skeletal muscle surface is measured at the level of the lumbar vertebra L5 (sceletal muscle mass L5), which you find by going more caudal.

The cross-sectional skeletal muscle mass area was measured with manually tracing inner and outer contours using a present Hounsfield unit (HU) range of −30 to +150 on the level of the third lumbar vertebra (L3) where both iliac crests were seen. The following muscles were included: psoas, paraspinal muscles (erector spinae, quadratus lumborum), transverse abdominal, external oblique, internal oblique, and rectus abdominis. (37)

In addition, the skeletal muscle surface is measured at the level of the fifth lumbar vertebral body (L5) (Sceletal muscle mass L5). After completion of the measurement at height L3, the patient will continue to scroll to the caudal angle until the bilateral anterior superior iliac spine appears. This corresponds to the height of the fifth lumbar vertebrae and is used for the measurement. In this setting, the two psoas muscle surfaces are measured analogously to the procedure at the height L3 and added to the total psoas muscle areas. To determine the total skeletal muscle area at height L5 (Sceletal muscle mass L5), the muscle areas of the two psoas muscles, the autochthonous back muscles, the abdominal muscles and the gluteal muscles are added together.

Fig. 16: The CT scan shows the marked muscle areas of the two psoas at height L3. The correct setting in a CT scan can be found by scrolling from cranial to caudal, where the left and right iliac crests are clearly seen.

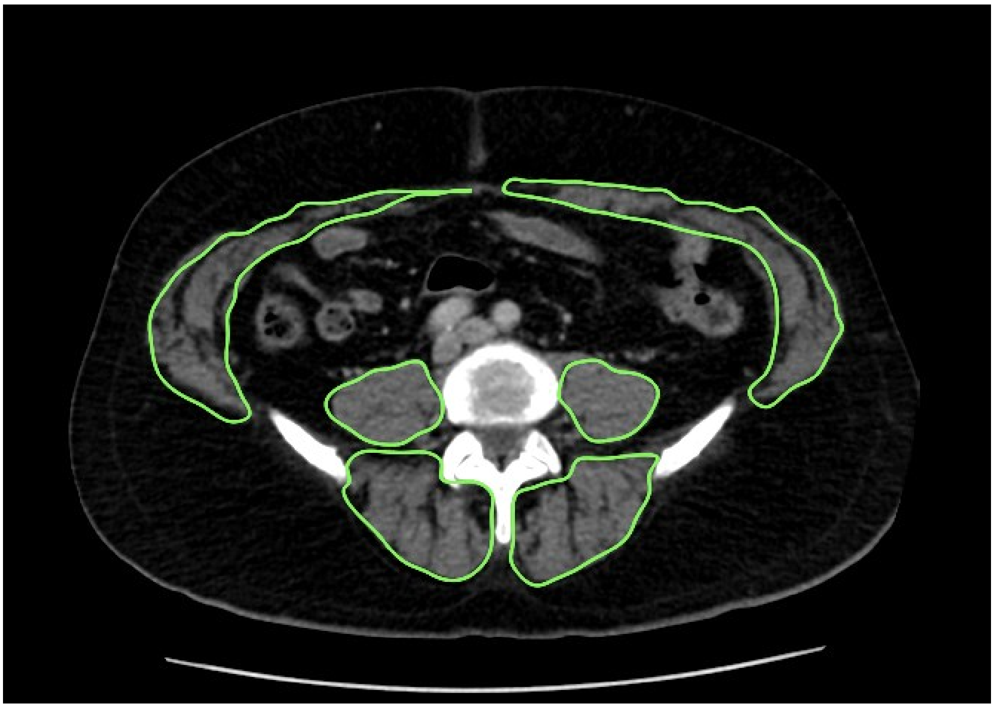

Fig. 17: In this CT scan at height L3, the total muscle area is marked.

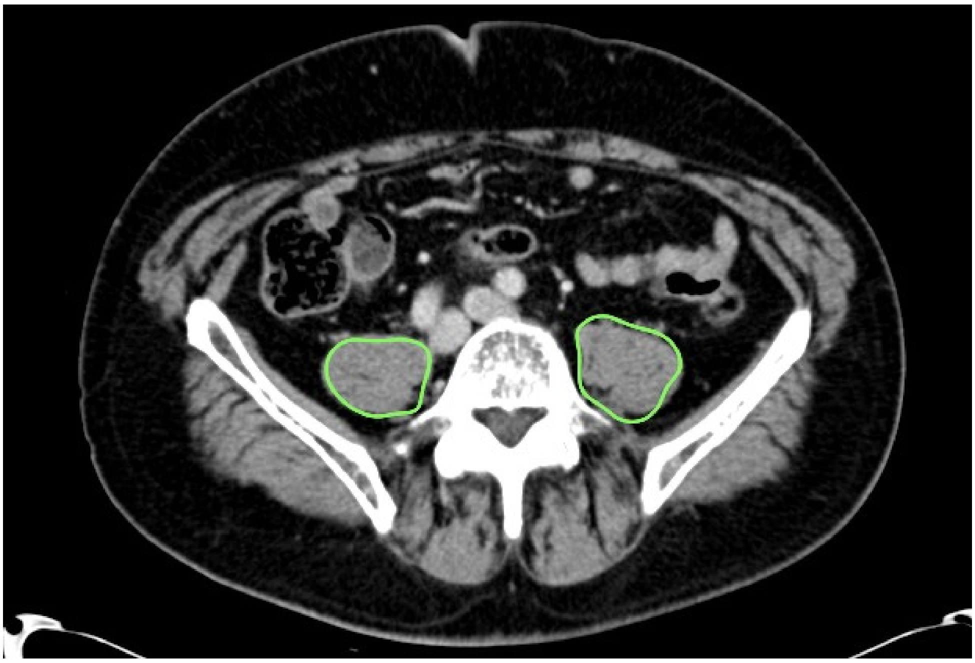

Fig. 18: This is a CT scan at height L5 with the marked muscle areas of the two psoas muscles. This position can be found by scrolling to the caudal angle until the bilateral anterior superior iliac spine appears

Fig. 19: The CT scan at height L5 shows the total muscle area marked.

For the objective determination of skeletal muscle mass (Sceletal muscle mass total), the mean value is calculated from the skeletal muscle masses of L3 and L5 (Sceletal muscle mass L3 and Sceletal muscle mass L5). This average is used to calculate the skeletal muscle index. The sceletal muscle index (SMI) is determined by dividing the median skeletal muscle mass (sceletal muscle mass total) by the body surface area, which is calculated using the body surface area calculator.

The Hounsfield scale describes the attenuation of X-rays in the computerized tomogram. HUAC (Hounsfield Unit Average Calculation) measures the muscle density and fat infiltration of the muscle. To calculate the HUAC left, the Hounsfield Units (HU) on the left are multiplied by the area of the left psoas muscle (LPA) and divided by the total psoas muscle area (TPA). Similarly, the HUAC is calculated right by multiplying the HU right and the area of the right psoas muscle (RPA) divided by the total psoas muscle area (TPA). The HUAC total is calculated from the total of the HUAC left and HUAC divided right by two.

8.2 Data acquisition

Data collection was carried out from April 2016 to December 2017 by a doctorate student. A retrospective data analysis of the patient group is carried out.

Standard demographic and clinical data are collected from the Open Medocs (data processing program of the Medical University of Graz / KAGES).

Demographic data such as age, sex, height, mass, BMI and survival as well as the time of death is collected to evaluate the data.

Clinical data from 966 patients were collected.

Preoperative abdominal computed tomography (CT) images and control CTs, 6 and 12 months after surgery, are measured and history is assessed. Sarcopenia is determined by measuring muscle mass on the abdominal CTs, and this data is related to the patient's postoperative course.

Several scores as the Charlson comorbidity index, the ASA classification and ECOG Score are used for the analysis.

The Charlson comorbidity index (38) predicts the one-year mortality for a patient who may have a range of comorbid conditions, such as heart disease, AIDS, or cancer (a total of 22 conditions). Each condition is assigned a score of 1, 2, 3, or 6, depending on the risk of dying associated with each one. Scores are summed to provide a total score to predict mortality.

Weight	Clinical condition
1	Myocardial infarct
	Congestive cardiac insufficiency
	Peripheral vascular disease
	Dementia
	Cerebrovascular disease
	Chronic pulmonary disease
	Conjunctive tissue disease
	Slight diabetes, without complications
	Ulcers
	Chronic diseases of the liver or cirrhosis
2	Hemiplegia
	Moderate or severe kidney disease
	Diabetes with complications
	Tumors
	Leukemia
	Lymphoma
3	Moderate or severe liver disease
6	Malignant tumor, metastasis
	Aids

Figure 1 - Charlson comorbidity index – weighting of the clinical conditions present among secondary diagnoses.

Fig. 20: Charlson comorbidity index (39)

The ASA classification is a widely used scheme in medicine for classifying patients into different groups (ASA physical status) with respect to the physical condition.

The ASA physical status classification system is a system for assessing the fitness of patients before surgery. In 1963 the American Society of Anesthesiologists (ASA) modified the five-category physical status classification system from the year 1941(40); a sixth category was later added.

These are:

- 1 - Healthy person.
- 2 - Mild systemic disease.
- 3 - Severe systemic disease.
- 4 - Severe systemic disease that is a constant threat to life.
- 5 - A moribund person who is not expected to survive without the operation.
- 6 - A declared brain-dead person whose organs are being removed for donor purposes.

In medicine a performance status is an attempt to quantify cancer patients' general well-being and activities of daily life. There are various scoring systems. A common system is the Eastern Cooperative Oncology Group (ECOG) system.

The Eastern Cooperative Oncology Group (ECOG) score), runs from 0 to 5, with 0 denoting perfect health and 5 death:

Its advantage lies in its simplicity.

- 0 – Asymptomatic (Fully active, able to carry on all predisease activities without restriction)

- 1 – Symptomatic but completely ambulatory (Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature. For example, light housework, office work)

- 2 – Symptomatic, <50% in bed during the day (Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours)

- 3 – Symptomatic, >50% in bed, but not bedbound (Capable of only limited self-care, confined to bed or chair 50% or more of waking hours)

- 4 – Bedbound (Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair)

- 5 – Death

8.3 Statistical Analysis

Continuous variables were provided as median values with interquartile range (IQR). Categorical variables were reported as totals and frequencies. Postoperative morbidity recorded as categorical variable was used as outcome parameter as well as postoperative mortality (within 30 days) complications recorded as Clavien Dindo > 2 were used to define severe complications and entered the statistical analysis as categorical outcome variable. The impact of low skeletal muscle mass was evaluated both as a continuous and a categorical variable. Low skeletal muscle mass was defined in categorical analyses as the lowest quartile in male and female patients seperately. The SMI cutoffs to define low skeletal muscle mass were 41 cm^2/m^2 in female and 43 cm^2/m^2 in males. The impact of low skeletal muscle mass on mortality was assessed using univariable and multivariable logistic regression analyses. Overall survival was analyzed using the Kaplan-Meier method, and differences in survival were evaluated with the log-rank test. The association of relevant clinicopathologic variables with postoperative mortality was assessed 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). Performance of the model was evaluated by Harrell's concordance index (C-index). All patients were analyzed together as well as according to their gender.

Low skeletal muscle mass reflecting sarcopenia was calculated preoperatively as well as 6 and 12 months postoperatively. The course of sarcopenia was assessed according to the patient gender and potential significancies in the course were tested via the EDGE test. Statistical analyses were performed with SPSS 22.0); all tests were two-sided and a P-value <0.05 was considered statistically significant.

9 Results

Nine hundred sixty six patients were included into the analysis. Of the included patients 497 (51.4%) were female and 469 were male. Most patients underwent liver resection due to existing malignancies (664/966, 70.4%) with a postoperative overall survival of 59.5% (572/966).

Preoperative condition of patients was comparable to the literature of these patients. Most patients had at least one remarkable history of hypertension or hyperlipidemia or diabetes. History of smoking or regular alcohol intake was quite prevalent in the patient cohort. Both facts are reflected by the fairly high Charlson Comorbidity Index (CCI) values and the relatively high ASA scores.

All demographics are compiled in Table 1 of all patients.

Demographics	Percentage and number of patients
Male patients %	48.6% (469/966)
Malignant diagnosis %	70.4% (664/966)
Indication of liver resection:	
Benign tumors and cysts	29.6% (286/966)
Liver metastases	49.3% (481/966)
Preoperative comorbidities:	
Diabetes mellitus	13.9% (135/966)
Hypertension	41.7% (403/966)
Hyperlipidemia	18.2% (176/966)
Metabolic Syndrome	28.2% (272/966)
Renal impairment	9.4% (91/966)
History of	
Smoking	23.1% (223/966)
Alcohol Abuse	59.7% (577/966)
Charlson Comorbidity Index preoperative	
Below 6	66.1% (639/966)
Above 6	33.8% (327/966)
Preoperative ASA score	
1-2	48.6% (469/966)
3-4	51.4% (497/966)

Table 1 includes all preoperative characteristics of the whole patient set.

Indications for resection were mostly colorectal liver metastases in 266 patients followed by primary liver tumors and tumors of the biliary tract. Some rare indications were prevalent as well, among them a large amount of patients with neuroendocrine tumors who underwent liver resection due to mestastases.

Indications for liver resection	
Malignant indications:	
Colon cancer liver metastases	16.3% (157/966)
Rectal cancer liver metastases	11.3% (109/966)
Cholangiocellular Carcinoma	5.6% (54/966)
Hepatocellular Carcinoma	8.7% (84/966)
Galbladder Carcinoma	7.6% (73/966)
Pancreatic Carcinoma	5.6% (49/966)
Melanoma	0.7% (7/966)
Breast Cancer	1.6% (15/966)
Neuroendocrine Tumors	3.1% (30/966)
Sarcoma	1.7% (16/966)
Gastric Cancer	1.0% (10/966)
Others	7.2% (70/966)
Benign Indications:	
Hemangioma	4.2% (41/966)
Liver zysts	12.0% (116/966)
Caroli Syndrome	0.5% (5/966)
Trauma	0.8% (8/966)
Adenoma	2.3% (22/966)
Focal Nodular Hyperplasia	5.1% (49/966)
Other	5.3% (51/966)

Table 2 All indications for live resection are summed up with respect to their ethiology.

Six hundred sixty four patients underwent resection due to malignant diagnosis. Most of them had colorectal liver metastases (43%). 18.2% (122/664) patients received neo adjuvant chemotherapy, 7.4% (49/664) had neo adjuvant radiation and 51.7% (340/664) of resections were followed by adjuvant chemotherapy. Patients with malignant diagnosis were more likely to be male (59.2%, 393/664).

Most patients were classified as completely active or only mildly impaired according to the preoperative ECOG score, most prevalent T stage in all resections was T3 indicating that patients mostly suffered from advanced tumor disease before resection.

There were no differences between female and male patients with respect to preoperative treatment or disease severity. Female patients had a slightly lower rate of neo adjuvant therapy (17%, 47/271) as compared to male patients (18%, 73/393). Male patients were as likely to have T3 and above staged carcinoma as were female patients (female: 51.6% - 140/271, male: 49.6% - 195/393, p=0.92) and patients of both genders showed equal performances in the preoperative ECOG assessment (ECOG 0 and 1 – male: 92% 362/393; female: 91% 249/271, p=0.18).

Patients with malignant diagnosis (n=664)	
Male gender (%)	59.2% (393/664)
Preoperative ECOG status:	
0	51.1% (339/664)
1	41% (272/664)
2	6.3% (42/664)
3	1.7% (11/664)
Primary T stage	
1	17.6% (98/664)
2	22.1% (123/664)
3	47.1% (262/664)
4	13.1% (43/664)
Neoadjuvant chemotherapy	18.2% (120/664)
Neoadjuvant radiotherapy	7.4% (49/664)
Adjuvant chemotherapy	51.7% (340/664)
Preoperative interventional treatment (portal vein embolization, transarterial chemoembolization)	14.8% (98/664)

Table 3 compiles all treatment characteristics of malignant patients.

Patients were followed for their whole time period after resection with a median follow up of 25 months in patients undergoing resections for malignancies and 35 months in the whole patient set.

Overall postoperative survival of all included patients was 88 months at median, 42 months for patients undergoing resections of malignancies. One month, 3 month and 12 months survival were 95%, 92% and 79% in malignant patients respectively. Survival significantly differed between patients who underwent resection for malignancies and those who did not (Log Rank: p=0.001).

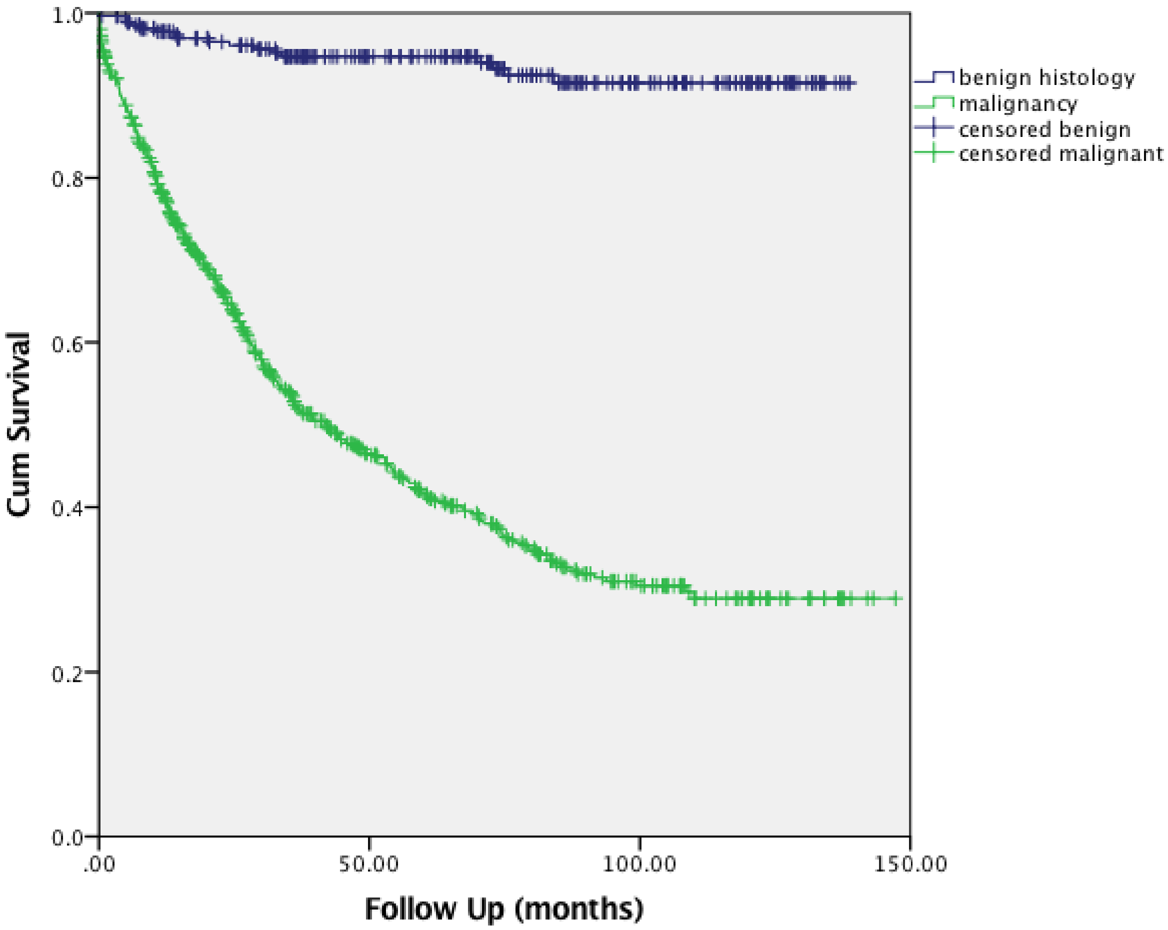

Figure 1 shows the cumulative survival of the included patients with respect to the underlying disease. Survival of patients who underwent liver resection for malignant diagnoses is significantly lower (p=0.001) as compared to patients with benign diagnoses.

The specific Follow Up of patients who underwent resection for malignant diagnoses is depicted in table 4.

Status Follow Up	
Alive with Disease	30.2%
Alive without evidence of Disease	25.7%
Dead of Disaese	33.3%
Dead of Other Causes	10.9%

Table 4 survival characteristics of patients underwent resection for malignancies.

Total operation time of patients was 165 minutes at median with a median of 7 red blood cell transfusions administered. Patients stayed 2 days at median in the ICU.

Operative characteristics (patients with malignancies)	
Total OR time (minutes)	165 (114-221)
Number of intraoperative transfusions (red blood cells, fluids)	7 (5-9)
Number of red blood cells	1 (0-2)
ICU days	2 (1-3)
Neoadjuvant radiotherapy	7.2% (49/664)
Adjuvant chemotherapy	51.7% (340/664)
Preoperative interventional treatment (portal vein embolization, transarterial chemoembolization)	14.8% (98/664)

Table 5 shows operative characteristics of the included patients with malignancies.

Significantly more patients were resected for malignancies (p=0.03). Benign indications were more prevalent in female patients (44%) as compared to male patients (14%, p=0.01).

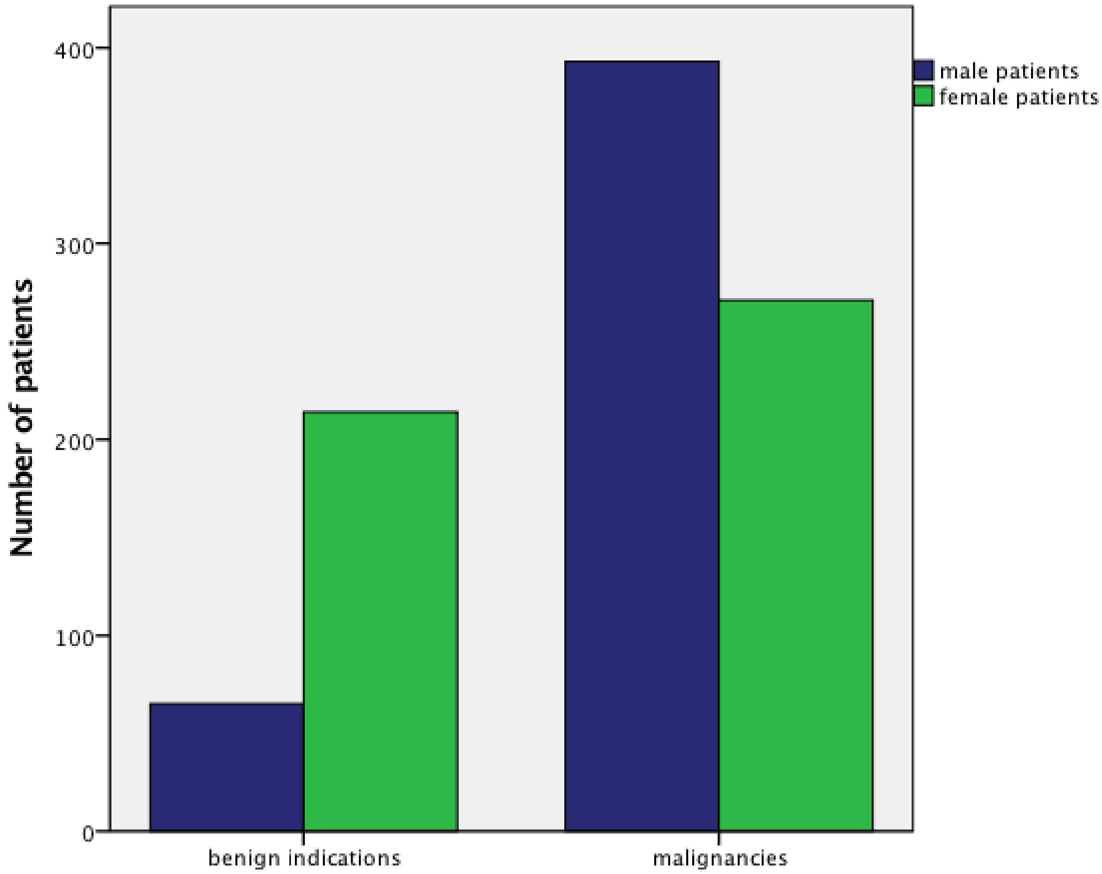

Figure 2 shows the distritbution between malignant and benign indications for liver resection with respect to the patients gender.

CT images to diagnose sarcopenia were available for 587 (61%) patients preoperatively, 464 (48%) at 6 months and for 333 patients (34%) at 12 months. In the whole patient set 146 patients showed sarcopenia preoperatively, 137 at 6 months and 92 at 12 months. This is an increase in the prevalence of sarcopenia of 3% throughout the first 12 postoperative months.

Female patients had a 3 times higher risk to show low skeletal muscle mass preoperatively as compared to male patients (OR 2.66, CI 95% 1.8-3.8; p=0.001) (Figure 3).

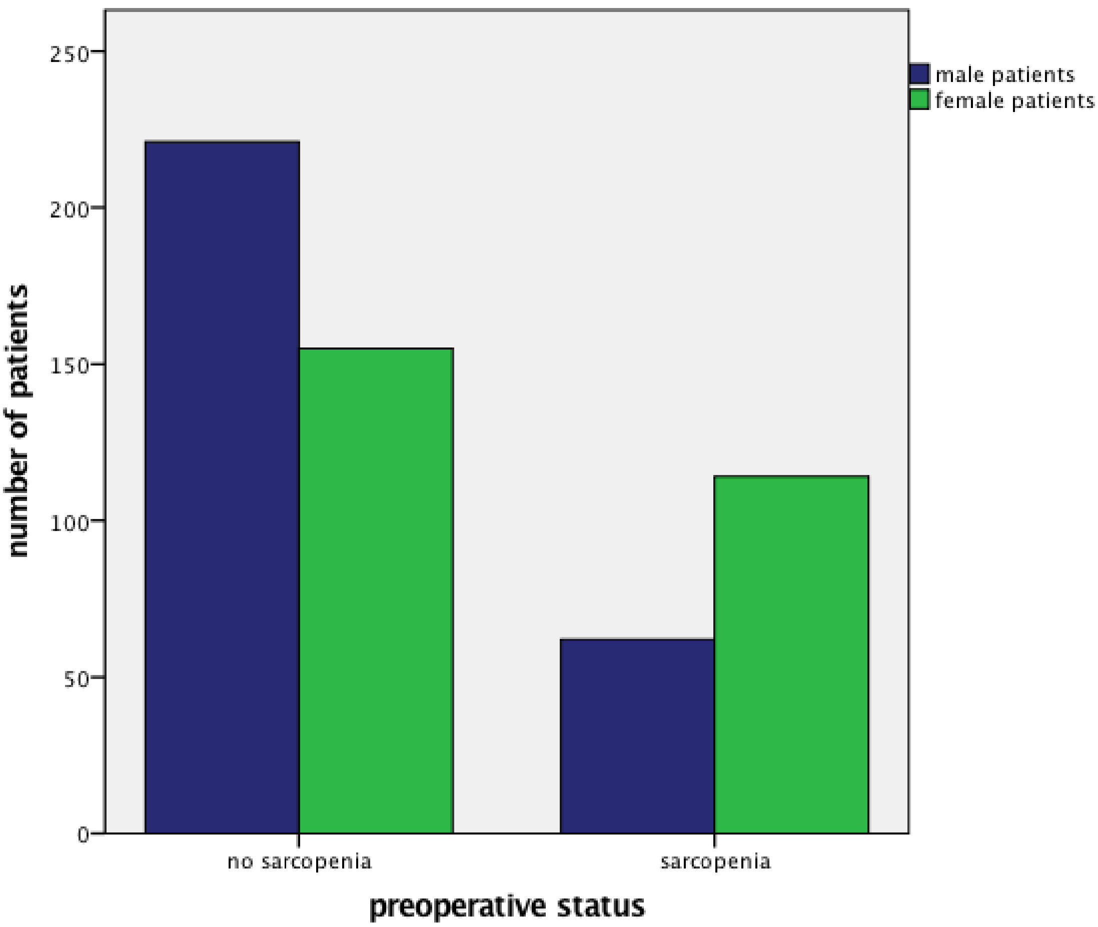

Figure 3 depicts the prevalence of low skeletal muscle mass in female and male patients. Sarcopenia was more prevalent among females as compared to males.

Throughout the investigated period of the first 12 postoperative months this difference evened out (prevalence sarcopenia 6 months: female gender 95/159, male gender: 64/159; prevalence sarcopenia 12 months: female gender: 53/99, male gender: 46/99) however, preoperatively and at 6 months females were significantly more affected with sarcopenia as compared to male patients (p values: preoperatively 0.01; 6 months 0.03).

Patients with sarcopenia showed significantly lower survival as compared to patients without sarcopenia (LOG rank p= 0.016). Median survival of patients undergoing liver resection without sarcopenia was 94 months, for patients without sarcopenia 74 months. This means a nearly 2-year shorter life span. This difference was even more pronounced in women as compared to men. Women with sarcopenia had a 25 months lower life expectancy as compared to women without sarcopenia. The life expectancy of male patients with sarcopenia was only 17 months lower as compared to the one of males without sarcopenia.

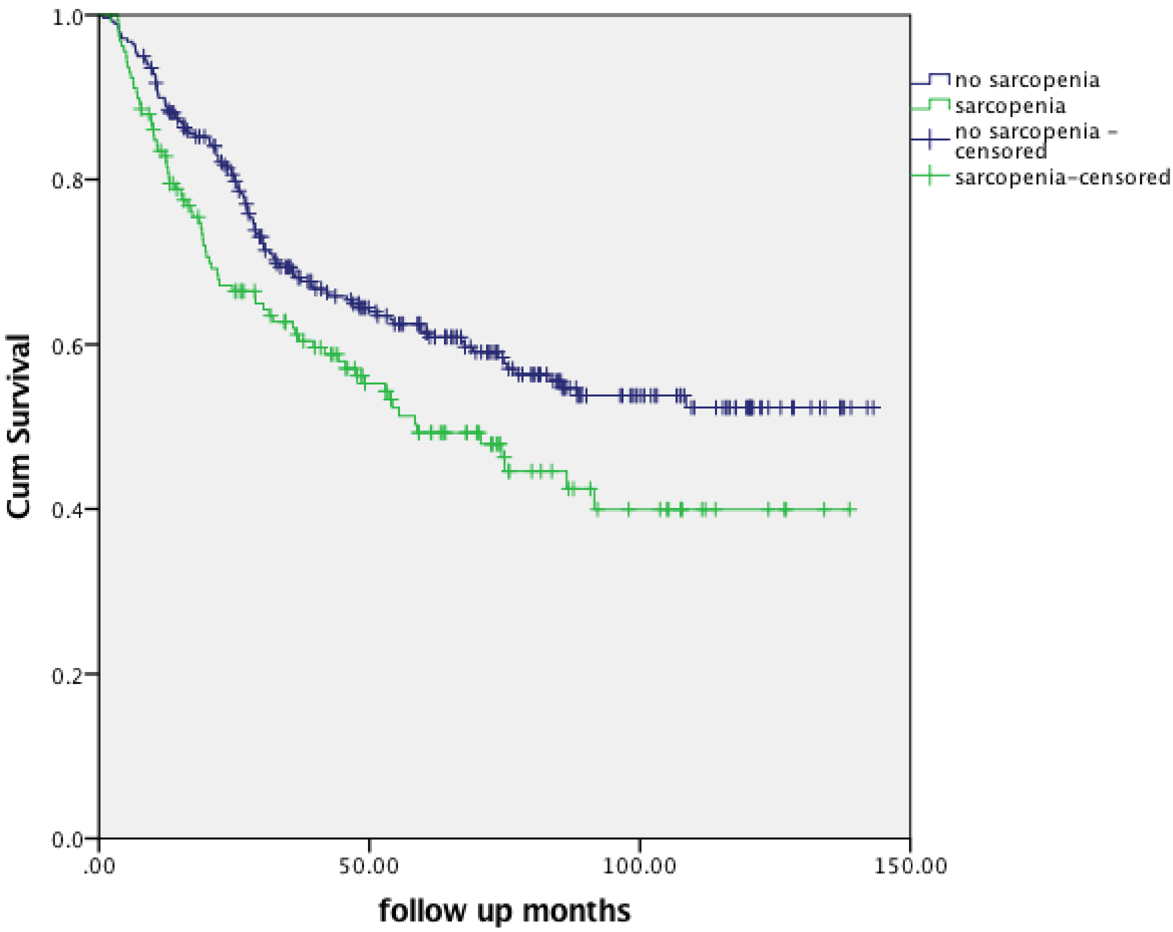

Figure 4 shows the overall survival of all patients undergoing liver resection with respect to their skeletal muscle mass. Patients with sarcopenia lived significantly shorter in the overall survival analysis as compared to patients without sarcopenia.

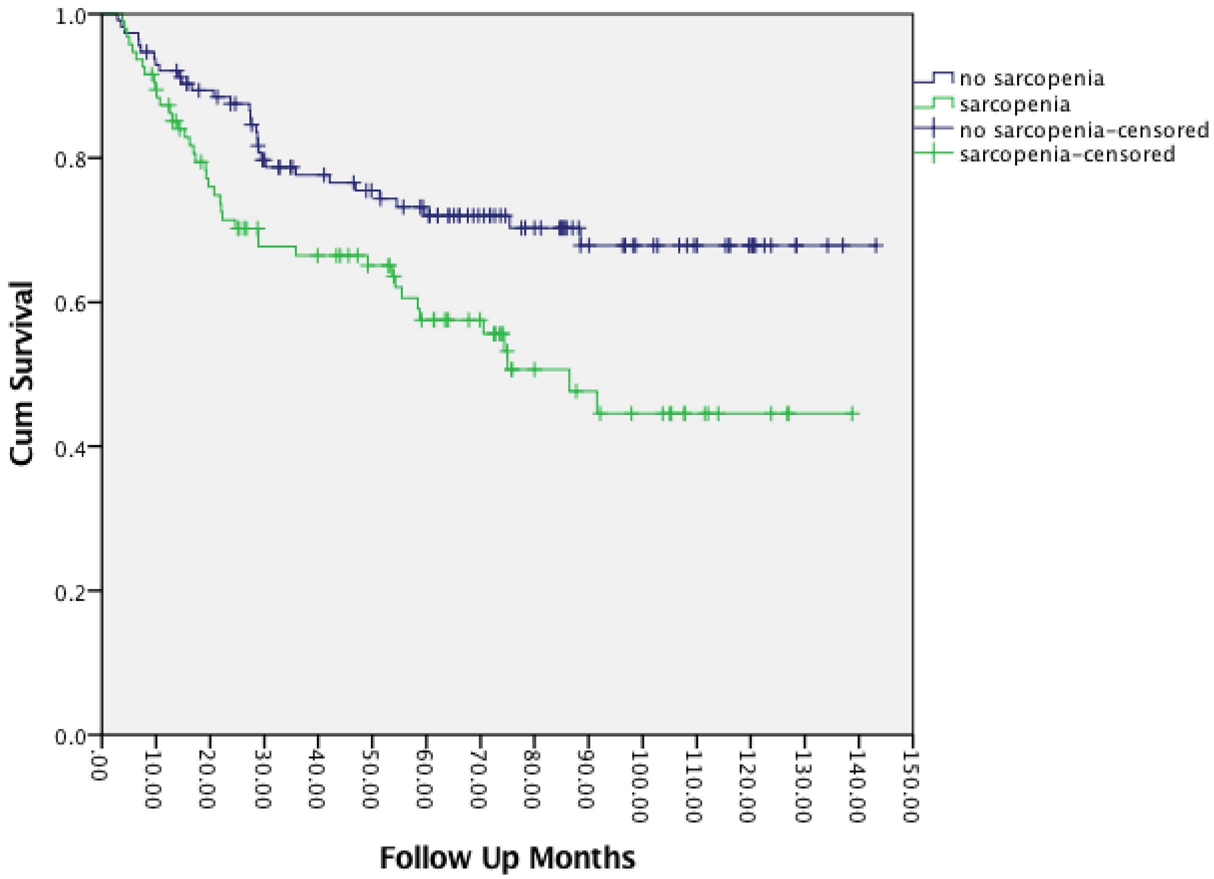

Figure 5 shows the survival curve of females with and without sarcopenia. The overall survival differed significantly between the two groups (p=0.001). Female patients with sarcopenia had a 30% higher risk to die within the observation period as compared to male patients (HR: 1.34, CI 95% 1.04-1.58, p=0.019).

10 Discussion

The human body consists of more than 600 skeletal muscles.(41) Stand straight, keep balance, walk, run, bend over, scratch your knee, get dressed, go shopping, carry a bag- all actions, which are all possible because of our skeletal muscles. The functionality of all skeletal muscles are only visible and realized by us when their function decreases. Difficulties may arise in performing activities of daily living and as a result quality of life and autonomy may decrease while the risk of care dependency and subsequent institutionalization increases.

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 the wish of the majority of older adults themselves, who prefer to stay at home as long as possible. Aging in place has several advantages for older adults, such as preservation of their personal network and environmental landmarks.(42)

In addition, aging in place is thought to reduce the burden of health care services and has therefore attracted attention of most western governments. Sarcopenia may threaten the trend towards aging in place, considering its association with difficulties performing activities of daily living and institutionalization. Insight in the prevalence of sarcopenia, its characteristics, health and economic outcomes is of importance to 1) know which community-dwelling older adults are at risk of sarcopenia, and 2) to know what are the target areas for a tailored-made approach to prevent/treat sarcopenia and contribute to a sustainable, affordable health care system.

Previous studies described sarcopenia as an independent prognostic factor in patients following hepatectomy and as a risk factor for postoperative complications.(43),(44),(45) Unfortunately, only a minority of patients presents with resectable disease. In the presented study, low skeletal muscle density identified with patients malignant diseases prone for an increased mortality rate in the long term and an increased morbidity rate in the short term.

One could hypothesize that once patients have survived the postoperative period, the effects of low skeletal muscle mass and density diminish.(46),(47) Other risk factors, such as age and comorbidity that are also strongly correlated with skeletal muscle mass and density, become more important for the clinical course of a given patient. (Wagner D Br J Surg 2016 and Wagner D EJSO 2018). In the literature it is hypothesized that cancer patients seem to reach a status of functioning in the long term, where even the effect of existing sarcopenia dimishes. We were able to prove this hypothesis in our patients.

The presented analysis is the first to show a potential amelioration of the physical status of patients after liver resection. Despite the fact that the majority of the included patients underwent resection for malignancies and therefore represent a patient cohort which is known to have higher prevalence of sarcopenia and low skeletal muscle mass, the overall quantity of muscle mass still improved over the time period, leading to a non significant difference between the groups of sarcopenic and non sarcopenic patients after 12 months. This improvement was significant in the included patients.

Therefore successful therapy seems to restore the patients physical functioning more than we know at the moment. This improvement was found despite the fact that liver cancer patients, have an increased risk of spiralling down a vicious circle of cancer development progressively enhancing physical impairment. Furthermore, tumor location, tumor biology, and tumor metabolism may determine the proportion of skeletal muscle wasting rather than tumor stage.

As already mentioned this is the first study to show that muscle wasting – which until now was only investigated at one time point – seems to change into a at least stable state at one postoperative point. This might be due to the effect that anticancer surgery may also halt further skeletal muscle wasting. A recent study found that advanced age, female gender, higher ASA classification, and an altered systemic inflammatory response were significantly associated with loss of skeletal muscle mass over time after colorectal surgery.(48) However, its prognostic value was not described and consequently remains unknown.

Postoperative skeletal muscle depletion after resection for hepatocellular carcinoma did indeed identify patients with recurrence. Future studies among patients with other tumors should therefore also elaborate on the question whether anticancer treatment may halt muscle wasting, and if postoperative skeletal muscle mass loss, which could be measured on sequential CT examinations, may predict mortality or could be used as a biomarker to identify disease recurrence in an early phase.

The WHO estimates that 2035 over one third of the world population will be aged above 65 years in industrial nations. Age is one of the major risk factors for cancer development.(49) In the presented study over half of the patients were patients who underwent liver resection for malignant diseases. Among the included patients age proved to be one of the major risk factors for worse outcome. Along with age sarcopenia was deeply associated with worse outcome and with older age in our analysis. These findings are in accordance with the existing literature.

Several conclusions can be drawn from this evaluation of the course of postoperative sarcopenia. Patients with sarcopenia had a significantly lower survival and more postoperative complications as compared to patients without sarcopenia. Therefore CT assessed sarcopenia seems to hold the potential to predict postoperative morbidities.

11 Conclusion

As the population ages, an increasing number of older patients will require complex gastrointestinal surgical procedures. While chronologic age is an important element in assessing a patient’s peri-operative risk, physiologic age is a more important determinant of outcomes. Geriatric assessment tools are important components of the pre-operative work-up and can help identify patients who suffer from frailty. Such data are important, as frailty has repeatedly been demonstrated to be one of the strongest predictors of both short- and long-term outcome following complicated surgical procedures such as esophageal, gastric, colorectal, and HPB resections. Frailty can sometimes, however, be difficult to assess in an accurate and timely manner. As such, there has been an increasing interest in determining a patient’s “morphometric age”. Sarcopenia, or wasting of lean muscle mass, has been noted to be an emerging important metric of frailty that is associated with peri-operative outcomes. As demonstrated by the data herein reviewed, screening of patients being considered for gastrointestinal surgery should include an assessment of frailty and sarcopenia to target high risk patients for pre-habilitation. Future studies will need to continue to define the optimal combination of factors (*e.g.*, clinical, performance, and morphometric) to predict optimally a patient’s peri-operative risk.

Conflict of Interest Statement

I declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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