Diplomarbeit

PANCREATIC CANCER IN THE ELDERLY: SARCOPENIA AS A PREDICTIVE FACTOR.

A retrospective study.

eingereicht von

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Graz, am 05.06.2023 Victoria Reitbauer eh.

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List of abbreviations

AJCC .... American Joint Committee on Cancer
BIA .... bioelectrical impedance analysis
BMI .... body mass index
BRCA2 .... breast cancer gene 2
CA 19-9 .... carbohydrate antigen 19-9
CT .... computed tomography
DXA .... dual-energy x-ray absorptiometry
ERCP .... endoscopic retrograde cholangiopancreatography
ESCEO .... European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis
EUS .... endoscopic ultrasound
EWGSOP .... European Working Group on Sarcopenia in Older People
FOLFIRINOX .... folinic acid, fluorouracil, irinotecan, oxaliplatin
HDI .... Human Development Index
ICD-10 .... 10th Revision of the International Statistical Classification of Diseases and Related Health Problems
IPMN .... intraductal papillary mucinous neoplasm
L3SMI .... skeletal muscle index measured on the level of the 3rd lumbar vertebra
LKH-Univ. Klinikum Graz .... Landeskrankenhaus-Universitätsklinikum Graz
MCN .... mucinous cystic neoplasm
MRI .... magnetic resonance imaging
NET .... neuroendocrine tumors
PET .... positron emission tomography
PMI .... psoas muscle index
PTBD .... percutaneous transhepatic biliary drainage
RCT .... randomized controlled trial
SCN .... serous cystic neoplasm
SMA .... superior mesenteric artery
SMI .... skeletal muscle index
SPN .... solid-pseudopapillary neoplasm
UICC .... Union for International Cancer Control

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Zusammenfassung

Immer mehr Studien beschäftigen sich mit dem Einfluss von Sarkopenie auf das postoperative Überleben von Patient*innen. Sarkopenie wird als Risikofaktor für erhöhte Mortalitätsraten und das Auftreten von Komplikationen nach Eingriffen unterschiedlicher Art angesehen.

Diese Studie untersucht einen möglichen Zusammenhang zwischen Sarkopenie und postoperativem Überleben von Patient*innen mit Pankreaskarzinom, einer hochmalignen Erkrankung mit besonders schlechten Überlebensraten.

Es wurden die Überlebensdaten von 206 Patient*innen, die an der Abteilung für Allgemeinchirurgie des LKH-Univ. Klinikum Graz behandelt wurden, analysiert. Dabei wurden nur jene Patient*innen eingeschlossen, bei denen eine operative Entfernung eines Pankreaskarzinoms mit kurativer Intention durchgeführt wurde.

Der Skeletal Muscle Index, gemessen auf Höhe des 3. Lendenwirbels (L3SMI), wurde unter Verwendung von präoperativen CT-Bildern berechnet und als Marker für Sarkopenie herangezogen. Patient*innen, deren L3SMI im niedrigsten geschlechtsspezifischen Quartil lag, wurden der Sarkopenie-Gruppe zugeordnet.

Es wurde eine Überlebenszeitanalyse nach Kaplan-Meier-Methode für 12 sowie 36 Monate nach Resektion durchgeführt.

Diese Analyse zeigte, dass das postoperative 1-Jahres-Überleben niedriger war in der Gruppe der Sarkopenie-Patient*innen (58.9 % vs. 72.6 %).

Die Überlebenszeitanalyse wurde zusätzlich getrennt nach Geschlechtern durchgeführt. In der Gruppe der Männer war der Unterschied im 1-Jahres-Überleben noch deutlicher zu sehen: 55.4 % der Männer mit Sarkopenie und 73.6 % der Männer ohne Sarkopenie waren nach einem Jahr noch am Leben. Allerdings erreichte keines dieser Ergebnisse im Log-Rank-Test statistische Signifikanz (p = 0.13 in der geschlechterunabhängigen Analyse und p = 0.1 in der Gruppe der Männer).

Im postoperativen 3-Jahres-Überleben zeigte sich kein Unterschied zwischen Patient*innen mit und ohne Sarkopenie.

Die Überlebenswahrscheinlichkeit nach Resektion eines Pankreaskarzinoms hängt von verschiedenen Faktoren ab. Die Ergebnisse dieser Studie deuten darauf hin, dass Sarkopenie einen negativen Einfluss auf das postoperative Überleben haben

könnte, der geschlechtsabhängig ist und mit wachsendem zeitlichem Abstand von der Operation abnimmt.

Abstract

A growing number of studies focusses on the impact of sarcopenia on postoperative outcome. Sarcopenia is considered a risk factor for increased rates of complications and mortality following different kinds of surgery.

This study evaluates a possible relationship between sarcopenia and postoperative survival in patients with pancreatic cancer which is a highly malignant disease with notably poor survival rates.

Survival data of 206 patients who underwent resection of pancreatic cancer at the Department of Surgery at the LKH-Univ. Klinikum Graz was analyzed. Only patients who were treated with curative intent were included in the study.

Skeletal muscle index measured at the level of the L3 vertebra (L3SMI) was chosen as a marker for sarcopenia and calculated using preoperative CT scans. The lowest sex-specific quartile of L3SMI was defined as sarcopenic. Survival analysis was conducted for 12 and 36 months following surgery using the Kaplan-Meier method.

Statistical analysis showed that postoperative 1-year survival rates were lower in the sarcopenia group (58.9 % vs. 72.6 %).

Survival analysis was also performed separated by sex. The difference in 1-year survival rates was even larger in men (55.4 % in the sarcopenic vs. 73.6 % in the non-sarcopenic group). However, none of these findings reached statistical significance ($p = 0.13$ for both sexes and $p = 0.1$ for men).

There was no difference in postoperative 3-year survival between sarcopenic and non-sarcopenic individuals.

Survival following surgery for pancreatic cancer is influenced by several factors. The results of the present study suggest that there might be an association between sarcopenia and poorer postoperative survival which is sex-dependent and decreases with growing distance from surgery.

Introduction: sarcopenia in pancreatic cancer patients

Motivation for this diploma thesis

Pancreatic cancer is a major contributor to mortality in industrial states. Although it represented only 2.6 % of new cancer cases, it accounted for 4.7 % of cancer deaths in 2020 (1).

Symptoms usually develop in advanced stages and are often unspecific (2). Even if there are typical symptoms, smaller tumors often cannot be detected by computed tomography (3).

Currently, we do not have reliable tests to screen patients with risk factors (4).

Despite efforts to enhance early diagnosis and therapy, 5-year survival has only improved marginally in recent years (5).

The term sarcopenia describes a loss of both muscle mass and function. Sarcopenia is common in pancreatic cancer patients (6).

Unfortunately, there are no definitive diagnostic criteria for the condition (7), hence it is vastly underdiagnosed and undertreated (8). Obese people can also be affected by sarcopenia and its negative effects on health, including falls and cardiac disease (9).

Early diagnosis and treatment are crucial to improve an individual patient's health and decrease social burden. However, screening for sarcopenia is no standard procedure for pancreatic cancer patients yet.

Sarcopenia awareness must be raised in order to identify cases and ensure proper treatment. This diploma thesis should contribute to the understanding of the disease and its effects on pancreatic cancer patients.

Problem description

During the last years, sarcopenia and its impacts especially on surgical outcomes gained growing attention amongst researchers (10).

Sarcopenia is associated with a variety of postoperative complications. These include increased rates of infections, postoperative delirium, longer hospital stays, shorter disease-free survival and increased risk of death (10).

The correlation between sarcopenia and increased numbers of postoperative infections, delirium and other surgical complications as well as longer hospital stays

and poorer overall survival could be shown for gastrointestinal surgery. A study done in orthopedic surgery suggests that sarcopenic patients are more often admitted to nursing homes and have a higher risk of death following hip fractures (10).
Researchers also found a connection between sarcopenia and poor outcomes in pancreatic cancer patients: According to Woo et al. and Peng et al., Sarcopenic patients have an increased 3-year mortality as well as more postoperative complications following resection (10,11).
There is a growing number of studies with a particular focus on postoperative survival of sarcopenic patients with pancreatic cancer. Since surgical treatment is a patient's only chance to be cured from the disease, the interrelation between sarcopenia and surgical outcome is of central significance.

Objectives/goals

The purpose of this diploma thesis is to investigate a potential link between sarcopenia and survival in patients who underwent resection of pancreatic cancer at the Department of Surgery at the LKH-Univ. Klinikum Graz.
Therefore, survival data of 206 patients were included to a retrospective study. 3-year survival as well as 1-year survival of sarcopenic and non-sarcopenic patients were analyzed. To show sex-specific differences, survival analysis was additionally performed for women and men separately.
This study uses computed tomography, a widely available technology, to assess sarcopenia. Therefore, the results are well reproducible.

Limitations

This study does not include benign or borderline-malignant lesions (e.g., adenoma of the pancreas, intraductal papillary mucinous neoplasm without invasion). Neuroendocrine neoplasia was also not included.
Other than pancreatic tumors (e.g., tumors of the biliary tract and the major duodenal papilla) as well as their metastases were excluded.
Patients who underwent palliative surgery without curative intent were not within the scope of this study. Those patients who had surgery of the pancreas for pancreatitis or traumatic reasons were also excluded.

Epidemiology of pancreatic cancer

Malignant diseases accounted for three out of ten premature deaths worldwide in 2019, according to the World Health Organization's Global Health Estimates (12). Incidences and mortality rates concerning cancer are increasing globally (1).
Currently, cardiovascular diseases are the most common cause of premature death in Europe (13).
Nevertheless, in 57 out of 183 countries, cancer was found to be the leading cause for premature death, defined as death between the ages of 30 and 70 years (12). It is assumed that malignant diseases will supersede cardiovascular diseases and become the most common cause of premature death over the course of the 21st century (12).
Thus, understanding the reasons for these rising incidences is crucial.

Progressive aging of the world's population and a considerable increase in risk factors for cancer contribute to the rising numbers of cancer patients. Both factors can be seen as a result of socioeconomic development (1).
The development status of any country can be described by the Human Development Index (HDI). This index takes into account a population's income as well as life expectancies and educational levels (14).
Sung et al. found that cancer incidences are higher in regions with high HDI compared to regions with low HDI (1).
This demonstrates the impact of social and economic factors on the distribution of malignant tumors.

Globally speaking, the cumulative risk of developing any kind of cancer prior to the age of 75 years was an estimated 22.4 % for men and 18.3 % for women in 2018. The figures for Europe were even higher (e.g., 34.9 % in males and 27.7 % in females in Western Europe) (15).
Cancer types are distributed differently between sexes. In men, lung cancer has the highest incidence and mortality of all cancer types. Breast cancer tops the worldwide incidence and mortality ranking in women (1).
Pancreatic cancer accounted for 2.6 % of new cancer cases and 4.7 % of deaths from cancer worldwide in 2020 (1).

As previously stated, connections between a country's developmental status and incidences of malignancies can be found. This applies particularly to pancreatic cancer: The age-standardized incidence rate for countries with high/very high HDI is 7.2 in men and 5.0 in women. By way of contrast, the incidence for countries with low/medium HDI is 1.6 in men and 1.0 in women (1). A similar trend can be shown for mortality rates (1).

Pancreatic cancer most commonly occurs in elderly patients. Nine out of ten patients are aged over 55 years at the time of the initial diagnosis, peaks can be shown for the 7th and 8th decade of life (5).

As mentioned above, incidence rates in men are slightly higher than in women. This holds true for both developed and developing countries (1).

Pathogenesis and risk factors

Risk factors for developing pancreatic cancer include non-modifiable parameters like age, male sex and family history of the disease (5).

There are also environmental components that can be modified such as cigarette smoking and chronic alcohol abuse (5). Furthermore, chronic pancreatitis, obesity, type-1 and type-2 diabetes are associated with pancreatic cancer (5).

Several genetic mutations were found to contribute to the development of the disease.

Germline mutations in the BRCA 2 gene, for example, result in a higher lifetime risk of developing pancreatic cancer as well as other types of malignancies such as breast, prostate or ovarian cancer (16).

There are also some familial cancer syndromes that are associated with pancreatic cancer, e.g. hereditary nonpolyposis colorectal cancer, better known as Lynch syndrome (5).

Lynch syndrome is caused by an autosomal dominant inherited defect in DNA mismatch repair genes. These mutations lead to microsatellite instability and malignant tumors in different organs. The syndrome is characterized by colon cancer occurring in young patients. Affected persons also have an increased risk of other gastrointestinal tumors including pancreatic cancer and urogenital malignancies (16).

Peutz-Jeghers syndrome is also inherited autosomal dominant. This genetic disorder causes intestinal polyposis and hyperpigmented macules of the oral region and mucosa. Peutz-Jeghers syndrome is also a risk factor for pancreatic cancer (16).
Another genetic disease which increases the risk of pancreatic cancer is hereditary pancreatitis. It causes recurrent episodes of acute pancreatitis. Symptoms occur in childhood and patients are usually left with pancreatic insufficiency at a young age (16).
As a matter of fact, pancreatic cancer can also arise from somatic gene mutations that have been acquired throughout the patient's life. Oncogene KRAS and tumor suppressor genes p16 and TP53, to name a few, are often involved in the pathogenesis of pancreatic adenocarcinoma (5).

Types of pancreatic tumors

There are several variants of pancreatic malignancies, which differ in their biological behavior. From a pathologically point of view, pancreatic neoplasms can be grouped into solid and cystic ones (16).

Ductal adenocarcinomas

When talking about pancreatic cancer, we usually address ductal adenocarcinomas of the pancreas. They are the most common solid tumors of the pancreas and make up for 85 % of all pancreatic malignancies (17).
The ductal adenocarcinoma is characterized by its specific growth pattern: It forms glands and is usually firm to the touch. It tends to invade nerves, small veins and lymphatic spaces. Consequently, malignant cells spread alongside nerves or metastasize to local lymph nodes and distant organs (16).
Up to 70 % of pancreatic adenocarcinomas are found in the head of the pancreas (5).

Neuroendocrine tumors

Neuroendocrine tumors (NET) of the pancreas are the second most common subtype of pancreatic tumors. They account for less than 5 % of pancreatic malignancies (17).
They are certainly malignant, yet their prognosis is better than that of ductal adenocarcinomas. Some NET produce hormones like insulin or glucagon (16).

Other pancreatic carcinomas

Adenosquamous carcinomas and undifferentiated carcinomas are examples of pancreatic tumors with highly aggressive behavior and especially poor prognosis (16). Colloid carcinomas and medullary carcinomas, on the other hand, do have a better prognosis (16).

Cystic tumors of the pancreas

Cystic tumors, the second type of pancreatic neoplasms, are often fully benign. However, some of them degenerate into invasive carcinomas (16). Cystic tumors of the pancreas include Intraductal papillary mucinous neoplasm (IPMN), Mucinous cystic neoplasm (MCN), Solid-pseudopapillary neoplasm (SPN) and Serous cystic neoplasm (SCN) (16).
IPMN and MCN are both defined as noninvasive neoplasms. While IPMN are found in larger ducts of the pancreas, MCN do not have contact with the duct system and typically occur in the tail of the pancreas. Both can develop into invasive pancreatic cancer and should therefor either be resected (in case of high-grade dysplasia) or observed conscientiously (in case of low-grade dysplasia) (16).
SPN consist of cells which lack cohesion, they are considered low grade malignant and should be resected (16,18). SCN are typically benign; resection is only necessary for large or symptomatic cysts (16,19).

Symptoms and diagnosis

Carcinomas of the pancreas usually cause unspecific symptoms and thus are diagnosed in advanced stages, when they are locally advanced or already have metastasized.
Pain of the epigastric region or the back, jaundice, nausea, unintentional weight loss and abnormal liver function tests are typical symptoms (2).

Chronic pancreatitis or new onset diabetes mellitus can also indicate the presence of a pancreatic tumor (16,20).

Diagnostic steps involve computed tomography (CT), magnetic resonance imaging (MRI), endoscopic ultrasound (EUS), positron emission tomography (PET) as well as laparoscopy (16,21).
CT and MR are considered equal imaging methods. Pathological examination is the gold standard for diagnosing pancreatic cancer (16).

Serum carbohydrate antigen (CA 19-9) can be used as a biomarker in symptomatic patients (4).
It provides prognostic information: A pre-operative elevation of CA 19-9 levels is associated with poorer median survival. Significant postoperative decreases of CA 19-9 levels are prognostically favorable (4).
However, CA 19-9 is not suitable for screening purposes as it has a low positive predictive value (4).

Staging

Exact staging is a crucial step during the diagnostic process, because treatment options depend on the stage of the disease (16,21,22).
Tumor staging includes clinical aspects as well as radiography and pathology. It provides clarification about a malignant tumor's dimension and location (22).
A staging system needs to meet several requirements: On the one hand, the patient must be assigned to a stage which reflects his or her individual prognosis. On the other hand, staging must be reproducible and easy implementable in clinical practice (22).

The TNM staging system, released by the American Joint Committee on Cancer (AJCC) and the Union for International Cancer Control (UICC), is widely used for staging pancreatic carcinoma (21,23).
This staging system considers the tumor's size, its proximity to large vessels and regional as well as distant metastases (23).
When performed at the time of initial diagnosis, it should also prognosticate the disease-related outcome (22).

The 8th edition of the AJCC/UICC TNM staging system describes Stages I to IV as well as two subsets of Stages I and II (IA, IB, IIA, IIB) (23). Tab. 1 provides an overview of this staging system.

Stages IA to IIA include tumors without regional or distant metastases. These stages are differentiated by tumor size (IA: maximum diameter ≤ 2cm, IB: > 2 ≤ 4cm, IIA: > 4cm).
Stage IIB includes tumors of any size without involvement of nearby major vessels (celiac axis, superior mesenteric artery or common hepatic artery), but with metastases in one to three (≥1 and ≤ 3) regional lymph nodes.
If the tumor involves one of these major vessels or more than three (≥4) positive lymph nodes are found, it is defined as stage III.
Stage IV means the presence of distant metastases (23). These are typically found in liver, lung and peritoneum (16).

Tumors of the endocrine pancreas (NET) have their own AJCC staging system, which deviates from the one mentioned above (24).

Tab. 1: Overview of tumor stages

Stage	Tumor size	Involvement of celiac axis, superior mesenteric artery and/or common hepatic artery	No. of positive lymph nodes	Distant metastases
IA	≤ 2cm	No	None	None
IB	> 2 ≤ 4cm	No	None	None
IIA	> 4cm	No	None	None
IIB	Any size	No	≥1 and ≤ 3	None
III	Any size	One or more of these vessels involved and/or ≥4 positive lymph nodes		None
IV	Any size	Irrelevant	Irrelevant	Yes

According to the 8th edition of the AJCC/UICC TNM staging system for pancreatic cancer (adapted from Cong et al. (23))

Resectability

According to the International Association of Pancreatology, adenocarcinomas of the pancreas can be divided into four groups: Resectable, borderline resectable, locally advanced and metastatic (2).

Resectable

To be considered resectable, the tumor must not have contact with the superior mesenteric artery (SMA), celiac axis or hepatic artery. If the major veins of the region (superior mesenteric vein or portal vein) are involved, narrowing must be unilateral (2).

Borderline resectable

The definition of a borderline resectable tumor is based on anatomical, biological and conditional features. Anatomical criteria include, for example, tumor contact with SMA of less than 180° without stenosis. Biological features include elevated CA19-9 levels. A patient's individual condition should also be considered (25).

Locally advanced disease

This group is characterized by extended involvement of nearby large vessels. It affects not less than one third of pancreatic cancer patients at time of initial diagnosis (2). In case of locally advanced pancreatic cancer, staging laparoscopy is recommended to search for peritoneal or hepatic metastases before treatment is determined (26).

Metastatic disease

Tumors which have already metastasized are considered not resectable.

Treatment of resectable tumors

According to Mizrahi et al. (2), management of borderline resectable tumors is the same as for resectable tumors.
Surgery is the only potentially curative therapy for pancreatic cancer and should be followed by six months of adjuvant chemotherapy (2).
Localization of the tumor determines the surgical technique that is used for resection (2).

Pancreaticoduodenectomy

A pancreaticoduodenectomy, also known as Whipple Procedure, is usually performed when the tumor is situated in the head of the pancreas (2).
Prior to a pancreaticoduodenectomy, the abdominal cavity must be examined to rule out occult peritoneal carcinomatosis. Furthermore, the liver must be palpated to identify any metastases (16).
There are two possible approaches: The standard pancreaticoduodenectomy and the pylorus preserving pancreaticoduodenectomy.
During a classic pancreaticoduodenectomy, the head of the pancreas, the gallbladder together with the distal common bile duct as well as the duodenum and a part of the stomach, more precisely the antrum, are resected. The jejunum is subsequently anastomosed with the stomach, the remaining part of the pancreas and the common hepatic duct (16).

In a pylorus preserving pancreaticoduodenectomy, the proximal part of the duodenum distal to the pylorus is removed. The stomach remains intact. The other steps of this procedure are identical to a classic pancreaticoduodenectomy, aside from the reconstruction at the end of the surgery: Following a pylorus preserving pancreaticoduodenectomy, the jejunum is anastomosed with the duodenum (16).
Following a Whipple resection, at least 12 regional lymph nodes should be evaluated microscopically (24). According to the 8th edition of AJCC staging system, the following surgical resection margins must be evaluated (24):

- pancreatic neck/parenchymal
- uncinate (retroperitoneal/superior mesenteric artery)
- bile duct
- proximal (gastric or duodenal)
- distal (duodenal or jejunal)

A positive margin is defined as “the presence of tumor at or within 1mm of resection” (24)

Distal pancreatectomy

A distal pancreatectomy is performed on tumors located in the body of the pancreas (2). In case of advanced disease, tumors located here often involve major vessels like celiac trunk or splenic artery. This can affect resectability and complicate the resection (16).
During the procedure, the distal part of the pancreas including the tail is removed. The spleen is resected simultaneously (16).
However, every surgical technique has its risks. Morbidity following resections of the pancreas is no less than 40 % (27).
Mortality rates for pancreatic surgery range from 16.3 % in very low volume hospitals to 3.8 % in very high-volume centers (27).

Minimally invasive surgery

There is evidence that laparoscopically performed pancreaticoduodenectomies are associated with decreased blood loss, better disease-free survival and shorter hospital stays (28).
The risk of complications and infections after laparoscopic distal pancreatectomy is significantly lower, compared to open pancreatectomy (29).
Laparoscopic pancreaticoduodenectomies are considered as safe as open procedures (30). However, laparoscopic pancreaticoduodenectomies take longer than the open procedure. Appropriate training for surgeons is needed to decrease operation time (30)

Treatment of locally advanced disease

Mainly due to vascular involvement, locally advanced disease is considered not resectable (2).
Treatment options include systemic chemotherapy with gemcitabine and nab-paclitaxel or FOLFIRINOX (folinic acid, fluorouracil, irinotecan, oxaliplatin) (2,31,32).
In the rare case restaging after initial treatment shows an operable tumor, resection is recommended (2).

Systemic therapy: neoadjuvant and postoperative chemotherapy

More and more centers use neoadjuvant chemotherapy (with or without radiotherapy) for resectable and borderline resectable tumors (2).
After neoadjuvant chemotherapy, restaging is done. If the disease is stable or responding to chemotherapy, resection takes place. In case of progressing disease, surgery is not recommended, as the patient would not profit from the procedure (33). Studies indicate that neoadjuvant approaches can increase the chance of negative resection margins and improve overall survival (2,25). However, there is no general recommendation for these due to a lack of data (2).

After resection, six months of chemotherapy with modified FOLFIRINOX (Fluorouracil + Leucovorin + Irinotecan + Oxaliplatin) are recommended for patients in good condition, regardless of the stage of the disease (2,34).
In case of contraindications, Gemcitabine can be used as an alternative (2).
Adjuvant chemotherapy is associated with improved overall survival, compared with surgery alone (2).

Palliative care and symptom control

50 % of pancreatic cancer patients already have metastatic disease at the time of initial diagnosis. Patients with stage IV disease should receive systemic chemotherapy to control symptoms and prolong life (2).

Nine of ten patients with ductal adenocarcinoma of the pancreas suffer from abdominal pain (3).
In the first place, analgesics are used to attain pain control. Depending on pain intensity, nonopioids or opioids are prescribed. The use of opioids is limited by side effects such as nausea and constipation (35).
In case the pain cannot be managed by pharmacotherapy alone, celiac plexus neurolysis is an option. During this procedure, ethanol or phenol is injected into the celiac plexus under endoscopic ultrasound guidance (35).

Biliary obstruction is another common problem in pancreatic cancer patients. It can lead to jaundice and pruritus (3).

Treatment options include endoscopic retrograde cholangiopancreatography (ERCP) with stent implantation and percutaneous transhepatic biliary drainage (PTBD) (3).
Fat malabsorption due to obstruction of the pancreatic duct is another potential complication within pancreatic cancer patients. Symptoms include pain as well as gastrointestinal problems like steatorrhea and abdominal bloating. These can be addressed by supplementation of pancreatic enzymes (2).

There is evidence that cancer patients in general benefit from an early integration of palliative care into the treatment process. Patients who systematically received palliative care from the beginning were found to have better life quality compared to those who received it later by demand (36).

Specifics of pancreatic cancer in elderly patients

According to the World Health Organization, people over 65 years are defined as "elderly" (37). As stated previously, incidence rates reach their highest peak in the 7^{th} and 8^{th} decade of life (5).
It is well established that advanced age is a risk factor for cancer in general. This also applies to pancreatic cancer (37,38).
This is due to the fact that aged body tissue has an increased vulnerability to carcinogens (38). Natural ageing of the immune system, called immunosenescence, as well as chronic inflammation also contribute to the pathogenesis of cancer in elderly individuals (38).
As the world's population is ageing (1), management of pancreatic cancer in elderly patients will become even more important in the future.
Advanced age is associated with undertreatment and poorer survival in cancer patients (38,39). Elderly patients are less likely to undergo surgery or receive a multimodal therapy (38,40).
Moreover, elderly people were found to have higher mortality rates as well as a higher risk of postoperative complications such as delayed gastric emptying and pancreatic fistula. Furthermore, they have more neurological complications and longer hospital stays following surgery (38).
There is a lack of clinical data regarding elderly persons as they are often underrepresented in studies. Statistical findings that were made in younger study

populations are not fully applicable to elderly patients because of altered organ function and the higher prevalence of comorbidities in elderly study groups (38).

There are several specifics in elderly patients, when it comes to pharmacotherapy. Changes in pharmacokinetics must be considered: Absorption as well as excretion of drugs are decreased. Metabolism is slower in the elderly, which can lead to reduced activation or deactivation of drugs (38).
Changes in pharmacodynamics can affect efficiency of cytotoxic drugs. Polypharmacy is also a common condition in elderly patients. It increases the risk of side effects and drug interactions (38).

However, it is important to consider a patient's individual biological age rather than his or her chronological age (38).
In order to meet the special demands of elderly people, they must get precise preoperative risk assessment. Following surgery, admission to an intensive care unit and proper antibiotic prophylaxis is supposed to be routine (38).

Sarcopenia: definition

According to the European Working Group on Sarcopenia in Older People (EWGSOP), Sarcopenia is "a progressive and generalized skeletal muscle disorder that is associated with increased likelihood of adverse outcomes including falls, fractures, physical disability and mortality" (9).
The prevalence of the disease is 13.3 % in women and 5.3 % in men (41).
The presence of low muscle strength is suggestive of sarcopenia.(9) Low grip strength was even identified as a predictor for adverse events like recurrent falling (42).
Male and female individuals are equally affected by sarcopenia (7).

The diagnosis is established when either low muscle quantity or quality can be found. The term "low muscle quality" describes alterations in muscle composition and architecture (9).
When a patient has low physical performance (e.g. assessed by gait speed) in addition, sarcopenia is classified as severe (9).
Fig. 1 shows the diagnostic process visualized in a flowchart.

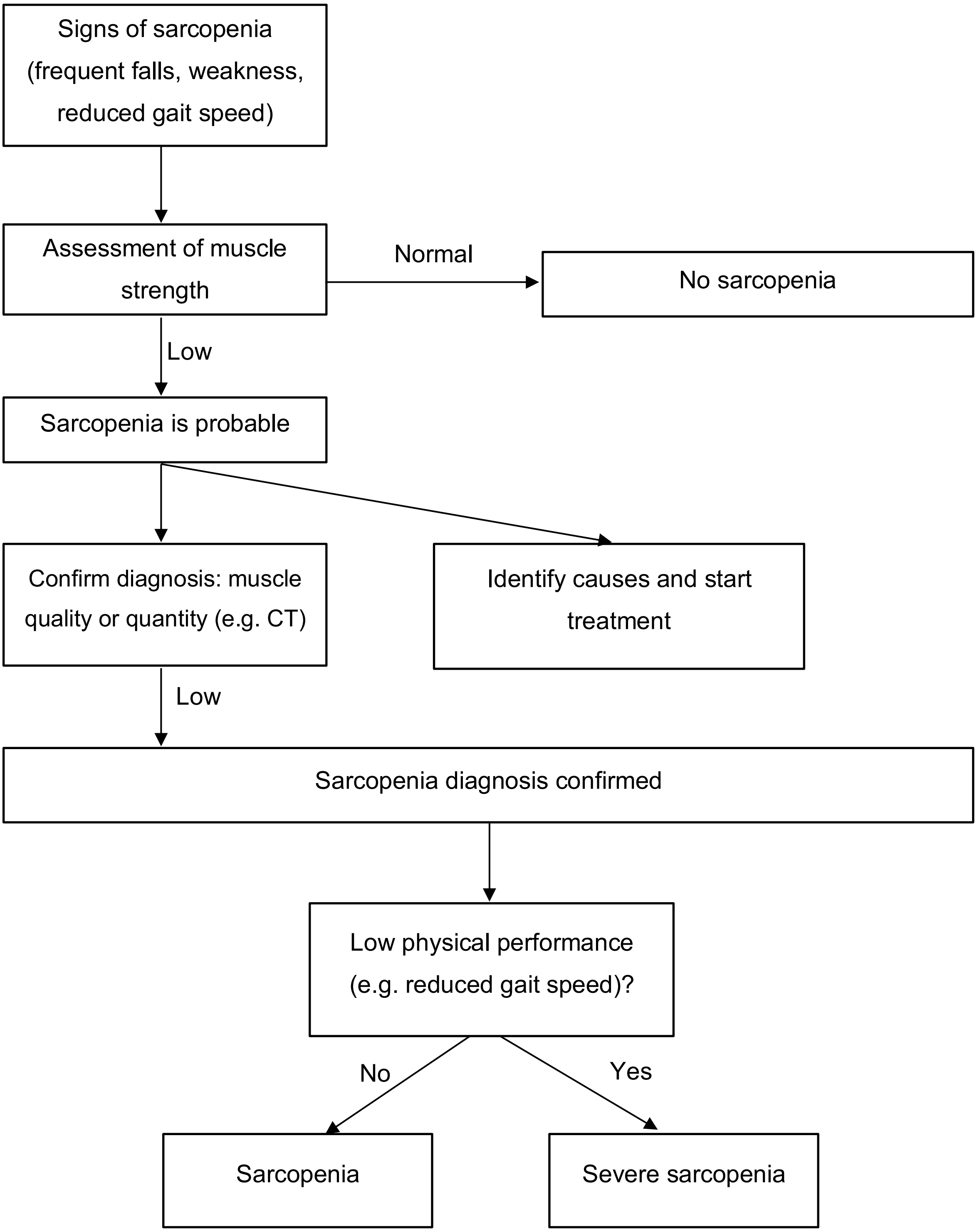

Fig. 1: Flowchart for diagnosing sarcopenia
Adapted from Cruz-Jentoft et al. (9)

Risk evaluation

If a patient describes symptoms such as a reduction in gait speed, frequent falls or weakness, sarcopenia should be considered, and further testing is indicated (43).
There are specific questionnaires which can easily be used in practice to screen for patients that are at risk of sarcopenia (9).
Doctors can also use methods which take into account a patient's physical performance, for instance the Ishii screening test. This test uses the patient's age as well as the grip strength and calf circumference to assess the risk of sarcopenia (44).
A normal Body Mass Index (BMI) does not rule out sarcopenia (45).

Diagnostic parameters

According to Cruz-Jentoft et al. there are three main parameters of sarcopenia which can be measured (9):

Muscular strength

Low muscle strength is a determining factor for sarcopenia. It is more important than muscle quantity (9).
Muscular strength can be evaluated by measuring a patient's grip strength with a handheld dynamometer (9).
Reduced grip strength is associated with poorer outcomes in terms of mortality (46) and functional decline (47).
Advantages of this method are ease of use and low costs (9).

Muscle quantity

Muscle quantity or muscle mass is widely used in research to identify sarcopenia (9).
There are several methods to estimate total body mass. These methods are described in the following chapter.

Evaluation of muscle mass

CT and MRI

Computed tomography and magnetic resonance imaging are gold standard for measuring muscle mass. But they are expensive, often not available and require specialized staff (48).

Muscle mass can be measured in different locations.
Cross-sectional images on the level of the 3rd lumbar vertebra are most frequently used. This section includes the following muscles: "rectus abdominis, transverse abdominis, internal and external obliques, quadratus lumborum, psoas major and minor, and erector spinae" (49).
The combined area of the skeletal muscles at L3 is representative for the skeletal muscle mass of the whole body (50). The total muscle area measured at the level of the 3rd vertebra, adjusted for the patient's height, is called skeletal muscle index (SMI) (49).
Psoas muscle area at the level of L3 is also used for estimating whole body muscle mass as the psoas muscle can easily be localized and measured (49).
The psoas muscle area measured at the level of the 3rd vertebra, adjusted for the patient's height, is called Psoas Muscle Index (PMI) (49).
However, studies suggest that SMI is a better predictor for mortality than PMI (51).

DXA

Dual-energy x-ray absorptiometry (DXA) is another non-invasive option to measure muscle quantity (9,52). It uses different x-ray attenuations of tissues to quantify three body compartments (bones, fat, lean mass) (49).
Values measured by DXA are reproducible, but only if the same instrument is used. Unfortunately, limited availability is a problem, as the instrument cannot be moved easily between locations (9).

BIA

Lastly, muscle mass can be estimated by using bioelectrical impedance analysis, short BIA. This method measures electrical conduction of a patient's body and approximates its composition, in this case muscular mass (9).

BIA is less expensive than DXA and transportable. However, further studies are needed to investigate this method's accuracy (53).
Dehydration can affect measured values of both DXA and BIA (9).

Ultrasound

Ultrasound provides information about muscle quantity as well as muscle quality. Usually the quadriceps femoris muscle is used for the assessment. Muscle thickness and cross-sectional area are measured to evaluate muscle mass. Decreases in quantity can be detected by repeated measurements (9).
Echogenicity provides information about the lipid content of the muscle and therefore muscle quality (9).
Ultrasound is a reliable technique for assessing muscle mass and considered equal to computed tomography, magnetic resonance imaging and dual-energy x-ray absorptiometry (9).
So far it has primarily been used in research. However, lately physicians started to utilize it in clinical practice (9).

Adjusting muscle mass for body size

There is a correlation between muscle mass and body size. Usually, patients with a larger body size have more muscle mass (9).
After measuring a patient's muscle mass using one of the methods described above, the findings must be adjusted for a patient's body size. Skeletal muscle index can be used to that end. Unfortunately, the term SMI has no consistent definition (54).
Authors use body height, weight or BMI to adjust the measured muscle area for body size. Various ways of calculating SMI and inconsistent cut-off values result in differing prevalence of sarcopenia within the same population (54).

Physical performance

According to the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO), physical performance is "an objectively measured whole body function related with mobility" (55).
Physical performance is not limited to measurable muscle function, but also involves the skeletal system, neurological functions like balance and many other factors (55).

Widely used tests for physical performance are the gait speed test and the chair stand test (55).
The gait speed test can be performed as short- or long-distance walk test. In clinical practice a 4-meter walk is used to assess gait speed as this test can be performed within short time and is still valid (55).
The 30-second chair stand test which was developed by Rikli and Jones is another good predictor of overall physical performance and ability to master activities of daily living. In this test, the patient is asked to repeatedly stand up and sit down. The investigator counts how often the patient can stand up and sit down again in 30 seconds. The chair stand test evaluates power of lower body muscles as well as the patient's balance and stamina (55).

Pathogenesis of sarcopenia

Sarcopenia can be grouped into two categories: First, primary sarcopenia which is related to aging and not caused by any specific disease or condition (9).
Second, there is secondary sarcopenia which is not necessarily age-related and has several causes. These include inflammation, a lack of physical activity, malnutrition and malignancies. Not only undernutrition is a risk factor for sarcopenia, but also excessive intake of food (9).
Genetics is also suspected of playing a role in the pathogenesis of sarcopenia. In elderly people expression of certain genes is decreased. Some of these genes are involved in cellular energy production within skeletal muscle tissue (7).
Though sarcopenia is associated with ageing, there is evidence that the disease starts to develop earlier, in the fourth decade of life (7).
Sarcopenia is considered chronic if it lasts longer than six months. Chronic sarcopenia is due to chronic diseases and associated with higher mortality rates (9).
Acute events such as severe illness or trauma can lead to acute sarcopenia (9).

Sarcopenic obesity

There is a condition called sarcopenic obesity, which is characterized by high body fat and decreased lean body mass. Obese individuals have higher mortality rates compared with non-obese patients. Furthermore, obesity is associated with decreased physical performance (9).

Pancreatic cancer patients with sarcopenic obesity have shorter overall survival following chemotherapy compared with those who suffer from sarcopenia alone (6).

The personal and social burden of sarcopenia

Untreated sarcopenia has several negative effects on the affected person and society. It is associated with falls and fractures, cardiac and respiratory disease, cognitive impairment and lower quality of life. In addition, health care costs are higher for patients with sarcopenia (9).

Sarcopenia is included in the 10th Revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10) (9).

Nevertheless, sarcopenia often is not adequately addressed by healthcare professionals. This may be due to a lack of clear guidelines for measuring, diagnosing and treating the disease (7–9).

Sarcopenia in pancreatic cancer patients

Pancreatic cancer patients often suffer from weight loss (56).

Anyway, there is a difference between sarcopenia and cachexia: In sarcopenic patients, muscle mass and/or function are impaired. In contrast, cachexia describes a loss of both muscle mass and body fat (10).

Both conditions are associated with poorer outcomes following abdominal surgeries (56).

According to Chan et al., 30 to 65 % of pancreatic cancer patients suffer from sarcopenia (6).

Peng et al. found that the disease is associated with significantly higher 3-year mortality after resection of pancreatic adenocarcinoma (11).

For pancreatic cancer patients with sarcopenic obesity, the risks of mortality and morbidity are even higher (6).

Sarcopenia also decreases response to systemic chemotherapy and increases its toxicity in pancreatic cancer patients (6). As chemotherapeutics are dosed based on a patient's body weight and height, the dose of the therapeutic substance in relation to muscle mass is relatively high in sarcopenic patients (6).

Conversely, chemotherapy leads to muscle loss and therefore increases sarcopenia (6).

Treatment of sarcopenia

Due to a lack of data, especially regarding surgical patients, treatment options are limited (10).
When sarcopenia is diagnosed in a cancer patient, preoperative treatment hardly ever takes place due to the short period of time before surgery (10).
Beaudart et al. conducted a systematic review of 37 randomized controlled trials (RCT) that analyzed the effect of physical exercise and nutritional supplements on sarcopenia. The review showed that physical exercise has positive effects on both muscle mass and function in elderly patients (57).
However, a clear benefit of additional dietary supplements could not be shown (57).
Up to this day, there is no pharmacological therapy available. There are clinical trials and studies on different hormones including testosterone, growth hormone and ghrelin. However, the use of these is limited by serious side effects and a lack of efficacy (10).

Methods

Skeletal muscle index was used to identify sarcopenia in our patients. Consequently, a survival analysis was conducted to investigate if there is a relation between sarcopenia and poorer outcomes in terms of shorter postoperative survival. According to the null hypothesis, there is no difference in postoperative overall survival between sarcopenic and non-sarcopenic individuals.

The alternative Hypothesis states that the postoperative overall survival is significantly lower in sarcopenic patients, compared with non-sarcopenic individuals.

Sampling methods

For this retrospective study, data of 448 patients who underwent surgery of the pancreas at the Department of Surgery at the LKH-Univ. Klinikum Graz between April 2000 and November 2019 was obtained from our hospital information system. Out of these cases, we selected those with a histologically verified adenocarinoma of the pancreas and a CT scan available for measuring the parameters of interest.

We tracked our patients until their date of death or, if they were still alive, April 2021. Patient’s condition at the time of their last documented medical contact was recorded. Using the available data, survival time after surgery in months was calculated.

Sampling size was determined by the number of available cases who fully met our criteria.

Data structure

Our data set includes, amongst other things, the following information:

- age (at the time of surgery)
- sex
- length of in-hospital stay (total and postoperative)
- 30-day-mortality (dead/alive)
- follow-up time in days/months
- status at the end of follow-up time: dead/alive
- body height and weight
- body mass index
- total muscle area (measured on the level of the 3rd lumbar vertebra)
- total psoas area (measured on the level of the 3rd lumbar vertebra)
- skeletal muscle index measured on the level of the 3rd lumbar vertebra (L3SMI)
- sarcopenia (yes/no)
- type of resection
- intensive care unit stay (postoperative, in days)

Assessment of sarcopenia

Muscle strength and physical performance could not be examined because this was a retrospective study.

SMI was used as a sarcopenia indicator because it allows the detection of decreased muscle mass using cross-sectional images. Since resections of pancreatic tumors are usually preceded by medical imaging of the abdomen, a cost-effective retrospective study could be done.

No additional imaging has been done, meaning that our patients were not exposed to further ionizing radiation for the purpose of this study.

The software OsiriX Lite was used to measure the area of the abdominal wall muscles on the level of the 3rd lumbar vertebra from pre-existing cross-sectional images (CT and MRI).

The L3 level was used because the combined muscle areas there correlate with the total body's skeletal muscle mass (50).

The following muscles were measured:

- rectus abdominis muscle
- internal abdominal oblique muscle
- external abdominal oblique muscle
- transversus abdominis muscle
- psoas major muscle
- psoas minor muscle
- quadratus lumborum muscle
- erector spinae muscle

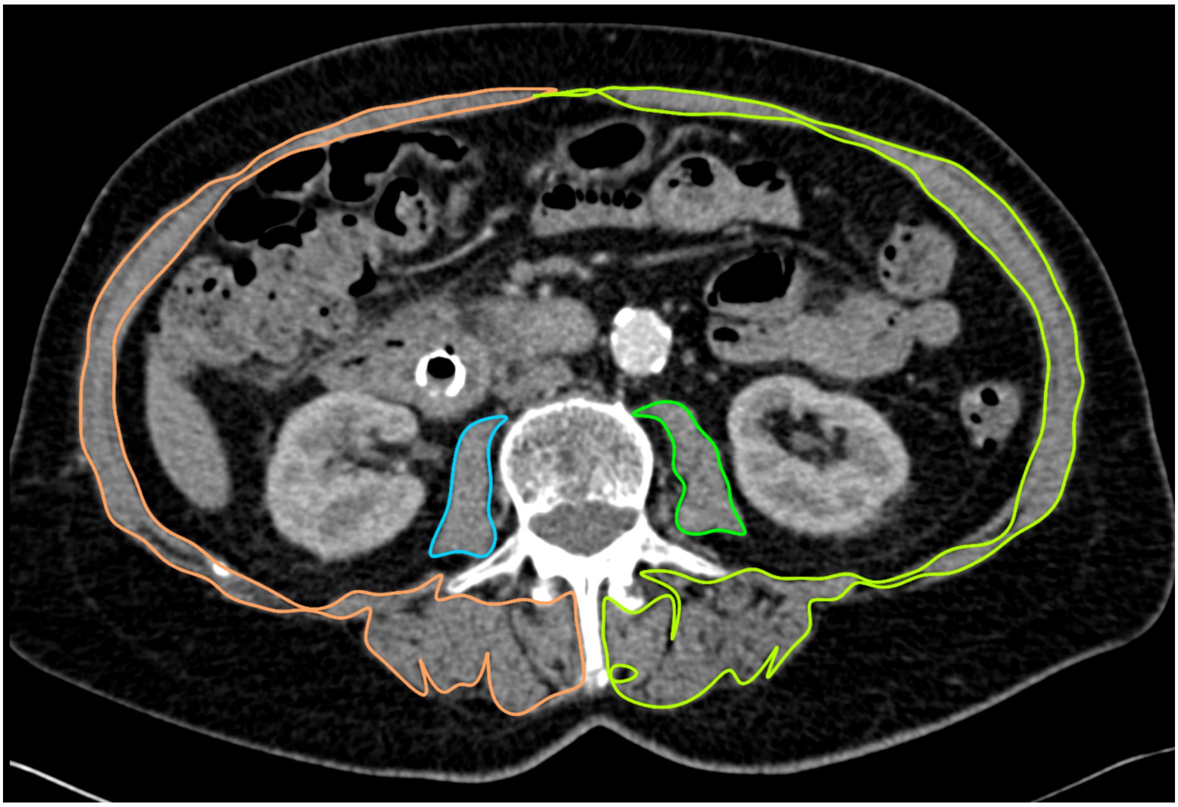

Fig. 2: Measurement of total muscle area with Osirix Lite

The skeletal muscles on level L3 were manually outlined (see Fig. 2). After that, the outlined areas were measured. The sum of all muscle areas makes up the Total Muscle Area.

Consequently, SMI was calculated using the formula shown in Fig. 3:

$$skeletal\ muscle\ index = \frac{total\ muscle\ area\ (cm^2)}{height\ (m)\ x\ height\ (m)}$$

Fig. 3: Formula for skeletal muscle index
According to Lee et al. (49)

Because there is a linear connection between skeletal muscle mass and body height, it is crucial to adjust the measured muscle mass for body height (9).
Depending on availability, either computed tomography or magnetic resonance images of our patients were used, since, according to Faron et al., CT and MRI deliver interchangeable results in measuring skeletal muscle area (58).

Statistical methods

Patients were stratified into quartiles according to L3 skeletal muscle index. The lowest sex-specific quartile was defined as sarcopenic, following the approach of Miyamoto et al. (59).
According to their study (59), sarcopenia, defined as lowest sex-stratified quartile of muscle mass index, is associated with poorer overall survival and shorter progression free survival in cancer patients following resection (59).
Male and female patients were stratified separately, to eliminate sex-specific differences in muscle mass.

To examine the impact of sarcopenia on postoperative survival, a survival analysis of sarcopenic and non-sarcopenic patients was performed using IBM SPSS Statistics (version 27).
The day of surgery was defined as starting point. Death, irrespective of cause, was defined as endpoint. The interval between surgery and death was defined as survival time.
Patients who did not reach this endpoint until April 2021 were censored at the time of their last known medical contact.
Survival analysis was limited to 36 and 12 months following surgery, as with growing temporal distance other factors than sarcopenia will have more important influence on survival.

In some cases, the follow-up-period was shorter than 36 respectively 12 months. Those patients who did not reach the endpoint before the end of the follow-up-period, were censored at the time of their last medical contact.

The Kaplan-Meier method was used to estimate survival probabilities of sarcopenic and non-sarcopenic patients over time. Using this method, data of individuals that were lost to follow-up still contributed to the study as censored cases.
Another advantage of the Kaplan-Meier method is the fact that individuals with different starting dates can be included. As the data for this study was collected over a long period of time (from year 2000 to 2019), starting points are widely dispersed. The Kaplan-Meier method considers not only the number of events in each group, but also the time that passes until the event occurs.

A log-rank test was performed to check if there is a statistically significant difference in postoperative survival times throughout the entire observation period between the two groups.
A p-value less than 0.05 was considered statistically significant. In case of a p-value smaller than 0.05, the null-hypothesis was rejected.
The statistical analysis was performed for both sexes together as well as separately, to examine any sex-related differences.
Kaplan-Meier survival curves of sarcopenic and non-sarcopenic patients were created to graphically display the survival of the two groups over time.

Results

Patient characteristics

448 patients (215 male, 233 female) underwent surgery of the pancreas between 2000 and 2019. 195 patients were excluded because they did not have a histologically verified adenocarcinoma of the pancreas.
5 patients (4 male, 1 female) were excluded for having palliative surgery.
Further 31 patients (14 male, 17 female) had to be excluded from the study because there was no CT or MRI scan of the 3rd lumbar vertebra level available. 11 patients had to be excluded due to missing data.
Finally, 206 patients were included into the present analysis as "patients under risk". 102 (49.5 %) of these were male, 104 (50.5 %) were female.
The patient sampling process is shown in Fig. 4.

The calculated threshold values for skeletal muscle index were ≤ 36.79 cm^2/m^2 for men and ≤ 32.57 cm^2/m^2 for women.
51 (24.8 %) of our patients were found to have sarcopenia (defined as lowest sex-stratified quartile of muscle mass index). Amongst these patients with sarcopenia, 25 (49 %) were male and 26 (51 %) were female (see Tab. 2).

Tab. 2: Prevalence of sarcopenia

			Sex		
			Male	Female	Total
Sarcopenia	Non-Sarcopenic	Count	77	78	155
		% within Sarcopenia	49,7%	50,3%	100,0%
		% within Sex	75,5%	75,0%	75,2%
	Sarcopenic	Count	25	26	51
		% within Sarcopenia	49,0%	51,0%	100,0%
		% within Sex	24,5%	25,0%	24,8%
Total		Count	102	104	206
		% within Sarcopenia	49,5%	50,5%	100,0%
		% within Sex	100,0%	100,0%	100,0%

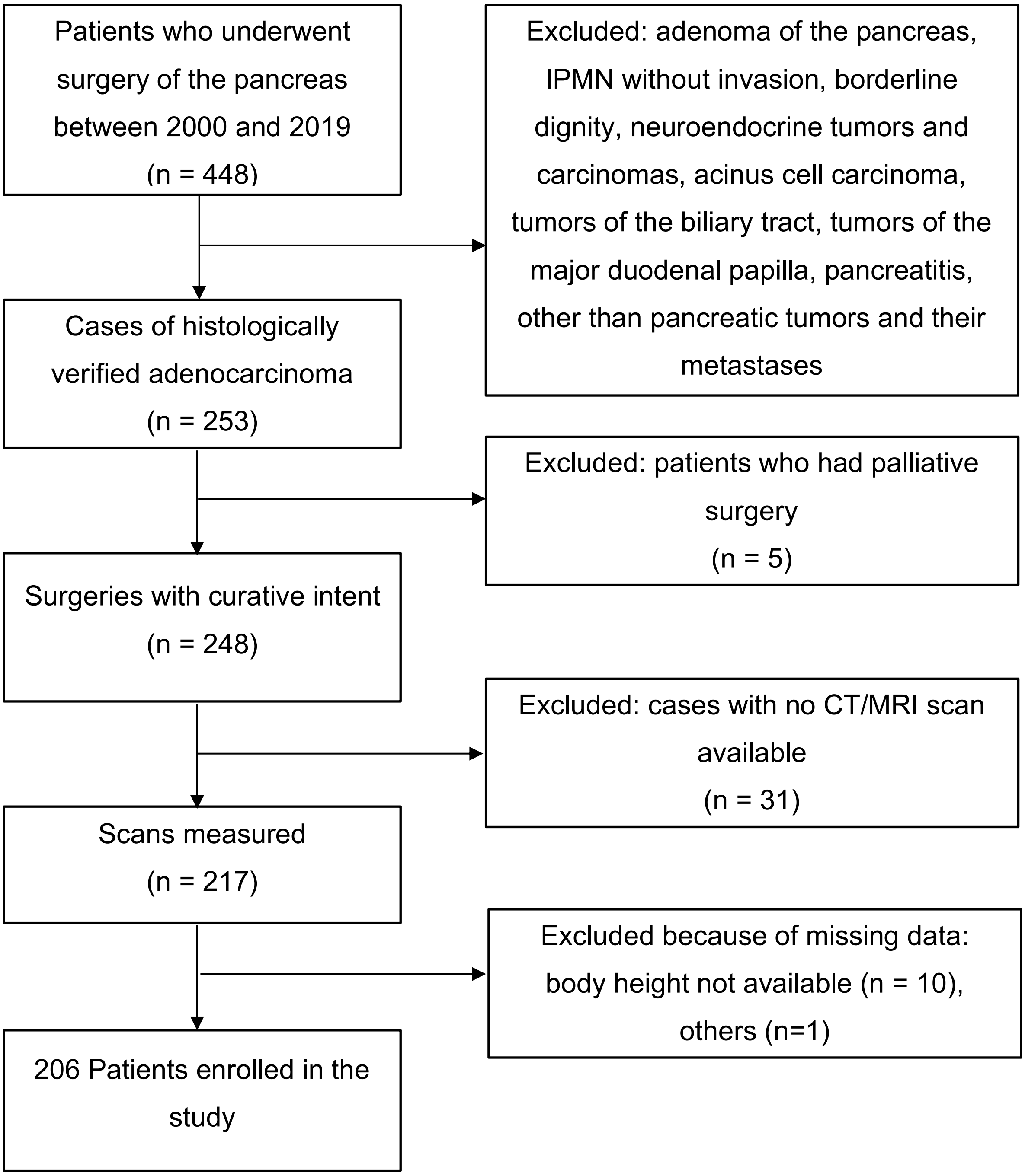

Fig. 4: Exclusion criteria and sampling size

The youngest patient was 40.8 years, the oldest 85.6 years old at the time of surgery. Mean average for age was 66.2 ± 9.3 years.

120 patients (58.3 %) were 65 years old or older at the time of surgery. 30 (25 %) of these elderly patients had sarcopenia. The prevalence of sarcopenia in younger individuals was identical (21 patients, 24.4 %).

Mean value for skeletal muscle index was 39.8 ± 7.8 cm^2/m^2, mean for BMI was 25.2 ± 4.2 kg/m^2 (see Tab. 3).

Four individuals (two female and two male) had particularly high SMI (over 60 cm^2/m^2).

Tab. 3: Descriptive statistics

	N	Minimum	Maximum	Mean	Std. Deviation
Age (years)	206	40,8	85,6	66,176	9,3310
Body mass index	206	17,58	39,86	25,2363	4,21209
L3 skeletal muscle index	206	22,97	64,32	39,7862	7,83097
Valid N (listwise)	206				

The average follow-up time (period from surgery until death or last known medical contact) was 16.39 ± 11.82 months, with a minimum of 0 months and a maximum of 36 months.

Average length of postoperative in-hospital stay was 19.8 ± 9.1 days, with a minimum of 2 and a maximum of 61 days. In one case, length of postoperative in-hospital stay could not be calculated, because the date of discharge was not available. One patient died on the day of surgery; this person was excluded from the calculation of average length of postoperative in-hospital stay, but not from the study.

63 (30.6 %) patients underwent a Whipple procedure, a pylorus-preserving pancreaticoduodenectomy was performed in 72 (35.0 %) cases. In 48 (23.3 %) patients, a distal pancreatectomy was performed. 23 (11.2 %) patients underwent a total pancreatectomy. Fig. 5 shows the distribution of the types of resections in a diagram.

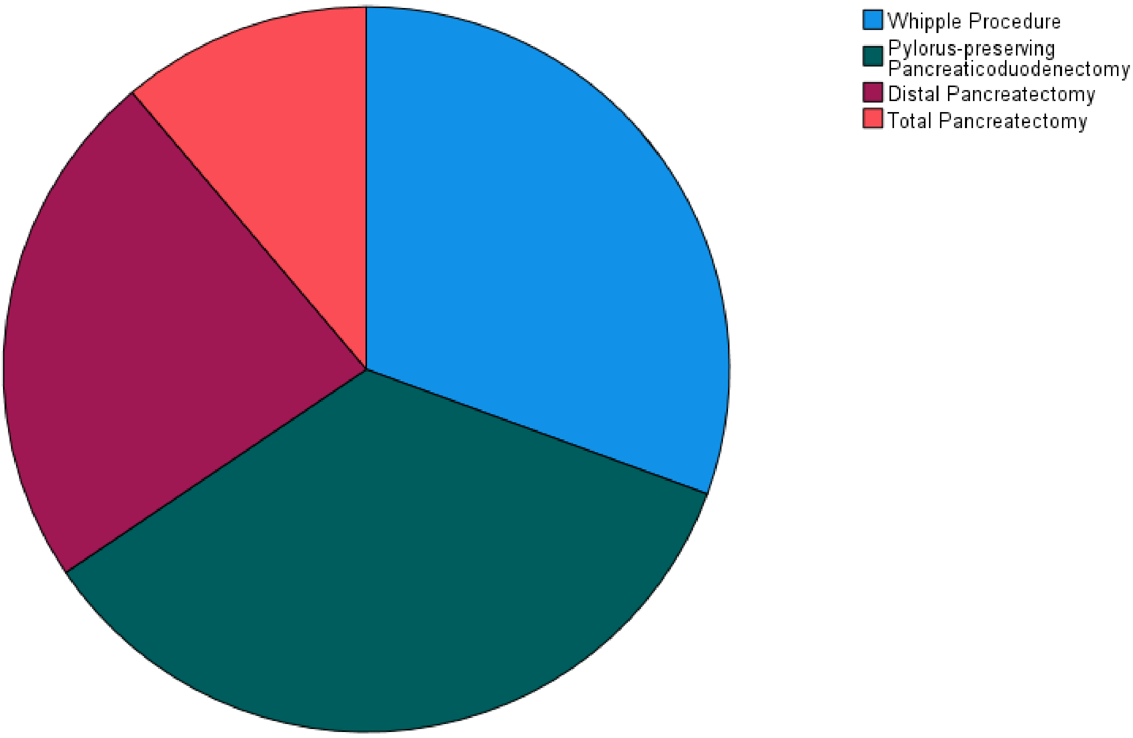

Fig. 5: Types of resections

109 patients (52.9 %) were dead at the end of their individual follow-up period, 97 (47 %) were alive (maximum of follow-up period was 36 months).

11 patients died within the first 30 days after surgery. 7 of these patients were male (63.6 %), 4 were female (36.4 %). Out of these 11 patients, 4 (36.4 %) were sarcopenic, 7 (63.6 %) were not (see Tab. 4).

Tab. 4: Sarcopenia and 30-day mortality

Sex			Sarcopenia		Total
			Non-Sarcopenic	Sarcopenic	
Male	30-Day mortality	Alive	73	22	95
		Dead	4	3	7
	Total		77	25	102
Female	30-Day mortality	Alive	75	25	100
		Dead	3	1	4
	Total		78	26	104
Total	30-Day mortality	Alive	148	47	195
		Dead	7	4	11
	Total		155	51	206

3-Year survival: both sexes

46.5 % of non-sarcopenic patients and 49.0 % of sarcopenic patients had to be censored (overall: 47.1 %) because they did not reach the endpoint (death) within 36 months from surgery or they were lost to follow-up. However, the data of these patients still contributed to the statistical analysis.

The Kaplan-Meier estimator shows a survival probability of 30.6 % after 36 months in the non-sarcopenic vs. 29 % in the sarcopenic group.

The survival curve is shown in Fig. 6.

A log-rank test was performed to compare overall 36-months-survival between the two study groups. It shows that survival distributions do not differ significantly (p = 0.46).

Non-sarcopenic patients had a median survival time of 23.2 months (95%-CI[17.38, 29.01]). In comparison, the median postoperative survival time of sarcopenic patients was with 19.09 months (95%-CI[12.2, 25.98]) slightly lower.

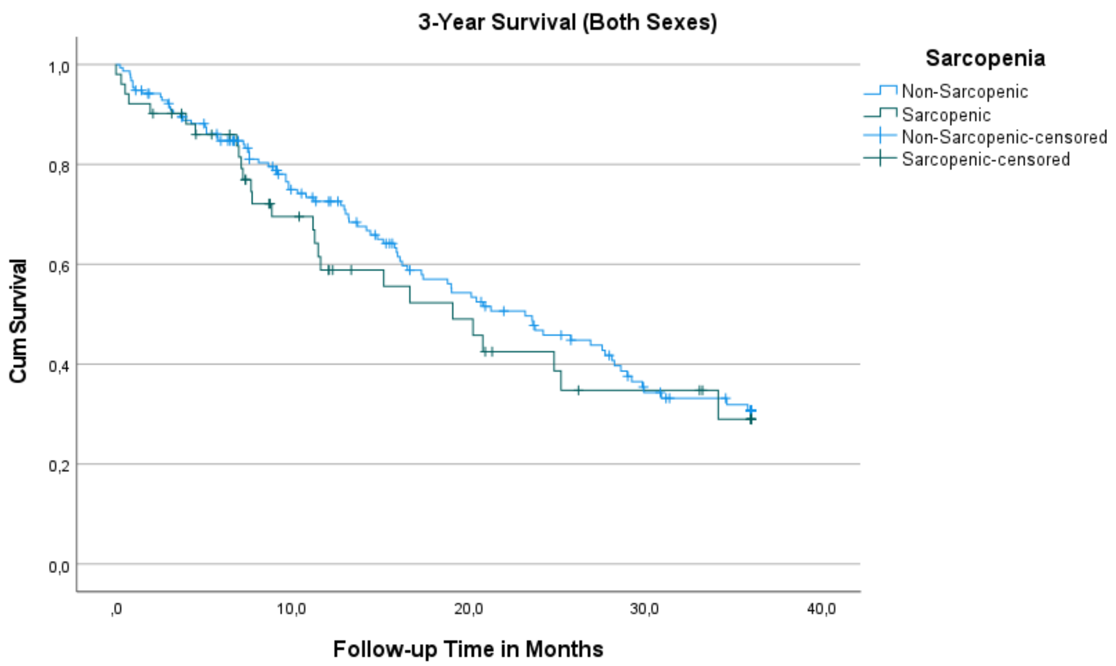

Fig. 6: 3-Year survival for both sexes

The x-axis of the Kaplan-Meier-curve in Fig. 6 indicates the months which have passed since surgery, the y-axis shows the estimated survival probability (cumulative survival).

Whenever an event (the death of an individual) occurs, the curve makes a step downwards.

Survival analysis was limited to 36 months following surgery. The small vertical lines indicate that patients got censored at time of their last known medical contact because they did not reach the endpoint (death) within 36 months from surgery or were lost to follow-up.

3-Year survival: men

45.1 % of male cases were censored (44.2 % of non-sarcopenic and 48.0 % of sarcopenic men).

The median postoperative survival time of sarcopenic men was lower, compared with non-sarcopenic men: 16.66 months (95%-CI[4.02, 29.3]) vs. 20.44 months (95%-CI[17.23, 27.6]).

3-Year survival rates are 30 % in the non-sarcopenic and 34.6 % in the sarcopenic group. The survival curve for men is shown in Fig. 7.

The log-rank test shows that differences in 3-year survival between sarcopenic and non-sarcopenic men are not significant (p = 0.469).

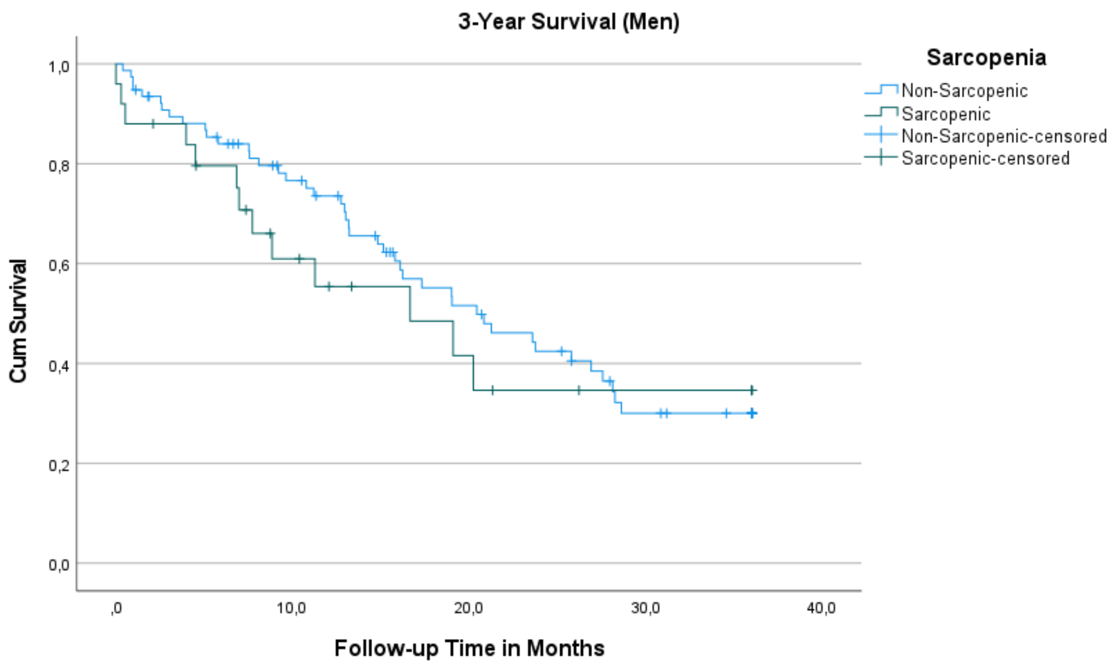

Fig. 7: 3-Year survival for men

3-Year survival: women

49.0 % of female cases were censored (48.7 % of non-sarcopenic and 50.0 % of sarcopenic women).

There was no difference in median postoperative survival time between sarcopenic and non-sarcopenic women: 24.84 months (95%-CI[7.93, 41.75]) vs. 24.21 months (95%-CI[14.7, 33.73]).

3-Year survival rates are 31.5 % (non-sarcopenic group) vs. 23.8 % (sarcopenic group). Fig. 8 shows the 3-year survival curve for women.

However, the log-rank test shows that there is no significant difference in 3-year survival between sarcopenic and non-sarcopenic women (p = 0.698).

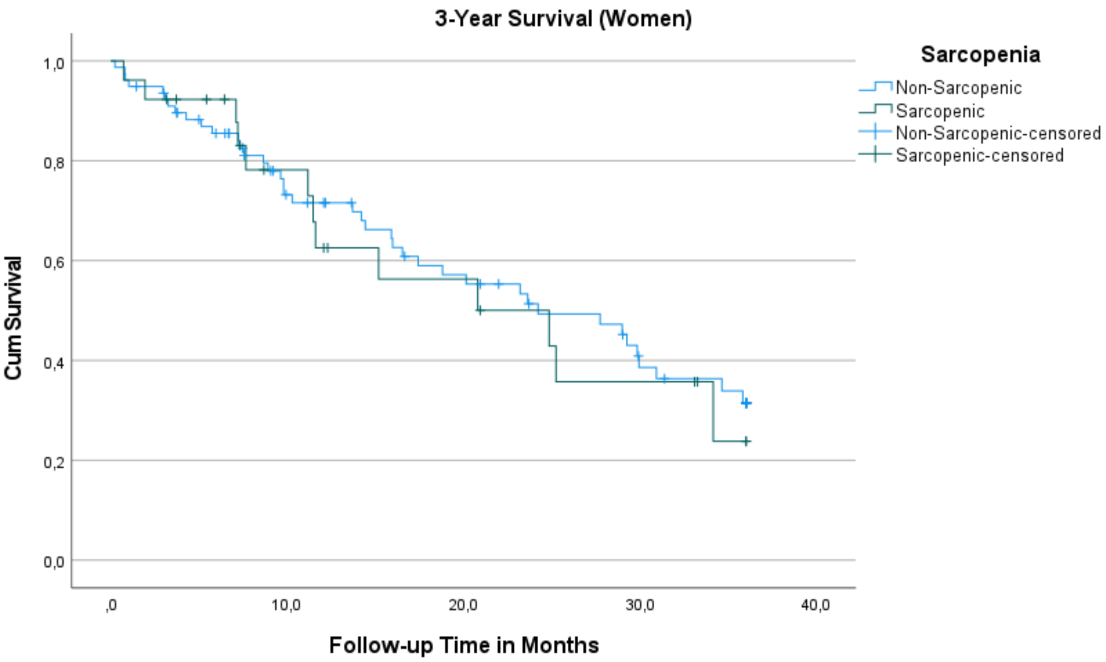

Fig. 8: 3-Year survival for women

1-Year survival: both sexes

74.8 % of non-sarcopenic patients and 64.7 % of sarcopenic patients were censored (overall: 72.3 %).

The median postoperative survival time could not be calculated because less than 50 % of patients did reach the endpoint (defined as death) until 12 months after surgery.

The survival probability after 1 year is 72.6 % for non-sarcopenic and 58.9 % for sarcopenic individuals. The result is visualized in Fig. 9.

The log-rank test shows that the difference in 1-year survival between sarcopenic and non-sarcopenic patients (both sexes) is not significant ($p = 0.13$).

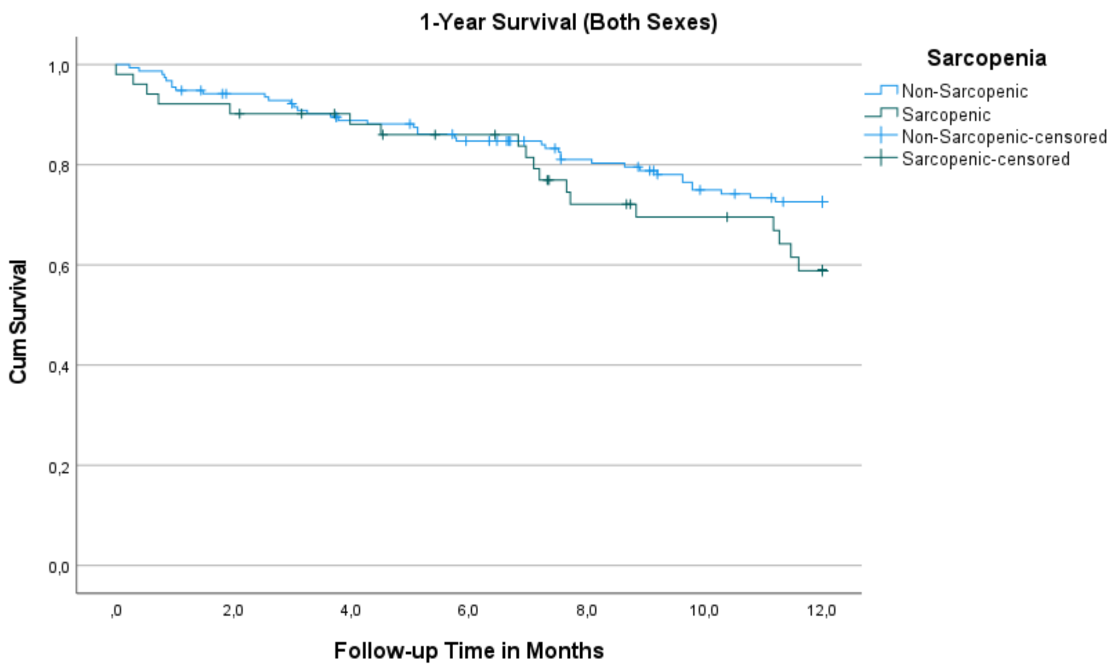

Fig. 9: 1-Year survival for both sexes

1-Year survival: men

1-Year survival rates for men diverge: 73.6 % in the non-sarcopenic vs. 55.4 % in the sarcopenic group. However, the results did not reach statistical significance (log-rank: $p = 0.1$).

Median survival time could not be calculated. The Kaplan-Meier curve is shown in Fig. 10.

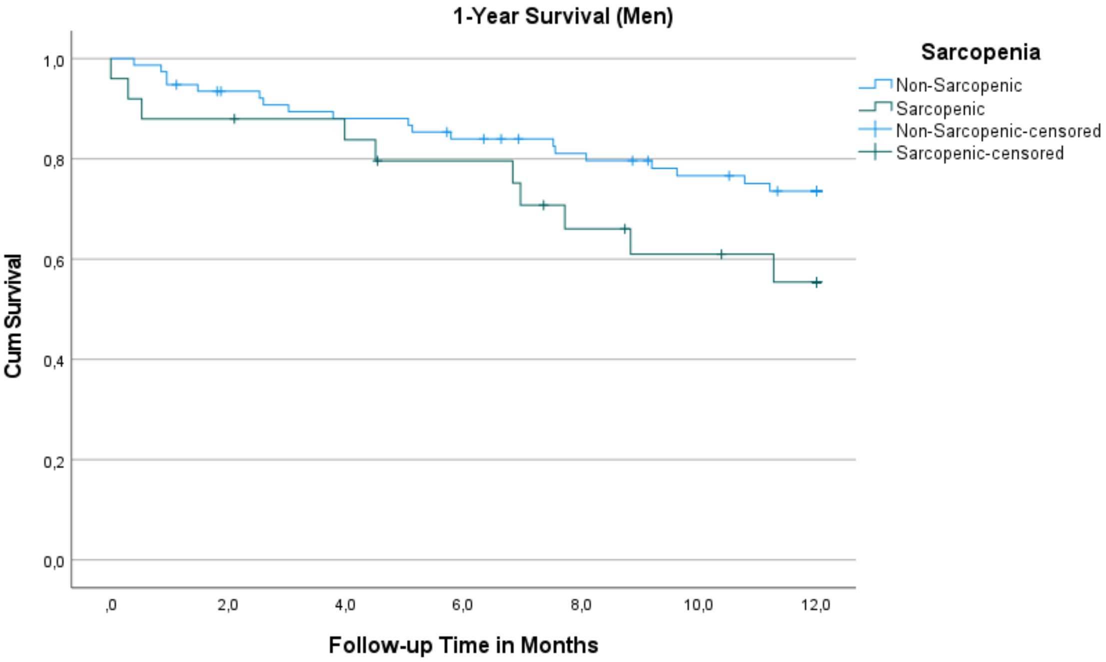

Fig. 10: 1-Year survival for men

1-Year survival: women

Amongst women, differences in 1-year survival rates are smaller: 71.6 % for non-sarcopenic vs. 62.6 % for sarcopenic individuals. Statistical significance was not reached (log-rank: $p = 0.618$).

Calculation of median survival time was not possible. Fig. 11 shows 1-year survival for women.

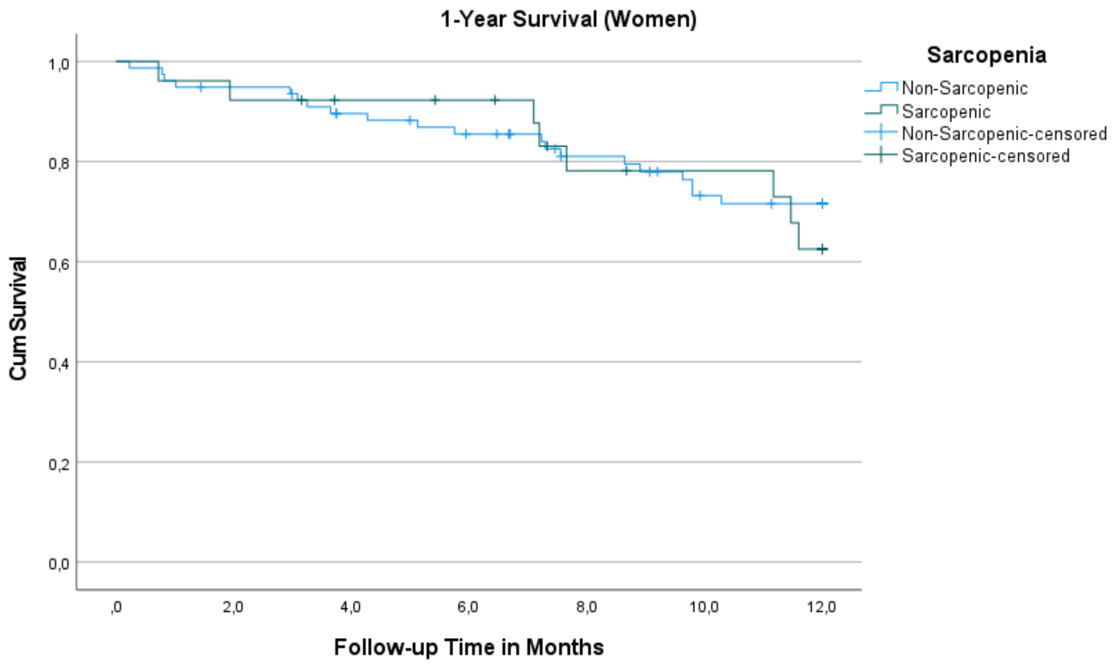

Fig. 11: 1-Year survival for women

Discussion

Pancreatic cancer is a highly malignant disease with poor 5-year survival rates, compared with other cancer types.
Despite advances in diagnostic and therapy, there was only a slight improvement in survival rates in recent years (5).
A growing number of studies focusses on the impact of sarcopenia on postoperative survival in sarcopenic patients.
We know that pancreatic cancer patients with sarcopenia have significantly higher 3-year mortality after resection (11).

The aim of this study was to analyze the relation between sarcopenia and postoperative survival in 206 patients who underwent resection of pancreatic cancer at the Department of Surgery at the LKH-Univ. Klinikum Graz. Therefore, survival analysis was conducted using the Kaplan-Meier method.
Statistical analysis showed that patients with sarcopenia had lower postoperative 1-year survival rates compared with those who were classified as non-sarcopenic (58.9 % vs. 72.6 %). When survival analysis was conducted separated by sex, it showed that the difference in 1-year survival rates was larger in men (55.4 % in the sarcopenic vs. 73.6 % in the non-sarcopenic group).
However, these findings were not statistically significant.
There was no difference in postoperative 3-year survival between sarcopenic and non-sarcopenic individuals. Sex-specific differences could also not be shown.
Analysis of 30-day mortality showed that 11 patients died within the first month after surgery. Only 4 (36.4 %) of these patients were sarcopenic.
The results of this study are different than expected, as most of the recent studies support the theory that sarcopenia is associated with significantly poorer postoperative survival in pancreatic cancer patients.

Common problems were missing data (e.g. no information about body height, therefore skeletal muscle index could not be calculated) and lack of utilizable CT-scans: Either preoperative imaging was done at another facility and not integrated into the hospital information system or scans did not include the level of the 3rd lumbar vertebra.

Definition of cut-off values

Finding the ideal cut-off values for defining low muscle mass based on skeletal muscle index has been the subject to several studies. Their results vary considerably:
Cai et al. (60) performed a retrospective study on 115 patients who underwent pancreatectomy. Only patients with resectable ductal adenocarcinoma of the pancreas were enrolled in the study. Skeletal muscle mass was measured on the level of the L3 vertebra and skeletal muscle index was calculated in the same way as in this diploma thesis.
The skeletal muscle index values that best predicted 1-year mortality were determined as cut-off values: 45.16 cm^2/m^2 for men and 34.65 cm^2/m^2 for women. Mean age was 65.1 ± 9 years.

The cut-off values used in this diploma thesis were ≤ 36.79 cm^2/m^2 for men and ≤ 32.57 cm^2/m^2 for women.
These cut-off values are considerably lower than the ones used in the study cited above. This applies especially to men (36.79 cm^2/m^2 in this study vs. 45.16 cm^2/m^2 in the study done by Cai et al. (60)).

Bahat et al. (61) assessed cut-off values for L3SMI in the Turkish population in two different ways: The 5th percentile was defined as cut-off on the one hand, the mean minus two standard deviations on the other hand.
The calculated cut-offs were 41.42 cm^2/m^2 for men and 30.70 cm^2/m^2 for women using the 5th percentile and 38.67 cm^2/m^2 (men)/ 27.8 cm^2/m^2 (women) using the mean minus two standard deviations.
However, these findings apply to a study population significantly younger than the one in this diploma thesis: mean age was 28.8 ± 5.9 years (vs. 66.2 ± 9.3 years in the present study).
Unfortunately, it is not specified how many of the study participants were classified as having low SMI, according to the calculated cut-off values. Potential relations between low SMI and patient outcome were also not part of the study.

Tab. 5 provides an overview of the cut-off values that were used in the studies cited above.

Tab. 5: Cut-off values for SMI to define low muscle mass

Author	Method of calculation	Cut-off value for males	Cut-off value for females	Mean age of study population
Cai et al. (60)	SMI values that best predicted 1-year mortality	45.16 cm^2/m^2	34.65 cm^2/m^2	65.1 ± 9 years
Bahat et al. (61)	5th percentile of SMI	41.42 cm^2/m^2	30.70 cm^2/m^2	28.8 ± 5.9 years
Bahat et al. (61)	Mean SMI minus two standard deviations	38.67 cm^2/m^2	27.8 cm^2/m^2	28.8 ± 5.9 years
Reitbauer (present thesis)	Lowest quartile of SMI	36.79 cm^2/m^2	32.57 cm^2/m^2	66.2 ± 9.3 years

The skeletal muscle index was used as a marker for sarkopenia in the present thesis. Some publications define sarcopenia using the psoas muscle index (PMI) which is defined as psoas muscle area measured at the level of the 3rd vertebra and adjusted for the patient's height, Therefore the area of the psoas muscle and the PMI were also included in the data set used for this study.
However, the author chose skeletal muscle index as a sarcopenia indicator because studies have shown that it is a better predictor of mortality than PMI (51).

Prevalence of low skeletal muscle mass

Naturally, differing threshold values for SMI lead to differing prevalence of sarcopenia.
A systematic review done by McGovern et al. (62) analyzed the prevalence of low skeletal muscle index amongst patients with different types of malignant tumors, including those with pancreatic cancer.
A total of 4689 pancreatic cancer patients from 23 studies was included. Cut-off values for defining low SMI differed between studies, ranging from ≤36.252 to ≤55.420 cm^2/m^2 in men and from ≤29.652 to ≤38.91 cm^2/m^2 in women.
They found that overall, 32.2 % of pancreatic cancer patients had low SMI.

In this diploma thesis, 24.8 % of patients (24.5 % of men and 25 % of women) were found to have sarcopenia, defined as lowest sex-stratified quartile of muscle mass index. As mentioned above the threshold values used in the present study (≤ 36.79 cm^2/m^2 for men and ≤ 32.57 cm^2/m^2 for women) are in the lower range, compared to other studies. This may explain the low prevalence of sarcopenia in the study cohort.

Cai et al. (60) found that 33 % of their patients had low SMI. Elderly patients were significantly more likely to have low SMI than patients aged younger than 65 (48.2 % vs. 18.6 %).

Furthermore, they found that a low skeletal muscle index predicted poor overall survival in patients aged 65 or older. This correlation could not be observed in younger patients (60).

By way of contrast, this diploma thesis did not find any age-related differences in the prevalence of sarcopenia: 25 % of elderly patients vs. 24.4 % of younger individuals were classified as sarcopenic.

Postoperative survival of pancreatic cancer patients

Statistical analysis showed that 30-day mortality was lower in individuals with sarcopenia compared to those who were not sarcopenic at the time of surgery.

It is possible that a potential effect of sarcopenia on postoperative survival becomes relevant later in clinical course.

However, only 11 patients died within the first 30 days after surgery. Due to the small sampling size this result is not valid enough to make a statement about the influence of sarcopenia on short-term survival following resection of pancreatic cancer.

The present study found that postoperative 1-year survival rates were lower in the sarcopenia group: 72.6 % (non-sarcopenic) vs. 58.9 % (sarcopenic).

This also applies when analysis is performed separated by sex: 73.6 % (non-sarcopenic) vs. 55.4 % (sarcopenic) in men and 71.6 % (non-sarcopenic) vs. 62.6 % (sarcopenic) in women.

The described differences in 1-year survival rates decreased with growing distance from surgery. However, they never reached statistical significance, neither in men nor in women.

A retrospective study by Beetz et al. (63) came to the same conclusion:
There was no significant difference in 1-year survival between sarcopenic and non-sarcopenic patients ($p = 0.25$).

Nevertheless, in the study conducted by Beetz et al. (63) low L3SMI was very well associated with poorer 3-year survival after pancreatic surgery ($p < 0.001$).
In comparison, the present study's results regarding 3-year survival are more complex: No differences in survival rates could be shown after 36 months in sex-independent analysis (30.6 % non-sarcopenic vs. 29 % sarcopenic).
When performing analysis separated by sex, the author of the present study found that the 3-year survival rate in sarcopenic men was, contrary to expectations, higher than in non-sarcopenic men.
Closer examination of the Kaplan-Meier curve (Fig. 7) shows that the survival curve of the non-sarcopenic cohort is higher compared with the curve of the sarcopenic cohort for most of the follow-up period, as expected.
Only after 28 months, the curves cross and the survival rate of the non-sarcopenic group falls below the one of the sarcopenic group. This circumstance is also shown in the related survival rates (see appendix, survival table).
However, the differences in 3-year survival did not reach statistical significance.

The study by Beetz et al. (63) cited above is not completely comparable with this diploma thesis.
Firstly, both patients who received surgical and non-surgical treatment (i.e., chemotherapy) were included to the study. 46 patients (45 %) underwent surgery, 57 (55 %) did not.
Secondly, threshold values for low SMI were different. Beetz et al. (63) defined L3SMI ≤ 52.4 cm^2/m^2 in men and ≤ 38.5 cm^2/m^2 in women as sarcopenia, these values are well above the ones used in the present study.
Based on these cut-off values, Beetz et al. (63) classified 63 % of their study cohort as sarcopenic (vs. 24.8 % in the present study). Mean SMI in their study was 45 ± 9 cm^2/m^2 (vs. 39.8 ± 7.8 cm^2/m^2 in the present study).
Furthermore, all the patients included in the study received chemotherapy. The study does not state whether this means adjuvant or neoadjuvant therapy for patients who underwent surgery.

The authors did also not specify the length of intervals between imaging and surgery. CT images were taken at time of initial diagnosis, hence before any treatment took place.

Not all patients included in the present study did receive chemotherapy. As stated in the theoretical background chapter, adjuvant chemotherapy is recommended for patients in good condition. Some individuals were not eligible for postoperative chemotherapy due to comorbidities or poor overall health status.

Preoperative chemotherapy might reduce muscle mass but improve a patient's prognosis. In other words, patients who have lower SMI due to neoadjuvant chemotherapy could have a better chance of survival.

In the present study, only patients who underwent surgery with curative intent were included. The authors cited above (63) did not specify if the examined cohort includes non-curative approaches.

Apart from these differences in study design, there are similarities regarding the patient cohort: Average age was similar (62 ± 11 years vs. 66.2 ± 9.3 years in the present study) and both studies were conducted in Central Europe (Germany and Austria). Unfortunately, it is not clear how many of the study participants were aged over 65 years.

Differences in study populations could be one reason why the results of this study diverge from other author's findings.

Ideal cut-off values for SMI may differ between regions of the world. Ethnicity and income levels were not part of the author's analysis, but the author assumes that the patients enrolled in this study were predominantly of Central European origin, as the data was collected from a hospital located in Austria. The study by Cai et al. (60) cited above was done in Asian population, Bahat et al.'s study (61) was conducted in Turkish population.

However, cut-off values in this diploma thesis were chosen based on the lowest sex-specific quartile of SMI within the study population. Further research is needed to assess comparability of sarcopenia prevalence and threshold values between different populations.

There is a study which came to the same conclusion as this diploma thesis.
Van Dijk et al. (64) conducted a prospective study on 199 pancreatic cancer patients undergoing pancreatic resection. The authors calculated L3SMI and classified the lowest tertile as sarcopenic.
Survival analysis found no statistically significant differences in survival between patients with low and normal SMI (cut-off values were 45.1 cm^2/m^2 for men and 36.9 cm^2/m^2 for women). Average age in the study cohort was 66.5 years, 54.8 % of participants were male.
In contrast to the present study, the one cited above included 62 patients who had surgery with palliative intent (accounting for 33.3 % of the study population). Apart from this fact, the study populations are comparable.

McGovern et al. (62) divided pancreatic cancer patients in two groups, based on TNM stages: A curative (TNM I-III) and a non-curative cohort (TNM IV/unresectable disease).
They found that the non-curative cohort had a significantly higher prevalence of sarcopenia (63.4 % in the non-curative vs. 32.5 % in the curative cohort).
This is most likely due to muscle loss in the course of this consuming disease.
In the present diploma thesis, 24.8 % of patients were classified as sarcopenic. The relatively low prevalence of sarcopenia in this study might be due to the fact that the present study included only patients who were treated with curative intent.

Amongst the study population of this thesis were four persons with remarkably high skeletal muscle index (> 60 cm^2/m^2, with a maximum of 64.3 cm^2/m^2).
Two of these patients were female, their body mass indices were 17.7 kg/m^2 and 24.6 kg/m^2 (both normal weight). The other two patients were male with body mass indices of 37 kg/m^2 (obesity) and 22.3 kg/m^2 (normal weight).
Inaccuracies in the evaluation of skeletal muscle area were ruled out by repeating the measurements. The documented values for the respective body heights were plausible.

Long-term survival of pancreatic cancer patients is influenced by several determinants, some of them are not related to the disease itself.
Preexisting comorbidities as well as overall health status before onset of the disease limit treatment options, especially when it comes to systemic therapy.

Patients with sarcopenia may not be eligible for chemotherapy due to bad overall condition, which could in turn have a negative effect on survival.
Furthermore, not every patient receives adequate oncological aftercare following resection of a tumor. This also applies to a high-development country like Austria where patients usually have access to medical care. Some individuals decline postoperative chemotherapy or do not keep their appointments for unknown reasons.
These factors may act as confounding variables in the conducted survival analysis.

Limitations

The author is aware of this study's limitations.
Firstly, the intervals between CT or MRI scan and surgery were not consistent. Time spans vary between one month and few days before surgery. In each case, the most recent scan prior to resection was chosen for measuring muscle mass.
In contrast to that, Cai et al. (60) used only CT scans which were taken within one week before surgery.
A few weeks can make a major difference when it comes to the physical condition of a cancer patient. If, hypothetically, imaging was done one month prior to surgery and the patient was then classified as non-sarcopenic, he or she might subsequently lose muscle mass due to the underlying disease. When resection takes place, the patient might then be sarcopenic according to the same definition.
Considering that, differing intervals between imaging and surgery can influence the results of the survival analysis.

Furthermore, this study does not distinguish between patients who underwent neoadjuvant chemotherapy before imaging and those who did not.
The data base used in the present study includes information about neoadjuvant as well as postoperative chemotherapy, in case such has taken place. Unfortunately, it does not indicate if the preoperative CT or MRI scans were taken before or after the start of such a chemotherapy regimen.
As stated above, neoadjuvant chemotherapy can increase the chance of negative resection margins and improve overall survival (2,25). Nevertheless, chemotherapy can contribute to loss of muscle mass and therefore decrease of skeletal muscle index.

Bearing that in mind, patients with low SMI due to preoperative chemotherapy can have a better prognosis compared to those who did not receive neoadjuvant treatment.

In addition, the survival analysis does not consider if the patient received postoperative chemotherapy.
According to Mizrahi et al., adjuvant chemotherapy is associated with improved overall survival, compared with surgery alone (2).
This issue can be addressed by doing a multivariate analysis. However, that would be beyond the scope of this diploma thesis.

Another problem was lack of survival data. For some of the patients who had a recurrence of their malignancy after resection and therefore received best supportive care, death was not reported to the hospital information system. Considering the poor survival of patients with stage IV pancreatic cancer, it is unlikely that they are still alive.
These patients were classified as lost to follow-up and censored at the time of their latest documented medical contact. In total, 47.1 % of the study group had to be censored. This number also includes patients who did not reach the endpoint (death) within 36 or 12 months from surgery.

Some authors such as Kong et al. (65) used medical imaging analysis software to automatically identify muscle tissue and measure its area.
Beetz et al. (63) used artificial intelligence-based software in combination with an experienced radiologist to identify skeletal muscle mass in computed tomography scans.
In the present study, skeletal muscles were manually outlined on CT or MRI images before their areas were measured. The author of this diploma thesis has anatomical knowledge and was trained in using OsiriX Lite software but is not specialized in radiology.

Muscle density was not considered in this diploma thesis in contrast to some of the other studies.
Van Dijk et al. (64) assessed the radiation attenuation of the measured muscle area in Hounsfield units. This method allowed conclusions about the amount of

intramuscular adipose tissue: The lower the radio attenuation of the measured muscle area, the higher the muscle fat content (64).
According to the study, low radiation attenuation of the L3 skeletal muscle area is associated with poorer survival in pancreatic cancer patients. However, the study did also not find an association between L3SMI and survival.
As mentioned above the cited study used the same method for calculating cut-off values and the study cohort was similar to the cohort of the present thesis. Given these facts, a possible connection between muscle density and survival in the patient collective of the present thesis should be subject of further studies.

Body composition in general can affect the outcome of cancer patients. Especially sarcopenic obesity is currently discussed as determinant of postoperative survival (6). However, evaluating sarcopenic obesity was beyond the scopes of this study.

This study includes data of patients who underwent surgery between April 2000 and November 2019. Within this period of time, there were advances in neoadjuvant and adjuvant chemotherapy as well as in radiochemotherapy.
The Kaplan-Meier estimator assumes that the survival probability is equal for every patient, regardless of the time when he or she was admitted to the study (66).
Therefore, it cannot be ruled out that advances in treatment options over the past 20 years interfered with this survival analysis.

Out of the 448 patients who underwent surgery of the pancreas, only 206 patients met all the criteria and were included in the study.
However, the sampling size for this study was relatively high and the study group is representative for Central European patients who underwent resection of invasive pancreatic cancer with curative intent. Few studies of a similar scale have been done in the Central European region so far.

Outlook

The prevalence of sarcopenia was remarkably low in the present study. Future analysis could use a method for calculating L3 skeletal muscle index threshold values that is more common in literature. This will improve comparability with other studies.

Clear criteria for the radiological diagnosis of sarcopenia have been requested by many researchers and will hopefully be published in the near future.

As mentioned above there is evidence that the correlation between sarcopenia and poor overall survival is age dependent. Multivariate analysis can determine whether this also applies to the patient cohort of this diploma thesis. Differing age structures in study populations should be taken into account when results of different studies are compared to each other.

Further research should focus on body composition rather than on quantitative muscle mass only. There is growing evidence that muscle quality is more important when it comes to diagnosing sarcopenia.

Researchers are only beginning to understand the pathomechanism behind sarcopenic obesity and its negative effects on health, especially its impact on postoperative morbidity and mortality.

Muscle density can easily be assessed in computed tomography images, especially with the help of medical imaging analysis software.

Some studies have been done on this topic, but there are still a lot of questions. The findings of this thesis can provide a basis for further research to answer some of them.

Conclusion

Pancreatic cancer is a major health issue. The disease has a remarkably high lethality rate and is an important cause of premature death. Incidence and mortality rates are rising, especially in high development countries.
Aging of the population as well as industrialization and the accompanying increased exposure to risk factors play an important role in this development.
Early diagnosis is crucial in order to detect this malignancy while there is still a chance for cure. Unfortunately, typical symptoms usually develop in advanced stages of the disease.
There is currently no reliable biomarker to screen patients at risk. Especially those with a family history of certain germline mutations would benefit from such a screening tool.
Radiological detection of small tumors is another challenge that hopefully will be mastered in the future.
As the incidence of pancreatic cancer peaks in the 7th and 8th decade of life, elderly persons account for a majority of pancreatic cancer cases. Therefore, specifics of geriatric patients must be considered. Undertreatment is a common problem in elderly patients that must be addressed. Furthermore, there are pharmacological issues such as altered metabolism, drug interactions due to polypharmacy and increased toxicity of chemotherapeutic substances.

Many pancreatic cancer patients are affected by sarcopenia. Identifying patients who are at risk for sarcopenia and initiating further investigations is crucial.
Several factors can contribute to the pathogenesis of sarcopenia, the presence of a malignant disease is one of them.
Assessment of muscle function is the best method for detecting sarcopenia, but it is also time-consuming and can only be done in prospective studies.
Evaluation of muscle quantity can easily be implemented in clinical routine, as every patient undergoes computed tomography or magnetic resonance imaging of the abdomen before surgery takes place.
Several methods for evaluation of muscle mass are currently used, which makes comparison between studies difficult. Standardized criteria for radiological diagnosis of sarcopenia, including sex-specific threshold values, are urgently needed.

Sarcopenia is associated with frequent falls and fractures. Furthermore, it is a risk factor for cardiovascular disease. Studies showed that sarcopenic patients have a poorer outcome and increased morbidity rates after surgery.
Therefore, it is important to raise awareness for sarcopenia in general and make diagnostic tools widely available. Diagnosis and proper treatment are necessary to increase life quality of affected patients and prevent complications.
There is evidence that physical exercise can be beneficial in order to increase muscle quantity and function. However, preoperative management of sarcopenia is barely implemented due to the short timeframe between diagnosis and surgical treatment.
Several studies suggest that sarcopenia is associated with poorer survival following different kinds of surgery. This association has been shown for pancreatic surgery as well, but it is still unclear if it applies to all groups of pancreatic cancer patients.
Understanding the factors that affect postoperative survival is crucial for successful treatment of this highly malignant disease, especially for patients who are eligible for a curative therapy approach.
Body composition plays a fundamental role when it comes to diagnosing sarcopenia. Especially sarcopenic obesity is associated with morbidity and poorer outcome following surgery. Researchers have taken up this topic, further findings hopefully can be expected in the near future.
Notwithstanding the above, it must be ensured that every pancreatic cancer patient has access to accurate medical support and is provided with sufficient analgesia, regardless of the stage of the disease.
It is also crucial to control typical symptoms such as nausea, biliary obstruction and fat malabsorption. Furthermore, psychological support should be offered.
Such a wide range of support can only be provided if the patient is treated by a multidisciplinary team.

The goal of this study was evaluating a possible connection between sarcopenia and overall survival.
Skeletal muscle index, measured on the level of the 3rd lumbar vertebra and adjusted for patient's height, was chosen as indicator for sarcopenia. Patients within the lowest sex-stratified quartile of L3SMI were classified as sarcopenic.

The results of the author's survival analysis suggest that sarcopenia does not significantly affect 1-year or 3-year survival following resection of invasive pancreatic cancer.
Though in the present study 1-year survival rates for sarcopenic individuals were lower compared with non-sarcopenic individuals, statistical significance was not reached.
The prevalence of sarcopenia within the study population was low, compared to other studies. This is most likely due to notably low threshold values. In contrast with other studies, the present study found no difference in prevalence between young patients and those aged 65 years or older

The main issue with evaluation of sarcopenia in pancreatic cancer patients is that there are several methods of measuring muscle mass and calculating cut-off values. The most common methods for evaluation muscle mass are measurement of the total psoas area or total muscle area on the level of the 3rd lumbar vertebra and adjusting the measured area for body height.
There are a lot of approaches for finding the right threshold values. Up to this day, it is not clear which approach correlates best with survival.
There are also considerable differences in patient cohorts between studies. Some authors include patients who undergo palliative surgery, some do not.
Study cohorts are also heterogeneous when it comes to systemic therapy. Neoadjuvant and postoperative chemotherapy as well as radiotherapy can influence postoperative survival, therefore they act as confounding factors and reduce comparability between studies.
Survival following resection of pancreatic cancer is influenced by several factors, sarcopenia is only one of them. Hopefully future advances in diagnosis and treatment will further decrease the lethality of this disease.
Even though the role of sarcopenia in postoperative survival is not clear yet, screening pancreatic cancer patients for sarcopenia is reasonable and should be established in clinical routine.
In case a patient is diagnosed with sarcopenia, modification of risk factors as well as pre- and postoperative physical exercise to increase muscle mass should be initiated. However, even if this does not affect postoperative survival, it can still improve quality of life and therefore be beneficial to the patient.

The frequently described inverse correlation between L3SMI and overall survival could not be shown in this study. This suggests that the correlation may not apply to all groups of patients.
Future studies should consider body composition, especially muscle density and sarcopenic obesity. To ensure comparability, studies should differentiate between patients who received chemotherapy and those who did not. The time span between imaging and surgery and pre-imaging chemotherapy must be considered as well.
There are only few studies in Central Europe with comparable sample size. This diploma thesis provides valuable information and can be the foundation for further investigations.
Future insights concerning diagnosis and treatment of pancreatic cancer will hopefully reduce the personal and social burden of this devastating disease. Evaluation of sarcopenia as potential risk factor for poor postoperative outcome should be implemented in clinical practice. The increasing awareness for sarcopenia amongst physicians raises hope that this will happen in the nearby future.

References

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin. 2021 May;71(3):209–49.

2. Mizrahi JD, Surana R, Valle JW, Shroff RT. Pancreatic cancer. www.thelancet.com [Internet]. 2020 [cited 2022 May 22];395. Available from: www.thelancet.com

3. Fogel EL, Shahda S, Sandrasegaran K, Dewitt J, Easler JJ, Agarwal DM, et al. A Multidisciplinary Approach to Pancreas Cancer in 2016: A Review. Am J Gastroenterol [Internet]. 2017 Apr 1 [cited 2022 May 26];112(4):537. Available from: /pmc/articles/PMC5659272/

4. Ballehaninna UK, Chamberlain RS. The clinical utility of serum CA 19-9 in the diagnosis, prognosis and management of pancreatic adenocarcinoma: An evidence based appraisal. J Gastrointest Oncol [Internet]. 2012 [cited 2022 May 22];3(2):105. Available from: /pmc/articles/PMC3397644/

5. McGuigan A, Kelly P, Turkington RC, Jones C, Coleman HG, McCain RS. Pancreatic cancer: A review of clinical diagnosis, epidemiology, treatment and outcomes. World J Gastroenterol. 2018;24(43):4846–61.

6. Chan MY, Chok KSH. Sarcopenia in pancreatic cancer - effects on surgical outcomes and chemotherapy. World J Gastrointest Oncol [Internet]. 2019 Jul 1 [cited 2022 Jul 11];11(7):527–37. Available from: https://pubmed-1ncbi-1nlm-1nih-1gov-10013b50g0362.han.medunigraz.at/31367272/

7. Han A, Bokshan SL, Marcaccio SE, Depasse JM, Daniels AH. Diagnostic Criteria and Clinical Outcomes in Sarcopenia Research: A Literature Review. J Clin Med [Internet]. 2018 Apr 1 [cited 2022 Jul 8];7(4). Available from: https://pubmed-1ncbi-1nlm-1nih-1gov-10013b50g0011.han.medunigraz.at/29642478/

8. Keller K. Sarcopenia. Wien Med Wochenschr [Internet]. 2019 May 1 [cited 2022 Jul 8];169(7–8):157–72. Available from: https://pubmed-1ncbi-1nlm-1nih-1gov-10013b50g0011.han.medunigraz.at/29411194/

9. Cruz-Jentoft AJ, Bahat G, Bauer J, Boirie Y, Bruyère O, Cederholm T, et al. Sarcopenia: Revised European consensus on definition and diagnosis. Age Ageing. 2019;48(1):16–31.

10. Woo EC, Rodis B. Sarcopenia in Elderly Surgery. 2019;48(11):363.

11. Peng P, Hyder O, Firoozmand A, Kneuertz P, Schulick RD, Huang D, et al. Impact of Sarcopenia on Outcomes Following Resection of Pancreatic Adenocarcinoma. Journal of Gastrointestinal Surgery. 2012;16(8):1478–86.

12. Bray F, Laversanne M, Weiderpass E, Soerjomataram I. The ever-increasing importance of cancer as a leading cause of premature death worldwide. Cancer. 2021 Aug 15;127(16):3029–30.

13. Townsend N, Kazakiewicz D, Lucy Wright F, Timmis A, Huculeci R, Torbica A, et al. Epidemiology of cardiovascular disease in Europe. Nat Rev Cardiol [Internet]. 2022 Feb 1 [cited 2022 Aug 7];19(2):133–43. Available from: https://pubmed-1ncbi-1nlm-1nih-1gov-10013b5la00b4.han.medunigraz.at/34497402/

14. Human Development Index (HDI) | Human Development Reports [Internet]. [cited 2022 May 7]. Available from: https://hdr.undp.org/en/content/human-development-index-hdi

15. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68(6):394–424.

16. CL W, JM H, DA L, AP K, MA E, EK F, et al. Recent progress in pancreatic cancer. CA Cancer J Clin [Internet]. 2013 [cited 2022 May 9];63(5):228–30. Available from: https://pubmed-1ncbi-1nlm-1nih-1gov-10013b5si0070.han.medunigraz.at/23856911/

17. Ilic M, Ilic I. Epidemiology of pancreatic cancer. World J Gastroenterol. 2016;22(44):9694–705.

18. Reddy S, Cameron JL, Scudiere J, Hruban RH, Fishman EK, Ahuja N, et al. Surgical Management of Solid-Pseudopapillary Neoplasms of the Pancreas (Franz or Hamoudi Tumors): A Large Single-Institutional Series. J Am Coll

Surg [Internet]. 2009 May [cited 2022 May 14];208(5):950. Available from: /pmc/articles/PMC3109868/

19. Wargo JA, Fernandez-del-Castillo C, Warshaw AL. Management of Pancreatic Serous Cystadenomas. Adv Surg. 2009 Sep 1;43(1):23–34.

20. Chari ST, Leibson CL, Rabe KG, Ransom J, de Andrade M, Petersen GM. Probability of Pancreatic Cancer Following Diabetes: A Population-Based Study. Gastroenterology. 2005 Aug 1;129(2):504–11.

21. Zar S, Kohoutová D, Bureš J. Pancreatic Adenocarcinoma: Epidemiology, Role of EUS in Diagnosis, Role of ERCP, Endoscopic Palliation. Acta Medica (Hradec Kralove) [Internet]. 2019;62(4):131–6. Available from: https://dx.doi.org/10.14712/18059694.2020.1

22. Allen PJ, Kuk D, Fernandez-del Castillo C, Basturk O, Wolfgang CL, Cameron JL, et al. Multi-Institutional validation study of the American Joint Commission on Cancer (8 th edition) changes for T and N staging in patients with pancreatic adenocarcinoma HHS Public Access Author manuscript. Ann Surg. 2017;265(1):185–91.

23. Cong L, Liu Q, Zhang R, Cui M, Zhang X, Gao X, et al. Tumor size classification of the 8th edition of TNM staging system is superior to that of the 7th edition in predicting the survival outcome of pancreatic cancer patients after radical resection and adjuvant chemotherapy. Sci Rep [Internet]. 2018 Dec 1 [cited 2022 May 14];8(1). Available from: /pmc/articles/PMC6039534/

24. Liao X, Zhang D. The 8th Edition American Joint Committee on Cancer Staging for Hepato-pancreato-biliary Cancer: A Review and Update. Arch Pathol Lab Med [Internet]. 2021 May 1 [cited 2022 May 14];145(5):543–53. Available from: https://pubmed-1ncbi-1nlm-1nih-1gov-10013b5s201b1.han.medunigraz.at/32223559/

25. Isaji S, Mizuno S, Windsor JA, Bassi C, Fernández-del Castillo C, Hackert T, et al. International consensus on definition and criteria of borderline resectable pancreatic ductal adenocarcinoma 2017. Pancreatology. 2018 Jan 1;18(1):2–11.

26. Suker M, Koerkamp BG, Coene PP, van der Harst E, Bonsing BA, Vahrmeijer AL, et al. Yield of staging laparoscopy before treatment of locally advanced pancreatic cancer to detect occult metastases. European Journal of Surgical Oncology. 2019 Oct 1;45(10):1906–11.

27. Hartwig W, Werner J, Jäger D, Debus J, Büchler MW. Improvement of surgical results for pancreatic cancer. Lancet Oncol. 2013 Oct;14(11).

28. Croome KP, Farnell MB, Que FG, ReidLombardo K, Truty MJ, Nagorney DM, et al. Total laparoscopic pancreaticoduodenectomy for pancreatic ductal adenocarcinoma: oncologic advantages over open approaches? Ann Surg [Internet]. 2014 [cited 2022 May 24];260(4):633–40. Available from: https://pubmed-1ncbi-1nlm-1nih-1gov-10013b5c00009.han.medunigraz.at/25203880/

29. Venkat R, Edil BH, Schulick RD, Lidor AO, Makary MA, Wolfgang CL. Laparoscopic distal pancreatectomy is associated with significantly less overall morbidity compared to the open technique: a systematic review and meta-analysis. Ann Surg [Internet]. 2012 Jun [cited 2022 May 24];255(6):1048–59. Available from: https://pubmed-1ncbi-1nlm-1nih-1gov-10013b5p90004.han.medunigraz.at/22511003/

30. Chen K, Liu X long, Pan Y, Maher H, Wang X fa. Expanding laparoscopic pancreaticoduodenectomy to pancreatic-head and periampullary malignancy: major findings based on systematic review and meta-analysis. BMC Gastroenterol [Internet]. 2018 Jul 3 [cited 2022 May 24];18(1). Available from: https://pubmed-1ncbi-1nlm-1nih-1gov-10013b5he0001.han.medunigraz.at/29969999/

31. Philip PA, Lacy J, Portales F, Sobrero A, Pazo-Cid R, Manzano Mozo JL, et al. Nab-paclitaxel plus gemcitabine in patients with locally advanced pancreatic cancer (LAPACT): a multicentre, open-label phase 2 study. Lancet Gastroenterol Hepatol [Internet]. 2020 Mar 1 [cited 2022 May 24];5(3):285–94. Available from: https://pubmed-1ncbi-1nlm-1nih-1gov-10013b5lg0004.han.medunigraz.at/31953079/

32. Suker M, Beumer BR, Sadot E, Marthey L, Faris JE, Mellon EA, et al. FOLFIRINOX for locally advanced pancreatic cancer: a systematic review and

patient-level meta-analysis. Lancet Oncol [Internet]. 2016 Jun 1 [cited 2022 May 24];17(6):801–10. Available from: https://pubmed-1ncbi-1nlm-1nih-1gov-10013b5yl0005.han.medunigraz.at/27160474/

33. Chatzizacharias NA, Tsai S, Griffin M, Tolat P, Ritch P, George B, et al. Locally advanced pancreas cancer: Staging and goals of therapy. Surgery [Internet]. 2018 May 1 [cited 2022 May 14];163(5):1053–62. Available from: https://pubmed-1ncbi-1nlm-1nih-1gov-10013b5s201b1.han.medunigraz.at/29331400/

34. Conroy T, Hammel P, Hebbar M, ben Abdelghani M, Wei AC, Raoul JL, et al. FOLFIRINOX or Gemcitabine as Adjuvant Therapy for Pancreatic Cancer. N Engl J Med [Internet]. 2018 Dec 20 [cited 2022 May 24];379(25):2395–406. Available from: https://pubmed-1ncbi-1nlm-1nih-1gov-10013b5oo0001.han.medunigraz.at/30575490/

35. Sachdev AH, Gress FG. Celiac Plexus Block and Neurolysis: A Review. Gastrointest Endosc Clin N Am. 2018 Oct 1;28(4):579–86.

36. Vanbutsele G, Pardon K, van Belle S, Surmont V, de Laat M, Colman R, et al. Effect of early and systematic integration of palliative care in patients with advanced cancer: a randomised controlled trial. Lancet Oncol [Internet]. 2018 Mar 1 [cited 2022 May 26];19(3):394–404. Available from: https://pubmed-1ncbi-1nlm-1nih-1gov-10013b54l0065.han.medunigraz.at/29402701/

37. Macchini M, Chiaravalli M, Zanon S, Peretti U, Mazza E, Gianni L, et al. Chemotherapy in elderly patients with pancreatic cancer: Efficacy, feasibility and future perspectives. Cancer Treat Rev. 2019 Jan 1;72:1–6.

38. Higuera O, Ghanem I, Nasimi R, Prieto I, Koren L, Feliu J. Management of pancreatic cancer in the elderly. World J Gastroenterol [Internet]. 2016 Jan 14 [cited 2022 May 26];22(2):764–75. Available from: https://pubmed-1ncbi-1nlm-1nih-1gov-10013b54l0065.han.medunigraz.at/26811623/

39. Quaglia A, Tavilla A, Shack L, Brenner H, Janssen-Heijnen M, Allemani C, et al. The cancer survival gap between elderly and middle-aged patients in Europe is widening. Eur J Cancer. 2009 Apr 1;45(6):1006–16.

40. Parmar AD, Vargas GM, Tamirisa NP, Sheffield KM, Riall TS. Trajectory of care and use of multimodality therapy in older patients with pancreatic adenocarcinoma. Surgery (United States). 2014;156(2):280–9.

41. Dam TT, Peters KW, Fragala M, Cawthon PM, Harris TB, McLean R, et al. An evidence-based comparison of operational criteria for the presence of sarcopenia. J Gerontol A Biol Sci Med Sci [Internet]. 2014 [cited 2022 Jul 8];69(5):584–90. Available from: https://pubmed-1ncbi-1nlm-1nih-1gov-10013b50g005e.han.medunigraz.at/24737561/

42. Schaap LA, van Schoor NM, Lips P, Visser M. Associations of Sarcopenia Definitions, and Their Components, With the Incidence of Recurrent Falling and Fractures: The Longitudinal Aging Study Amsterdam. J Gerontol A Biol Sci Med Sci [Internet]. 2018 Aug 10 [cited 2022 Jul 7];73(9):1199–204. Available from: https://pubmed-1ncbi-1nlm-1nih-1gov-10013b5ki0340.han.medunigraz.at/29300839/

43. Morley JE, Abbatecola AM, Argiles JM, Baracos V, Bauer J, Bhasin S, et al. Sarcopenia with limited mobility: an international consensus. J Am Med Dir Assoc [Internet]. 2011 [cited 2022 Jul 7];12(6):403–9. Available from: https://pubmed-1ncbi-1nlm-1nih-1gov-10013b5ki0340.han.medunigraz.at/21640657/

44. Ishii S, Tanaka T, Shibasaki K, Ouchi Y, Kikutani T, Higashiguchi T, et al. Development of a simple screening test for sarcopenia in older adults. Geriatr Gerontol Int [Internet]. 2014 Feb [cited 2022 Jul 7];14 Suppl 1(SUPPL.1):93–101. Available from: https://pubmed-1ncbi-1nlm-1nih-1gov-10013b5ki0340.han.medunigraz.at/24450566/

45. Merchant RA, Seetharaman S, Au L, Wong MWK, Wong BLL, Tan LF, et al. Relationship of Fat Mass Index and Fat Free Mass Index With Body Mass Index and Association With Function, Cognition and Sarcopenia in Pre-Frail Older Adults. Front Endocrinol (Lausanne). 2021 Dec 24;12:1779.

46. Leong DP, Teo KK, Rangarajan S, Lopez-Jaramillo P, Avezum A, Orlandini A, et al. Prognostic value of grip strength: findings from the Prospective Urban Rural Epidemiology (PURE) study. Lancet [Internet]. 2015 Jul 18 [cited 2022

Jul 7];386(9990):266–73. Available from: https://pubmed-1ncbi-1nlm-1nih-1gov-10013b5ki0357.han.medunigraz.at/25982160/

47. Schaap LA, Koster A, Visser M. Adiposity, muscle mass, and muscle strength in relation to functional decline in older persons. Epidemiol Rev [Internet]. 2013 Jan 1 [cited 2022 Jul 7];35(1):51–65. Available from: https://pubmed-1ncbi-1nlm-1nih-1gov-10013b5ki0357.han.medunigraz.at/23221972/

48. Beaudart C, McCloskey E, Bruyère O, Cesari M, Rolland Y, Rizzoli R, et al. Sarcopenia in daily practice: assessment and management. BMC Geriatr [Internet]. 2016 [cited 2022 Jul 7];16(1):1–10. Available from: https://pubmed-1ncbi-1nlm-1nih-1gov-10013b5ki03ed.han.medunigraz.at/27716195/

49. Lee CM, Kang BK, Kim M. Radiologic Definition of Sarcopenia in Chronic Liver Disease. Life (Basel) [Internet]. 2021 Feb 1 [cited 2022 Jul 8];11(2):1–16. Available from: https://pubmed-1ncbi-1nlm-1nih-1gov-10013b50g0011.han.medunigraz.at/33504046/

50. Mourtzakis M, Prado CMM, Lieffers JR, Reiman T, McCargar LJ, Baracos VE. A practical and precise approach to quantification of body composition in cancer patients using computed tomography images acquired during routine care. Appl Physiol Nutr Metab [Internet]. 2008 Oct [cited 2022 Jul 8];33(5):997–1006. Available from: https://pubmed-1ncbi-1nlm-1nih-1gov-10013b50g0011.han.medunigraz.at/18923576/

51. Ebadi M, Wang CW, Lai JC, Dasarathy S, Kappus MR, Dunn MA, et al. Poor performance of psoas muscle index for identification of patients with higher waitlist mortality risk in cirrhosis. J Cachexia Sarcopenia Muscle [Internet]. 2018 Dec 1 [cited 2022 Jul 8];9(6):1053–62. Available from: https://pubmed-1ncbi-1nlm-1nih-1gov-10013b50g004a.han.medunigraz.at/30269421/

52. Buckinx F, Landi F, Cesari M, Fielding RA, Visser M, Engelke K, et al. Pitfalls in the measurement of muscle mass: a need for a reference standard. J Cachexia Sarcopenia Muscle [Internet]. 2018 Apr 1 [cited 2022 Jul 7];9(2):269–78. Available from: https://pubmed-1ncbi-1nlm-1nih-1gov-10013b5ki03ed.han.medunigraz.at/29349935/

53. Reiss J, Iglseder B, Kreutzer M, Weilbuchner I, Treschnitzer W, Kässmann H, et al. Case finding for sarcopenia in geriatric inpatients: performance of

bioimpedance analysis in comparison to dual X-ray absorptiometry. BMC Geriatr [Internet]. 2016 Feb 29 [cited 2022 Jul 7];16(1). Available from: https://pubmed-1ncbi-1nlm-1nih-1gov-10013b5ki03ed.han.medunigraz.at/26928275/

54. Kim KM, Jang HC, Lim S. Differences among skeletal muscle mass indices derived from height-, weight-, and body mass index-adjusted models in assessing sarcopenia. Korean J Intern Med [Internet]. 2016 Jul 1 [cited 2022 Jul 7];31(4):643–50. Available from: https://pubmed-1ncbi-1nlm-1nih-1gov-10013b5ki03ed.han.medunigraz.at/27334763/

55. Beaudart C, Rolland Y, Cruz-Jentoft AJ, Bauer JM, Sieber C, Cooper C, et al. Assessment of Muscle Function and Physical Performance in Daily Clinical Practice: A position paper endorsed by the European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCEO). Calcif Tissue Int [Internet]. 2019 Jul 15 [cited 2022 Jul 7];105(1):1–14. Available from: https://link-1springer-1com-10013b5ki03ed.han.medunigraz.at/article/10.1007/s00223-019-00545-w

56. Onesti JK, Wright GP, Kenning SE, Tierney MT, Davis AT, Doherty MG, et al. Sarcopenia and survival in patients undergoing pancreatic resection. Pancreatology [Internet]. 2016;16(2):284–9. Available from: http://dx.doi.org/10.1016/j.pan.2016.01.009

57. Beaudart C, Dawson A, Shaw SC, Harvey NC, Kanis JA, Binkley N, et al. Nutrition and physical activity in the prevention and treatment of sarcopenia: systematic review. Osteoporos Int [Internet]. 2017 Jun 1 [cited 2022 Jul 11];28(6):1817–33. Available from: https://pubmed-1ncbi-1nlm-1nih-1gov-10013b50g02bc.han.medunigraz.at/28251287/

58. Faron A, Sprinkart AM, Kuetting DLR, Feisst A, Isaak A, Endler C, et al. Body composition analysis using CT and MRI: intra-individual intermodal comparison of muscle mass and myosteatosis. Sci Rep [Internet]. 2020 Dec 1 [cited 2022 Aug 15];10(1). Available from: https://pubmed-1ncbi-1nlm-1nih-1gov-10013b50t00ab.han.medunigraz.at/32678260/

59. Miyamoto Y, Baba Y, Sakamoto Y, Ohuchi M, Tokunaga R, Kurashige J, et al. Sarcopenia is a Negative Prognostic Factor After Curative Resection of

Colorectal Cancer. Ann Surg Oncol [Internet]. 2015 Aug 1 [cited 2023 Apr 10];22(8):2663–8. Available from: https://pubmed-1ncbi-1nlm-1nih-1gov-10013b521050d.han.medunigraz.at/25564158/

60. Cai ZW, Li JL, Liu M, Wang HW, Jiang CY. Low preoperative skeletal muscle index increases the risk of mortality among resectable pancreatic cancer patients: A retrospective study. World J Gastrointest Surg [Internet]. 2022 Dec 12 [cited 2023 Apr 4];14(12):1350. Available from: /pmc/articles/PMC9827571/

61. Bahat G, Turkmen BO, Aliyev S, Catikkas NM, Bakir B, Karan MA. Cut-off values of skeletal muscle index and psoas muscle index at L3 vertebra level by computerized tomography to assess low muscle mass. Clinical Nutrition. 2021 Jun 1;40(6):4360–5.

62. McGovern J, Dolan RD, Horgan PG, Laird BJ, McMillan DC. Computed tomography-defined low skeletal muscle index and density in cancer patients: observations from a systematic review. J Cachexia Sarcopenia Muscle [Internet]. 2021 Dec 1 [cited 2023 Apr 10];12(6):1408. Available from: /pmc/articles/PMC8718024/

63. Lasse Beetz N, Geisel D, Maier C, Auer TA, Shnayien S, Malinka T, et al. Influence of Baseline CT Body Composition Parameters on Survival in Patients with Pancreatic Adenocarcinoma. 2022 [cited 2023 Apr 11]; Available from: https://doi.org/10.3390/jcm11092356

64. J van Dijk DP, A M Bakens MJ, E Coolsen MM, Rensen SS, van Dam RM, L Bours MJ, et al. Low skeletal muscle radiation attenuation and visceral adiposity are associated with overall survival and surgical site infections in patients with pancreatic cancer. 2016 [cited 2023 Apr 11]; Available from: https://onlinelibrary.wiley.com/doi/10.1002/jcsm.12155

65. Kong M, Geng N, Zhou Y, Lin N, Song W, Xu M, et al. Defining reference values for low skeletal muscle index at the L3 vertebra level based on computed tomography in healthy adults: A multicentre study. Clinical Nutrition. 2022 Feb 1;41(2):396–404.

66. Kishore J, Goel M, Khanna P. Understanding survival analysis: Kaplan-Meier estimate. Int J Ayurveda Res. 2010;1(4):274.

Appendix

Survival Table

Sarcopenia		Time	Status	Cumulative Proportion Surviving at the Time Estimate	Cumulative Proportion Surviving at the Time Std. Error	N of Cumulative Events	N of Remaining Cases
Non-Sarcopenic	1	,394	Dead	,987	,013	1	76
	2	,854	Dead	,974	,018	2	75
	3	,953	Dead	.	.	3	74
	4	,953	Dead	,948	,025	4	73
	5	1,117	Alive	.	.	4	72
	6	1,478	Dead	,935	,028	5	71
	7	1,807	Alive	.	.	5	70
	8	1,873	Alive	.	.	5	69
	9	2,530	Dead	,921	,031	6	68
	10	2,595	Dead	,908	,033	7	67
	11	3,023	Dead	,894	,035	8	66
	12	3,778	Dead	,881	,037	9	65
	13	5,060	Dead	,867	,039	10	64
	14	5,125	Dead	,854	,041	11	63
	15	5,717	Alive	.	.	11	62
	16	5,782	Dead	,840	,042	12	61
	17	6,341	Alive	.	.	12	60
	18	6,637	Alive	.	.	12	59
	19	6,932	Alive	.	.	12	58
	20	7,524	Dead	,825	,044	13	57
	21	7,556	Dead	,811	,046	14	56
	22	8,082	Dead	,796	,047	15	55
	23	8,871	Alive	.	.	15	54
	24	9,133	Alive	.	.	15	53
	25	9,199	Dead	,781	,049	16	52
	26	9,626	Dead	,766	,050	17	51
	27	10,513	Alive	.	.	17	50
	28	10,776	Dead	,751	,051	18	49
	29	11,203	Dead	,736	,052	19	48
	30	11,335	Alive	.	.	19	47
	31	12,583	Alive	.	.	19	46
	32	12,747	Dead	,720	,054	20	45
	33	12,945	Dead	,704	,055	21	44
	34	13,010	Dead	,688	,056	22	43
	35	13,175	Dead	,672	,057	23	42
	36	13,207	Dead	,656	,058	24	41
	37	14,686	Alive	.	.	24	40
	38	14,817	Dead	,639	,058	25	39
	39	15,146	Dead	,623	,059	26	38
	40	15,310	Alive	.	.	26	37
	41	15,507	Alive	.	.	26	36
	42	15,671	Alive	.	.	26	35

Appendix: survival table for 3-year survival (both sexes), part 1/3

	43	15,803	Dead	,605	,060	27	34
	44	16,099	Dead	,587	,061	28	33
	45	16,230	Dead	,570	,062	29	32
	46	17,314	Dead	,552	,062	30	31
	47	19,000	Dead	,534	,063	31	30
	48	19,023	Dead	,516	,063	32	29
	49	20,435	Dead	,498	,063	33	28
	50	20,698	Alive	.	.	33	27
	51	20,830	Dead	,480	,064	34	26
	52	21,257	Dead	,461	,064	35	25
	53	23,589	Dead	,443	,064	36	24
	54	23,754	Dead	,425	,064	37	23
	55	25,232	Alive	.	.	37	22
	56	25,791	Dead	,405	,064	38	21
	57	25,791	Alive	.	.	38	20
	58	26,908	Dead	,385	,064	39	19
	59	27,565	Dead	,365	,064	40	18
	60	27,959	Alive	.	.	40	17
	61	28,123	Dead	,343	,063	41	16
	62	28,255	Dead	,322	,063	42	15
	63	28,616	Dead	,300	,062	43	14
	64	30,850	Alive	.	.	43	13
	65	31,179	Alive	.	.	43	12
	66	34,563	Alive	.	.	43	11
	67	36,000	Alive	.	.	43	10
	68	36,000	Alive	.	.	43	9
	69	36,000	Alive	.	.	43	8
	70	36,000	Alive	.	.	43	7
	71	36,000	Alive	.	.	43	6
	72	36,000	Alive	.	.	43	5
	73	36,000	Alive	.	.	43	4
	74	36,000	Alive	.	.	43	3
	75	36,000	Alive	.	.	43	2
	76	36,000	Alive	.	.	43	1
	77	36,000	Alive	.	.	43	0

Appendix: survival table for 3-year survival (both sexes), part 2/3

Sarcopenic	1	,000	Dead	,960	,039	1	24
	2	,296	Dead	,920	,054	2	23
	3	,526	Dead	,880	,065	3	22
	4	2,103	Alive	.	.	3	21
	5	3,975	Dead	,838	,074	4	20
	6	4,501	Dead	,796	,081	5	19
	7	4,534	Alive	.	.	5	18
	8	6,834	Dead	,752	,088	6	17
	9	6,965	Dead	,708	,093	7	16
	10	7,359	Alive	.	.	7	15
	11	7,721	Dead	,661	,098	8	14
	12	8,739	Alive	.	.	8	13
	13	8,838	Dead	,610	,103	9	12
	14	10,382	Alive	.	.	9	11
	15	11,269	Dead	,554	,108	10	10
	16	12,057	Alive	.	.	10	9
	17	13,339	Alive	.	.	10	8
	18	16,657	Dead	,485	,114	11	7
	19	19,088	Dead	,416	,117	12	6
	20	20,238	Dead	,346	,116	13	5
	21	21,322	Alive	.	.	13	4
	22	26,218	Alive	.	.	13	3
	23	36,000	Alive	.	.	13	2
	24	36,000	Alive	.	.	13	1
	25	36,000	Alive	.	.	13	0

Appendix: survival table for 3-year survival (both sexes), part 3/3