Universidade de Lisboa

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BODY COMPOSITION AND CLINICAL OUTCOME IN PATIENTS WITH GASTROINTESTINAL CANCER AND CROHN´S DISEASE

Sónia Denise Ferreira Velho

Orientador(es): Professora Doutora Marília Lopes Cravo

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Tese especialmente elaborada para obtenção do grau de Doutor em Ramo de Ciências e Tecnologias da Saúde, especialidade de Nutrição

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2024

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"A impressão desta tese foi aprovada pelo Conselho Científico da Faculdade de Medicina de Lisboa em reunião de 17 de setembro de 2024."

ABSTRACT/SUMÁRIO

ABSTRACT

This thesis aims to explore the intricate role of body composition in chronic inflammatory diseases as gastrointestinal cancer and Crohn's disease. The relationship between sarcopenia, visceral obesity and outcomes varies within different contexts of GI cancers, emphasizing the need for tailored studies addressing its clinical significance based on disease stage and treatment plans. Additionally, geographical variations in obesity prevalence and dietary patterns further highlight the complexity of these relationships.

The impact of adiposity-related phenotypes, such as sarcopenic obesity and low muscle radiation attenuation, remains underexplored. Through retrospective studies focusing on gastric and pancreatic cancers, we observed the negative influence of adiposity-related phenotypes. These observations emphasize the importance of utilizing informative techniques like CT-scan body composition analysis, which can capture these phenotypes overlooked by traditional methods like anthropometry and bioimpedance analysis. Furthermore, we identified a dietary pattern potentially protective of sarcopenia and pursued an intervention study which demonstrated that a multimodal intervention with combined exercise and diet is feasible and may have beneficial effects on body composition and weight in cancer patients undergoing neoadjuvant treatment.

In parallel, our research delved into the influence of body composition on Crohn's disease (CD) phenotypes, given the significant variability in disease progression among patients. Our studies revealed that adiposity-related phenotypes, particularly visceral fat index and low muscle radiation attenuation, were predominantly associated with the risk of complicated CD. Additionally, longitudinal analyses demonstrated that visceral obesity was associated with a 5-fold increase in the risk and shorter time until abdominal surgery.

In conclusion, our thesis underscores the importance of considering body composition in understanding disease outcomes in GI cancers and Crohn's disease. By elucidating these complex relationships, we aim to contribute to more personalized and effective management strategies for patients with these conditions.

Keywords

Cancer, Crohn's Disease, Body composition, Diet, Exercise

SUMÁRIO

Nos últimos anos, tem sido observada uma mudança importante nos padrões alimentares, amplamente influenciada pelo crescimento económico e pela globalização, e que deu origem ao que é vulgarmente conhecido como a dieta ocidental. De acordo com a Organização Mundial da Saúde, em 2022, a prevalência a nível mundial de pré-obesidade era de 43%, enquanto a obesidade se situava nos 16%. No que diz respeito à obesidade, uma tendência preocupante tem sido observada, uma vez que a sua estimativa em 2022 corresponde aproximadamente ao dobro da prevalência mundial da obesidade em 1990. A dieta ocidental e o seu respetivo estilo de vida, predispõem para o aumento de peso e podem desencadear um estado de inflamação sistémica crónica de baixo grau. A inflamação sistémica é uma característica conhecida dos distúrbios relacionados com a obesidade e um fator de risco reconhecido para várias doenças não transmissíveis (DNTs), incluindo a resistência à insulina, diabetes tipo 2, síndrome metabólica, cancro, distúrbios respiratórios, autoimunes e relacionados ao sistema imunológico (por exemplo, doença de Crohn), artrite e depressão. Durante o curso da doença, a transição da obesidade/pré-obesidade para a desnutrição/caquexia pode ocorrer, gerando um espectro de condições nutricionais e fenótipos de composição corporal, que podem ser determinantes para o *outcome* clínico destas doenças. Nas últimas décadas, os avanços nas técnicas de composição corporal, que permitem uma avaliação precisa dos fenótipos de composição corporal, permitiram aprofundar os conhecimentos a este respeito. Esta tese, tem por objetivo investigar o papel das especificidades da composição corporal no cancro gastrointestinal e na doença de Crohn e qual a sua relação com o prognóstico das várias patologias.

No que diz respeito ao cancro gastrointestinal, nos últimos anos, diversos estudos têm identificado a sarcopenia como um preditor independente de sobrevida global. No entanto, as evidências atuais demonstram a existência de particularidades dentro dos diferentes tipos de cancro gastrointestinal relativamente à associação entre a sarcopenia e o desfecho clínico, o que fundamenta a necessidade de estudos direcionados para abordar o seu significado clínico em contextos específicos nomeadamente num determinado estadio da doença e plano

terapêutico. Além disso, estas particularidades podem ser específicas da região geográfica, uma vez que a pandemia da obesidade tem tido um impacto com diferentes proporções a nível mundial. A influência da adiposidade no resultado clínico tem sido substancialmente menos estudada. Nesta tese começamos por realizar estudos retrospetivos, que incidiram sobre o cancro gástrico devido à sua elevada taxa de mortalidade em Portugal e o cancro do pâncreas, que apesar dos notáveis avanços no seu tratamento permanece com uma sobrevida a 5 anos excessivamente baixa, prevendo-se que a sua incidência aumente a um ritmo acelerado no Mundo Ocidental.

1. No primeiro estudo que incluiu doentes com cancro gástrico sob quimioterapia neoadjuvante, para além de confirmar a relação com a sarcopenia, observou-se um risco aumentado de interrupção da quimioterapia por toxicidade, associado a fenótipos relacionados com a adiposidade como a obesidade sarcopenica e a baixa atenuação radiológica da massa muscular. Este estudo foi um dos primeiros no qual foi utilizada a metodologia relativa à avaliação da composição corporal tendo por base imagens de Tomografia Axial Computorizada (TAC) e como tal foi importante no desenvolvimento e integração desta técnica. Assim, este estudo contribuiu para aprofundar o conhecimento a respeito das particularidades da composição em doentes com cancro gástrico, num momento em que existia pouca informação a esse respeito.

2. No segundo estudo retrospetivo que incidiu sobre uma população de doentes com cancro pancreático ressecável, verificou-se que o rácio da área do tecido adiposo visceral: tecido muscular esquelético, que é um parâmetro associado à obesidade sarcopenica, demonstrou estar significativamente associado ao risco de complicações pós-operatórias e à sobrevivência aos 90 dias. Neste estudo observou-se também uma associação significativa entre a atenuação muscular e a sobrevivência global. Estes resultados suportam a necessidade de técnicas informativas e precisas como a análise da composição corporal por TC, uma vez que estes fenótipos, tais como a atenuação radiológica da muscular, podem ser negligenciados por outros métodos como antropometria e análise por bioimpedância, como tivemos oportunidade de observar, após a comparação destas diferentes técnicas no estudo prospetivo seguinte.

3. Posteriormente, foi realizado um estudo prospetivo em doentes com cancro gastrointestinal, no qual abordamos o papel da dieta em relação ao risco de desenvolver sarcopenia, uma vez que uma melhor compreensão desta associação pode permitir intervenções dietéticas otimizadas. Historicamente, Portugal está associado a uma dieta mediterrânica, com as suas particularidades devido à sua proximidade geográfica com o mar. Embora o padrão alimentar identificado como protetor da sarcopenia, inclua alimentos da dieta mediterrânica, como o azeite e o peixe, não foi encontrado um padrão mediterrâneo explícito, e alimentos ricos em gordura saturada também foram identificados no âmbito deste padrão protetor, mas presumivelmente em menor quantidade.

4. Prosseguiu-se para a implementação de um estudo de intervenção com o objetivo de avaliar a adesão, às intervenções dietéticas e ao exercício físico durante o tratamento neoadjuvante. Selecionamos este contexto clínico porque tínhamos como hipótese que poderia ser uma janela de oportunidade para melhorar a composição corporal dos doentes oncológicos, aumentando assim a reserva fisiológica para lidar com o stress cirúrgico. De facto, foi possível demonstrar que a adesão à nossa intervenção foi razoavelmente elevada e que terá potenciais benefícios no peso e na composição corporal.

Simultaneamente, investigámos a influência da composição corporal no fenótipo da doença de Crohn (DC), dada a acentuada heterogeneidade na progressão desta doença. Os estudos foram realizados, sob a premissa de que um maior conhecimento dos fatores preditivos que contribuem para esta heterogeneidade, pode melhorar o tratamento da DC, particularmente no que toca à decisão de iniciar tratamentos farmacológicos mais intensivos, cuja indicação deve estar reservada a doentes com maior risco de desenvolver doença complicada. A gordura mesentérica, também conhecida como “creeping fat”, tem sido reconhecida como uma característica da DC, mas o seu papel preciso na etiopatogenia e evolução da doença permanece pouco esclarecido. A gordura mesentérica tem sido associada a efeitos prejudiciais e benéficos na progressão da DC, e persiste incerteza quanto à sua presença no diagnóstico versus o seu desenvolvimento durante a progressão da doença. O paradigma do estado nutricional dos pacientes com DC tem sofrido uma evolução significativa nas últimas décadas, em grande parte devido ao aparecimento da terapêutica com biológicos no início dos anos

2000, que melhoraram substancialmente a questão da desnutrição através da melhoria do tratamento da DC. Isto, juntamente com o aumento global na prevalência de obesidade, levou a um aumento notável nas taxas de obesidade nos pacientes com DC.

5. O primeiro estudo retrospetivo realizado no âmbito da DC, teve por objetivo examinar a composição corporal e caracterizar esta população em relação aos diferentes fenótipos e explorar sua associação com a probabilidade de desenvolver doença complicada. Neste estudo observou-se que em comparação com os parâmetros associados à musculatura, os fenótipos associados à adiposidade, como o índice de gordura visceral e a baixa atenuação radiológica da massa muscular, estavam predominantemente ligados ao risco de doença complicada, estenosante ou perfurante. No entanto, devido ao desenho do estudo não foi possível aferir se as alterações da composição corporal estavam presentes no diagnóstico ou se seriam consequência da progressão da doença. Por esse motivo foi realizado um segundo estudo longitudinal prospetivo que incluiu apenas doentes nos quais era possível avaliar a composição corporal no diagnóstico.

6. No segundo estudo que incluiu doentes com diagnóstico recente de CD, observámos que as alterações na composição corporal estão de facto presentes no diagnóstico e foi ainda possível perceber que a adiposidade corporal total e a obesidade visceral estão associadas ao aparecimento de fenótipos complicados da doença e a uma necessidade de cirurgia mais precoce, respetivamente. Na análise longitudinal, observamos um aumento significativo nos parâmetros associados à musculatura e à adiposidade nos doentes com evolução desfavorável da doença. No entanto, o aumento foi notavelmente mais pronunciado para a gordura corporal total, mostrando um aumento de aproximadamente quatro vezes ao longo do tempo de estudo.

Os estudos realizados, tanto a nível do cancro gastrointestinal como na DC, demonstraram que as medidas de adiposidade foram principalmente relacionadas com um pior resultado clínico. Este efeito reforça a necessidade de avaliações da composição corporal por TC, uma vez que certos fenótipos, como a atenuação radiológica da massa muscular, só podem ser detetados por técnicas de imagem. Dada a relevância das informações fornecidas por esta técnica,

acreditamos que a sua integração na prática clínica, pode ter o potencial para otimizar o plano de cuidados destes doentes. Em meio hospitalar, os nutricionistas podem ser treinados para realizar essa tarefa e reportar os resultados à equipa multidisciplinar, bem como traduzi-los em planos alimentares personalizados.

Palavras-chave: Cancro, Doença de Crohn, Composição Corporal, Dieta, Exercício.

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PROLOGUE AND ACKNOWLEDGMENTS

My journey began during my final years of my degree in Nutrition Sciences when I had the privilege of being supervised by Professor Pedro Marques Vidal. His ability to simplify and explain research methods sparked my interest in biostatistics and research in the field of Nutrition. Professor Marques Vidal's mentorship laid the foundation for my development in these areas, and I am deeply grateful for his inspiration.

Continuing my education with a Master's degree in Clinical Nutrition at Faculdade de Medicina de Lisboa in 2002, I had the opportunity to work with Professor Marques Vidal once again, as well as with other influential figures like Professors Ermelinda Camilo and Marília Cravo. Realizing the importance of clinical research in nutrition, I am thankful to Professor Camilo for her support in clarifying my career direction.

Reaching out to Professor Marília Cravo marked the beginning of an incredible journey. Her unwavering support, both professionally and personally, has been invaluable. I am profoundly grateful for her guidance and mentorship, which have had a profound impact on my life and career. Being part of Professor Cravo's research group is an honour, and I cannot express enough gratitude for her belief in me and her extraordinary guidance.

I had the pleasure of meeting Professor Vickie Baracos at the 36th European Society of Parenteral and Enteral Nutrition (ESPEN) conference in Geneva in 2014. I was truly amazed by Professor Baracos's scientific expertise and generosity. Her guidance was vital in implementing the technique of body composition assessment using CT scan images. Without her insights and support, the studies in my doctoral thesis would not have been possible. I am deeply grateful to Professor Baracos for her guidance and knowledge, which have been instrumental in my research journey.

I also want to express my gratitude to the individuals who have supported and facilitated the studies herein presented. During the development of these studies, I was fortunate to work at Hospital Beatriz Ângelo (HBA) under the leadership of Professor Rui Maio, who served as the

clinical director at the time. Professor Maio's support for research in clinical nutrition was essential in motivating me to pursue this PhD, and for that, I am deeply grateful. I would also like to extend my appreciation to the members of the board administration at that time, including Dr. Artur Vaz, Dr. Francisco Mota, and Engenheira Isabel Vaz, for creating the necessary conditions to conduct these studies. A heartfelt thank you goes to Marisa Raposo, whose inspirational leadership and support were precious at the beginning of this journey. I am also grateful to Cátia Calisto for enabling the continuity of this work and to Carolina Santo for her support until the end. I will always be thankful to each of them for allowing me to develop my skills and contribute to this field. Furthermore, I would like to thank Dr. Luísa Gloria, the head of the Department of Gastroenterology at Hospital Beatriz Ângelo, for her support and guidance throughout this endeavor. Their contributions have been integral to the success of these studies, and I am truly grateful for their assistance and encouragement. I would like to extend my gratitude to Prof. Paula Pereira and Prof. Renata Ramalho for their support.

The Department of Radiology played a crucial role in advancing this work, and I am immensely grateful for their contributions. I extend my sincere thanks to Dr. João Stretch, who served as the head of the department at the time, for his leadership and support. I would also like to express my gratitude to Dr. Rita Cruz and Dr. Lisa Agostinho for their efforts in operationalizing computed tomography image selection and postprocessing validation. Their dedication and expertise were vital to the success of this project.

Special recognition is also due to gastroenterologists Carolina Palmela, Maria Pia Santos, and Barbara Morão for their valuable work in creating databases related to gastric cancer, pancreatic cancer, and Crohn’s disease studies. Their contributions have been instrumental in expanding our understanding of these conditions. I am deeply thankful to Prof. Joana Torres for her guidance and thoughtful suggestions throughout this journey. Her expertise and support have been precious, and I am grateful for the impact she has had on this research.

I would like to express my gratitude to Professor José Passos Coelho, the head of the Oncology department at Hospital da Luz, for providing valuable feedback. I am also thankful to Dr. José

Alberto Teixeira, head of the Oncology department at Hospital Beatriz Ângelo, for his support and patient referrals. I extend my appreciation to the oncologists who participated in data collection, including Dr. Fábio Lopes, Dr. João Godinho, and Dr. Luísa Leal da Costa. Their dedication has been essential to the progress of our research. I am grateful to the nursing team, particularly Chief Nurse Sónia Caixeirinho, Nurse Pedro Vivas, Nurse Ana Helena, and Nurse Ana Rosado, for their important support throughout the intervention study. Also, this study greatly benefited from the expertise of the Physical Medicine and Rehabilitation Department, under the leadership of Dr. Ana Borges. I extend special thanks to physiotherapists Claudia Abreu, Rute Alves, and head physiotherapist Filipa Pires for their brilliant contributions. I also want to acknowledge the efforts of my colleagues Sara Moço, Carolina Capitão, and Mariana Branco for their collaboration has been invaluable to the success of this research endeavour. Also, I would like to express my appreciation to all patients who participated in our studies, to whom I am truly grateful.

I want to express my deepest gratitude to my beloved friends and family, who have been my pillars of strength throughout this journey. To my mother, Maria José Ferreira Velho, your unwavering love, support, and patience have been a constant source of comfort and motivation. I am endlessly grateful for your encouragement and understanding, which have guided me through every challenge. To my sister, Sara Velho, for all your support, you have been our family's rock, your commitment has made this achievement possible, I am truly grateful. To my father, Olimpio Velho, your joy, and encouragement have given me the resilience needed to persist in every challenge. I also extend my gratitude to my parents and sister-in-law, António, Otilia, and Teresa Vilar, whose support has been crucial in seeing this project through to completion.

Last but certainly not least, I want to extend my heartfelt appreciation to Carlos Vilar. His expertise, patience, understanding, and belief in me have guided me throughout this challenging journey. His endless support, both emotionally and practically, has been instrumental in achieving this milestone. To my son Simão, you are my greatest joy and source of inspiration. You have my heart, always, and I am grateful for the happiness you bring into my life.

ABBREVIATIONS

5-FU,5-fluorouracil

6MWT-6 min walking test

AM- Anthropometric measures

ASA, American Society of Anaesthesiologists

AT, Adipose Tissue

AUC, Area Under the Curve

BAT, Brown Adipose Tissue

BIA, Bioelectrical Impedance Analysis

BIVA, Bioelectrical Impedance Vector Analysis

BMI, Body Mass Index

CD, Crohn's Disease

CDS, Carbohydrate Specific Diet

CEDI, Combined Exercise and Dietary Intervention

CI, Confidence Interval

CRP, C Reactive Protein

CT, Computed Tomography

CTE, Computed Tomography Enterography

DALYS, Disability Adjusted Life Years

DEXA, Dual-energy X-ray absorptiometry

DLT, Dose-Limiting Toxicity

ECF, Epirubicin, Cisplatin, and infused 5-Fluorouracil

ECOG, Eastern Cooperative Oncology Group

EEN, Exclusive Enteral Nutrition

E-MRI, Entero Magnetic Resonance

EORTC, European Organization for Research and Treatment of Cancer

EPA, Eicosapentaenoic Acid

ES, Effect size

ESPEN, European Society of Parenteral and Enteral Nutrition

EWGSOP, European Working Group on Sarcopenia in Older People

FFQ, Food Frequency Questionnaire

FO, Favourable Outcome

FODMAP, Fermentable Oligosaccharides, Disaccharides, Monosaccharides and Polyols

GC, Gastric Cancer

GEJ, Gastroesophageal Junction

GI, Gastrointestinal

HBA, Hospital Beatriz Ângelo

HR, Hazard Ratio

HU, Hounsflield Units

IL, Interleukin

IQR, Interquartile Range

KMO, Kaiser-Meiyer-Olkin

LPS, lipopolysaccharide

MAFBx, Muscle Atrophy F-box

MCP-1, Monocyte Chemoattractant Protein-1

MRI, Magnetic Resonance Imaging

mTOR, mechanistic/mammalian target of rapamycin

MUFA, Monounsaturated Fatty Acids

MuRF1, Muscle Ring Finger 1

NAC, Neoadjuvant Treatment

NCD, Non Communicable Diseases

NF-Kβ, Nuclear Factor-Kβ

NPV, Negative Predictive Value

OR, Odds Ratio

PCA, Principal Component Analysis

PEN, Partial Enteral Nutrition

PG-SGA- Patient Generated Subjective Global Assessment

PPARγ, Peroxisome Proliferator-Activated Receptor Gamma

PPV, Positive Predictive Value

PUFA, Polyunsaturated Fatty Acids

ROC, Receiver Operating Characteristic

ROS, Reactive Oxigen Species

SAT, Subcutaneous Adipose Tissue

SCFA, Short-Chain Fatty Acid

SFA, Subcutaneous Fat Area

SMA,Skeletal Muscle Area

SMI, Skeletal Muscle Index

SO, Sarcopenic Obesity

SPSS, Statistical Package for Social Sciences

TLR, Toll Like Receptors

TNF-α, Tumor Necrosis Factor-α

UO,Unfavourable Outcomes

VAT, Visceral Adipose Tisse

VFA, Visceral Fat Area

VFA:SMA ratio, Visceral Fat Area-to- Skeletal Muscle Area ratio

VFI, Viscera Fat Index

WAT, White Adipose Tissue

CHAPTER 1

INTRODUCTION

I. Background

In recent years, the global shift in dietary patterns, largely influenced by economic growth and globalization, has given rise to what is commonly known as the Western Diet[1]. This dietary transition involves increased consumption of refined carbohydrates, sugar, saturated fat, sodium, coupled with a decreased intake of essential nutrients, fiber, vitamins, minerals, and plant-based bioactive compounds. The western diet is characterized not only by excessive calorie intake but also by a substantial reliance on processed foods, fast food, additives, snacks, and sugary soft drinks, often accompanied by a sedentary lifestyle[2]. Hence, the western diet exhibits a high energy density and elevated glycemic index, which inadvertently promotes rapid weight gain, thereby enhancing overweight, obesity development and related diseases as the metabolic syndrome, among others[2].

The global prevalence of pre-obesity and obesity estimates of the World Health Organization in 2022, was of 43% and 16%, respectively. A concerning trend has been observed regarding obesity as its global prevalence has doubled since 1990. In Portugal, the situation is noteworthy, with approximately 28.7% of the adult population classified as obese and 39.1% as overweight[3]. The significant repercussions of obesity contribute to 9% of mortality and 7.9% of Disability Adjusted Life Years (DALYs), while inadequate dietary intake alone is associated with 11.4% of mortality and 7.3% of DALYs in Portugal[4]. This problem contributes to 86% of the total disease burden, particularly due to its links with diabetes mellitus, hypertension, and cardiovascular diseases, the later responsible for 29.7% of all deaths in 2015[4].

The process of weight gain, driven by sustained positive energy balance, manifests at the cellular level through the storage of excess energy as triglycerides in adipocytes[5]. This can lead to cell hypertrophy and local hypoxia, impacting angiogenesis and increasing oxidative stress[6]. The activation of toll-like receptors (TLR) and the nuclear factor (NF)-kB pathway sets off an inflammasome, resulting in low-grade chronic systemic inflammation[6].

Notably, systemic inflammation isn't solely attributed to the western diet; other facets of the Western lifestyle, including increased exposure to pollution, microbial infections, and

heightened stress, can also trigger this inflammatory state[2]. Systemic inflammation is a known characteristic of obesity-related disorders and a recognized risk factor for various Non-Communicable Diseases (NCDs), such as insulin resistance, type 2 diabetes, metabolic syndrome, cancer, respiratory, auto-immune and immune-related disorders (e.g. Crohn's disease)[7], arthritis, and depression[8]. In addition, obesity-related disorders may be associated with the risk of gastrointestinal cancers, such as colorectal and pancreas[9,10], which reinforces the need to address risk factors like overweight and obesity in a preventive perspective.

Fighting obesity is crucial as this state can lead to an increase in proinflammatory adipokines, which elicit a proinflammatory cytokine response[11]. Chronic inflammation and insulin resistance create an ideal environment for disease promotion[11]. It's noteworthy that, although distinct, both obesity and cachexia, also prevalent in advanced chronic conditions, share common underlying mechanisms, including insulin resistance, adipose tissue lipolysis, skeletal muscle atrophy, and systemic inflammation[11]. By addressing body composition, particularly low muscle mass[12], excess body adiposity, and obesity, not only we decrease the incidence of obesity related chronic non-communicable as cancer, but also we may potentially improve outcomes once these diseases are present and treated.

1. Body composition assessment and phenotypes

1.1. Body composition assessment techniques.

Over the past decades, a robust scientific foundation has emphasized the importance of body composition assessment, associating it with clinical outcomes in patients with inflammatory chronic conditions[13–16], mostly neoplastic diseases. Various methods have been used for body composition assessment, including anthropometry, Bioelectrical Impedance Analysis (BIA), imaging techniques (computed tomography or magnetic resonance imaging), and Dual-energy X-ray absorptiometry (DEXA). A concise review of body composition techniques for inflammatory chronic diseases will be provided in this section.

1.1.1. Anthropometry and Bioelectrical Impedance Analysis

Anthropometry and BIA stand out as cost-effective and non-invasive techniques[17,18]. However, in patients with inflammatory chronic diseases, fluid imbalances[19,20] resulting from the disease, treatments, and the underlying conditions can challenge these methods due to their impact on electric conductibility[21]. Despite BIA being considered less reliable than DEXA[22], parameters like phase angle and Bioelectrical Impedance Vector Analysis (BIVA) have proven valuable in assessing patients with inflammatory chronic diseases, since they rely on raw impedance measures. Phase angle, indicative of cellular health, has been explored as a prognostic factor[23] and nutritional status indicator[24–27]. Moreover, BIVA aids in hydration status assessment and facilitates body composition analysis through comparisons with a reference population[28].

1.1.2. Dual-energy X-ray absorptiometry

DEXA, renowned for its accuracy and reproducibility, is considered the gold standard in body composition assessment[22,29]. It is a non-invasive and reliable technique suitable for tracking longitudinal body composition changes[30]. DEXA estimates of bone density and soft-tissue

composition are based on x rays beams[19], therefore using reduced radiation. Although recent developments have allowed to quantify visceral adipose tissue (VAT) with DEXA, yielding estimates highly correlated with imaging techniques, there are some issues regarding concordance[31]. Besides, other limitations include its inability to assess total water and ectopic fat depots within skeletal muscle.

1.1.3. Computed Tomography and Magnetic Resonance Imaging

In recent decades, imaging methods as CT and MRI have emerged as gold standards for body composition analysis in patients with inflammatory chronic diseases[22,32–35] who perform these exams for other clinical reasons. Initially developed for obesity research[36], these methods have been refined for patients with inflammatory chronic diseases, as cancer, providing detailed data on skeletal mass tissue quantity and quality, adipose tissue quantity and distribution (visceral, subcutaneous, and intramuscular). Imaging techniques, notably the analysis of CT scan images, have received acclaim for their informative capabilities, easily accessible through the opportunistic utilization of diagnostic exams performed for other reasons in cancer patients and/ or other chronic conditions.

Automated body composition assessment using CT imaging, validated for patients with inflammatory chronic diseases[37,38], employs image processing software, which is progressing by including artificial intelligence like neuronal networks and deep learning, to reduce human effort and integrate it into clinical practice[39,40,41]. CT images can be processed automatically based on tissue-specific Hounsfield Units (HU) thresholds, facilitating developments in this technique. MRI image processing is mostly manual and anatomy dependent.

Until now, body composition image analysis has mostly been based on the segmentation of a single slice at the third lumbar vertebrae level, since it strongly correlates with whole body composition[22]. However, more developments have been undertaken, aiming at using several CT images at the same time and identifying other valid locations to conduct body composition analysis, since not all patients have CT scans at the third lumbar vertebrae level, as well as to

investigate if this landmark correlates with body composition changes overtime. For instance, a recent study from Arribas L *et al.* demonstrated the need for precision studies when assessing body composition changes overtime. In their study with head and neck cancer patients, the rate of muscle loss was higher in the limbs, when compared with chest, abdomen and upper limbs[42].

Notably, CT scan imaging for body composition assessment has expanded to various inflammatory chronic diseases. All mentioned techniques are applicable to this population, and the same holds true regarding their methodological limitations. **Table 1** provides a summarized review of the pros and cons of different body composition techniques. In addition, evidence regarding the agreement between these methods remains limited. Since CT-derived body composition is conducted opportunistically, determining whether other parameters from methods as BIA or anthropometry provide concordat results, could improve nutritional assessment especially when CT is not feasible.

Imaging techniques as CT scan and MRI have become golden standards for body composition assessment, and these are the focus of this thesis, the subsequent exploration on the role of body composition in patients with inflammatory chronic diseases primarily centers on these methods. Moreover, body composition estimates derived from these imaging methods can play a valuable role in enhancing clinical decisions and tailoring nutritional interventions for patients dealing with chronic inflammatory diseases[39].

Methods	**Pros**	**Cons**
Anthropometry *E.g. body mass index, arm and calf circumference and arm muscle cross-sectional area as a function of arm muscle circumference and skinfold thickness*	Portable Low cost	Lacks precision. Expertise is required. Assess mostly adiposity. Influenced by hydration status. Estimates rely on equations, with substantial prediction error at an individual level.

Methods	Pros	Cons
Bioelectrical Impedance Analysis (BIA) *E.g. Free Fat Mass, Muscle Mass, Total Body Water, Intracellular Water, Extra Cellular Water, Phase Angle, Bioimpedance Vector Analysis*	Portable Low cost (depending on the device) Not much expertise is required	Estimates rely on equations (which are not available for most cancer locations). Influenced by hydration. Contraindicated in patients with implanted electronic devices (e.g. pacemaker).
Dual- energy X-ray absorptiometry *Fat mass, fat free mass, bone mineral content*	Accuracy and reliability Low radiation (compared with CT scans)	Unable to assess total body water. Expertise is required. Opportunistic use is not possible. High-cost device. Inaccessible to most patients. Correct positioning of obese and elderly patients may be challenging.
Imaging techniques *E.g., Skeletal muscle, visceral, subcutaneous, and intramuscular adipose tissue area, muscle radiation attenuation*	Very informative (e.g. allows the determination of muscle radiation attenuation- CT scans only) Opportunistic use	Radiation exposure limits longitudinal use (CT scans). Time consuming (MRI). Cost Expertise Accessibility

Table 1- Pros and cons of different body composition techniques.

1.2. Nutritional Status definitions and body composition phenotypes in cancer.

1.2.1. Malnutrition and cachexia

In a consensus paper issued by the European Society of Parenteral and Enteral Nutrition (ESPEN), malnutrition (synonym for undernutrition) is defined as a condition resulting from decreased intake or uptake, emphasizing altered body composition (decreased fat-free mass) and body cell mass leading to diminished physical and mental function, along with impaired clinical outcomes from disease[43]. Cachexia, a form of malnutrition, is classified as chronic disease-related malnutrition with inflammation, characterized by the loss of muscle mass, with or without the loss of fat mass[43]. Notably, the consensus also emphasizes the importance of body composition assessment in understanding these conditions. Fearon et al. introduced a groundbreaking definition in 2011, describing cancer cachexia as a "multifactorial syndrome characterized by ongoing loss of skeletal muscle mass (with or without loss of fat mass), which cannot be fully reversed by conventional nutrition support and leads to progressive functional impairment"[44]. This definition includes stages as pre-cachexia, cachexia, and refractory cachexia, with recent endorsement by the Global Leadership Initiative on Malnutrition (GLIM) as core criteria in diagnosing cancer cachexia[45].

1.2.2. Sarcopenia

Skeletal muscle is attached to bones, tendons and nerves and is responsible for voluntary movements, making it paramount for movement, posture, and stability. Besides this, skeletal muscle is important for heat production, glucose homeostasis (insulin sensitivity), organ protection, health, and well-being. This tissue is also known to act as an endocrine organ with the production of multiple myokines, one of the most studied being IL-6 and its anti-inflammatory effect[46].

Sarcopenia, initially defined as age-associated skeletal muscle deficiency[47], has been revised over the years. In 2010, the European Working Group on Sarcopenia in Older People (EWGSOP) characterized it as "a syndrome marked by progressive and generalized loss of skeletal muscle mass and strength, posing a risk of adverse outcomes as physical disability, poor quality of life, and death"[48]. A significant shift occurred in the 2018 revision, highlighting muscle strength as a key diagnostic criterion due to its technical feasibility and its role as a predictor of outcomes[49].

Clinical oncology research predominantly reports sarcopenia using muscularity measures from imaging techniques as Computed Tomography (CT) or Magnetic Resonance Imaging (MRI) scans. These techniques convey accurate data of skeletal mass tissue quantity and quality, adipose tissue quantity and distribution (visceral, subcutaneous, and intramuscular). Globally, in the most frequently used procedure, MRI or CT scan images are selected at L3 vertebrae level and are processed with a specific software which executes an automatic processing of tissue cross-sectional areas, based on Hounsfield unit (UH) thresholds: –29 to 150 for skeletal muscle, –190 to –30 for subcutaneous and intra-muscular adipose tissue and –50 to –150 for visceral adipose tissue (**Figure 3**). Afterwards manual corrections are conducted. Finally, specific thresholds are used to determine the different body composition phenotypes, whereas the most used are presented on **table 2**. Notably, there exists a broad spectrum of thresholds extending beyond those outlined here, coupled with a lack of consistency in both tissue-specific cutoffs and the reporting of body composition phenotypes.

Martin et al. cut-offs are widely used for determining CT or MRI-derived sarcopenia at L3 vertebrae [50]. Previously in 2008, sex-specific cut-offs were defined for a population of obese cancer patients by Prado et al.[51] with the same methodology, afterwards the sample was further increased by Martin et al. to compute sex and BMI specific thresholds (**table 2**). **Figure 4** illustrates processed CT images of cancer patients with and without sarcopenia.

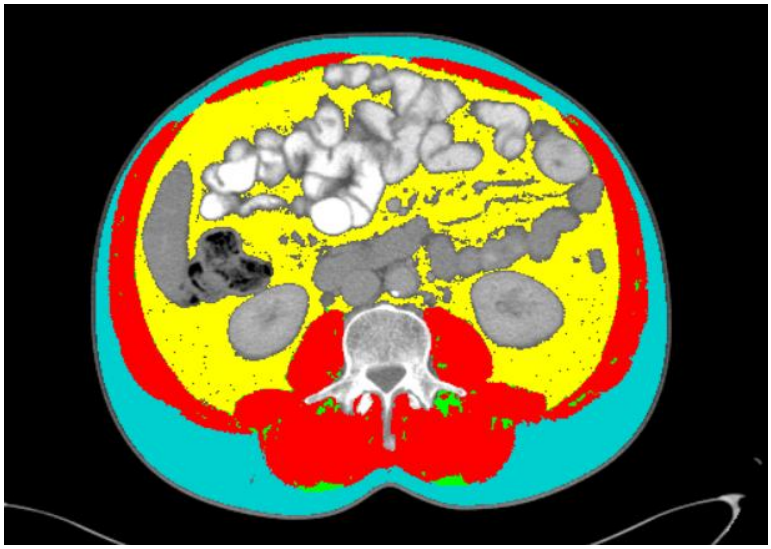

Figure 3- Processed Computed Tomography image at third lumbar vertebrae for body composition assessment. Psoas, paraspinal muscles, quadratus lumborum, rectus abdominis and obliques are segmented together with a red tag. Visceral, subcutaneous, and intramuscular adipose tissue are depicted in yellow, blue, and green tags, respectively.

Body composition Phenotype	Reference	Thresholds
Sarcopenia	[50]	M: SMI, <43 cm/m^2 if BMI <25 kg/m2, SMI <53 cm/m^2 if BMI ≥25 kg/m2 F: SMI<41 cm/m^2
	[51]	M: SMI <52.4 cm/m^2 F: SMI <38.5 cm/m^2
Low Muscle Radiation Attenuation	[50]	MA <41 HU, if BMI <25 kg/m^2, MA <33 HU, if BMI >25 kg/m^2
Visceral Obesity	[52]	M: VFA, 124.3-163.8 cm^2 F: VFA, 80.1-173.0 cm^2
	[53]	M: VFI, 38.7 cm^2/m^2 F: VFI, 24.9 cm^2/m^2

Table 2-Most frequently used thresholds to determine body composition phenotypes, based on L3 Computed Tomography scan. M-Male, F-Female, SMI-Skeletal Muscle Index, MA-Muscle Radiation Attenuation, VFA-Visceral Fat Area, VFI-Visceral Fat Index.

a) **b)**

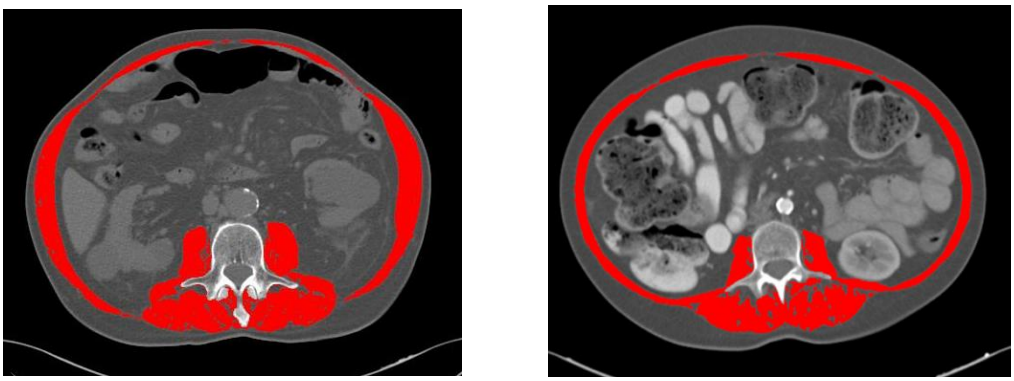

Figure 4- Skeletal muscle tissue area of a) non-sarcopenic and b) sarcopenic patient.

1.2.3. Sarcopenic obesity

Another noteworthy body composition phenotype is sarcopenic obesity, characterized by both low muscle mass quantity and excessive adiposity. While specific cutoffs for this phenotype are yet to be universally established[54,55], studies often define sarcopenic obesity using cutoffs from Martin et al.[50]and Prado et al.[51], combined with BMI to identify obese and overweight patients[52,55]. Additionally, measures such as visceral fat area, percentage body fat, and the ratio of total/visceral fat to total skeletal muscle have been employed to define sarcopenic obesity, with various studies proposing their own cut-offs [54,55].

1.2.4. Low muscle radiation attenuation

In addition to assessing muscle quantity, CT scan imaging techniques enable the analysis of muscle radiodensity. Myosteatosis, characterized by altered radiodensity due to ectopic fat depots within skeletal muscle, is identified using mean muscle radiation attenuation (HU), intramuscular adipose tissue, either alone or in conjunction with BMI. Previous studies have explored sex-specific cutoffs, as well as a single cutoff for both sexes[56]. **Figure 5** illustrates processed images of two cancer patients (A and B); although both have the same skeletal muscle area, patient A exhibits a higher proportion of low radiation attenuation muscle area,

indicating lower muscle density. **Table 3** presents the results from body composition analysis for patients A and B.

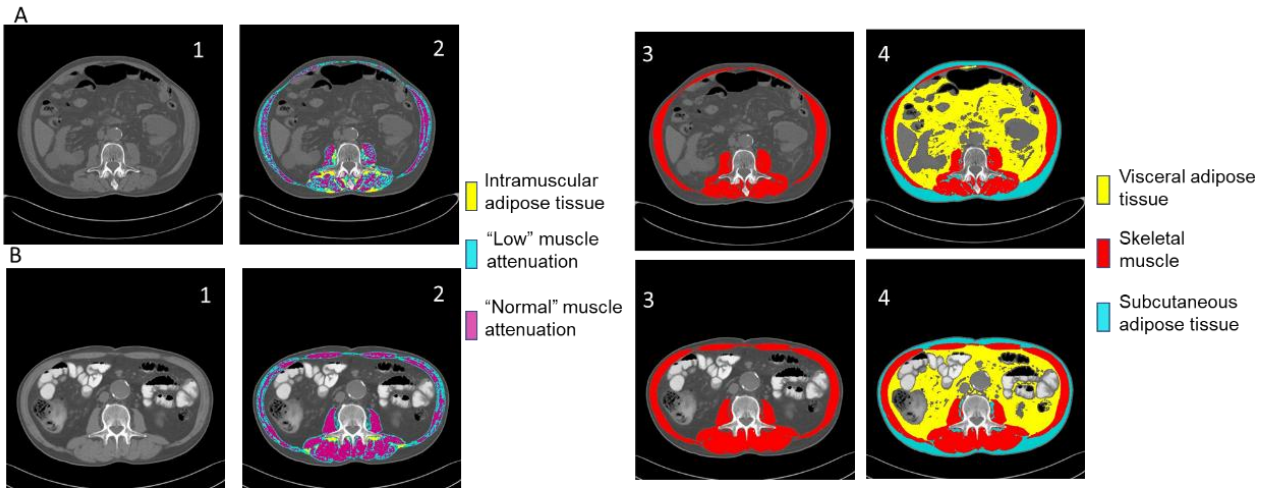

Figure 5- Body composition assessment of two cancer patients (A and B). 1) CT scan image at L3 without processing, 2) muscle density analysis, showing intramuscular adipose tissue, low and normal radiation attenuation areas, 3) skeletal muscle area, and 4) skeletal muscle, visceral and subcutaneous adipose tissue.

Patient	Visceral adipose tissue area	Subcutaneous adipose tissue area	Skeletal muscle area	Skeletal muscle area with low attenuation	% of skeletal muscle area	Intramuscular adipose tissue area	% of skeletal muscle area
A	284.8 cm^2	99.1 cm^2	134.2 cm^2	68.7 cm^2	51.2	10.3 cm^2	7.7
B	162.9 cm^2	65.0 cm^2	134.2 cm^2	51.2 cm^2	38.2	3.4 cm^2	2.5

Table 3- Results from body composition analysis for patient A and B based on images shown on **Figure 5**.

1.2.5. Visceral Obesity

White Adipose Tissue (WAT) is broadly divided in subcutaneous adipose tissue (SAT) and visceral AT (VAT) based on its location, under the skin or surrounding internal organs,

respectively[57]. VAT is found in the abdominal cavity and can be divided in mesenteric, omental, perirenal and peritoneal depots[58]. SAT and VAT differ in relation to their venous draining system and metabolic activity. Compared with SAT, VAT is known to be a more important risk factor for metabolic syndrome, hepatic steatosis, cardiovascular disease, and insulin resistance. This may be attributed to VAT localization, which favors drainage of fatty acids and inflammatory molecules produced by VAT into the portal vein, therefore reaching the liver in high concentrations, this is known as "the portal theory". In contrast SAT drains to the vena cava and thus to systemic circulation[57]. However this theory has been challenged in previous studies and is therefore not straightforward[59].

AT can produce several molecules, named adipokines, which impact glucose homeostasis and metabolic health, through an endocrine, autocrine, or paracrine action. Adipokine secretion appears to be distinct depending on its location (e.g. VAT vs. SAT) and may also vary according to type of adipocyte size and number[60]. Adipokines participate in inflammation modulation since they can have an anti-inflammatory or pro-inflammatory nature. VAT is associated with higher production of pro-inflammatory adipokines such as Retinol Binding Protein 4 (RBP4), TNF-α, MCP-1, IL-8, and IL-6[59], whereas SAT has a greater production of adipokines such as leptin and adiponectin.

Concerning visceral obesity, various cutoffs have been employed in prior studies. Visceral obesity is defined by a visceral fat area >100[61] or >130 cm^2[62], a ratio of visceral fat to subcutaneous fat >0.4[63], gender-specific visceral fat area[52], or visceral fat index cutoffs[53]. It is important to note that these cutoffs were primarily determined with focus on the metabolic risk associated with visceral fat and are not disease specific. Consequently, they have been applied in various clinical contexts[61,63–65].

2. Gastrointestinal Cancer.

Cancer rates are rising globally, with gastrointestinal (GI) cancers accounting for over a quarter of all cancer cases[66]. This phenomenon has been attributed to an increase and ageing of the

population, as well as to human development which entails a shift to less healthy dietary habits and lifestyle, obesity, smoking and alcohol consumption, among others[67]. GI cancer profoundly impacts nutritional status, thus predisposing these patients to be at higher nutritional risk. The presence of a tumor in the digestive tract, or the anatomic remodeling due to surgery, can precipitate mechanic and physiological alterations to its functioning[68]. The dysfunction and inflammation of the gastrointestinal tract due to the tumor can hinder the intake of food and the absorption of nutrients, resulting in symptoms such as dysphagia, pain, and vomiting. For instance, patients with gastroesophageal, colon and pancreatic cancer may be obese at diagnosis and experience significant weight loss, potentially causing various body composition changes as disease progresses, ultimately leading to undernutrition/cachexia[68]. This section provides an overview of gastrointestinal cancer, the impact of body composition in outcomes, and intervention strategies aiming at preserving/improving nutritional and functional status.

2.1. Epidemiology

Recent global estimates indicate that in 2020, there were 19.3 million new cancer cases diagnosed and approximately 10.0 million cancer deaths[69]. Gastrointestinal cancers, including colorectal, liver, pancreatic and gastric cancer, are ranked among the top five cancers with higher mortality[69]. Projections for 2040 suggest a 47% increase in the global burden of cancer reaching 28.4 million cases, with a more pronounced rise in transitioning countries (64% to 95%), then transitioned countries (32% to 56%)[69]. This surge is attributed to demographic changes and risk factors associated with globalization and growing economy.

In 2020, Portugal recorded 60 467 new cases and 30 168 cancer-related deaths[70]. Specifically, the number of new cases (NC) versus deaths (D) for digestive tumors was as follows: colon (NC:5367 vs D:2972), gastric (NC:2950 vs. D:2332), pancreas (NC:1792 vs. D:1770) and esophagus (NC:683 vs. D:588). Gastrointestinal cancer held the leading position in cancer diagnosis in Portugal in 2019[71].

Estimates propose that 30-50% of all cancers could be prevented by lifestyle changes[72], leading to a reduction in cancer incidence. Adopting a favorable lifestyle has been associated with a 40% lower risk of cancer mortality compared to unfavorable lifestyles[73]. These lifestyle

changes encompass increased fruit, vegetables and wholegrains intake and reduced consumption of red and processed meats, physical activity, maintaining an appropriate body weight, and abstaining from tobacco and alcohol[72]. Adherence to recommendations, reduces the risk of gastrointestinal cancers, among others, and may even be more beneficial in those with higher genetic risk[72].

Furthermore, existing evidence supports diet and exercise as modifiable factors with the potential to reduce the likelihood of cancer mortality[74]. Notably, both interventions are linked with body composition, which has been found to be associated with cancer patients' outcome. This supports the hypothesis that lifestyle changes may play an important role both in cancer prevention, as well as benefit patients during anticancer treatments and survivorship.

2.2. Causes and pathophysiology.

Gastrointestinal cancers affect multiple digestive organs, driven by an interplay of genetic and environmental factors like age, tobacco use, alcohol, diet, and obesity. It manifests when mutations disrupt essential gene functions regulating cell growth, programmed cell death (apoptosis), and cellular differentiation, consequently leading to aberrant and uncontrolled cell proliferation[75]. Extensive laboratory and clinical investigations have delineated various contributors to neoplastic transformation, encompassing hereditary susceptibilities, exposure to carcinogenic agents, chronic inflammatory states, and the accrual of sporadic mutations and epigenetic alterations over time[75]. For instance, exposure to carcinogenic agents can result from dietary intake. Nitrites that are used as preservatives in processed meats, can be converted to N-nitrosamines by gastric bacteria and by gastric acid secretion. N-nitrosamine is a genotoxic substance proven to be associated with increased risk of esophagus, gastric and colorectal cancer[76].

Furthermore, chronic inflammation of gastrointestinal tissues may also increase the risk of gastrointestinal cancer. Inflammation can be promoted by infections (e.g. chronic gastritis by *Helicobacter pylori*), recurrent chemical abrasion (e.g. gastroesophageal reflux disease) or

enzymatic damage (e.g. chronic pancreatitis) or immunity related diseases (e.g.Crohn's disease)[75].

There are several underlying mechanisms linking inflammation to neoplastic transformation. Increased levels of highly reactive oxygen and nitrogen species (ROS and RNS) produced by inflammatory cells, can damage RNA, DNA, lipids, and proteins, thus causing mutations and alterations in protein functions, which have been implicated in neoplastic transformation. Immune mediators (cytokines, e.g. TNFα, IFNγ, and IL-6 and chemokines, e.g. CXCL8, CXCL12) produced by inflammatory cells have also demonstrated to stimulate growth and metastasis of tumors. These mediators exert a paracrine and autocrine effect thereby promoting cell proliferation and migration, apoptosis inhibition, stromal degradation and elicit angiogenesis[75]. Moreover, tumor-derived immune mediators can further contribute to the immune response, by inhibiting normal surveillance mechanisms, such as those targeting neoplastic cells. Additionally, immune cell infiltration in the tumor milieu can result in the degradation of stromal elements, facilitating the migration and spread of neoplastic cells[75].

Eicosanoids, lipid signalling molecules produced by tumor cells and surrounding cells, are linked to cancer development[77]. They originate from arachidonic acid metabolism via pathways like cyclooxygenases (COX) and lipoxygenases (LOX), leading to products such as prostaglandins and leukotrienes[77]. Prostaglandin E2, for example, promotes cell proliferation and metastasis. Eicosanoids also trigger inflammation and can generate reactive compounds that damage DNA, potentially initiating or advancing cancer[77].

Most gastrointestinal cancers are of sporadic nature, thereby developing throughout one's lifetime. The underlying hypothesis is that accumulation of random DNA mutations at some point result in neoplastic transformation. However, certain exposures, habits, diets, among others, can modulate the risk of gastrointestinal cancer. Particularly, the western diet is related to an increased risk of colorectal cancer, whereas increased salt intake has been shown to be linked with the risk of gastric cancer. Additionally, obesity has been related to an increased risk of gastrointestinal cancers[78]. Excessive weight and adiposity can result in elevated concentrations of free fatty acids, leptin, plasminogen activator inhibitor 1 (PAI-1), tumor

necrosis factor α (TNF-α), and resistin, while concurrently reducing levels of adiponectin. This imbalance contributes to insulin resistance and higher concentrations of insulin-like growth factor-binding protein 1 (IGFBP1) and IGFBP2[78], which can inhibit apoptosis and promote cell proliferation[78]. Additionally, obesity promotes a low-grade chronic systemic inflammation, characterized by elevated inflammatory cells and proteins within white adipose tissue. Inflammation serves as a hallmark of cancer, supported by evidence from both experimental models and epidemiological studies, which corroborate a causal relationship between inflammation and the development of cancer[5].

2.3. Gastrointestinal cancer diagnosis and treatments.

The therapeutic arsenal for GI cancers encompasses a range of modalities as surgery, radiation therapy, and systemic treatments namely chemotherapy, targeted therapy and immunotherapy, or a strategic combination of these modalities. Treatment selection depends on factors such as the tumor's location, histological type, stage, the patient's overall health status (e.g. comorbidities, physiological reserve) and individual preferences.

Surgery often plays a primary role in managing localized GI cancers, aiming to remove the tumor and any adjacent/regional lymph nodes containing cancer cells. Chemotherapy and radiation therapy may be administered before or after surgery to reduce tumor size, eradicate residual cancer cells, or alleviate symptoms. The introduction of targeted therapies and immunotherapies has transformed the management of advanced or metastatic GI cancers, offering selective targeting of cancer cells or enhancing the body's immune response against tumors.

Despite significant advances in gastrointestinal cancer treatments leading to improved survival rates, the incidence and mortality of this disease remains high. Variability in treatment response and overall quality of life persists, prompting exploration into potential factors, such as body composition, that may contribute to explain this diversity.

2.4. Body composition and clinical outcome in gastrointestinal cancers.

2.4.1. Survival

- Sarcopenia

Skeletal muscle wasting is key feature of cancer associated cachexia, with protein being the predominant component of this tissue. The conservation of skeletal muscle relies on the balance between synthesis and breakdown[79]. In the context of cancer, muscle wasting can be attributed to factors such as higher energy requirements, anorexia, inflammation and metabolic unbalances of the host in response to disease[80]. Additionally, tumor secretions, including inflammatory cytokines, can stimulate the release of activin A, inhibit Akt/mTOR pathway and simultaneously activate muscle ring finger-containing protein 1 (MURF-1) and muscle atrophy F box protein (MAFbx/atrogin), which contribute significantly to protein catabolism. Other substances as lactate, tryptophan and parathormone-related peptide, induce anorexia by acting on the central nervous system[81]. Proteolysis inducing factor, produced by the tumor, has also been associated with weight loss in patients with GI cancer[82]. Moreover, low dietary intake, resulting of anatomic alterations related to disease location and the effects of anti-cancer therapies (systemic treatments, surgery and radiotherapy) can also limit dietary intake due to symptoms as vomiting, dysgeusia, anorexia and pain[80].

The biological and biochemical explanation linking sarcopenia with poor prognosis is still uncertain. However, it is believed to influence survival in several ways, because it predisposes to a higher risk of chemotherapy toxicity, delay, or early termination, which may also contribute to a less efficient chemotherapy treatment[83]. Furthermore, sarcopenia has been related with frailty, with increased vulnerability to several conditions such as infections.

The impact of sarcopenia on survival of cancer patients has been explored in various studies. Research from Prado et al.[51] and Linda et al.[50] prompted discussions on the need of body composition analysis in cancer patients. Linda et al. demonstrated that muscle depletion and low muscle radiation attenuation or muscle quality are associated with worse prognosis

independently of BMI[50]. Reinforcing the role of body composition on prognosis, models predicting overall survival incorporating BMI, weight loss, muscle radiation attenuation and skeletal muscle index, outperformed models with only conventional variables such as sex, age, performance status, disease stage and location[50].

In recent years, additional studies have reported sarcopenia as an independent predictor of overall survival in specific gastrointestinal cancer locations, namely esophagus[84,85], gastric[86–88], pancreas[89,90], and colorectal disease[91–93]. However, current evidence demonstrates the existence of particularities within GI cancers regarding the relationship sarcopenia and outcome, which substantiates the need for studies driven to address its clinical significance within specific contexts regarding disease stage and therapeutic plan, among others. Moreover, we can only speculate which other factors are involved in this particularities, specifically whether geographic variability can interfere in this association, given that globalization is negatively affecting dietary intake and obesity prevalence in different proportions throughout the world[1]. Furthermore, there is limited evidence in respect to the role of dietary patterns as a predictor of sarcopenia, which again can be specific to geographic region and could shed light on nutritional interventions to counteract wasting. Taken together and bearing in mind the paucity of studies regarding this issue in Portugal, further studies in this field of research are highly warranted to address this gap in knowledge. Additionally, compared with skeletal muscle, the influence of adiposity on outcome, is still significantly underexplored.

- Low muscle radiation attenuation

Muscle radiodensity, assessed by CT derived muscle radiation attenuation, has emerged as a prognosis factor in prior studies[56]. Low muscle radiation attenuation has been linked with metabolic dysfunction, such as insulin resistance[55,94]. Insulin resistance or low insulin sensibility highly contributes to reduced muscle anabolism by favoring muscle proteolysis, by enhancing nuclear translocation of FoxO transcription factors and upregulation of both Atrogin 1 and MurF1[55].

The coexistence of low skeletal muscle quantity and radiodensity has also been documented showing a significant association with overall survival[95]. However, muscle radiodensity has also been identified as an independent predictor of poor prognosis in cancer patients[96]. Those with comparable skeletal muscle quantity, but low muscle radiation attenuation, exhibit worse outcomes, such as increased chemotherapy toxicity, and reduced time to disease progression[56].

- Sarcopenic Obesity

Sarcopenic obesity (SO), characterized by the combination of low skeletal muscle quantity and excess adiposity, has consistently been linked to a poorer prognosis in cancer patients[51,54,55,97–99]. Baracos et al. found that in cancer patients with advanced solid tumors, the prevalence of sarcopenic obesity was approximately 9%, but broader estimates ranged from 1% to 47% due to inconsistencies in defining criteria across studies.[100].

From a molecular perspective, sarcopenic obesity has been associated with a shift from type II muscle fibers to slow type I muscle fibers, as well as inter and intramuscular lipid infiltration, closely aligning with myosteatosis[55]. Consequently, SO has been associated with the same metabolic derangements as low muscle radiation attenuation. Indeed, SO cancer patients are considered to be at greater risk of worse outcomes[55], bearing a double, if not triple burden due to the concurrent presence of obesity, muscle loss and potential skeletal muscle fat infiltration.

The initial study establishing the relationship between SO and survival in cancer patients was published by Prado et al. in 2008, which demonstrated SO as an independent predictor of worse prognosis[51]. Subsequent findings from a review by Carneiro et al. reinforced this association, concluding that SO was associated with worse outcomes, including shorter survival[99].

A decade after the initial SO study by Prado et al., Baracos et al. provided a review of existing studies on SO and its association with outcomes. Remarkably, in 2018, when compared with

numerous sarcopenia studies in cancer, only a small subset had specifically addressed SO (a total of 22 studies: 6 on patients with SO and 16 on patients with SO and overweight sarcopenia)[54]. Findings from this review supported the association between SO and higher mortality[54].

- Visceral adipose tissue and the obesity paradox

The association between VAT and survival is less studied than skeletal muscle, with contradictory results. Negative associations between VAT and survival have been observed, particularly in colorectal[101–103] and pancreatic cancers[104], while abrupt VAT loss has also been linked to worse outcomes[105], suggesting complex relationships requiring further studies. The positive association between adiposity and survival, known as the "obesity paradox," is debated, with arguments against it emphasizing the importance of considering muscle measures and adipose tissue location[106,107].

2.4.2. Adverse effects of systemic cancer treatments relation with body composition.

The early 2000s marked a significant milestone with the progression of body composition imaging techniques, allowing for a more nuanced assessment in cancer patients. In 2007, Prado et al. demonstrated a poor correlation between estimated free fat mass and Body Surface Area (BSA) (r^2=0.37), in patients with lung and gastrointestinal cancer, revealing a three-fold variation in the volume of distribution[51]. By 2011, this research group had provided evidence linking low lean body mass relative to weight and height with severe toxicity to fluoropyrimidines (5-fluorouracil (5FU) and capecitabine), single agent tyrosine kinase inhibitor (TKI) (sorafenib), or combination of drugs (adjuvant FEC: 5FU, epirubicin and cyclophosphamide)[108]. A subsequent review in 2016, expanded this list, adding additional drugs as sunitinib, vendetabin, imatinib, ECX and CF (Epirubicin, Cisplatin, Capecitabine) and CF (Cisplatin and 5-Fluorouracil)[109].

The association between cachexia and Dose Limiting Toxicity (DLT) in gastrointestinal cancers has been previously reported[110,111], with inconsistent results observed in studies focusing on cancer of specific digestive organs namely esophagus[112,113], gastric[87,114], pancreatic[95,115] and colorectal location[116,117]. In the context of neoadjuvant therapies, there's a lack of substantial evidence regarding the influence of body composition. This knowledge could enhance treatment tolerance by identifying patients more resilient to the physiological demands of these rigorous protocols, which entail chemotherapy prior to surgery. Thus, studies focusing on this specific scenario are essential for establishing individualized treatment plans.

2.4.3. Influence of body composition on post-operative complications.

Significant strides have been achieved in systemic cancer treatments, yet surgery remains the cornerstone of gastrointestinal cancer patients, offering a potential cure[118]. However, surgery decisions must carefully balance prognostic benefits against complications, as post-operative issues including anastomotic leakage, stenosis, cardiorespiratory complications, and infections can occur, thereby delaying the beginning of adjuvant treatments and impact survival[119]. Precise pre-operative evaluation of surgical risk, along with identifying modifiable factors for prophylactic strategies, is crucial, especially for patients requiring combination therapies. Post-operative complications are often graded using Clavien Dindo criteria, providing a standardized assessment of complications[120].The underlying mechanisms linking body composition alterations to post-operative complications are not fully elucidated.

The surgical stress response is characterized by an increased release of glucocorticoids, catecholamines, and glucagon, mediated by afferent nerves and humoral factors such as cytokines released from the injury site. This response is triggered by the activation of the hypothalamic-pituitary-adrenal axis and the sympathetic nervous system[121]. These metabolic alterations result in the mobilization of energy substrates and hyperglycemia. Hyperglycemia is a consequence of insulin resistance and increased hepatic glucose production through neoglycogenesis, which is fueled by proteolysis and lipolysis. Additionally, amino acids efflux from proteolysis is used for acute phase protein synthesis[121].

The Enhanced Recovery After Surgery (ERAS) approach, aligns with specialized perioperative care, aiming to enhance recovery by addressing potential key factors involved in surgery stress. This multimodal approach, focusing on pain relief, stress reduction, early nutrition, and mobilization, allows for standardized care plans that evaluate prognostic factors such as nutritional and functional status[119]. More recently a prehabilitation strategy has been proposed, which is a multimodal approach encompassing nutrition, exercise, psychological, and medical optimization interventions[122]. Both prehabilitation and ERAS aim to manage stress response to surgery using multimodal strategies, through different focuses.

Sarcopenia has been linked with postoperative complications in gastrointestinal cancer, but with inconsistent results[49,90,119,123]. Beyond sarcopenia, low muscle radiation attenuation, an indicator of myosteatosis that may precede the decline in muscle quantity, has arose as an independent risk factor for short-term major post-operative complications[124,125]. While studies exploring the relationship between post-operative complications and adiposity are limited, a recent study suggests that increasing weight class defined by BMI is associated with higher odds of surgical complications[126].

2.5. The role of single and multimodal interventions in cancer cachexia.

Cancer cachexia is not a static condition, it evolves as a continuum and is conceptualized as a spectrum. In this context, the inclusion of rehabilitation components alongside anticancer treatments has been advocated to either treat or alleviate cancer cachexia. This section provides a review of the effects of isolated and multimodal pharmacological, exercise, and nutritional interventions in the treatment of cancer cachexia.

2.5.1. Pharmacological Interventions

In the realm of pharmacological treatments for cancer cachexia, three primary approaches have been explored: appetite stimulation, anti-inflammatory treatment, and anabolic

enhancement[127]. Among these, Megestrol Acetate (Megace), a progesterone derivative, has been commonly employed to enhance the appetite of patients with cancer cachexia. Its underlying mechanism, thought to be related to neuropeptide Y release, remains unclear[128]. While there is some evidence suggesting a positive impact of Megace on appetite and weight gain in cancer cachexia patients, these effects have not been consistently reported.

Other appetite stimulation agents, such as cannabis sativa, nabilone, and melatonin, have not demonstrated success in modulating appetite in cancer patients[127]. In contrast, anamorelin, a selective ghrelin agonist, shows greater promise as it has been linked to improved weight and lean body mass in cachectic cancer patients[127].

Concerning anti-inflammatory treatments, a systematic review by Solheim et al. reported that, of thirteen trials investigating NSAIDs, all but two showed improvements or stabilization in weight, with evidence suggesting a positive impact on quality of life[129]. Other anti-inflammatory agents such as etanercept, infliximab, pentoxifylline, and thalidomide have demonstrated inconsistent results or reduced clinical benefit, limiting their applicability. Anabolic substances like insulin and enobosarm show potential in addressing cancer cachexia, but the evidence remains limited[127]. Nevertheless, as of today, none of these agents is routinely recommended to counteract cancer cachexia.

2.5.2. Exercise

Exercise in the context of oncology has demonstrated numerous benefits, encompassing reductions in cancer-related fatigue[130] and treatment side effects[131], improved mental health[131], enhanced quality of life[132], and favourable effects on mortality and recurrence[133].

Molecular investigations, primarily conducted in cancer animal models, have shed light on the anti-inflammatory [134,135] and anti-proliferative effects[136] of exercise. Myokines released during exercise have been identified as key mediators of these effects. Muscle-derived gp130 receptor cytokine interleukin-6 (IL-6) is a pivotal myokine known for its acute increase (up to 100-fold) in response to exercise, functioning in autocrine, paracrine, and endocrine manners.

This includes enhancing glucose uptake and fat oxidation in muscles, glucose production in the liver, or lipolysis in adipose tissue[134]. Muscle-derived IL-6 has a dual nature, with tumor and immune cell-derived IL-6 exhibiting a pro-inflammatory role, while muscle-derived IL-6 mediates an anti-inflammatory response[137]. Consequently, IL-6 is associated with both pro and anti-cancer effects[138]. Studies have shown that muscle-derived IL-6 infusion inhibits endotoxin-induced TNF production and stimulates the release of anti-inflammatory cytokines[134].

Although numerous studies have explored the role of exercise on inflammation and cytokine expression in cancer patients, particularly those undergoing treatment and survivors[139–144], only a limited number have addressed its effect on cancer cachexia[145]. Colorectal cancer, in particular, has been a primary focus, but more research is needed to fully understand its impact[138].

Beyond its anti-inflammatory effects, an experimental study also suggested that exercise can also exert a direct anti-proliferative effect. During exercise, there is a coupled release of epinephrine from adrenal glands, leading to the epinephrine-dependent mobilization of IL-6-sensitive natural killer (NK) cells. These NK cells, equipped with epinephrine receptors, migrate into tumors, potentially sensitizing them to immunotherapy[146]. While some evidence supports these effects in human studies, inconsistent results have been reported, highlighting the need for further research[146–149].

2.5.3. Nutrition

Achieving adequate dietary intake in cancer patients poses significant challenges, given the prevalence of symptoms such as anorexia, a major component of cachexia, which affects a substantial percentage of cancer patients at the time of diagnosis[150,151]. Additionally, anticancer treatments may lead to gastrointestinal abnormalities, such as nausea, vomiting, constipation, and diarrhoea, further reducing dietary intake. Anatomic alterations due to tumour localization, along with pain and fatigue, also negatively impact nutrient intake[151].

Maintaining a positive energy and protein balance has been found to be essential for promoting muscle anabolism in cancer patients[152–154]. The current ESPEN guidelines recommend 25-30kcal/kg/day and a protein intake above 1.0g/kg/day, targeting 1.2-2.0g/kg/day. [155]

Protein metabolism alterations, characterized by increased protein breakdown and branched-chain amino acid oxidation in skeletal muscle, are prominent in cancer cachexia. These alterations aim to maintain energy production via gluconeogenesis and supply amino acids for acute phase protein synthesis by the liver. Therefore, adequate protein intake is crucial to maintain or promote skeletal muscle. Muscle anabolism is known to be enhanced in the circumstance of a positive protein balance and elevated plasma amino acids levels[153,154]. Although still warranting further research, lipids and in particular n-3 fatty acids have been related to a beneficial effect, as a strategy to counteract cancer cachexia[156].

2.5.4. Multimodal interventions

Given that cancer cachexia is a complex syndrome, emerging evidence advocates for a multimodal approach in its treatment. However, despite ongoing efforts, establishing conclusive evidence for this concept has proven challenging. Recent trials, have explored interventions encompassing pharmacological, nutritional, exercise, and psychosocial elements[157]. For instance, the Multimodal-Exercise Nutrition and Anti-inflammatory medication for Cachexia (MENAC) trial incorporated a combination of interventions, including pharmacological (NSAIDs), n-3 fatty acids supplementation (2g of EPA and 1g of DHA), nutritional (dietary counselling and oral nutritional supplements), and exercise interventions (home-based exercise program)[157–159] with promising results.

Therefore, the capacity of multimodal interventions to reverse cachexia or other alterations in body composition, leading to improved clinical outcomes, has not been conclusively established. As such, there is a critical need for further extensive research in this field.

3. Crohn's disease

Inflammatory Bowel Disease (IBD) comprises a group of chronic conditions characterized by recurrent inflammation in the gastrointestinal (GI) tract, with periods of relapse and remission. There are two major types of IBD: Crohn´s Disease (CD) and Ulcerative Colitis. CD is an autoimmune gastrointestinal disorder known for its chronic, relapsing-remitting course with a pattern of discontinuous inflammation[160]. CD can manifest in any part of the GI tract, extending from the mouth to the anus, with the most common locations being the terminal ileum and proximal colon. Intestinal involvement in CD can exhibit characteristics of being segmental, asymmetrical, and transmural. While most patients typically present with an inflammatory phenotype, about half of them may progress to more complex phenotypes, potentially requiring surgery, due to the development of strictures, fistulas, and abscesses[161]. Therapeutics for CD have evolved over the years, aiming to achieve deep and prolonged remission. The primary objective is to prevent complications and cease disease progression[161].

In recent years, research has increasingly shed light on the significant role of diet in both the pathogenesis and treatment of CD. Moreover, the association between CD and obesity/overweight, often associated with a Western diet, has emerged as a noteworthy area of research. This connection suggests that excess adiposity may play a role in the pathogenesis of CD and it is conceivable that this association contributes to the observed variability in the course of CD. While considerable attention has been devoted to understanding the role of body composition in cancer, its relevance in CD has received comparatively less scrutiny, underscoring the need for further research in this domain.

3.1. Epidemiology

While there is generally no sex-specific distribution identified in the adult Crohn's disease population[161], it may exhibit a slightly higher prevalence in women[162]. CD can affect individuals of all ages, but it typically peaks in onset between 20 to 40 years, with a smaller peak from 50 to 60[161]. CD is more common in the industrialized world and in urban areas. In Europe, there's

a geographical variation in the incidence of IBD, characterized by a north-south and east-west gradient[163]. Northern Europe reports an incidence of CD at 6.3 per 100,000 compared to 3.6 per 100,000 in Southern Europe. Furthermore, in Portugal, CD prevalence has increased over the years and is situated between countries with the highest and lowest CD prevalence[164].

3.2. Cause and pathophysiology.

Pathogenesis of CD is believed to be multifactorial, resulting from the interaction between genetics, environmental factors (e.g.: smoking, medications, and diet), host microbiome and immune system[165,166].

3.2.1. Genetics and family history

Genetics significantly influences Crohn's disease (CD), impacting its onset, complications, and treatment response[162]. CD appears more common in individuals of Ashkenazi Jewish origin compared to non-Jews and is less prevalent in African Americans or Hispanics. About 10-25% of IBD patients have a family history, and extensive genetic studies have revealed over 200 IBD-associated genes, including 37 specific to CD[161,167]. Insights into disease development include genes associated with bacterial sensing, innate immunity, Th17-cell function (including NOD2, ATG16L1, LRRK2, IRGM, IL23R, HLA, STAT3, JAK2, and Th17 pathways), and an altered mucus layer[161]. However, genetic factors explain only a small portion (13.1%) of disease heritability, highlighting the significance of non-genetic factors like epigenetics[161].

3.2.2. Environmental and dietary factors

Given that genetic factors alone cannot fully account for the incidence of Crohn's disease (CD), attention has turned to environmental influences in shaping CD risk. Environmental factors are implicated in promoting gut dysbiosis, reducing microbiome diversity, introducing non-

commensal microorganisms, compromising epithelial barrier integrity, and inducing altered immune responses[168]. This includes factors such as cigarette smoking, obesity, physical activity, and adherence to a Western-type diet, characterized by high intake of saturated fat, refined carbohydrates, red and processed meat, and low intake of fruits, vegetables, fibre, and fish[168].

Dietary choices also contribute to CD risk, acting as gut antigens that impact mucosal inflammation and the composition of the intestinal microbiota[169]. Evidence supports the relevance of diet to IBD development as early as breastfeeding and complementary feeding. Breastfeeding, particularly sustained for 12 months, is associated with a reduced risk of IBD in a dose-dependent manner[170].

Furthermore, components of the Western-type diet, such as processed foods, rich in food additives like emulsifiers (e.g., carrageenan, carboxymethylcellulose, and polysorbate-80) and preservatives (e.g., sulphites, aluminium silicates, and titanium dioxide), have been linked to the development of IBD[171]. Emulsifiers, for instance, may impact intestinal mucosal integrity, bacterial translocation, and promote alterations in the microbiota[172].

Insight from animal models has shown that gluten (wheat-protein composed of gliadin and glutenin), may modulate immune pathways in the small intestine in TNFα knock out mice model, whereas other wheat-protein components as amylase trypsin inhibitors, may further contribute to inflammation.

High animal protein intake, specifically red meat, processed meat, or fish have been associated with a higher risk of IBD (HR:3.31; 95%IC:1.41-7.77, p=0.007)[173]. Interestingly, in this study a dose dependent association was only found for UC, probably due to lack of power.

Insight from animal models has shown that a high-fat intake, particularly in the context of obesity, is linked to more severe CD. Studies indicate that a diet rich in fat is associated with inflammation in the mesenteric fat and increased leptin levels[172]. It's worth noting that the type of fat matters; for instance, saturated fats are associated with an increased risk of CD[174].

Conversely, patients with a balanced n-3/n-6 polyunsaturated fat ratio are more likely to be in remission[171].

In humans, a high dietary fibre intake, especially from fruits and cruciferous vegetables, has been linked to a lower risk of CD (HR = 0.59; 95% CI: 0.39-0.90)[174]. The protective effect of fibre was significant, particularly for those consuming more than 22.1 g/d[174]. Moreover, a high fruit intake was associated with a 73%-80% decreased risk of CD in the same study[174]. The positive effect of fibre is proposed to be due to the production of short-chain fatty acids, such as acetate, propionate, and butyrate, which influence gut microbial, metabolic, and immune homeostasis[175].

The intricate interplay between genetic predisposition, environmental factors, lifestyle choices, and dietary habits plays a crucial role in the development and management of IBD, especially CD.

3.2.3. Microbiota

The human gut microbiota is composed of a vast array of microorganisms, encompassing bacteria, fungi, viruses, eukaryotes, and archaea[176]. In healthy individuals, the gut microbiota typically harbours commensal bacteria predominantly from three principal phyla: Firmicutes, Bacteroidetes, and Actinobacteria[176]. In the context of CD, the bacterial community has been extensively studied, and early dysbiosis is recognized as a characteristic feature[177].

In CD, the bacterial signature involves decreased β-diversity, with a decline in obligate anaerobes and an increase in facultative anaerobes[176]. Additionally, CD is characterized by a reduction in the abundance of beneficial bacteria, such as Faecalibacterium prausnitzii and Roseburia spp., which produce short-chain fatty acid (SCFA) as butyrate. Butyrate is an energy source for colonocytes, enhancing gut integrity through re-enforcing tight junction and exhibiting anti-inflammatory effects by inhibiting interleukin (IL)-6 release and suppressing the NF-κB inflammatory pathway[176]. Moreover, a microbial signature associated with CD severity reveals a loss of major anti-inflammatory SCFA producers like Roseburia, Eubacterium,

Subdoligranumum, and Ruminococcus, coupled with a higher abundance of pro-inflammatory pathogens like Proteus and Finegoldia. Other minor SCFA producers show elevated abundance, indicating a complex dysregulation[178].

Dietary factors play a role in microbiota modulation. High sugar intake correlates with diminished abundance of anti-inflammatory bacteria, while plant-based diets increase SCFA producers[179]. Exclusive Enteral Nutrition (EEN), has been associated with reduced microbiota diversity, but with increased Firmicutes abundance, and shows rebound effects post-treatment[180]. Partial Enteral Nutrition (PEN) plus ad libitum diet and other diets like Carbohydrate Specific Diet (CSD), Low Fermentable Oligosaccharides, Disaccharides, Monosaccharides and Polyols (FODMAP) diet, and Mediterranean diet impact microbiota diversity and composition, but evidence varies[179]. Both CSD and Mediterranean diet have been associated with increased diversity with a reduction in Proteobacteria and Bacillaceae abundance, while the low FODMAP diet has been related to a decrease in Firmicutes, including Clostridium cluster XIVa and F. prausnitzii[179].

3.3. Diagnostic criteria, classification, disease activity and activity indexes.

The diagnosis of CD primarily relies on clinical evaluation, including physical assessment and various diagnostic methods such as laboratory tests, radiographic imaging, endoscopy, and histological examination[181]. CD clinical presentation may encompass various symptoms as abdominal pain, diarrhoea, weight loss and fever. Extraintestinal manifestations can also occur in approximately 50% of patients, namely primarily peripheral arthritis, ankylosing spondylitis, uveitis, and erythema nodosum[181]. CD classification in adults may be conducted according to Montreal classification, which includes age of onset, disease location and behaviour (**table 4**)[182].

Furthermore, disease activity can be defined as mild, moderate, and severe, depending on response to therapy, presence of malnutrition, mass or obstruction, among others[161]. In the context of research, the Crohn's Disease Activity Index (CDAI) is used to assess disease activity.

Besides CDAI, the Harvey-Bradshaw index (HBI) comprehends exclusively clinical parameters as: general wellbeing, abdominal pain, number of liquid stools, abdominal mass, and complications including perianal and extra-intestinal manifestations. This score is computed by attributing one point for each positive parameter[181].

	Montreal classification
Age at diagnosis	
<16 years	A1
17-40 years	A2
>40 years	A3
Disease location	
Ileal disease	L1
Colonic disease	L2
Ileocolonic disease	L3
Upper-isolated gastrointestinal disease*	L4
Disease behaviour	
Non-stricturing and non-penetrating	B1
Stricturing	B2
Penetrating	B3
Perianal disease†	P

Table 4- **Montreal Classification**. L4 serves as an adjunct to the L1-L3 classification in the presence of concurrent upper gastrointestinal illness. †Perianal disease (p) functions similarly as a modifier within the B1-B3 classification when occurring simultaneously.

3.4. Therapeutic management

3.4.1. Pharmacological

CD treatment centres on effectively inducing and maintaining remission, managing symptoms, and averting potential complications. Based on remarkable advances in CD pathogenesis comprehension in the last decades, therapeutics for CD has progressed significantly. To achieve remission, various medications were employed to diminish inflammation, encompassing antibiotics (e.g., metronidazole), corticosteroids (such as prednisolone and budesonide), immunomodulators (azathioprine, 6-mercaptopurine, and methotrexate). However, an important turning point was accomplished with the discovery of biologics (monoclonal antibodies targeting TNF-α) in the early 2000, and that continues to evolve to date with more treatment options. Throughout this journey of advances, the treatment paradigm changed substantially, from symptom control to more demanding outcomes as clinical and endoscopic remission[166]. Notably, these advances had a positive impact on patients' nutritional status, as they succeeded to control CD activity more effectively, thus reducing long term use of corticoids and related complications and the need for surgery[183], thus avoiding complications linked to increased nutritional risk as short bowel syndrome.

It is crucial to highlight the notable variability in treatment response[184] and disease behaviour in CD[166]. For instance, approximately one-third of patients exhibit primary nonresponse to biological therapy and 50% to vedolizumab, and 20% of responders experience loss of response[167]. This variability underscores the need for a deeper understanding of the underlying factors contributing to such diversity. Besides, biologics are more efficient, but are considered more intensive treatments that should be reserved to patients with potential to develop complicated disease. Numerous studies have attempted to identify, upon diagnosis, features of disease predictive of worse outcome so that aggressive therapies could be started early. Most of these include the presence of perianal disease, extensive involvement, and endoscopic features as large ulcers, among others. To our knowledge very few studies assessed body composition alterations as predictors of complicated phenotypes. In our studies we hypothesized that body composition parameters could have prognostic value and contribute

to aid therapeutic decisions directed to optimized care plans. Emerging evidence suggests that diet and body composition may play pivotal roles, prompting active investigations in these areas.

3.4.2. Nutrition as primary treatment

Several studies have underscored the efficacy of exclusive enteral nutrition (EEN) in inducing remission in pediatric CD patients[185–187]. EEN is currently recommended as first line treatment for inducing remission in children with active luminal CD, exhibiting efficacy comparable or even superior to oral corticosteroids[188,189]. EEN is known to achieve remission in approximately 50-80% of pediatric patients and to promote mucosal healing [172,186], thereby forming a robust link between diet and CD activity. Furthermore, whole food-based diets with or without partial enteral nutrition have shown promising results, with rates of clinical and endoscopic remission very similar to the observed with EEN[190–192].

3.5. Body composition in CD

3.5.1. Undernutrition and sarcopenia

Undernutrition has long been linked to CD, but overweight and obesity are significantly increasing in CD patients. Guerreiro et al. found that overweight (32%) and obesity (8%) were the most common forms of malnutrition in their study population of CD patients[193]. This advent is connected to the increase in worldwide prevalence of obesity, as well as the progress regarding CD therapeutics, especially regarding the era of biologic therapy after the year 2000, which positively impacted CD course, thereby alleviating undernutrition[193].

Although few studies are published on this topic, the estimated prevalence of undernutrition and sarcopenia in CD ranges from approximately 20-40% and 60%, respectively[194]. However, these estimates can vary due to several factors. Disease location plays a role, with

undernutrition being more prevalent when the small intestine is affected, leading to compromised food digestion and nutrient absorption. Additionally, reduced dietary intake, either due to hospitalization or disease-related symptoms such as nausea, vomiting, diarrhoea, and abdominal pain, further contribute to undernutrition[194].

Small Intestinal Bacterial Overgrowth (SIBO), commonly seen in CD, can exacerbate malabsorption, especially in cases with ileal involvement or ileocecal valve removal[194]. Increased energy expenditure due to inflammation, combined with physical inactivity or disability, further compounds the risk of malnutrition. Therapy side effects, particularly from corticosteroids, that can directly lead to reduced muscularity and increased adiposity, as well as the impact of surgery, depending on the location and size of the resected segment, as well as with the length of remnant intestine, can also interfere with nutrient absorption[194].

3.5.2. Visceral adipose tissue and mesenteric fat

In addition to undernutrition, adiposity, particularly visceral adipose tissue and its mesenteric component known as "creeping fat," has drawn attention for its potential involvement in CD pathogenesis[195]. This "creeping fat" is often observed around more active and aggressive inflammatory lesions of the intestine[196] and is one of the firstly described features of CD[195]. “Creeping fat” results from adipocyte hyperplasia and is strongly correlated with intestinal transmural inflammation, muscular hypertrophy, fibrosis, and stricture formation[197].

However, it remains uncertain whether “creeping fat” is a cause or consequence of CD. Mesenteric fat comprises various cells and structures, including adipocytes, macrophages, fibroblasts, extracellular matrix, and increased vasculature, which can influence intestine inflammation and immunity[195]. Mesenteric fat has been associated with a dual nature. It can result from the activation of peroxisome proliferator-activating receptor-gamma (PPAR-γ) by pro-inflammatory cytokines such as TNF-α and transforming growth factor (TGF) produced by the intestinal mucosa and macrophages. Additionally, mesenteric fat is also known to produce proinflammatory cytokines, triggered by bacteria translocation and this can potentially result

in transmural intestine inflammation[195]. Conversely, mesenteric fat has been described as a physical barrier to bacterial translocation as well as produce adipokines that favour anti-inflammatory macrophage polarization (M2)[195]. Despite these complexities, consensus on the role of mesenteric fat in CD has yet to be reached.

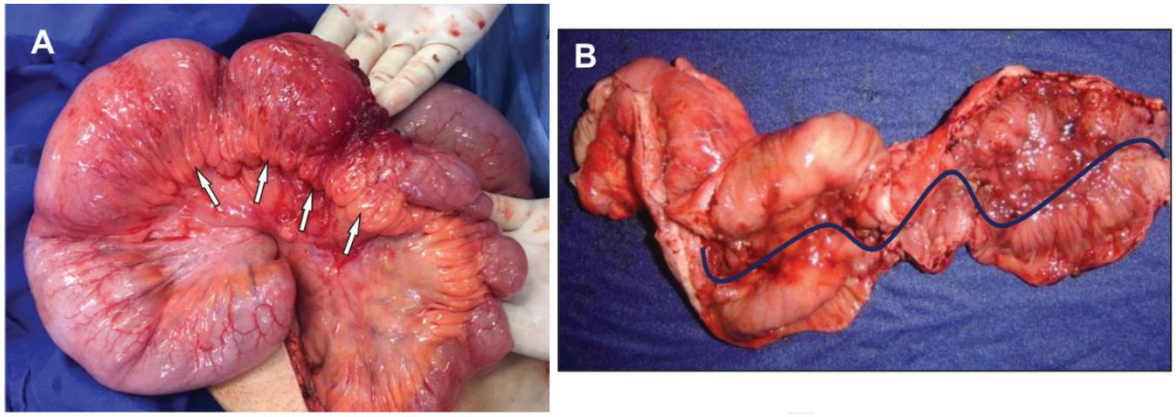

Figure 6- Mesenteric or creeping fat in the inflamed ileum with the presence of Crohn's Disease. The arrows in (A) show the creeping fat around inflamed small bowel. The blue line in (B) indicates a longitudinal intestinal mucosa ulcer in the mesenteric face of the bowel (source: Archives of Colorectal Surgery Unit—Universidade Estadual de Campinas (UNICAMP)). Figure reproduced with the permission from the editors of IntechOpen and Leal, R. F. et al. (2018) The Role of Mesenteric Adipose Tissue in Crohn's Disease; https://doi.org/http://dx.doi.org/10.5772/intechopen.73872.

3.5.3. Clinical outcomes in CD

Several studies have aimed to determine the role of prognostic factors, as age and genetic predisposition, among others, to optimize treatment decisions in CD patients, namely concerning the initiation of potent pharmacological therapies as biologics. Body composition alterations are hypothesized to be related to CD behaviour and response to treatments,[194] and therefore could be considered a natural candidate to such markers. However, body composition's clinical significance has been less extensively studied in Crohn's disease.

An early and small sampled study by Erhayiem et al., shed light on this association, since a high ratio of visceral to subcutaneous fat area was identified as marker of a more aggressive CD phenotype[198]. In addition only few studies have addressed the role of body composition in postoperative endoscopic and clinical recurrence, with the most related body composition parameter being visceral fat[199,200]. However, uncertainty remains regarding whether mesenteric fat is primarily involved in CD pathogenesis or if it is a secondary consequence of the disease.

Although evidence is more suggestive of an association between CD behaviour and visceral adiposity, again only few studies investigated the role of sarcopenia. Therefore, limited evidence exists linking sarcopenia with indication for surgery[201] and secondary failure of biologics defined as loss of response in CD patients[64]. Even less evidence exists regarding body composition phenotypes as low radiation attenuation and sarcopenic obesity.

The limited research on body composition's clinical significance in CD, highlights the need for further investigation in this area. More comprehensive, and longitudinal studies are warranted to fully elucidate the role of body composition in CD prognosis and management. Expanding our understanding in this domain could potentially lead to more personalized and effective approaches to CD care.

II. Rationale and research questions

A mounting body of international research has provided a conceptual framework linking body composition to outcomes of chronic inflammatory diseases. The availability of accurate body composition techniques as CT or MRI imaging, has brought a better understanding of this connection, which can ultimately lead to an optimized management of these diseases.

Gastrointestinal Cancer

Regarding GI cancer, body composition phenotypes as sarcopenia have been associated with outcome, but inconsistencies have been reported, meaning that particularities may exist, and further studies addressing specific tumor locations, stage and therapeutics are highly warranted. Also, prevalence of obesity is on the rise worldwide, due to globalization and human development, but at different rates[202]. Therefore, it can be hypothesized that geographic location due its obesity prevalence and unique dietary habits further adds to these particularities and substantiates the need for region specific studies. Further concerning geographic specificities, although gastric cancer mortality has declined at a worldwide level, it remains one of the deadliest cancers in Portugal, and prevails as an important public health issue in our country[203]. Alike pancreatic cancer, while remarkable improvements have been made concerning treatment options of this disease, it remains with an extremely low 5-year survival, whereas its incidence is projected to increase at an accelerated rate in the next decades[204].

Additionally, delving into dietary habits region-wise, can also elucidate as to which dietary patterns are more protective of unfavourable body composition phenotypes, as sarcopenia, eliciting optimized dietary approaches. Furthermore, it is conceivable that modifiable factors as dietary intervention and exercise can play an important role in modulating body composition, and these, in turn, result in improved outcomes.

The following questions were addressed:

a) Are CT-derived body composition parameters concordant with parameters measured by BIA or anthropometry in patients with GI cancer?
b) Are body composition abnormalities present in gastric cancer patients undergoing neoadjuvant treatment associated with survival and chemotherapy toxicity?
c) Are body composition abnormalities present in patients with resectable pancreatic cancer related to postoperative complications and survival?
d) Is there a dietary pattern protective of sarcopenia in GI cancer?
e) Are patients willing to participate in behavioural changes as diet and exercise during neoadjuvant chemotherapy? Can these interventions modulate body composition parameters and influence outcome?

Crohn's Disease

The obesity prevalence is increasing worldwide, and accordingly patients with inflammatory disease as Crohn's disease have been found to follow this trend[205]. While CD has been traditionally associated with undernutrition, due to the obesity pandemics and important improvements in CD therapeutics, such as the biologics discovery in the early 2000s, obesity/overweight is becoming the most prevalent form of malnutrition of these patients.

Although mesenteric fat has histologically been related to CD, its role remains unclear, whereas both a harmful and a protective effect has been described regarding this tissue[206]. Besides, there is uncertainty, if mesenteric fat is present upon diagnosis, thereby participating in disease pathogenesis, or if it is a consequence of disease progression.

The CD disease course exhibits a high variability, it can follow an indolent course or a more aggressive one, leading to complicated phenotypes requiring more intensive treatments and ultimately surgery. Therefore, efforts have been made to determine predictors of complicated disease phenotype, since this information has the potential to improve CD patients'

management, specifically concerning therapeutics. Herein, we hypothesized that body composition could have a prognostic value in this respect.

The following questions were addressed:

a) Are body composition abnormalities present in CD patients?
b) Are they related to the odds of complicated CD phenotype?
c) Are body composition abnormalities present upon diagnosis?
d) Are body composition abnormalities related to risk and time until surgery?

III. Objectives

The primary objective of this PhD was to examine the association between CT/MRI-derived body composition and clinical outcomes in chronic inflammatory gastrointestinal diseases. These investigations shared a common thread: the utilization of imaging techniques to precisely assess body composition, providing valuable insights into the influence of skeletal muscle, adipose tissue, and muscle density on the outcome of chronic inflammatory gastrointestinal (GI) diseases such as cancer and Crohn's disease. Given the considerable variability in treatment response observed in both conditions, a deeper understanding of how body composition modulates response to treatments could help to elucidate underlying mechanisms.

In the context of gastrointestinal cancers, despite a growing body of international evidence suggesting a link between body composition and clinical outcomes, research in Portugal remains scarce, thereby prompting us to further explore this topic. Furthermore, we aimed to identify predictors of sarcopenia in this population, uniquely incorporating dietary intake data to inform tailored nutritional interventions. Building upon our prior findings of a significant association between body composition and dietary patterns and outcomes, we subsequently designed a multimodal interventional study focusing on nutrition and exercise as part of prehabilitation during chemotherapy, with the goal of evaluating adherence and assessing the intervention's impact on physical status. Moreover, we envisage investigating whether improving body composition could translate into better outcomes.

Similarly, Crohn's disease presents an opportune scenario for CT or MR-derived body composition analysis, alike gastrointestinal cancer, as these patients frequently perform CT scans or MRI upon diagnosis or later during course of disease either to map the extension of disease or the rule out complications. While a growing body of evidence underscores the role of diet and body composition in CD pathogenesis and treatment, this area remains relatively understudied compared to cancer. Hence, our objective was to explore the associations

between body composition and clinical outcomes, aiming to enhance disease understanding and support tailored interventions.

CHAPTER 2

MATERIALS AND METHODS

To accomplish established objectives, six distinct studies were conducted and are detailed within this PhD thesis. In all studies body composition was assessed with computed tomography (CT).

Cross-sectional imaging evaluation

Images were selected at the third lumbar vertebra (L3) by radiologists or by the PhD candidate and were processed using a software built on Matlab or with Slice-o-Matic (Tomovison Magog, QC, Canada) and the ABCS plugin, which automatically segmented tissue cross-sectional areas of CT scan images. MRI images were segmented manually. Subsequently, the processed images were validated by a nutritionist and radiologist, with manual adjustments made as required. Tissue cross-sectional areas were segmented based on specific Hounsfield Unit (HU) thresholds: -29 to 150 for skeletal muscle, -190 to -30 for subcutaneous and intramuscular adipose tissue, and -50 to -150 for visceral adipose tissue. The areas of cross-sectional skeletal muscle, visceral fat, and subcutaneous fat were measured in square centimetres, and the mean muscle radiation attenuation was measured in Hounsfield units. The skeletal muscle area (SMA) was adjusted for stature to calculate the skeletal muscle index (SMI) in cm^2/m^2. Sarcopenia was defined as SMI lower than 41 cm^2/m^2 in women, lower than 43 cm^2/m^2 in men with a body mass index (BMI) <25 Kg/m^2, and <53 in men with a BMI > 25 Kg/m^2, as described by Martin et al.[50]. Sarcopenic obesity was defined as patients exhibiting concomitantly an BMI in the obesity category and sarcopenia according to Martin et al. thresholds. The visceral adipose tissue area: skeletal muscle area ratio, was also computed and used as a proxy of sarcopenic obesity. Visceral obesity was mostly defined as a visceral fat area ≥80.1 cm^2 for women and ≥163.8 cm^2 for men, according to Doyle et al.[207].

Gastrointestinal cancer

1. Study Design

To explore the impact of CT or MRI derived body composition on gastrointestinal cancer, a series of studies were undertaken, encompassing retrospective, prospective, and interventional approaches. Retrospective studies primarily aimed to investigate the association between body composition and outcomes, including studies 1 and 2. Study 3, designed as a prospective study, presents baseline findings focused on comparing body composition techniques and identifying predictors of sarcopenia as dietary patterns, among others. Study 4, an interventional endeavour, sought to elucidate the potential for altering body composition and functional status through personalized nutrition and exercise interventions. Details for each of the four studies are outlined below.

2. Study plan and methodology.

2.1. Study 1 (n=48) - Body Composition as a Prognostic Factor of Neoadjuvant Chemotherapy Toxicity and Outcome in Patients with Locally Advanced.

The purpose of this longitudinal retrospective study was to determine the prognostic value of CT-derived body composition alterations in patients with gastric cancer submitted to neo-adjuvant chemotherapy.

Patients with diagnosis of locally advanced gastric or gastroesophageal junction (Siewert type III only) adenocarcinoma submitted to neoadjuvant chemotherapy in our institution were enrolled in this study. All patients had histological confirmation of adenocarcinoma and no evidence of metastasis. Chemotherapy side effects were assessed using the National Cancer Institute Common Toxicity Criteria, while dose-limiting toxicity (DLT) was determined by severe toxicity (grade 3/4) leading to dose reduction or treatment termination. Chemotherapy effectiveness was evaluated using the Response Evaluation Criteria in Solid Tumors (RECIST)

criteria[208], confirmed with surgical specimens when possible. Information on the last follow-up, date, and cause of death was recorded, and overall survival was measured from cancer diagnosis to death from any cause. All patients performed a CT scan at diagnosis at our institution, that was opportunistically used to assess body composition.

Statistical procedures included an exploratory and descriptive analysis, using Student's t-test or Mann-Whitney U test for continuous variables according to their adjustment with the normal distribution; and χ^2 test or Fisher's exact test were used for categorical variables. Simple and multiple logistic regression was preformed to identify potential predictors of early treatment termination, which included CT-derived body composition parameters, as sarcopenia and muscle radiation attenuation, among others. Kaplan Meier survival curves were also computed and were compared with log rank test. Statistical analysis was performed using Statistical Package for Social Sciences version 22 (SPSS Inc., Chicago, IL, USA) and R software (R Foundation, Vienna, Austria).

2.2. Study 2 (n=91) - Body Composition Influences Post-Operative Complications and 90-Day and Overall Survival in Pancreatic Surgery Patients.

This retrospective study was performed to determine the influence of body composition in post-operative outcome of pancreatic cancer patients. This study focused on investigating the association of body composition parameters, i.e., skeletal muscle, visceral fat, and muscle radiation attenuation with postoperative complications, 90- day survival, and overall survival in patients undergoing pancreatic surgery.

We examined all patients who underwent pancreatic surgery at Hospital Beatriz Ângelo from March 2012 to December 2017. To qualify for our study, patients had to have undergone an abdominal computed tomography (CT) scan at our institution within 30 days of their surgery to enable analysis of body composition. Post-operative complications were classified with Clavien-Dindo criteria[120], which were subsequently dichotomized as grade I–IIIa versus grade IIIb–V. 90-day survival was defined in months ranging from date of hospitalization for surgery

until censor or death date at 90 days after surgery. Overall survival was recorded as the number of months between the date of elective hospitalization for surgery and censor (last visit to the hospital) or death date. Body composition analysis using CT scan images was performed, and variables as sarcopenia, low muscle radiation attenuation, visceral obesity, and visceral fat area: skeletal muscle area ratio were retrieved, among others.

Regarding statistical analysis, potential predictors of post operative complications (classified as Clavien-Dindo ≥IIIb), including conventional clinical variables and body composition variables, were identified with simple and multiple logistic regression. Overall survival was first analysed with Kaplan Meier curves, whereas comparisons were performed with log rank test. Subsequently, two proportional hazards Cox models concerning overall survival were adjusted, one comprising only conventional clinical variables and the other encompassed body composition variables, to compare the discriminatory ability of these models. Finally, proportional hazards Cox model regarding 90-day survival was adjusted to investigate if variables associated immediate post-operative mortality differ from those affecting overall survival. Statistical analysis was conducted with SPSS v20 and R v3.0.2.

2.3. Study 3 (n=100) - Dietary patterns and its relationship to sarcopenia in Portuguese patients with gastrointestinal cancer: An exploratory study.

In this prospective study we aimed to compare different body composition techniques and to identify factors related with sarcopenia in patients with gastrointestinal cancer.

In this study we included patients with mixed gastrointestinal cancers, namely hepatic-biliary-pancreatic, esophagus, gastric and colorectal cancer at diagnosis. Disease stage was also registered and was dichotomized in stages I, II, and III versus stage IV disease for non-metastatic and metastatic disease, respectively. An holistic assessment was performed including 1) performance status with Eastern Cooperative Oncology Group Performance Status scale, 2) quality of life with European Organization for Research and Treatment of Cancer

Version 3.0 questionnaire, 3) physical activity was assessed with the International Physical Activity Questionnaire, 4) nutritional status with Patient-generated Subjective Global Assessment (SGA) assessment, 5) anthropometric measures and body composition analysis with bioimpedance and CT imaging techniques, and 6) dietary intake with a semiquantitative food frequency questionnaire validated for the Portuguese population.

Statistical analysis encompassed an exploratory analysis, where adjustment of continuous variables to a normal distribution was analysed using Shapiro-Wilk's test, and these variables were further analysed with t test or Mann-Whitney U test, as appropriate. Categorical variables were analysed with χ^2 test or Fisher's exact test. Comparison between different body composition techniques was conducted using Pearson and Spearman correlation tests, as appropriate. Principal Component Analysis (PCA) was used for reducing the dimensionality of the dietary intake data. This statistic strategy allows the determination of dietary patterns by grouping correlated foods. Simple and multiple logistic regression were performed to analyse potential predictors of sarcopenia. Data analysis was performed with SPSS Version 20 (IBM Corp., Armonk, NY) and R Version 3.0.2 (R Foundation for Statistical Computing, Vienna, Austria).

2.4. Study 4 (n=46) - Adherence to Combined Exercise and Dietary Intervention in Patients with Gastrointestinal Cancer Undergoing Neo-Adjuvant Therapy: An Open-Label, Pilot, Randomized Controlled Trial.

This study was designed as an open label randomized controlled trial aiming to investigate the adherence to Combined Exercise and Dietary Intervention (CEDI) in patients with GI cancer.

Recruitment took place at the Oncology Centre of Hospital Beatriz Ângelo. Patients diagnosed with esophageal, gastric, pancreatic, and rectal cancer were included, provided they were eligible for neo-adjuvant chemo/radiotherapy (ChT) and were between 18 and 80 years old. Demographic and clinical data, as tumor site, histological type, TNM staging chemotherapy toxicity, among others, were retrieved from electronic records. Nutritional assessment encompassed Patient Generated Subjective Global Assessment (PG-SGA), anthropometric

measures and CT-derived body composition analysis. Dietary intake was assessed with semiquantitative food frequency questionnaire before and after neoadjuvant treatment, 24h recalls were used to assess dietary intake during CEDI. Functional status was evaluated with handgrip strength (dynamometer, JAMAR®), 6-minute walking test and functional score of the EORTC quality of life questionnaire. The intervention group received a combined exercise and dietary intervention with a duration of 8-12 weeks. Exercise consisted of moderate aerobic and resistance training with a duration of 40-60 minutes once per week, and daily home exercises. Dietary intervention was based on nutritional counselling with tailored dietary plans plus oral nutritional supplements, targeting the European Society of Parenteral and Enteral Nutrition estimated nutritional requirements. The control group received standard care.

Adherence to CEDI was evaluated using an intention-to-treat approach, while anthropometric measures, body composition, functional status, quality of life, and dietary intake were assessed using a per-protocol approach. Associations between categorical variables were examined using the Chi-square test or Fisher exact test. Differences in means for continuous variables were analysed using the t-test or Mann-Whitney U test, depending on the adjustment to a normal distribution, assessed with Shapiro-Wilk test. Effect size was calculated using Cohen's d. Longitudinal data within the control and intervention groups were analysed using paired-samples t-tests or Wilcoxon Signed Rank Tests. Statistical analyses were performed using Posit software.

Crohn's Disease

3. Study Design

In parallel to the previously described studies, we conducted two retrospective studies focusing on exploring the association between body composition and outcomes in Crohn´s Disease. The first study had a more descriptive nature, where we committed to explore the role of the skeletal muscle and fat compartments in complicated phenotypes in a transversal study. The second, was a longitudinal retrospective study, aiming to further elucidate whether these changes were present upon diagnosis of CD and, as such, could be used as predictive and prognostic markers for severe phenotypes warranting more intensive therapies from the beginning.

3.1. Study 5 (n=71) - Lower skeletal muscle attenuation and high visceral fat index are associated with complicated disease in patients with Crohn's disease: An exploratory study.

In this retrospective cross-sectional study patients were eligible for inclusion if they underwent either computed tomography enterography (CTE) or computed tomography as part of their clinical assessment within one month of completing a full clinical, laboratory, and, whenever possible, endoscopic evaluation. Phenotypic characteristics obtained from medical records included demographic information, age of disease onset, disease extent, and behaviour based on the Montreal classification, as well as previous treatments such as surgery. Patients with a history of stricturing (B2) or penetrating (B3) complications and/or prior resection surgery at any stage of their clinical history were classified as having a complicated phenotype. Body composition analysis was obtained by the analysis of CT scans.

An exploratory analysis was first performed to characterize the study population. Simple logistic regression was performed using complicated behaviour (B1 vs B2 or B3 and/or previous resection surgery) as the dependent variable, whereas independent variables included demographic, clinical and body composition parameters as skeletal muscle area, subcutaneous

and visceral fat area, visceral obesity, visceral fat index, muscle radiation attenuation and sarcopenia. Successively, significant predictors or those with clinical relevance, were included in a multiple logistic regression. Other two models were created using stepwise variables selection. Taken together a total of 3 models were devised, and the final model was chosen based on the lowest Akaike Information Criteria (AIC). A Receiver Operating Characteristic (ROC) curve was plotted to assess the model's ability to predict complicated CD phenotype. Statistical analysis was performed with Statistical Package for the Social Sciences (SPSS, IBM) and R software.

Study 6 (n=72) - Body composition and Crohn's disease behavior: Is adiposity the main game changer?

In this study longitudinal retrospective study we included only patients with recently diagnosed disease and analysed the association between body composition and outcome, namely 1) disease phenotype and 2) time until abdominal surgery. Furthermore, we also explored longitudinal body composition alterations in patients with favourable and unfavourable CD progression.

Patients were enrolled if they underwent either CT enterography or magnetic resonance enterography as part of their clinical evaluation within six months of diagnosis, which encompassed clinical, laboratory, and endoscopic assessments. Phenotypic traits were retrieved retrospectively from medical records, encompassing demographic information, age of disease onset, disease extent, and behaviour (B), as per the Montreal classification. A complicated disease phenotype was delineated by the presence of B2 (stricturing) or B3 (penetrating) characteristics, as outlined in the Montreal classification. The duration until abdominal surgery was defined as the time in years between diagnosis and the abdominal surgical procedure. CT scans or MRIs were performed at both diagnosis and subsequent follow-up visits were retrieved. These scans were then analysed for body composition by a single investigator who was blinded to clinical and endoscopic data. This approach was adopted to ensure unbiased and objective interpretation of the imaging results.

Regarding statistical analysis simple logistic regression was conducted to examine the association between the dependent variable, complicated behavior (B1, non-stricturing vs. B2, stricturing, or B3, penetrating), and relevant clinical and body composition variables. Variables with clinical significance and/or with $p<0.25$ in simple logistic regression were included in a multiple logistic regression analysis. Time until abdominal surgery was assessed using Kaplan-Meier survival curves, and a multiple proportional hazards Cox model was adjusted accordingly.

In the longitudinal analysis of body composition and its correlation with clinical outcomes, a composite endpoint was defined to classify Favourable Outcomes (FO) or Unfavourable Outcomes (UO), including abdominal surgery, therapy intensification, and complicated disease phenotype at follow-up. Differences between baseline and follow-up body composition cross-sectional areas were calculated, and comparisons between outcome groups were performed. Statistical analysis was conducted using Posit software.

CHAPTER 3

RESULTS[1]

[1]In the next chapter additional results beyond what is presented in the published articles has been included to better integrate the information.

Study 1

Body Composition as a Prognostic Factor of Neoadjuvant Chemotherapy Toxicity and Outcome in Patients with Locally Advanced Gastric Cancer

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Contribution of the PhD candidate:

The candidate operationalized the technique regarding CT derived body composition assessment in collaboration with Lisa Agostinho. She then proceeded to analyze the body composition data, using reported thresholds to identify body composition phenotypes. She conducted part of the statistical analysis in collaboration with Carolina Palmela, including the multivariate logistic regression. She drafted the manuscript, namely the section regarding body composition analysis procedure, and part of the statistical analysis section. She participated in the revision of the draft leading up to its publication. The paper was then published in the Journal of Gastric Cancer (Quartile 2 in Gastroenterology).

J Gastric Cancer. 2017 Mar;17(1):74-87 https://doi.org/10.5230/jgc.2017.17.e8 pISSN 2093-582X·eISSN 2093-5641

ABSTRACT

Purpose: Neoadjuvant chemotherapy has been shown to improve survival in locally advanced gastric cancer, but it is associated with significant toxicity. Sarcopenia and sarcopenic obesity have been studied in several types of cancers and have been reported to be associated with higher chemotherapy toxicity and morbi-mortality. The aim of this study was to assess the prevalence of sarcopenia/sarcopenic obesity in patients with gastric cancer, as well as its association with chemotherapy toxicity and long-term outcomes.

Materials and Methods: A retrospective analysis was performed using an academic cancer center patient cohort diagnosed with locally advanced gastric cancer between January 2012 and December 2014 and treated with neoadjuvant chemotherapy. We analyzed body composition (skeletal muscle and visceral fat index) in axial computed tomography images.

Results: A total of 48 patients met the inclusion criteria. The mean age was 68±10 years, and 33 patients (69%) were men. Dose-limiting toxicity was observed in 22 patients (46%), and treatment was terminated early owing to toxicity in 17 patients (35%). Median follow-up was 17 months. Sarcopenia and sarcopenic obesity were found at diagnosis in 23% and 10% of patients, respectively. We observed an association between termination of chemotherapy and both sarcopenia (P=0.069) and sarcopenic obesity (P=0.004). On multivariate analysis, the odds of treatment termination were higher in patients with sarcopenia (odds ratio=4.23; P=0.050). Patients with sarcopenic obesity showed lower overall survival (median survival of 6 months [95% confidence interval (95% CI)=3.9–8.5] vs. 25 months [95% CI=20.2–38.2]; log- rank test P<0.001).

Conclusions: Sarcopenia and sarcopenic obesity were associated with early termination of neoadjuvant chemotherapy in patients with gastric cancer; additionally, sarcopenic obesity was associated with poor survival**.**

Keywords: Stomach neoplasms; Body composition; Sarcopenia; Neoadjuvant therapy; Prognosis

Abbreviations

5-FU – 5-fluorouracil

AUC – area under the curve

BMI – body mass index

95%CI – confidence interval

CT – computed tomography

DLT – dose-limiting toxicity

ECF – epirubicin, cisplatin, and infused 5-fluorouracil

GC – gastric cancer

GEJ – gastroesophageal junction

HBA – hospital Beatriz Ângelo

HR – hazard ratio

HU – Hounsfield unit

MA – muscle radiation attenuation

OR – odds ratio

ROC – receiver-operator characteristic

SFA – subcutaneous fat area

SMA – skeletal muscle area

SMI – skeletal muscle index

SPSS – statistical package for social sciences

VFA – visceral fat area

VFI – visceral fat mass index

INTRODUCTION

Gastric cancer (GC) is the fifth most common cancer worldwide and the third leading cause of cancer-related death[209]. It is often diagnosed at an advanced stage and has a low 5-year survival rate[210]. Neoadjuvant chemotherapy improves survival in locally advanced GC[211]. In 2006, the MRC Adjuvant Gastric Infusional Chemotherapy (MAGIC) trial showed that in patients with operable esophagogastric adenocarcinomas, a perioperative regimen of epirubicin, cisplatin, and infused 5-fluorouracil (ECF) resulted in downstaging of the disease and significantly improved both disease-free and overall survival when compared with surgery alone[211]. However, in the MAGIC trial, only 41.6% of the patients assigned to perioperative chemotherapy completed all 6 cycles of chemptherapy, with some discontinuation owing to toxic effects[114]. Therefore, there is a great need to identify host or tumor factors that might explain individual variation in therapeutic efficacy and toxicity.

Body composition (i.e., the proportions of skeletal muscle and fat) has been studied in several types of tumors in the context of various anti-cancer treatments. The evaluation of skeletal muscle and fat using cross-sectional computed tomography (CT) imaging is gaining popularity due to its wide availability, high precision, and low incremental costs[51]. Sarcopenia, which is the depletion of skeletal muscle, is associated with higher chemotherapy toxicity and higher morbi-mortality in cancer patients, with an overall worse[212–214]. Recent reports in patients with GC demonstrate that sarcopenia is a significant predictor of chemotherapy toxicity[114], worse postoperative outcomes[215–217], and reduced overall survival[218,219]. One of the reasons for the variable chemotherapy toxicity among individuals may be different body composition, which is not currently taken into account when prescribing chemotherapy.

Not only skeletal muscle mass depletion but also the distribution of adipose tissue might influence survival[220]. The presence of both sarcopenia and obesity has been associated with worse prognosis in a series of reports[51,220,221]. In the specific setting of GC, sarcopenic obesity was shown to be an independent predictive factor of postoperative complications in patients undergoing radical gastrectomy[222,223].

The aim of this study was to assess the prevalence of sarcopenia and sarcopenic obesity in a population of patients with GC, as well as its association with chemotherapy toxicity, response, and long-term outcomes.

MATERIALS AND METHODS

We conducted a single-center retrospective study in a secondary care hospital — Hospital Beatriz Ângelo (HBA). The study protocol was approved by the Scientific and Ethics Committee of HBA. The requirement for informed consent from patients was waived because of the retrospective design of the study.

Patients

We selected all patients diagnosed between January 2012 and December 2014 with locally advanced adenocarcinoma from the stomach or gastroesophageal junction (GEJ, Siewert type III only) who received neoadjuvant chemotherapy in our institution. Locally advanced gastric/GEJ cancer was defined as tumor stage greater than cT2 or positive locoregional lymph nodes (cN+), according to the tumor, node, and metastasis (TNM) staging classification (American Joint Committee on Cancer). Included patients had histologically confirmed adenocarcinoma with no evidence of distant metastasis on preoperative staging. CT was performed at diagnosis in all cases. Endoscopic ultrasound was used to confirm T stage in the absence of suspicious lymph nodes. Staging laparoscopy was not uniformly used in this cohort of patients because it was not yet systematically included in the staging protocol of our unit at that time.

Patient data were obtained from the electronic records at HBA. Demographic and clinical data, such as age, sex, tumor site and histological type, chemotherapy regimens used, and chemotherapy response and toxicity, were retrieved. Chemotherapy toxicity was graded according to National Cancer Institute Common Toxicity Criteria. Dose-limiting toxicity (DLT) was defined as any grade 3/4 toxicity associated with physician-ordered dose reduction or termination of therapy. Response to chemotherapy was evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST) criteria[208] and confirmed on surgical specimens

(when available). Date of the last follow-up and date and cause of death were collected. Overall survival was measured from the date of histologic diagnosis until the date of death from any cause.

Body composition evaluation

Weight and height at diagnosis were recorded by hospital staff. Body mass index (BMI) was calculated as weight (kg)/height (m^2).

CT scans were obtained and evaluated for body composition data by one investigator (SV) who was blinded to clinical and endoscopic data to ensure objective interpretation of image findings. Skeletal muscle and fat tissue cross-sectional areas were measured on axial CT images, at the level of the third lumbar vertebra (L3) with the patient lying supine (Fig. 1). Skeletal muscle area (SMA), visceral fat area (VFA), and subcutaneous fat area (SFA) were measured in square centimeters on the basis of the pixel count using appropriate software[50]. Mean muscle radiation attenuation was calculated for muscle area and was also recorded. Skeletal muscle and visceral fat were normalized for height to obtain the skeletal muscle index (SMI) and visceral fat mass index (VFI) — cm^2/m^2. Sarcopenia was defined as SMI lower than 41 cm2/m2 in women or lower than 43 cm^2 /m^2 in men with BMI <25 kg/m^2 and<53 cm^2/m^2 in men with BMI ≥25 kg/m2, as described by Martin et al. [50]. Sarcopenic obesity was defined as sarcopenia in patients with BMI ≥25 kg/m^2.

Body composition data were evaluated at the time of cancer diagnosis using the CT scan performed for staging. We were also able to access a follow-up CT scan after completion of neoadjuvant chemotherapy in a subset of 43 patients. These scans were used to perform a longitudinal analysis of body composition over time. The mean interval (± standard deviation [SD]) between CT scans was 86.4±29.0 days.

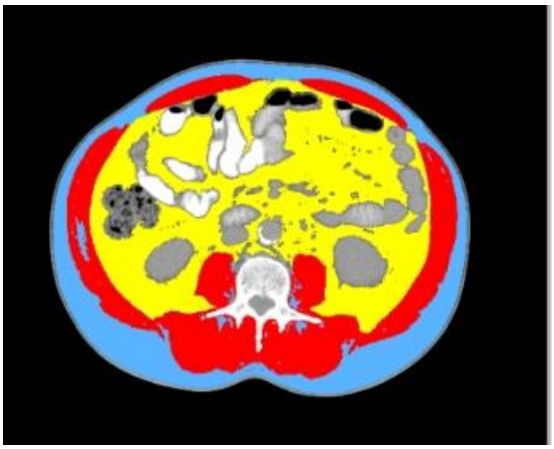

Fig. 1. Axial CT images of the third lumbar vertebra region. CT was analyzed for muscle and fat tissue cross sectional areas and analyzed using appropriate software. SMA (shown in red) was quantified within a HU range of −29 to 150, VFA (shown in yellow) ranged from −150 to −50 HU, and SFA (shown in blue) ranged from −190 to −30 HU. CT = computed tomography; SMA = skeletal muscle area; HU = Hounsfield unit; VFA = visceral fat area; SFA = subcutaneous fat area**.**

Statistical analysis

All continuous variables were described as median and range, while categorical variables were expressed as frequency and percentage. Differences in mean continuous variables with a normal distribution were analyzed using an independent Student's t-test. The other continuous variables were compared using the Mann-Whitney U test. To explore univariate associations in the distribution of categorical data, the $\chi 2$ test or Fisher's exact test was used as appropriate. On multivariate analysis, treatment termination was used as the dependent variable since we considered this variable the most clinically relevant. Any variable with a P-value <0.250 on univariate analysis or that was considered clinically relevant was included, and variable selection was performed with a stepwise analysis. Logistic regression was used for dichotomous outcomes, to determine the effect estimates, which are presented as odds ratio (OR) and 95% confidence intervals (CI). It is noteworthy that all patients with sarcopenic obesity experienced early treatment termination, so a high OR was obtained, and it was not possible to calculate the upper 95% CI limit. For this reason, this variable was not included in

the final model to avoid error in parameter estimation. For continuous variables in the model, cubic spline graphs and the Wald test of linearity were used to test linearity in the logit model. For the Wald test of linearity, age and muscle radiation attenuation did not demonstrate statistically significant P-values (P=0.430 and P=0.270, respectively). However, linearity was not clear for both muscle radiation attenuation and age on cubic spline graphs, so these variables were categorized. Age was categorized using 65 years as a cut-off. Muscle radiation attenuation was categorized with a cut-off (35 Hounsfield units [HUs]) provided by cubic spline graph analysis. Survival curves were estimated using the Kaplan-Meier method and compared using a log-rank test. A P-value <0.05 was considered statistically significant. Statistical analysis was performed using Statistical Package for Social Sciences version 22 (SPSS Inc., Chicago, IL, USA) and R software (R Foundation, Vienna, Austria).

RESULTS

A total of 160 cases of gastric/GEJ (Siewert type III) cancers were diagnosed in our institution during the study period, of which 48 were locally advanced cancers treated with neoadjuvant chemotherapy. Survival was 93.8% at 3 months, 62.5% at 1 year, and 41.7% at 2 years. Response to neoadjuvant chemotherapy was observed in 30 patients (63%), with 3 cases of complete pathological response (6%). DLT was observed in 22 patients (46%), among whom 17 patients (35%) terminated chemotherapy early (i.e., before completion of 3 cycles of neoadjuvant chemotherapy).

Mean BMI at diagnosis was 23.8±3.5 kg/m2, with 42% of patients categorized as overweight (BMI 25–29 kg/m2) or obese (BMI ≥30 kg/m2). Body composition data at diagnosis are shown in **Table 1**. Sarcopenia was present in 23% and sarcopenic obesity in 10% of patients at diagnosis. We did not find a significantly higher proportion of sarcopenia in older patients, but patients older than 65 years had a lower value of muscle radiation attenuation (30.0±6.0 vs. 39.8±8.1 HU; P=0.001). We also assessed patient demographics and body composition characteristics according to the presence/absence of sarcopenia (**Table 2**). Sarcopenic patients were more frequently female (64% vs. 22%; P=0.023), but were otherwise similar with respect to age, tumor site, histology and stage of disease, BMI, VFI, and muscle attenuation radiation.

We found no significant association between chemotherapy response and the presence of sarcopenia or sarcopenic obesity.

Although not statistically significant, we found a trend toward a higher percentage of DLT in patients with sarcopenia (64% vs. 39%; P=0.181) and sarcopenic obesity (80% vs. 42%; P=0.165). We found an association between early termination of chemotherapy and the presence of sarcopenia (64% vs. 28%; P=0.069) and sarcopenic obesity (100% vs. 28%; P=0.004). Seven of 11 patients with sarcopenia (64%) and all patients with sarcopenic obesity (n=5) required early chemotherapy termination.

Univariate and multivariate analysis were performed to assess factors that could contribute to termination of treatment (**Table 3**). On univariate analysis, both sarcopenia and muscle radiation attenuation were associated with treatment termination. Additionally, a strong effect was found for sarcopenic obesity since treatment termination was observed in all patients with sarcopenic obesity. There was no significant association between disease stage and termination of treatment.

On multivariate analysis, the odds of treatment termination were reduced in patients with higher muscle radiation attenuation, as compared to patients with lower muscle radiation attenuation (OR=0.20; P=0.040). In addition, the odds of treatment termination were higher in patients with sarcopenia as compared to patients without sarcopenia (OR=4.23; P=0.050). The receiver operating characteristic (ROC) curve showed an acceptable power of discrimination of treatment termination using a model with age, sarcopenia, and muscle radiation attenuation as independent variables (area under the curve [AUC] of 0.755) (**Fig. 2**).

There was no significant difference in overall survival between patients with and without sarcopenia (**Fig. 3A**). However, patients with sarcopenic obesity showed reduced survival (median survival 6 months [95% CI=3.9–8.5] vs. 25 months for patients who were obese and did not have sarcopenia [95% CI=20.2–38.2]; log-rank test P<0.001) (**Fig. 3B**).

Table 1 – Body composition data at diagnosis.

	Number of patients (%) n=48
BMI (mean ± SD) (kg/m^2)	23.8 ± 3.5
Underweight (BMI < 20)	5 (10%)
Normal (BMI 20-25)	23 (48%)
Overweight (BMI 25-29)	18 (38%)
Obese (BMI ≥30)	2 (4%)
Skeletal muscle index (SMI**)** (cm^2/m^2)	48.7 ± 9.7
Males	52 ± 9
Females	41 ± 7
Fat mass index (FMI) (cm^2/m^2)	50.4 ± 36.3
Males	59 ± 39
Females	33 ± 23
Muscle attenuation (HU)	34.2 ± 7.9
Sarcopenia	11/47 (23)
Sarcopenic obesity	5/47 (10)

Table 2 – Patient demographics according to the presence/absence of sarcopenia.

	Sarcopenia n=11	**Non-sarcopenia n=36**	**p value**
Age (mean±SD) (years)	69.3 ± 9.1	67.1 ± 10.4	0.534
Gender			0.023
Male	4	28	
Female	7	8	
Tumour site			0.924
Body	5	18	
Antrum	5	14	
Esophago-gastric junction (Siewert III)	1	4	
Histology			0.111
Intestinal	6	27	
Diffuse	5	6	
Mixed	0	3	
Clinical TNM stage			0.322
II	0	5	
III	11	31	
Type of chemotherapy used (n)			0.388
ECF / EOF / EOX / ECX	2 / 0 / 6 / 0	9 / 2 / 17 / 1	
XELOX / FOLFOX / Xeloda / DCF	1 / 0 / 1 / 1	6 / 1 / 0 / 0	
Chemotherapy response			1.000
Yes	7	22	
No	4	14	
Chemotherapy toxicity (n)			
Grade 2 / 3 / 4	3 / 6 / 0	11 / 14 / 0	0.455

	Sarcopenia n=11	Non-sarcopenia n=36	p value
Chemotherapy toxicity (n)			
Type: GI / haematological / other	5 / 2 / 3	12 / 12 / 4	0.135
Dose-limiting toxicity (DLT)	7	14	0.181
Termination of chemotherapy due to toxicity	7	10	0.069
BMI (kg/m^2)	22.7 ± 3.6	24 ± 3.3	0.278
Fat mass index (cm^2/m^2)	39.1 ± 34	53.9 ± 36.7	0.241
Muscular attenuation (HU)	31.2 ± 7.4	35.1 ± 8	0.151
Follow-up, months (median) [IQR]	10 [6-36]	20 [9.25-33.75]	0.551

E – epirubicin; C – cisplatin; F - 5-fluorouracil; O - oxaliplatin, X and Xeloda - capecitabine; D – docetaxel; FOLFOX – folinic acid plus 5-fluorouracil plus oxaliplatin; XELOX – capecitabine plus oxaliplatin; GI – gastrointestinal; SD – standard deviation; IQR – interquartile range.

A second CT scan after completion of neoadjuvant chemotherapy was available in a subset of 43 patients. No second CT scan was available for 5 patients, either owing to obvious clinical disease progression or because either magnetic resonance imaging or ultrasonography was used. The mean interval (± SD) between CT scans was 86.4±29.0 days. The mean loss of SMA during follow-up (mean 86 days) was 15.4±2.8 cm2. In the second CT scan, sarcopenia and sarcopenic obesity were found in 38% and 17% of patients, respectively, after neoadjuvant chemotherapy. Over time, there was a significant loss of skeletal muscle and adipose tissue (**Table 4**). Stratification of patients according to chemotherapy response demonstrated that only those patients who did not respond to chemotherapy experienced a significant reduction in SMI (49.9±10.1 to 44.6±9.5 cm^2/m^2; P=0.001) and VFI (57.5±33.6 to 42.1±26.3 cm^2 /m2; P=0.002) **(Fig. 4A).** Similarly, only those patients who experienced DLT had a significant reduction in SMI (47.0±10.2 to 43.0±10.8 cm^2/m^2; P=0.001) and VFI (52.7±31.2 to 39.2±28.5 cm^2/m^2; P<0.001) **(Fig. 4B).**

Table 3 – Univariate and multivariate analysis assessing the odds ratio (OR) of treatment termination associated with clinical variables and body composition markers in GC patients.

	Univariate Analysis			Multivariate Analysis		
	OR	**95% CI**	**p-value**	**OR**	**95% CI**	**p-value**
Age						
<65 years	1.00		0.92	1.00		0.308
≥65 years	1.06	0.30-3.81		0.44	0.077-2.08	
Gender				Excluded		
Male	1.00		0.70			
Female	1.27	0.34-4.50				
Tumour site				Excluded		
Body	1.00		0.42			
Antrum/GEJ	1.63	0.49-5.61				
Stage				Excluded		
II	1.00		0.26			
III	0.33	0.04-2.23				
Histology type				Excluded		
Intestinal	1.00		0.64			
Diffuse/Mixed	1.36	0.34-5.24				
Skeletal muscle area (SMA)	0.98	0.96-1.00	0.25	Excluded		
Visceral fat area (VFA)	1.00	0.99-1.01	0.12	Excluded		
Subcutaneous fat area (SFA)	1.00	0.99-1.01	0.28	Excluded		
Muscle radiation attenuation						
<35HU	1.00		0.04	1.00		0.04
≥ 35HU	0.27	0.06-0.95		0.20	0.33-0.95	

	Univariate Analysis			Multivariate Analysis		
	OR	**95% CI**	**p-value**	**OR**	**95% CI**	**p-value**
Sarcopenia						
No	1.00		0.03	1.00		0.05
Yes	4.55	1.13-20.7		4.23	0.98-20.8	
Sarcopenic Obesity				Not Included*		
No	1.00					
Yes	106362030.9	$2.81x10^{-72}$-NA	0.0007			

GC=Gastric Cancer; OR = odds ratio; CI = confidence interval; GEJ = gastroesophageal junction; HU = Hounsfield unit. *All patients with sarcopenic obesity experienced treatment termination, and for that reason a high OR was obtained, and the upper 95%IC limit was not possible to compute. This variable was not included in the final model to avoid error in parameter estimation.

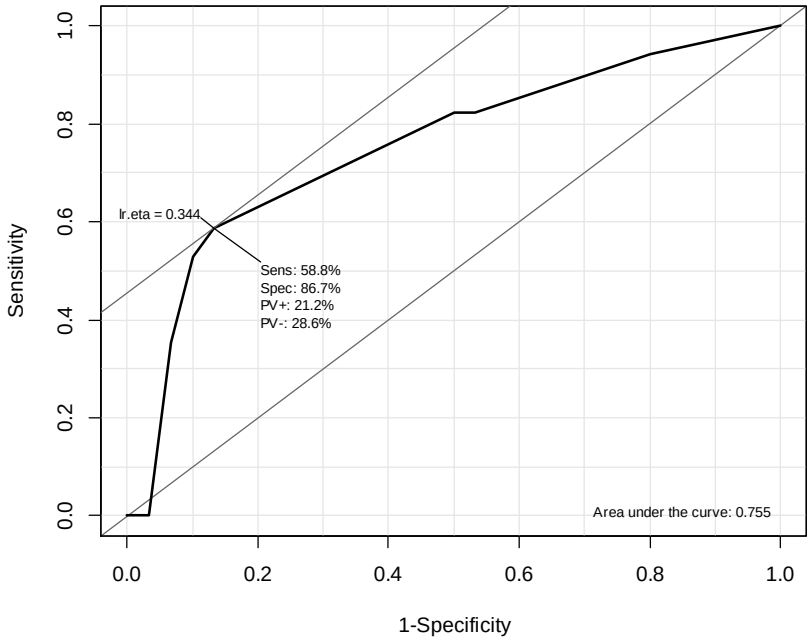

Figure 2 – ROC curve using treatment termination as dependent variable and age, sarcopenia, and muscle radiation attenuation as independent variables.

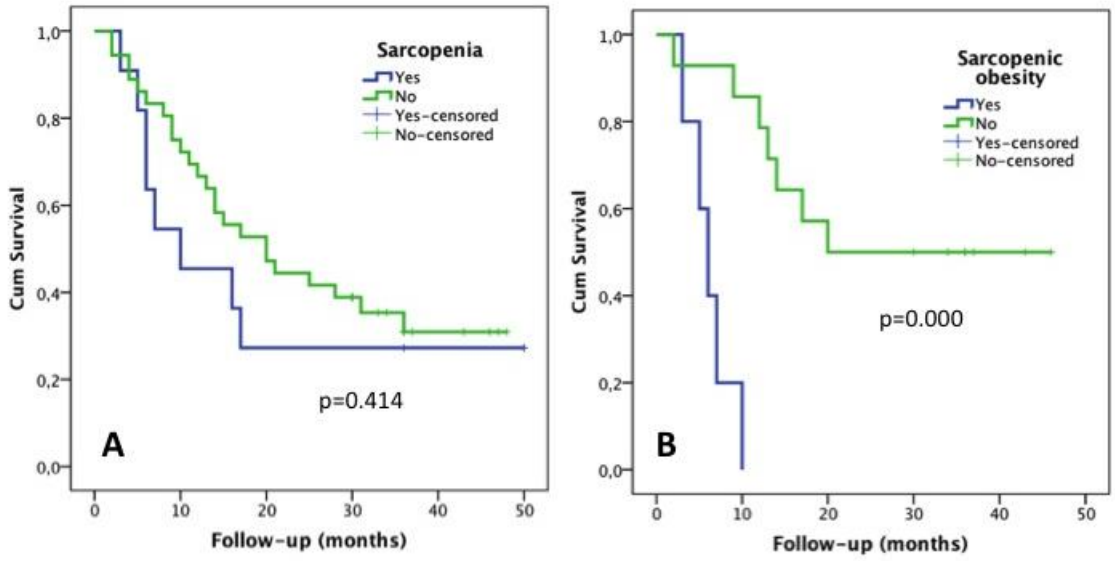

Figure 3 – Survival Kaplan-Meier curves of patients with and without sarcopenia (A) and of obese patients with and without sarcopenia (B) (Log-rank p-value).

Table 4 – Change in body composition over time in gastric cancer patients (n=43).

	First CT scan	Second CT scan	p value
Skeletal muscle area (cm^2)	132.1 ± 30.9	123.9 ± 29.6	0.001
Muscle attenuation (HU)	34 ± 7.2	31.7 ± 6.7	0.006
Visceral fat area (cm^2)	137.8 ± 96.2	113.5 ± 86.4	0.001
Subcutaneous fat area (cm^2)	136.2 ± 76.3	119.6 ± 78.7	0.002
Skeletal muscle index (cm^2/m^2)	48.2 ± 9.6	45.3 ± 9.5	0.001
Visceral fat mass index (cm^2/m^2)	49.8 ± 34	41 ± 30.1	0.001

Mean interval (± SD) between CT scans: 86.4 ± 29 days.

CT = computed tomography; HU = Hounsfield unit; SD = standard deviation.

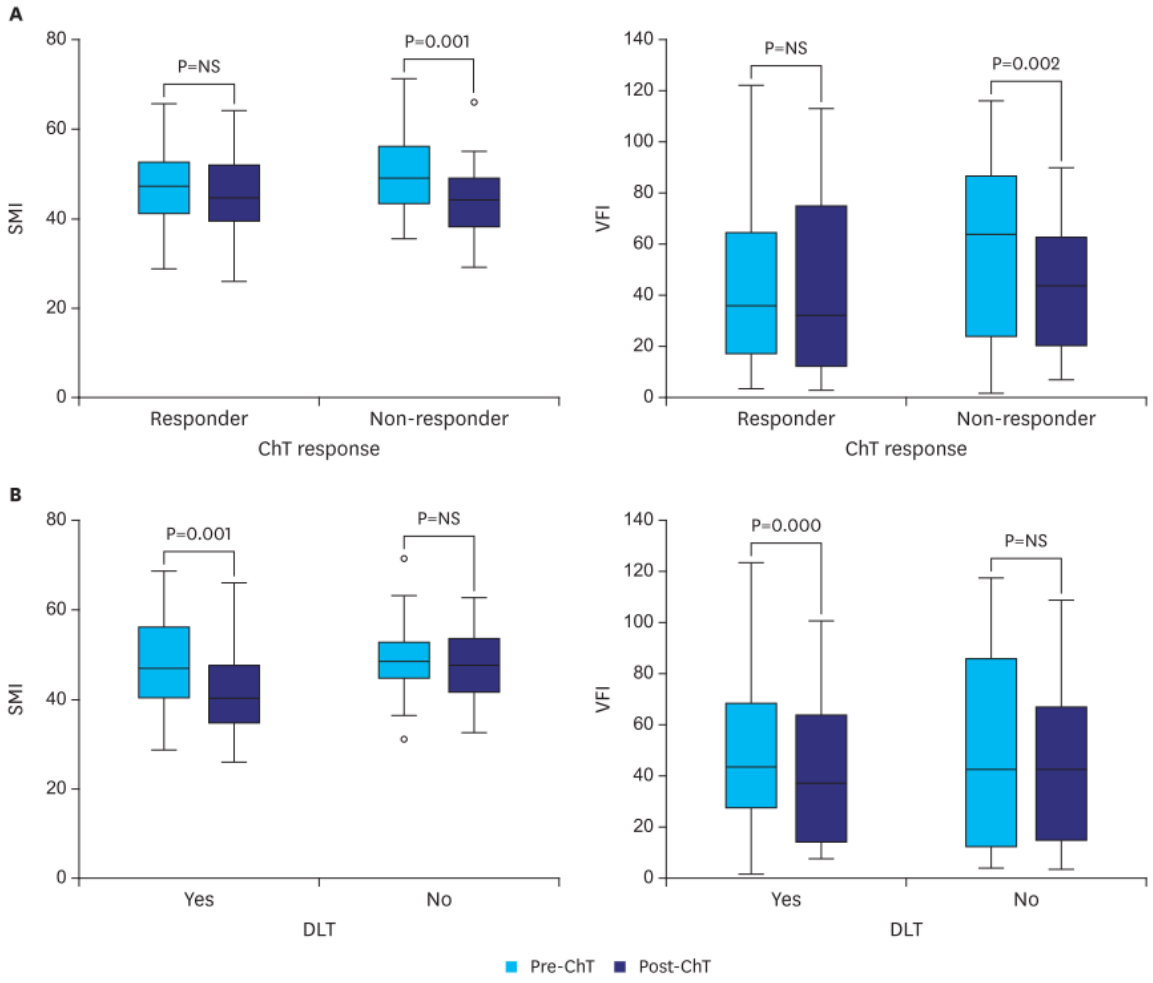

Fig. 4. Body composition changes (namely SMI and VFI in cm^2/m^2) before and after neoadjuvant chemotherapy, according to chemotherapy response (A) and DLT (B). SMI = skeletal muscle index; VFI = visceral fat mass index; ChT = chemotherapy; DLT = dose-limiting toxicity; NS = non-significant

DISCUSSION

In this observational study in patients with locally advanced GC who underwent neoadjuvant chemotherapy we observed that sarcopenic obesity was associated with poorer outcome, with a high likelihood of early termination of treatment and lower overall survival. Additionally, we confirmed that neoadjuvant chemotherapy was associated with important catabolic losses of

muscle and fat over time, although these occurred only in patients who did not respond to chemotherapy or in those who developed toxicity.

Several recent studies have reported a high prevalence of sarcopenia at diagnosis in patients with gastrointestinal cancers **(Table 5)**[224–230]**.** Comparison of sarcopenia prevalence among studies is rather difficult because of the use of different methodologies: axial CT cross-sectional imaging of SMAs, muscle mass using dual-energy X-ray absorptiometry, or a combination of anthropometric and physical performance measurements[231–234]. Furthermore, even when the same methodology is employed, different cut-offs for sarcopenia are often used (**Table 5**).

In the specific setting of patients with GC, the reported prevalence in the literature of sarcopenia ranges from 12.5% to 69.8% at diagnosis (**Table 5**). In our population, a quarter of the patients had sarcopenia at diagnosis. Additionally, the prevalence of sarcopenia increased following neoadjuvant chemotherapy. Similarly, Awad et al.[212] reported an increase in sarcopenia prevalence from 57% pre-chemotherapy to 79% in patients with esophagogastric cancer.

Several recent studies show a relationship between skeletal muscle mass depletion and treatment toxicity. In a recent systematic review by Kazemi-Bajestani et al.[235], there were 14 published articles relating CT-based body composition to the prevalence of chemotherapy-induced toxicity. These were mainly single-center investigations with small samples Bajestani et al., 2016), and only one addressed patients with GC[114]. In a prospective study in patients with colon cancer by Prado et al.[213], the authors found an increase in DLT in patients with lower muscle mass treated with 5-fluorouracil (5-FU). Likewise, in a prospective randomized trial in patients with colon cancer by Ali et al.[236], low lean body mass was an independent predictor of DLT and neuropathy in patients administered folinic acid plus 5-fluorouracil plus oxaliplatin (FOLFOX)-based regimens. More recently, data analysis from a randomized controlled trial in advanced non-small cell lung cancer also showed an association between low muscle mass and chemotherapy-induced hematological toxicity[237].

However, studies addressing the impact of sarcopenia in chemotherapy toxicity in patients with GC are scarce. Recently, Tan et al.[114] demonstrated that sarcopenia at the time of

diagnosis in patients with esophagogastric cancer was a significant predictor of DLT. In the present study, we found that the odds of treatment termination were higher in patients with sarcopenia. The mechanism that links sarcopenia with increased chemotherapy toxicity is currently unknown. Some authors speculate that different proportions of lean and adipose tissue compartments may be associated with alterations in the distribution, metabolism, and clearance of chemotherapy agents[213].

Although the impact of sarcopenia in DLT in patients with GC needs further prospective characterization, there are several recent reports demonstrating the important predictive role of low muscle mass in short- and long-term outcomes in patients with GC. In patients who undergo radical gastrectomy for GC, there is a significant relationship between sarcopenia and postoperative[215–217,232]. In a recent prospective study by Huang et al.[219] including 173 elderly patients undergoing curative gastrectomy for GC, sarcopenia was predictive of higher 1-year mortality (hazard ratio [HR]=3.615; 95% CI=1.459–8.957). Similarly, a large retrospective study of 937 patients with GC showed that sarcopenia was an independent predictor of low overall survival after gastrectomy[215]. Nonetheless, it is important to highlight that the impact of sarcopenia in postoperative and long-term outcomes has not been universally reported[238]. Further prospective studies using a consensual definition for sarcopenia are needed.

Although cachexia is a frequent feature of patients with advanced cancer, a substantial increase has been observed in the past decades in the proportion of cancer patients with a BMI in the overweight range[239]. In the present study, 42% of patients were overweight or obese at the time of diagnosis of GC. Abdominal adipose fat distribution might have an influence on tumor growth and therefore on cancer outcome[220]. The negative impact of visceral obesity has been previously reported in patients with colon, pancreatic, and renal cancer[240–242]; however, few studies in GC have addressed this issue.

The simultaneous presence of sarcopenia and obesity (especially visceral obesity) is a worse-case scenario associated with poorer prognosis[51]. The inflammatory cytokines produced by adipose cells are thought to play an important role in insulin resistance, resulting in an increase in muscle protein loss[243]. In addition, in patients with sarcopenic obesity, the increased body

mass inflates the overall administered chemotherapy dose, which is then distributed within a reduced lean tissue compartment, thus resulting in a disproportionately small volume of drug distribution and hence higher toxicity[51]. A population-based study by Prado et al.[51] that included 250 obese patients with solid tumors of the respiratory and gastrointestinal tracts showed that patients with sarcopenic obesity had poorer functional status and lower survival. In a recent prospective study of 206 overweight or obese patients with GC after radical gastrectomy, sarcopenic obesity was an independent predictor of postoperative complications[222]. Likewise, Nishigori et al.[223] retrospectively reported a prevalence of 24% of sarcopenic obesity (45 of 157 patients with GC) and found an association between sarcopenic obesity and surgical site infection.

Limitations of our study include its retrospective design, single-center recruitment, and small sample size. One important limitation was the lack of staging laparoscopy that is now routinely used in our unit. Some of the patients included in the study might have already had peritoneal disease, and this may explain the notable percentage of patients with disease progression during neoadjuvant chemotherapy. Another important limitation, associated with the retrospective nature of the study, was the use of different regimens of chemotherapy drugs according to patient characteristics. Nonetheless, 77% of our cohort received ECF or a similar regimen, with no difference between patients with and without sarcopenia. The relationship between chemotherapy toxicity and body composition has been observed in patients receiving a variety of different chemotherapy regimens[237,244]**.** One possible explanation is that the measurements of body composition reveal reduced fitness and low ability to tolerate cancer therapy independently of the type of chemotherapy.

Table 5 – Sarcopenia prevalence at diagnosis of gastrointestinal tumors.

Study reference	Country	Type of tumour	Number of patients	Sarcopenia (%)	Sarcopenia definition
Yip *et al.* (2014)[230]	United Kingdom	Oesophageal cancer	35	26	1
Reisinger et al. (2015)[229]	The Netherlands	Oesophageal cancer	108	56	1
Awad *et al.* (2012)[212]	United Kingdom	Oesophago-gastric cancer	47	57	1
Tan *et al.* (2015)[114]	United Kingdom	Oesophago-gastric cancer	89	49.4	1
Tegels *et al.* (2015)[238]	The Netherlands	Gastric cancer	152	57.7	2
Huang *et al.* (2016)[245]	China	Gastric cancer	470	16.8	3
Chen *et al.* (2016)[246]	China	Gastric cancer	158	24.7	3
Zhuang *et al.* (2016)[215]	China	Gastric cancer	937	41.5	4
Wang *et al.* (2016)[216]	China	Gastric cancer	255	12.5	5
***Hayash et al.* (2016)** [218]	Japan	Gastric cancer	53	69.8	2
Huang *et al.* (2016)[219]	China	Gastric cancer	173	30.1	3
Fukuda *et al.* (2016)[217]	Japan	Gastric cancer	99	21.2	6
Nishigori *et al.* (2016)[223]	Japan	Gastric cancer	157	57	1
Lieffers *et al.* (2012)[224]	Canada	Colorectal cancer	234	39	1
Reisinger *et al.* (2015)[225]	The Netherlands	Colorectal cancer	310	47.7	1
Huang *et al.* (2015) [219]	China	Colorectal cancer	142	12	5
Tan *et al.* (2009)[226]	Canada	Pancreatic cancer	111	56	1
Peng *et al.* (2012)[214]	USA	Pancreatic cancer	557	25	7
Joglekar *et al.* (2015)[227]	USA	Pancreatic cancer	118	26.3	8
***Harimoto et al.* (2013)** [228]	Japan	Hepatocellular carcinoma	186	40.3	9

Sarcopenia definition:

1. SMI ≤38.5 cm^2/m^2 for women and ≤52.4 cm^2/m^2 for men
2. SMI <41 cm^2/m^2 for women and <43 cm^2/m^2 in men with BMI <25 Kg/m^2 and <53 cm^2/m^2 in men with BMI ≥25 Kg/m^2
3. SMI <34.9 cm^2/m^2 for women and ≤40.8 cm^2/m^2 for men plus handgrip strength <18 kg for women and <26 kg for men and/or 6-m usual gait speed <0.8 m/s
4. SMI <34.9 cm^2/m^2 for women and ≤40.8 cm^2/m^2 for men
5. SMI <29 cm^2/m^2 for women and ≤36 cm^2/m^2 for men plus handgrip strength <18 kg for women and <26 kg for men and/or 6-m usual gait speed <0.8 m/s
6. SMI <6.42 kg/m^2 for women and ≤8.87 kg/m^2 for men plus handgrip strength <20 kg for women and <30 kg for men and/or 6-m usual gait speed <0.8 m/s
7. Total psoas muscle index <362 mm^2/m^2 for women and <492 mm^2/m^2 for men
8. Total psoas muscle index <4.0 cm^2/m^2 for women and <5.2 mm^2/m^2 for men
9. SMI ≤41.1 cm^2/m^2 for women and ≤43.75 cm^2/m^2 for men

CONCLUSIONS

Sarcopenic obesity is a strong risk factor for chemotherapy toxicity, premature termination of chemotherapy, and reduced overall survival. Future studies are required to define chemotherapy dosages that are within the limits of tolerability for this unique and vulnerable subgroup.

Study 2

Body Composition Influences Post-Operative Complications and 90-Day and Overall Survival in Pancreatic Surgery Patients

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Contribution of the PhD candidate:

The candidate operationalized the technique regarding CT derived body composition assessment in collaboration with Lisa Agostinho and Rita Cruz. She then proceeded to analyze the body composition data, using reported thresholds to identify body composition phenotypes. She completed the database created by Maria Pia Santos, with CT-derived body composition parameters, conducted the statistical analysis and interpreted the results. She drafted the paper and participated in its revision until its publication. The paper was then published in the Portuguese Journal of Gastroenterology (Quartile 3 in Gastroenterology).

GE - Port. J. Gastroenterol. **2020**, 1–13. https://doi.org/10.1159/000507206.

Abbreviations list

ASA, American Society of Anaesthesiologists

BMI, Body Mass Index

95% CI, 95% Confidence Interval

SMI, Skeletal Muscle Index

VFA:SMA ratio, Visceral Fat Area: Skeletal Muscle Area ratio

ABSTRACT

Introduction: Pancreatic surgery still carries a high morbidity and mortality even in specialized centres. The aim of this study was to evaluate the influence of patients' body composition on postoperative complications and survival of pancreatic surgery.

Methods: Retrospective study in patients undergoing pancreatic surgery between March 2012 and December 2017. Demographic, clinical data and postoperative complications classified according to Clavien-Dindo were recorded. Body composition was assessed using routine diagnostic or staging Computed Tomography (CT). Multiple Cox proportional hazards models were adjusted.

Results: Ninety patients were included, 55% male, mean age of 68 ± 10.9 years. Of those, 92% underwent total pancreatectomy or pancreaticoduodenectomy, 7% distal pancreatectomy and 1% pancreaticoduodenectomy with multivisceral resection; 84% had malignant disease. The incidence of major complications was 27.8% and 90-day mortality was 8.8%. Visceral Fat Area/Skeletal Muscle Area (VFA: SMA) ratio was associated with increased risk of complications (OR=2.24, 95%CI=1.14-4.87, p=0.03) and 90-day survival (HR=2.13, 95%CI=1.13-4.01, p=0.019). On simple analysis lower overall survival was observed in patients aged ≥70 years (p=0.0009), with postoperative complications ≥IIIb (p=0.01), with an increased VFA: SMA (p=0.007) and a decreased muscle radiation attenuation ($p=1.6x10^{-5}$). In an overall survival model adjusted for age, disease malignancy, postoperative complications and body composition parameters, muscle radiation attenuation remained significantly associated with survival (HR:0.94; IC95%:0.90-0.98; p=0.0016). A model which included only body composition variables had a discrimination ability (C-statistic 0.76) superior to a model which comprised conventional clinical variables (C-statistic 0.68).

Conclusion: Body composition is a major determinant of postoperative complications and survival in pancreatic surgery patients.

Keywords: pancreatic surgery, body composition, survival, postoperative complications, muscle attenuation, visceral fat area: skeletal muscle area ratio.

INTRODUCTION

Pancreatic cancer incidence is increasing, and surgery remains the only curative treatment. However, even in specialized centres the incidence of postoperative complications remains as high as 40-60% with 5-years survival of 10-20%[214].

Operative mortality has improved through surgical technique and perioperative care optimization. In particular, the Enhanced Recovery After Surgery (ERAS) pathway allows a standardized, multimodal, multidisciplinary approach, aiming at favouring postoperative recovery, by reducing surgical metabolic stress and limiting organ dysfunction[247].

Regarding nutritional status, recent studies have suggested that body composition phenotypes may influence postoperative and long-term clinical outcome. Most studies focused primarily on the impact of sarcopenia (low skeletal muscle) on major postoperative complications[248] and overall survival[214,226,233,249–255] and secondarily on visceral adipose tissue[104,248,252,254] and low muscle radiation attenuation (a marker of fat infiltration of skeletal muscle)[104,253–255]. Although some of these studies have included body mass index (BMI)[226] as a proxy of body fatness, still the influence of skeletal muscle infiltration by adipose tissue, as well as the proportion of visceral adipose tissue in regard to skeletal muscle tissue has been strikingly less studied.

Bearing in mind that obesity is a recognized risk factor for pancreatic cancer and that many of these patients experience weight loss at diagnosis which will certainly translate in a decline of skeletal muscle mass, we hypothesized that all tissues namely skeletal muscle, visceral fat and skeletal muscle infiltration by adipose tissue, may be equally relevant. We believe that this approach could lead us to a more comprehensive view, were all tissues have a different role but are equally important and expected to interplay. We therefore aimed to study the relationship between body composition parameters, namely skeletal muscle, visceral fat and muscle radiation attenuation and postoperative complications, 90-day as well as overall survival in patients undergoing pancreatic surgery.

MATERIALS AND METHODS

We conducted a single centre retrospective study at Hospital Beatriz Ângelo (HBA).

Subjects

We reviewed all patients undergoing pancreatic surgery in our Hospital between March 2012 and December 2017. To be considered eligible for our study, patients needed to have an abdominal Computed Tomography (CT) scan performed in our institution within 30 days of surgery to allow body composition analysis.

Demographic and clinical data including age, gender, American Society of Anaesthesiologists (ASA) score, disease location and histology according to surgical specimen were retrieved from patients' electronic charts. 90-day mortality and postoperative complications classified according to Clavien-Dindo classification. We considered rate of complications grade I–IIIa *versus* grade IIIb–V[120].Date of last follow-up and death were recorded as well. Primary outcome was overall survival, measured in months from date of elective hospitalization for surgery until death or until the censor date that was the last visit to the hospital. The 90-day survival was recorded in months from date of elective hospitalization for surgery until death or until censor date that was set at 90 days post-surgery.

Body composition assessment

Weight and reported height were recorded on admission and BMI was computed. BMI classification was done according to the following categories for adults: < 18.5 kg/m^2, underweight; 18.5 to 24.9 kg/m^2, normal weight; 25.0 to 29.9 kg/m^2, overweight; and 30.0 to 34.9 kg/m^2, class I obesity, 35 to 39.9 class II obesity and ≥40 class III obesity. BMI classification for the elderly was used for patients aged $\geq$ 65 years: <24 kg/m^2, underweight; 24-27 kg/m^2, normal weight; and > 27 kg/m^2, overweight. Opportunistic body composition assessment was conducted in diagnostic or staging CT scan. CT methodology is highly precise to quantify specific tissues and to predict whole-body composition[22]. Images were selected by radiologists on the axial plane at the level of the 3rd lumbar vertebra including both transverse processes using a portal venous phase and were processed with a program built with Matlab. This software performs an automatic segmentation of tissue cross-sectional areas, using the following Hounsfield unit (UH) thresholds: –29 to 150 for skeletal muscle, –190 to –30 for subcutaneous and intra-muscular adipose tissue and –50 to –150 for visceral adipose tissue.

Posterior validation of processed images was conducted, and manual corrections were executed by Radiologists. Cross-sectional skeletal muscle, visceral fat and subcutaneous fat were recorded in cm^2 and mean muscle radiation attenuation in HU. Skeletal Muscle Index (SMI=Skeletal Muscle Area (cm^2)/(height(m))^2 and visceral fat area:skeletal muscle area (VFA:SMA) ratio were calculated as previously described[50,248]. Sarcopenia, low muscle radiation attenuation and high visceral fat were defined according to sex-specific previously published cut-offs[50,62].

Statistical Analysis

Thresholds for CT-derived body composition parameters to define sarcopenia and low muscle radiation attenuation have been determined for a population with mixed cancer disease location[50,51] whereas reported thresholds for visceral obesity have been obtained from obesity related research[63,229] The above mentioned thresholds for sarcopenia and low muscle radiation attenuation have already been used in pancreatic cancer patients [97,104,226,248,249,256]. Besides this, candidate thresholds for sarcopenia based on skeletal muscle area/ body surface area were determined for gastric cancer patients[97]. However, there has been some criticism about generalization of reported thresholds due to ethnic and disease site differences. As such, in recent studies with pancreatic cancer patients different strategies to determine specific thresholds for each study population have been used, such as optimal stratification of total psoas area[233], sex-specific lowest quartile/tertile of skeletal muscle area[253,254] and Receiver Operator Characteristic (ROC) curve analysis[250,255].

Since thresholds for body composition are not established for the Portuguese population and bearing in mind that using thresholds that were not validated specifically for patients with pancreatic tumours may be misleading, we decided to use body composition variables in their continuous form, except for Kaplan-Meier curve comparison, where dichotomization is necessary. From a statistical point of view the use of continuous variables is a better option than discrete data, since continuous data convey more information. However, to account for gender specific differences in body composition, variables were mean centred in order to be

scaled by sex. We decided not to use optimal stratification strategies, since this approach is considered unstable for our sample size.

Simple and multiple Logistic Regression was used to relate each variable with complications Clavien-Dindo equal or higher than IIIb. For continuous variables, linearity of the logit in the predictor was assessed using a cubic spline and Wald test of linearity[257]. Only variables with p-value≤0.25 or considered clinically relevant were selected to multiple logistic regression. Multicollinearity was also analysed through the observation of variance inflation factors. A stepwise both-selection technique was used to create the multiple regression model. ROC curve was computed and the respective area under the curve (AUC) was calculated to assess accuracy of the model. The positive predictive value (PPV) and the negative predictive value (NPV) were also given. The association between major post-operative complications and type of surgery was assessed with fisher exact test.

Survival analysis was conducted with Kaplan-Meier estimate, and survival curves were compared with Log-rank test. Body composition variables such as Skeletal Muscle Index and Muscle Radiation Attenuation were dichotomized according to the lowest sex specific quartile and Visceral fat area: Skeletal muscle area with respect to the highest sex specific quartile to allow for comparison of survival curves.

First, two multiple Cox proportional hazards models with conventional clinical variables and body composition variables were adjusted and C-statistic was computed to assess model prediction ability.

Lastly, a multiple Cox proportional hazards model was adjusted regarding 90-day survival, to allow the comparison between variables associated with 90-day and overall survival. In this comparison, we used the overall survival model containing both clinical and body composition variables which yielded the highest c-statistics.

Data analysis was performed with SPSS (IBM, version 20) and R (version 3.0.2) and statistical significance was set at $p \leq 0.05$.

RESULTS

Population

A total of 125 patients undergoing surgery for pancreatic tumours at our institution during the study period were screened for eligibility. Thirty-five patients were excluded since diagnostic CT scan was performed at another hospital. Excluded patients were compared with the included patients and no differences were found for demographic, postoperative complications, and mortality rate. Demographic and clinical data are presented in **Table 1**. Ninety patients were included, 56% were male, with mean age of 68 ± 10.9 years; 16% (14/90) of patients had benign or pre-malignant tumours on the surgical specimen (10 IPMN, 1 serous cystadenoma, 1 chronic focal pancreatitis and 2 mucinous cysts). Among the patients with malignant tumours although the large majority were pancreatic ductal adenocarcinomas, we also found 17 adenocarcinomas of de ampulla of Vater, 7 distal cholangiocarcinoma, 1 duodenal carcinoma, 3 malignant neuroendocrine tumours, 1 acinar cell carcinoma of the pancreas. 92% underwent total pancreatectomy or pancreaticoduodenectomy, 7% distal pancreatectomy and 1% pancreaticoduodenectomy with multivisceral resection. The rate of major complications was 27.8%, the 90-day mortality rate was 8.8% and 28.9% died during the study period. Survival was 81.1% at 1 year and 73.3% at 2 years. Mean follow-up period was of 12.5 [0.26-49.8] months.

BMI categories and body composition parameters at diagnosis are presented in **Table 2**. Number of patients per body composition phenotypes according to published cut-offs are shown on **Figure 1**. Mean BMI was 25.1± 4.03 and 27.8% were underweight, 37.8% had normal weight, 20.0% had overweight and 13.3% had class I obesity and 1.1% class II obesity. Furthermore, 2.2% patients presented sarcopenic obesity.

Table 1. Demographic and clinical data

	Number of patients *(n=90)
Age (years, mean ± standard deviation)	68 ± 10.9
Male	50 (56%)
ASA grade	
I/II	60 (66.6%)
III	30 (33.3%)
Preoperative biliary drainage	38 (42.2%)
Type of surgery	
Duodenopancreatectomy /total	84 (92%)
Distal resection body-tail	6 (7%)
Duodenopancreatectomy with multivisceral resection	1(1%)
Post-operative histology	26 (54%)
Benign	14 (16%)
Malignant	76 (84%)
Stage I	22 (28.9%)
Stage II/III	54 (71.1%)
Preoperative Chemotherapy	9 (10.0%)
Major post-operative Complications	25 (27.8%)
90 –day Mortality	8 (8.8%)
Overall Mortality	26 (28.9%)

* Results expressed as number (percentage) unless indicated otherwise. N=90 patients.

Table 2. Body Mass Index and Body Composition at Diagnosis.

	Values *(n=90)
Body Mass Index (kg/m^2)	
Underweight	25 (27.8%)
Normal weight	34 (37.8%)
Overweight	18 (20.0%)
Class I Obesity	12 (13.3%)
Class II Obesity	1 (1.1%)
SMI (cm^2/m^2)	
Men	49.4±8.2
Women	41.2±4.9
Fat Mass Index (cm^2/m^2)	
Men	105.3±50.3
Women	139.3±66.8
Visceral Fat Index (cm^2/m^2)	
Men	58.6±32.2
Women	51.6±33.6
Muscle Radiation Attenuation (HU)	
Men	34.8±7.9
Women	30.8±10.0
VFA:SMA ratio	
Men	1.2±0.6
Women	1.2±0.9

Results are expressed as number (percentage) or mean (standard deviation); SMI-Skeletal Muscle Index; FMI - Fat Mass Index; VFA:SMA ratio - Visceral Fat Area: Skeletal Muscle Area. N=90 patients.

Postoperative Complications

Twenty-five out of 90 patients had post-operative complications ≥IIIb. We observed that 24/25 patients with complications ≥IIIb were submitted to total pancreatectomy or pancreaticoduodenectomy, 1/25 was submitted to pancreaticoduodenectomy with multivisceral resection, and none of the patients submitted to distal resection experienced major complications. In this analysis we obtained a near significant association between type of surgery and major postoperative complications (p=0.087). **Table 3** shows Simple and Multiple logistic regression exploring the relationship of each variable with postoperative complications. Results from simple logistic regression, showed that postoperative complications ≥IIIb were significantly associated with visceral fat index and VFA:SMA ratio, and an almost significant association was found for muscle radiation attenuation and ASA score. However, in multiple logistic regression analysis, only VFA:SMA ratio remained significantly associated with postoperative complications≥IIIb. In this model, the odds of major complications were two times higher per (increase of one) unit of VFA:SMA ratio. Regarding ASA score, although perceived as relevant to major postoperative complications (since it was selected in stepwise analysis), lost statistical significance when adjusted for VFA:SMA ratio. The area under the curve (AUC) obtained through ROC curve analysis was 0.691, which shows a fair discrimination ability of the selected model **Figure 2**. Sensitivity was 68.0%, specificity was 67.7%, positive predictive value was 15.4% and negative predictive value was 55.3%. Lastly, we conducted a subset analysis including only patients with malignant disease, were VFA:SMA ratio was the only variable to be selected for the final model with a near significant association (OR:1.77; 95%IC:0.925-3.77; p=0.10).

Table 3-Simple and Multiple Logistic Regression with post-operative complications as dependent variable.

	Post-Operative Complications		Simple Logistic Regression			Multiple Logistic Regression		
	Yes (n=25)	**No (n=65)**	**OR**	**95%CI**	**p-value**	**OR**	**95%CI**	**pvalue**
Continuous Variables	**Mean (Max-Min)**	**Mean (Max-Min)**						
Age	70[48-85]	67[34-89]	1.03	0.98-1.07	0.28	Excluded		
Body Mass Index	25.8[19.4-33.5]	24.9[18.2-35.0]	1.05	0.93-1.18	0.39	Not Included		
Skeletal Muscle Index	44.4[31.4-74.3]	46.4[32.9-65.9]	0.96	0.89-1.03	0.34	Not Included		
Visceral Fat Index	68.4[11.5-168.2]	50.6[1.91-104.2]	1.90	1.07-3.65	0.04	Excluded		
VFA:SMA ratio	1.55[0.31-4.9]	1.09[0.04-2.54]	2.30	1.21-4.92	0.02	2.24	1.14-4.87	0.03
Muscle Radiaton Attenuation	30.21[11.4-47.2]	34.14[8.22-48.12]	0.95	0.90-1.00	0.07	Excluded		
Categorical Variables	**Number**	**Number**						
Gender								
Female	13	37	1.00					
Male	12	28	0.82	0.32-2.09	0.67	Not Included		
Age								
<70 years	14	39	1.00					
≥70 years	11	26	1.17	0.45-2.99	0.73	Not Included		

Table 3-Simple and Multiple Logistic Regression with post-operative complications as dependent variable (*cont*.).

	Post-Operative Complications		Simple Logistic Regression			Multiple Logistic Regression		
	Yes (n=25)	**No (n=65)**	**OR**	**95%CI**	**p-value**	**OR**	**95%CI**	
ASA								
I	13	47	1.00			1.00		
II/III	12	18	2.41	0.92-6.32	0.07	2.26	0.83-6.20	0.11
Histology								
Benign	3	11	1.00			Excluded		
Malignant	22	54	1.49	0.42-7.07	0.56			
Neoadjuvant Chemotherapy								
No	24	57	1.00					
Yes	1	8	0.29	0.01-1.74	0.26	Excluded		

Excluded- variables excluded with stepwise analysis. Not Included- variables not included since p-value>0.25. Although gender had a p-value higher than 0.25, this variable was included in the model due to expected between gender body composition differences. VFA: SMA ratio, Visceral Fat Area: Skeletal Muscle Area ratio.

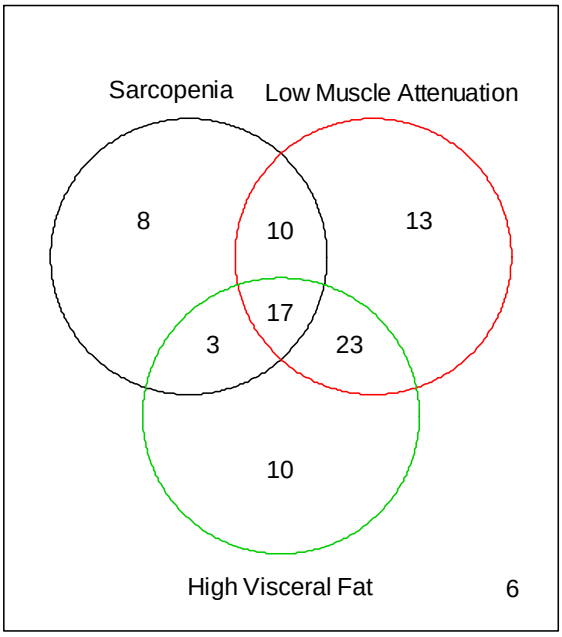


Figure 1: Venn diagram with number of patients with sarcopenia, low muscle attenuation and high visceral fat defined with published cut-offs. N=90 patients.

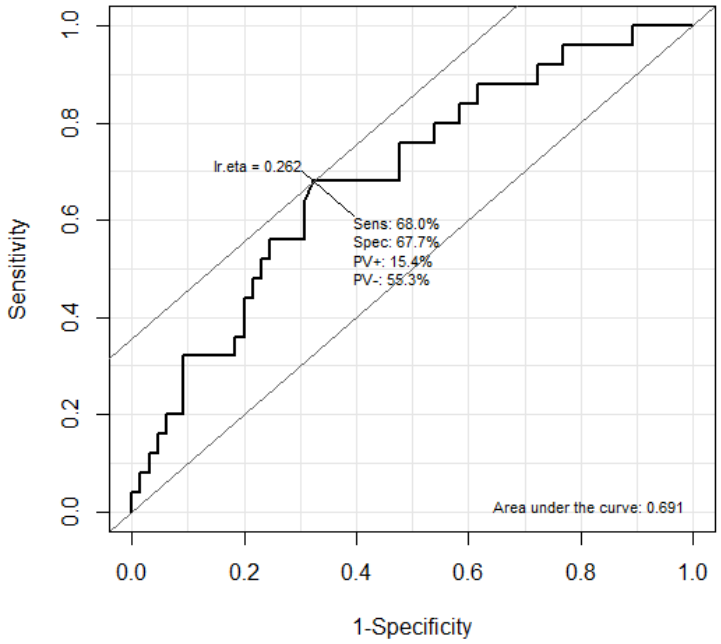


Figure 2-Receiver Operating Characteristic Curve (ROC) for Major Complications as dependent variable and ASA score and Visceral Adipose Tissue: Skeletal Muscle Tissue ratio as independent variables. N=90 patients.

Survival

Estimated overall mean survival was 31.15 months. Kaplan-Meier survival curves for overall survival as well as their comparison with clinical and body composition variables are reported on **Figures 3, 4 and 5**. Dichotomization of body composition parameters was conducted using the first sex specific quartile for skeletal muscle index (male-43.9 cm^2/m^2, female-37.2 cm^2/m^2), muscle radiation attenuation (male-30.9 HU, female-23.42 HU) and the third sex specific quartile for the VFA:SMA (male-1.52, female-1.67) to allow for Kaplan-Meier curve comparison. Comparison of survival curves was also conducted in respect to BMI categories (low/normal weight vs. overweight/obese), but no statistically significant differences were found (p=0.332).

Table 4 presents simple and multiple analyses for overall survival. Regarding clinical variables, on simple analysis, shorter survival was observed in patients aged ≥ 70 years, those submitted to pancreaticoduodenectomy with multivisceral resection, postoperative complications ≥ IIIb, and a near significant p-value was found for ASA score (I/II vs. III). In respect to body composition variables, an increase of 1 unit in muscle radiation attenuation was associated with an 8% reduction in the estimated risk of death, whereas an increase of one unit of VFA: SMA ratio was associated with an increase of 90% in the estimated risk of death. Lastly, a near significant association was found between overall survival and skeletal muscle index, where an increase of one unit was associated with a 5% reduction in the estimated risk of death.

Two multiple proportional hazards Cox models were adjusted using variables significantly associated with overall survival or considered clinically pertinent and c-statistics were compared. In the first model, only conventionally used clinical variables were included, namely age, ASA score, histology, and postoperative complications. In this model both age and postoperative complications were significantly associated with overall survival. The estimated risk of death was 3.34 times higher in patients aged ≥ 70 years. Hazard ratios for major complications could not be computed because this variable was adjusted by stratification, since it violated the proportional hazards assumption. At first, we decided not to include type of surgery since most patients were submitted to total pancreatectomy or

pancreaticoduodenectomy, whereas the remainder categories, namely distal pancreatectomy and multivisceral resection, had very few patients, which may influence estimates. However, bearing in mind the clinical relevance of this variable, we performed the same analysis including type of surgery, but since this variable did not alter the previous results or increase model performance (c-statistics remained the same), we decided not to include it to avoid overfitting (data not shown). A second model was adjusted using body composition variables. In this model we included, skeletal muscle index, muscle radiation attenuation and VAF:SMA ratio. According to this model the only significant variable was muscle radiation attenuation, where an increase of 1 HU was associated a reduction of 8% in the estimated risk of death. Interestingly the model which included 3 body composition variables had a discrimination ability (c-statistic 0.76) superior to the model which included 4 conventional clinical variables (c-statistic 0.68).

To compare postoperative survival with overall survival, **Table 5** shows the results obtained for the model that yielded the highest c-statistics regarding overall survival and results of a Cox proportional hazards model for the analysis of 90-day survival. Ninety-day survival was associated with age, with patients aged ≥ 70 years displaying an 8.2 times higher estimated risk of postoperative death when compared with patients aged < 70 years. Although in this analysis we could not compute hazards ratio for postoperative complications≥ IIIb due to model stratification, it is worth noting that all patients who died at 90 days had had major complications. Also, the estimated risk of death was two times higher per (an increase of 1) unit of VFA:SMA ratio, adjusted for age, histology, and post-operative complications.

On the other hand, when we analysed overall survival, age was no longer a determinant factor. Regarding body composition parameters, results differed from 90-day survival, and muscle radiation attenuation was the only significant variable, where an increase in 1 unit was associated to a reduction of 6% in the estimated risk of death, independently of age, histology, and postoperative complications.

Finally, 90-day and overall survival analysis was conducted including only patients with malignant disease, in this analysis similar results were obtained. In a model that adjusted for post-operative complications and age, VFA:SMA ratio (HR: 2.02; 95% CI:1.07- 3.81, p=

0.03) was significantly associated with 90-day survival. In a model adjusted for post-operative complications and age, muscle attenuation was significantly associated with overall survival (HR: 0.94; 95% CI: 0.89- 0.99, p= 0.019).

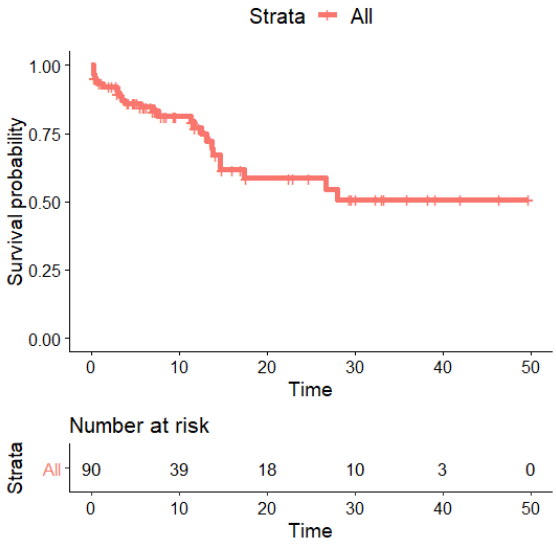
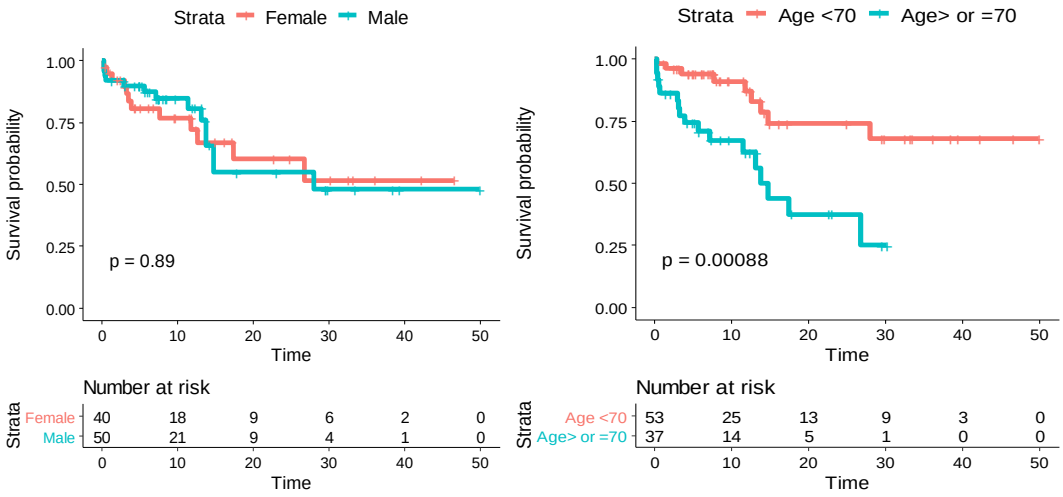


Figure 3- Overall survival. N=90 patients.



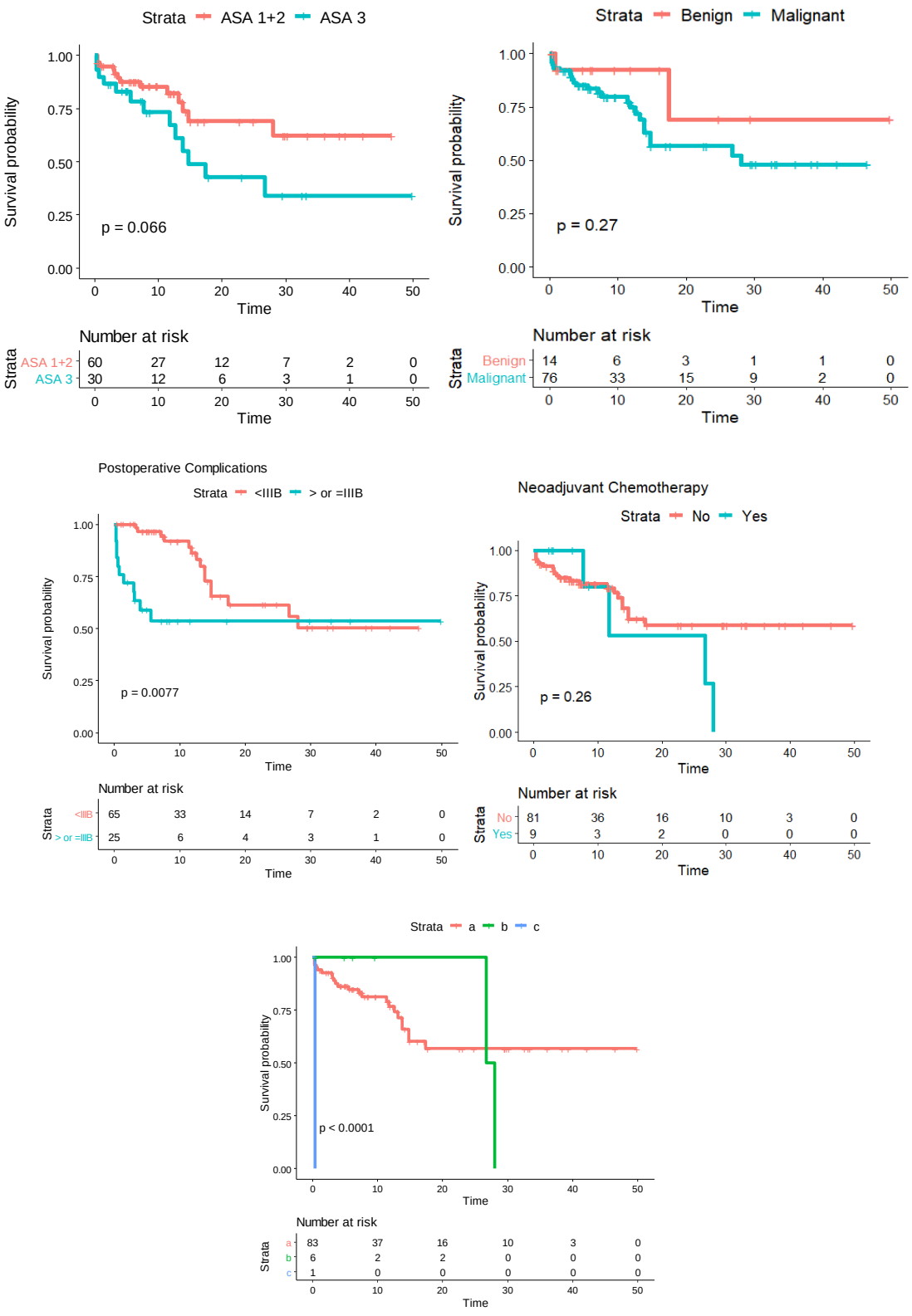


Figure 4- Overall survival according to clinical variables: sex, age, ASA score, disease malignancy, post-operative complications, neoadjuvant chemotherapy, postoperative complications, and type

of surgery: a) total pancreatectomy or pancreaticoduodenectomy, b) distal pancreatectomy and c) pancreaticoduodenectomy with multivisceral resection. N=90 patients.

Table 4- Mean survival and Simple and Multiple Proportional Hazards Cox Models.

	Pts.	Dths.	Survival	Simple analysis					Multiple analysis -Conventional					Multiple analysis –Body composition				
			Mean	Coef	SE	HR	95%CI	p	Coef	SE	HR	95%CI	p	Coef	SE	HR	95% CI	p
Sex																		
Female	40	12	30.3			1.00			Excl					Excl				
Male	50	14	29.6	-0.05	0.4	0.95	0.4-2.0	0.9										
Age, years																		
<70	53	9	31.5			1.00					1.00			Excl				
≥70	37	17	18.5	1.29	0.4	3.66	1.6-8.3	0.0009	1.2	0.4	3.34	1.4-7.9	0.0006					
Histology																		
Benign	14	2	37.4			1.00					1.00			Excl				
Malignant	76	24	29.2	0.79	0.7	2.22	0.5-9.4	0.3	0.69	0.7	2.0	0.4-8.5	0.34					

Table 4- Mean survival and Simple and Multiple Proportional Hazards Cox Models (*cont*.).

	Pts	Dths.	Survival	Simple analysis					Multiple analysis – Conventional					Multiple analysis –Body composition				
			Mean	Coef	SE	HR	95%CI	P	Coef	SE	HR	95%CI	P	Coef	SE	HR	95%CI	P
Type of Surgery																		
Total pancreatectomy/ pancreaticoduo-denectomy	83	23	19.9			1.00			Excl					Excl				
Distal pancreatectomy	6	2	27.34	0.13	0.7	1.15	0.3-4.8	0.84										
Pancreaticoduo-denectomy with Multivisceral resection	1	1	0.36	3.38	1.1	29.4	3.0-284.0	0.003										
Complications																		
<III B	65	15	32.0			1.00			Controlled with model stratification[1]					Excl				
≥III B	25	11	26.7	1.02	0.4	2.77	1.2-6.1	0.01										

Table 4-Mean survival and Simple and Multiple Proportional Hazards Cox Models (*cont*.)

Pts.-number of patients, Dths.-number of deaths, Coef- Coefficient, SE-Standard Error, HR- Hazard Ratio, 95%CI -95% Confidence Interval, Excl-

	Pts.	Dth	Survi-val	Simple analysis					Multiple analysis -Coventional					Multiple analysis –Body composition				
			Mean	Coef	SE	HR	95%CI	P	Coef	SE	HR	95%CI	P	Coef	SE	HR	95%CI	p
ASA score																		
I/II	60	13	34.5			1.00					1.00			Excl				
III	30	13	23.9	0.70	0.4	2.0	0.9-4.4	0.07	0.20	0.4	1.2	0.5-2.7	0.62					
Skeletal Muscle Index	90	26	31.15	-0.04	0.02	0.95	0.9-1.0	0.09	Excl					-0.01	0.03	0.98	0.9-1.0	0.65
Muscle Radiation Atenuation	90	26	31.15	-0.09	0.02	0.92	0.8-0.9	$1.6x10^{-5}$	Excl					-0.08	0.03	0.92	0.8-0.9	0.004
VFA:SMA ratio	90	26	31.15	0.64	0.2	1.9	1.9-3.0	0.007	Excl					0.03	0.32	1.03	0.5-1.9	0.92
C-statistics											**0.68**					**0.76**		

Excluded; [1]In the multiple analysis with conventional variables model complications were accounted for through stratification since this variable violated the proportional hazards assumption. VFA: SMA ratio, Visceral Fat Area: Skeletal Muscle Area ratio. N=90 patients, with 26 deaths during overall follow up.

Table 5- 90-day survival *vs* overall survival- stratified Cox proportional hazards models.

	90-day Survival							Overall survival						
	Dths. (n=8)	**Survival Mean**	**Coef**	**SE**	**HR**	**95%CI**	**p**	**Dths. (n=26)**	**Survival Mean**	**Coef**	**SE**	**HR**	**95%CI**	**P**
Age, years														
<70	2	2.92			1.00			9	31.5			1.00		
≥70	6	2.65	2.1	0.9	8.2	1.3-51.8	0.02	17	18.5	0.74	0.48	2.09	0.81-5.39	0.12
Histology														
Benign	1	2.84			1.00			2	37.4			1.00		
Malignant	7	2.80	0.76	1.09	2.14	0.24-18.5	0.48	24	29.2	0.53	0.74	1.70	0.39-7.34	0.51
Complications														
<III B	0	3.00	Controlled with model stratification[1]					15	32.0	Controlled with model stratification[1]				
≥III B	8	2.31						11	26.7					
SMI	8	2.8	Excluded[2]					26	31.1	Excluded[2]				
Muscle Radiation Attenuation	8	2.8	Excluded[2]					26	31.1	-0.05	0.02	0.94	0.90-0.98	0.016
VFA:SMA ratio	8	2.8	0.75	0.32	2.13	1.13-4.01	0.019	26	31.1	Excluded[2]				
C-statistics					**0.767**							**0.735**		

N = 90 patients, with 8 and 26 deaths at the 90-day and overall follow-ups, respectively. [1]Complications were accounted for through stratification since this variable violated the proportional hazards assumption. [2]Nonsignificant body composition parameters were excluded to avoid numerous predictors. SMI-Skeletal Muscle Index.

DISCUSSION

In this observational study performed in one single reference centre for pancreatic surgery we observed that body composition is a major determinant of the outcome of surgically treated patients. We found that, for predicting survival, the discrimination achieved with a model that includes 3 body composition parameters was superior to a model with 4 conventional clinical variables such as age, ASA score, disease histology and postoperative complications. Regarding postoperative complications, which is a major determinant of overall survival, we observed a significant association with VFA:SMA ratio independently of ASA score. It is worth pointing out that in our sample only 2 patients meet conventional criteria for sarcopenic obesity.

Considering the high morbidity and mortality of pancreatic surgery, our findings are highly relevant. Although age, ASA score and disease stage are non-modifiable factors, we can certainly aim at modifying preoperative body composition, especially during neoadjuvant chemotherapy. This being more frequently prescribed even in tumours which seem resectable upfront. Criteria for considering a tumour borderline resectable have been recently expanded and as of today, neoadjuvant chemo or chemoradiotherapy is now strongly recommended in a substantial proportion of operated patients if not all[258–261]. This period usually lasts 6 months or even more, which is an excellent opportunity to intervene with combined programs of exercise and/or dietary intervention aiming at modifying body composition.

Most studies that addressed the relationship between body composition and clinical outcome of pancreatic surgery patients have focused mainly on skeletal muscle tissue and overall survival with contradictory results. These studies have approached this issue using different methods to tackle skeletal muscle tissue, namely L3 CT scan derived sarcopenia [50,249,254,262], skeletal muscle area loss [263], accelerated loss of muscle mass[229], total psoas area [214,255] and volume[233], which have been associated with shorter overall survival in pancreatic cancer patients submitted to surgery or palliative care.

In contrast, other studies failed to demonstrate such an association[97,253], or were only able to show an association with sarcopenia if BMI was accounted for (which may be thought of as a proxy of body fatness)[226,252]. Some studies include both patients submitted to curative and palliative procedures which obviously have different outcomes[104]. In the present study, we only included patients submitted to curative surgery, 84% had malignant tumours while the remaining ones had pre-malignant lesions, and all patients were treated by the same team of 3 surgeons. Although skeletal muscle *per se* was not associated to a worse prognosis, it is worth noting that both VFA:SMA ratio and muscle attenuation, which incorporate both visceral fat and skeletal muscle tissues analysis, were strong determinants of postoperative complications and 90-day and overall survival, respectively. This suggests that these body compartments should not be considered isolated as they seem to exert a joint influence on outcome.

Noticeably most studies published so far have addressed overall survival and only a small number have investigated body composition effect on postoperative survival. Joglekar et al [227] found that sarcopenia was an independent predictor of grade III complications but visceral fat and muscle radiation attenuation were not analysed. In the present series, VFA: SMA was independently associated with 90-day survival and postoperative complications on multivariate analysis, while ASA score lost significance. Our findings are in line with the only published study that investigated the influence of VFA:SMA ratio on 60-day mortality, which found that VFA:SMA ratio exceeding 3.2 and ASA III were the strongest predictors of mortality[248].

In our study, muscle radiation attenuation was the most relevant body composition parameter associated with overall survival independently of age, postoperative complications, and disease histology. This result supports the hypothesis that muscle quality may be one of the most important body composition parameters influencing overall survival. In agreement with our results, Van Dijk et al.[104] also found that low skeletal muscle radiation attenuation was associated with worse overall survival while high skeletal/visceral adipose tissue index was related to increased surgical site infection rate. In this study 50% of patients had non-pancreatic cancer and 30% of them were submitted to palliative

procedures which increases substantially the heterogeneity of the study population. Also, in a recent study Stretch et al.[253], found that myosteatosis was associated to an increase in postoperative complications but no correlation was found between body composition and overall survival. Of note, the reported incidence of major postoperative complications and deaths in this study was exceedingly low which may be an explanation for this lack of correlation. They concluded that sarcopenia and myosteatosis represent 2 separate and distinct clinical phenotypes, but they did not include VFA:SMA ratio in their analysis.

CONCLUSIONS

To our knowledge this is the first study examining the effect of body composition in its most holistic perspective including the ratios between visceral fat and skeletal muscle tissues in both postoperative outcome and overall survival. Although well powered prospective studies are still needed, our results suggest that muscle radiation attenuation may be an independent prognostic factor of overall survival and that VFA:SMA ratio is significantly associated with 90-day survival and postoperative complications.

Study 3

Dietary patterns and their relationships to sarcopenia in Portuguese patients with gastrointestinal cancer: An exploratory study

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Contribution of the PhD candidate:

The candidate created the study protocol, aiming at exploring the role of dietary patterns on body composition. She operationalized the technique regarding CT derived body composition assessment in collaboration with Lisa Agostinho and Rita Cruz. She then proceeded to analyze the body composition data, using reported thresholds to identify body composition phenotypes. She created the database in collaboration with Sara Moço and conducted the statistical analysis and interpreted the results. She drafted the paper and participated in its revision util its publication. The paper was then published in Nutrition (**Quartile 2** in Nutrition and Dietetics).

Nutrition 2019, *63–64*, 193–199. https://doi.org/10.1016/j.clnu.2018.06.1731

Abbreviations list

AUC, Area Under the Curve

ECOG, Eastern Cooperative Oncology Group

EORTC, European Organization for Research and Treatment of Cancer

ESPEN, European Society of Parenteral and Enteral Nutrition

EPA, Eicosapentaenoic Acid

FFQ**,** Food Frequency Questionnaire

GI, Gastrointestinal

MUFA, Monounsaturated Fatty Acids

MDP, Mediterranean Dietary Pattern

PG-SGA, Patient Generated Subjective Global Assessment

PUFA, Polyunsaturated Fatty Acids

ROC, Receiver Operating Characteristic

Abstract

Background and aims: The purpose of this exploratory study was to identify the main dietary patterns of a Portuguese population of patients with GI cancer and to analyze their association with sarcopenia.

Methods: This was a prospective study with a consecutive sample of 100 patients with gastrointestinal cancer enrolled at diagnosis. Dietary intake was assessed with a Semi-quantitative Food Frequency questionnaire, and dietary patterns were obtained with principal component analysis. Nutritional assessment was done using the Patient Generated Subjective Global Assessment and body composition was evaluated with anthropometric measures, bioelectrical impedance (BIA), and Computerized Tomography image processing obtained at the third lumbar vertebrae. Sex and Body Mass Index specific cutoffs by Martin et al. were used to define sarcopenia[50].

Results: Sarcopenia prevalence was 32% (n=32). Sarcopenic patients were older (69.92±10.64 vs. 67.53±10.9, p=0.003) and had a worse performance status (ECOG≥3 25% vs. 6% p=0.06). Sarcopenic patients had a lower mean BMI (24.2±3.7 vs. 26.9±5.9, p=0.03) although 53.1% of them were overweight/obese. CT defined sarcopenia could not be detected with many commonly used anthropometric and BIA measurements. Four major patterns were identified: high fat dairy products, fried snacks and processed meat diet, legumes, vegetables and fruit diet, fat and fish diet and alcohol, cereal, and animal protein diet. On simple logistic regression, the occurrence of sarcopenia in subjects in the second (OR: 0.30; CI95%:0.10-0.83, p=0.02) and third tertile (OR: 0.24; IC: 0.08-0.69, p=0.01) of adhesion to the high fat and fish diet was reduced in comparison with the first tertile. On multiple logistic regression, the second tertile (OR: 0.38, CI95%:0.11-1.19, p=0.10) of the fat and fish dietary pattern maintained a trend towards a reduction of the odds of sarcopenia, compared with the first tertile, independently of calorie intake, age, disease location and stage.

Conclusion: The Fat and fish pattern was associated with lower odds of sarcopenia in this population of GI cancer.

Keywords: Dietary patterns, cancer, body composition

1. Introduction

Cancer cachexia is a highly prevalent multifactorial syndrome characterized by the ongoing muscle loss, with or without fat loss[111]. Sarcopenia (severe muscle depletion), is a key feature of cancer cachexia and affects 26-78.7% of gastrointestinal (GI) cancer patients[44,264]. Sex and Body Mass Index (BMI) specific cutoffs for computed tomography (CT) derived skeletal muscle index, have been previously reported to define sarcopenia[50]. It is well established that sarcopenia is associated with a worse outcome and recent research has focused on feasibility and effects of diet and exercise on body composition[121,159,265–267] , but scientific evidence is still lacking.

Previous studies have shown that: 1) cancer patients are able to maintain protein synthesis provided that they receive a higher amount and type of protein/amino acids [268,269]; 2) n-3 polyunsaturated fatty acids may be linked to skeletal muscle maintenance[270] and 3) cancer patients maintain a capacity for muscle anabolism even until advanced stages[271], suggesting opportunity for nutritional status optimization through dietary intervention.

Given the known effects of single nutrients on skeletal muscle and that dietary patterns may be more relevant than single nutrient intake, due to an expected synergistic effect of foodstuffs consumed, we hypothesized that dietary patterns could be linked to the odds of cancer-related sarcopenia. Furthermore, as a secondary objective, our aim was to compare various body composition techniques.

Materials and Methods:

Study population

The study protocol was approved by the Scientific and Ethics Committee of Hospital Beatriz Ângelo in Loures, Portugal. From October 2014 till December 2015 a total of 100 outpatients aged 18 or more, with a recent diagnosis of GI cancer and untreated, were consecutively enrolled in this prospective study. Informed consent was obtained. Clinical data was

prospectively collected from electronic charts, however the present study reports on baseline data. Data was coded to maintain pseudo anonymity. Variables concerning disease location were categorized as hepatic-biliary-pancreatic cancer, upper (esophagus, gastric) and lower (colorectal cancer) GI. Disease stage was categorized in stage I, II, III versus stage IV disease for non-metastatic and metastatic disease respectively.

Performance Status was assessed with Eastern Cooperative Oncology Group (ECOG) Performance Status scale[272] and Quality of life with the European Organization for Research and Treatment of Cancer (EORTC) version 3.0 questionnaire[273]. Physical activity was assessed with the International Physical Activity Questionnaire[274], previously validated for the Portuguese population.

Patient Generated Subjective Global Assessment (PG-SGA) assessment[275,276] was conducted by a single experienced dietitian (SV) and patients were classified as well nourished (SGA A), moderately or suspected of being malnourished (SGA B) or severely malnourished (SGA C). Body weight was measured with a digital scale (SECA) and height with a stadiometer. Body Mass Index (BMI) was calculated, and BMI classification was done according to the following categories: < 20.0, underweight; 20.0 to 24.9, normal weight; 25.0 to 29.9, overweight; and 30.0 kg/m^2, obese. Other anthropometric measurements as triceps skinfold, arm and waist circumference were also recorded. Moreover, fat free mass, body fat, total body water, phase angle, as well as raw data as resistance and reactance were obtained with bioelectrical impedance analysis (BIA) (Bodystat 1500 MDD).

Since Computed Tomography (CT) imaging is part of the clinical staging of GI cancer patients, CT images were used for body composition analysis. CT methodology is highly precise to quantify specific tissues and to predict whole-body composition[22]. Images were selected by Radiologists at the 3rd lumbar vertebra (L3) using a portal venous phase and were processed with specific software which performed an automatic segmentation of tissue cross-sectional areas, with manual corrections by the Radiologist. Segmentation of tissue cross-sectional areas was conducted according to the following Hounsfield unit (UH) thresholds: –29 to 150 for skeletal muscle, –190 to –30 for subcutaneous and intra-muscular

adipose tissue and –50 to –150 for visceral adipose tissue. Cross-sectional skeletal muscle, visceral fat and subcutaneous fat were recorded in cm^2 and mean muscle radiation attenuation in HU. Skeletal Muscle Index (SMI-cm^2/height^2) was calculated. Sex specific cut-offs for SMI and Muscle Radiation Attenuation as defined by Martin L et al.[50] were used to define sarcopenia and low muscle radiation attenuation, since there are no published cut-offs for the Portuguese population.

Dietary intake

Dietary intake was assessed with Semi-quantitative Food Frequency Questionnaire (FFQ) developed for the Portuguese population[277,278]. This questionnaire includes 86 commonly eaten food, or drinks and participants were asked to estimate the amount and frequency of intake of each food/drink according to frequency and amount. Conversion of foodstuffs to nutrients was conducted with software Food Processor Plus (ESHA Research, Salem, Oregon) adapted to the Portuguese commonly eaten food or drinks. This questionnaire was filled out during the interview with the Dietitian.

Statistical Analysis

Data analysis was performed with SPSS (IBM, version 20) and R (version 3.0.2) and statistical significance was set at $p \leq 0.05$.

Shapiro-Wilk test was used to test for the adjustment of continuous variables to the normal distribution and differences in means were analyzed by t-test or Mann Whitney U test as appropriate. The association between categorical variables was tested with Chi-squared test. Correlations among body composition techniques were evaluated using Pearson or Spearman coefficients, selected based on the normality of the variables. Analysis of Covariance (ANCOVA) was conducted to test for differences in mean dietary intakes while adjusting for BMI.

A total of 86 food items were categorized in 23 food groups (**table 1**), according to their nutritional composition similarity. Principal Component Analysis (PCA) with varimax rotation, was performed as previously described [279], [280]. The suitability of the data for PCA

was analyzed with Kaiser-Meiyer-Olkin (KMO) and Bartlett´s test of sphericity. The KMO, a measure of sampling adequacy for PCA was 0.61, which is above the established cut-off of 0.5, indicating that PCA can be performed[281]. Barlett test which tests the null hypothesis that the correlation matrix is an identity matrix, was statistically significant (<0.001) thereby showing that variables are correlated, and ACP is appropriate. The decision to retrieve dietary patterns was based on an eigenvalue above 1, visual scree plot analysis and interpretability[281]. Food groups were considered as relevant to a dietary pattern if the loading coefficient was greater than 0.3[282]. The score of each subject to each specific dietary pattern was computed with SPSS during PCA analysis, which was converted to percentiles and categorized in tertiles.

Simple logistic regression was used to relate each variable with sarcopenia. For continuous variables, linearity of the logit in the predictor was assessed using a cubic spline and Wald test of linearity[257]. Since for age linearity was not clear on cubic spline graphs (p-values of Wald test of linearity was 0.15), this variable was categorized as less than 70 years and 70 years or older. Only variables with p-value≤0.25 or considered clinically relevant were selected to multiple logistic regression. Two multiple logistic regression models were adjusted without automatic stepwise variable selection, since with this method, important variables, such as calorie intake and disease location were discarded. Multicollinearity was also analyzed through the observation of variance inflation factors. Receiver Operating Characteristic (ROC) curve were computed and the respective area under the curve (AUC) was calculated to assess accuracy of both models. The positive predictive value (PPV) and the negative predictive value (NPV) were also given.

Because assumptions of ANOVA failed namely homogeneity of variances (tested with Levene's test) and/or adjustment of the dependent variable to a normal distribution within each tertile (graphical analysis of P-P plots of studentized residuals), Kruskal Wallis test was used to test for differences between the means of continuous variables and tertiles of adhesion to the fat and fish diet. Post-hoc multiple comparisons were conducted with pairwise analysis.

Table 1- Food groupings for dietary pattern analysis.

Food Group	Examples
Processed meat	Sausage, Bacon, Ham
Animal protein	Eggs, Chicken, Turkey, Rabbit, Pork, Cow, Liver, Cow ‘s Tongue
Fish	Sardines, Cod fish, Tuna, Squid, Octopus, Shrimp
Low fat dairy products	Skim milk, low fat milk, low fat yogurt
High fat dairy products	Whole milk, Desserts, Ice Cream
Vegetables	Cabbage, Broccoli, Cauliflower, Green beans, Carrots, Onions, Turnip, Tomato
Fresh fruits	Pear, Apple, Orange, Banana, Kiwi, Strawberry, Cherries, Peach, Fig
Low sugar drinks	Tea, coffee
High sugar drinks	Commercial fruit juice, Cola, Commercial Iced tea
Alcohol drinks	Beer, Wine, Whiskey
Legumes	Chickpea, kidney bean, black-eyed beans
Potato	
Cereal derived	Whole-grain bread, pasta, rice, cereals
Nuts	
Olive oil	Olive oil, olives
Sugar	
High fat snacks	Cookies, chocolates
Processed fruit	Jam, marmalade, canned fruit
Margarine	
Butter	
Portuguese fried snacks	Fried cod fish cakes, “croquetes”, “rissois”
Plant oil	
Soup	

Food Group	Examples
Fast food	Pizza, French fries, Hamburger, Ketchup

Results

Characteristics of the studied population

Table 2 presents characteristics of the population. 32% of patients presented with sarcopenia. Sarcopenic patients were older, had a more advanced disease stage, worse performance status and lower mean BMI. Regarding BMI categories both normal weight and overweight had the highest percentage of sarcopenic patients. In respect to dietary intake, we observed that sarcopenic patients had a significantly lower total calorie, protein, and fat daily intake, whereas no difference was found for carbohydrate intake. After adjusting for BMI, differences in calorie (p=0.013), protein (p=0.013) and fat (p=0.002) remained statistically significant, whereas differences in carbohydrate (p=0.454) intake remained non-significant.

Table 2 - General characteristics of participants.

	Total (n=100)	Sarcopenic (n=32)	Non-sarcopenic (n=68)	p-value	OR	95%CI	p-value
Age	69.49±11.15	69.92±10.64	67.53±10.9	0.003	1.05	1.01- 1.10	0.01
Age categorized							
<70 (years)	50 (50%)	10 (31.2%)	40 (58.8%)	0.010	1.00		
≥70 (years)	50 (50%)	22 (68.8%)	28 (41.2%)		3.14	1.31-7.912	0.01
Gender							
Female	34 (34%)	11 (34.4%)	23 (33.8%)	0.957	1.00		
Male	66 (66%)	21 (65.6%)	45 (66.2%)		0.97	0.40-2.41	0.95
Disease Location							
Upper GI	37 (37%)	9 (28.1%)	28 (41.2%)	0.276	1.00		
Lower GI	54 (54%)	21 (65.6%)	33 (48.5%)		1.97	0.79- 5.19	0.15
hepatic-biliary-pancreatic	9 (9%)	2 (6.2%)	7 (10.3%)		0.88	0.11- 4.53	0.89
Disease Stage							
Non-metastatic	76 (76.0)	20 (62.5%)	56 (82.4%)	0.03	1.00		
Metastatic	24 (24.0)	12 (37.5%)	12 (17.6%)		2.80	1.08-7.32	0.03

	Total (n=100)	Sarcopenic (n=32)	Non-sarcopenic (n=68)	p-value	OR	95%CI	p-value
High GI Obstruction[1]							
No	74 (74%)	26 (81.2%)	48 (70.6%)	0.26	1.00		
Yes	26 (26%)	6 (18.8%)	20 (29.4%)		0.55	0.18- 1.48	0.26
Smoking habits							
No	82 (82%)	27 (84.4%)	55 (80.9%)	0.67	1.00		
Yes	18 (18%)	5 (15.6%)	13 (19.1%)		0.78	0.23-2.31	0.67
Performance Status							
0	35 (35.4%)	11 (34.4%)	24 (35.8%)	0.06	1.00		
1	37 (37.4%)	8 (25.0%)	29 (43.3%)		0.60	0.20- 1.72	0.34
2	15 (15.2%)	5 (15.6%)	10 (14.9%)		1.09	0.28-3.89	0.89
3	11 (11.1%)	7 (21.9%)	4 (6.0%)		4.36[2]	1.12-19.41	0.04
4	1 (1.0%)	1 (3.1%)	0 (0%)				
Quality of life							
Function	52.50±24.24	54.39±23.94	51.5±24.78	0.592	1.00	0.98- 1.02	0.58
Symptoms	33.56±23.07	35.88±22.09	32.42±23.62	0.314	1.00	0.98- 1.02	0.48
Global score	47.91±21.76	44.79±25.64	49.47±19.57	0.367	0.98	0.97-1.00	0.31

	Total (n=100)	Sarcopenic (n=32)	Non-sarcopenic (n=68)	p-value	OR	95%CI	p-value
Patient Generated Subjective Global Assessment							
Well Nourished	27 (27%)	7 (21.9%)	20 (29.4%)	0.579	1.00		
Severely Malnourished	34 (34%)	13(40.6%)	21 (30.9%)		1.26	0.43- 3.95	0.66
Moderately Malnourished	39 (39%)	12 (37.5%)	27 (39.7%)		1.76	0.59-5.55	0.31
Physical activity							
Low physical activity	60 (60%)	22 (68.8%)	38 (55.9%)	0.220	1.00		
Moderate physical activity	40 (40%)	10 (31.2%)	30 (44.1%)		0.57	0.22-1.37	0.22
Body Mass Index (kg/m^2)	26.08±5.4	24.2±3.7	26.9±5.9	0.03	0.89	0.81-0.97	0.02
Body Mass Index							
Low weight	6 (6%)	2 (6.2%)	4 (5.9%)	0.005	1.00		
Normal weight	42 (42%)	13 (40.6%)	29 (42.6%)		0.89	0.15- 7.05	0.90
Overweight	31 (31%)	16 (50.0%)	15 (22.1%)		2.13	0.36- 17.05	0.41
Obesity	21 (21%)	1 (3.1%)	20 (29.4%)		0.10	0.004-1.27	0.09

	Total (n=100)	Sarcopenic (n=32)	Non-sarcopenic (n=68)	p-value	OR	95%CI	p-value
Dietary Intake							
Calorie intake (kcal/day)	2782.3±889.0	2451.6±803.1	2937.9±890.2	0.013	0.99	0.998-0.999	0.01
Calorie intake (kcal/kg)	41.1±14.6	37.3±12.6	43.0±15.1	0.07	0.97	0.93- 1.00	0.07
Protein(g/day)	105.5±33.3	93.9±34.2	111.0±31.7	0.01	0.98	0.96-0.99	0.02
Protein (g/kg)	1.56±0.6	1.42±0.5	1.63±0.6	0.08	0.51	0.21-1.09	0.09
Carbohydrates (g/day)	290.3±106.9	277.7±103.5	296.2±108.8	0.261	0.99	0.99-1.00	0.42
Carbohydrates (g/kg)	4.3±1.7	4.2±1.5	4.37±1.5	0.674	0.94	0.72-1.20	0.63
Fat (g/day)	125.7±49.25	103.1±44.64	136.3±48.0	0.001	0.98	0.97-0.99	0.003
Fat (g/kg)	1.9±0.8	1.6±0.7	2.0±0.8	0.01	0.47	0.24-0.85	0.02
High fat dairy products, fried snacks, and processed meat							
1st Tertile	33 (33%)	9 (28.1%)	24 (35.3%)	0.12	1.00		
2nd Tertile	33(33%)	15 (46.9%)	18 (26.5%)		2.22	0.80-6.39	0.12
3rd Tertile	34 (34%)	8 (25.0%)	16 (38.2%)		0.82	0.26-2.48	0.72
Legumes, vegetables, and Fruit diet							
1st Tertile	33 (33%)	13 (40.6%)	20 (29.4%)	0.53	1.00		
2nd Tertile	33(33%)	9 (28.1%)	24 (35.3%)		0.57	0.19-1.61	0.29

	Total (n=100)	Sarcopenic (n=32)	Non-sarcopenic (n=68)	p-value	OR	95%CI	p-value
Legumes, vegetables, and Fruit diet (cont.)							
3rd Tertile	34 (34%)	10 (31.2%)	24 (35.3%)		0.64	0.22-1.76	0.39
High fat and fish diet							
1st Tertile	33 (33%)	17 (53.1%)	16 (23.5%)	0.01	1.00		
2nd Tertile	33(33%)	8 (25.0%)	25 (36.8%)		0.30	0.10-0.83	0.02
3rd Tertile	34 (34%)	7 (21.9%)	27 (39.7%)		0.24	0.07-0.69	0.01
Alcohol, cereal, and animal protein diet							
1st Tertile	33 (33%)	11 (34.4%)	22 (32.4%)	0.92	1.00		
2nd Tertile	33(33%)	11 (34.4%)	22 (32.4%)		1.00	0.35-2.80	1.00
3rd Tertile	34 (34%)	10 (31.2%)	24 (35.3%)		0.83	0.29-2.35	0.73

Comparison of body composition techniques

CT defined sarcopenia could not be detected by many commonly used anthropometric measures, since no differences between sarcopenic and non-sarcopenic patients were found for waist circumference, triceps skin fold, arm muscle and fat area. When sarcopenic and non-sarcopenic patients were compared according to body composition data from BIA, the only significant differences refer to higher mean body water (p=0.05) and lower phase angle (p=0.04) in sarcopenic patients (**table 3**).

Table 3- Anthropometric measurements and bioelectrical impedance analysis for sarcopenic and no-sarcopenic patients.

	Total (n=100)	**Sarcopenic (n=32)**	**Non-Sarcopenic (n=68)**	**p-value**
Anthropometric measures				
Weight (kg)	61.57±16.21	67.71±14.49	71.38±16.55	0.286
Weight loss (kg)	4.40±8.27	5.58±8.20	2.82±7.74	0.05
BMI (kg/m^2)	26.07±9.07	24.20±3.70	26.95±5.92	0.03
Waist Circumference (cm)	92,77±16.06	97.25±12.25	96.61±14.50	0.832
Triceps Skinfold (mm)	21.91±8.21	17.25±7.42	20.22±9.24	0.115
Arm Muscle Area (cm^2)	30.59±11.63	27.80±8.47	31.10±11.41	0.149
Arm Fat Area (cm^2)	13.30±13.49	9.38±7.56	15.17±15.24	0.127
Bioelectrical Impedance Analysis				
Fat Free Mass (kg)	39.60±12.51	49.04±12.95	48.49±12.11	0.839
Fat Mass (kg)	28.32±13.94	20.54±11.45	24.50±10.73	0.10
Body Water	53.69±9.21	59.86±8.96	55.95±8.24	0.05
Phase Angle	5.12±1.10	5.57±2.53	5.82±1.47	0.04

Considering CT imaging as the golden standard, total fat area correlated with BMI (r=0.862, p<0.001) and waist circumference (r=0.852, p<0.001); subcutaneous fat area with fat mass

from BIA (r=0.810, p<0.001) and visceral fat area with waist circumference (r=0.782, p<0.001). Skeletal muscle area from CT imaging was correlated with fat free mass from BIA (r=0.745, p<0.001). However, in absolute values no agreement was found between estimated whole body skeletal muscle using CT and BIA. Either weak or non-significant correlations were mostly observed between muscle radiation attenuation and anthropometry/BIA **(table 4).**

Table 4- Correlations between body composition measurements assessed with anthropometry, bioelectrical impedance and computed tomography.

		Anthropometric measures				**Bioelectrical impedance**	
		BMI	Arm Muscle Area	Arm Fat Area	Triceps Skinfold	Waist Circumf.	FFM	FM
CT-scan imaging	Skeletal muscle area	r=0.452 p<0.001	r=0.214 p=0.03	--	--	r=0.424 p<0.001	r=0.722 p<0.001	--
	Visceral fat area	r=0.679 p<0.001	--	r=0.253 p=0.01	r=0.207 p=0.04	r=0.782 p<0.001	--	r=0.493 p<0.001
	Subcutaneous fat area	r=0.768 p<0.001	--	r=0.531 p<0.001	r=0.471 p<0.001	r=0.645 p<0.001	--	r=0.810 p<0.001
	Total fat area	r=0.862 p<0.001	---	r=0.515 p<0.001	r=0.450 p<0.001	R=0.852 P<0.001	--	r=0.719 p<0.001
	Muscle Radiation Attenuation	r=-0.215 p=0.03	ns	ns	ns	r=-0.448 p<0.001	ns	r=-0.306 p=0.002

BMI-Body Mass Index, FFM-Fat Free Mass, FM-Fat Mass, Waist Circumf. – circumference.

Dietary patterns

Four major patterns were identified with PCA: 1) high fat dairy products, fried snacks and processed meat pattern, 2) legumes, vegetables and fruit pattern, 3) fat and fish pattern and 3) alcohol, cereal, and animal protein pattern. These patterns explained 37.2% of the overall variance. The first pattern was defined with food stuffs such as high fat dairy products, fried Portuguese snacks, processed meat, and nuts (with or without salt), which presented high loadings (>0.3). The second pattern had high loadings for legumes, vegetables, potatoes, soup, and fresh fruit. The third pattern had high loadings for olive oil, butter, high fat snacks (cookies and chocolates) and fish. Lastly the fourth pattern had high loadings for alcoholic drinks, cereal derived products, fast food, and animal protein. **Table 1** shows food groupings for dietary pattern analysis and **Table 5** summarizes the results from PCA.

Table 5- Factor loading matrix for main dietary patterns.

	High fat dairy products, fried snacks, and processed meat diet	**Legumes, vegetables, and Fruit diet**	**Fat and fish diet**	**Alcohol, cereal, and animal protein diet**
High fat dairy products	0.877			
Portuguese fried snacks	0.846			
Processed meat	0.791			
Nuts (with and without salt)	0.346			
Legumes		0.828		
Vegetables		0.805		
Potatoes		0.464		
Soup		0.424		
Fresh fruit		0.319		
Olive Oil			0.751	
Butter			0.728	
High Fat snacks			0.381	
Fish			0.344	
Alcoholic drinks				0.776
Cereal derived products				0.627
Fast Food				0.551
Animal protein				0.424
% of Variance explained	12.2	9.4	7.8	7.8

Values <0.30 were excluded for simplicity.

Dietary patterns and sarcopenia

Simple logistic regression was performed to explore which variables are associated with sarcopenia. The results of this analysis are presented on **Table 2**. This analysis indicated that patients with higher odds of sarcopenia were older, had worse performance status and more advanced disease stage, whereas calorie intake was associated with lower odds of sarcopenia. Regarding dietary patterns, patients in the second and third tertile of adhesion to the fat and fish pattern presented significantly lower odds of sarcopenia. No association was found with other patterns.

Since the fat and fish diet was the only pattern with a significant association with sarcopenia, multiple logistic regressions focused on this pattern. **Table 6** reports on the results from multiple logistic regressions. Interpretation of the variables was done considering that the subjects had the same values on all variables, except for the one being compared. In **Model I** we adjusted for age, fat and fish pattern and calorie intake. According to this analysis the odds of sarcopenia was almost three times higher in patients with age ≥ 70 compared with patients with age <70. The odds of sarcopenia were reduced in 67% in patients in the second tertile and 68% in the third tertile, compared with the first tertile of adhesion to the fat and fish diet, independently of calorie intake.

Model II further adjusts for clinical variables namely disease location, disease stage, age, and calorie intake. Again, the odds of sarcopenia were three times higher in patients age ≥70, compared with patients age <70. Besides age, disease stage was the only clinical variable associated with sarcopenia, as the odds of sarcopenia was three times higher in patients with metastatic disease, when compared with non-metastatic patients. Lastly, a trend was found for a reduction of 62% of the odds of sarcopenia for patients in the second tertile of the fat and fish diet when compared with the first tertile of adhesion to the fat and fish diet.

The area under the curve (AUC) obtained through Receiver Operating Characteristic (ROC) curve analysis was 0.727 and 0.767, for Model I and Model II, respectively (**Figure 1**). These

AUC show a fair discriminatory ability of both models in the prediction of sarcopenia. ROC curves are presented on figure 1. Sensitivity was 59.4%, specificity was 76.5%, positive predictive value was 20% and negative predictive value was 45.7% for Model I. Sensitivity was 62.5%, specificity was 82.4%, positive predictive value was 17.6% and negative predictive value was 37.5% for Model II.

Participant's characteristics according to compliance to Fat and Fish pattern

Table 7 shows the studied population characteristics across tertiles of adhesion to the fat and fish pattern. According to this analysis patients did not differ in respect to clinical, anthropometric and body composition, except for the proportion of sarcopenic patients. Patients with a lower adhesion to the fat and fish pattern, showed a higher proportion of sarcopenia.

Regarding dietary intake, patients in the second tertile were characterized as having a similar calorie and protein intake normalized by body weight and carbohydrate intake as patients in the first tertile. The main difference was a higher lipid intake, but not as high as observed for the third tertile and the highest mono+polyunsaturated fat: saturated fat ratio. Also, patients in the second tertile had an energy intake predominantly above 30kcal/kg, a high lipid intake (only one patient had a lipid intake below 30% of total calorie intake) and a higher proportion of patients were within the ESPEN recommendations of protein intake.

Table 6: Model I and II for sarcopenia as dependent variable obtained with multiple logistics regression.

	Model I			Model II		
Variables	**OR**	**95%CI**	**p-value**	**OR**	**95%CI**	**p-value**
Disease location	Not Included					
Upper GI				1.00		
Lower GI				1.75	0.62-5.13	0.28
Hepatic-biliary-pancreatic				0.58	0.06-3.69	0.59
Disease Stage	Not Included					
Non-metastatic				1.00		
Metastatic				3.4	1.13-10.87	0.03
Age						
<70	1.00			1.00		
≥70	2.83	1.09- 7.71	0.03	3.2	1.17-9.23	0.03
Fat and fish Diet						
1st Tertile	1.00			1.00		
2nd Tertile	0.33	0.10- 0.98	0.05	0.38	0.11-1.19	0.10
3rd Tertile	0.32	0.08-1.18	0.08	0.45	0.11-1.84	0.26
Calories	0.99	0.99-1.00	0.38	0.99	0.99-1.00	0.37

OR-Odds Ratio, 95% IC-95% Confidence Interval.

Table 7- Fat and fish diet and participants clinical characteristics, anthropometric measures, body composition and dietary intake.

	Fat and fish diet			
	1st Tertile (n=33)	2nd Tertile (n=33)	3rd Tertile (n=34)	p-value
Age				
<70	15(30.0)	17(34.0)	18(36.0)	0.810
≥70	18(36.0)	16(32.0)	16(32.0)	
Gender				
Female	14(41.2)	9(26.5)	11(32.4)	0.417
Male	19(28.8)	24(36.4)	23(34.8)	
Disease location				
Upper GI	11(23.9)	18(39.1)	17(37.0)	0.190
Lower GI	22(40.7)	15(27.8)	17(31.5)	
Disease stage				
<IV	22 (28.9)	24(31.6)	30(39.5)	0.102
IV	11(45.8)	9(37.5)	4(16.7)	
Physical activity				
Low	30(33.7)	27(30.3)	32(36.0)	0.250
Moderate	3 (27.3)	6 (54.5)	2 (18.2)	
Anthropometric measures				
Weight loss	5.29±9.4	3.82±6.2	2.00±7.8	0.292
BMI	25.7±5.6	26.3±4.5	26.2±6.2	0.866
Arm circumference	27.5±3.7	28.2±3.7	28.0±3.67	0.707
Triceps skinfold	19.1±9.9	18.61±7.3	20.1±9.1	0.793
Waist circumference	96.7±12.7	97.8±12.8	96.1±15.9	0.880

	Fat and fish diet			
	1st Tertile (n=33)	2nd Tertile (n=33)	3rd Tertile (n=34)	p-value
Body Composition				
Skeletal Mass Area				
Female	104.3±15.4	106.3±16.7	108.9±21.7	0.918
Male	136.0±30.2	148.82±28.5	145.03±23.4	0.353
Skeletal Mass Index				
Female	43.4±8.1	45.5±6.3	44.5±7.2	0.684
Male	47.9±10.3	52.2±9.3	51.5±9.6	0.264
Sarcopenia	17 (17%)	8 (8%)	7 (7%)	0.013
Muscle attenuation	28.8±9.8	29.5±8.5	31.2±8.7	0.528
Low Muscle radiation attenuation	29 (29%)	30 (30%)	29 (29%)	0.779
Visceral fat area	165.3±112.1	200.5±89.4	158.1±126.6	0.100
Subcutaneous fat area	149.5±91.4	159.7±67.2	178.9±126.2	0.648
Total Fat area	314.81±174.9	360.2±137.7	337.1±214.1	0.445
Dietary Intake				
Calories (Kcal/kg)	35.4±17.1	38.5±10.2	49.3±12.0†	<0.001
Calorie intake (<25 kcal/kg)	11 (33.3%)	2 (6.1%)	0(0%)	<0.001
Calorie intake (>30 kcal/kg)	17 (51.5%)	28(84.8%)	34 (100%)	
Protein (g/kg)	1.4±0.6	1.6±0.4	1.8±0.6‡	0.012
Protein intake (1.2-2g/kg)	14 (42.4%)	22 (66.7%)	20 (58.8%)	0.003
Carbohydrates (g/day)	274.0±116.4	267.3±82.3	328.4±111.0‡	0.023
Lipids (g/day)	84.6±42.1†	122.0±28.3†	169.0±33.8†	<0.001
Lipids (% Total calorie daily intake)	33.7±8.3†	41.4±6.4	45.9±8.3	<0.001
Lipid intake <30% of Total calorie daily intake	12 (85.7%)	1(7.1%)	1(7.1%)	<0.001
Monounsaturated:saturated ratio	2.0±0.6†	2.5±0.6	2.3±0.3	0.003
Mono+Poliunsaturated:saturated ratio	2.6±0.7†	3.0±0.7†	2.8±0.6†	<0.001

†Significantly different from the other groups, ‡ pairwise significant difference between the lowest and highest tertile.

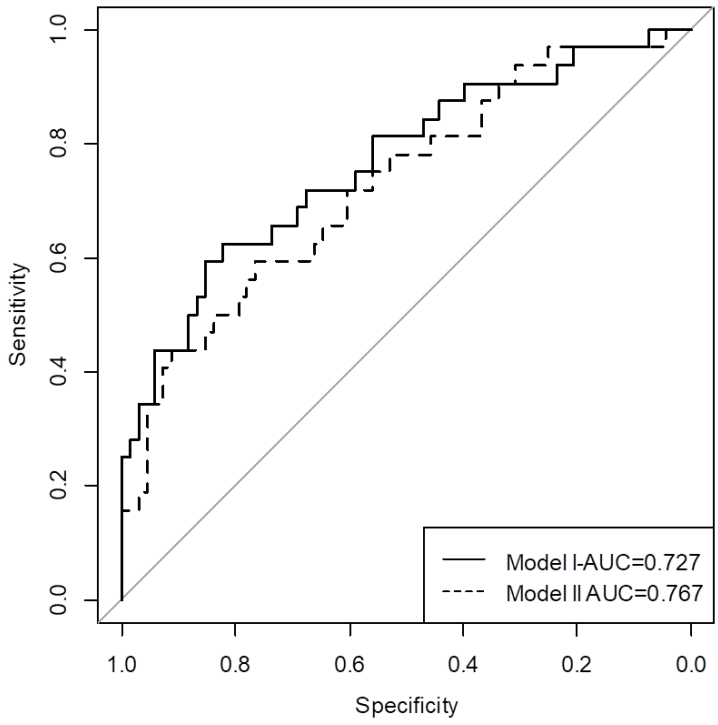


Figure 1- Receiver Operating Characteristic (ROC) curve analysis for Model I and II.

Discussion

To our knowledge this is the first study examining the relationship between dietary patterns and sarcopenia in a population of GI cancer patients. We identified 4 dietary patterns but only the fat and fish diet were associated with a lower odds of sarcopenia. Furthermore, in our study, we observed correlations between CT scans and anthropometry/BIA. However, relying solely on anthropometry and BIA for body composition assessment proved insufficient in identifying crucial phenotypes such as sarcopenia and fat infiltration in skeletal muscle tissue.

After the seminal paper of Martin et al.[50], several other studies have clearly demonstrated that alterations in body composition, namely sarcopenia, in cancer patients is a very important prognostic marker[235], with a high discriminant power in regard to long term survival[50]. However, the most effective way of tackling these alterations with the aim of improving outcome is less clear.

Four main dietary patterns were identified in this prospective study: high fat dairy products, fried snacks and processed meat pattern, legumes, vegetables and fruit pattern, fat and fish pattern and alcohol, cereal, and animal protein pattern. Total variance of dietary intake was mostly explained by a dietary pattern characterized by the first pattern and no explicit Mediterranean dietary pattern was found.

Although in the 60's Portugal was known to have a Mediterranean dietary pattern[283], according to the results of the National Portuguese Report of Dietary Intake and Exercise, Mediterranean dietary pattern is becoming less predominant and only 12% of the Portuguese population are highly compliant with the Mediterranean dietary pattern[284]. This shift in the dietary intake paradigm supports the findings in our study, in which Mediterranean dietary pattern was not explicit, but still foods from Mediterranean dietary pattern were found.

In our study the fat and fish pattern were the only pattern exhibiting a protective effect regarding sarcopenia. This pattern correlated highly with olive oil which is a source of monounsaturated fatty acids (MUFA), butter and high fat snacks which are sources of saturated fatty acids, fish which provides both protein and polyunsaturated n-3 fatty acids and was associated with calorie intake. Interestingly, a trend was found for reduced odds of sarcopenia for patients in the second tertile of the fat and fish pattern, when compared with the first tertile, independently of calorie intake, age, disease location and stage. Patients in the second tertile had a higher percentage of compliance to the target supply of 1.2-2g protein/kg/day, a fat intake higher than general recommendations, but also a higher mono+polyunsaturated fat: saturated fat ratio. In other words, this pattern consisted of a nutrient and energy dense diet that may be protective of muscle loss. It is worth pointing out that high fat snacks such as cookies and chocolate, also contributed for this association. We hypothesized that these foodstuffs, if consumed within a dietary pattern with healthy fat sources, may facilitate an adequate calorie intake and a balanced overall lipid intake (MUFA+PUFA: saturated fat) depending on the amounts consumed. In our study, patients in the second tertile of the fat and fish diet presented the highest mean MUFA+PUFA: saturated fat ratio.

There is some evidence that in cancer patients lipid oxidation may be normal or increased[285], and according to our results, a higher fat intake may be needed to reduce the odds of sarcopenia. Most studies have focused on the effect of PUFA intake in cancer cachexia, namely n-3 polyunsaturated fatty acids which have demonstrated a beneficial effect in the treatment of age-related sarcopenia[286] and cancer associated muscle wasting[268,287,288]. Eicosapentanoic acid (EPA) is thought to improve anabolism by increasing muscle sensitivity to insulin, but also has been shown to inhibit muscle degradation by down regulation of acute phase response and by decreasing the expression of proteasome subunits[289].

It has been hypothesized that oleic acid, may also be important for muscle health. Data from an animal model of muscular dystrophy (Mdx mice), suggest that high monounsaturated fat (MUFA) may assist muscle in coping with this pathology. In Mdx mice, high oleic acid intake was associated with reduced serum creatine kinase as compared with high PUFA intake[286]. Conflicting results have been shown in regard to MUFA effect on cancer cells[290,291].

Still, studies concerning the relationship of dietary patterns and cancer-related sarcopenia are lacking. In a cross sectional study in Iranian community dwelling elderly, which addressed the association between dietary patterns and sarcopenia, demonstrated that a higher adherence to a dietary pattern consistent with the Mediterranean diet (higher consumption of olive oil, fruits, vegetables, fish and nuts) was associated with a lower odds of age-related sarcopenia[279], which is in line with our results. In a recent systematic review, the authors conclude that there is some cross sectional evidence of an association between diet quality and the odds of sarcopenia[292].

In comparing body composition techniques, it's notable that inconsistencies between CT-derived body composition and BIA have been documented in previous studies[293]. This underlines the necessity of integrating CT-derived body composition assessments into clinical practice, as they can offer more comprehensive insights, especially regarding specific phenotypes like low muscle radiation attenuation, which may not be effectively

captured by other methods. Nevertheless, this doesn't discredit techniques such as anthropometry or BIA, as each approach has its merits and limitations. Therefore, it's imperative that these techniques be employed by skilled professionals and that results be interpreted judiciously. Further studies are needed to explore and validate the comparative effectiveness of these techniques.

Lastly, several limitations must be considered in our study. Due to logistic and budget limitations, we performed an exploratory study, with a consecutive convenience sample. We used a FFQ which is susceptible to under or overestimation bias, but is validated for the Portuguese population and is useful in dietary patterns determination[294].

Conclusions

The fat and fish pattern was associated with lower odds of sarcopenia in this Portuguese population of GI cancer. We consider that our study has contributed as a first step in unraveling the association between dietary patterns and sarcopenia. Although correlations between CT scan and anthropometry/BIA were found, body composition assessment with anthropometry and BIA may be insufficient to identify sarcopenia and ow muscle radiation attenuation. Therefore, CT scan analysis should be routinely used in the nutritional assessment of GI cancer patients.

Study 4

Adherence to Combined Exercise and Dietary Intervention in Patients with Gastrointestinal Cancer Undergoing Neo-Adjuvant Therapy: An Open-Label, Pilot, Randomized Controlled Trial

Sónia Velho, Sara Moço, Carolina Capitão, Mariana Branco, Luísa Costa, Sílvia Rodrigues, Cláudia Abreu, Rute Alves, Filipa Pires, Pedro Sousa, Lisa Agostinho, Rita Cruz, Susana Clemente, Ana Borges, Fábio Lopes, João Godinho, Ana Faria, José Alberto Teixeira, José Luís Passos Coelho, Rui Maio, Vickie E Baracos, Marília Cravo.

Contribution of the PhD candidate:

The candidate created and implemented the study protocol and was therefore responsible for coordinating the participation of the departments involved namely Nutrition and Dietetics, Oncology, Pneumology, Physical Medicine and Rehabilitation. She was actively involved in the nutritional intervention of this study and collaborated closely with physiotherapist Claudia Abreu, which was responsible for the exercise component of the intervention. She operationalized the technique regarding CT derived body composition assessment in collaboration with Lisa Agostinho, Rita Cruz, and Pedro Sousa. She then proceeded to analyze the body composition data, using reported thresholds to identify body composition phenotypes. She created the database in collaboration with Carolina Capitão and Mariana Branco, conducted the statistical analysis and interpreted the results. She drafted the paper and participated in its revision util its publication. The paper was then published in Journal of Food Science and Nutrition Research.

Journal of Food Science and Nutrition Research, 05(04), 669–681. https://doi.org/10.26502/jfsnr.2642-110000113

Abbreviations

AM- Anthropometric measures

CEDI- Combined Exercise and Dietary Intervention

CT- Computed Tomography

DLT- Dose-limiting toxicity

ES- Effect size

EORTC- European Organization for Research and Treatment of Cancer

EWGSOP- European Working Group on Sarcopenia in Older People

FFQ- Food Frequency Questionnaire

GI-Gastrointestinal

PG-SGA- Patient Generated Subjective Global Assessment

6MWT-6 min walking test

SMA- Skeletal muscle area

SMI- skeletal muscle index

Abstract

Background: To assess adherence of gastrointestinal cancer patients to a Combined Exercise and Dietary Intervention (CEDI) during neo-adjuvant chemotherapy.

Methods: Parallel randomized controlled, open label, pilot trial. A table from a web-based randomization system was used to allocate treatments. 46 patients were screened at diagnosis of esophageal, gastric, pancreatic, and rectal cancer from June 2018 to November 2019 at a teaching hospital in Loures, 39 were randomized. A planned interim analysis was performed, and results are herein presented. Patients were randomized to receive either 8-week individualized CEDI, with moderate aerobic and resistance training, dietary counseling and oral nutritional supplements or standard care. Follow up was conducted after neo-adjuvant treatment. Main outcome measures were adherence to CEDI, change in weight, body composition and functional status. Adherence to CEDI was analyzed with an intention to treat approach, other outcome measures were analyzed with a per protocol approach**.** Data analysis was conducted with Chi-square test or Fisher exact test and t-test or Mann Whitney U test. Effect size was computed with Cohen's d for t tests and r for Mann-Whitney U tests. Paired-samples t test or Wilcoxon Signed Rank Test were used to analyze longitudinal data.

Results: 39 patients (CEDI n=19 or control n=20) were randomized and included in the intention to treat analysis (29 (74.3%) male, median age 63.5 (Interquartile Range (IQR):11.75)). 32 patients completed follow up. 13/19 (68.4%) were fully adherent to CEDI. CEDI patients maintained weight (Effect size (EF):0.91; 95% Confidence Interval (95%CI): [0.15,1.67]), waist circumference (EF:0.83, 95%CI: [0.05, 1.61]), had a lower skeletal muscle loss (EF:0.79; [-0.18;1.77]) and improved 6 minute walking test distance (EF:1.51; 95%CI: [0.44;-2.57]) and quality of life function score (EF:0.99; 95%CI:[0.13,1.86]). There were 4 serious adverse events, 3 in the intervention and 1 in the control arm but none related to the intervention.

Conclusions: CEDI is feasible, and patients are willing to participate even under neo-adjuvant chemoradiotherapy, resulting in potential nutritional and functional benefits.

Trial registration Trial registry: www.clinicaltrials.gov; Identifier: NCT05237921, 14-2-22, retrospectively registered, https://www.clinicaltrials.gov/ct2/results?cond=&term=NCT05237921&cntry=&state=&city=&dist=

Keywords: Adhesion, Exercise, Diet, Oral Nutritional Supplements, Gastrointestinal Cancer.

Background

Body composition alterations, namely sarcopenia and sarcopenic obesity, are known to have a negative impact on cancer patients outcome[50,51,213,224,235,295–298], but the benefit of intervention strategies, remain unclear.

Exercise has been associated with improved functional status and patient reported outcomes in cancer patients[299,300], but mostly in breast and colorectal cancer survivors[301,302]. In patients undergoing treatment a positive effect has also been observed and exercise has been considered safe and feasible even in advanced cancer[303]. However, optimal exercise frequency, intensity and duration is still open to debate.

On the other hand, dietary intake is also relevant since it seems to have an important role in skeletal muscle maintenance. It has been suggested that cancer patients may experience an anabolic resistance to protein stimuli, but protein synthesis is not completely blunted and may respond to an elevated protein intake[269]. In fact, protein supplementation has proven to improve protein synthesis [268], body composition, muscle strength[304] and walking capacity [121] in cancer patients. Besides the effect of single nutrients, dietary patterns namely a high fat and fish diet, is associated with a reduced odds of sarcopenia[305] and simultaneous energy and protein intake seem to result in a more robust effect on muscle mass and strength[306].

Few studies have investigated the influence of a combined exercise and dietary intervention[307]. Solheim et al have reported on a phase II Multimodal Intervention Exercise, Nutrition and Anti-Inflammatory medication in cachexia (pre-MENAC) versus standard care, showing that this intervention is feasible and safe in patients with incurable lung and pancreatic cancer and may have a positive effect on patients weight[159]. This multimodal approach was designed to address cachexia which is known to be a multidimensional condition[158], and therefore is expected to be a more suitable approach for cancer patients.

The aim of this randomized controlled, open label pilot study was to assess the adherence to a Combined Exercise and Dietary Intervention (CEDI) in patients with GI cancer submitted

to neo-adjuvant chemo(radio)therapy, to pursue other outcome associated studies in the future. Bearing in mind that compliance is a limiting factor to the benefit provided from exercise and diet, assessing adherence to these interventions is paramount before pursuing further studies.

Methods:

Study design and participants.

A parallel randomized controlled, open label pilot trial was conducted. This trial is registered at ClinicalTrials.gov: NCT05237921 and conforms to CONSORT guidelines for randomized controlled trials. Study protocol is available online www.clinicaltrials.gov. Recruitment was conducted at the Oncology center of Hospital Beatriz Ângelo, and patients were consecutively selected by Oncologists during the weekly multidisciplinary meeting. Patients with esophageal, gastric, pancreatic, and rectal cancer, were enrolled at diagnosis if they were eligible for neo-adjuvant chemo/radiotherapy and with age higher than 18 years and lower than 80 years. Before enrollment initiation, besides upper gastrointestinal cancer (as initially planned for), we decided to also include patients with rectal cancer to have a broader view of adherence to CEDI in patients with gastrointestinal cancer under neo-adjuvant treatment, which is in line with the exploratory nature of this study.

Combined Dietary and Exercise Intervention arm.

The intervention group received a supervised combined moderate aerobic and resistance training, once a week with duration of 40-60 minutes plus daily home exercise. All patients were evaluated in respect to their physical condition by a physical medicine and rehabilitation physician, and exercise was administered by a physiotherapist. Exercise was planned within a “slow and low” approach and was personalized according to patients’ age and functional status. The first exercise session was dedicated to full patient evaluation to perceive individual tolerance and to educate regarding home exercises. Most common exercises were aerobic exercises as 10-15 minutes of walking and resistance exercises as squatting with theraband around knees, shoulder flexor strengthening in standing using

theraband and stretching. Educational written and illustrated materials as well as therabands were provided to each patient for home-based exercise.

Besides exercise, the intervention group received a one-on-one nutritional counseling, by a senior and research Dietitian (SV). In the first visit a dietary plan was designed and one daily oral nutritional supplement (Forticare®, Nutricia) was given to meet the European Society of Parenteral and Enteral Nutrition (ESPEN) recommended intake of 25-30kcal/kg/day and 1-1.5g of protein/kg/day[308]. Also, patients were recommended to maintain a fat intake of 30% of total daily calories, with mostly being provided by monounsaturated fat. Patients were suggested to drink the supplements after exercise. All dietary plans were created with Nutrium® software, to obtain personalized dietary plan prescriptions that conveyed nutritional needs targets. Nutrium is a Portuguese software that allows rigorous dietary planning, since it enables the user to set energy and nutrient estimated requirements and to create dietary plans with nutritional composition information determined for Portuguese foodstuffs[309]. Written materials were given to patients and/or caregivers. Follow up visits took place every week during exercise.

Total duration of the intervention was set at 8 weeks, although patients with longer neo-adjuvant treatments, namely patients with rectal cancer, maintained the intervention for a longer period, with a maximum of 12 weeks. Patients were recommended to maintain the dietary plan and exercise during the whole chemotherapy treatment plan. Due to possible symptoms after chemotherapy, namely nausea and vomiting, patients were asked to intensify compliance on the week preceding chemotherapy when there is a higher probability that patients are less symptomatic. Whenever patients did not attend the weekly exercise activity, they were contacted to provide support and to assess if any diet or exercise adjustment was needed with the intention to maximize adherence.

Control arm- Standard care.

Patients allocated to the control arm received standard care, in which patients were referred to the dietitian only when the attending physicians felt there was a need for dietary

intervention. Whenever relevant, exercise was recommended but without personalized training program, which is in accordance to our current practice.

Outcome measures

The primary outcome was intervention adherence, that was evaluated according to five criteria: 1) proportion of patients willing to engage in CEDI; 2) adherence to dietary plan, patients were considered adherent if they have met ≥ 75% of their calorie and protein estimated requirements; 3) adherence to oral nutritional supplements, one supplement per day was prescribed, and supplement intake ≥ 4 weeks was considered acceptable; 4) adherence to exercise, were attendance to the exercise class for at least 4 consecutive weeks was considered acceptable; 5) adherence to CEDI, patients were considered adherent if they were able to meet more than 75% of their calorie and protein estimated requirements/oral nutritional supplementation and adhered to exercise, approximately one month after initiation of CEDI. Dropout rates and reasons for leaving the study were also recorded.

The secondary outcomes included change in weight, waist circumference, CT derived body composition and functional status assessed with hand grip strength, 6MWT and functional score of EORTC quality of life questionnaire. Measurements were conducted before and after neo-adjuvant treatment.

Sample size.

Sample size per group was calculated bearing in mind that according to data form the World Health Organization, 14% of Portuguese adults are compliant to moderate exercise, and in our study adherence will be set as compliance ≥ 50%. Considering a power of 0.80 and an α set at 0.05, 25 patients will be needed per group. A planned interim analysis was performed to substantiate preparation of further study protocols using CEDI, and results are reported in this paper.

Randomization

A table was created by a web-based randomization system to allocate treatments, with an allocation ratio of 1:1. Stratified block randomization using random block size (2, 4 and 6) was conducted to allocate patients to standard care and to intervention with CEDI. Stratification was performed according to disease location. Patients eligible to enter the study were referred by Oncologists, and after obtaining consent patients were enrolled in the study by researcher (SV), which was responsible for allocation consignment.

Procedures

Clinical data

Demographic and clinical data as age, gender, tumor site, histological type, TNM staging, Chemotherapy toxicity, overall survival were prospectively recorded and retrieved from electronic records. Chemotherapy toxicity was graded according to National Cancer Institute Common Toxicity Criteria. Dose-limiting toxicity (DLT) was defined as any grade 3/4 toxicity associated with physician-ordered dose reduction or termination of therapy and chemotherapy delay. This data was collected by Oncologists. The most common neoadjuvant treatments were: FLOT (5-Fluorouracil, Folinic acid, Oxaliplatin, Docetaxel) for gastric, XELOX (Oxaliplatine and Capecitabine) followed by Capecitabine plus radiotherapy for rectal, Carboplatine/Paclitaxel and radiotherapy for esophagus and FOLFIRINOX (5-Fluorouracil, Irinotecan and Oxaliplatin) for pancreatic cancer patients. Duration of neo-adjuvant therapies varied from 8 to 12 wks.

Anthropometric measures and nutritional assessment

Anthropometric measures (AM) such as weight and height were obtained, and Body Mass Index was calculated. All AM were performed according to previously established protocols [310]. Patient Generated Subjective Global Assessment (PG-SGA) was conducted by an experienced dietitian and patients were classified as well nourished (SGA A), moderately or

suspected of being malnourished (SGA B) or severely malnourished (SGA C). Assessments were conducted before and after neo-adjuvant treatments.

Body composition assessment

Cross-sectional imaging evaluation

Body composition analysis was conducted with Computed Tomography (CT) scan image analysis[50]. Images were selected at the third lumbar vertebra (L3) using a portal venous phase. CT scans were used opportunistically, as CT is performed at diagnosis and after neo-adjuvant treatment. Image thickness was 5mm and tube voltage was 100kv. Images were processed with Slice-o-Matic (Tomovison) and ABCS module that performs automatic segmentation of tissue cross-sectional areas, whereas posterior validation of image processing was done by the Radiologist, with manual corrections as necessary. Segmentation of tissue cross-sectional areas was conducted according to the following Hounsfield unit thresholds: -29 to 150 for skeletal muscle, -190 to -30 for subcutaneous and intramuscular adipose tissue, and -50 to -150 for visceral adipose tissue. Cross-sectional skeletal muscle, visceral fat, and subcutaneous fat was recorded in squared centimeters and mean muscle radiation attenuation in Hounsfield units. Skeletal muscle area (SMA) was normalized for stature to calculate the skeletal muscle index (SMI) - cm^2/m^2. Sarcopenia was defined as SMI lower than 41 cm^2/m^2 in women, lower than 43 cm^2/m^2 in men with body mass index (BMI) <25 Kg/m^2 and lower than 53 in men with BMI > 25 Kg/m^2 as described by Martin et al.[50]. Visceral obesity was defined as visceral fat area >130cm^2 [62]. An inter-reliability analysis was conducted, and variance coefficients computed for two duplicate CT scans was 0.32%, 1.09%, 0.39% and 4.04%, for skeletal muscle, visceral adipose tissue, subcutaneous adipose tissue, and intramuscular adipose tissue areas, respectively.

Dietary Intake assessment

Dietary intake was assessed with a Semi-quantitative Food frequency questionnaire to estimate dietary intake of both the intervention and control group before and after neo-adjuvant therapy and 24h recalls to assess dietary intake of patients undergoing CEDI at every 2 weeks to estimate compliance to established dietary goals.

The Semi-quantitative Food Frequency Questionnaire (FFQ) used, was developed for the Portuguese population[278] and is designed to evaluate usual dietary intake. This questionnaire includes 86 commonly eaten food, or drinks and participants were asked to estimate the amount and frequency of intake of each food/drink according to frequency and amount, at baseline and before surgery. Conversion of foodstuffs to nutrients was conducted with software Food Processor Plus (ESHA Research, Salem, Oregon) which has been adapted to the Portuguese commonly eaten food or drinks.

The 24h recall using a modified USDA five-pass method consists in 5 steps where the first is to list all foods consumed on the previous 24h. On the second step the interviewer asks about possible forgotten food items. In the third step the interviewer clarifies the time and occasion of the consumed foods and on the fourth step clarifies portion size[311]. Conversion of foodstuffs to nutrients was conducted with Nutrium® software which has been developed for the Portuguese population[309].

Functional status assessment

Performance Status was assessed with Eastern Cooperative Oncology Group Performance Status scale. According to these criteria patients are classified from grade 0 (fully active) to grade 4 (bedridden). Prior to initiation and after neo-adjuvant treatment a 6 min walking test (6MWT) was conducted by cardiopulmonary technicians blinded to the intervention groups, were walking distance and percentage of predicted normal values were recorded.

Handgrip strength was measured with a dynamometer (JAMAR®) and measurements were recorded in kg. Handgrip strength was measured 3 times with the non-dominant arm according to manufacturer's instructions. Mean handgrip strength was analyzed with gender specific thresholds from the revised guidelines of the European Working Group on Sarcopenia in Older People (EWGSOP) (<27kg in men and <16kg in women)[312].

Patient Reported Outcome Measures

Quality of life was assessed before and after neo-adjuvant treatment with the European Organization for Research and Treatment of Cancer (EORTC) questionnaire. This questionnaire allows determination of functional, symptoms and overall quality of life score.

Statistical analysis

Adherence to CEDI was analyzed with an intention to treat approach, whereas anthropometric measures, body composition, functional status, quality of life and dietary intake were analyzed with a per protocol approach**.** Continuous variables were described as median and inter-quartile range, while categorical variables were expressed as frequency and percentage. Chi-square test or Fisher exact test were used to assess association between categorical variables. Differences in means from continuous variables were analyzed by t-test or Mann Whitney U test as appropriate, according to variables' adjustment to a normal distribution. Shapiro-Wilk test was used to test for normality. Effect size was computed with Cohen's d for t tests and r for Mann-Whitney U tests. Paired-samples t test or Wilcoxon Signed Rank Test were used to analyze longitudinal data within the control and intervention arm. Statistical analysis was conducted with Posit software.

Results

Study population.

From June 2018 to November 2019, 46 patients were screened resulting in 39 patients being randomly allocated either to the intervention (n=19) or to the control arm (n=20). All patients had indication for neo-adjuvant treatment. All patients had stages II/III disease, except for one patient randomly allocated to the intervention arm with gastric cancer and a single liver metastasis (stage IV disease) who was included since the patient was eligible for neo-adjuvant treatment. **Figure 1** presents the trial profile and reasons for exclusion. A total of 32 patients completed follow up evaluations.

Baseline characteristics are shown on **Table 1**. Patients in both groups were well matched regarding age, sex, disease site, serum C-reactive protein, albumin and total proteins, Body Mass Index (BMI), nutritional assessment (PG-SGA and CT-derived body composition), functional status (handgrip strength and 6-minute walking test), quality of life score and dietary intake. Regarding ECOG scale we found a higher proportion of patients with ECOG 0 in the control arm and a lower proportion of patients ECOG 2, than in the intervention arm (p=0.026).

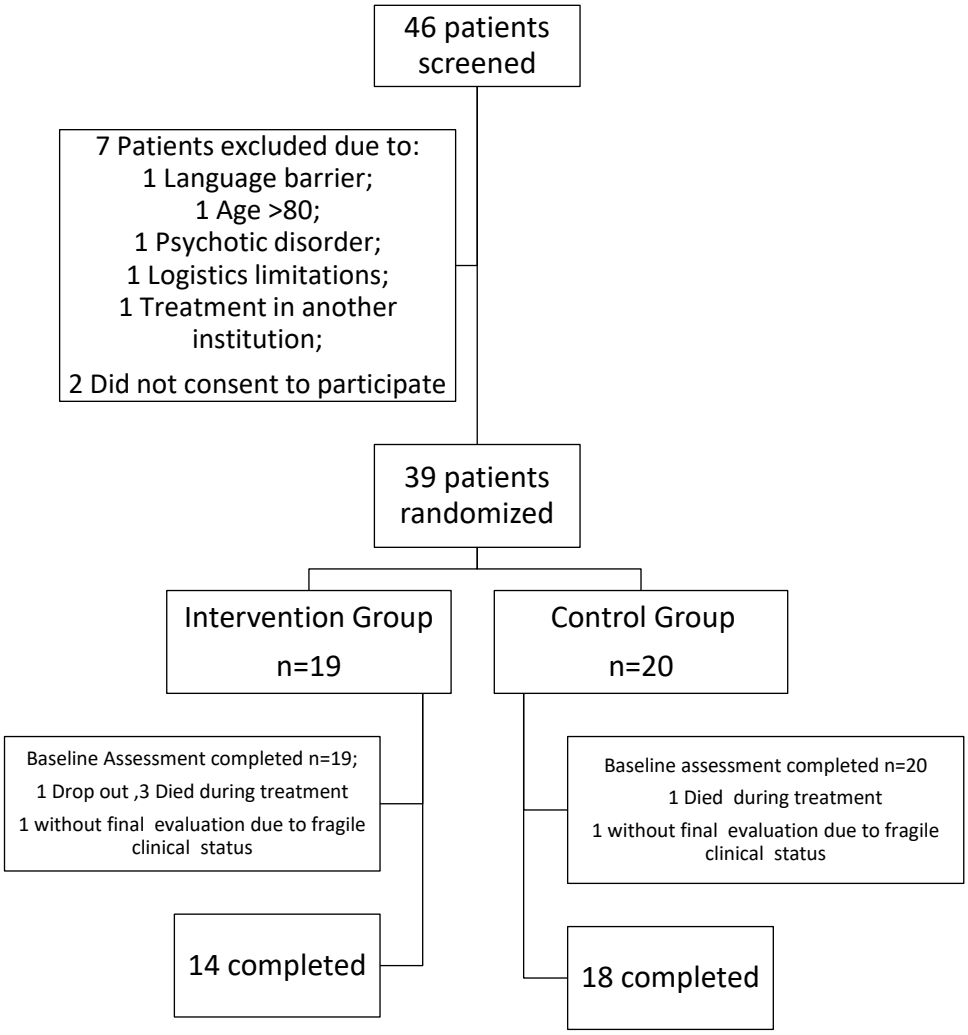


Figure 1-Trial profile.

Table 1- Baseline study population characteristics.

	Intervention n=19				Control n=20				
	N	**%**	**Med**	**IQR**	**n**	**%**	**Med**	**IQR**	**P**
Age			64	9.5	20		64.5	19.0	0.978
Male	14	73.3			15	75			0.925
Disease Site									
Esophagus	2	10.5			1	5.0			0.899
Gastric	9	47.4			9	45.0			
Pancreas	2	10.5			3	15.0			
Rectum	6	31.6			7	35.0			
C-Reactive Protein			0.5	0.6			0.4	0.9	1.00
Albumin			4.2	0.5			4.1	0.7	0.670
Total proteins			6.8	0.8			6.7	1.1	0.665
Body Mass Index			24.9	6.5			26.0	5.8	0.737
Body Mass Index Categories									
Underweight	3	15.8				2	10.0		0.927
Normal weight	7	35.0				7	35.0		
Overweight	6	31.6				8	40.0		
Obese	3	15.8				3	15.0		
PG-SGA									
Suspected Malnutrition	6	31.6			11	55.0			0.324
Malnourished	2	10.5			1	5.0			
ECOG									0.026
0	8	42.1			12	60.0			
1	9	47.4			2	10.0			
2	2	10.5			6	30.0			

	Intervention n=19				Control n=20				
	n	**%**	**Med**	**IQR**	**n**	**%**	**Med**	**IQR**	**P**
CT Body Composition									
Skeletal Muscle Area									
Male			158.5	32.5			166.1	20.3	0.679
Female			99.8	11.8			101.0	22.0	0.739
Skeletal Muscle Index									
Male			54.2	13.4			56.5	8.4	0.431
Female			41.5	7.8			41.6	8.9	0.828
Visceral Adipose Tissue									
Male			133.4	102.4			175.4	153.9	0.20
Female			83.1	65.8			91.9	64.8	0.904
Subcutaneous Adipose Tissue									
Male			98.6	113.2			112.5	81.3	0.538
Female			137.3	50.5			249.2	60.4	0.246
Total Adipose Tissue									
Male			274.7	200.9			342.5	182.9	0.238
Female			248.7	67.8			362.4	145.4	0.433
Intramuscle Adipose Tissue									
Male			9.1	5.6			9.7	5.7	0.92
Female			9.0	6.7			16.2	8.3	0.109
Sarcopenia	4	23.5			3	21.4			0.889
Low Muscle Attenuation	8	47.1			6	42.9			0.815
Visceral Obesity	7	41.2			8	57.1			0.376
Sarcopenic Obesity	1	5.26			0	0			0.310
Handgrip Strength			33.0	18.5			29.0	14.0	0.713

	Intervention n=19				Control n=20				
	N	**%**	**Med**	**IQR**	**n**	**%**	**Med**	**IQR**	**P**
Low Handgrip Strength	5	27.8			5	25.0			0.846
6MWT-Distance (m)			400	127.5			444.0	182.0	0.183
Low 6MWT-Distance (m)	9	47.4			7	41.2			0.708
Quality of life Global			66.7	37.5			58.3	29.2	0.997
Calorie Intake (kcal)[a]			3847	1278			3208	1308	0.517
Calorie Intake (kcal/kg)[a]			55	26			47	25	0.158
Protein (g)[a]			159	59			131	59	0.515
Protein (g/kg)[a]			2.2	0.7			1.7	1.1	0.376
Carbohydrates (g)[a]			369	167			334	144	0.275
Carbohydrates (g/kg)[a]			5.3	1.5			4.9	1.5	0.289
Fat (g)[a]			172	71			131	60	0.463
Fat (g/kg)[a]			2.3	1.1			1.9	1.3	0.239

Med-Median; **IQR-**Interquartile Range; **PG-SGA**-Patient Generated Subjective Global Assessment; **ECOG-**Eastern Cooperative Oncology Group Performance Status scale; **CT**- Computed Tomography; **6MWT-**6 Minute Walking Test; [a]Semi Quantitative Food Frequency questionnaire derived estimated daily calorie, protein, carbohydrates, and fat intake for usual daily intake before disease.

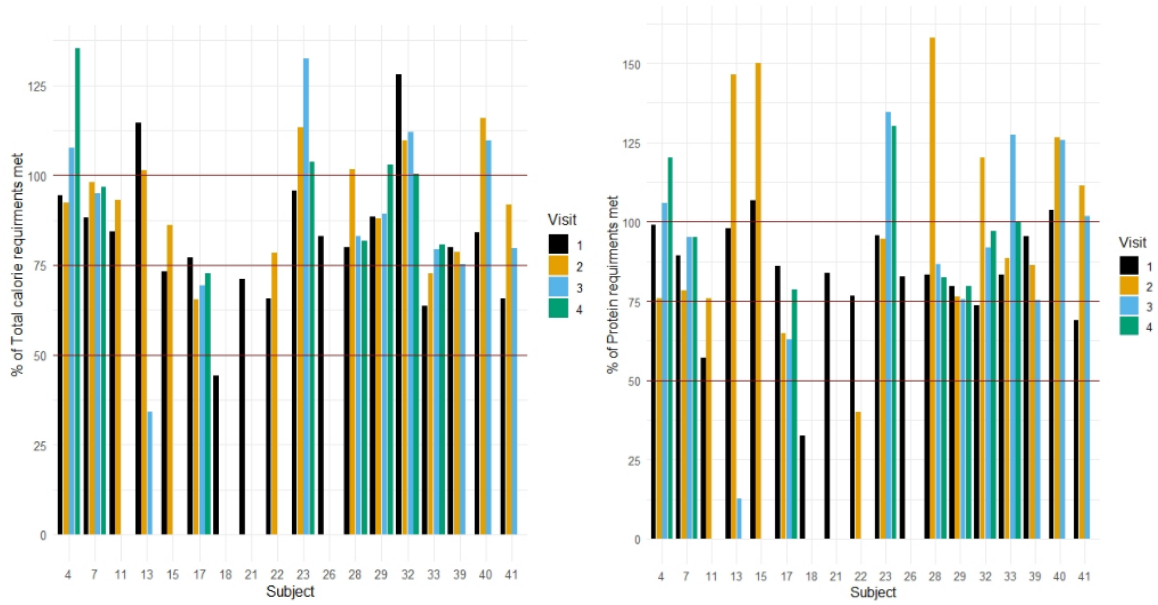
Adherence analysis

Analysis was conducted for 19 patients that gave consent and completed baseline measurements. One patient dropped out on the second week of intervention because CEDI was viewed as an additional burden. During follow up 3 patients who entered CEDI, died and one refused to pursue further evaluations due to decline of performance status. In the control group 1 patient died and 1 patient refused to pursue further evaluations due to decline of performance status.

Adherence to estimated nutritional requirements.

Globally, 17/19 (89.4%), 14/19 (73.6%) and 6/19 (31.5%) were able to meet a daily calorie intake above 50%, 75% and 100% of estimated total calorie daily requirements on at least one visit, respectively. Regarding protein intake, 17/19 (89.4%), 17/19 (89.4%) and 9/19 (47.3%) were able to meet a protein intake above 50%, 75% and 100% of estimated protein requirements, respectively. Concerning total fat intake, most patients were able to maintain fat intake within 25-30% of total calorie intake and 7/19 (36.8%) patients had a total fat intake exceeding 35% on at least one visit. As planned all patients had a monounsaturated fat intake above 30% of total fat intake on at least one visit. Details for each patient concerning percentage of nutritional requirements met are presented in **Figure 2**.

a) **b)**



c) **d)**

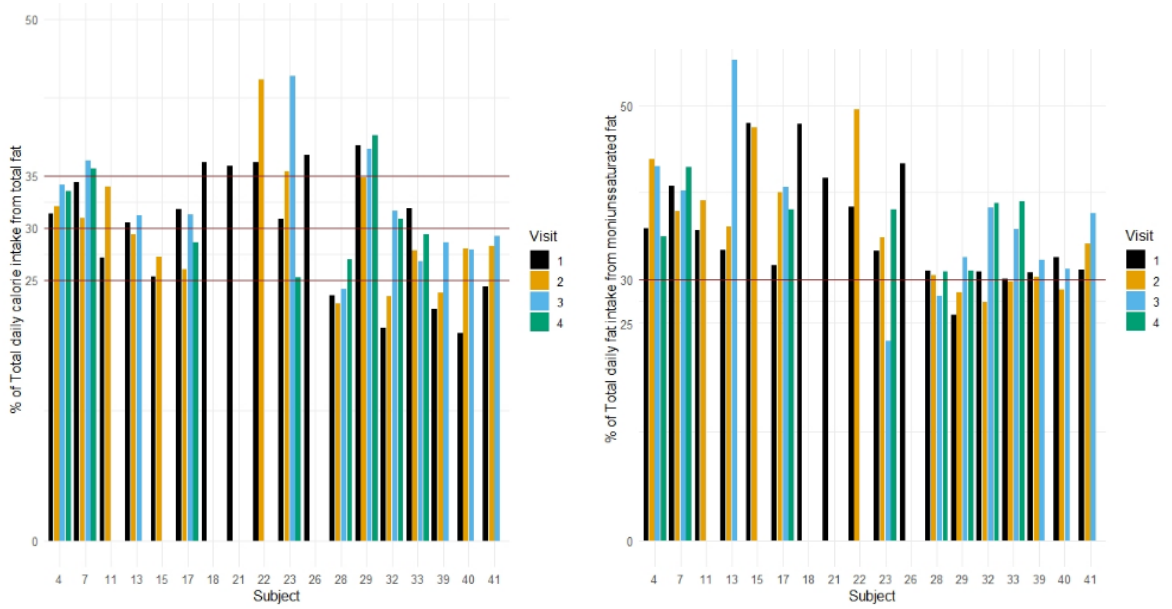


Figure 2 a) Percentage of estimated total calorie intake met; **b)** Percentage of estimated total protein intake met; **c)** Percentage of estimated total fat intake of total estimated daily calorie intake and **d)** Percentage of monounsaturated fat intake regarding total fat estimated intake, per subject per visit during Combined Exercise and Diet Intervention (CEDI).

Adherence to oral nutritional supplements and exercise

A total of 13/19(68.4%) adhered to oral nutritional supplements and 13/19 (68.4%) to the exercise program. Patients that adhered to oral nutritional supplements (ONS) were found to have a significantly higher median daily calorie intake (ONS Adherent- 1781kcal/day, Interquartile Range (IQR)-633 vs. ONS non-Adherent- Median (Med)-1537kcal, IQR-332; p=0.022), but no difference in regard to protein intake (ONS Adherent-91g/day, IQR- 22 vs ONS non-Adherent-84g/day, IQR-25, p=0.707). Adherence to supplementation was not influenced by tumor location (esophagus-2/2(15.4%), gastric-6/8 (46.2%), pancreatic-1/2 (7.7%) and rectal-4/6 (30.8%); p=1).

Concerning exercise, no differences were found in respect to daily calorie (Exercise Adherent: Med-1659kcal/day, IQR-452, Exercise non-Adherent: Med-1470kcal/day, IQR-319; p=0.208) and protein (Exercise Adherent: Med-91g/day, IQR-19, Exercise non-

Adherent: Med-81g/day, IQR-25; p=0.593) intake. In respect to tumor location, we found that all patients with gastric cancer adhered to exercise (1/2(7.7%) esophagus, gastric-8/8 (61.5%), pancreatic-0/2 (0.0%) and rectal-4/6 (30.8%) (p=0.02)).

Adherence to Combined Exercise and Dietary Intervention (CEDI)

At the second visit, approximately one month after CEDI initiation, 13/19 (68.4%) were able to meet more than 75% of their calorie and protein estimated requirements or maintained oral nutritional supplement intake and exercise for 1 month and thus were considered fully adherent to CEDI. Adhesion to all studied criteria is presented on **Figure 3.**

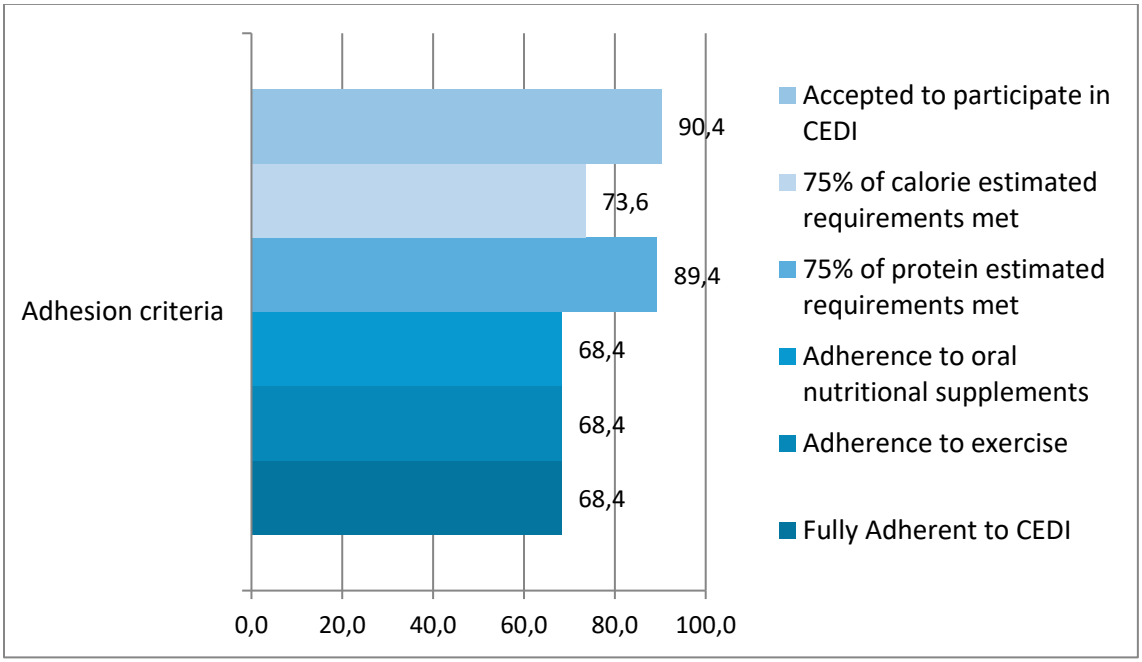


Figure 3- Adherence to Combined Exercise and Dietary Intervention after 1 month follow up.

Longitudinal analysis

CEDI vs. Control

Anthropometric, bioelectrical impedance, CT scan body composition measures, as well as grip strength, 5-minute walking distance, percentage of predicted normal values and quality of life score at baseline (before neo-adjuvant treatment) and at follow up (after neo-adjuvant treatment) are presented per trial arm on **Table 2**. For more information regarding body composition and functional status change refer to supplementary material (**Figure S1**).

Patients in the intervention arm were able to maintain weight during neo-adjuvant therapy, in contrast to patients in the control arm who lost a median weight of 3.34kg, which represents 5.10% of their initial weight. Similarly, patients in the intervention arm, maintained waist circumference, whereas patients in the control arm lost a median 2.5 cm.

Concerning CT scan derived body composition, a near significant difference was found for skeletal muscle area, where patients in the control arm had a higher median loss of skeletal muscle area when compared with the intervention arm. In respect to visceral adipose tissue, we observed a significantly higher loss in the control group. There were no differences between study groups in bioelectrical impedance measurements.

Regarding functional status, patients in the intervention group improved median walking distance and median percentage of predicted normal values from the 6-minute walking test. Also, functional score from quality-of-life questionnaire differed significantly between groups with a significant improvement for the intervention group.

In respect to daily caloric and protein intake estimated with food frequency questionnaire, no differences were found between control and intervention arm in regard to the median difference before and after neo-adjuvant treatment (Calories-Intervention: Med:-1243, IQR: 1159 vs. Control: Med:-478, IQR:1216, p=0.483; Protein- Intervention: Med:-11, IQR: 69 vs. Control:Med:17, IQR:44, p=0.91).

Table 2: Anthropometric measures, bioelectrical impedance, computed tomography (CT) derived body composition, functional status, and quality of life at baseline and follow up.

		Intervention arm Median (IQR) n=19	Control arm Median (IQR) n=20	P[a]	Effect Size[b]
Anthropometric Measures					
Weight (kg)		n=14	n=18		
	Baseline	67.0 (18.4)	68.7(21.9)		
	Follow Up	72.5(17.0)	61.2(25.5)		
	Difference	-0.05 (2.9)	3.4 (6.3)		
	%Difference	0.062(4.5)	5.1(10.7)	**0.008**	**0.91 [0.15,1.67]**
Waist Circumference (cm)		n=14	n=18		
	Baseline	91.0(14.5)	94.5(13.5)		
	Follow Up	96.0(11.5)	89.5(16.7)		
	Difference	0(4.5)	2.5(9.5)	**0.028**	**0.83 [0.05,1.61]**
Bioelectrical impedance					
Fat Free Mass (kg)		n=13	n=16		
	Baseline	52.6(16.5)	53.9(23.4)		
	Follow Up	56.5(18.9)	49.8(21.7)		
	Difference	-0.1 (1.8)	0.70(3.9)	0.455	-
Fat Mass (kg)		n=14	n=16		
	Baseline	17.10(6.0)	16.30(7.4)		
	Follow Up	15.20(7.2)	15.15(6.8)		
	Difference	-1.80(5.2)	0.75(4.9)	0.580	-
Phase angle		n=13	n=16		
	Baseline	6.00(1.3)	6.30(1.1)		
	Follow Up	5.80(0.8)	5.25(1.8)		
	Difference	0.60(1.1)	0.6(0.8)	0.126	-

		Intervention arm Median (IQR) n=19	Control arm Median (IQR) n=20	P[a]	Effect Size[b]
CT scan image analysis					
Skeletal Muscle tissue area (cm^2)		n=11	n=14		
	Baseline	151.3(56.0)	147.25(51.3)		
	Follow Up	153.6(32.4)	128.15(45.4)		
	Difference	8.2(16.2)	12.15(15.7)	**0.09**	**0.79 [-0.18;1.77]**
Visceral adipose tissue area (cm^2)		n=11	n=14		
	Baseline	115.4(132.1)	141.50(136.7)		
	Follow Up	108.1(103.3)	107.(130.0)		
	Difference	4.0(38.6)	57.9(102.1)	**0.027**	**1.10 [0.09;2.10]**
Subcutaneous adipose tissue area (cm^2)		n=11	n=14		
	Baseline	115.0(83.4)	123.0(83.4)		
	Follow Up	77.41(91.6)	141.85(150.3)		
	Difference	-9.40(41.1)	20.93(23.4)	0.519	-
Intramuscular Adipose Tissue area (cm^2)		n=11	n=14		
	Baseline	9.0(4.0)	10.6(6.9)		
	Follow Up	11.3(4.3)	9.6(10.0)		
	Difference	-1.5(3.1)	0.5(4.6)	0.311	-
Muscle Radiation Attenuation		n=11	n=14		
	Baseline	39.6(8.5)	37.6(10.3)		
	Follow Up	37.4(5.6)	37.4(13.9)		
	Difference	-1.5(1.7)	-0.12(3.2)	0.725	-

		Intervention arm Median (IQR) n=19	Control arm Median (IQR) n=20	P[a]	Effect Size[b]
Functional Status					
Handgrip Strength		n=13	n=15		
	Baseline	33.0(14.0)	29.0(18.5)		
	Follow Up	39.0(11.0)	29.0(19.0)		
	Difference	-1.0(8.0)	-1.0(7.5)	0.680	
6MWT-Distance (m)		n=10	n=10		
	Baseline	400.0(127.5)	444.0(182.0)		
	Follow Up	486.0(151.75)	451.0(163.0)		
	Difference	-65.0(81.25)	6.0(64.5)	**0.004**	**1.51 [0.44; 2.57]**
Quality of life					
Symptoms score		n=13	n=15		
	Baseline	18.8(30.3)	27.3(30.3)		
	Follow Up	9.09(12.1)	18.2(18.2)		
	Difference	9.09(16.8)	6.0(10.6)	0.412	
Functional score					
	Baseline	82.3(21.6)	78.43(16.7)		
	Follow Up	88.2(13.7)	82.35(20.6)		
	Difference	-7.8(10.8)	0.00(8.8)	**0.027**	**0.99 [0.13; 1.86]**
Global Score					
	Baseline	66.7(36.5)	58.3(29.2)		
	Follow Up	66.7(41.7)	66.7(41.7)		
	Difference	8.3(37.5)	0.0(33.3)	0.757	

[a] Between group differences- 2-sample t test or Mann-Whitney U test; [b] Effect size computed with Cohen's d for t tests and r for Mann-Whitney U tests; **6MWT**-6 Minute Walking Test; **6MWT-% Predicted**-Percentage of predicted normal values.

Pairwise analysis-CEDI group

Patients in the intervention arm had a near significant skeletal muscle area loss (Baseline: Med: 151.30, IQR:56.0 vs. follow up: Med: 153.60, IQR:32.40, p=0.052), but probably clinically negligent, since they were able to improve significantly their 6MWT distance (Baseline:Med-400.0, IQR: 127.5; follow up: Med: 486.00, IQR:151.75, p=0.02), percentage of predicted normal value of 6MWT (Baseline:75.97, IQR: 21.24; follow up: Med: 89.54, IQR:23.07, p=0.08) and median functional score from quality of life questionnaire (Baseline:82.35, IQR:21.56; follow up: Med: 88.24, IQR:13.73, p=0.009). Improvement in symptoms was observed (intervention-Baseline: 18.8, IQR:30.3; follow up: Med: 9.09, IQR:12.12, p= 0.035).

Pairwise analysis-control group

Patients in the control arm had a significant reduction in in their median weight (Baseline:Med:68.7 (21.87), follow up: Med: 61.20 (25.55), p=0.017), waist circumference (Baseline: Med:94.5(13.5), follow up: Med:89.5, p=0.017), median skeletal muscle area (Baseline: Med: 147.25, IQR: 51.30 vs. follow up: Med: 128.15, IQR:51.30, p=0.0008) and visceral adipose tissue (Baseline: Med: 141.5, IQR: 136.67 vs. follow up: Med: 107.05, IQR:130.0, p=0.0097), as well as a near significant reduction in 6MWT distance (Baseline:444.0, IQR: 182.0; follow up: Med: 451.00, IQR:163.00, p=0.09). Also, there was a significant reduction in phase angle (baseline: Med: 6.30, IQR: 1.15 vs. follow up: Med: 5.29, IQR: 0.85, p=0.003). Improvement in symptoms was observed (Baseline:27.27, IQR:30.3; follow up: Med:18.18, IQR:18.18, p=0.010).

Chemotherapy toxicity and adverse events

A total of 20/39 (51.28%) experienced toxicity to neo-adjuvant treatment with no differences between groups (CEDI-8/19 (42.1%) vs. control-12/20 (60.0%); p=0.33). No

between groups differences were found in regard to the percentage of patients that had to reduce dosage (CEDI-4/7 (57.1%); control-3/7 (42.9%), p=0.56), dose limiting toxicity (CEDI-2/4 (50.0%); control 2/4 (50.0%), p=0.92) or delay treatment (CEDI-1 (100%); control-0 (0%), p=0.28). There were 4 serious adverse events, 3 in the intervention and 1 in the control arm but none related to the intervention. Details regarding neo-adjuvant treatment can be found in **Table S1** of supplemental material.

Discussion

This open label randomized controlled trial demonstrated that a Combined Exercise and Dietary Intervention (CEDI) in patients with gastrointestinal cancer under neo-adjuvant treatment is feasible and has a reasonably high adherence. Also, CEDI patients were able to maintain their pre-treatment nutritional status and improve functional status. To our knowledge this is the first combined exercise and nutritional intervention program performed in cancer GI patients during neo-adjuvant treatment.

Recent studies have reported that adherence to behavioural interventions varies substantially, from 8 to 93%[159,313–315]. It is noteworthy that this high adhesion variability, may be attributed to heterogeneity in the type of intervention, namely the time of implementation (pre-treatment, post-treatment, survivors), aim (ex: weight loss in overweight survivors, nutritional status optimization preoperatively, implementation of specific dietary recommendations as high fiber diet, etc.), duration, type (dietary intervention, supplements, and exercise), disease stage, site and treatment. Another challenge that further adds to the complexity of studying adherence rates is the inexistence of specific criteria to define optimal adherence, although some studies have defined an adherence equal or higher to 50% as acceptable[159]

In our study 68.4% of patients were fully adherent to CEDI, which we consider as reasonably high, comparing with previously reported adherence rates as low as 48% for oral nutritional supplements and 60% for exercise[159], and bearing in mind that these patients had locally

advanced disease, were under neo-adjuvant treatment and therefore may be more symptomatic. This adhesion study was deemed by us as crucial, since adhesion rates are variable and we are aiming to pursue further studies to explore the influence of CEDI in patients under neo-adjuvant treatments, and thus it would be imprudent to tackle this issue before knowing if these patients were willing to participate in CEDI.

Although cancer cachexia is known to impair anti-cancer treatments, cause distress in patients and families and decreased survival, it remains to date without standard care, and therefore strategies to deal with this condition are highly warranted[316]. During the past decades a multimodal intervention has been advocated, due to the existing knowledge that cancer cachexia is a multidimensional condition[307,317,318]. Still, further increasing the complexity is the uncertainty of the most appropriate endpoint regarding cancer cachexia, were besides weight, muscle mass quantity and quality, measures of function such as 6MWT, handgrip strength, quality of life and activities of daily living are at present considered equally or even more relevant[316].

When addressing multimodal interventions in cancer patients the MENAC study clearly stands out. Solheim T et al.[159] have reported on an intervention Exercise, Nutrition and Anti-Inflammatory medication in cachexia (pre-MENAC) versus standard care, conducted with patients with stage III/IV small cell lung cancer or inoperable pancreatic cancer with indication for chemotherapy, showing a positive effect on weight. Indeed, our results are consistent with those of MENAC, since patients in CEDI group were also able to maintain weight, and in addition we were able to show that these patients lose less muscle mass and improve functional status. In contrast, patients in the control arm lost skeletal muscle, visceral adipose tissue and worsened functional status. Visceral adipose tissue loss could seem like a positive characteristic of the control group, however it is important to note that 1)concomitant reduction of skeletal muscle and visceral adipose tissue is inherent to dietary restriction[319], meaning that these patients probably did not meet their nutritional requirements during treatment; 2) evidence supports a survival advantage for patients with higher content in skeletal muscle mass in obese patients with cancer[320], showing that muscle mass is presumably a key component. Moreover, our findings further support the

use of sophisticated and reliable body composition techniques for the optimization of dietary intervention, since besides calculating nutritional requirements with established calories and macronutrients per kg, body composition should also be considered in the estimation of nutritional requirements.

The open label nature of our study design is a limitation of this study, but we did address this issue providing an intervention individualized for each patient, that would be difficult to mimic, and all professionals involved except for Nutritionists and Physiotherapist were blinded to the study intervention. Also, sample size is one of the limiting aspects of generalizability of results and cautious interpretation, and further studies are needed in this field.

Conclusions

Our study has allowed us to understand that CEDI is feasible, and that most patients are willing to participate even under neo-adjuvant chemotherapy, resulting in potential benefits regarding nutritional and functional status. To our knowledge there are no studies evaluating intervention programs with the characteristics of CEDI in patients with gastrointestinal cancer undergoing neo-adjuvant treatment. We are aware that due to sample size interpretation of results should be conscious, however we feel that the encouraging results of this study are a starting point to pursue further well powered studies namely to investigate the role of CEDI in post-operatory complications, cancer cachexia and inflammation.

Study 5

Lower skeletal muscle attenuation and high visceral fat index are associated with complicated disease in patients with Crohn's disease: An exploratory study.

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Contribution of the PhD candidate:

The candidate operationalized the technique regarding CT derived body composition assessment in collaboration with Rita Cruz and João Stretch. She then proceeded to analyze the body composition data, using reported thresholds to identify body composition phenotypes. She completed the database with body composition parameters, conducted the statistical analysis and drafted part of the methods and materials, namely the section regarding body composition analysis procedure, and statistical analysis section. She participated in the revision of the draft leading up to its publication. The paper was then published in Clinical Nutrition ESPEN (**Quartile 2** in Nutrition and Dietetics).

Clinical Nutrition ESPEN (2017), 21. https://doi.org/10.1016/j.clnesp.2017.04.005

Abbreviations

95%CI, 95% Confidence Interval

CD, Crohn's Disease

CRP, C reactive protein

CT, Computed Tomography

CTE, Computed Tomography Enterography

HU, Hounsfield Units

MA, Muscle Radiation Attenuation

NPV, Negative Predictive Value

PPV, Positive Predictive Value

ROC, Receiver Operating Characteristic curve

SFA, Subcutaneous Fat Area

SMA, Skeletal Muscle Area

SMI, Skeletal Muscle Index

VFA, Visceral Fat Area

VFI, Viscera Fat Index

Abstract

Background and aims: The prognostic value of body composition analysis in patients with Crohn's disease (CD) is poorly explored. The aims of the present study were to assess fat and skeletal muscle compartments including muscle radiation attenuation (MA) in patients with CD, and to analyse its predictive value to identify complicated phenotypes.

Methods: Seventy-one patients with CD who have had an abdominal CT within one month of clinical, laboratory, and endoscopic evaluation were included. Skeletal muscle area (SMA) and index (SMI), visceral fat area (VFA) and index (VFI), subcutaneous fat area (SFA), and mean MA were measured using appropriate software. Sarcopenia, as defined by Martin´s criteria was assessed. Montreal classification was used to characterize disease phenotype.

Results: Mean muscle radiation attenuation was lower in patients> 40 years (p=0.001), L2 (p=0.09) and stricturing/penetrating disease (p=0.02) whereas SMA and SMI were significantly lower in patients with positive CRP and previous hospital admissions (p<0.01). On multivariate analysis, higher muscle radiation attenuation was protective against complicated disease phenotype (stricturing/penetrating disease and/or previous surgeries) (OR:0.81, p=0.002) whereas a high visceral fat index increased such risk (OR:26.1, p=0.02). A ROC curve showed an 82.4% sensibility, 90.3% specificity, 17.6% PPV, 9.7% NPV and an AUC of 0.91 for body composition analysis to predict complicated disease.

Conclusions: A lower muscle radiation attenuation and a high visceral fat index (VFI) seem to be associated with more severe phenotypes in patients with CD.

Keywords: Body composition, Crohn's Disease, Computed Tomography.

Introduction

In recent years, the relationships between body composition and clinical outcomes have been extensively studied in the field of oncology, facilitated by the advent of appropriate software applied to diagnostic imaging technologies such as computed tomography. Body composition parameters such as sarcopenia, visceral obesity, and low muscle radiation attenuation are now recognized as important prognostic factors predicting, toxicity and response to chemotherapy, post-operative complications and even survival, more accurately than other variables classically associated to a better prognosis such as TNM stage[50,51,224,321,322].

Changes in body composition evaluated by various methods such as Computed Tomography, Magnetic Resonance or abdominal ultrasound, have also been described in Crohn´s disease (CD), but their clinical significance and predictive value remain unclear [323,324]. Changes in mesenteric fat, also known as fat wrapping, have been recognized in patients with CD since its initial description[325]. Studies performed during the last decade show that increased body mass index in CD patients is associated with poorer prognosis, early need for surgery, higher risk of active disease and earlier loss of response to therapy [326,327,328]. Further supporting the active role of mesenteric fat in promoting intestinal inflammation, recent studies showed that visceral fat in patients with CD undergoing intestinal resection was associated with higher risk of postoperative complications and post-operative recurrence[199,323]. However, whether visceral fat accumulation is a consequence of long standing disease or a primary event involved in the pathogenesis of the disease is still unclear[329,330]. Sarcopenia (severe muscle depletion) has been shown to be highly prevalent in CD, possibly as a result of poor nutrition, uncontrolled inflammation, and physical inactivity among others[331], and to be associated with major postoperative complications. Treatment with anti-TNF was shown to reverse sarcopenia, further supporting the concept that it may represent a biomarker of chronic inflammation and wasting[160]. Finally, skeletal muscle radiation attenuation is a radiologic metric inversely related to muscle fat content[321]. A reduction in muscle radiation attenuation, mirroring excess fat deposition in the muscle tissue, has been described in several chronic

inflammatory conditions such as obesity, type 2 diabetes , and in cancer patients[321] in whom it is associated with a poorer prognosis[50]. The value of these body composition variations, as markers of chronic inflammation and in predicting more severe phenotypes in patients with CD has not been previously tested. The aims of the present study were to perform a comprehensive description of the skeletal muscle and fat compartments in patients with CD, to analyse the recently described variable muscle radiation attenuation, and to explore possible associations of these body composition measurements with complicated phenotypes with the aim of assessing its potential use as early predictors of severe disease.

Materials and Methods

Study population.

The study protocol was approved by the Scientific and Ethics Committee of Hospital Beatriz Ângelo in Loures, Portugal. We retrospectively reviewed all the clinical records of CD patients followed in our clinic between 2012 and 2015. Patients were included if they had a Computed Tomography Enterography (CTE) or Computed Tomography ordered as part of clinical workup within one month of full clinical, laboratorial and, whenever possible, endoscopic evaluation. Phenotypic characteristics retrospectively collected from charts included demographic data, age of disease onset, disease extension, and behaviour according to Montreal classification[182], and previous therapies including surgery. Patients with a history of a stricturing (B2) or penetrating (B3) complication and/or previous resection surgery at any time point during their clinical course were considered as having a complicated phenotype. Laboratory values were abstracted from electronic charts. Anemia defined as a hemoglobin value lower than 12 gr/dl for women or 13 gr/dl in men. C-Reactive protein (CRP) was considered positive when higher than 0.5 mg/dl.

Cross-sectional imaging evaluation

CT scans were obtained and evaluated for body composition data by two investigators who were blinded to clinical and endoscopic data to ensure objective interpretation of image findings. Skeletal muscle and fat tissue cross-sectional areas were measured on CT images, at the level of the third lumbar vertebrae (L3) with the patient lying supine as shown on **Figure 1**. Skeletal muscle area (SMA), visceral fat area (VFA) and subcutaneous fat area (SFA) were measured in square centimetres based on pixel count using appropriate software[50]. Briefly, muscle is annotated and is quantified within a Hounsfield unit (HU) ranging from -29 to 150; visceral fat ranges from -150 to -50 HU, and subcutaneous fat from -190 to -30 HU. Muscle radiation attenuation was calculated for muscle area from -190 to -30 HU. Skeletal muscle area (SMA) was normalized for stature to calculate the skeletal muscle index (SMI) - cm^2/m^2. Visceral Fat Index (VFI) was defined as the ratio of areas of visceral to subcutaneous fat. Sarcopenia was defined as SMI lower than 41 cm^2/m^2 in women, lower than 43 cm^2/m^2 in men with body mass index (BMI) <25 Kg/m^2 and < 53 cm^2/m^2 in men with BMI > 25 Kg/m^2 as described by Martin et al[50] based on the International Consensus of Sarcopenia [44]. Visceral obesity was defined as visceral fat area >130cm^2[62].

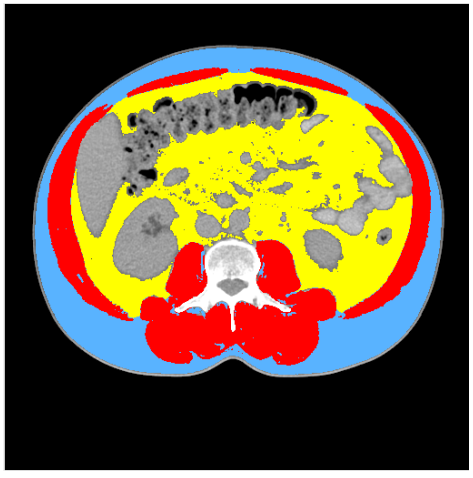

Figure 1- Axial computed tomography (CT) images at the level of the third lumbar vertebrae were analysed for muscle and fat tissue cross sectional areas and analysed using an appropriate software. Muscle mass is shown in red and was quantified within a Hounsfield unit (HU) range of -29 to 150, visceral fat shown in yellow, range from -150 to -50 and subcutaneous fat shown in blue range from -190 to 30. Muscle radiation attenuation was calculated for muscle area.

Statistical analysis

Continuous variables were described as mean, median and range, while categorical variables were expressed as frequency and percentage. Differences in mean continuous variables and dichotomous variables were analysed by t-test or Mann Whitney U test as appropriate, according to variable´s adjustment to a normal distribution. Difference in mean continuous variables and categorical variables with more than two levels was conducted with One-way analysis of variance (ANOVA) or KrusKal-Wallis test, as appropriate. Chi-squared test and Fisher's Exact Test were used to explore associations between categorical variables. A p-value <0.05 was considered statistically significant. Univariate logistic regression was first performed using complicated behavior (B1 vs B2 or B3 and/or previous resection surgery) as the dependent variable and clinically relevant factors as independent variables namely gender, age, disease duration and location, weight and BMI, skeletal muscle area, subcutaneous and visceral fat area, visceral obesity, mesenteric fat index, muscle radiation attenuation and sarcopenia, anemia and CRP positivity.

On multivariate analysis both manual and automatic variable selection methods were performed. Hosmer and Lemeshow (HL) method was used for manual variable selection, and, as part of this method, a p-value cut-off of 0.25 on univariate analysis was used. Also, an automatic variable selection with backward, forward and both stepwise regression was performed. In this analysis all predictors that were significant or clinically relevant were included. Three possible models were obtained: HL model, both stepwise (backward stepwise was identical to both stepwise) and forward stepwise. Finally, models were compared using Akaike Information Criteria (AIC), and the selected model had lowest AIC, which was the model obtained through both stepwise analysis and is presented in this paper. Receiver Operating Characteristic (ROC) curve was plotted for the selected model; sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and area under the curve were calculated. Statistical analysis was performed with Statistical Package for the Social Sciences (SPSS, IBM) and R software.

Results

Demographics and clinical features

Overall, 71 patients fulfilled inclusion criteria and were reviewed. 18/89 CD patients were excluded because they did not have a CT scan with one month of clinical, laboratorial, and endoscopic evaluation. Clinical and demographic data are shown in **Table 1**. CTE was ordered to evaluate disease extension in 37% patients with recently diagnosed disease, to rule out disease complications in 52%, and to evaluate response to therapy in the remaining 11% patients. Body composition data did not differ according to reason for performing CTE (data not shown).

Table 1 – Clinical characteristics of patients included in the study.

N	**71**
Median age	43
Male/Female	36/35
Montreal classification	
A1/ A2/ A3	5/ 47/ 19
L2/L3/L3/ + L4	27/ 7/ 37/3
B1/ B2/ B3/ p	36/24/11/ 25
Duration of disease (years)	9.7 (0-32)
Smoking habits	
Yes/No/ Unknown	36/31/5
Previous surgery	
Yes/ No	26/45

N	**71**
Previous hospital Admission	
Yes/ No	51/20
Recent corticosteroids	
Yes/No	8/63
Current medication	
5-ASA	22
Azathioprine	21
Biologics	2
Biologics+Azathioprine	5
Harvey-Bradshaw Index	
Remission	25
Mild disease	24
Moderate disease	21
Severe disease	1
Mean C-reactive protein (mg/dL)	4.0±6.0
C-reactive protein	
Positive/ negative	47/20
Mean Hemoglobin (mg/dL)	12.5±2.3
Anemia	30/36
Endoscopic activity	
Yes/no	39/23

Body composition

- BMI, sarcopenia, and visceral obesity

According to BMI, 11.3% of patients were underweight (BMI <18.5 Kg/m^2), 49.3% had a normal BMI, 28.2% were overweight and 11.3% were obese with a BMI equal or greater than 30 kg/m^2. Sarcopenia was observed in 31% patients, whereas visceral obesity was present in 28.2% of the total population. Sarcopenia was more frequently observed in patients with a BMI lower than 25 Kg/m^2 (39%) as compared to those with BMI higher than 25Kg/m^2 (13.5%) (p=0.05). Previously hospitalized patients were more frequently sarcopenic (39% vs 9%, p=0.014). As expected, visceral obesity was more frequent in patients with BMI higher than 25 Kg/m^2 (64.3% vs 4.7%, p<0.001); also mean subcutaneous fat area (84.2±57.3 vs 233.6±100.6 cm^2; p<0.001) and mean total fat area (127.3±97.0 vs 396.8±150.7 cm^2, p<0.001) were higher in patients with BMI over 25 Kg/m^2.

- Sarcopenia and visceral obesity

Table 2 shows the associations between body composition parameters as measured by CT which evaluate skeletal muscle and visceral fat. SMA and SMI were significantly higher in patients with visceral obesity. In contrast, muscle radiation attenuation, which is a negative prognostic factor, was lower is patients with visceral obesity (34.1+9.0 vs 44.7+9.2 HU; p<0.001).

Table 3 shows values for body composition data according to demographics, clinical and biological variables. We observed significant direct correlation between fat areas and visceral fat index with aging, both for subcutaneous and visceral fat, as opposed to muscle radiation attenuation which decreased with age. SMA and SMI were not influenced by age, as opposed to gender with females exhibiting significantly lower skeletal muscle values. No significant associations were observed with duration of disease except for subcutaneous fat

area for which a positive correlation was found. When we explored whether there were any associations with Montreal classification, we observed that patients diagnosed >40 years of age (A3) had a higher value for visceral fat and visceral fat index whereas muscle radiation attenuation was significantly lower. Regarding disease location, we also observed significant associations, with L2 patients exhibiting a distinct pattern of visceral fat distribution with higher VFI and lower muscle radiation attenuation although the latter did not reach statistical significance (p=0.09). Patients with complicated phenotype (B2 or B3, and/or history of surgery), presented lower muscle radiation attenuation – 39.5±9.4 vs 44±10 HU, p=0.02. Visceral obesity was more prevalent in patients with L2 disease (62.5% vs 27% in L1 and 21% in L3 patients – p=0.06). We then used positive CRP and previous hospital admission as surrogate markers for disease activity and severity, respectively. When we compared patients with a positive CRP or with previous hospital admission, we observed that SMA and SMI were significantly lower (127±33 vs 155±35 cm^2, p=0.003; 52±8.6 vs 45.2±9.9 cm^2/m^2, p=0.008, respectively), as well as muscle radiation attenuation in previous hospitalized patients (45±9.4 vs 40±10 HU, p=0.047). Visceral fat area, subcutaneous fat area and total fat area weren´t associated to CRP or previous hospital admission. Also, no significant associations were observed between muscle radiation attenuation and endoscopic activity, Harvey Bradshaw index, or current medical treatment. However, patients on recent (one month or less) corticosteroid therapy had a lower muscle radiation attenuation as compared to non-steroid treated patients (33.8 ± 13.6vs 42.7 ± 9.5HU; p=0.056), and more frequent visceral obesity (62.5% vs 23.8%, p=0.035). Mean total fat area (217.9±167.3 vs 356.8±229.1 cm^2, p=0.098) and mean subcutaneous fat area (220.5±148.7 vs 133.3±96.8 cm^2, p=0.1) were higher for patients on recent corticosteroid therapy, although not statistically significant.

Table 2 - Associations between Sarcopenia and Visceral Obesity and CT derived parameters of body composition.

	Sarcopenia			Visceral Obesity		
	No (n=49)	**Yes (n=22)**	**p-value**	**No (n=51)**	**Yes (n=20)**	**p-value**
Skeletal Muscle Area (cm^2)	150.1±32.0	102.5±101.2	<0.001	127.7±29.2	154.9±44.7	0.019
Skeletal Muscle Index (cm^2/m^2)	51.9±7.9	36.6±4.8	<0.001	44.8±8.8	53.1±10.7	<0.001
Subcutaneous Fat Area (cm^2)	153.3±104.4	120.4±109.0	0.132	105.4±79.0	239.4±107.5	<0.001
Visceral Fat Area(cm^2)	105.0±101.1	58±72.9	0.055	37.2±35.0	226.4±57.1	<0.001
Visceral Fat Index (cm^2/m^2)	0.66±0.53	0.47±0.48	0.896	0.40±0.33	1.1±0.54	<0.001
Muscle Radiation Attenuation (HU)	42.35±9.1	40.3±12.6	0.105	44.7±9.2	34.1±9.0	<0.001

*HU - Hounsfield Unit

Table 3 - Association between body composition data and demographics, clinical and biological variables.

	Skeletal Muscle Area	Skeletal Muscle Index	Subcut. Fat area	Visceral Fat area	Visceral Fat Index	Muscle attenuation
Age (years)	Male NS Female NS	Male NS Female NS	R=0.46 P=0.000	R=0.58 P=0.000	R=0.44 P=0.000	R=-0.67 P=0.000
Gender						
Female	107.8±16.4	41.1±6.6	NS	NS	NS	NS
Male	162.1±29 P=0.000	53.0±9.2 P=0.000				
Duration of disease (years)	NS	NS	R=0.36 P=0.002	NS	NS	NS
Age on onset						
A1 (<16)				89±85	0.56±0.60	46±5
A2 (17-40)	NS	NS	NS	64±85	0.46±0.45	44±9.7
A3 (>40)				156±92 P=0.001	0.96±0.50 P=0.002	34±9.2 P=0.001
Location						
L1				154±72	0.71±0.51	43.3±8.3
L2	NS	NS	NS	70±90	1.02±0.66	32.1±14.4
L3				130±69 P=0.02	0.44±0.43 P=0.009	42.6±9.6 P=0.09
C-reactive protein (mg/dL)	151.9±39	52.6±11.1				
<0.5	127±30	44.3±8.1	NS	NS	NS	NS
≥0.5	P=0.007	P=0.001				
Previous Hospitalization						
No	155+35	52+8.6				45+9.4
Yes	127+33 P=0.003	45.2+9.9 P=0.008	NS	NS	NS	40+10 P=0.047

Association between body composition measurements and age and disease duration are presented as coefficient of correlation and p-value, whereas age of onset and location variables, CRP lower or higher than 0.5 mg/dL and previous hospitalizations are presented as mean ± standard deviation and p-value; NS-non-significant.

Model for complicated disease incorporating body composition parameters.

We performed multiple logistic regression analysis to assess the prognostic value of these body composition variables in predicting our primary outcome – complicated disease: B2 or B3 disease and/or previous resection surgeries. As shown on **Table 4**, on univariate analysis we observed that anemia was associated with complicated phenotypes (OR 5.2, 95% IC 1.7-18.3; p=0.0005). On multivariate analysis the selected model included muscle radiation attenuation, disease location, visceral fat index and anemia. We observed that a higher muscle radiation attenuation (continuous variable) was a protective factor for complicated phenotypes (OR 0.81 95%CI 0.70-0.91; p=0.002). Isolated colonic disease was associated with a decreased risk of complicated disease (OR 0.03; 95%CI 0.001-0.45; p=0.02). A high visceral fat index was associated with increased risk of complicated phenotype (OR 26.1 95%CI 2.0-754, p=0.02). Anemia remained as a significant risk factor for complicated phenotype (OR 36, 95% IC .5.6-418.3; p=0.0007) after adjusting for muscle radiation attenuation, disease site, and visceral obesity and CRP. Positive CRP was associated with a reduced risk of complicated phenotypes (OR 0.075 IC-0.006-0.49, p=0.015). The reason for this protective effect is not apparent but we may hypothesize that when a complication like stricture or fistula is present there is no longer active inflammation but mostly fibrosis which is not associated with increased CPR. A ROC curve was plotted for the previous model showing an 82.4% sensibility, 90.3% specificity, 17.6 PPV, 9.7% NPV and an AUC of 0.91 (**Figure 2**) for predicting complicated disease.

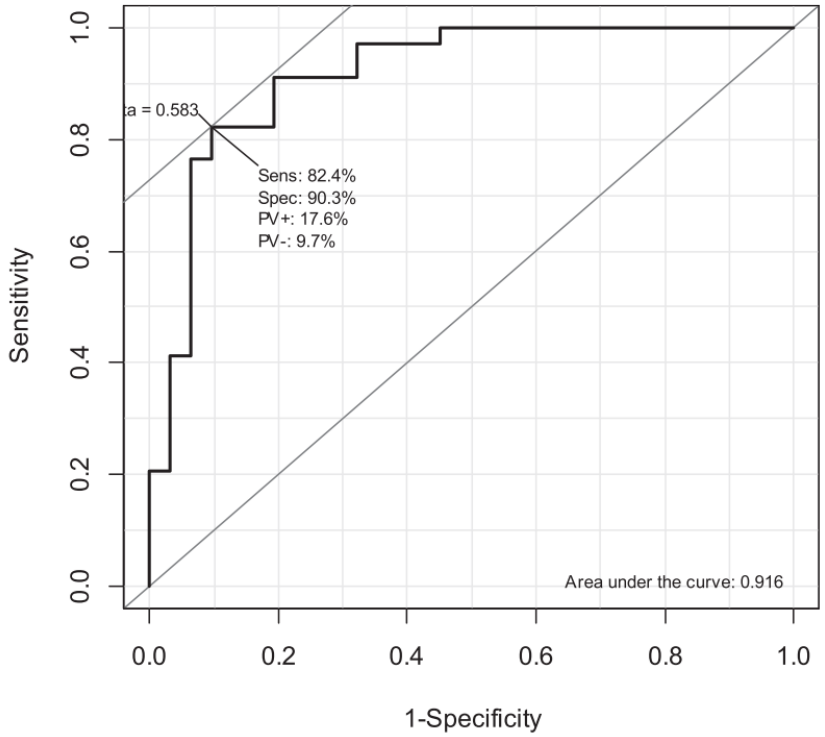

Figure 2-Receiver operating characteristic (ROC) curve for model assessment. Multivariate logistic regression model; dependent variable: B2 or B3 phenotype and/or previous resection surgery; independent variables: disease duration and location, muscle attenuation, visceral fat area, visceral fat index, anaemia, and positive C-reactive protein. Sens-Sensitivity; Spec-Specificity; PV+ - Positive predictive value; PV- - Negative predictive value.

Table 4- Univariate and Multivariate Logistic Analysis with Disease Behaviour as dependent variable.

Disease Behaviour B2+B3 vs B1	**Univariate analysis**			**Multivariate analysis**		
	OR	**95% IC**	**p-value**	**OR**	**95%IC**	**p- value**
Age	1.02	0.99-1.06	0.089	Excl.		
Gender				Excl.		
Female	1.00					
Male	1.05	0.41-2.69	0.904	Excl.		
Weight	0.98	0.94-1.01	0.229	Excl.		
Body Mass Index (kg/m^2)	0.96	0.86-1.06	0.434	Excl.		
Disease Duration	1.03	0.98-1.09	0.166	1.2	1.07-1.40	0.004
Disease Localization						
L1	1.00		0.134	1.00		
L2	0.45	0.058-2.42		0.034	0.001-0.45	0.023
L3+L4	2.0	0.72-5.65		1.86	0.33-8.72	0.53
Skeletal Muscle Area (cm^2)	0.99	0.97-1.00	0.304	Excl.		
Visceral Fat Area (cm^2)	0.99	0.993-1.00	0.508	0.97	0.94-0.98	0.005
Visceral Fat Index (cm^2/m^2)	1.28	0.52-3.25	0.583	26.1	2.0-754.0	0.026
Subcutaneous Fat Area (cm^2)	0.99	0.99-1.00	0.477	Excl.		
Muscle Radiation Attenuation (HU)	0.96	0.91-1.00	0.081	0.81	0.70-0.91	0.002
Visceral Obesity			0.129	Excl.		
No	1.00					
Yes	0.44	0.14-1.2				
Sarcopenia			0.553	Excl.		
No	1.00					
Yes	1.35	0.49-3.78				

Disease Behaviour B2+B3 vs B1	Univariate analysis			Multivariate analysis		
Anemia			0.027			
No	1.00			1.00		
Yes	3.2	1.13-10.1		36.3	5.6-418.3	0.007
C-reactive protein			0.282			
Negative	1.00			1.00		
Positive	0.56	0.18-1.60		0.075	0.006-0.49	0.01

OR-odds ratio; 95% CI- 95% confidence interval; Excl.- excluded; NI- not included.

Discussion

Herein we have assessed the prevalence of sarcopenia, visceral obesity, and muscle attenuation in patients with CD, and its associations with complicated phenotypes. Changes in body composition have been reported in patients with Crohn's disease as compared to controls, but the methods used are various and the clinical significance of these changes remain unclear. A recently published study[38] showed that body composition evaluation using CT imaging correlates strongly with DEXA analysis which is the gold standard method to evaluate body composition. Also, the recently described MA can only be assessed in CT scans. In the present study, we observed that 1) sarcopenia was highly prevalent even in overweight CD patients, 2) and more prevalent in patients with prior history of hospitalization, 3) and that a reduction in muscle radiation attenuation (reflecting increased deposition of fat in the skeletal muscle) and an increase in VFI were positively associated with more complicated phenotypes. A model using these body composition parameters showed a AUC value of 0.91 to discriminate complicated disease (B2/B3 phenotypes and/or previous surgery). These results are in line with those obtained by Erhayiem et al.[198] although the latter did not measure skeletal muscle area or index nor did they measure muscle attenuation. In our study we found that SMA and SMI were significantly lower in patients with positive CRP and previous hospital admissions reflecting patients with a more chronic and protracted course of disease.

Although we used the cutoff points to identify sarcopenia[50] validated in cancer patients, which might not be adequate to estimate sarcopenia in CD patients[332], we believe our findings strengthen the concept that in the era of obesity we cannot draw any conclusions about the nutritional status of CD patients based on weight only. More importantly, we also observed that patients with visceral obesity were the ones who had higher SMA and SMI but lower muscle radiation attenuation. This is different from the sarcopenic obesity described in certain cancer sub-populations[50] where expansion of visceral fat is associated with depletion of skeletal muscle, both reflecting a more inflammatory and catabolic setting. Our observations are consistent with the hypothesis that, by contrast to cancer patients, in CD, excess of visceral fat may not be the result of a chronic inflammatory process as it is not associated to depletion of skeletal muscle, but rather constitute a primary process in disease pathogenesis. This is further supported by the lack of association found between visceral fat or muscle radiation attenuation and disease duration. Furthermore, in our multivariate model, adjusted for age, muscle radiation attenuation was still predictive of complicated phenotypes. The only fat compartment which was found to increase with duration of disease was subcutaneous fat which plays no specific role in chronic inflammation as cytokine production profiles differ between subcutaneous and visceral fat[333].

Interestingly, we also observed significant associations between visceral fat area, visceral fat index and muscle radiation attenuation and Montreal characteristics such as age of disease onset, disease location and behaviour. Specifically, lower muscle radiation attenuation, reflecting infiltration of muscle by fat, was associated with complicated disease, raising the possibility whether this parameter could be used to predict disease severity and progression. As opposed to visceral fat parameters which correlated with disease characteristics, SMA and SMI and index were significantly lower in patients with positive CRP and previous hospital admissions which certainly reflect patients with a more chronic and protracted course of disease. Muscle radiation attenuation was also lower in previous hospitalized patients probably identifying more wasted patients.

Previous studies in CD patients found that mesenteric fat hypertrophy could be present at disease presentation and be a primary event involved in disease pathogenesis[333,334]. Most available data suggest that mesenteric fat promotes intestinal inflammation, with some studies linking expansion of visceral fat with more aggressive phenotypes, earlier need of surgery and poor response to therapy[323,326–328]. These observations are not consistent across all studies with some observations favouring the hypothesis that mesenteric fat may constitute a host response, a mean of containing inflammation and decreasing the risk of fistula formation[335]. Simultaneously, decrease of skeletal muscle mass has been shown to exist in the majority of patients with CD[331] but to our knowledge, no previous study has simultaneously evaluated both body compartments. These changes in body composition are most probably related to each other and the stimuli responsible for expansion of mesenteric fat could be the ones which promote wasting of skeletal muscle and/ or increased infiltration of skeletal muscle by fat tissue – muscle radiation attenuation.

Lower MA has been shown to be an important prognostic factor in cancer patients [321] although the mechanism whereby this contributes to worsen the prognosis remains to be clarified. To our knowledge this is the first study showing that a lower MA might also represent a negative prognostic factor in CD. In contrast to disease location which tends to remain quite stable over years, disease behaviour changes over the years with most patients being diagnosed as an inflammatory phenotype (B1) but some of these moving into more complicated phenotypes such as B2/B3. Numerous attempts have been made to identify early predictors of complicated phenotypes to select patients who could benefit from early aggressive therapy. Although our data needs to be confirmed in future prospective and longitudinal studies, low muscle radiation attenuation in patients with a recent diagnosis of CD could be a predictive biomarker of increased risk to progress into complicated phenotypes, which could benefit from the early institution of more effective therapies. In our institution, CT is often performed as the first cross-sectional imaging investigation to map disease extent in adult patients, since it is prone to less artifacts and more accessible, and therefore this could be a tool used to predict disease behaviour in CD at diagnosis. Due to radiation exposure, there is a tendency to replace it by MRI but, with

the available technology, it is not possible to measure muscle radiation attenuation using MRI.

This study has several limitations namely the heterogeneity of the study population and the fact that CT was not performed in all patients upon diagnosis. Although in the present study we did not find any association with current medical therapy, except for recent corticosteroid intake, we cannot exclude that changes in body composition observed were not primary but secondary to disease evolution and/or therapies performed. However, if we only included patients with recently diagnosed CD where CT was being performed as part of the initial staging process, we could not explore possible associations with complicated phenotypes which, in most patients, develop with 5-10 years. Another limitation is the small number of patients included in the present study. However, this exploratory study enabled us to identify possible biomarkers of body composition with a potential prognostic value.

Conclusion

This is the first study where a significant association between fat and fat-free compartments and Crohn's disease phenotype according to Montreal classification was found. We identified that body composition, namely lower muscle radiation attenuation and increased visceral obesity were associated with complicated disease. We believe that these findings together indicate that the systematic assessment of body composition parameters may have a predictive value in identifying patients who will develop complicated phenotypes. Body composition analysis can be made using CT scans ordered as part of routine clinical care in patients with Crohn's disease. Prospective multicentre studies are needed to confirm the findings of this study and assess the utility of these parameters to predict disease behaviour and act as a prognostic tool for patients with CD.

Study 6

Body composition and Crohn's disease behavior: Is adiposity the main game changer?

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Contribution of the PhD candidate:

The candidate operationalized the technique regarding CT derived body composition assessment in collaboration with Lisa Agostinho. She then proceeded to analyze the body composition data, using reported thresholds to identify body composition phenotypes. She completed the database with body composition parameters, conducted the statistical analysis and drafted the article. She participated in the revision of the draft leading up to its publication. The paper was then published in Nutrition (**Quartile 1** in Nutrition and Dietetics).

Nutrition (2023), 108. https://doi.org/10.1016/j.nut.2022.111959

Abbreviations

CD, Crohn's Disease

CT, Computed Tomography

MRI, Magnetic Resonance Imaging

DEXA, Dual-energy X-ray absorptiometry

BMI, Body Mass Index

CTE, Computed Tomography Enterography

E-MRI, Entero Magnetic Resonance

CRP, C-Reactive Protein

SMA, Skeletal Muscle Area

SMI, Skeletal Muscle Index

Abstract

Objective: We investigated the association between body composition upon diagnosis and complicated phenotypes and time until surgery in patients with Crohn´s disease (CD).

Methods: retrospective cohort study including patients with CD who had a computed tomography enterography or an entero magnetic resonance performed within 6 months of diagnosis. Skeletal muscle, visceral and subcutaneous adipose tissue cross-sectional areas were determined with CT or MR images at L3 vertebrae level, processed with Slice-o-Matic (Tomovison) and ABCS plugin.

Results: We included 63 patients: 33(52%) men, median age of 35 years. Disease location and behaviour according to Montreal classification was: L1 (ileal disease)=28(44%), L2(colonic disease)=13(21%), L3(ileocolonic disease)=18(28%), L1+L4(ileal and isolated upper disease)=1(2%), L3+L4(ileocolonic and isolated upper disease)=3(5%); B1(non-sticturing)=39(62%), B2(structuring)=11(17%), B3(penetrating)=13(21%); 20(32%) patients had perianal disease. Visceral obesity was present in 12(19%) patients and was associated with higher age of CD onset (median 60 vs. 34 years, p=0.002) and complicated disease behaviour (B2/B3) (66.7% vs. 31.7%, p=0.021). After adjusting for age and perianal disease, total adipose tissue was associated with 4% increase in the odds of complicated behaviour per 10 cm^2 of total adipose tissue (OR 1.004,95%CI 1.00-1.008, p=0.043). Median follow-up time was 3.35 years, during which 15 (24%) of patients underwent abdominal surgery. Visceral obesity was associated with 5.10 times higher risk of abdominal surgery (95%CI 1.52-17.09, p=0.008); after adjusting for disease behaviour, visceral obesity, maintained a near significant association with 2.90 times higher risk of surgery (95%CI 0.83-10.08, p=0.09).

Conclusion: Total fat was associated with complicated disease phenotype and visceral obesity with higher risk of abdominal surgery and shorter time until surgery.

Keywords: Body composition, Total Fat, Visceral obesity, Crohn´s disease behaviour, abdominal surgery

Introduction

CD is a chronic and relapsing disease, characterized by a discontinuous and transmural inflammatory process, affecting the entire gastrointestinal tract[336] with extraintestinal manifestations and associated immune disorders[337]. Mesenteric fat wrapping is considered a hallmark of Crohn's disease and has been recognized as a key feature since its initial description. Recent research has suggested that obesity, visceral fat, and in special mesenteric fat may be involved in the pathogenesis and course of Crohn´s disease (CD)[336].

Body composition analysis with computed tomography (CT) has been recently validated in Crohn's disease patients, and this technique has shown to accurately predict fat mass, fat-free mass and appendicular skeletal muscle by processing a single CT slice[38]. MRI (Magnetic Resonance Imaging) has also been validated using dual-energy X-ray absorptiometry (DEXA) as golden standard, and demonstrated a high correlation with CT scan derived measurements[338]. Body composition assessment with these sophisticated techniques is highly warranted since these are more informative than commonly used anthropometric measures such as Body Mass Index (BMI), which is known to be a poor predictor of body composition abnormalities such as sarcopenia[50,109], visceral obesity[339] and sarcopenic obesity[54].

Noticeably, comparing with BMI, visceral adiposity derived from imaging techniques as CT scan or MRI, has been more constantly related to IBD outcomes. Indeed in CD, visceral fat or its mesenteric fat component has been associated with unfavourable therapeutic outcomes such as complicated disease[198,340], increased risk of postoperative complications after elective ileocolectomy[15], higher post-operative recurrence after ileocolic ressection[199], higher risk of surgery and penetrating disease[341] and has been determined as an independent risk factor for endoscopic recurrence[200].

Although the link between excess adiposity and CD is still not completely understood several plausible biological mechanisms have come forward. Adipose tissue is both a storage and an endocrine organ that is able to release a number of adipokines, such as adiponectin (APN), IL-1, IL-6, IL-8, IFNγ, TNF-α, leptin, apelin, chemerin, and resistin[336]. The

expanding adipose tissue is known to release proinflammatory cytokines such as tumor necrosis factor-alpha (TNFα), interleukin-(IL)-6 (IL-6), IL-8 (CXCL8) and inflammatory ligands like lipopolysaccharide (LPS) which activate Toll- like receptor (TLR) and consequently NF-κB, further fueling inflammation[342].

In a previous study[340] we observed that excess of visceral fat was associated with stricturing and penetrating phenotypes. Whether this excess of fat was previous, or a consequence of chronic inflammation could not be clarified as body composition measures were not performed upon diagnosis. In the present study all measurements of body composition were made within 6 months of diagnosis, and we sought to analyse the association between body composition and outcome, namely disease phenotype and time until abdominal surgery. Furthermore, we compared longitudinal body composition evolution between baseline matched patients with favourable and unfavourable outcomes.

Materials and Methods

Study population.

The study protocol was approved by the Scientific and Ethics Committee of Hospital Beatriz Ângelo in Loures, Portugal. Clinical records of patients with an incident diagnosis of CD in our clinic between January 2012 and June 2017 were retrospectively reviewed. Patients were included if they had either a Computed Tomography Enterography (CTE) or an Entero Magnetic Resonance (E-MRI) as part of clinical workup within six months of diagnosis which included clinical, laboratorial, and endoscopic evaluation. Phenotypic characteristics were retrospectively collected from charts including demographic data, age of disease onset, disease extension and behaviour according to Montreal classification[182]. Complicated disease phenotype was defined as B2 (structuring) or B3(penetrating) phenotype according to Montreal classification. Time until abdominal surgery was defined in years between diagnosis and abdominal surgery. Therapies prescribed, response and disease evolution, hospital admission, surgery and post-operative complications were also recorded.

Laboratory values were abstracted from electronic charts. Anemia was defined as a hemoglobin value lower than 12 gr/dl for women or 13 gr/dl in men. C-Reactive protein (CRP) values was also registered.

Cross-sectional imaging evaluation

CT scans or MRI images taken during diagnosis and subsequent follow-up were acquired and analysed for body composition by one investigator blinded to clinical and endoscopic data to ensure objective interpretation of images findings. Images were selected by radiologists at the third lumbar vertebra (L3) using a portal venous phase and processed using Slice-o-Matic (Tomovison Magog, QC, Canada) and the ABCS plugin, which automatically segmented tissue cross-sectional areas of CT scan images. MRI images were segmented manually. Posterior validation of image processing was done by a nutritionist and radiologist, with manual corrections made as necessary. Image thickness was set at 5mm, and the tube voltage was 100kv. Segmentation of tissue cross-sectional areas was conducted according to the following Hounsfield unit thresholds: -29 to 150 for skeletal muscle, -190 to -30 for subcutaneous and intramuscular adipose tissue, and -50 to -150 for visceral adipose tissue. Cross-sectional skeletal muscle, visceral fat, and subcutaneous fat areas were measured in square centimetres, and mean muscle radiation attenuation was measured in Hounsfield units. Skeletal muscle area (SMA) was normalized for stature to calculate the skeletal muscle index (SMI) in cm^2/m^2. Sarcopenia was defined as SMI lower than 41 cm^2/m^2 in women, lower than 43 cm^2/m^2 in men with a body mass index (BMI) <25 Kg/m^2, and <53 in men with a BMI > 25 Kg/m^2, as described by Martin et al.[50] based on an International Consensus of Sarcopenia[44]. Visceral obesity was defined as a visceral fat area ≥80.1 cm2 for women and ≥163.8 cm2 for men, according to Doyle et al.[207]. An inter-reliability analysis was conducted, and variance coefficients were calculated for two duplicate CT scans, yielding values of 1.2%, 1.9%, and 4.2% for skeletal muscle, visceral adipose tissue, and subcutaneous adipose tissue, respectively.

Statistical analysis

Continuous variables were described as mean, median and interquartile range (IQR), while categorical variables are expressed as frequency and percentage. Differences in mean continuous variables and dichotomous variables were analysed by t-test or Mann Whitney U test as appropriate, according to variable´s adjustment to a normal distribution. Chi-squared test and Fisher's Exact Test was used to explore associations between categorical variables. A p-value <0.05 was set as statistically significant.

Simple logistic regression was performed to analyse the relationship between dependent variable, complicated behaviour (B1, non-stricturing vs. B2, stricturing or B3, penetrating), and relevant clinical and body composition variables. Multiple logistic regression was performed using variables clinically relevant and/or with p-value <0.25 in simple logistic regression. Time until abdominal surgery was analysed with Kaplan Meier survival curves and a Multiple Proportional Hazards Cox Model was also adjusted.

In the longitudinal analysis of body composition and its association with clinical outcome, a composite endpoint was used to define favourable (FO) or unfavourable outcome (UO), which comprised the following components: abdominal surgery, therapy intensification and complicated disease phenotype at follow up. The difference between baseline and follow up body composition cross sectional areas were computed, and outcome group comparisons were performed. Statistical analysis was performed with Posit software.

Results

Demographics and clinical features

Overall, 72 patients fulfilled inclusion criteria and were reviewed. 9/72 patients were excluded due to missing CT scan (6 patients) or MR images with artifact (3 patients). Clinical and demographic data are shown on **Table 1**.

Table 1 – Clinical Characteristics of patients included in the study.

N	**63**
Median Age (years)/IQR	35/22.5
Male/Female	
Montreal classification	
A1/A2/A3	5/34/24
L1/L2/L3/ L1+L4/L3+L4	29/13/21/1/3
B1/B2/B3	39/11/13
Perianal disease	
Yes/No	20/43
Median Duration of Disease (years)/IQR	3.35/4.19
Smoking habits	
Yes/no/ex-smoker	21/36/6
Surgery after diagnosis	
Yes/No	25/38
Corticosteroids	
Yes/No	17/46
Medication	
Azathioprine	42
Biologics	31
C- reactive protein	
Positive/negative	45/8
Median hemoglobin (mg/dl)/IQR	13.4/2.8
Anemia	
Yes/No	18/38
Endoscopic Activity	
Yes/No	10/45

IQR-Interquartile range.

Body Mass Index and Body composition

According to BMI classification, 17/63 (26.9%) were underweight (BMI<20 kg/m^2), 31/63 (49.2%) had normal weight, 15/63 (23.8%) were overweight or obese. 12/63 (19%) presented visceral obesity, 32/63 (50.8%) were sarcopenic and 5/63 (7.9%) had sarcopenic obesity. A Venn diagram presenting body composition phenotypes can be viewed on **Figure 1**. Results from the analysis of the association between BMI, body composition and sex are presented in **Table 2**. Sarcopenia was more prevalent among women (22/30 (73.3%) vs. 10/33 (30.3%), p<0.001), accordingly median Skeletal Muscle Index (SMI) was higher for men (Median-48.07 (IQR-12.46) vs. Median-37.50 (IQR-9.63), p<0.001). No other significant associations were found between sex and body composition.

Associations between disease characteristics and body composition are presented on **Table 3**. Sarcopenia was found to be significantly associated with ileocolonic disease location (14/21 (66.6%) vs 7/21 (33.4%), p=0.054) and anemia, as the number of sarcopenic patients with anemia was almost threefold the number of non-sarcopenic patients with anemia (13/18 (72.2%) vs 5/18 (22,8%), p=0.035). Visceral obesity was associated with older age of onset in both continuous (Median-59.5 (IQR-16.5) vs Median-34.0 (IQR-21.0), p=0.002) and categorized form (9/12 (75%) patients with visceral obesity had age higher than 40, p=0.021), and also with complicated disease phenotype, where 8/12 (66.7%) patients with visceral obesity and 16/51 (31.7%) patients without visceral obesity had complicated disease phenotype (p=0.021).

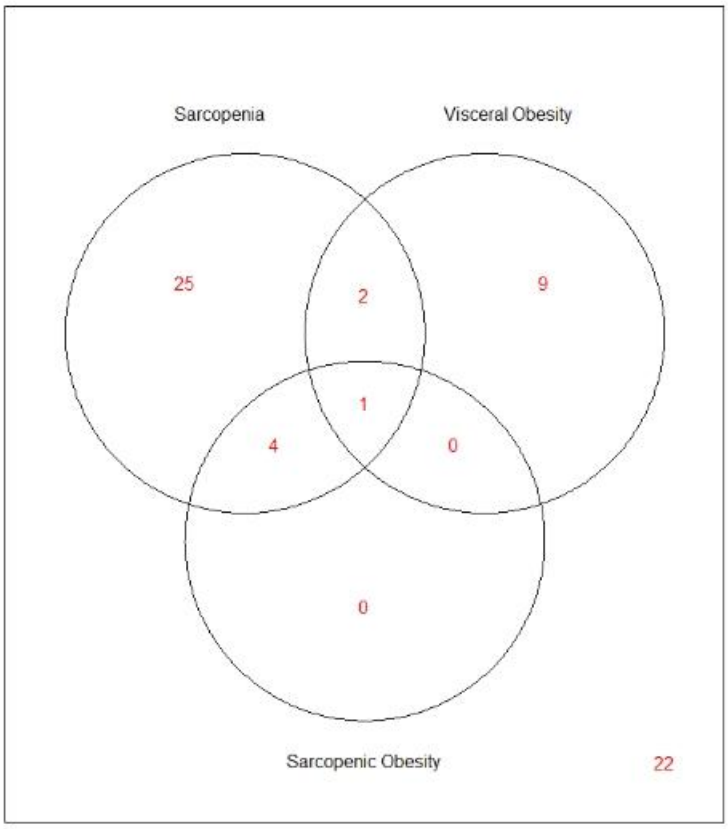


Figure 1- Venn diagram of body composition phenotypes: Sarcopenia, Visceral Obesity and Sarcopenic Obesity

Table 2-Body Mass Index and Body Composition at Diagnosis.

	Values (n=63)			
	Total	**Women**	**Men**	**p-value**
		n=30	**n=33**	
Body Mass Index (kg/m^2)	21.97 (5.07)	22.66 (5.08)	21.80 (4.63)	0.316
Body Mass Index Categories				
<20.0	17 (26.9)	7 (23.3)	10(30.3)	0.288
20.0-24.9	31 (49.2)	15(50.0)	16(48.5)	
25.0-29.9	12 (19.0)	5(16.7)	7(21.2)	
≥30	3 (4.8)	3(10.0)	0(0.0)	
SMI (cm^2/m^2)	42.9(13.5)	37.5(9.63)	48.07(12.46)	<0.001
Visceral Fat Index (cm^2/m^2)	12.11(33.49)	11.07 (17.19)	18.36(42.25)	0.270
Subcutaneous Fat Index (cm^2/m^2)	38.72(41.15)	61.12(61.21)	30.44(26.84)	0.0008
Total Fat (cm^2)	168.58(227.24)	176.86(243.89)	157.21(219.71)	0.362
Muscle Radiation Attenuation (HU)	46.88(17.72)	44.64 (14.53)	49.99(19.91)	0.640
VFA: SMA ratio	0.31(0.62)	0.31 (0.51)	0.46 (0.83)	0.656
Visceral obesity	12 (19.0)	5 (16.7)	7 (21.2)	0.646
Sarcopenia	32 (50.8)	22 (73.3)	10 (30.3)	<0.001
Sarcopenic Obesity	5 (7.9)	4 (13.3)	1(3)	0.130

Results are expressed as number (percentage) or median (interquartile range); SMI-Skeletal Muscle Index; VFA:SMA ratio- Visceral Fat Area-to- Skeletal Muscle Area**.**

Table 3- Association between body composition phenotypes and demographics, clinical and biological variables.

	Sarcopenia			Visceral Obesity		
	Yes (n=32)	**No (n=31)**	**P**	**Yes (n=12)**	**No (n=51)**	**P**
Age	34 (22.75)	39(30.0)	0.119	59.5(16.5)	34.0(21.0)	0.0002
Age of onset						
A1	3 (9.4)	2 (6.5)	0.51	0(0)	5(9.8)	0.012
A2	19 (59.4)	15 (48.4)		3(25.0)	31(60.8)	
A3	10 (31.2)	14 (45.2)		9(75.0)	15(29.4)	
Location						
L1	10(31.2)	19(61.3)	0.054	7(58.3)	22(43.1)	0.634
L2	8(25.0)	5(16.1)		2(16.7)	11(21.6)	
L3	14(43.8)	7(22.6)		3(25.0)	18(35.3)	
Phenotype						
B1	19(59.4)	20(64.4)	0.672	4(33.3)	35(68.6)	0.029
B2	5(15.6)	6(19.4)		5(41.7)	6(11.8)	
B3	8(25.0)	5(16.1)		3(25.0)	10(19.6)	
Perianal disease						
No	22(68.8)	21(67.7)	0.931	9(75.0)	34(66.7)	0.57
Yes	10(31.2)	10(32.3)		3(25.0)	17(33.3)	
C-reactive protein (mg/dl)						
<0.5	4(14.3)	4(16.0)	0.51	1(12.5)	7(15.6)	0.82
≥0.5	24(85.7)	21(84.0)		7(87.5)	38(84.4)	

	Sarcopenia			Visceral Obesity		
	Yes (n=32)	**No (n=31)**	**P**	**Yes (n=12)**	**No (n=51)**	**p**
Anemia						
No	16(55.2)	22(81.5)	0.035	9(81.8)	16(35.4)	0.268
Yes	13(44.8)	5(18.5)		2(18.2)	29(64.4)	
Hospitalization after diagnosis						
No	15(46.9)	17(54.8)	0.527	5(41.7)	27(52.9)	0.482
Yes	17(53.1)	14(45.2)		7(58.3)	24(47.1)	

Results expressed as number(percentage) or median (IQR): Age at diagnosis: A1, ≤16; A2, 17-19; A3, ≥40, Behaviour: B1, non-stricturing, B2, structuring, B3 penetrating, L1, ileal, L2 colonic, L3, ileocolonic.

Clinical and body composition features associated with complicated phenotype at diagnosis.

According to results obtained with simple logistic regression, age at diagnosis was associated with a 3% increase in the odds of complicated disease per year (OR=1.03, 95%IC=1.00-1.06, p=0.05). Regarding body composition, visceral obesity was associated with approximately four times higher risk of complicated phenotype, when compared with patients without visceral obesity (OR=4.37, 95%IC=1.19-18.44, p=0.03). Likewise, total adipose tissue was associated with a 4% increase in the odds of complicated disease per 10 units of total adipose tissue (OR=1.004, 95%IC=1.001-1.008, p=0.006). It is noteworthy that other significant associations were found for other continuous variables concerning body composition such as visceral adipose tissue area (OR=1.007, 95%IC= 1.00-1.014, p=0.0242) and index (OR=1.02, 95%IC=1.00-1.04, p=0.0244), subcutaneous adipose tissue area (OR=1.006, 95%IC=1.00-1.01, p= 0.0247) and total fat-to-skeletal muscle ratio (OR=1.67, 95%IC=1.27-2.66, p=0.016). On the other hand, non-significant associations were found for

sex (women: OR=0.28; 95%CI=0.06- 1.03, p=0.075), disease location (L2 OR=0.37, 95%CI= 0.07- 1.50, p=0.188; L3 OR=0.75, 95%CI=0.24-2.36, p=0.634), corticosteroid therapy (OR=0.59, 95%IC=0.16-1.88, p=0.391), sarcopenia (OR=1.24, 95%CI=0.44-3.49, p=0.675), skeletal muscle area (OR=1.00, 95%CI=0.98-1.01, p=0.95) and skeletal muscle index (OR=1.00, 95%IC=0.94-1.05, p=0.988).

On multiple logistic regression (**Table 4**) we included all variables with p value ≤0.05 and limited the number of variables selected to avoid overfitting. Thus, regarding body composition we decided to use total fat alone in the final model, since all other significant variables are accounted for in total fat, which means that including others would be redundant, and because total fat was substantially more significant. In order to account for between biological sex variability, we mean-centred total fat per sex. After adjusting for age and perianal disease, total fat remained statistically significant and was associated with a 4% increase in the odds of complicated disease per 10 units of total adipose tissue (OR=1.004, 95%IC=1.00-1.008, p=0.043). According to ROC curve analysis this model had a fair ability of discriminating complicated disease phenotype with an area under de curve of 0.728; sensibility of 70.8. specificity of 69.2, positive predicted value of 20.6 and negative predictive value of 41.4 (**Figure 2**).

Table 4- Results from simple and multiple logistic regression form the analysis of predictive factors associated with disease phenotype.

	Disease Phenotype		Simple Logistic Regression			Multiple Logistic Regression		
	B1 (n=39)	**B2/B3 (n=24)**	**OR**	**95%IC**	**P**	**OR**	**95%IC**	**P**
Age at diagnosis	34(24)	41.5(31.25)	1.03	1.00-1.06	0.05	1.004	0.11-3.49	0.576
Age								
≥ 25 years	26	21	1.00					
<25 years	13	3	0.28	0.06- 1.03	0.075			
Sex								
Men	20	13	1.00					
Women	19	11	1.12	0.40-3.41	0.824			
Disease Location								
L1	16	13	1.00					
L2	10	3	0.37	0.07- 1.50	0.188			
L3/L4	13	8	0.75	0.24-2.36	0.634			
Perianal disease								
Yes	23	20	1.00			1.00		
No	16	4	0.28	0.07-0.93	0.05	0.40	0.09-1.52	0.195
Body composition								
Sarcopenia								
No	20	11	1.00					
Yes	19	13	1.24	0.44-3.49	0.675			
Low Muscle Radiation Attenuation								
No	28	13	1.00					
Yes	4	5	2.69	0.62-12.53	0.187			

	Disease Phenotype		Simple Logistic Regression			Multiple Logistic Regression		
	B1 (n=39)	B2/B3 (n=24)	OR	95%IC	P	OR	95%IC	P
Visceral Obesity								
No	35	16	1.00					
Yes	4	8	4.37	1.19-18.44	0.030			
Total Adipose Tissue	129.06 (156.95)	261.31 (295.05)	1.004	1.001-1.008	0.007	1.004	1.00-1.01	0.043

Results expressed as number or median (IQR). L, Location; L1, ileal; L2, colonic, L3, ileocolonic, L4, isolated upper disease; CI, confidence interval; OR, odds ratio.

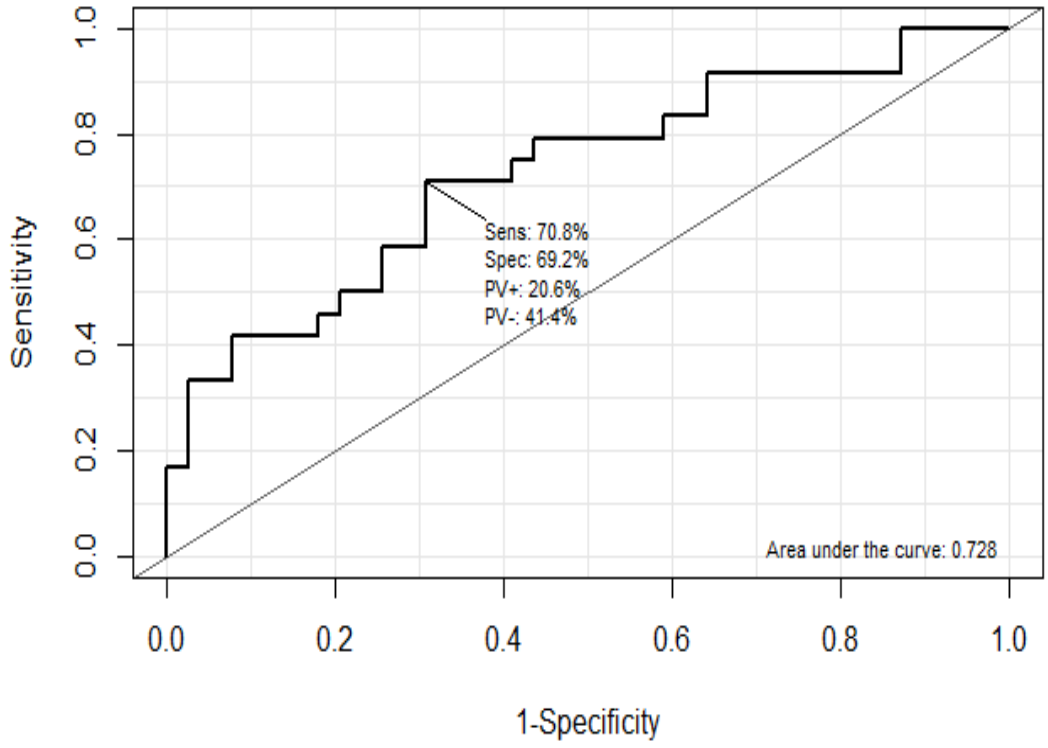


Figure 2-Receiver-operating characteristics (ROC) curve for complicated disease phenotype as the dependent variable and age at diagnosis, perianal disease and mean centred total adipose tissue per sex (n = 63). Sens, sensitivity; Spec, specificity; PV+, positive predictive value; PV–, negative predictive value.

Time until surgery and body composition

Estimated mean time until surgery was 2.57 years. According to Kaplan Meier curve comparison disease phenotype (B1, non-stricturing=7.49, B2, structuring=3.16, B3, penetrating=4.00, p<0.0001), and visceral obesity (yes=4.13 vs. no=6.16 p=0.0035) were associated with time until abdominal surgery (**Figures 3 and 4)**. Non-significant variables included Montreal A (A1, ages≤16-6.91, A2,17-19=6.34, and A3≥40 years=5.32, p=0.22), Montreal L (L1 (ileal)=5.62, L2(colonic disease)= 7.10, and L3(ileocolonic)=5.99, p=0.4), corticosteroids (yes=6.41, no=5.93, p=0.58) and sarcopenia (yes=6.09, no=5.83, p=0.79), whereas a near significant association was found for perianal disease (yes=7.20, no=5.35, p=0.05) and sarcopenic obesity (yes=4.13, no=6.16, p=0.09). **Table 5** presents restricted mean time to abdominal surgery and results from simple and multiple proportional hazards cox models. For a matter of simplicity only statistically significant results are presented on **Table 5**, non-significant variables included Montreal A (A2:Hazard Ratio (HR)=1.50, 95%CI-0.18-12.39, p=0.70; A3:HR=3.55, 95%CI-0.41-30.68, p=0.24), Montreal L (L2:HR=0.25, 95%CI-0.03-2.07, p=0.202; L3- HR=0.85, 95%CI-0.29-2.4, p=0.77), corticosteroids (HR=0.71, 95%IC-0.218-2.32, p=0.575), sarcopenia (HR=0.87, 95%IC-0.31-2.42, p=0.787), sarcopenic obesity (HR=2.91,95%CI-0.80-10.53, p=0.103) and a near significant association was found for perianal disease (HR= 0.25, 95%CI-0.05-1.12, p=0.07). Patients with B2 and B3 phenotype had 18- and 12-times higher risk of abdominal surgery compared with B1, respectively. Regarding body composition, patients with visceral obesity presented 5-times higher risk of abdominal surgery compared with patients without visceral obesity.

Furthermore, a proportional hazards Cox model was defined including variables with p-value <0.25 in simple analysis or deemed as clinically relevant, namely perianal disease, disease phenotype and visceral obesity. However, after stepwise variable selection only disease phenotype and visceral obesity remained in the final model. In this model visceral obesity-maintained a near significant association with a risk of surgery 2.90-times higher in patients with visceral obesity when compared with patients without visceral obesity, after adjusting for disease phenotype.

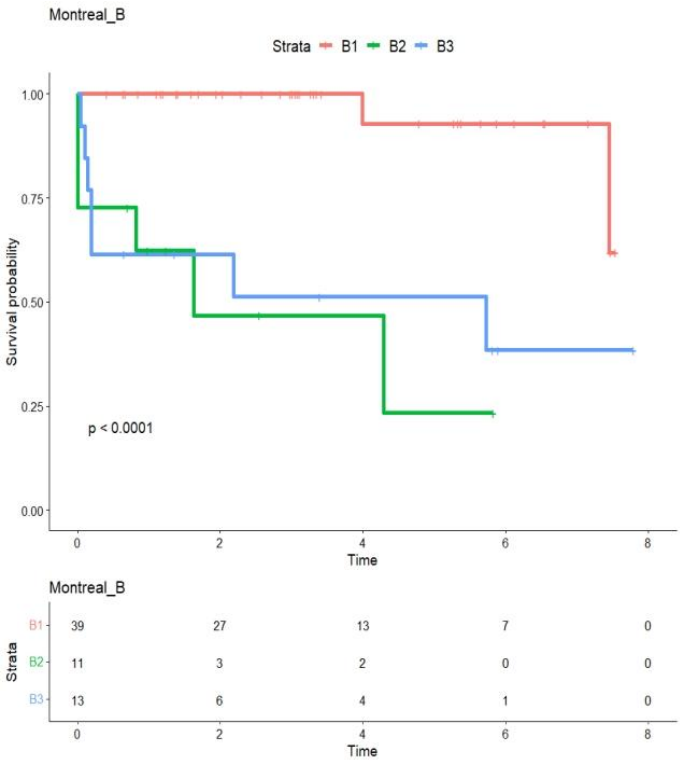


Figure 3-Kaplan Meier curves for time until abdominal surgery and disease phenotype.

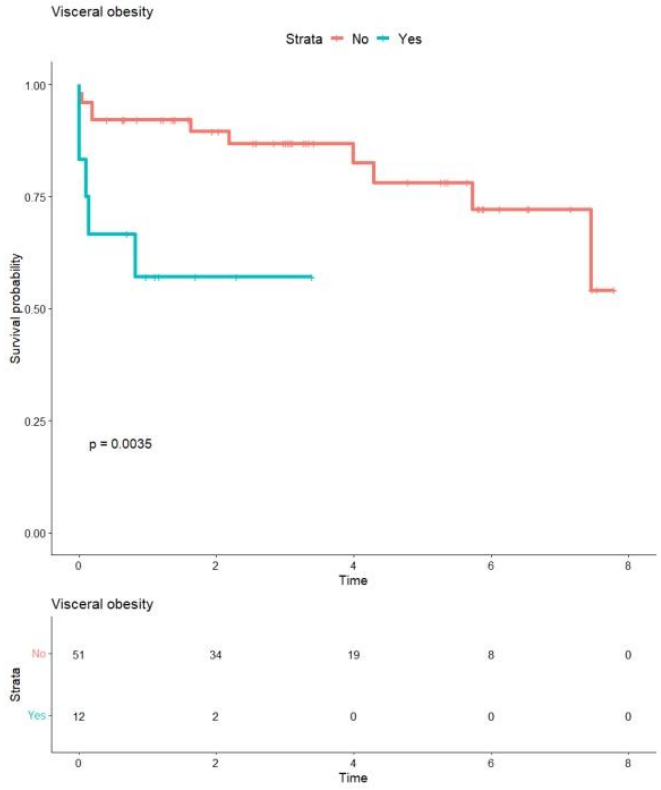


Figure 4-Kaplan Meier curves for time until abdominal surgery and visceral obesity.

Table 5- Mean time to abdominal surgery and Simple and Multiple Proportional Hazards Cox Model

	n	Abd. Surg.	Restricted Mean time to surgery (years)	Simple analysis					Multiple analysis				
				Coef	SE	HR	95%CI	p	Coef	SE	HR	95%CI	p
Perianal Disease													
No	43	13	5.35			1.00					Excluded		
Yes	20	2	7.20	-1.4	0.76	0.52	0.05-1.12	0.07					
Montreal classification													
B1	39	2	7.41			1.00					1.00		
B2	11	6	3.16	2.9	0.82	18.04	3.50-91.10	0.0005	2.7	0.84	14.50	2.76-76.02	0.001
B3	13	7	4.00	2.5	0.80	12.01	2.48-58.12	0.002	2.4	0.80	10.99	2.26-53.46	0.003
Visceral Obesity													
No	51	10	6.37			1.00					1.00		
Yes	12	5	4.35	1.6	0.61	5.10	1.52-17.09	0.008	1.1	0.63	2.90	0.83-10.08	0.09
c-statistics											0.865		

Abd. Surg.-Abdominal Surgery; CI, confidence interval; Coef, coefficient; HR, hazard ratio; B, Behavior; B1, non-stricturing, B2, stricturing, B3, penetrating.

Body composition evolution and outcome.

In a subset of 30 patients, we were able to obtain information regarding body composition at follow up, with a median follow up of 3.29 years. Favourable and unfavourable outcome was defined with a composite endpoint which included the following components: abdominal surgery, treatment intensification and complicated disease phenotype at follow up. 19/30 were categorized as having an unfavourable outcome (UO) and were compared with 11/30 who had a favourable outcome (FO). At baseline patients with favourable and unfavourable outcome were well matched regarding Montreal classification, perianal disease, age and gender and corticosteroid therapy (data not shown). In regard to

treatment during follow up period, unfavourable outcome group had more frequently azathioprine medication (FO-5 (22.7%) vs. OU-17(77.3%), p=0.008) and biologic therapy (FO-4 (23.5%) vs.UO-13(76.5%), p=0.09).Patients with unfavourable outcome had a significantly higher increase of skeletal muscle (Median difference-12.20,IQR-16.45 vs. Median-7.9, IQR-10.8, p=0.0005), subcutaneous adipose tissue (Median-47.48,IQR-108.10 vs. Median-24.80, IQR-57.71, p=0.005) and total adipose tissue (Median-114.03, IQR-154.40 vs. Median-27.57, IQR-136.21, p=0.034), whereas a near significant p value was obtained for visceral adipose tissue (Median- 23.84, IQR-64.77 vs. Median-1.16, IQR-42.87, p=0.1), when compared with patients with favourable outcome. **Figure 5** presents a waterfall plot analysing total fat according to disease course.

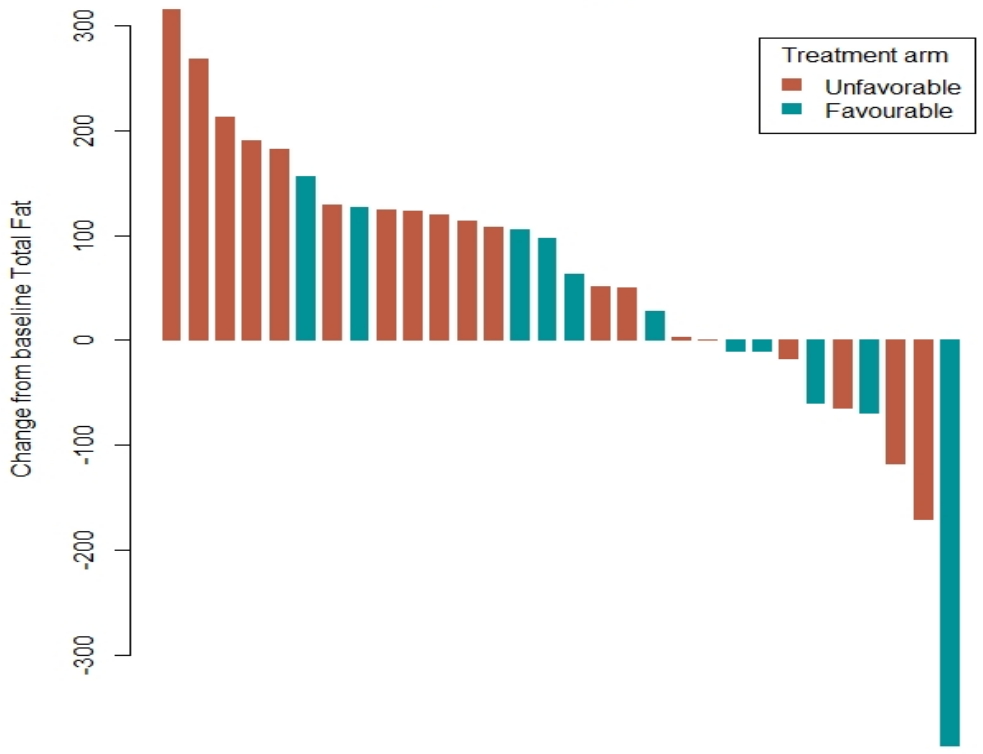


Figure 5- Waterfall plot analysing the evolution of total fat according to disease course.

Discussion

Herein, we have assessed the association between body composition on diagnosis in patients with CD and disease outcome, such as complicated phenotypes and time until abdominal surgery. We found that total fat is independently associated with complicated disease phenotypes (B2, stricturing and B3 penetrating) independently of age and perianal disease; visceral fat seems to be present at diagnosis and is the only body composition compartment that comes near to a significant association with time until abdominal surgery, when adjusted for disease phenotype. Moreover, patients with UO had an almost 4-times increase in the amount of total body fat from baseline until follow-up, compared with patients with FO.

The association between body composition and disease phenotype is in line with the results from a previous study conducted by our group, in which lower muscle attenuation and high visceral fat index were associated with more severe phenotypes in patients with CD. However, in our previous study, body composition was not measured on diagnosis, which did not allow drawing conclusions on whether these changes were causes or consequences of these complicated phenotypes. In the present study, we found that visceral obesity and more significantly total fat area were associated with complicated disease phenotype. In the present study, we were not able to explore muscle radiation attenuation, because, besides CT scans, we also used MRIs and, in these images, muscle radiation attenuation cannot be measured. Nevertheless, we included total fat, which may in fact be even more important. Previous studies focused on the association between the visceral fat-to-subcutaneous fat ratio and disease phenotype with contradictory results [198,343]. These were smaller studies and did not assess the association between total fat and disease phenotype. To our knowledge this is the first study analysing the association between total fat derived from sophisticated body composition techniques, such as CT or MRI, and disease phenotype.

In our study, a near-significant association was found for visceral obesity and time until abdominal surgery, which means patients with visceral obesity may need earlier surgery.

This result is concordant with a recent study, where patients with both high visceral fat-to-subcutaneous fat and sarcopenia had the highest probability of surgery[344] and, in another study, where both sarcopenia and visceral obesity were associated with the occurrence of abdominal surgery[345]. It is worth pointing out that in our study population, only 3 patients presented both visceral obesity and sarcopenia and were all included in the visceral obesity group.

Furthermore, in longitudinal analysis of body composition, patients with UO had a significantly higher increase in skeletal muscle, visceral adipose tissue, subcutaneous adipose tissue, and total adipose tissue. Although this may seem a paradox, because skeletal muscle did increase in patients with UO, interpretation of this result should be done, considering that in these patients we also observed a significant and concomitant increase in adipose tissue. Patients with UO had an increase of total body fat >4-times the increase of body fat in patients with FO, whereas we observed a more modest increase in skeletal muscle. In the natural process of weight gain, skeletal muscle development may occur to support extra weight resulting from the expanding fat mass[346]. However, we believe that the proinflammatory environment, because of an increase in adipokines released by the expanding adipose tissue, may hinder the supposed beneficial effect of skeletal muscle increase. Indeed, the prevalence of obesity and overweight measured with BMI has increased in CD patients and has been associated with both CD etiology and worse disease course[336], thus supporting the hypothesis that total body fat may have an effect on CD outcome.

There are two major types of adipose tissue, white adipose tissue, and brown adipose tissue. Beige adipose tissue may be considered a third type, identified in recent years. Brown adipose tissue is located in the neck and interscapular region and has been considered a heat-producing tissue mostly associated with maintaining body temperature of newborns; however, brown adipose tissue has also been recognized in adults, and its role in obesity treatment through energy dissipation as heat has been hypothesized[347]. Beige adipose tissue may be present within white adipose tissue and supraclavicular location and consists of adipocytes with thermogenic proprieties, because like brown adipose tissue,

beige adipose tissue has numerous mitochondria[347]. White adipose tissue comprises visceral adipose tissue and subcutaneous adipose tissue, which are known to have distinct metabolic and immunologic profiles. In particular, visceral obesity has been associated with higher inflammatory potential. In particular, mesenteric fat deposition leads to the disturbance of homeostasis of the intestine, participating directly or indirectly in low-grade inflammation, imbalance between the leptin-to-adiponectin ratio, disruption of the intestinal mucosa, and intestinal permeability, which again favours adipokine release, bacterial translocation, and T-cell infiltration, all of which are involved in the pathogenesis of IBD[336]. On the other hand, although inconsistently, subcutaneous adipose tissue has been associated with altered pharmacokinetics of drugs. Increased subcutaneous adipose tissue has been associated with decreasing levels of 6-thioguanine and adalimumab and speeded loss of response to infliximab[195]. All these observations support the findings of the present study, because total body fat may be implicated in CD etiology and behaviour and may also influence response to therapy.

Besides the previously stated physiologic effect of body fat, increasing body fat is a result of excess nutrition, in which the ingestion of dietary components (e.g., xenobiotics and food additives) that may alter gut microbiota is highly likely and has been previously reported[186,348] to have an effect on CD pathogenesis and behaviour. Indeed, diet seems to play a leading role in the pathogenesis of IBD along with sedentary lifestyle and genetic susceptibility, because it is involved in gut homeostasis. In particular, diet has been associated with the composition and functioning of gut microbiota, gut barrier host immunity, and hormone release[349]. The adoption of western nutritional habits is known to shift traditionally plant-based diets to animal-sourced food, supporting a substantial change in microbiota and microbiome, with reduction of bacteria, such as *Prevotella* and *Treponema*, which are involved in fibre degradation[350]. The western dietary pattern is characterized by an overall higher calorie intake, mostly derived from sugar, refined carbohydrates, animal proteins, and processed foods and has been associated with higher risk of obesity, type 2 diabetes mellitus, cardiovascular disease [351], and apparently IBD.

Conclusion

This study has allowed us to confirm the relationship between body composition, specifically total fat and visceral obesity upon diagnosis, and CD outcome, namely, disease phenotype and time until abdominal surgery. Also, this study further clarified that patients exhibiting worse outcome do actually change body composition with time, indicating a significant increase in all body composition compartments, but the greatest one is in total fat. We are aware that sample size is one of the limiting aspects of generalizability of our results, and cautious interpretation is therefore needed. Well-powered intervention studies focusing on body com- position in CD are mandatory, because confirming the link between body composition and outcome may have an effect on treatment by including body composition changing interventions, such as diet and exercise in standard treatment of patients with CD.

CHAPTER 4

Discussion

Chronic inflammatory diseases are becoming more prevalent worldwide and have been linked to the obesity pandemics. Obesity has been associated with the western lifestyle, which includes an excessive dietary intake and reduced physical activity, among others. Body composition alterations, such as increased adiposity, visceral obesity, sarcopenia, sarcopenic obesity and low muscle radiation attenuation have reportedly been linked with inflammation[352]. As such, these body composition phenotypes can be viewed as a hallmark of an inflammatory state and is suggested to be related to disease pathogenesis, as well as a potential key factor involved in the high variability often observed regarding disease course and/or response to therapies.

In this thesis, we have tried to gain insight into specificities regarding the association of body composition in chronic inflammatory gastrointestinal diseases including gastric and pancreatic cancer and Crohn's disease. The findings from the presented studies highlight the importance of CT-derived body composition analysis in clinical practice, due to its prognostic value, and its potential to enhance care plans. This connection further suggests that dietary interventions and exercise, are important modifiable factors which may play a leading role in counteracting unfavorable body composition alterations, and this, in turn, may lead to improved outcomes.

Gastrointestinal cancers

Cancer cachexia is characterized primarily by weight loss, resulting from a decrease in skeletal muscle mass, with or without the loss of adipose tissue. This condition arises from a combination of reduced food intake due to symptoms associated with the disease and anticancer treatments, but also from metabolic alterations, including heightened energy expenditure, neuro-hormonal changes, and chronic inflammation[353]. Various mediators produced by cancer cells and those within the tumor microenvironment can contribute to the development of cancer cachexia. In addition, anticancer therapies are known to exert cytotoxic effects on muscle cells that accelerate atrophy[353,354].

While many patients experience wasting, in some gastrointestinal cancers, such as pancreatic and colorectal cancers, obesity is a predisposing factor and therefore patients may begin their journey with excess adiposity, and as disease progresses, cachexia may arise, adding to the diversity of body composition phenotypes among patients and within patients over the disease course. The increasing prevalence of obesity is changing malnutrition's paradigm as phenotypes linked with adiposity, such as low muscle radiation attenuation and sarcopenic obesity are likely to become more prevalent, and as captured by our studies, can have clinical implications in the outcome of these patients. This emphasizes the importance of incorporating CT-based assessments into clinical practice, as it can provide more detailed insights, particularly regarding specific characteristics like low muscle radiation attenuation and sarcopenic obesity, which are not adequately detected by methods of nutrition risk screening[263]. Furthermore, these data may become incorporated in the definition of patient fitness which is increasingly used when deciding upon anti-cancer treatments, either medical (chemotherapy) or surgical.

In the last decade studies have established a relationship between body composition alterations and major outcome variables as overall survival[83,355–357], chemotherapy toxicity[358,359] and post operative complications[215,360] in patients with solid tumors, including gastrointestinal cancer. However, contradictory results have also been reported. In a study with patients with gastric/gastroesophageal junction cancer with advanced disease, muscle radiodensity (HR:0.979, 95%CI:0.96-0.99, p<0.0001), not quantity (HR:0.99, 95% CI:0.98-1.003, p=0.129), was significantly associated with overall survival, while skeletal muscle index was associated with PFS (HR:0.99, 95%CI:0.97-0.99, p=0.02)[361]. Confirming the role of sarcopenia in PFS, a recent systematic review with meta-analysis, reported a significant reduced PFS in cancer patients with sarcopenia (HR:1.56, 95% CI:1.19–2.03, p<0.001) in a mixed population that included gastrointestinal cancer[362]. These inconsistent results, probably reflect particularities that may exist regarding the association between body composition and outcome. Indeed, this connection is presumably dependent on factors inherent to the disease as tumor location, stage, treatment regimen, as well as factors

related to the host, which can be non-modifiable as age, genetics, among others, or modifiable as dietary intake, exercise, and ultimately body composition.

In a broader view, we can hypothesize that this association can be geographically specific since obesity prevalence and dietary intake inadequacies are known to vary at a worldwide level. In 2022, USA was at the leading position with an estimated prevalence of obesity of 42.4%[363]. In Europe in the same year the prevalence of obesity varied across countries with Romania (34%) and Turkey (33.3%) having higher rates, while France (9.7%) was among the lowest[363], and Portugal in between (17%)[364]. In China the estimated prevalence of obesity was of 8.3%, according to BMI≥30, however there is evidence that Chinese people exhibit greater adiposity comparing with Caucasian counterparts, and this criteria may potentially lead to an underestimated prevalence[365,366]. In contrast Japan has the lowest estimated prevalence of obesity, with a rate of 5.5%[366].

Bearing in mind this variability of obesity worldwide and that most existing studies relating body composition with cancer outcome have been conducted in the USA, East Asia (Japan and China) and to a lesser extent in Europe, in our view the results obtained from these studies may not be applicable to Portugal. The known differences in obesity prevalence between regions, can reflect significant differences in dietary habits. Portugal is known by its Mediterranean diet and together with its specific prevalence of obesity, highlights the need for country specific research in this field, due to its particularities, since existing evidence may not reflect our country's reality. This led us to pursue such research in Portugal, since none of a kind had been conducted in our country.

Another explanation for these inconsistencies is the diversity in methods and cutoffs used to define all body composition phenotypes. For instance, recent studies have indicated a notable occurrence of sarcopenia in gastrointestinal cancer patients upon diagnosis. However, comparing the prevalence of sarcopenia across these studies poses challenges due to variations in methodologies[224–230,367]. These methodologies include the utilization of bioimpedance, axial CT cross-sectional imaging, dual-energy X-ray absorptiometry for assessing muscle mass, alone or combined with physical performance measurements[231–

[234,356,357,367]. Additionally, even when employing the same methodology, differing sarcopenia thresholds are frequently applied[215,356,357], which can hinder interpretation of results.

1., Body composition assessment with anthropometry and BIA may be insufficient to identify sarcopenia and low muscle radiation attenuation although significant correlations between CT scan and anthropometry/BIA were found.

The comparability of various body composition assessment techniques remains inadequately substantiated, urging further investigation of this topic. In our study BIA was significantly correlated with CT-derived body composition but was insufficient to assess sarcopenia and low muscle radiation attenuation. These results are supported by Ní Bhuachalla et al. who also documented discrepancies between CT-based body composition analysis and BIA[368]. This clearly demonstrates the importance of integrating CT-derived body composition techniques into clinical practice, since it provides valuable information that can contribute to determine patients level of fitness, and this in turn, has the potential to aid therapy decision-making. In other words, CT-derived body composition can be used as a marker of patient's physiological reserve to cope with demanding treatments, and to identify patients in greater need of multimodal interventions, as prehabilitation. Oncology centres have started to integrate this approach, but to our knowledge no publications have reported their experience.

While CT-derived body composition can bring important, reliable, and impacting information, this does not diminish the value of techniques such as anthropometry or BIA, as each method has its own strengths and weaknesses. Thus, it's crucial for trained professionals to utilize these techniques and interpret the results thoughtfully. Further research is necessary to explore and validate the comparative efficacy of these various approaches.

2. Patients with gastric cancer undergoing neoadjuvant chemotherapy with low muscle radiation attenuation, sarcopenia or sarcopenic obesity had an increased likelihood of treatment toxicity.

The first study from this PhD thesis focusing on gastric cancer patients improved our understanding of the role of body composition in systemic treatment toxicity in a unique setting as neoadjuvant chemotherapy (NAC). It is noteworthy that at the time of our publication, as reported by a systematic review published in 2023, only two out of fourteen currently existing studies on the effect of NAC on body composition in gastric cancer, had been conducted in preceding years[369]. To our knowledge, no other studies on this topic have been published since. Although gastric cancer mortality is on a worldwide decline, Portugal exhibits the highest mortality rates compared to other Western European nations[203], which further adds to the pertinence of our study.

In our study, we found that low muscle radiation attenuation, sarcopenia and sarcopenic obesity were significantly associated with neoadjuvant chemotherapy toxicity. It is worth noting that except for the very early lesions for which endoscopic resection is recommended or direct surgery (<T2), most of gastric cancer diagnosed patients are treated with NAC which has been shown to improve overall survival in a significant manner[370]. However, this beneficial effect must consider the great toxicity of these regimens. Accordingly, it is of paramount importance to identify predictive factors of tolerance/effectivity as well as of strategies designed to improve tolerance. Regarding sarcopenia which is the most studied phenotype, existing evidence has reported both a significant[114] and non-significant[371,372] association with short-term outcomes as DLT in gastric cancer perioperative chemotherapy. While our study and that from Tan et al. which found a significant association, included patients undergoing the MRC Adjuvant Gastric Infusional Chemotherapy from MAGIC trial with Epirubicin, Cisplatin and 5-FU, in the other two studies which found no association, patients were treated with FLOT (fluorouracil, oxaliplatin, docetaxel, leucovorin) regimens. Toxicity may vary substantially with these two different regimens. However, there is preliminary evidence showing no difference concerning changes in adiposity or muscle losses between neoadjuvant treatment with

FLOT and MAGIC regimens in esophageal-gastric junction cancer patients[373], suggesting that other factors as sample size and sarcopenia cutoffs may have influenced the results.

In a meta-analysis, which included mostly studies with gastrointestinal cancer conducted in Europe and Asia, the authors analyzed the prognostic value of body composition. This study demonstrated that evidence linking sarcopenic obesity and DLT is limited [374]. In this meta-analysis published in 2022, few studies were eligible to analyze the effect of sarcopenic obesity on chemotherapy toxicity. The authors used studies enrolling patients with esophagogastric, pancreatic, esophageal cancer, which were associated with different chemotherapy toxicities[113,375,376]. While these results support our findings, they clearly demonstrate the paucity of existing evidence. In particular, the study from Dijksterhuis et. al. involving 88 patients with metastatic esophagogastric cancer, treated with standard first-line palliative systemic therapy with capecitabine and oxaliplatin showed that pre-treatment sarcopenic obesity and muscle radiodensity were independently associated with grade 2-4 neurotoxicity (OR:3.82, 95%:1.2-12.18 p=0.024) and grade 3-4 overall toxicity (OR:0.94, 95%:0.89-1.00; p=0.037), respectively[375]. Furthermore, a retrospective study by Kim et al. which included gastric cancer patients reported sarcopenic obesity as an independent risk factor for increased mortality (HR: 2.608; 95% CI:1.313–5.179, $p<0.05$)[377]. Although results from a meta-analysis published in 2023, which included mostly Asian studies, established that myosteatosis is associated with worse prognosis in gastric cancer, thereby increasing mortality risk in 46%[378], the association between myosteatosis and chemotherapy toxicity has been explored, with some evidence suggesting a link[379,380], but to our knowledge none specific to gastric cancer.

Therefore, we believe that our study contributed to bring light on this topic, since evidence is globally lacking regarding the effect of these specific phenotypes on chemotherapy toxicity in gastric cancer patients. Beyond that, it is a topic with national interest, since gastric cancer is an important public health issue in Portugal due to its increased mortality, and because existing evidence produced from studies in other geographic regions may fail to represent the particularities of the Portuguese population, which exhibit their specific obesity prevalence. While Portugal has an intermediate obesity prevalence, the USA

presents the highest and Japan with the lowest rate of obesity. These two regions have contributed with substantial research in the field of body composition and outcomes in cancer, but may not be valid to the Portuguese population, due to its dissimilarities.

The interplay between body composition phenotypes and survival is thought to be significantly influenced by toxicity to systemic treatments, a pivotal factor in the treatment journey. DLT stands out as a critical clinical outcome, often leading to treatment discontinuation, termination, hospitalization, and in severe cases, fatalities[109]. DLT is characterized by dose reduction, treatment delays or discontinuation due to adverse events graded by the National Cancer Institute Comon Toxicity Criteria for Adverse Events[116]. Notably, drugs dosage calculations, based on body surface area (BSA) derived from weight and height, or capped for patients with BSA ≥ 2.0m^2 [381], do not account for body composition, potentially impacting drugs' pharmacokinetics. Initially this association was linked with lean body mass (LBM), which contains skeletal muscle as an important component, due to its role in the volume of distribution of hydrophilic drugs as platin-based substances (e.g. cisplatin, carboplatin, oxaliplatin), 5-fluorouracil, cyclophosphamide and gemcitabine and anticancer drug clearance[382]. Recent evidence suggests that fat mass may, in addition, influence pharmacokinetics of lipophilic drugs as Irinotecan, capecitabine, epirubicin, docetaxel and/or paclitaxel and tyrosine kinase inhibitors (e.g. sorafenib and vandetanib).

The complexity of these interactions is heightened by the frequent simultaneous administration of drugs encompassing both hydrophilic and lipophilic characteristics. Additionally, anticancer treatments may induce skeletal muscle loss[109,354,383], further affecting tolerance to treatment. A recent meta-analysis by Surov et al., spanning 48 studies and 4803 patients with different malignant diseases, concluded that low skeletal muscle mass is a pivotal factor in treatment toxicity, with strongest impact observed in kinases inhibitors and the lowest in checkpoint inhibitors[382]. In conclusion, body composition in patients with gastric cancer submitted to NAC should be considered and whenever possible, optimized to reduce toxicity and improve outcome.

3. Sarcopenic obesity was significantly associated with postoperative complications and 90-day survival, whereas muscle radiation attenuation was an independent predictor of overall survival in patients undergoing pancreatic surgery.

Pancreatic cancer is currently the seventh leading cause of mortality worldwide, and its incidence is projected to increase at an accelerated rate in the next decades[204]. It presents a 5-year survival rate as low as 8.5%, therefore estimated mortality, is almost coincident with its incidence[204]. Important modifiable risk factors for this disease include obesity, smoking habits[204], and dietary patterns, including alcohol consumption[384] and high fat diet[385], among others. Although impressive improvements have been made in the treatment of this disease, with operative mortality rates below 3% in high volume centers, it remains associated with high operative morbidity ranging from 40-50% for pancreatoduodenectomy[386]. Moreover, since approximately only 20% of patients have indication for up front surgery, neoadjuvant treatments are increasingly used in these patients[387]. Neoadjuvant chemotherapy with FOLFIRINOX (5-fluorouracyl, irinotecan, oxaliplatin), is associated with a significant increase in overall survival, compared with other alternatives as gemcitabine based regimens[388], but is also related with higher toxicity, thereby being an option only for fit patients. Therefore, patients' optimization through multimodal interventions as ERAS or prehabilitation programs, may be paramount for these patients to endure combination therapies as neoadjuvant treatment[387]. Implementation of ERAS appears to modify the relationship between sarcopenia and complications positively[119,387]. Moreover, prehabilitation strategies have also been associated with reduced risk of post-operative complications in malnourished (incidence of infectious RR: 0.58, 95% CI: 0.50-0.68; $p<0.01$, and non-infectious complications RR: 0.74; 95% CI: 0.63-0.88; $p<0.01$)[389] and in high risk patients (RR:0.62, 95%: CI 0.43-0.89, $p=0.01$)[390].

The association between chemotherapy toxicity and body composition in pancreatic cancer has limited evidence, with a recent systematic review reporting a wide range of results[391]. A recent study observed an association regarding muscle radiodensity and chemotherapy toxicity (OR:0.96; 95% CI:0.95-0.98;$p<0.05$), but in patients with locally advanced pancreatic adenocarcinoma undergoing gemcitabine and nab-paclitaxel[392]. A study including

pancreatic cancer patients with indication for gemcitabine-based chemotherapy, revealed a positive correlation between skeletal muscle quantity and radiodensity and co-existence of low skeletal muscle index and low muscle radiodensity, were associated with overall survival (HR: 1.58, 95% CI: 1.12–2.23, p= 0.010)[95]. However, in a recent systematic review focusing on pancreatic cancer patients with incurable cancer, authors did not find a significant association between muscle loss and reduced overall survival[393]. In contrast, in the same review, the authors included four studies, which reported a significant association of muscle mass deficit with reduced overall survival, but in overweight or obese patients, meaning that compared with sarcopenia, adiposity phenotypes as myosetatosis or sarcopenic obesity may have a more significant impact in outcome of patients with incurable pancreatic cancer[393]. Regarding pancreatic cancer in the surgery setting there is more evidence, but inconsistent findings have been reported regarding sarcopenia and post-operative complications[49,119,394,395].

In our study sarcopenic obesity, but not sarcopenia by itself, was found to be significantly associated with 90-day post operative complications in patients submitted to pancreatic surgery mostly for malignant diseases. In our study sarcopenic obesity was defined using Visceral Fat Area: Skeletal Muscle Area ratio (VFA:SMA ratio), since it combines visceral adipose tissue, which is known to produce proinflammatory cytokines, and muscularity. Meta-analyses support the association between sarcopenia and an increased risk of major and total post-operative complications in gastrointestinal cancer patients[49,119], but particularities may exist regarding pancreatic cancer patients, since several other studies failed to demonstrate a link with sarcopenia alone in this population[90,123]. There is evidence suggesting that sarcopenic obesity might pose a more important risk, regarding main postoperative complications as pancreatic fistula, which is in line with our results[387,394,395]. The combination of sarcopenic obesity and myosteatotsis may further increase the risk of major complications (OR: 1.34, 95%CI: 1.01-1.74) and ICU admission (OR: 1.39, 95%CI 1.04-1.90), emphasizing its impact on patient outcomes[396]. Also, VAT has been linked to an increased risk of postoperative complications, possibly due to proinflammatory adipokines exacerbating surgical stress[124,126].

In our study, while sarcopenic obesity was associated with 90-day mortality, muscle radiation attenuation was significantly associated with overall survival. This result is supported by findings of Pecorelli et al., which also found a significant association between VFA:SMA ratio higher than 3.2 (OR:6.76; 95%CI:2.41-18.99, p<0.001) with 60-day postoperative complications adjusted to ASA score[248]. In our study, we focused on 90-day postoperative complications because we believe it offers a more comprehensive evaluation of this outcome, encompassing a broader understanding of the recovery process. The association between myosteatosis and overall survival of patients with gastrointestinal cancer has been reported. In a meta-analysis by Aleixo et al., myosteatosis was observed in 48% (range 11–85 %) of patients, whereas myosteatotic patients presented a 75% higher mortality risk when compared to non-myosteatotic counterparts (HR:1.75 95% CI: 1.60–1.92, p<0.00001)[56]. This study highlighted that myosteatosis was associated with worse prognosis across various cancer types, including periampullary/pancreatic, hepatocellular, gastroesophageal, colorectal carcinoma, among others, and included mostly studies that recruited patients treated with chemotherapy and surgery[56]. In addition, in a very recent study which included 354 patients with all stage pancreatic ductal adenocarcinomas, demonstrated that myosteatosis (HR: 1.53; 95% CI:1.10–2.14, p=0.01), and not sarcopenia or sarcopenic obesity, was independently associated with overall survival, adjusted for age, sex, disease stage, curative resection, sarcopenia and sarcopenic obesity[397]. Since myosteatosis is known to be linked with sarcopenic obesity, it is worth mentioning the results from a meta-analysis by Mintziras et al., that analyzed studies on pancreatic ductal adenocarcinoma, yielded a 2 fold increased risk of death ((HR:2.01; 95% CI:1.55-2.61,p<0.001) for patients with SO, compared with non-SO patients, adjusted for age, extent of disease, CA19-9 and tumor size[98].

Thus, we believe that our study was able to underpin the relationship between body composition and important outcomes in patients undergoing pancreatic surgery in a comprehensive approach, since we dealt with postoperative complications, 90-day, and overall survival, and went beyond sarcopenia, by investigating the role of all body composition phenotypes. To our knowledge there is no study of this kind in Portugal, and

we believe that this holistic approach has contributed to further elucidate this subject and set the stage for optimized nutritional interventions in pancreatic cancer patients. As such we should reinforce all pre-habitation strategies which aim at improving body composition status in these patients, and this may translate in less post-operative complications and better short and long-term survival.

At this stage of our research, it became obvious that body composition is related with gastric and pancreatic cancer clinical outcome and that the opportunistic CT imaging is a powerful technique that allowed us to obtain accurate information regarding body composition. As such, we decided to pursue our research aiming at analyzing the prognostic importance of diet in predicting sarcopenia. A better understanding of the relationship between diet and sarcopenia could convey insight for optimized nutritional interventions to fight muscle wasting. Moreover, unlike other features as age and tumor type or stage, diet is potentially modifiable, and could be a feasible approach to optimize patients' body composition.

4. The fat and fish pattern were associated with lower odds of sarcopenia in a Portuguese population with GI cancer.

Since cancer cachexia is partially attributed to nutritional deficits, which can be prevented or reversed, there is a theoretical possibility that dietary intake can modulate anabolism[398]. There is evidence that sustained hyper-aminoacidemia can contribute to achieve maximal levels of anabolism, prior to end-stage disease, characterized by an estimated survival of less than 3 months[271,399]. Recognizing the importance of the anabolic window, strategies to treat/prevent cachexia should be implemented at the time of diagnosis, before or at the time of therapeutic decision.

Optimal nutrition care, emphasizing both the quantity and quality of nutrient intake, stands as a fundamental strategy in supporting muscle anabolism, reducing catabolism, and improving overall prognosis throughout the continuum of cancer care[400]. While nutrition alone cannot reverse cancer cachexia, it can contribute significantly to maintain nutritional status, minimize its decline, control symptoms, and improve quality of life and overall

outcomes in cancer patients[400]. Thus, this study focused on improving our knowledge regarding diet and its impact on sarcopenia, since this information has the potential to improve nutritional interventions. This study allowed us to characterize the dietary patterns of patients with GI cancer, and we four distinct patterns: 1) high fat dairy products, fried snacks and processed meat pattern,2) legumes, vegetables, and fruit pattern, 3) fat and fish pattern, and 4) alcohol, cereal, and animal protein pattern. The pattern that explained more of the variance concerning the dietary intake data, was the high fat dairy products, fried snacks, and processed meat pattern, which are foods rich in saturated fat. This finding, together with the inexistent pattern explicitly describing the Mediterranean diet in our data, further supports the "westernization" of dietary habits in Portugal. In fact, compliance to the Mediterranean diet in a Portuguese population is estimated to be as low as 12-26%[284,401]

Most interestingly, in our study, the second tertile of high fat and fish pattern was associated with a protective effect regarding sarcopenia. Patients in this tertile showed a predominant energy intake above 30 kcal/kg, higher adherence to targeted protein intake (1.2-2 g/kg/day), and fat intake exceeding general recommendations (>30% of total calorie intake), with a higher ratio of mono- and polyunsaturated fats to saturated fat. In other words, this pattern consisted of an energy and protein dense diet, encompassing high quality lipids, that demonstrated to have protective effects on sarcopenia. Our findings suggest that sustaining a positive energy and protein balance is essential for promoting muscle anabolism in cancer patients[152–154].

While the importance of protein intake is recognized, evidence regarding specific requirements in terms of quantity and quality are still lacking[402]. Existing guidelines suggest an intake above 1.0g/kg/day, with a target of 1.2-2.0g/kg/day, mostly based on expert consensus[155]. Also, 2g/kg/day of protein has been found to be safe in patients with normal renal function. Animal-based proteins have been associated with higher anabolic potential due to their complete amino acid composition[402], but plant-based proteins, when properly combined, may also be considered.

Branched-Chain Amino Acids (BCAA), particularly leucine, have been attributed a therapeutic effect in cancer cachexia due to their role in activating the mTOR pathway, stimulating protein synthesis, and modulating inflammation[153,403]. In experimental models there is some evidence that leucine supplementation may be beneficial in cancer cachexia, by minimizing muscle decline and upregulation of protein synthesis[153]. Deutz et al. conducted a randomized, controlled, double-blind, parallel-group trial aiming at measuring muscle protein synthesis response to an experimental medical food consisting of 40g of casein and whey protein (the latter being a natural source of leucine but further enriched with 10% free leucine) plus n-3 fatty acids versus a conventional oral nutritional supplement with 24g of casein alone[268]. In this study, which included 25 patients with mostly lung and colon cancer, the experimental medical food was associated with a significant increase in fractional rate of muscle protein synthesis, whereas no effect was found for the conventional supplement[268]. In another cross-over study in patients with non-small-cell lung cancer, intake of essential amino acids (EEA)/leucine mixture resulted in a higher protein synthesis and net protein anabolism ($p<0.001$) than a balanced amino acid mixture[404]. This study showed a strong significant correlation between serum amino acid levels and protein anabolism (R^2:0.85, $p<0.001$)[404]. Additionally, higher levels of EAA/leucine mixture added no anabolic benefit, possibly implying the existence of an optimal threshold[404]. Furthermore, other metabolites, peptides and amino acids as β-hydroxy β-methylbutyrate (HMB), carnitine, creatine and glutamine, which traditionally have been used in sports nutrition for muscle gain and increased performance are now being studied in the context of cancer to counteract muscle loss. Although promising, current evidence is still insufficient to recommend their use in clinical practice[403].

Regarding lipids, monounsaturated and polyunsaturated fatty acids have been related to an anti-atrophic effect, further supporting our results. The underlying mechanisms include their ability to improve insulin sensitivity and generate anti-inflammatory eicosanoids, as well as by enhancing mitochondrial oxidative capacity and protein synthesis, while concurrently diminishing pro-inflammatory responses[405]. N-3 fatty acids supplementation, including alpha-linolenic acid (ALA), eicosapentaenoic acid (EPA), and docosahexaenoic acid

(DHA), has been proposed to counteract skeletal muscle loss in cancer cachexia patients. EPA, in particular, has been associated with reducing pro-inflammatory cytokines and decreasing proteolysis-inducing factors. An intake ranging from 1.8 and 2.2 has been associated with body weight and muscle mass increase or maintenance in the context of pancreatic[406], oesophageal[407] cancer, and cancer cachexia[156]. However, conflicting results exist regarding the benefit of polyunsaturated fatty acid supplementation in cancer cachexia. While some studies suggest positive outcomes, heterogeneity and varied study designs limit definitive conclusions[270].

This study deepened our understanding regarding the role of dietary patterns and sarcopenia. The Mediterranean diet was not explicitly identified in our data, but foods such as olive oil and fish which derive from the Portuguese history of Mediterranean diet, and that are characteristic of the Portuguese dietary habits (due to its geographic proximity to the sea and its natural ideal conditions allowing the production of olive oil), were identified in the protective dietary pattern of sarcopenia. Notably, this pattern also picked up on unhealthy foods, rich in saturated fat, as butter and high fat snacks as cookies and chocolates, which clearly shows the decline of Mediterranean diet in Portugal. As the protective effect was more prominent for the second tercile of this pattern, which presented a higher mono+polyunsaturaded: saturated fat ratio, we assumed that the healthy fats are more relevant to this association.

To date evidence regarding this issue is in fact deficient. In a scoping review published in 2022, which aimed at exploring the association between dietary patterns and malnutrition, low muscle mass and sarcopenia, found only 7 eligible studies, including our own study[408]. Furthermore, only two out of seven studies, addressed gastrointestinal cancer[408]. Therefore, we believe that our study contributed to explain this association and provided a greater comprehension of nutritional intervention needed to promote muscle anabolism. This insight was essential to plan for our future intervention studies, aiming at modulating body composition.

5. A Combined Exercise and Dietary Intervention (CEDI) is feasible in gastrointestinal cancer under neoadjuvant treatment. CEDI resulted in potential benefits regarding nutritional and functional status.

The skills and knowledge obtained from our previous studies led us to further pursue our research and proceeded to an interventional design. We planned to investigate the role of CEDI in an unique setting as neoadjuvant chemotherapy (NAC). Our hypothesis was that the window of opportunity provided by the treatment, could be used to optimize nutritional status, leading to improved body composition and this, in turn, could result in better outcomes. In other words, we aimed to implement what is now known as a prehabilitation approach during NAC.

First, we decided to tackle adherence to CEDI, to better understand if patients are willing to participate, since it required more visits to the hospital therefore increasing treatment burden. Additionally, reported adherence to behavioural interventions have proven to vary substantially[159,313–315]. In our study 68.5% of patients adhered to CEDI, which we considered reasonably high, compared to other studies of similar design such as the preMENAC study[159]. This study, involving patients with lung and pancreatic cancer initiating chemotherapy, was deemed feasible and safe, whereas compliance rates varied for different components of the intervention: 76% for celecoxib, 60% for exercise and 48% for oral nutritional supplements[159]. The most relevant difference from our study, was the studied population, since they implemented a multimodal approach in patients with inoperable lung and pancreatic cancer advanced stage III/IV, while our study was conducted in patients with gastrointestinal cancer stage II/III undergoing NAC. The type of intervention also differed, since the preMENAC study included a pharmacologic intervention with anti-inflammatory drugs (celecoxib), nutritional intervention was provided by a dietitian and/or nursing staff aiming to increase the number of meals and incorporate foods that are rich in energy and exercise was homebased. In contrast, our intervention had no pharmacologic intervention, nutritional intervention was performed solely by nutritionists with tailored dietary plans plus supplements targeting ESPEN guidelines recommendations and incorporating food associated with a protective effect of muscle wasting, as olive oil and

fish, and exercise included a weekly presential session supervised by a physiotherapist at the hospital Physical Medicine and Rehabilitation department gym.

More recently an on-going randomized controlled multicentric trial in Portugal, recruiting gastric cancer patients with indication for NAC, by Gonçalves et al. aims to determine the acceptability, feasibility, and safety of adding an internet-based exercise intervention with aerobic, resistance and inspiratory muscle training to the usual care plan encompassing medical, nutrition and psychological optimization[409]. Patients in the control group receive standard care plus written educational materials with physical activity aims[410]. Regarding nutritional intervention, patients are screened by the Nutritionist using the patient generated subjective global assessment (PG-SGA), and whenever the score is equal or greater than 9, a tailored nutritional plan is provided to the patient. A total of 39 patients have been recruited (17 in the control and 22 in the intervention group) and preliminary results point to adherence of 68.5% for the control group and in the intervention group 87.5% adhered to aerobic, 50% to resistance and 26.5% to inspiratory muscle training[410]. This intervention differs from ours, since in CEDI besides home-based exercise, a presential weekly session was performed, and concerning nutrition, all patients received an individualized nutritional plan, and were monitored weekly during NAC.

Additionally, studies with various designs have contributed to the evidence supporting multimodal approaches to cancer cachexia. A retrospective analysis of quality of life in mixed population with advanced cancer subjected to a multidisciplinary cachexia approach (including a physician, nurse, physiotherapist, and a dietitian) showed improved quality of life, irrespective of patients' baseline characteristics[411]. Another study, the Nutrition and Exercise Treatment for Advanced Cancer (NEXTAC) program, designed for elderly patients with advanced pancreatic and non-small-cell lung cancer, demonstrated feasibility and safety, with a high compliance rate of 96.7%[412].

As a secondary aim, we explored the effect of CEDI on body composition. Although this was an exploratory study, and results should be cautiously interpreted, they demonstrate the potential that a behavioral intervention as CEDI can have in modulating body composition,

even under NAC. Patients in CEDI group were able to maintain weight, loose less muscle mass and improve functional status. These results were in agreement with those from the MENAC trial, as it resulted in weight maintenance, whereas patients receiving standard care had a notable weight loss[159]. Regarding functional status, our results showed a positive effect which is supported by two randomized controlled trials recently published, which included gastric and esophagogastric cancer patients that analysed the impact of prehabilitation encompassing exercise, nutrition and psychological intervention, demonstrating a significant improvement in 6 min walk test distance[413,414]. However, in these studies most patients underwent NAC, but patients with indication to upfront surgery were also included[413,414].

Furthermore, in our study, patients in the control arm had a significant loss of skeletal muscle, visceral adipose tissue and worsened functional status. These findings are supported by longitudinal retrospective studies aiming at describing the association of body composition with outcome. They focused on patients undergoing FLOT, and observed a significant decrease in skeletal muscle and visceral adipose tissue, but failed to demonstrate a clinical significance for this finding, since it did not affect clinical outcome[371,372].

While excessive visceral adipose tissue (VAT) has been linked with a negative effect, increasing evidence also demonstrates that steep VAT losses in patients undergoing chemotherapy or surgery may also contribute to worse outcomes. In a study with colon cancer patients with high-risk stage II or III, VAT loss of less than 46% during FOLFOX chemotherapy was associated with a protective effect on overall survival (HR: 0.31, 95% CI: 0.14–0.69, p=0.004)[415]. Similarly, in a study analyzing patients undergoing resection of colorectal liver metastasis, concomitant systemic inflammation and sarcopenia and/or low VAT were associated with worse prognosis[416]. In a recent Chinese population-based multicenter prospective cohort study with 14018 patients encompassing various cancer types, stages and anti-cancer treatments, lower VAT was associated with an increased risk of death (HR: 1.33, 95% CI: 1.08-1.64, P=0.007), among gastric (HR: 2.13, 95%IC: 1.3-3.49, p=0.003), colorectal (HR:1.81 , 95%IC:1.06-3.08, p=0.03), and non-small cell lung cancer (HR:1.27, 95%IC:1.01-1.59, p=0.04)[105].

The next natural step is to ascertain if promoting beneficial modifications of body composition during NAC, results in improved outcomes. While prehabilitation strategies have been associated with reduced risk of post-operative complications[389,390,417], the role of this approach is less studied regarding NAC and is currently being investigated. A study published in 2023, which included gastric cancer patients with all stages of disease, the vast majority undergoing NAC, demonstrated that home-based prehabilitation (exercise, nutrition and psychological support) with a minimum of 4 weeks, was associated with a reduced rate of postoperative complications and improved quality of life[413]. This study did not assess body composition, therefore the intervention impact at this level remained undetermined. In another study which included gastroesophageal cancer patients which aimed to study the influence of prehabilitation, with exercise, nutritional and psychological support, demonstrated an enhanced completion rate for chemotherapy[418]. But again, this study did not analyze body composition. The preliminary results from the study by Gonçalves et al. are in line with these findings, as the authors observed a significant reduction in post-operative complications and increased tolerance to NAC[410]. Data regarding body composition, to our knowledge has not been reported, but is planned to be assessed with bioimpedance[410].

While our study has shown the feasibility of altering body composition during NAC, our next objective is to investigate the potential advantages of these changes on clinical outcomes such as post operative complications and short-term survival. The growing body of literature on this subject, along with ongoing research projects such as NCT02330926[307] underscores the significance of this area of research in potentially improving outcomes and enhancing patients' quality of life.

Crohn´s disease

The following topics are dedicated to discuss the associations between body composition in CD patients and complicated phenotypes of this disease.

1. Sarcopenia was highly prevalent even in overweight CD patients, and skeletal muscle area and index were significantly lower in patients with active chronic disease as reflected by a positive C-reactive protein and previous hospital admissions.

In Crohn´s disease (CD), disruption of intestinal integrity, may be triggered by dysbiosis and transmural injury, allowing the inflow of xenobiotics and invasion of luminal microbiota[206]. The anatomical proximity between peri-intestine fat and the gut suggests a direct reciprocal immunological relationship. Adipocytes possess innate immune sensors that react to external stimuli. Consequently, adipocytes and their precursor cells undergo significant immunophenotypic changes, leading to remodeling of adipose tissue and to hypertrophy of mesenteric fat also known as "creeping fat"[206].

Mesenteric fat is a component of visceral adipose tissue, which can be described as a continuous collection of fat tissue surrounding various sections of the intestines[419]. Furthermore, creeping fat is distinctive from normal mesenteric fat by exhibiting a larger size and increased infiltration of immune and inflammatory cells[336]. Prior research on CD patients suggests that mesenteric fat hypertrophy may manifest at the onset of the disease and play a significant role in its development although other studies show that it increases at disease evolves. Also, some studies suggest that mesenteric fat exacerbates intestinal inflammation, with some linking it to more severe disease phenotypes, increased disease activity, earlier surgical interventions, reduced therapy efficacy and quality of life[206]. The underlying mechanism explaining this association is the fact that creeping fat can modulate immune responses through the production of cytokines of pro and anti-inflammatory nature, pro-fibrotic factors and adipokines[195]. However, not all studies align with this perspective; some suggest that mesenteric fat might act as a host response, serving to contain inflammation and reduce the risk of fistula formation[206]. Notably, these inconsistencies, also reflect methodological issues, since most studies are of retrospective nature and with limited sample sizes. Besides, unstandardized measures regarding "creeping fat", and distinguishing it from normal mesenteric fat, further adds to the complexity of research in this field, whereas most studies use VAT as a proxy for mesenteric fat, but mesenteric fat associated with CD is known to differ from obesity related VAT[206].

Body composition alterations are a common occurrence in CD patients, but are often underlooked[324]. This is particularly notable when nutritional assessment relies solely on body mass index (BMI). In our study, we found patients with sarcopenia in all categories of BMI. Data from a cohort study involving 90 patients with inflammatory bowel disease (IBD), support our results, where nearly half were found to be sarcopenic, despite many of them being categorized as normal or overweight based on BMI[420]. This finding highlights the need for body composition assessment in CD patients, with imaging techniques that are able to detect accurately different body composition phenotypes.

Traditionally, undernutrition has been prevalent in Crohn's disease (CD), but there's a remarkable rise in overweight and obesity among CD patients, which is now estimated to be present in 15-40% of cases[205]. This trend is linked to the global increase in obesity prevalence but also with the improvement in CD treatment, particularly with the advent of biologic therapy post-2000. These therapeutic innovations have had a positive impact on the course of this disease, leading to improvements in controlling disease activity that mitigate undernutrition[193]. Recent studies support this hypothesis. In a prospective study involving 23 CD patients with moderate to severe CD, the authors demonstrated a significant increase, in all nutritional status parameters assessed with anthropometric measures such as BMI and waist circumference, as well as BIA analysis, namely lean mass and fat mass, probably reflecting a good control of disease activity with anti-TNF therapy and other biologics[24]. In another study, investigating the effect of biologics on body composition, using CT-derived body composition analysis, only patients exhibiting low skeletal muscle experienced a significant increase in SMI, VFA and SFA[421]. Additionally, a recent retrospective study including 115 CD patients, aiming at investigating the role of early anti-TNF therapy demonstrated that it is related to a reduced odds of undernutrition (OR:0.217; 95%CI:0.057-0.821, p=0.024)[422].

Although obesity is becoming more prevalent in CD patients, in the context of disease flares or/and hospitalization, weight loss and wasting still occur, thereby predisposing to undernutrition[194]. Additionally, sarcopenia has been considered a hallmark of inflammation. In our study we found that skeletal muscle area and index were significantly

lower in patients with positive C-reactive protein and previous hospital admissions, but we found no association between sarcopenia and CD disease phenotype. These findings are supported by another retrospective study including 79 patients newly diagnosed with CD (CT within 3 months), where the same association between C-reactive protein and sarcopenia were found, and likewise no prognostic value was attributed to sarcopenia[423].

Intestinal inflammation has been associated with muscle wasting, by upregulation of pathways common with sarcopenia. For instance, research has demonstrated that elevated serum levels of TNF-α correlate with muscle deterioration. TNF-α controls the activation of the NF-kB signalling pathway by inducing the expression of genes associated with atrophy and facilitating protein breakdown through the transcription of ubiquitin proteasome E3 ligases, including muscle RING-finger protein-1 (MurF1) and Atrogin[424]. Therefore, the occurrence of undernutrition appears to be greatly influenced by the extent and severity of intestinal inflammation, as well as duration of CD.

2. Lower muscle radiation attenuation and increased visceral fat index were associated with complicated disease phenotype.

At the time of our first publication on this topic, to our knowledge, no other study had explored the role of muscle radiation attenuation on disease phenotype. In fact, according to a systematic review published in 2023, research focusing on body composition and CD was in general lacking. Prior to 2017, merely 7 out of 39 studies included in this review had been published, and only 2[198,425] out of 7 addressed the relationship between body composition and CD behaviour[426]. To date the link with muscle radiation attenuation remains underexplored. Low muscle radiation attenuation is a marker of myosteatosis, which is known to be linked to muscle and metabolic disfunction, namely insulin resistance[427]. The latter is highly correlated with hyperinsulinemia[428], which has been linked to increased levels of Insulin Like Growth Factor (IGF)-1[429]. We can hypothesize that this connection may be relevant to CD, since IGF-1 has been shown to be implicated in the fibrogenic process of CD[430]. Fibrosis is a major cause of stricture and obstruction in CD, leading patients to surgery, and therefore is related with more complicated phenotypes[430].

Notably, detection of low muscle radiation attenuation is dependent on accurate techniques as CT-derived body composition analysis, and without such assessment, this body composition phenotype can be largely ignored. Besides, muscle radiation attenuation is an indicator of muscle quality, that can be as important or even more than muscle quantity[56].

In our study, we observed that muscle radiation attenuation is a potential predictor of disease phenotype, as it was associated with a more complicated disease phenotype. We believe that this is a useful finding since it can improve management of these patients. Abdominal CT studies are part of disease mapping at diagnosis, and an opportunistic use of these images for body composition assessment is feasible. Muscle radiation attenuation assessment can contribute to predict a more complicated disease course and allow for personalized care plans, regarding therapeutics and the need for interventions focusing on factors known to influence body composition as diet and exercise. However, to date, evidence regarding the importance of low muscle radiation attenuation on CD phenotype is limited[431], and the existing studies showing this association have focused mostly on surgical series of CD. For instance, in a recent prospective observational study, including 124 consecutive CD patients, myosteatosis (defined by intramuscular adipose area analysed as a continuous variable), was related with an increased odds of postoperative complications according to Clavien Dindo classification (OR: 1.08; 95% CI: 1.01-1.16; p= 0.037)[431].

However conflicting results have been reported. Studies by Pozios I et al. and Cankurtaran et al. that approached myosteatosis by determining average muscle signal intensity normalized against cerebrospinal fluid to dorsal skeletal muscle area (SMA), found no association between myosteatosis and post-operative complications[432,433]. Regarding these studies only Cankurtaran et al. found a significant association with sarcopenia[433]. Possibly, methodological issues can partly explain these discrepancies. Further studies are therefore necessary to clarify this association.

In contrast to studies which explored the association with surgical complications/outcomes, we were interested in investigating whether specific body composition phenotypes are

related to disease behaviour, namely complicated disease with strictures and fistulae. In our study, increased Visceral Fat Index (VFI) was associated with an increased risk of complicated disease phenotype (B2/B3). These results are in line with observations from a study by Erhayiem et al. who demonstrated that a high visceral to subcutaneous ratio was associated with more aggressive disease[198]. Subsequently, in another study by Büning et al., the authors observed that CD patients with complicated disease had a higher visceral adipose tissue area to total fat[425], which also support our results. However, these two studies by Erhayiem et al. and Büning et al. recruited a smaller sample than in our study and did not perform multivariate analysis. More recently, Bryant et al. reported on prospective data, from a study which recruited 97 CD patients, showing an increased odds of stricturing behaviour associated with visceral adipose tissue to subcutaneous adipose tissue ratio (OR:1.7; 95%CI:0.32-3; p=0.01)[434].

Our results are also reinforced by findings of a retrospective study with 72 CD patients who underwent ileocolic resection, since visceral fat area emerged as an independent prognostic factor for postoperative endoscopic (HR: 8.643, 95% CI: 1.59–47.06, p= 0.013) and clinical recurrence (HR: 2.63, 95% CI: 1.03–6.74, p = 0.044). This result was supported by a subsequent study which included 44 CD patients with the aim of investigating endoscopic recurrence at 18 months. In this study all patients (100%) with VFI >1.5 times the gender-specific mean, had endoscopic recurrence at 18 months, whereas patients with VFI≤ 1.5 (47%) experienced lower recurrence rates (relative risk 2.1, 95% CI 1.5– 3.0, p= 0.012). Another interesting finding of this study was that while low skeletal muscle was highly prevalent (41%), it was not associated with endoscopic recurrence, although appendicular skeletal muscle was inversely correlated with faecal calprotectin[200].

Another study investigating CD behaviour, has focused on the association of body composition and response to CD treatments. In a very recent study, which included 69 patients with ulcerative colitis and 72 patients with CD who received intravenous corticosteroids, CD patients responding to therapy presented a lower visceral adipose tissue index and mesenteric fat index[435]. These observations may be explained by the fact that mesenteric fat promotes the amplification of the inflammatory response. This study also

found a correlation between a more active disease and increased visceral adipose tissue index, mesorectal adipose tissue index and mesenteric fat index[435]. Another recent study reported that a higher intra-abdominal visceral adipose tissue (IA-VAT) was associated with worse outcomes. This prospective study recruited 141 IBD patients and 51 matched controls, and demonstrated that higher IA-VAT% (OR:0.4; 95% CI:0.16–0.98; p=0.03), previous exposure to biologics (OR:3.49; 95% CI: 1.43–8.53, p<0.01), baseline C-reactive protein (OR:0.72; 95%CI:1.02-1.09; p=0.03) and drug levels in the 2 highest quartiles for each biologic (OR:2.97; 95% CI: 1.20–7.32, p=0.02) were independent predictors of achievement of corticosteroid-free deep remission at weeks 14–16[436]. Interestingly, in comparison with responders and patients with low IA-VAT, non-responders with high IA-VAT had significantly higher serum IL-6 and TNFα, thereby demonstrating a more proinflammatory environment[436].

In conclusion our findings together with reported data support the fact that expression of visceral fat is a potential negative predictor factor. We believe that our study contributed to elucidate this subject, specially at a time when most existing studies focusing on body composition relied on anthropometry/BIA/DEXA. However, since body composition was not performed at diagnosis, we were not able to determine whether body composition phenotypes are a cause or a consequence of the disease, prompting us to pursue further studies.

3. Total fat was independently associated with complicated CD phenotype (B2/B3) independently of age and perianal disease.

This association was reported in our second study regarding body composition and CD phenotype. Besides total fat, visceral obesity showed a significant association with more complicated disease phenotype, which supports the findings of the previous study. However, in this study body composition was assessed at diagnosis, suggesting that body composition alterations are present *ab initio*, and are not a consequence of disease course. Besides CT images, in this study we decided to also include MRI images, which limited the analysis of muscle radiation attenuation. However, nowadays most physicians prefer entero

MRI, instead of abdominal CT to map extent of disease to spare radiation in this population. As such, and as we are using imaging techniques opportunistically, it is important to adapt to this trend. According to our data, compared with visceral obesity, total fat was more significantly associated with disease phenotype, which led us to focus more on this association. Another study which included 69 patients with Crohn's disease, showed a relevant association between total fat area and a heightened risk of secondary loss of response in patients treated with adalimumab (HR:1.01, 95%IC: 1.002-1.016, p=0.011), but not with infliximab[437], which supports our results. Total fat encompasses both visceral and subcutaneous adipose tissue, which are metabolically very different and may influence disease course in different ways. Visceral adipose tissue is likely to be associated with CD phenotype, because of its pro-inflammatory nature, as previously reviewed in this thesis, while subcutaneous adipose tissue has been suggested to be involved in drugs pharmacokinetics. For instance, elevated subcutaneous adipose tissue (SAT) has been linked to reduced levels of 6-thioguanine and adalimumab, as well as accelerated loss of response to infliximab[195]. In another study, which focused on BMI categories, the authors found that the time until infliximab optimization was significantly shorter for patients with BMI>25, whereas the rate of optimization was meaningfully higher when compared to normal weight patients[438].

4. Visceral obesity was the only body composition phenotype significantly associated with time until abdominal surgery but reduced its statistical significance when adjusted for disease phenotype.

Although the association of skeletal muscle was also analysed, in this study only adiposity parameters were significantly associated with disease outcomes as disease phenotype and time until abdominal surgery. Particularly, visceral obesity may be of value in predicting time to abdominal surgery since patients with visceral obesity exhibiting an almost 5-fold increased risk of abdominal surgery when compared to non-visceral obese counterparts. This result is supported by an initial study focusing on BMI, which showed that patients with BMI≥25kg/m^2, exhibited a significant shorter time until first surgery, compared with

patients with BMI<18.5kg/m^2 (252 vs. 24 months, p=0.043). In a retrospective study including 482 CD patients, those in the highest quartile of VAT volume had approximately a 2 fold increase in the risk of undergoing surgery (OR:2.01, 95%CI: 1.09-3.76, p=0.006), when compared to patients in the lowest quartile of VAT, after adjusting for age at diagnosis, sex, smoking habits and disease duration[341]. Also, the risk of penetrating disease appeared to be associated with VAT. This was not observed for stricturing or perianal disease[341]. Furthermore, results from another study which included 91 patients who received anti-TNF therapy as their first biologic treatment, are in line with our results, since high visceral adipose tissue/subcutaneous adipose tissue ratio was associated with increased risk of bowel resection (HR: 4.31, 95% CI: 1.36–13.7, p=0.013), independently of younger age of induction of anti-TNFα therapy, body weight, BMI and Skeletal Mass Index (SMI) [64].

It is worth noting that after adjusting for disease phenotype, visceral obesity reduced its statistical significance, which may mean that body composition is probably one in many factors which can influence time until abdominal surgery. Therefore, more studies are needed to clarify this association.

5. Patients with unfavourable outcome increased almost four times the amount of total body fat from baseline until follow up, when compared with patients with favourable outcome.

Finally, we observed in a longitudinal analysis, that patients experiencing worse disease course significantly increased their total body fat when compared to patients with more benign disease course. In this analysis, we observed that besides expansion of adipose tissue, that more markedly affected subcutaneous adipose tissue, skeletal muscle also increased, but with a more modest variation. Skeletal muscle has been described to increase in response to augmented mechanical overload exerted by the expanding adiposity[346].

Increased total body fat adiposity is a hallmark of obesity. Our results depict body composition evolution which is consistent with the increasing prevalence of obesity.

Increasing adiposity has been related to the western diet. If CD patients inactive disease due to modern biologic medication, they will follow western epidemic of obesity. Therefore, we can hypothesize that these patients have a dual burden predisposing to CD unfavourable course, namely adiposity and its pro-inflammatory nature, as well as a westernized dietary intake, which can negatively impact microbiota, and intestinal immune system[172,439].

In conclusion, together with the existing evidence, our findings lead us to think that body composition and particularly adiposity parameters are potential predictors of worse outcome in CD. This insight further contributes to a better understanding of possible interventions to enhance CD outcome. However, it is yet to be established if besides pharmacologic treatments, interventions focusing on body composition, as diet and exercise, can alter disease course. We believe that we have contributed to lay the groundwork for future studies in this field, which we consider are highly warranted to improve management of CD.

Conclusions

Body composition assessment with imaging techniques as part of clinical practice.

The preceding sections underscore the importance of assessing body composition using imaging techniques in both GI cancer and CD patients, highlighting existing evidence suggesting that optimizing body composition can lead to improved clinical outcomes. Over the years, operational aspects of these techniques have evolved, making them increasingly applicable to clinical practice and setting the stage for their integration into routine care. A critical consideration is the availability of expertise and software within hospital settings for conducting these assessments. Once expertise is established and recognized by multidisciplinary therapy teams, the groundwork is laid for integrating body composition assessment into standard care.

Managing the increased workload associated with expanded body composition assessment capacity requires a strategic approach. Training Nutritionists to assist in this task presents a viable solution, as previous experience has shown that these professionals can be efficiently trained for this purpose[440]. An adequately scaled team of Nutritionists can play a pivotal role in operationalizing body composition assessment, staying scientifically updated on these techniques, and facilitating the dissemination of crucial findings supporting their use.

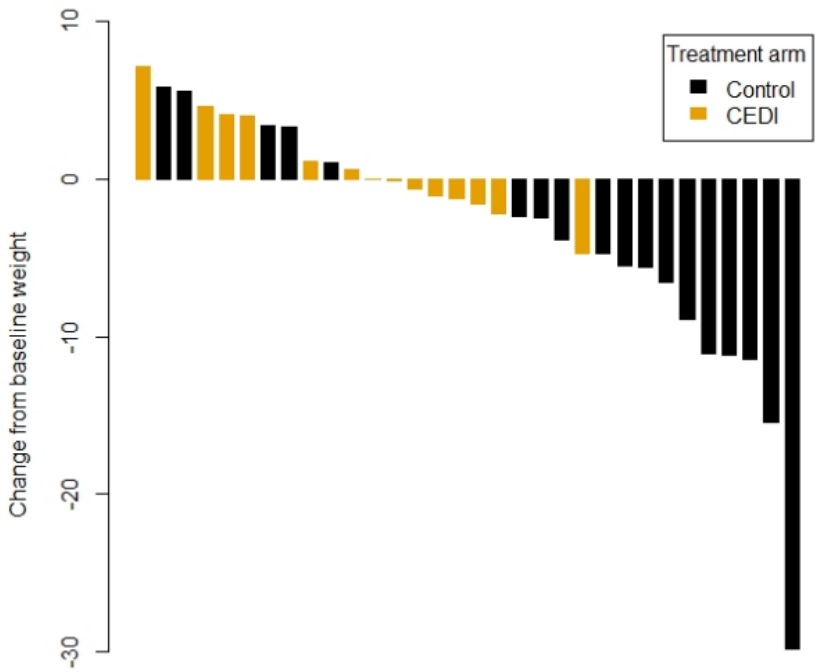
Furthermore, information obtained from body composition analysis can actively inform individualized treatment plans, spanning pharmacology, nutrition, and exercise, thus promoting a multimodal approach. Nutritionists can translate body composition phenotype information into tailored dietary plans and collaborate with other healthcare professionals, to promote holistic and individualized care. This is particularly crucial regarding body composition phenotypes such as low muscle radiation attenuation, sarcopenic obesity, and visceral adiposity, which are challenging to detect with other techniques.

Moreover, as with chemotherapy, it has been proposed that nutritional requirements be computed based on body composition rather than body weight, as a path to precision nutrition.

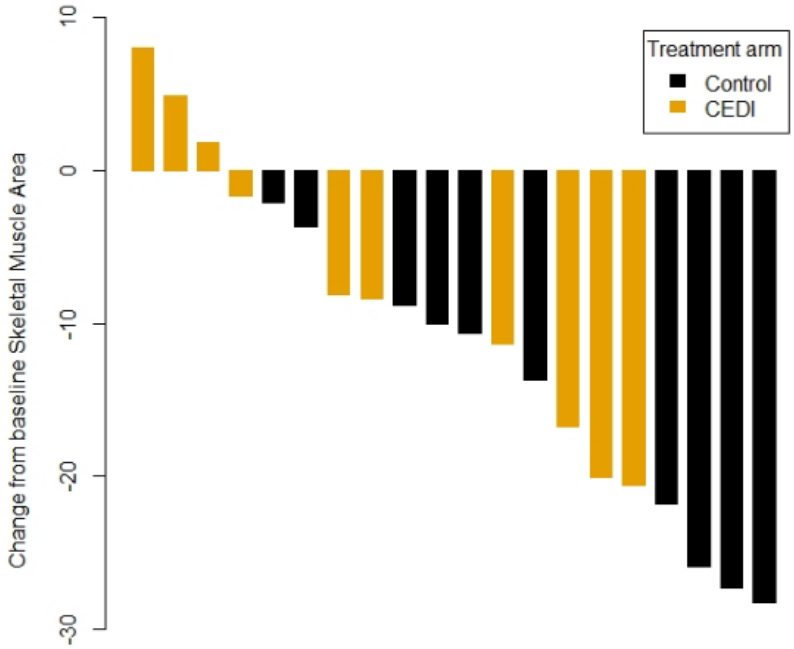
These imaging techniques hold tremendous potential and are supported by a substantial body of evidence, as elucidated in the preceding sections. Nutritionists can contribute to the hospital setting by facilitating the implementation of these techniques, potentially leading to more effective therapeutic plans and, consequently, reduced negative outcomes, lower hospital costs, and ultimately, improved quality of life for patients.

SUPPLEMENTARY MATERIAL

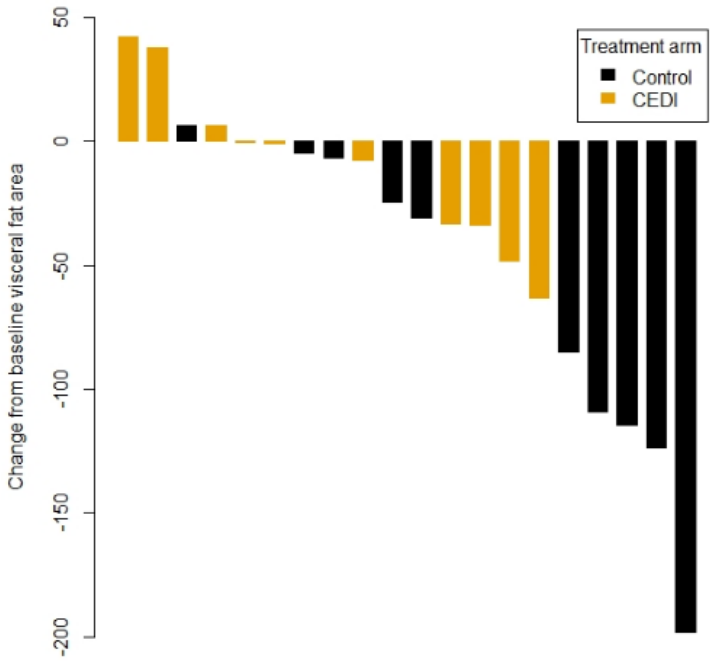
a)


Treatment arm
Control
CEDI
Change from baseline weight
10
0
-10
-20
-30

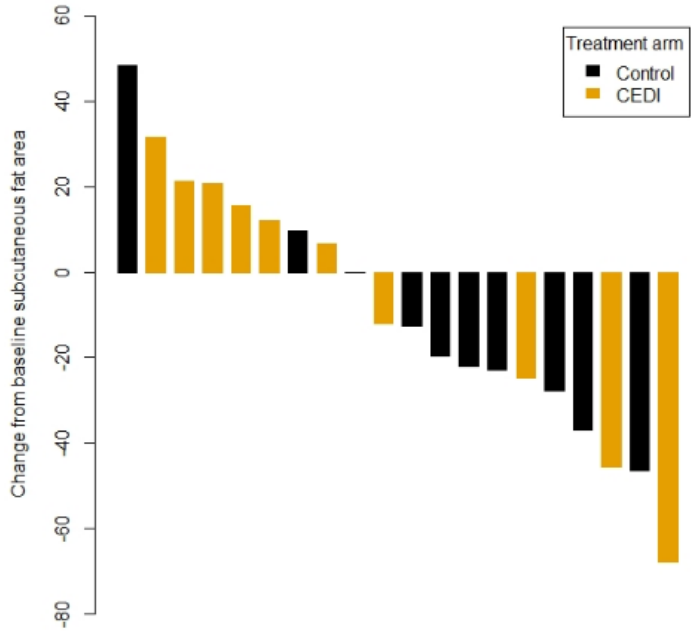
b)


Treatment arm
Control
CEDI
Change from baseline Skeletal Muscle Area
10
0
-10
-20
-30

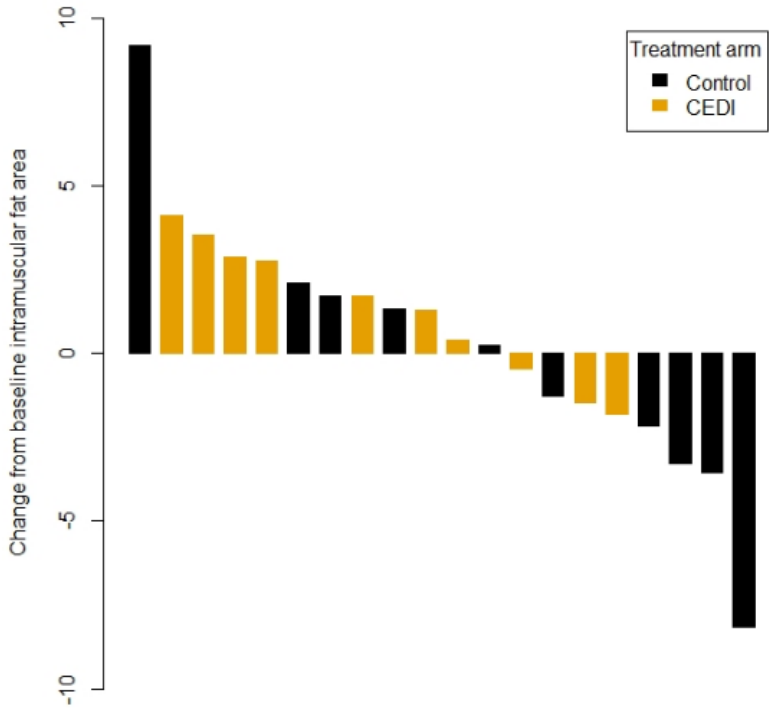
c)


Treatment arm
Control
CEDI
Change from baseline visceral fat area
50
0
-50
-100
-150
-200

d)


Treatment arm
Control
CEDI
Change from baseline subcutaneous fat area
60
40
20
0
-20
-40
-60
-80

e)


Change from baseline intramuscular fat area
10
5
0
-5
-10
Treatment arm
Control
CEDI

f)

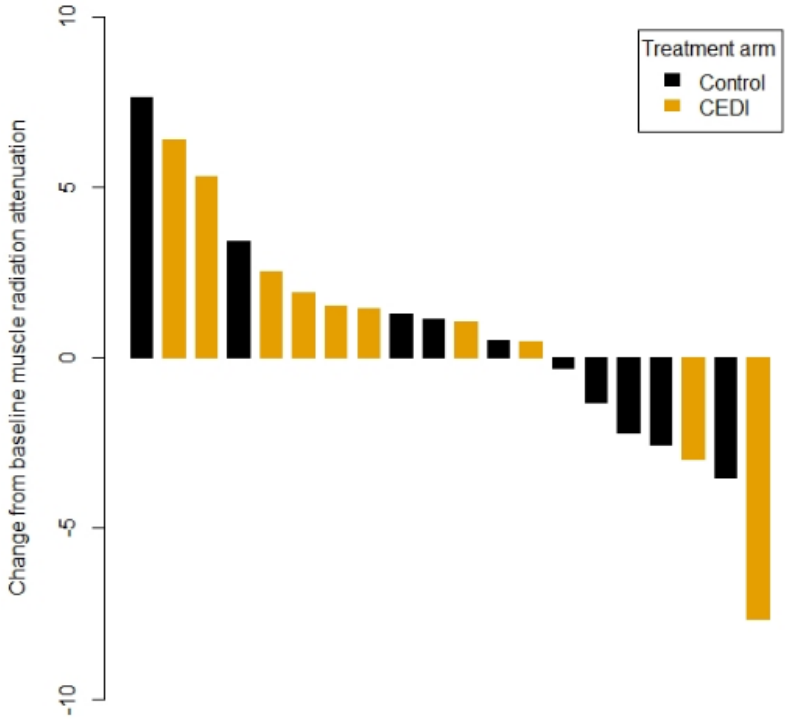

Change from baseline muscle radiation attenuation
10
5
0
-5
-10
Treatment arm
Control
CEDI

Figure S1-Waterfall plots for change in **a)** weight, **b)** skeletal muscle tissue, **c)** visceral adipose tissue, **d)** subcutaneous adipose tissue, **e)** intramuscular adipose tissue and **f)** muscle radiation attenuation, from baseline to after neo-adjuvant treatment.

Supplementary tables

Patient Number	Disease Site	Neo-adjuvant Chemotherapy	Neo-adjuvant Radiotherapy	Study arm	Follow Up	ONS	Exercise	Adequate Dietary Intake[a]	Fully Adherent to CEDI
4	Retal	Capecitabine	Yes	CEDI	Complete	Yes	Yes	Yes	Yes
7	Gastric	FLOT, 4 cycles	No	CEDI	Complete	Yes	Yes	Yes	Yes
11	Gastric	FLOT, 4 cycles	No	CEDI	Complete	Yes	Yes	Yes	Yes
13	Rectal	XELOX, 2 cycles - > Chemotherapy and radiotherapy with Capecitabine- > XELOX, 2 cycles	Yes	CEDI	Complete	Yes	Yes	Yes	Yes
15	Gastric	FLOT, 4 cycles	No	CEDI	Complete	No	Yes	Yes	Yes
17	Pancreas	FOLFIRINOX, 4 cycles -> QRT with capecitabine	Yes	CEDI	Complete	Yes	No	No	No
18	Gastric	FLOT, 3 cycles	No	CEDI	Died during NAT	Yes	Yes	No	Yes
21	Esophagus	ChRT with Carboplatin/Paclitaxel	Yes	CEDI	Died during NAT	Yes	Yes	No	Yes
22	Gastric	FLOT, 3 cycles	No	CEDI	Died during NAT	Yes	Yes	No	Yes

Patient Number	Disease Site	Neo-adjuvant Chemotherapy	Neo-adjuvant Radiotherapy	Study arm	Follow Up	ONS	Exercise	Adequate Dietary Intake*	Fully Adherent to CEDI
23	Esophagus	Chemotherapy and Radiotherapy with Carboplatin/Paclitaxel	Yes	CEDI	Complete	Yes	No	Yes	No
26	Pancreas	FOLFIRINOX, 2 cycles	No	CEDI	Complete	No	No	No	No
28	Gastric	FLOT, 4 cycles	No	CEDI	Complete	Yes	Yes	Yes	Yes
29	Rectal	XELOX, 1 cycle - > RT short duration	Yes	CEDI	Complete	Yes	Yes	Yes	Yes
32	Gastric	FLOT, 4 cycles	No	CEDI	Complete	Yes	Yes	Yes	Yes
33	Rectal	XELOX, 2 cycles - > Chemotherapy and Radiotherapy with capecitabine - > XELOX, 5 cycles	Yes	CEDI	Complete	No	No	No	No
38	Gastric	FLOT, 4 cycles	No	CEDI	Drop out	No	No	No	No
39	Rectal	Chemotherapy and Radiotherapy with capecitabine	Yes	CEDI	Incomplete	No	No	Yes	No
40	Rectal	Chemotherapy and Radiotherapy with capecitabine - > XELOX, 7 cycles	Yes	CEDI	Complete	Yes	Yes	Yes	Yes
41	Gastric	FLOT, 8 cycles	No	CEDI	Complete	No	Yes	Yes	Yes
1	Pancreas	FOLFIRINOX - > FOLFIRI - > Gemcitabine	No	Control	Complete				
2	Gastric	FLOT 4 cycles	No	Control	Complete				

Patient Number	Disease Site	Neo-adjuvant Chemotherapy	Neo-adjuvant Radiotherapy	Study arm	Follow Up	ONS	Exercise	Adequate Dietary Intake*	Fully Adherent to CEDI
3	Rectal	Chemotherapy and radiotherapy with 5FU	Yes	Control	Complete				
5	Gastric	FLOT 1 cycle	No	Control	Died during NAT				
6	Rectal	Chemotherapy and radiotherapy with capecitabine	Yes	Control	Complete				
8	Gastric	FLOT, 4 cycles	No	Control	Complete				
9	Pancreas	FOLFIRINOX, 4 cycles -> Chemotherapy and Radiotherapy with capecitabine	Yes	Control	Complete				
10	Pancreas	GEMOX, 6 cycles	No	Control	Complete				
14	Rectal	XELOX, 2 cycles - > Chemotherapy and radiotherapy com capecitabine - > XELOX 2 cycles	Yes	Control	Complete				
16	Rectal	Chemotherapy and radiotherapy with capecitabine	Yes	Control	Complete				
20	Rectal	XELOX, 3 cycles - > chemotherapy and radiotherapy with capecitabine - > XELOX, 2 cycles	Yes	Control	Complete				
24	Esophagus	Chemotherapy and radiotherapy with Carboplatin/paclitaxel	Yes	Control	Complete				

Patient Number	Disease Site	Neo-adjuvant Chemotherapy	Neo-adjuvant Radiotherapy	Study arm	Follow Up	ONS	Exercise	Adequate Dietary Intake*	Fully Adherent to CEDI
25	Gastric	FLOT 4 cycles	No	Control	Complete				
27	Gastric	FLOT, 4 cycles	No	Control	Complete				
30	Gastric	FLOT, 3 cycles	No	Control	Complete				
31	Rectal	XELOX, 3 cycles - > Chemotherapy and radiotherapy with capecitabine - > XELOX, 3 cycles	Yes	Control	Complete				
34	Gastric	FLOT, 4 cycles	No	Control	Complete				
35	Gastric	FLOT, 4 cycles	No	Control	Complete				
36	Gastric	FLOT, 8 cycles	No	Control	Complete				
37	Rectal	XELOX, 1 cycle - > Chemotherapy and radiotherapy with capecitabine - > XELOX 2 cycles	Yes	Control	Incomplete				

Table S1- Neo-aduvant treatment regimens and adherence to Combined Exercise and Dietary Intervention (CEDI). **ChTRT-**Chemotherapy with radiotherapy**, FLOT-**5-Fluorouracil, Folinic acid, Oxaliplatin, Docetaxel, **XELOX-** Oxaliplatin and Capecitabine; **FOLFIRINOX-**5-Fluorouracil, Irinotecan and Oxaliplatin; **FOLFOX**- folinic , fluorouracil (**5FU**), oxaliplatin.; **NAT**-Neo-adjuvant Treatment;[a]Dietary intake above 75% of estimated energy and protein requirements; **ONS**- Oral Nutritional Supplements.

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APENDIUM

BODY COMPOSITION AS A PROGNOSTIC FACTOR OF NEOADJUVANT CHEMOTHERAPY TOXICITY AND OUTCOME IN PATIENTS WITH LOCALLY ADVANCED GASTRIC CANCER

J Gastric Cancer. 2017 Mar;17(1):74-87
https://doi.org/10.5230/jgc.2017.17.e8
pISSN 2093-582X·eISSN 2093-5641

jgc Journal of Gastric cancer

Original Article

Body Composition as a Prognostic Factor of Neoadjuvant Chemotherapy Toxicity and Outcome in Patients with Locally Advanced Gastric Cancer

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Received: Jan 29, 2017
Revised: Mar 3, 2017
Accepted: Mar 3, 2017

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Conflict of Interest
No potential conflict of interest relevant to this article was reported.

ABSTRACT

Purpose: Neoadjuvant chemotherapy has been shown to improve survival in locally advanced gastric cancer, but it is associated with significant toxicity. Sarcopenia and sarcopenic obesity have been studied in several types of cancers and have been reported to be associated with higher chemotherapy toxicity and morbi-mortality. The aim of this study was to assess the prevalence of sarcopenia/sarcopenic obesity in patients with gastric cancer, as well as its association with chemotherapy toxicity and long-term outcomes.

Materials and Methods: A retrospective analysis was performed using an academic cancer center patient cohort diagnosed with locally advanced gastric cancer between January 2012 and December 2014 and treated with neoadjuvant chemotherapy. We analyzed body composition (skeletal muscle and visceral fat index) in axial computed tomography images.

Results: A total of 48 patients met the inclusion criteria. The mean age was 68±10 years, and 33 patients (69%) were men. Dose-limiting toxicity was observed in 22 patients (46%), and treatment was terminated early owing to toxicity in 17 patients (35%). Median follow-up was 17 months. Sarcopenia and sarcopenic obesity were found at diagnosis in 23% and 10% of patients, respectively. We observed an association between termination of chemotherapy and both sarcopenia (P=0.069) and sarcopenic obesity (P=0.004). On multivariate analysis, the odds of treatment termination were higher in patients with sarcopenia (odds ratio=4.23; P=0.050). Patients with sarcopenic obesity showed lower overall survival (median survival of 6 months [95% confidence interval {CI}=3.9–8.5] vs. 25 months [95% CI=20.2–38.2]; log-rank test P=0.000).

Conclusions: Sarcopenia and sarcopenic obesity were associated with early termination of neoadjuvant chemotherapy in patients with gastric cancer; additionally, sarcopenic obesity was associated with poor survival.

Keywords: Stomach neoplasms; Body composition; Sarcopenia; Neoadjuvant therapy; Prognosis

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INTRODUCTION

Gastric cancer (GC) is the fifth most common cancer worldwide and the third leading cause of cancer-related death [1]. It is often diagnosed at an advanced stage and has a low 5-year survival rate [2]. Neoadjuvant chemotherapy (ChT) improves survival in locally advanced GC [3]. In 2006, the MRC Adjuvant Gastric Infusional Chemotherapy (MAGIC) trial showed that in patients with operable esophagogastric adenocarcinomas, a perioperative regimen of epirubicin, cisplatin, and infused 5-fluorouracil (ECF) resulted in downstaging of the disease and significantly improved both disease-free and overall survival when compared with surgery alone [3]. However, in the MAGIC trial, only 41.6% of the patients assigned to perioperative ChT completed all 6 cycles of ChT, with some discontinuation owing to toxic effects [4]. Therefore, there is a great need to identify host or tumor factors that might explain individual variation in therapeutic efficacy and toxicity.

Body composition (i.e., the proportions of skeletal muscle and fat) has been studied in several types of tumors in the context of various anti-cancer treatments. The evaluation of skeletal muscle and fat using cross-sectional computed tomography (CT) imaging is gaining popularity due to its wide availability, high precision, and low incremental costs [5]. Sarcopenia, which is the depletion of skeletal muscle, is associated with higher ChT toxicity and higher morbi-mortality in cancer patients, with an overall worse prognosis [6-8]. Recent reports in patients with GC demonstrate that sarcopenia is a significant predictor of ChT toxicity [4], worse postoperative outcomes [9-13], and reduced overall survival [11,14,15]. One of the reasons for the variable ChT toxicity among individuals may be different body composition, which is not currently taken into account when prescribing ChT.

Not only skeletal muscle mass depletion but also the distribution of adipose tissue might influence survival [16]. The presence of both sarcopenia and obesity has been associated with worse prognosis in a series of reports [5,16,17]. In the specific setting of GC, sarcopenic obesity was shown to be an independent predictive factor of postoperative complications in patients undergoing radical gastrectomy [18,19].

The aim of this study was to assess the prevalence of sarcopenia and sarcopenic obesity in a population of patients with GC, as well as its association with ChT toxicity, response, and long-term outcomes.

MATERIALS AND METHODS

We conducted a single-center retrospective study in a secondary care hospital — Hospital Beatriz Ângelo (HBA). The study protocol was approved by the Scientific and Ethics Committee of HBA. The requirement for informed consent from patients was waived because of the retrospective design of the study.

Patients

We selected all patients diagnosed between January 2012 and December 2014 with locally advanced adenocarcinoma from the stomach or gastroesophageal junction (GEJ, Siewert type III only) who received neoadjuvant ChT in our institution. Locally advanced gastric/GEJ cancer was defined as tumor stage greater than cT2 or positive locoregional lymph nodes (cN+), according to the tumor, node, and metastasis (TNM) staging classification (American

https://doi.org/10.5230/jgc.2017.17.e8

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Joint Committee on Cancer). Included patients had histologically confirmed adenocarcinoma with no evidence of distant metastasis on preoperative staging. CT was performed at diagnosis in all cases. Endoscopic ultrasound was used to confirm T stage in the absence of suspicious lymph nodes. Staging laparoscopy was not uniformly used in this cohort of patients because it was not yet systematically included in the staging protocol of our unit at that time.

Patient data were obtained from the electronic records at HBA. Demographic and clinical data, such as age, sex, tumor site and histological type, ChT regimens used, and ChT response and toxicity, were retrieved. ChT toxicity was graded according to National Cancer Institute Common Toxicity Criteria. Dose-limiting toxicity (DLT) was defined as any grade 3/4 toxicity associated with physician-ordered dose reduction or termination of therapy. Response to ChT was evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST) criteria [20] and confirmed on surgical specimens (when available). Date of the last follow-up and date and cause of death were collected. Overall survival was measured from the date of histologic diagnosis until the date of death from any cause.

Body composition evaluation

Weight and height at diagnosis were recorded by hospital staff. Body mass index (BMI) was calculated as weight (kg)/height (m^2).

CT scans were obtained and evaluated for body composition data by one investigator (SV) who was blinded to clinical and endoscopic data to ensure objective interpretation of image findings. Skeletal muscle and fat tissue cross-sectional areas were measured on axial CT images, at the level of the third lumbar vertebra (L3) with the patient lying supine (**Fig. 1**). Skeletal muscle area (SMA), visceral fat area (VFA), and subcutaneous fat area (SFA) were measured in square centimeters on the basis of the pixel count using appropriate software [21]. Mean muscle radiation attenuation (MA) was calculated for muscle area and was also

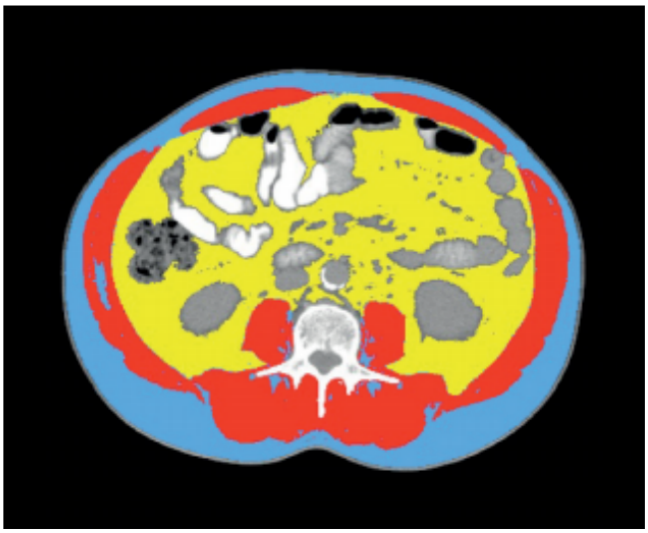

Fig. 1. Axial CT images of the third lumbar vertebra region. CT was analyzed for muscle and fat tissue cross sectional areas and analyzed using appropriate software. SMA (shown in red) was quantified within a HU range of −29 to 150, VFA (shown in yellow) ranged from −150 to −50 HU, and SFA (shown in blue) ranged from −190 to −30 HU.
CT = computed tomography; SMA = skeletal muscle area; HU = Hounsfield unit; VFA = visceral fat area; SFA = subcutaneous fat area.

https://doi.org/10.5230/jgc.2017.17.e8

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recorded. Skeletal muscle and visceral fat were normalized for height to obtain the skeletal muscle index (SMI) and visceral fat mass index (VFI) — cm^2/m^2. Sarcopenia was defined as SMI lower than 41 cm^2/m^2 in women or lower than 43 cm^2/m^2 in men with BMI <25 kg/m^2 and <53 cm^2/m^2 in men with BMI ≥25 kg/m^2, as described by Martin et al. [21]. Sarcopenic obesity was defined as sarcopenia in patients with BMI ≥25 kg/m^2.

Body composition data were evaluated at the time of cancer diagnosis using the CT scan performed for staging. We were also able to access a follow-up CT scan after completion of neoadjuvant ChTin a subset of 43 patients. These scans were used to perform a longitudinal analysis of body composition over time. The mean interval (± standard deviation [SD]) between CT scans was 86.4±29.0 days.

Statistical analysis

All continuous variables were described as median and range, while categorical variables were expressed as frequency and percentage. Differences in mean continuous variables with a normal distribution were analyzed using an independent Student's t-test. The other continuous variables were compared using the Mann-Whitney U test. To explore univariate associations in the distribution of categorical data, the χ^2 test or Fisher's exact test was used as appropriate. On multivariate analysis, treatment termination was used as the dependent variable, since we considered this variable the most clinically relevant. Any variable with a P-value <0.250 on univariate analysis or that was considered clinically relevant was included, and variable selection was performed with a stepwise analysis. Logistic regression was used for dichotomous outcomes, in order to determine the effect estimates, which are presented as odds ratio (OR) and 95% confidence intervals (CI). It is noteworthy that all patients with sarcopenic obesity experienced early treatment termination, so a high OR was obtained, and it was not possible to calculate the upper 95% CI limit. For this reason, this variable was not included in the final model to avoid error in parameter estimation. For continuous variables in the model, cubic spline graphs and the Wald test of linearity were used to test linearity in the logit model. For the Wald test of linearity, age and MA did not demonstrate statistically significant P-values (P=0.430 and P=0.270, respectively). However, linearity was not clear for both MA and age on cubic spline graphs, so these variables were categorized. Age was categorized using 65 years as a cut-off. MA was categorized with a cut-off (35 Hounsfield units [HUs]) provided by cubic spline graph analysis. Survival curves were estimated using the Kaplan-Meier method and compared using a log-rank test. AP-value <0.05 was considered statistically significant. Statistical analysis was performed using Statistical Package for Social Sciences version 22 (SPSS Inc., Chicago, IL, USA) andR software (R Foundation, Vienna, Austria).

RESULTS

A total of 160 cases of gastric/GEJ (Siewert type III) cancers were diagnosed in our institution during the study period, of which 48 were locally advanced cancers treated with neoadjuvant ChT. Survival was 93.8% at 3 months, 62.5% at 1 year, and 41.7% at 2 years. Response to neoadjuvant ChT was observed in 30 patients (63%), with 3 cases of complete pathological response (6%). DLT was observed in 22 patients (46%), among whom 17 patients (35%) terminated ChT early (i.e., before completion of3 cycles of neoadjuvant ChT).

Mean BMI at diagnosis was 23.8±3.5 kg/m^2, with 42% of patients categorized as overweight (BMI 25–29 kg/m^2) or obese (BMI ≥30 kg/m^2). Body composition data at diagnosis are shown

https://doi.org/10.5230/jgc.2017.17.e8

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in **Table 1**. Sarcopenia was present in 23% and sarcopenic obesity in 10% of patients at diagnosis. We did not find a significantly higher proportion of sarcopenia in older patients, but patients older than 65 years had a lower value of MA (30.0±6.0 vs. 39.8±8.1 HU; P=0.001). We also assessed patient demographics and body composition characteristics according to the presence/absence of sarcopenia (**Table 2**). Sarcopenic patients were more frequently female (64% vs. 22%; P=0.023), but were otherwise similar with respect to age, tumor site, histology and stage of disease, BMI, VFI, and MA. We found no significant association between ChT response and the presence of sarcopenia or sarcopenic obesity.

Although not statistically significant, we found a trend toward a higher percentage of DLT in patients with sarcopenia (64% vs. 39%; P=0.181) and sarcopenic obesity (80% vs. 42%; P=0.165). We found an association between early termination of ChT and the presence of sarcopenia (64% vs. 28%; P=0.069) and sarcopenic obesity (100% vs. 28%; P=0.004). Seven of 11 patients with sarcopenia (64%) and all patients with sarcopenic obesity (n=5) required early ChT termination.

Univariate and multivariate analysis were performed to assess factors that could contribute to termination of treatment (**Table 3**). On univariate analysis, both sarcopenia and MA were associated with treatment termination. Additionally, a strong effect was found for sarcopenic obesity, since treatment termination was observed in all patients with sarcopenic obesity. There was no significant association between disease stage and termination of treatment.

On multivariate analysis, the odds of treatment termination were reduced in patients with higher MA, as compared to patients with lower MA (OR=0.20; P=0.040). In addition, the odds of treatment termination were higher in patients with sarcopenia as compared to patients without sarcopenia (OR=4.23; P=0.050). The receiver operating characteristic (ROC) curve showed an acceptable power of discrimination of treatment termination using a model with age, sarcopenia, and MA as independent variables (area under the curve [AUC] of 0.755) (**Fig. 2**).

There was no significant difference in overall survival between patients with and without sarcopenia (**Fig. 3A**). However, patients with sarcopenic obesity showed reduced survival

Table 1. Body composition data at diagnosis

Variables	Values (n=48)
BMI (kg/m^2)	23.8±3.5
Underweight (BMI <20)	5 (10)
Normal (BMI 20–24)	23 (48)
Overweight (BMI 25–29)	18 (38)
Obese (BMI ≥30)	2 (4)
SMI (cm^2/m^2)	48.7±9.7
Men	52±9
Women	41±7
FMI (cm^2/m^2)	50.4±36.3
Men	59±39
Women	33±23
MA (HU)	34.2±7.9
Sarcopenia	11/47 (23)
Sarcopenic obesity	5/47 (10)

Values are presented as number of patients (%) or mean±SD.

BMI = body mass index; SMI = skeletal muscle index; FMI = fat mass index; MA = muscle radiation attenuation; HU = Hounsfield unit; SD = standard deviation.

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Table 2. Patient demographics according to the presence/absence of sarcopenia

Variables	Sarcopenia (n=11)	Non-sarcopenia (n=36)	P-value
Age (yr)*	69.3±9.1	67.1±10.4	0.534
Sex			0.023
Male	4	28	
Female	7	8	
Tumor site			0.924
Body	5	18	
Antrum	5	14	
Esophagogastric junction (Siewert III)	1	4	
Histology			0.111
Intestinal	6	27	
Diffuse	5	6	
Mixed	0	3	
Clinical TNM stage			0.322
II	0	5	
III	11	31	
Type of ChT used			0.388
ECF/EOF/EOX/ECX	2/0/6/0	9/2/17/1	
XELOX/FOLFOX/Xeloda/DCF	1/0/1/1	6/1/0/0	
ChT response			1.000
Yes	7	22	
No	4	14	
ChT toxicity			
Grade 2/3/4	3/6/0	11/14/0	0.455
Type: GI/hematological/other	5/2/3	12/12/4	0.135
DLT	7	14	0.181
Early termination of ChT due to toxicity	7	10	0.069
BMI (kg/m^2)	22.7±3.6	24.0±3.3	0.278
FMI (cm^2/m^2)	39.1±34.0	53.9±36.7	0.241
MA (HU)	31.2±7.4	35.1±8.0	0.151
Follow-up (mo)†	10 [6–36]	20 [9.25–33.75]	0.551

TNM = tumor, node, and metastasis; ChT = chemotherapy; ECF = epirubicin,cisplatin, and 5-fluorouracil; EOF = epirubicin, oxaliplatin, and 5-fluorouracil; EOX = epirubicin, oxaliplatin, and capecitabine; ECX = epirubicin,cisplatin, and capecitabine; XELOX = capecitabine plus oxaliplatin; FOLFOX = folinic acid plus 5-fluorouracil plus oxaliplatin; Xeloda = capecitabine; DCF = docetaxel, cisplatin, and 5-fluorouracil; GI = gastrointestinal; DLT = dose-limiting toxicity; BMI = body mass index; FMI = fat mass index; MA = muscle radiation attenuation; HU = Hounsfield unit; SD = standard deviation; IQR = interquartile range.
Values are presented differently follow as *mean±SD; †median [IQR].

(median survival 6 months [95% CI=3.9–8.5] vs. 25 months for patients who were obese and did not have sarcopenia [95% CI=20.2–38.2]; log-rank test P=0.000) (**Fig. 3B**).

A second CT scan after completion of neoadjuvant ChT was available in a subset of 43 patients. No second CT scan was available for 5 patients, either owing to obvious clinical disease progression or because either magnetic resonance imaging or ultrasonography was used. The mean interval (± SD) between CT scans was 86.4±29.0 days. The mean loss of SMA during follow-up (mean 86 days) was 15.4±2.8 cm^2. In the second CT scan, sarcopenia and sarcopenic obesity were found in 38% and 17% of patients, respectively, after neoadjuvant ChT. Over time, there was a significant loss of skeletal muscle and adipose tissue (**Table 4**). Stratification of patients according to ChT response demonstrated that only those patients who did not respond to ChT experienced a significant reduction in SMI (49.9±10.1 to 44.6±9.5 cm^2/m^2; P=0.001) and VFI (57.5±33.6 to 42.1±26.3 cm^2/m^2; P=0.002) (**Fig. 4A**). Similarly, only those patients who experienced DLT had a significant reduction in SMI (47.0±10.2 to 43.0±10.8 cm^2/m^2; P=0.001) and VFI (52.7±31.2 to 39.2±28.5 cm^2/m^2; P=0.000) (**Fig. 4B**).

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Table 3. Univariate and multivariate analysis assessing the OR of treatment termination associated with clinical variables and body composition markers in patients with GC

Variables	Univariate analysis			Multivariate analysis		
	OR	95% CI	P-value	OR	95% CI	P-value
Age (yr)						
<65	1.00		0.920	1.00		0.308
≥65	1.06	0.30–3.81		0.44	0.08–2.08	
Sex				Excluded		
Male	1.00		0.700			
Female	1.27	0.34–4.50				
Tumor site						
Body	1.00		0.420			
Antrum/GEJ	1.63	0.49–5.61				
Stage				Excluded		
II	1.00		0.260			
III	0.33	0.04–2.23				
Histology type				Excluded		
Intestinal	1.00		0.640			
Diffuse/mixed	1.36	0.34–5.24				
SMA	0.98	0.96–1.00	0.250	Excluded		
VFA	1.00	0.99–1.01	0.120	Excluded		
SFA	1.00	0.99–1.01	0.280	Excluded		
MA (HU)						
<35	1.00		0.040	1.00		0.040
≥35	0.27	0.06–0.95		0.20	0.33–0.95	
Sarcopenia						
No	1.00		0.030	1.00		0.050
Yes	4.55	1.13–20.70		4.23	0.98–20.80	
Sarcopenic obesity				Not included*		
No	1.00					
Yes	106,362,030.9	2.81×10^{-72}–NA	<0.001			

OR = odds ratio; GC = gastric cancer; CI = confidence interval; GEJ = gastroesophageal junction; SMA = skeletal muscle area; VFA = visceral fat area; SFA = subcutaneous fat area; MA = muscle radiation attenuation; HU = Hounsfield unit.

*All patients with sarcopenic obesity experienced treatment termination, and for that reason a high OR was obtained, and the upper 95% CI limit was not possible to calculate. This variable was not included in the final model to avoid error in parameter estimation.

DISCUSSION

In this observational study inpatients with locally advanced GC who underwent neoadjuvant ChT, we observed that sarcopenic obesity was associated with poorer outcome, with a high likelihood of early termination of treatment and lower overall survival. Additionally, we confirmed that neoadjuvant ChT was associated with important catabolic losses of muscle and fat over time, although these occurred only inpatients who did not respond to ChT or in those who developed toxicity.

Several recent studies have reported a high prevalence of sarcopenia at diagnosis inpatients with gastrointestinal cancers (**Table 5**) [22-28]. Comparison of sarcopenia prevalence among studies is rather difficult because of the use of different methodologies: axial CT cross-sectional imaging of SMAs, muscle mass using dual-energy X-ray absorptiometry, or a combination of anthropometric and physical performance measurements [29-32]. Furthermore, even when the same methodology is employed, different cut-offs for sarcopenia are often used (**Table 5**).

In the specific setting of patients with GC, the reported prevalence in the literature of sarcopenia ranges from 12.5% to 69.8% at diagnosis (**Table 5**). In our population, a quarter of

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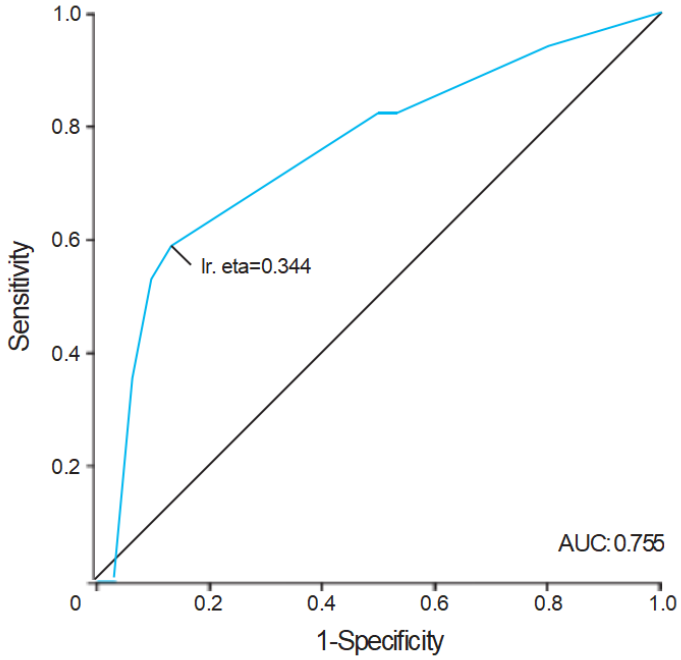

Fig. 2. ROC curve using treatment termination as dependent variable and age, sarcopenia, and MA as independent variables. Sensitivity: 58.8%; Specificity: 86.7%; Positive predictive value: 21.2%; Negative predictive value: 28.6%.
ROC = receiver operating characteristic; MA = muscle radiation attenuation; AUC = area under the curve.

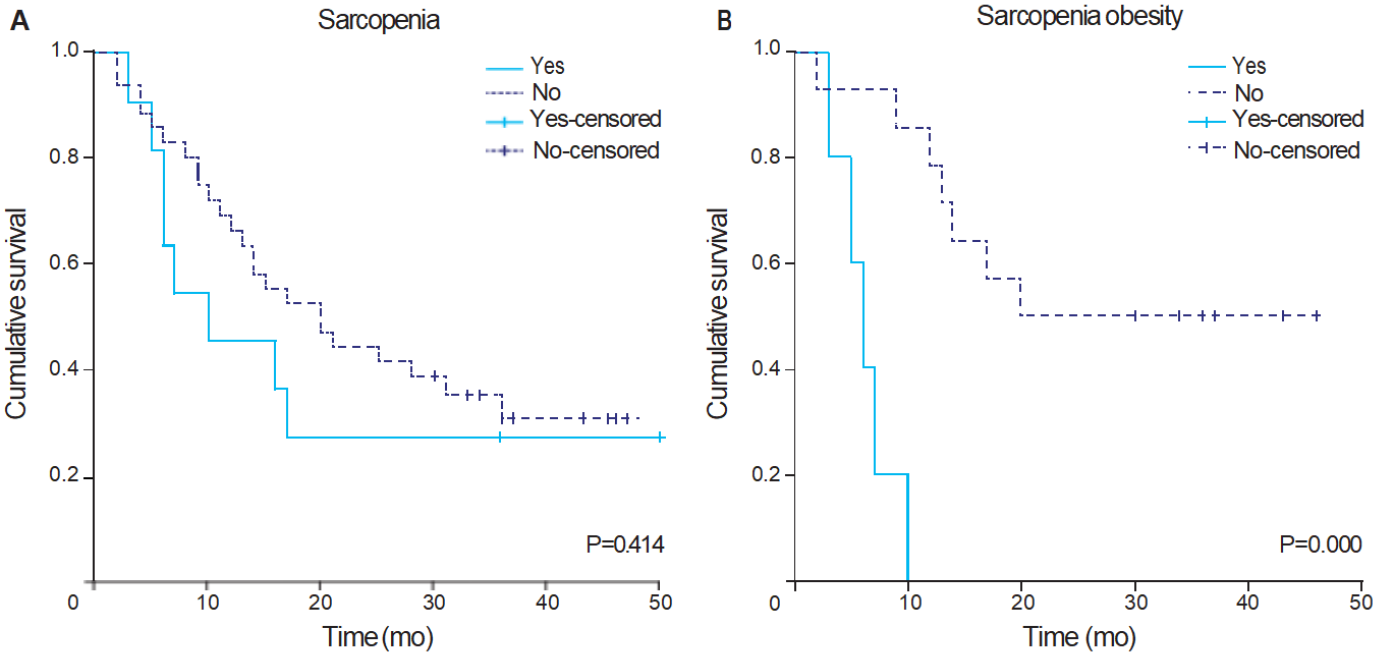

Fig. 3. Kaplan-Meier survival curves of patients with and without sarcopenia (A) and of obese patients with and without sarcopenia (B) (log-rank P-value).

the patients had sarcopenia at diagnosis. Additionally, the prevalence of sarcopenia increased following neoadjuvant ChT. Similarly, Awad et al. [6] reported an increase in sarcopenia prevalence from 57% pre-ChT to 79% in patients with esophagogastric cancer.

https://doi.org/10.5230/jgc.2017.17.e8

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Table 4. Change in body composition over time inpatients with GC (n=43)

Variables	First CT scan	Second CT scan	P-value
SMA (cm^2)	132.1±30.9	123.9±29.6	0.001
MA (HU)	34.0±7.2	31.7±6.7	0.006
VFA (cm^2)	137.8±96.2	113.5±86.4	0.001
SFA (cm^2)	136.2±76.3	119.6±78.7	0.002
SMI (cm^2/m^2)	48.2±9.6	45.3±9.5	0.001
VFI (cm^2/m^2)	49.8±34.0	41.0±30.1	0.001

Mean interval (± SD) between CT scans: 86.4±29.0 days.

GC = gastric cancer; CT = computed tomography; SMA = skeletal muscle area; MA = muscle radiation attenuation; HU = Hounsfield unit; VFA = visceral fat area; SFA = subcutaneous fat area; SMI = skeletal muscle index; VFI = visceral fat mass index; SD = standard deviation.

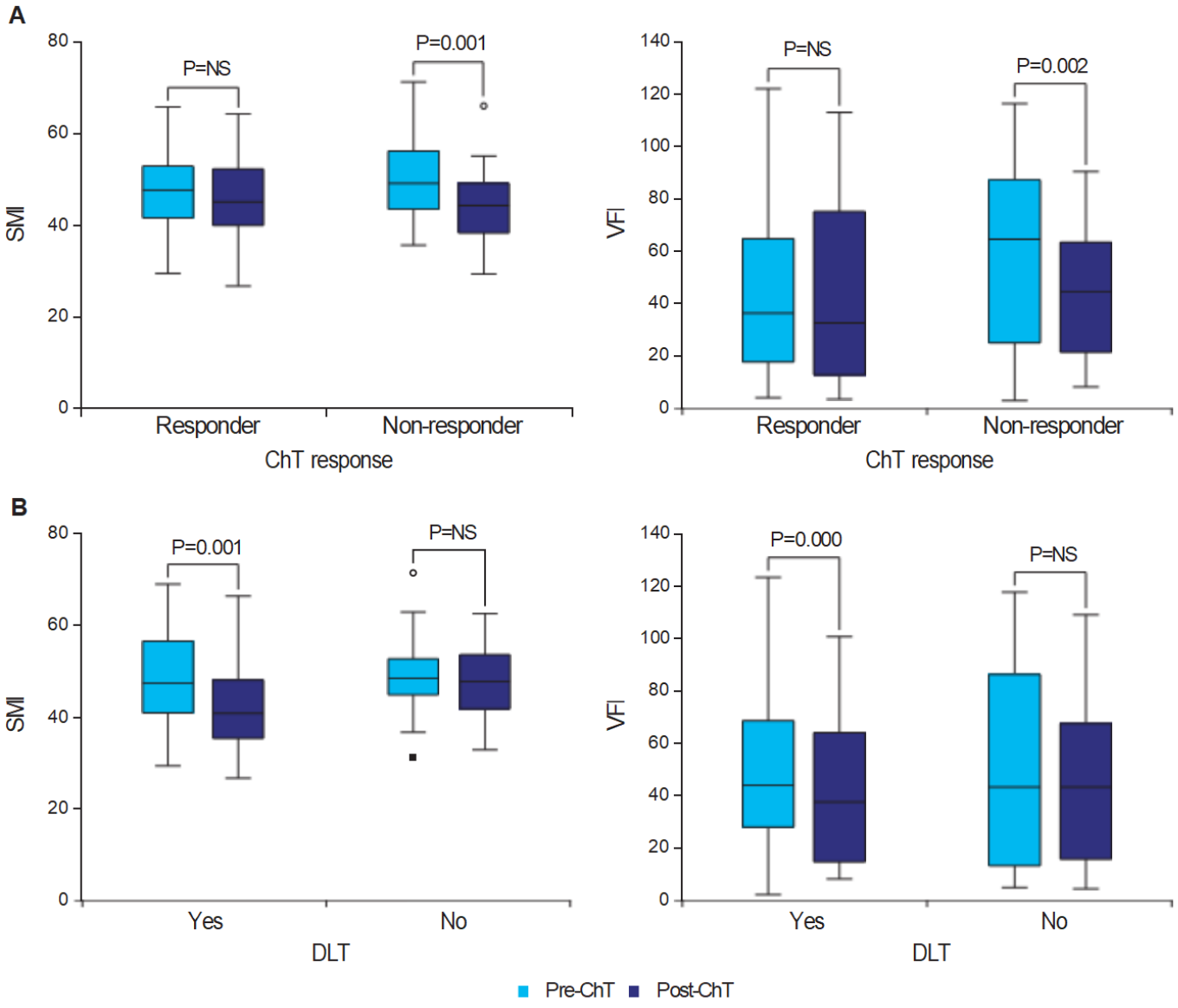

Fig. 4. Body composition changes (namely SMI and VFI in cm^2/m^2) before and after neoadjuvant ChT, according to ChT response (A) and DLT (B).
SMI = skeletal muscle index; VFI = visceral fat mass index; ChT = chemotherapy; DLT = dose-limiting toxicity; NS = non-significant.

https://doi.org/10.5230/jgc.2017.17.e8

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Table 5. Sarcopenia prevalence at diagnosis of gastrointestinal tumors

Study reference	Country	Type of tumor	No. of patients	Sarcopenia (%)	Sarcopenia definition
Yip et al. [28]	United Kingdom	Esophageal cancer	35	26.0	1
Reisinger et al. [27]	The Netherlands	Esophageal cancer	108	56.0	1
Awad et al. [6]	United Kingdom	Esophagogastric cancer	47	57.0	1
Tan et al. [4]	United Kingdom	Esophagogastric cancer	89	49.4	1
Tegels et al. [36]	The Netherlands	GC	152	57.7	2
Huang et al. [9]	China	GC	470	16.8	3
Chen et al. [10]	China	GC	158	24.7	3
Zhuang et al. [11]	China	GC	937	41.5	4
Wang et al. [12]	China	GC	255	12.5	5
Hayashi et al. [14]	Japan	GC	53	69.8	2
Huang et al. [15]	China	GC	173	30.1	3
Fukuda et al. [13]	Japan	GC	99	21.2	6
Nishigori et al. [19]	Japan	GC	157	57.0	1
Lieffers et al. [22]	Canada	Colorectal cancer	234	39.0	1
Reisinger et al. [24]	The Netherlands	Colorectal cancer	310	47.7	1
Huang et al. [30]	China	Colorectal cancer	142	12.0	5
Tan et al. [23]	Canada	Pancreatic cancer	111	56.0	1
Peng et al. [8]	USA	Pancreatic cancer	557	25.0	7
Joglekar et al. [25]	USA	Pancreatic cancer	118	26.3	8
Harimoto et al. [26]	Japan	Hepatocellular carcinoma	186	40.3	9

Sarcopenia definition:

1. SMI ≤38.5 cm^2/m^2 for women and ≤52.4 cm^2/m^2 for men
2. SMI <41 cm^2/m^2 for women and <43 cm^2/m^2 in men with BMI <25 kg/m^2 and <53 cm^2/m^2 in men with BMI ≥25 kg/m^2
3. SMI <34.9 cm^2/m^2 for women and ≤40.8 cm^2/m^2 for men plus handgrip strength <18 kg for women and <26 kg for men and/or 6-m usual gait speed <0.8 m/s
4. SMI <34.9 cm^2/m^2 for women and ≤40.8 cm^2/m^2 for men
5. SMI <29 cm^2/m^2 for women and ≤36 cm^2/m^2 for men plus handgrip strength <18 kg for women and <26 kg for men and/or 6-m usual gait speed <0.8 m/s
6. SMI <6.42 kg/m^2 for women and ≤8.87 kg/m^2 for men plus handgrip strength <20 kg for women and <30 kg for men and/or 6-m usual gait speed <0.8 m/s
7. Total psoas muscle index <362 mm^2/m^2 for women and <492 mm^2/m^2 for men
8. Total psoas muscle index <4.0 cm^2/m^2 for women and <5.2 mm^2/m^2 for men
9. SMI ≤41.1 cm^2/m^2 for women and ≤43.75 cm^2/m^2 for men

GC = gastric cancer; SMI = skeletal muscle index; BMI = body mass index.

Several recent studies show a relationship between skeletal muscle mass depletion and treatment toxicity. In a recent systematic review by Kazemi-Bajestani et al. [33], there were 14 published articles relating CT-based body composition to the prevalence of ChT-induced toxicity. These were mainly single-center investigations with small samples [33],and only one addressed patients with GC [4]. In a prospective study inpatients with colon cancer by Prado et al. [7], the authors found an increase in DLT inpatients with lower muscle mass treated with 5-fluorouracil (5-FU). Likewise, in a prospective randomized trial inpatients with colon cancer by Ali et al. [34], low lean body mass was an independent predictor of DLT and neuropathy inpatients administered folinic acid plus 5-fluorouracil plus oxaliplatin (FOLFOX)-based regimens. More recently, data analysis from a randomized controlled trial in advanced non-small cell lung cancer also showed an association between low muscle mass and ChT-induced hematological toxicity [35].

However, studies addressing the impact of sarcopenia in ChT toxicity inpatients with GC are scarce. Recently, Tan et al. [4] demonstrated that sarcopenia at the time of diagnosis in patients with esophagogastric cancer was a significant predictor of DLT. In the present study, we found that the odds of treatment termination were higher inpatients with sarcopenia. The mechanism that links sarcopenia with increased ChT toxicity is currently unknown. Some authors speculate that different proportions of lean and adipose tissue compartments maybe associated with alterations in the distribution, metabolism, and clearance of ChT agents [7].

https://doi.org/10.5230/jgc.2017.17.e8

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Although the impact of sarcopenia in DLT inpatients with GC needs further prospective characterization, there are several recent reports demonstrating the important predictive role of low muscle mass in short-and long-term outcomes inpatients with GC. In patients who undergo radical gastrectomy for GC, there is a significant relationship between sarcopenia and postoperative complications [10-13,30]. In a recent prospective study by Huang et al. [15] including 173 elderly patients undergoing curative gastrectomy for GC, sarcopenia was predictive of higher 1-year mortality (hazard ratio [HR]=3.615; 95% CI=1.459–8.957). Similarly, a large retrospective study of 937 patients with GC showed that sarcopenia was an independent predictor of low overall survival after gastrectomy [11]. Nonetheless, it is important to highlight that the impact of sarcopenia in postoperative and long-term outcomes has not been universally reported [36]. Further prospective studies using a consensual definition for sarcopenia are needed.

Although cachexia is a frequent feature of patients with advanced cancer, a substantial increase has been observed in the past decades in the proportion of cancer patients with a BMI in the overweight range [37]. In the present study, 42% of patients were overweight or obese at the time of diagnosis of GC. Abdominal adipose fat distribution might have an influence on tumor growth and therefore on cancer outcome [16]. The negative impact of visceral obesity has been previously reported inpatients with colon, pancreatic, and renal cancer [38-40]; however, few studies in GC have addressed this issue.

The simultaneous presence of sarcopenia and obesity (especially visceral obesity) is a worst-case scenario associated with poorer prognosis [5]. The inflammatory cytokines produced by adipose cells are thought to play an important role in insulin resistance, resulting in an increase in muscle protein loss [41]. In addition, inpatients with sarcopenic obesity, the increased body mass inflates the overall administered ChT dose, which is then distributed within a reduced lean tissue compartment, thus resulting in a disproportionately small volume of drug distribution and hence higher toxicity [5]. A population-based study by Prado et al. [5] that included 250 obese patients with solid tumors of the respiratory and gastrointestinal tracts showed that patients with sarcopenic obesity had poorer functional status and lower survival. In a recent prospective study of 206 overweight or obese patients with GC after radical gastrectomy, sarcopenic obesity was an independent predictor of postoperative complications [18]. Likewise, Nishigori et al. [19] retrospectively reported a prevalence of 24% of sarcopenic obesity (45 of 157 patients with GC) and found an association between sarcopenic obesity and surgical site infection.

Limitations of our study include its retrospective design, single-center recruitment, and small sample size. One important limitation was the lack of staging laparoscopy that is now routinely used in our unit. Some of the patients included in the study might have already had peritoneal disease, and this may explain the notable percentage of patients with disease progression during neoadjuvant ChT. Another important limitation, associated with the retrospective nature of the study, was the use of different regimens of ChT drugs according to patient characteristics. Nonetheless, 77% of our cohort received ECF or a similar regimen, with no difference between patients with and without sarcopenia. The relationship between ChT toxicity and body composition has been observed inpatients receiving a variety of different ChT regimens [35,42]. One possible explanation is that the measurements of body composition reveal reduced fitness and low ability to tolerate cancer therapy independently of the type of ChT.

https://doi.org/10.5230/jgc.2017.17.e8

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CONCLUSIONS

Sarcopenic obesity is a strong risk factor for ChT toxicity, premature termination of ChT, and reduced overall survival. Future studies are required to define ChT dosages that are within the limits of tolerability for this unique and vulnerable subgroup.

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Body Composition Influences Post-Operative Complications and 90-Day and Overall Survival in Pancreatic Surgery Patients

Research Article

Portuguese Journal of Gastroenterology

GE Port J Gastroenterol
DOI: 10.1159/000507206

Received: November 25, 2019
Accepted: January 20, 2020
Published online: May 19, 2020

Body Composition Influences Post-Operative Complications and 90-Day and Overall Survival in Pancreatic Surgery Patients

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Keywords

Pancreatic surgery · Body composition · Survival · Postoperative complications · Muscle attenuation · Ratio of visceral fat area/skeletal muscle area

Abstract

Introduction: Pancreatic surgery still carries a high morbidity and mortality even in specialized centers. The aim of this study was to evaluate the influence of patients' body composition on postoperative complications and survival after pancreatic surgery. ***Methods:*** This was a retrospective study on patients undergoing pancreatic surgery between March 2012 and December 2017. Demographics, clinical data, and postoperative complications classified according to Clavien-Dindo were recorded. Body composition was assessed using routine diagnostic or staging computed tomography (CT). Multiple Cox proportional hazards models were adjusted. ***Results:*** Ninety patients were included, 55% were male, and the mean age was 68 ± 10.9 years. Of these 90, 92% had a total pancreatectomy or pancreaticoduodenectomy, 7% a distal pancreatectomy, and 1% a pancreaticoduodenectomy with multi-visceral resection; 84% had malignant disease. The incidence of major complications was 27.8% and the 90-day mortality was 8.8%. The ratio of visceral fat area/skeletal muscle area (VFA:SMA) was associated with an increased risk of complications (OR 2.24, 95% CI 1.14–4.87, $p = 0.03$) and 90-day survival (HR 2.13, 95% CI 1.13–4.01, $p = 0.019$). On simple analysis, shorter overall survival (OS) was observed in patients aged ≥70 years ($p = 0.0009$), with postoperative complications ≥IIIb ($p = 0.01$), an increased VFA:SMA ($p = 0.007$), and decreased muscle radiation attenuation ($p = 1.6 \times 10^{-5}$). In an OS model adjusted for age, disease malignancy, postoperative complications, and body composition parameters, muscle radiation attenuation remained significantly associated with survival (HR 0.94, 95% CI 0.90–0.98, $p = 0.0016$). A model which included only body composition variables had a discrimina-

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tion ability (*C*-statistic 0.76) superior to a model which comprised conventional clinical variables (*C*-statistic 0.68). ***Conclusion:*** Body composition is a major determinant of postoperative complications and survival in pancreatic surgery patients.

A composição corporal influencia a taxa de complicações pós-operatórias, a sobrevivência aos 90 dias e global em doentes submetidos a cirurgia pancreática

Palavras Chave
Cirurgia pancreatica · Composição corporal · Sobrevivência · Complicações pós-operatórias · Atenuação muscular · Racio da área de gordura visceral / área de tecido muscular esquelético

Resumo
Introdução: A cirurgia pancreática continua associada a uma elevada morbimortalidade mesmo em centros de referência. O objetivo do presente estudo foi avaliar a influência da composição corporal nas complicações e sobrevivência após cirurgia pancreática. ***Métodos:*** Estudo retrospetivo em doentes submetidos a cirurgia pancreática entre Março 2012 e Dezembro 2017. Foram registadas variáveis demográficas, clínicas, complicações pós-cirúrgicas classificadas de acordo com a classificação de a classificação de Clavien Dindo. A composição corporal foi avaliada utilizando imagens de Tomografia Axial Computorizada (TAC) realizada no diagnóstico. Modelos de riscos porporcionais de Cox foram ajustados. ***Resultados:*** Incluídos 90 doentes, 55% homens e média de idade de 68 ± 10.9 anos; 92% submetidos a pancreatectomia/pancreatoduodenectomia, 7% pancreatectomia distal e 1% pancreatoduodenectomia com ressecção multivisceral; 84% tinham doença maligna. A incidência de complicações major foi de 27.8% e a mortalidade aos 90 dias de 8.8%. O racio da Área de Gordura Visceral (AGV) / Área de Tecido Muscular Esquelético (ATME) associou-se a um risco acrescido de complicações (OR 2.24, 95% CI 1.14–4.87, $p = 0.03$) e de morte aos 90 dias (HR 2.13, 95% CI 1.13–4.01, $p = 0.019$). Observámos uma sobrevivência global mais baixa em doentes com idade ≥70 anos ($p = 0.0009$), com complicações ≥IIIb ($p = 0.01$), com AGV/ ATME aumentada e atenuação muscular diminuída ($p = 1.6 \times 10^{-5}$). A atenuação muscular ajustada para a idade, malignidade, complicações, manteve-se associada à sobrevivência global (HR 0.94, IC 95% 0.90–0.98, $p = 0.0016$). Um modelo que inclua apenas variáveis de composição corporal mostrou uma capacidade discriminatória (C-statistic 0.76) superior a um modelo convencional com variáveis clínicas (C-statistic 0.68). ***Conclusão:*** A composição corporal é um determinante major de complicações pós-cirúrgicas e de sobrevivência de doentes submetidos a cirurgia pancreática.

Introduction

Pancreatic cancer incidence is increasing, and surgery remains the only curative treatment. However, even in specialized centers, the incidence of postoperative complications remains as high as 40–60% with a 5-year survival rate of 10–20% [1].

Operative mortality has improved through surgical technique and perioperative care optimization. In particular, the enhanced recovery after surgery (ERAS) pathway allows a standardized, multimodal, multidisciplinary approach aimed at favoring postoperative recovery by reducing surgical metabolic stress and limiting organ dysfunction [2].

With regard to nutritional status, recent studies have suggested that body composition phenotypes may influence postoperative and long-term clinical outcomes. Most studies have focused primarily on the impact of sarcopenia (low skeletal-muscle mass) on major postoperative complications [3] and overall survival (OS) [1, 4–12], and secondarily on visceral adipose tissue [3, 8, 10, 13] and low muscle radiation attenuation (a marker of fat infiltration of skeletal muscle) [9–11, 13]. Although some of these studies have included body mass index (BMI) [4, 12] as a proxy of body fatness, the influence of skeletal muscle infiltration by adipose tissue as well as the proportion of visceral adipose tissue with regard to skeletal-muscle tissue has been strikingly less studied.

Bearing in mind that obesity is a recognized risk factor for pancreatic cancer and that many of these patients experience weight loss at diagnosis which will certainly translate into a decline of skeletal muscle mass, we hypothesized that all tissues, namely skeletal muscle, visceral fat, and skeletal muscle infiltration by adipose tissue, may be equally relevant. We believe that this approach could lead us to a more comprehensive view where all tissues have a different role but are equally important and expected to interplay. We therefore aimed

to study the association of body composition parameters, i.e., skeletal muscle, visceral fat, and muscle radiation attenuation with postoperative complications, 90-day survival, and OS in patients undergoing pancreatic surgery.

Materials and Methods

We conducted a single-center retrospective study at the Beatriz Ângelo Hospital (HBA). We reviewed all patients undergoing pancreatic surgery at our hospital between March 2012 and December 2017. To be eligible for our study, patients needed to have an abdominal computed tomography (CT) scan performed at our institution within 30 days of surgery to allow body composition analysis.

Demographic and clinical data including age, gender, American Society of Anesthesiologists (ASA) score, disease location, and histology according to surgical specimens were retrieved from patients' electronic charts. The 90-day mortality and postoperative complications were classified according to Clavien-Dindo classification. We considered the rate of complications as grade I–IIIa versus grade IIIb–V [14]. The date of the last follow-up and death were recorded as well. Primary outcome was OS measured in months from the date of elective hospitalization for surgery until death or until the censor date of the last visit to the hospital. The 90-day survival was recorded in months from the date of elective hospitalization for surgery until death or until the censor date set at 90 days after surgery.

Body Composition Assessment

Weight and reported height were recorded on admission and body mass index (BMI) was computed. BMI classification was done according to the following categories for adults: <18.5 = underweight, 18.5–24.9 = normal weight, 25.0–29.9 = overweight, 30.0–34.9 = class I obesity, 35–39.9 = class II obesity, and ≥40 = class III obesity. The BMI classification for the elderly was used for patients aged ≥65 years, i.e., <24 = underweight, 24–27 = normal weight, and >27 = overweight. Opportunistic body composition assessment was conducted from the diagnostic or staging CT scan. CT methodology is highly precise for quantifying specific tissues and predicting whole-body composition [15]. Images were selected by radiologists on the axial plane at the level of the 3rd lumbar vertebra including both transverse processes using a portal venous phase, and then processed with a program built with Matlab. This software performs an automatic segmentation of tissue cross-sectional areas, using the following Hounsfield unit (HU) thresholds: –29 to 150 for skeletal muscle, –190 to –30 for subcutaneous and intramuscular adipose tissue, and –50 to –150 for visceral adipose tissue. Validation of the processed images was conducted and manual corrections were executed by radiologists. Cross-sectional skeletal muscle, visceral fat, subcutaneous fat, and mean muscle radiation attenuation were recorded. The skeletal muscle index (SMI [in cm^2/m^2] = skeletal muscle area [SMA]/height) and ratio of visceral fat area/SMA (VFA:SMA) were calculated as previously described [3, 16]. Sarcopenia, low muscle radiation attenuation, and high visceral fat were defined according to sex-specific previously published cut-offs [16, 17].

Statistical Analysis

The thresholds for CT image-derived body composition parameters to define sarcopenia and low muscle radiation attenuation have been determined for a population with mixed cancer disease locations [16, 18] whereas those for visceral obesity have been obtained from obesity-related research [19, 20]. The above-mentioned thresholds for sarcopenia and low muscle radiation attenuation have already been used in pancreatic cancer patients [3, 4, 12, 13, 21, 22]. Besides this, candidate thresholds for sarcopenia based on SMA/body surface area (BSA) have been determined for gastric cancer patients [23]. However, there has been some criticism about the generalization of the reported thresholds due to ethnic and disease-site differences. As such, in recent studies with pancreatic cancer patients, different strategies to determine specific thresholds for each study population have been used, such as optimal stratification of total psoas area [5], sex-specific lowest quartile/tertile of SMA [9, 10], and receiver-operating characteristics (ROC) curve analysis [6, 11].

Since no thresholds for body composition have yet been established for the Portuguese population and bearing in mind that using thresholds not validated specifically for patients with pancreatic tumors may be misleading, we decided to use body composition variables in their continuous form, except for the Kaplan-Meier curves comparison, where dichotomization is necessary. From a statistical point of view, the use of continuous variables is a better option than discrete data, since continuous data convey more information. However, to account for gender-specific differences in body composition, variables were mean-centered in order to be scaled by sex. We decided not to use optimal stratification strategies, since this approach was considered unstable for our sample size.

Simple and multiple logistic regression were used to relate each variable with complications as Clavien-Dindo ≥IIIb. For continuous variables, linearity of the logit in the predictor was assessed using a cubic spline and the Wald test of linearity [24]. Only variables with a p value ≤0.25 or considered clinically relevant were selected for multiple logistic regression. Multicollinearity was also analyzed via the observation of variance inflation factors. A stepwise both-selection technique was used to create the multiple regression model. The ROC curve was computed and the respective area under the curve (AUC) was calculated to assess the accuracy of the model. The positive and negative predictive values (PPV and NPV) were also given. The association between major postoperative complications and type of surgery was assessed with the Fisher exact test.

Survival analysis was conducted with the Kaplan-Meier estimate, and survival curves were compared with the log-rank test. Body composition variables such as SMI and muscle radiation attenuation were dichotomized according to the lowest sex-specific quartile and VFA:SMA, with respect to the highest sex-specific quartile to allow for the comparison of survival curves.

First, 2 multiple Cox proportional hazards models with conventional clinical variables and body composition variables were adjusted and the *C*-statistic was computed to assess model prediction ability.

Lastly, a multiple Cox proportional hazards model was adjusted for 90-day survival, in order to allow the comparison between variables associated with 90-day survival and OS. In this comparison, we used the OS model containing both clinical and body composition variables which yielded the highest *C*-statistics.

Data analysis was performed with SPSS v20 and *R* v3.0.2 and statistical significance was set at $p \leq 0.05$.

Table 1. Demographic and clinical data of 90 patients

Age, years (mean ± SD)	68±10.9
Male sex	50 (56)
ASA grade	
I/II	60 (66.6)
III	30 (33.3)
Preoperative biliary drainage	38 (42.2)
Type of surgery	
Duodenopancreatectomy/total	84 (92)
Distal resection body-tail	6 (7)
Duodenopancreatectomy with multivisceral resection	1 (1)
Postoperative histology	26 (54)
Benign	14 (16)
Malignant	76 (84)
Stage I	22 (28.9)
Stage II/III	54 (71.1)
Preoperative chemotherapy	9 (10.0)
Major postoperative complications	25 (27.8)
90-Day mortality	8 (8.8)
Overall mortality	26 (28.9)

Values express *n* (%), unless otherwise indicated.

Table 2. BMI and body composition of 90 patients at diagnosis

BMI	
Underweight	25 (27.8)
Normal weight	34 (37.8)
Overweight	18 (20.0)
Class I obesity	12 (13.3)
Class II obesity	1 (1.1)
SMI	
Men	49.4±8.2 cm^2/m^2
Women	41.2±4.9 cm^2/m^2
Fat mass index	
Men	105.3±50.3 cm^2/m^2
Women	139.3±66.8 cm^2/m^2
Visceral fat index	
Men	58.6±32.2 cm^2/m^2
Women	51.6±33.6 cm^2/m^2
Muscle radiation attenuation	
Men	34.8±7.9 HU
Women	30.8±10.0 HU
VFA:SMA	
Men	1.2±0.6
Women	1.2±0.9

Values are expressed as *n* (%) or mean (SD). BMI, body mass index; SMI, skeletal muscle index; FMI, fat mass index; VFA:SMA, ratio of visceral fat area/skeletal muscle area.

Results

Population

A total of 125 patients undergoing surgery for pancreatic tumors at our institution during the study period were screened for eligibility. Thirty-five patients were excluded because their diagnostic CT scan had been performed at another hospital. Excluded patients were compared to included patients, and no differences were found in demographics, postoperative complications, or mortality rate. Demographic and clinical data are presented in Table 1. Ninety patients were included, 56% of whom were male, and the mean age was 68 ± 10.9 years. Fourteen of 90 patients (16%) had evidence of benign or premalignant tumors on the surgical specimen (10 intraductal papillary mucinous neoplasms, 1 serous cystadenoma, 1 case of chronic focal pancreatitis, and 2 mucinous cysts). Among the patients with malignant tumors, although the large majority were pancreatic ductal adenocarcinomas, we also found 17 adenocarcinomas of the ampulla of Vater, 7 distal cholangiocarcinomas, 1 duodenal carcinoma, 3 malignant neuroendocrine tumors, and 1 acinar-cell carcinoma of the pancreas. Of the 90 patients, 92% had a total pancreatectomy or pancreaticoduodenectomy, 7% a distal pancreatectomy, and 1% a pancreaticoduodenectomy with multivisceral resection. The rate of major complications was 27.8%, the 90-day mortality rate was 8.8%, and 28.9% died during the study period. Survival was 81.1% at 1 year and 73.3% at 2 years. The mean follow-up period was 12.5 (0.26–49.8) months.

BMI categories and body composition parameters at diagnosis are presented in Table 2. The number of patients per body composition phenotype according to published cut-offs is shown in Figure 1. Mean BMI was 25.1 ± 4.03; 27.8% of the patients were underweight, 37.8% were of normal weight, 20.0% were overweight, 13.3% had class I obesity, and 1.1% had class II obesity. Furthermore, 2.2% patients presented sarcopenic obesity.

Postoperative Complications

Twenty-five of 90 patients had postoperative complications ≥IIIb. We observed that 24 of these 25 patients were referred for total pancreatectomy or pancreaticoduodenectomy, 1 for pancreaticoduodenectomy with multivisceral resection, and none for distal resection experienced major complications. In this analysis, we obtained a near-significant association between the type of surgery and major postoperative complications (p = 0.087). Table 3 shows simple and multiple logistic regressions exploring the association of each variable with the

Table 3. Simple and multiple logistic regression with postoperative complications as the dependent variable

	Postoperative complications		Simple logistic regression			Multiple logistic regression		
	yes (n = 25)	no (n = 65)	OR	95% CI	p value	OR	95% CI	p value
Continuous variables								
Age	70 (48–85)	67 (34–89)	1.03	0.98–1.07	0.28	excluded		
BMI	25.8 (19.4–33.5)	24.9 (18.2–35.0)	1.05	0.93–1.18	0.39	not included		
SMI	44.4 (31.4–74.3)	46.4 (32.9–65.9)	0.96	0.89–1.03	0.34	not included		
Visceral fat index	68.4 (11.5–168.2)	50.6 (1.91–104.2)	1.90	1.07–3.65	0.04	excluded		
VFA:SMA	1.55 (0.31–4.9)	1.09 (0.04–2.54)	2.30	1.21–4.92	0.02	2.24	1.14–4.87	0.03
Muscle radiation attenuation	30.21 (11.4–47.2)	34.14 (8.22–48.12)	0.95	0.90–1.00	0.07	excluded		
Categorical variables								
Gender								
Female	13	37	1.00					
Male	12	28	0.82	0.32–2.09	0.67	not included		
Age								
<70 years	14	39	1.00					
≥70 years	11	26	1.17	0.45–2.99	0.73	not included		
ASA score								
I	13	47	1.00			1.00		
II/III	12	18	2.41	0.92–6.32	0.07	2.26	0.83–6.20	0.11
Histology								
Benign	3	11	1.00			excluded		
Malignant	22	54	1.49	0.42–7.07	0.56			
Neoadjuvant chemotherapy								
No	24	57	1.00					
Yes	1	8	0.29	0.01–1.74	0.26	excluded		

Values are presented as mean (range) or n. "Excluded" pertains to variables excluded in the stepwise analysis and "not included" to variables not included since $p > 0.25$. BMI, body mass index; SMI, skeletal muscle index; VFA:SMA, ratio of visceral fat area/skeletal muscle area.

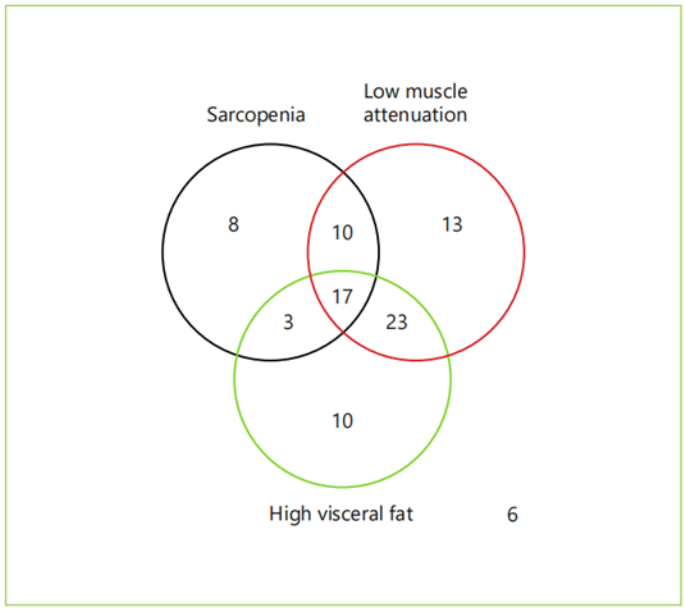

Fig. 1. Venn diagram of number of patients with sarcopenia, low muscle attenuation, and high visceral fat defined with published cut-offs (n = 90).

postoperative complications. Simple logistic regression showed that postoperative complications ≥IIIb were significantly associated with the visceral fat index and VFA:SMA, and an almost significant association was found for muscle radiation attenuation and ASA score. However, in the multiple logistic regression analysis, only VFA:SMA remained significantly associated with postoperative complications ≥IIIb. In this model, the odds of major complications were 2-fold greater per (an increase of 1) unit of VFA:SMA. Regarding ASA score, although it was perceived as relevant to major postoperative complications (since it was selected in the stepwise analysis), it lost statistical significance when adjusted for VFA:SMA. The AUC obtained through the ROC curve analysis was 0.691, which shows a fair discrimination ability of the selected model (Fig. 2). Sensitivity was 68.0%, specificity was 67.7%, PPV was 15.4%, and NPV was 55.3%. Lastly, we conducted a subset analysis including only patients with malignant disease, where VFA:SMA was the only variable to be selected for the final model with a near-significant association (OR 1.77, 95% CI 0.925–3.77, p = 0.10).

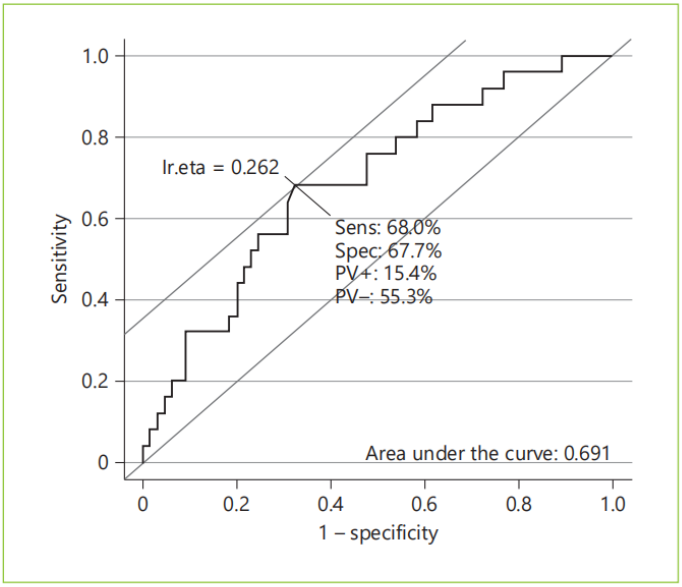

Fig. 2. Receiver-operating characteristics (ROC) curve for major complications as the dependent variable and ASA score and ratio of visceral fat area/skeletal muscle area as independent variables ($n = 90$). Sens, sensitivity; Spec, specificity; PV+, positive predictive value; PV–, negative predictive value.

Survival

Estimated mean OS was 31.15 months. Kaplan-Meier survival curves for OS as well as their comparison with clinical and body composition variables are reported in Figures 3–5. Dichotomization of body composition parameters was conducted using the first sex-specific quartile for SMI (males 43.9 cm^2/m^2 and females 37.2 cm^2/m^2), muscle radiation attenuation (males 30.9 HU and females 23.42 HU), and the third sex-specific quartile for the VFA:SMA (males 1.52 and females 1.67) to allow for the Kaplan-Meier curves comparison. Comparison of survival curves was also conducted for BMI categories (low/normal weight vs. overweight/obese), but no statistically significant differences were found ($p = 0.332$).

Table 4 presents the results of the simple and multiple analyses for OS. Regarding clinical variables, in the simple analysis, shorter survival was observed in patients aged ≥70 years, those submitted to pancreaticoduodenectomy with multivisceral resection, with postoperative complications ≥IIIb, and when a near-significant p value was found for ASA score (I/II vs. III). Regarding body composition variables, an increase of 1 unit in muscle radiation attenuation was associated with an 8% reduction in the estimated risk of death, whereas an increase of 1 unit in VFA:SMA was associated with an increase of 90% in the estimated risk of death. Lastly, a near-significant association was found between OS and SMI, where an increase of 1 unit was associated with a 5% reduction in the estimated risk of death.

Two multiple proportional hazards Cox models were adjusted using variables significantly associated with OS or considered clinically pertinent, and the *C*-statistics were compared. In the first model, only conventionally used clinical variables were included, namely age, ASA score, histology, and postoperative complications. In this model, both age and postoperative complications were significantly associated with OS. The estimated risk of death was 3.34 times greater in patients aged ≥70 years. HRs for major complications could not be computed because this variable was adjusted by stratification as it violated the proportional hazards assumption. At first, we decided not to include the type of surgery because most patients were submitted to total pancreatectomy or pancreaticoduodenectomy, and there were very few patients who underwent distal pancreatectomy and multivisceral resection which can influence estimates. However, bearing in mind the clinical relevance of this variable, we performed the same analysis including the type of surgery; this did not alter the previous results or increase the performance of the model (the *C*-statistics remained the same), so we decided to not include it after all to avoid overfitting (data not shown). A second model was adjusted using body composition variables. In this model, we included SMI, muscle radiation attenuation, and VFA:SMA. The only significant variable was muscle radiation attenuation, where an increase of 1 HU was associated with an 8% reduction in estimated risk of death. Interestingly, the model which included 3 body composition variables had a discrimination ability (a *C*-statistic of 0.76) superior to the model which included 4 conventional clinical variables (a *C*-statistic of 0.68).

To compare postoperative survival with OS, Table 5 shows the results obtained for the model that yielded the highest *C*-statistics with regard to OS and the results of the Cox proportional hazards model for the analysis of 90-day survival. Ninety-day survival was associated with age, with patients aged ≥70 years displaying an 8.2-fold greater estimated risk of postoperative death compared with patients aged <70 years. Although in this analysis we could not compute the HR for postoperative complications ≥IIIb due to model stratification, it is worth noting that all patients who had died at 90 days had experienced major complications. Also, the estimated risk of death was 2 times higher per (an increase of 1) unit of VFA:SMA adjusted for age, histology, and postoperative complications.

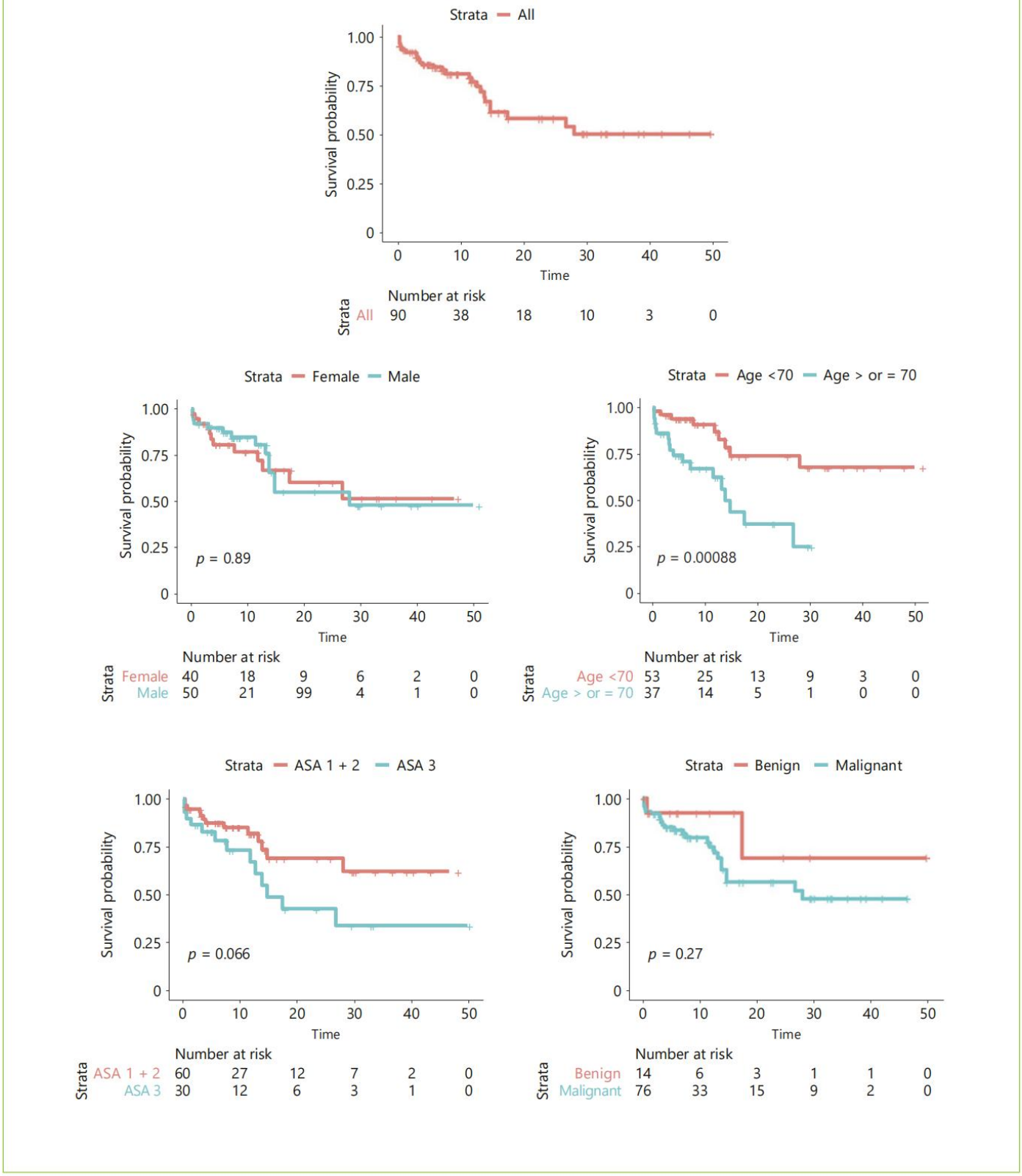

Fig. 3. Overall survival ($n = 90$).

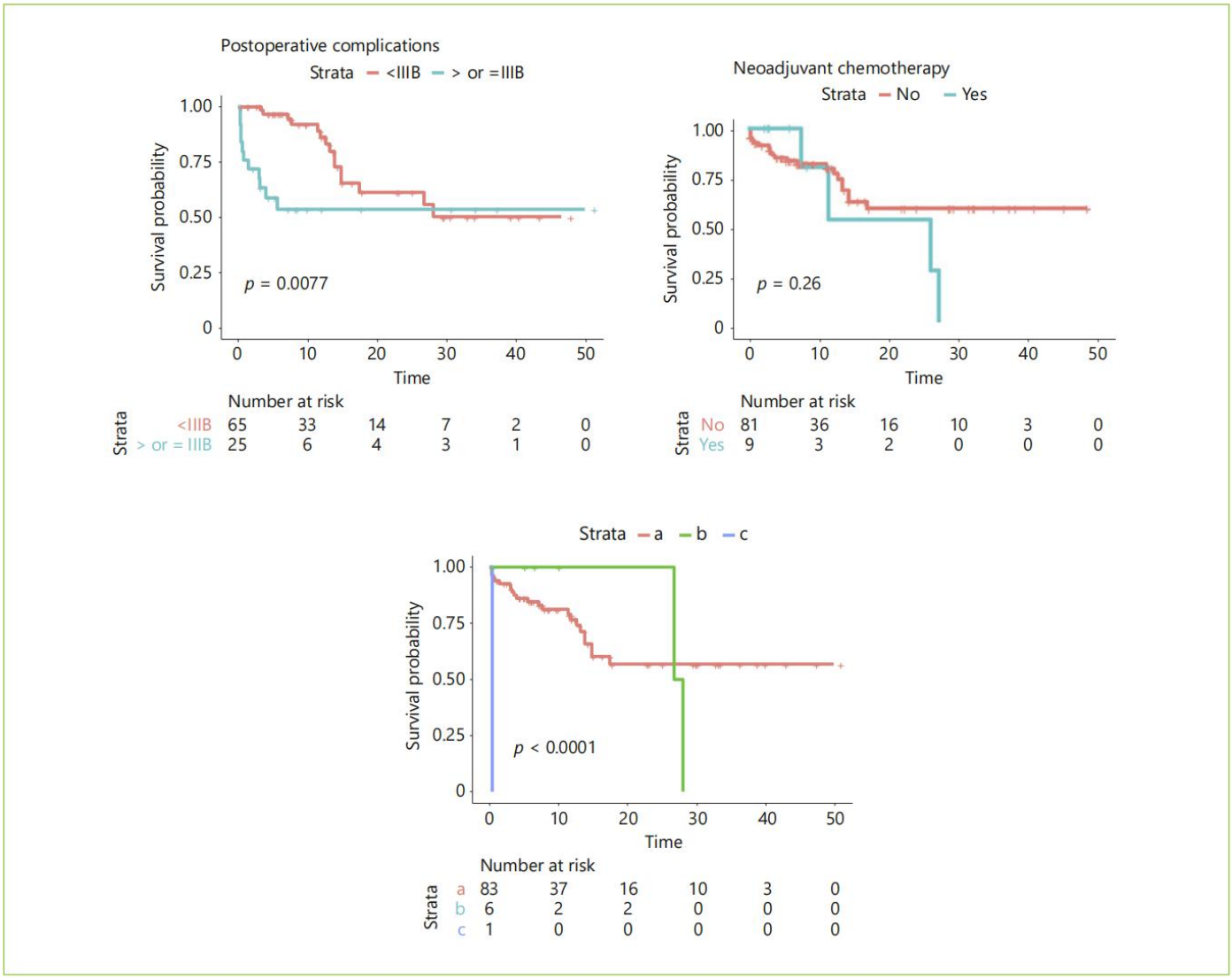

Fig. 4. Overall survival according to clinical variables: sex, age, ASA score, disease malignancy, neoadjuvant chemotherapy, postoperative complications, and type of surgery. **a** Total pancreatectomy or pancreaticoduodenectomy. **b** Distal pancreatectomy. **c** Pancreaticoduodenectomy with multivisceral resection ($n = 90$). IIIB, Clavien-Dindo class IIIb.

On the other hand, when we analyzed OS, age was no longer a determinant factor. With regard to body composition parameters, the results differed from those for 90-day survival, and muscle radiation attenuation was the only significant variable where an increase in 1 unit was associated with a 6% reduction in estimated risk of death, independently of age, histology, and postoperative complications.

Finally, the 90-day survival and OS analyses were conducted only for patients with malignant disease, and similar results were obtained. In a model that adjusted for postoperative complications and age, VFA:SMA (HR 2.02, 95% CI 1.07–3.81, $p = 0.03$) was significantly associated with 90-day survival. In a model adjusted for postoperative complications and age, muscle attenuation was significantly associated with OS (HR 0.94, 95% CI 0.89–0.99, $p = 0.019$).

Discussion

In this observational study performed in a single reference center for pancreatic surgery, we observed that body composition is a major determinant of the outcome of

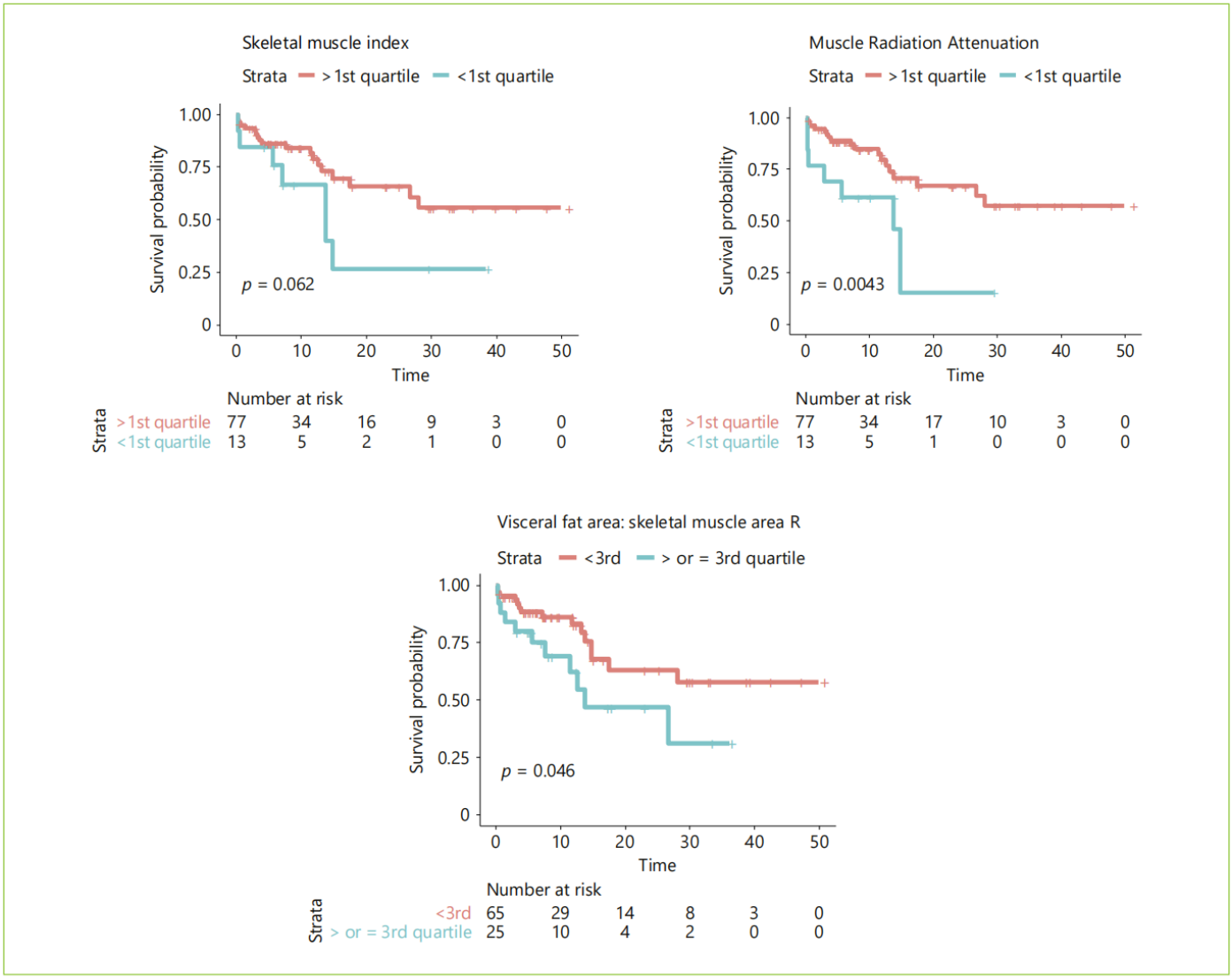

Fig. 5. Overall survival according to body composition variables dichotomized according to quartiles: skeletal muscle index, muscle radiation attenuation, and ratio of visceral fat area/skeletal muscle area (VFA:SMA) (n = 90).

surgically treated patients. We found that, for predicting survival, the discrimination achieved with a model that includes 3 body composition parameters proved superior to a model with 4 conventional clinical variables such as age, ASA score, disease histology, and postoperative complications. With regard to postoperative complications, a major determinant of OS, we observed a significant association with VFA:SMA independently of ASA score. It is worth pointing out that, in our sample, only 2 patients met conventional criteria for sarcopenic obesity.

Considering the high morbidity and mortality associated with pancreatic surgery, our findings are highly relevant. Although age, ASA score, and disease stage are non-modifiable factors, we can certainly aim at modifying preoperative body composition, especially during neoadjuvant chemotherapy. This is being more frequently prescribed even in tumors which seem resectable upfront. Criteria for considering a tumor as borderline resectable have been recently expanded and, as of today, neoadjuvant chemo/chemoradiotherapy is now strongly recommended in a substantial proportion of operated patients, if not all [25–28]. This period usually lasts 6 months or even more, which is an excellent opportunity to intervene with combined programs of exercise and/or dietary intervention aimed at modifying body composition.

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DOI: 10.1159/000507206

Table 4. Mean survival and simple and multiple proportional hazards cox models

	Patients, *n*	Deaths, *n*	Survival, months (mean)	Simple analysis					Conventional multiple analysis					Body composition multiple analysis				
				Coeff.	SE	HR	95% CI	*p*	Coeff.	SE	HR	95% CI	*p*	Coeff.	SE	HR	95% CI	*p*
Sex																		
Female	40	12	30.3			1.00			Excl					Excl				
Male	50	14	29.6	−0.05	0.4	0.95	0.4–2.0	0.9										
Age																		
<70 years	53	9	31.5			1.00					1.00			Excl				
≥70 years	37	17	18.5	1.29	0.4	3.66	1.6–8.3	0.0009	1.2	0.4	3.34	1.4–7.9	0.0006					
Histology																		
Benign	14	2	37.4			1.00					1.00			Excl				
Malignant	76	24	29.2	0.79	0.7	2.22	0.5–9.4	0.3	0.69	0.7	2.0	0.4–8.5	0.34					
Type of surgery																		
Total pancreatectomy/ pancreaticoduodenectomy	83	23	19.9			1.00			Excl					Excl				
Distal pancreatectomy	6	2	27.34	0.13	0.7	1.15	0.3–4.8	0.84										
Pancreaticoduodenectomy with multivisceral resection	1	1	0.36	3.38	1.1	29.4	3.0–284.0	0.003										
Complications																		
<IIIb	65	15	32.0			1.00			controlled with model stratification[2]					Excl				
≥IIIb	25	11	26.7	1.02	0.4	2.77	1.2–6.1	0.01										
ASA score																		
I/II	60	13	34.5			1.00					1.00			Excl				
III	30	13	23.9	0.70	0.4	2.0	0.9–4.4	0.07	0.20	0.4	1.2	0.5–2.7	0.62					
Skeletal muscle index	90	26	31.15	−0.04	0.02	0.95	0.9–1.0	0.09	Excl					−0.01	0.03	0.98	0.9–1.0	0.65
Muscle radiation attenuation	90	26	31.15	−0.09	0.02	0.92	0.8–0.9	1.6×10^{-5}	Excl					−0.08	0.03	0.92	0.8–0.9	0.004
VFA:SMA	90	26	31.15	0.64	0.2	1.9	1.9–3.0	0.007	Excl					0.03	0.32	1.03	0.5–1.9	0.92
C–statistic									**0.68**					**0.76**				

N = 90 patients, with 26 deaths during overall follow-up. VFA:SMA, ratio of visceral fat area/skeletal muscle area; Coeff., coefficient; SE, standard error; HR, hazard ratio; CI, confidence interval; Excl, excluded.
[1] Log rank test; [2] in the multiple analysis with conventional variables, complications were accounted for through stratification since this variable violated the proportional hazards assumption.

Table 5. Stratified Cox proportional hazards models of 90-day and overall survival

	90-Day survival							Overall survival						
	deaths (n = 8)	survival (mean)	Coeff.	SE	HR	95% CI	p	deaths (n = 26)	survival (mean)	Coeff.	SE	HR	95% CI	p
Age, years														
<70	2	2.92			1.00			9	31.5			1.00		
≥70	6	2.65	2.1	0.9	8.2	1.3–51.8	0.02	17	18.5	0.74	0.48	2.09	0.81–5.39	0.12
Histology														
Benign	1	2.84			1.00			2	37.4			1.00		
Malignant	7	2.80	0.76	1.09	2.14	0.24–18.5	0.48	24	29.2	0.53	0.74	1.70	0.39–7.34	0.51
Complications														
<IIIb	0	3.00	Controlled with model stratification[1]					15	32.0	Controlled with model stratification[1]				
≥IIIb	8	2.31						11	26.7					
Skeletal muscle index	8	2.8	Excluded[2]					26	31.1	Excluded[2]				
Stratified Cox proportional hazards models														
Muscle radiation attenuation	8	2.8	Excluded[2]					26	31.1	–0.05	0.02	0.94	0.90–0.98	0.016
VFA:SMA	8	2.8	0.75	0.32	2.13	1.13–4.01	0.019	26	31.1	Excluded[2]				
C-statistic			**0.767**							**0.735**				

N = 90 patients, with 8 and 26 deaths at the 90-day and overall follow-ups, respectively.
[1] Complications were accounted for through stratification since this variable violated the proportional hazards assumption.
[2] Nonsignificant body composition parameters were excluded to avoid numerous predictors.

Most studies that have addressed the relationship between body composition and the clinical outcome of pancreatic surgery patients focused mainly on skeletal muscle tissue and OS, with contradictory results. The studies have approached this issue using different methods to tackle skeletal muscle tissue, namely L3 CT scan-derived sarcopenia [4, 10, 16, 29], SMA loss [30], accelerated loss of muscle mass [20], total psoas area [1, 11] and volume [5], which have been associated with shorter OS in pancreatic cancer patients submitted to surgery or palliative care.

In contrast, other studies failed to demonstrate such an association [9, 22], or were only able to show an association with sarcopenia if BMI was accounted for (which may be thought of as a proxy of body fatness) [8, 12]. Some studies included patients submitted to curative and palliative procedures which obviously have different outcomes [13]. In this study, we enrolled patients submitted to curative surgery only; 84% had malignant tumors while the remaining ones had premalignant lesions, and all patients were treated by the same team of 3 surgeons. Although skeletal muscle per se was not associated with a worse prognosis, it is worth noting that both VFA:SMA and muscle attenuation, which incorporate both fat and skeletal muscle tissue, were strong determinants of postoperative complications, 90-day survival, and OS, respectively. This suggests that these body compartments should not be considered isolated as they seem to exert a joint influence on the final outcome.

Notably, most studies published so far have addressed OS; only a small number have investigated the effect of body composition on postoperative survival. Joglekar et al. [31] found that sarcopenia was an independent predictor of grade-III complications, but they did not analyze visceral fat or muscle attenuation. In our study series, VFA:SMA was independently associated with 90-day survival and postoperative complications on multivariate analysis, while ASA score lost significance. Our findings are in line with the only published study to investigate the influence of VFA:SMA on 60-day mortality, and found that a VFA:SMA exceeding 3.2 and ASA III were the strongest predictors of mortality [3].

In our study, muscle radiation attenuation was found to be the most relevant body composition parameter associated with OS independently of age, postoperative complications, and disease histology. This result supports the hypothesis that muscle quality may be one of the most important body composition parameters influencing OS. In agreement with our results, van Dijk et al. [13] also found that low skeletal-muscle radiation attenuation was associated with worse OS and a high skeletal/visceral adipose tissue index was related to an increased

surgical-site infection rate. In this particular study, 50% of patients had non-pancreatic cancer and 30% of them were submitted to palliative procedures which substantially increased the heterogeneity of the study population. In a recent study, Stretch et al. [9] found that myosteatosis was associated with an increase in postoperative complications but found no correlation between body composition and OS. Of note, the reported incidence of major postoperative complications and deaths in their study was exceedingly low, which could explain this lack of correlation. They concluded that sarcopenia and myosteatosis represent 2 separate and distinct clinical phenotypes, but they did not include VFA:SMA in their analysis.

To our knowledge, this is the first study examining the effect of body composition in its most holistic perspective including the ratios between visceral fat and skeletal muscle tissues in both postoperative outcomes and OS. Although well-powered prospective studies are still needed, our results suggest that muscle radiation attenuation may be an independent prognostic factor of OS and that VFA:SMA is significantly associated with 90-day survival and postoperative complications.

Statement of Ethics

The study protocol was approved by the Scientific and Ethics committee of the HBA. The requirement for informed consent from patients was waived because of the retrospective design of the study.

Disclosure Statement

There were no conflicts of interest.

Funding Sources

There was no funding.

Author Contributions

S.V.: formal analysis and writing of original draft; M.P.C.S.: investigation and formal analysis; F.C. and C.C.: clinical data collection; L.A. and R.C.: computed tomography image acquisition and validation of processed images; M.G. and P.O.: investigation; R.M.: resources and supervision; V.E.B.: writing, review, and editing; M.C.: conceptualization, writing, review, and editing.

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DIETARY PATTERNS AND THEIR RELATIONSHIP TO SARCOPENIA IN PORTUGUESE PATIENTS WITH GASTROINTESTINAL CANCER: AN EXPLORATORY STUDY

Nutrition 63–64 (2019) 193–199

Contents lists available at ScienceDirect

Nutrition

journal homepage: www.nutritionjrnl.com

Applied nutritional investigation

Dietary patterns and their relationships to sarcopenia in Portuguese patients with gastrointestinal cancer: An exploratory study

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ARTICLE INFO

Article History:
Received 22 October 2018
Received in revised form 15 December 2018
Accepted 21 January 2019

Keywords:
Dietary patterns
Cancer
Body composition
Gastrointestinal
sarcopenia

ABSTRACT

Objectives: The purpose of this exploratory study was to identify the main dietary patterns of a Portuguese population of patients with gastrointestinal cancer and to analyze their association with sarcopenia.
Methods: This was a prospective study with a consecutive sample of 100 patients with gastrointestinal cancer enrolled at diagnosis. Dietary intake was assessed with a semiquantitative Food Frequency Questionnaire, and dietary patterns were obtained with principal component analysis. Nutritional assessment was done using the Patient-Generated Subjective Global Assessment, and body composition was evaluated with anthropometric measures and computed tomography image processing obtained at the third lumbar vertebrae. Sex and body mass index specific cutoffs were used to define sarcopenia.
Results: Four major patterns were identified: high-fat dairy products, fried snacks, and processed meat diet; legumes, vegetables, and fruit diet; fat and fish diet; and alcohol, cereal, and animal protein diet. On simple logistic regression, the occurrence of sarcopenia in participants in the second tertile (odds ratio [OR] 0.30; 95% confidence interval [CI] 0.10–0.83; $P = 0.02$) and third tertile (OR 0.24; 95% CI 0.08–0.69; $P = 0.01$) of adherence to the high-fat and fish diet was reduced compared with the first tertile. On multiple logistic regression, the second tertile (OR 0.38, 95% CI 0.11–1.19; $P = 0.10$) of the fat and fish dietary pattern maintained a trend toward a reduction of the odds of sarcopenia compared with the first tertile, independently of calorie intake, age, disease location, and stage.
Conclusions: The fat and fish dietary pattern was associated with lower odds of sarcopenia in this population of patients with gastrointestinal cancer.

Introduction

Cancer cachexia is a highly prevalent multifactorial syndrome characterized by ongoing muscle loss, with or without fat loss [1]. Sarcopenia (severe muscle depletion) is a key feature of cancer cachexia and affects 26% to 78.7% of gastrointestinal (GI) cancer patients [2,3]. Sex and body mass index (BMI) specific cutoffs for computed tomography (CT)–derived skeletal muscle index have been previously reported to define sarcopenia [4]. It is well established that sarcopenia is associated with a worse outcome, and recent research has focused on feasibility and effects of diet and exercise on body composition [5–9], but scientific evidence is still lacking.

Previous studies have reported the following: 1) cancer patients are able to maintain protein synthesis provided they receive a higher amount and type of protein or amino acids [10,11]; 2) ω-3 polyunsaturated fatty acids may be linked to skeletal muscle maintenance

M. Salomé Cabral was partially funded by FCT-Fundação para a Ciência e a Tecnologia, Portugal, through the project UID/MAT/00006/2013.
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https://doi.org/10.1016/j.nut.2019.01.014
0899-9007/

[12]; and 3) cancer patients maintain a capacity for muscle anabolism even until advanced stages [13], suggesting an opportunity for nutritional status optimization through dietary intervention.

Given the known effects of single nutrients on skeletal muscle and that dietary patterns may actually be more relevant than single nutrient intake, because of an expected synergistic effect of foodstuffs consumed, we hypothesized that dietary patterns could be linked to the odds of cancer-related sarcopenia.

Materials and methods

Study population

The study protocol was approved by the Scientific and Ethics Committee of Hospital Beatriz Ângelo in Loures, Portugal. From October 2014 to December 2015 a total of 100 outpatients age 18 or older, with a recent diagnosis of GI cancer and untreated, were consecutively enrolled in this prospective study. Informed consent was obtained. Clinical data were prospectively collected from electronic charts; however, the present study reports on baseline data. Data were coded to maintain pseudo-anonymity. Variables concerning disease location were categorized as hepatic-biliary-pancreatic cancer or upper (esophagus, gastric) and lower (colorectal cancer) GI. Disease stage was dichotomized in stages I, II, and III versus stage IV disease for non-metastatic and metastatic disease, respectively.

Performance status was assessed with the Eastern Cooperative Oncology Group Performance Status scale [14] and quality of life with the European Organization for Research and Treatment of Cancer Version 3.0 questionnaire [15]. Physical activity was assessed with the International Physical Activity Questionnaire [16], previously validated for the Portuguese population.

Body weight was measured with a digital scale (SECA) and height with a stadiometer. BMI was calculated and BMI classification was done according to the following categories: <20.0, underweight; 20.0 to 24.9, normal weight; 25.0 to 29.9, overweight; and 30.0 kg/m^2, obese. Patient-generated Subjective Global Assessment (SGA) assessment [17,18] was conducted by a single experienced dietitian (S.V.), and patients were classified as well nourished (SGA A), moderately malnourished or suspected of being malnourished (SGA B), or severely malnourished (SGA C).

Because CT imaging is part of the clinical staging of GI cancer patients, CT images were used for body composition analysis. CT methods are highly precise to quantify specific tissues and to predict whole-body composition [16]. Images were selected by radiologists at the third lumbar vertebra (L3) using a portal venous phase and were processed with specific software that performed an automatic segmentation of tissue cross-sectional areas, with manual corrections by the radiologist. Segmentation of tissue cross-sectional areas was conducted according to the following Hounsfield unit thresholds: −29 to 150 for skeletal muscle, −190 to −30 for subcutaneous and intramuscular adipose tissue, and −50 to −150 for visceral adipose tissue. Cross-sectional skeletal muscle, visceral fat, and subcutaneous fat were recorded in centimeters squared and mean muscle radiation attenuation in Hounsfield units. Skeletal Muscle Index (cm^2 / height^2) was calculated. Sex-specific cutoffs for Skeletal Muscle Index and muscle radiation attenuation as defined by Martin et al. [4] were used to define sarcopenia and low muscle radiation attenuation because there are no published cutoffs for the Portuguese population.

Dietary intake

Dietary intake was assessed with a semiquantitative food frequency questionnaire developed for the Portuguese population [19,20]. This questionnaire includes 86 commonly eaten food or drinks, and participants were asked to estimate the amount and frequency of intake of each food and drink according to frequency and amount. Conversion of foodstuffs to nutrients was conducted with Food Processor Plus software (ESHA Research, Salem, OR, USA) adapted to Portuguese commonly eaten food and drinks. This questionnaire was filled out during the interview with the dietitian.

Statistical analysis

Data analysis was performed with SPSS Version 20 (IBM Corp., Armonk, NY) and R Version 3.0.2 (R Foundation for Statistical Computing, Vienna, Austria), and statistical significance was set at $P \leq 0.05$.

Shapiro-Wilk's test was used to test for the adjustment of continuous variables to the normal distribution and differences in means were analyzed by t test or Mann-Whitney U test as appropriate. The association between categorical variables was tested with χ^2 test. Analysis of covariance was conducted to test for differences in mean dietary intakes while adjusting for BMI.

A total of 86 food items were categorized in 23 food groups (Table 1) according to their nutritional composition similarity. Principal component analysis (PCA) with varimax rotation was performed as previously described [21,22]. The suitability of the data for PCA was analyzed with Kaiser-Meyer-Olkin and Bartlett's test of sphericity. The Kaiser-Meyer-Olkin, a measure of sampling adequacy for PCA, was 0.61, which is greater than the established cutoff of 0.5, indicating that PCA could be performed [23]. Barlett's test, which tests the null hypothesis that the correlation matrix is an identity matrix, was statistically significant (<0.001), thereby indicating that variables are correlated and PCA is appropriate. The decision to retrieve dietary patterns was based on an eigenvalue >1, visual scree plot analysis, and interpretability [23]. Food groups were considered as relevant to a dietary pattern if the loading coefficient was >0.3 [24]. The score of each participant to each specific dietary pattern was computed with SPSS during PCA analysis, which was converted to percentiles and categorized in tertiles.

Table 1
Food groupings for dietary pattern analysis

Food group	Examples
Processed meat	Sausage, bacon, ham
Animal protein	Eggs, chicken, turkey, rabbit, pork, cow, liver, cow's tongue
Fish	Sardines, cod fish, tuna, squid, octopus, shrimp
Low-fat dairy products	Skim milk, low-fat milk, low-fat yogurt
High-fat dairy products	Whole milk, desserts, ice cream
Vegetables	Cabbage, broccoli, cauliflower, green beans, carrots, onions, turnip, tomato
Fresh fruits	Pear, apple, orange, banana, kiwi, strawberry, cherries, peach, fig
Low sugar drinks	Tea, coffee
High sugar drinks	Commercial fruit juice, cola, commercial iced tea
Alcohol drinks	Beer, wine, whiskey
Legume	Chickpea, kidney bean, black-eyed beans
Potato	
Cereal derived	Whole-grain bread, pasta, rice, cereals
Nuts	
Olive oil	Olive oil, olives
Sugar	
High-fat snacks	Cookies, chocolates
Processed fruit	Jam, marmalade, canned fruit
Margarine	
Butter	
Plant oil	
Portuguese fried snacks	Fried codfish cakes, croquettes, *rissois*
Soup	
Fast food	Pizza, french fries, hamburger, ketchup

Simple logistic regression was used to relate each variable with sarcopenia. For continuous variables, linearity of the logit in the predictor was assessed using a cubic spline and Wald's test of linearity [25]. Because for age linearity was not clear on cubic spline graphs (P value of Wald's test of linearity was 0.15), this variable was categorized as younger than 70 years and 70 years or older. Only variables with $P \leq 0.25$ or considered clinically relevant were selected for multiple logistic regression. Two multiple logistic regression models were adjusted without automatic stepwise variable selection because with this method, important variables, such as calorie intake and disease location, were discarded. Multicollinearity was also analyzed through the observation of variance inflation factors. Receiver operating characteristic (ROC) curves were computed and the respective area under the curve (AUC) was calculated to assess accuracy of both models. The positive predictive value and the negative predictive value were also given.

Because assumptions of analysis of variance failed—namely, homogeneity of variances (tested with Levene's test) or adjustment of the dependent variable to a normal distribution within each tertile (graphical analysis of P-P plots of studentized residuals)—a Kruskal-Wallis test was used to test for differences between the means of continuous variables and tertiles of adhesion to the fat and fish diet. Post hoc multiple comparisons were conducted with pairwise analysis.

Results

Characteristics of the studied population

Table 2 presents demographic characteristics of the studied population. A total of 32% of patients presented with sarcopenia. Sarcopenic patients were older and had a more advanced disease stage, worse performance status, and lower mean BMI. Regarding BMI categories, both normal weight and overweight had the highest percentage of sarcopenic patients. In respect to dietary intake we found that sarcopenic patients had a significantly lower total calorie, protein, and fat daily intake, whereas no difference was

Table 2
General characteristics of participants

Variables	Total (n = 100)	Sarcopenic (n = 32)	Nonsarcopenic (n = 68)	P	OR	95% CI	P
Age	69.49 ± 11.15	69.92 ± 10.64	67.53 ± 10.9	0.003	1.05	1.01– 1.10	0.01
Age categorized							
<70 (y)	50 (50%)	10 (31.2%)	40 (58.8%)	0.010	1.00		
≥70 (y)	50 (50%)	22 (68.8%)	28 (41.2%)		3.14	1.31–7.912	0.01
Sex							
Female	34 (34%)	11 (34.4%)	23 (33.8%)	0.957	1.00		
Male	66 (66%)	21 (65.6%)	45 (66.2%)		0.97	0.40–2.41	0.95
Disease location							
Upper GI	37 (37%)	9 (28.1%)	28 (41.2%)	0.276	1.00		
Lower GI	54 (54%)	21 (65.6%)	33 (48.5%)		1.97	0.79– 5.19	0.15
Hepatic-biliary-pancreatic	9 (9%)	2 (6.2%)	7 (10.3%)		0.88	0.11– 4.53	0.89
Disease stage							
Nonmetastatic	76 (76.0)	20 (62.5%)	56 (82.4%)	0.03	1.00		
Metastatic	24 (24.0)	12 (37.5%)	12 (17.6%)		2.80	1.08–7.32	0.03
High GI obstruction*							
No	74 (74%)	26 (81.2%)	48 (70.6%)	0.26	1.00		
Yes	26 (26%)	6 (18.8%)	20 (29.4%)		0.55	0.18– 1.48	0.26
Smoking habits							
No	82 (82%)	27 (84.4%)	55 (80.9%)	0.67	1.00		
Yes	18 (18%)	5 (15.6%)	13 (19.1%)		0.78	0.23–2.31	0.67
Performance status							
0	35 (35.4%)	11 (34.4%)	24 (35.8%)	0.06	1.00		
1	37 (37.4%)	8 (25.0%)	29 (43.3%)		0.60	0.20– 1.72	0.34
2	15 (15.2%)	5 (15.6%)	10 (14.9%)		1.09	0.28–3.89	0.89
3	11 (11.1%)	7 (21.9%)	4 (6.0%)		4.36†	1.12–19.41	0.04
4	1 (1.0%)	1 (3.1%)	0 (0%)				
Quality of life							
Function	52.50 ± 24.24	54.39 ± 23.94	51.5 ± 24.78	0.592	1.00	0.98– 1.02	0.58
Symptoms	33.56 ± 23.07	35.88 ± 22.09	32.42 ± 23.62	0.314	1.00	0.98– 1.02	0.48
Global score	47.91 ± 21.76	44.79 ± 25.64	49.47 ± 19.57	0.367	0.98	0.97–1.00	0.31
Patient-generated Subjective Global Assessment							
Well nourished	27 (27%)	7 (21.9%)	20 (29.4%)	0.579	1.00		
Severely Malnourished	34 (34%)	13(40.6%)	21 (30.9%)		1.26	0.43– 3.95	0.66
Moderately Malnourished	39 (39%)	12 (37.5%)	27 (39.7%)		1.76	0.59–5.55	0.31
Physical activity							
Low physical activity	60 (60%)	22 (68.8%)	38 (55.9%)	0.220	1.00		
Moderate physical activity	40 (40%)	10 (31.2%)	30 (44.1%)		0.57	0.22–1.37	0.22
Body mass index (kg/m^2)	26.08 ± 5.4	24.2 ± 3.7	26.9 ± 5.9	0.03	0.89	0.81–0.97	0.02
Body mass index							
Low weight	6 (6%)	2 (6.2%)	4 (5.9%)	0.005	1.00		
Normal weight	42 (42%)	13 (40.6%)	29 (42.6%)		0.89	0.15– 7.05	0.90
Overweight	31 (31%)	16 (50.0%)	15 (22.1%)		2.13	0.36– 17.05	0.41
Obesity	21 (21%)	1 (3.1%)	20 (29.4%)		0.10	0.004–1.27	0.09
Dietary intake							
Calorie intake (kcal/d)	2782.3 ± 889.0	2451.6 ± 803.1	2937.9 ± 890.2	0.013	0.99	0.998–0.999	0.01
Calorie intake (kcal/kg)	41.1 ± 14.6	37.3 ± 12.6	43.0 ± 15.1	0.07	0.97	0.93– 1.00	0.07
Protein(g/d)	105.5 ± 33.3	93.9 ± 34.2	111.0 ± 31.7	0.01	0.98	0.96– 0.99	0.02
Protein (g/kg)	1.56 ± 0.6	1.42 ± 0.5	1.63 ± 0.6	0.08	0.51	0.21– 1.09	0.09
Carbohydrates (g/d)	290.3 ± 106.9	277.7 ± 103.5	296.2 ± 108.8	0.261	0.99	0.99– 1.00	0.42
Carbohydrates (g/kg)	4.3 ± 1.7	4.2 ± 1.5	4.37 ± 1.5	0.674	0.94	0.72–1.20	0.63
Fat (g/d)	125.7 ± 49.25	103.1 ± 44.64	136.3 ± 48.0	0.001	0.98	0.97– 0.99	0.003
Fat (g/kg)	1.9 ± 0.8	1.6 ± 0.7	2.0 ± 0.8	0.01	0.47	0.24– 0.85	0.02
High-fat dairy products, fried snacks, and processed meat diet							
First tertile	33 (33%)	9 (28.1%)	24 (35.3%)	0.12	1.00		
Second tertile	33(33%)	15 (46.9%)	18 (26.5%)		2.22	0.80–6.39	0.12
Third tertile	34 (34%)	8 (25.0%)	16 (38.2%)		0.82	0.26–2.48	0.72
Legumes, vegetables, and fruit diet							
First tertile	33 (33%)	13 (40.6%)	20 (29.4%)	0.53	1.00		
Second tertile	33(33%)	9 (28.1%)	24 (35.3%)		0.57	0.19–1.61	0.29
Third tertile	34 (34%)	10 (31.2%)	24 (35.3%)		0.64	0.22–1.76	0.39
High-fat and fish diet							
First tertile	33 (33%)	17 (53.1%)	16 (23.5%)	0.01	1.00		
Second tertile	33(33%)	8 (25.0%)	25 (36.8%)		0.30	0.10–0.83	0.02
Third tertile	34 (34%)	7 (21.9%)	27 (39.7%)		0.24	0.07–0.69	0.01
Alcohol, cereal, and animal protein diet							
First tertile	33 (33%)	11 (34.4%)	22 (32.4%)	0.92	1.00		
Second tertile	33(33%)	11 (34.4%)	22 (32.4%)		1.00	0.35–2.80	1.00
Third tertile	34 (34%)	10 (31.2%)	24 (35.3%)		0.83	0.29–2.35	0.73

CI, confidence interval; GI, gastrointestinal; OR, odds ratio
Results expressed as mean ± standard deviation or number (percentage)
ORs and 95% CIs from simple logistics regression with sarcopenia as dependent variable
*Performance status categories 3 and 4 were merged to allow 95% CI determination.
†Patients classified as having GI obstruction presented endoscopic documentation of high GI stenosis and clinical manifestations of stenosis such as dysphagia for solid foods, regurgitation, or vomiting.

Table 3
Factor loading matrix for main dietary patterns

Variables	High-fat dairy products, fried snacks, and processed meat diet	Legumes, vegetables, and fruit diet	Fat and fish diet	Alcohol, cereal, and animal protein diet
High-fat dairy products	0.877			
Portuguese fried snacks	0.846			
Processed meat	0.791			
Nuts (with and without salt)	0.346			
Legumes		0.828		
Vegetables		0.805		
Potatoes		0.464		
Soup		0.424		
Fresh fruit		0.319		
Olive oil			0.751	
Butter			0.728	
High-fat snacks			0.381	
Fish			0.344	
Alcoholic drinks				0.776
Cereal-derived products				0.627
Fast food				0.551
Animal protein				0.424
% of variance explained	12.2	9.4	7.8	7.8

Values <0.30 were excluded for simplicity

found for carbohydrate intake. After adjusting for BMI, differences in calorie ($P = 0.013$), protein ($P = 0.013$), and fat ($P = 0.002$) remained statistically significant, whereas differences in carbohydrate ($P = 0.454$) intake remained non-significant.

Dietary patterns

Four major patterns were identified with PCA: high-fat dairy products, fried snacks, and processed meat diet; legumes, vegetables, and fruit diet; fat and fish diet; and alcohol, cereal, and animal protein diet. These patterns explained 37.2% of the overall variance. The first pattern was defined with food stuffs such as high-fat dairy products, fried Portuguese snacks, processed meat, and nuts (with or without salt), which presented high loadings (>0.3). The second pattern had high loadings for legumes, vegetables, potatoes, soup, and fresh fruit. The third pattern had high loadings for olive oil, butter, high-fat snacks (cookies and chocolates), and fish. The fourth pattern had high loadings for alcoholic drinks, cereal-derived products, fast food, and animal protein. Table 1 shows food groupings for dietary pattern analysis and Table 3 summarizes the results from PCA.

Dietary patterns and sarcopenia

Simple logistic regression was performed to explore which variables are associated with sarcopenia. The results of this analysis are presented in Table 2. This analysis indicated that patients with higher odds of sarcopenia were older, had worse performance status, and had more advanced disease stage, whereas calorie intake was associated with lower odds of sarcopenia. Regarding dietary patterns, patients in the second and third tertiles of adhesion to the fat and fish pattern presented significantly lower odds of sarcopenia. No association was found with other patterns.

Because the fat and fish diet was the only pattern with a significant association with sarcopenia, multiple logistic regressions focused on this pattern. Table 4 reports on the results from multiple logistic regressions. Interpretation of the variables was done considering that the participants had the same values on all variables, except for the one being compared. In model I we adjusted for age, fat and fish pattern, and calorie intake. According to this analysis the odds of sarcopenia were almost three times greater in patients with age ≥70 compared with patients with age <70. The odds of sarcopenia were reduced in 67% in patients in the second tertile and 68% in the third tertile, compared with the first tertile of adhesion to the fat and fish diet, independently of calorie intake.

Table 4
Models I and II for sarcopenia as dependente variable obtained with multiple logistic regression

	Model I			Model II		
Variables	OR	95% CI	*P*	OR	95% CI	*P*
Disease location	Not included					
Upper GI				1.00		
Lower GI				1.75	0.62–5.13	0.28
Hepatic-biliary-pancreatic				0.58	0.06–3.69	0.59
Disease stage	Not included					
Non-metastatic				1.00		
Metastatic				3.4	1.13–10.87	0.03
Age						
<70	1.00			1.00		
≥70	2.83	1.09– 7.71	0.03	3.2	1.17–9.23	0.03
Fat and fish diet						
First tertile	1.00			1.00		
Second tertile	0.33	0.10– 0.98	0.05	0.38	0.11–1.19	0.10
Third tertile	0.32	0.08–1.18	0.08	0.45	0.11–1.84	0.26
Calories	0.99	0.99–1.00	0.38	0.99	0.99–1.00	0.37

CI, confidence interval; GI, gastrointestinal; OR, odds ratio

Model II further adjusts for clinical variables—namely, disease location, disease stage, age, and calorie intake. Again the odds of sarcopenia was three times higher in patients age ≥70, compared with patients age <70. Besides age, disease stage was the only clinical variable associated with sarcopenia because the odds of sarcopenia were three times greater in patients with metastatic disease compared with non-metastatic patients. Lastly, a trend was found for a reduction of 62% of the odds of sarcopenia for patients in the second tertile of the fat and fish diet compared with the first tertile of adhesion to the fat and fish diet.

The AUC obtained through ROC curve analysis was 0.727 and 0.767 for model I and model II, respectively (Fig. 1). These AUCs indicate a fair discriminatory ability of both models in the prediction of sarcopenia. ROC curves are presented in Figure 1. Sensitivity was 59.4%, specificity was 76.5%, positive predictive value was 20%, and negative predictive value was 45.7% for model I. Sensitivity

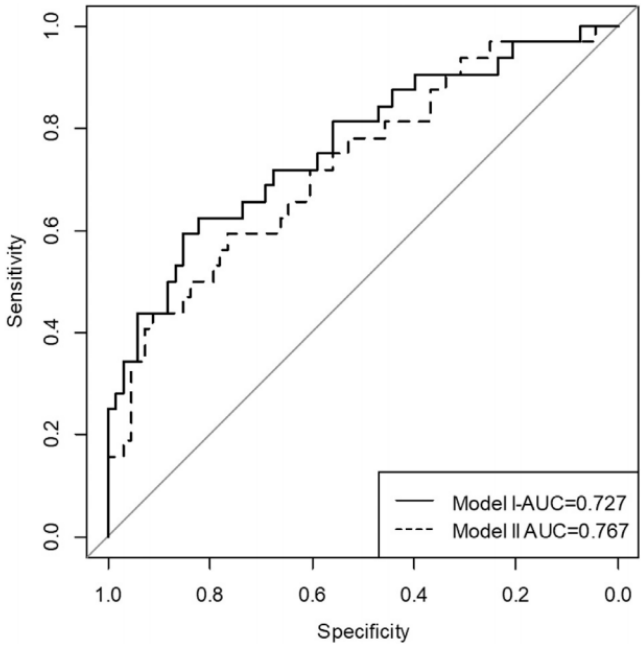

Fig. 1. Receiver operating characteristic curve analysis for models I and II. AUC, area under the curve.

was 62.5%, specificity was 82.4%, positive predictive value was 17.6%, and negative predictive value was 37.5% for model II.

Participant's characteristics according to compliance to fat and fish pattern

Table 5 shows the studied population characteristics across tertiles of adhesion to the fat and fish pattern. According to this analysis, patients did not differ in respect to clinical and anthropometric characteristics and body composition, except for the proportion of sarcopenic patients. Patients with a lower adhesion to the fat and fish pattern had a higher proportion of sarcopenia.

Regarding dietary intake, patients in the second tertile were characterized as having a similar calorie and protein intake normalized by body weight and carbohydrate intake as patients in the first tertile. The main difference was a higher lipid intake, but not as high as identified for the third tertile and the highest monounsaturated + polyunsaturated fat/saturated fat ratio. Also, patients in the second tertile had an energy intake predominantly >30 kcal/kg and a high lipid intake (only one patient had a lipid intake <30% of total calorie intake), and a higher proportion of patients were within the European Society of Parenteral and Enteral Nutrition recommendations of protein intake.

Discussion

To our knowledge this is the first study examining the relationship between dietary patterns and sarcopenia in a population of GI cancer patients. We identified four dietary patterns, but only the fat and fish diet was associated with a lower odds of sarcopenia.

After the seminal paper of Martin et al. [4], several other studies have clearly found that alteration in body composition—namely, sarcopenia—in cancer patients is a very important prognostic marker [26], with a high discriminant power regarding long-term survival [4]. However, the most effective way of tackling these alterations with the aim of improving final outcome is less clear.

Four main dietary patterns were identified in this prospective study: high-fat dairy products, fried snacks, and processed meat pattern; legumes, vegetables, and fruit pattern; fat and fish pattern; and alcohol, cereal, and animal protein pattern. Total variance of dietary intake was mostly explained by a dietary pattern characterized by the first pattern, and no explicit Mediterranean dietary pattern (MDP) was found.

Although in the 1960s Portugal was known to have an MDP [27], according to the results of the National Portuguese Report of Dietary Intake and Exercise, MDP is becoming less predominant and only 12% of the Portuguese population are highly compliant with the MDP [28]. This shift in the dietary intake paradigm supports the findings in our study, in which MDP was not explicit, but still foods from MDP were found.

In our study the fat and fish pattern was the only pattern exhibiting a protective effect in regard to sarcopenia. This pattern correlated highly with olive oil, which is a source of monounsaturated fatty acids (MUFA); butter and high-fat snacks, which are sources of saturated fatty acids; and fish, which provides both protein and polyunsaturated ω-3 fatty acids and was associated with calorie intake. Interestingly, a trend was found for reduced odds of sarcopenia for patients in the second tertile of the fat and fish dietary compared with the first tertile, independently of calorie intake, age, disease location, and stage. Patients in the second tertile had a higher percentage of compliance to the target supply of 1.2 to 2 g protein/kg/day, a fat intake higher than general recommendations but also a higher monounsaturated + polyunsaturated fat (PUFA)/saturated fat ratio. In other words, this pattern consisted of a nutrient- and energy-dense diet that may be protective of muscle loss. It is worth pointing out that high-fat snacks such as cookies and chocolate also contributed to this association. We hypothesized that these foodstuffs, if consumed within a dietary pattern with healthy fat sources, may facilitate an adequate calorie intake and a balanced overall lipid intake (MUFA + PUFA/saturated fat) depending on the amounts consumed. In our study, patients in the second tertile of the fat and fish diet presented the highest mean MUFA + PUFA/saturated fat ratio.

There is some evidence that in cancer patients lipid oxidation may be normal or increased [29], and according to our results, a higher fat intake may be needed to reduce the odds of sarcopenia. Most studies have focused on the effect of PUFA intake in cancer cachexianamely, ω-3 PUFAs, which have been found to have a beneficial effect in the treatment of age-related sarcopenia [30] and cancer-associated muscle wasting [10,31,32]. Eicosapentaenoic acid (EPA) is thought to improve anabolism by increasing protein synthesis and muscle sensitivity to insulin, but it has also been found to inhibit muscle degradation by down-regulation of acute phase response and by decreasing the expression of proteasome subunits [33].

It has been hypothesized that oleic acid may also be important for muscle health. Data from an animal model of muscular dystrophy (Mdx mice) suggest that high MUFA may assist muscle in coping with this pathologic condition. In Mdx mice, high oleic acid intake was associated with reduced serum creatine kinase compared with high PUFA intake [30]. Conflicting results have been reported regarding MUFA effect on cancer cells [34,35].

Still, studies concerning the relationship of dietary patterns and cancer-related sarcopenia are lacking. A cross-sectional study in Iranian community-dwelling elderly adults, which addressed the association between dietary patterns and sarcopenia, found that a higher adherence to a dietary pattern consistent with the Mediterranean diet (higher consumption of olive oil, fruits, vegetables, fish, and nuts) was associated with a lower odds of age-related sarcopenia [21], which is in line with our results. In a recent systematic review, the authors conclude that there is some cross-sectional evidence of an association between diet quality and the odds of sarcopenia [36].

Table 5
Fat and fish diet and participants' clinical characteristics, anthropometric measures, body composition, and dietary intake

Variables	Fat and fish diet First tertile(n = 33)	Second tertile(n = 33)	Third tertile(n = 34)	P
Age				
<70	15 (30.0)	17 (34.0)	18 (36.0)	0.810
≥70	18 (36.0)	16 (32.0)	16 (32.0)	
Sex				
Female	14 (41.2)	9 (26.5)	11 (32.4)	0.417
Male	19 (28.8)	24 (36.4)	23 (34.8)	
Disease location				
Upper GI	11 (23.9)	18 (39.1)	17 (37.0)	0.190
Lower GI	22 (40.7)	15 (27.8)	17 (31.5)	
Disease stage				
<IV	22 (28.9)	24 (31.6)	30 (39.5)	0.102
IV	11 (45.8)	9 (37.5)	4 (16.7)	
Physical activity				
Low	30 (33.7)	27 (30.3)	32 (36.0)	0.250
Moderate	3 (27.3)	6 (54.5)	2 (18.2)	
Anthropometric measures				
Weight loss	5.29 ± 9.4	3.82 ± 6.2	2.00 ± 7.8	0.292
BMI	25.7 ± 5.6	26.3 ± 4.5	26.2 ± 6.2	0.866
Arm circumference	27.5 ± 3.7	28.2 ± 3.7	28.0 ± 3.67	0.707
Triceps skinfold	19.1 ± 9.9	18.61 ± 7.3	20.1 ± 9.1	0.793
Waist circumference	96.7 ± 12.7	97.8 ± 12.8	96.1 ± 15.9	0.880
Body composition				
Skeletal mass area				
Female	104.3 ± 15.4	106.3 ± 16.7	108.9 ± 21.7	0.918
Male	136.0 ± 30.2	148.82 ± 28.5	145.03 ± 23.4	0.353
Skeletal mass index				
Female	43.4 ± 8.1	45.5 ± 6.3	44.5 ± 7.2	0.684
Male	47.9 ± 10.3	52.2 ± 9.3	51.5 ± 9.6	0.264
Sarcopenia	17 (17%)	8 (8%)	7 (7%)	0.013
Muscle attenuation	28.8 ± 9.8	29.5 ± 8.5	31.2 ± 8.7	0.528
Low muscle attenuation	29 (29%)	30 (30%)	29 (29%)	0.779
Visceral fat area	165.3 ± 112.1	200.5 ± 89.4	158.1 ± 126.6	0.100
Subcutaneous fat area	149.5 ± 91.4	159.7 ± 67.2	178.9 ± 126.2	0.648
Total fat area	314.81 ± 174.9	360.2 ± 137.7	337.1 ± 214.1	0.445
Dietary intake				
Calories (kcal/kg)	35.4 ± 17.1	38.5 ± 10.2	49.3 ± 12.0*	<0.001
Calorie intake (<25 kcal/kg)	11 (33.3%)	2 (6.1%)	0(0%)	<0.001
Calorie intake (>30 kcal/kg)	17 (51.5%)	28(84.8%)	34 (100%)	
Protein (g/kg)	1.4 ± 0.6	1.6 ± 0.4	1.8 ± 0.6†	0.012
Protein intake (1.2–2 g/kg)	14 (42.4%)	22 (66.7%)	20 (58.8%)	0.003
Carbohydrates (g/d)	274.0 ± 116.4	267.3 ± 82.3	328.4 ± 111.0†	0.023
Lipids (g/d)	84.6 ± 42.1*	122.0 ± 28.3*	169.0 ± 33.8*	<0.001
Lipids (% total calorie daily intake)	33.7 ± 8.3*	41.4 ± 6.4	45.9 ± 8.3	<0.001
Lipid intake <30% of total calorie daily intake	12 (85.7%)	1 (7.1%)	1 (7.1%)	<0.001
saturated ratio/saturated ratio	2.0 ± 0.6*	2.5 ± 0.6	2.3 ± 0.3	0.003
Monounsaturated + polyunsaturated/saturated ratio	2.6 ± 0.7*	3.0 ± 0.7*	2.8 ± 0.6*	<0.001

BMI, body mass index; GI, gastrointestinal
*Significantly different from the other groups.
†Pairwise significant difference between the lowest and highest tertile.

Lastly, several limitations must be considered in our study. Because of logistic and budget limitations, we performed an exploratory study, with a consecutive convenience sample. We used a food frequency questionnaire, which is susceptible to under- or overestimation bias but has been validated for the Portuguese population and is useful in dietary patterns determination [37].

In conclusion, the fat and fish pattern was associated with lower odds of sarcopenia in this Portuguese population of patients with GI cancer. We consider that our study has contributed as a first step in unraveling the association between dietary patterns and sarcopenia.

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Research Article

JOURNAL OF FOOD SCIENCE AND NUTRITION RESEARCH

ISSN: 2642-1100

Adherence to Combined Exercise and Dietary Intervention in Patients with Gastrointestinal Cancer Undergoing Neo-Adjuvant Therapy: An Open-Label, Pilot, Randomized Controlled Trial

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Abstract

Background: To assess adherence of gastrointestinal cancer patients to a Combined Exercise and Dietary Intervention (CEDI) during neo-adjuvant chemotherapy.

Methods: Parallel randomized controlled, open label, pilot trial. A table from a web based randomization system was used to allocate treatments. 46 patients were screened at diagnosis of esophageal, gastric, pancreatic and rectal cancer from June 2018 to November 2019 at a teaching hospital in Loures, 39 were randomized. A planned interim analysis was performed and results are herein presented. Patients were randomized to receive either 8 week individualized CEDI, with moderate aerobic and resistance training, dietary counseling and oral nutritional supplements or standard care. Follow up was conducted after neo-adjuvant treatment. Main outcome measures were adherence to CEDI, change in weight, body composition and functional status. Adherence to CEDI was analyzed with an intention to treat approach, other outcome measures were analyzed with a per protocol approach. Data analysis was conducted with Chi-square test or Fisher exact test and t-test or Mann Whitney U test. Effect size was computed with Cohen's d for t tests and r for Mann-Whitney U tests. Paired-samples t test or Wilcoxon Signed Rank Test were used to analyze longitudinal data.

Results: 39 patients (CEDI n=19 or control n=20) were randomized and included in the intention to treat analysis (29 (74.3%) male, median age 63.5 (Interquartile Range (IQR):11.75)). 32 patients completed follow up. 13/19 (68.4%) were fully adherent to CEDI. CEDI patients maintained weight (Effect size (EF):0.457; 95% Confidence Interval (95%CI): [0.44,0.46]), waist circumference (EF:-0.56, 95%CI: [-1.08, -0.034]), had a lower skeletal muscle loss (EF:-0.79; [-1.77;0.18]) and improved 6 minute walking test distance (EF:-1.51; 95%CI: [-2.57;-0.44]) and quality of life function score (EF:0.45; 95%CI:[0.43,0.45]). There were 4 serious adverse events, 3 in the intervention and 1 in the control arm but none related to the intervention.

Conclusions: CEDI is feasible and patients are willing to participate even under neo-adjuvant chemoradiotherapy, resulting in potential nutritional and functional benefits.

Trial registration Trial registry: www.clinicaltrials.gov; Identifier: NCT05237921, 14-2-22, retrospectively registered, https://www.clinicaltrials.gov/ct2/results?cond=&term=NCT05237921&cntry=&state=&city=&dist=

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Citation: Velho S, Moço S, Capitão C, Branco M, Costa L, Rodrigues S, Abreu C, Alves R, Pires F, Sousa P, Agostinho L, Cruz R, Clemente S, Borges A, Lopes F, Godinho J, Faria A, Teixeira JA, Passos Coelho JL, Maio R, Baracos VE, Cravo M. Adherence to Combined Exercise and Dietary Intervention in Patients with Gastrointestinal Cancer Undergoing Neo-Adjuvant Therapy: An Open-Label, Pilot, Randomized Controlled Trial. Journal of Food Science and Nutrition Research 5 (2022): 669-681.

Received: August 30, 2022
Accepted: September 06, 2022
Published: October 11, 2022

Velho S et al., J Food Sci Nutr Res 2022
DOI:10.26502/jfsnr.2642-110000113

Keywords: Adhesion; Exercise; Diet; Oral nutritional supplements; Gastrointestinal cancer

Background

Body composition alterations, namely sarcopenia and sarcopenic obesity, are known to have a negative impact on cancer patients outcome [1-10], but the benefit of intervention strategies, remain unclear. Exercise has been associated with improved functional status and patient reported outcomes in cancer patients [11,12], but mostly in breast and colorectal cancer survivors [13,14]. In patients undergoing treatment a positive effect has also been observed and exercise has been considered safe and feasible even in advanced cancer [15]. However, optimal exercise frequency, intensity and duration is still open to debate. On the other hand, dietary intake is also relevant since it seems to have an important role in skeletal muscle maintenance. It has been suggested that cancer patients may experience an anabolic resistance to protein stimuli, but protein synthesis is not completely blunted and may respond to an elevated protein intake [16]. In fact, protein supplementation has proven to improve protein synthesis [17], body composition, muscle strength [18] and walking capacity [19] in cancer patients. Besides the effect of single nutrients, dietary patterns namely a high fat and fish diet, is associated with a reduced odds of sarcopenia [20] and simultaneous energy and protein intake seem to result in a more robust effect on muscle mass and strength [21].

Few studies have investigated the influence of a combined exercise and dietary intervention [22]. Solheim et al have reported on a phase II Multimodal Intervention Exercise, Nutrition and Anti-Inflammatory medication in cachexia (pre-MENAC) versus standard care, showing that this intervention is feasible and safe in patients with incurable lung and pancreatic cancer and may have a positive effect on patients weight [23]. This multimodal approach was designed to address cachexia which is known to be a multidimensional condition [24], and therefore is expected to be a more suitable approach for cancer patients. The aim of this randomized controlled, open label pilot study was to assess the adherence to a Combined Exercise and Dietary Intervention (CEDI) in patients with GI cancer submitted to neo-adjuvant chemo(radio)therapy, in order to pursue other outcome associated studies in the future. Bearing in mind that compliance is a limiting factor to the benefit provided from exercise and diet, assessing adherence to these interventions is paramount before pursuing further studies

Methods

Study design and participants

A parallel randomized controlled, open label pilot trial was conducted. This trial is registred at CinicalTrials.gov: NCT05237921 and conforms to CONSORT guidelines for randomized controlled trials. Study protocol is available online www.clinicaltrials.gov. Recruitment was conducted at the Oncology center of Hospital Beatriz Ângelo and patients were consecutively selected by Oncologists during the weekly multidisciplinary meeting. Patients with esophageal, gastric, pancreatic and rectal cancer, were enrolled at diagnosis provided that they were eligible for neo-adjuvant chemo/radiotherapy (ChT) and with age higher than 18 years and lower than 80 years. Before enrollment initiation, besides upper gastrointestinal cancer (as initially planned for), we decided to also include patients with rectal cancer to have a broader view of adherence to CEDI in patients with gastrointestinal cancer under neo-adjuvant treatment, which is in line with the exploratory nature of this study.

Combined Dietary and Exercise Intervention arm

The intervention group received a supervised combined moderate aerobic and resistance training, once a week with duration of 40-60 minutes plus daily home exercise. All patients were evaluated in respect to their physical condition by a physical medicine and rehabilitation physician, and exercise was administered by a physiotherapist. Exercise was planned within a “slow and low“ approach and was personalized according to patients’ age and functional status. The first exercise session was dedicated to full patient evaluation in order to perceive patients individual tolerance and to educate in regard to home exercises. Most common exercises were aerobic exercises as 10-15 minutes of walking and resistance exercises as squatting with theraband around knees, shoulder flexor strengthening in standing using theraband and stretching. Educational written and illustrated materials as well as therabands were provided to each patient for home based exercise.

Besides exercise, the intervention group received a one-on-one nutritional counseling, by a senior and research Dietitian (SV). In the first visit a dietary plan was designed and one daily oral nutritional supplement (Forticare®, Nutricia) was given to meet the European Society of Parenteral and Enteral Nutrition (ESPEN) recommended intake of 25-30kcal/kg/day and 1-1.5g of protein/kg/day [25]. Also, patients were recommended to maintain a fat intake of 30% of total daily calories, with mostly being provided by monounsaturated fat. Patients were suggested to drink the supplements after exercise. All dietary plans were created with Nutrium® software, in order to obtain personalized dietary plan prescriptions that conveyed nutritional needs targets. Nutrium is a Portuguese software that allows rigorous dietary planning, since it enables the user to set energy and nutrient estimated requirements and to create dietary plans with nutritional composition information determined for Portuguese foodstuffs [26]. Written materials were given to patients and/or caregivers. Follow up visits took place every

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DOI:10.26502/jfsnr.2642-110000113

week during exercise. Total duration of the intervention was set at 8 weeks, although patients with longer neo-adjuvant treatments, namely patients with rectal cancer, maintained the intervention for a longer period of time, with a maximum of 12 weeks. Patients were recommended to maintain the dietary plan and exercise during the whole ChT treatment plan. Due to possible symptoms after ChT, namely nausea and vomiting, patients were asked to intensify compliance on the week preceding ChT when there is a higher probability that patients are less symptomatic. Whenever patients did not attend the weekly exercise activity, they were contacted to provide support and to assess if any diet or exercise adjustment was needed in order to maximize adherence.

Control arm- Standard care

Patients allocated to the control arm received standard care, in which patients were referred to the dietitian only when the attending physicians felt there was a need for dietary intervention. Whenever relevant, exercise was recommended but without personalized training program, according to our current practice.

Outcome measures

The primary outcome was intervention adherence, that was evaluated according to five criteria: 1) proportion of patients willing to engage in CEDI; 2) adherence to dietary plan, patients were considered adherent if they have met ≥ 75% of their calorie and protein estimated requirements; 3) adherence to oral nutritional supplements, one supplement per day was prescribed, and supplement intake ≥ 4 weeks was considered acceptable; 4) adherence to exercise, were attendance to the exercise class for at least 4 consecutive weeks was considered acceptable; 5) adherence to CEDI, patients were considered adherent if they were able to meet more than 75% of their calorie and protein estimated requirements/oral nutritional supplementation and adhered to exercise, approximately one month after initiation of CEDI. Dropout rates and reasons for leaving the study were also recorded. The secondary outcomes included change in weight, waist circumference, CT derived body composition and functional status assessed with hand grip strength, 6MWT and functional score of EORTC quality of life questionnaire. Measurements were conducted before and after neo-adjuvant treatment.

Sample size

Sample size per group was calculated bearing in mind that according to data form the World Health Organization, 14% of Portuguese adults are compliant to moderate exercise, and in our study adherence was set as compliance ≥ 50%. Considering a power of 0.80 and an α set at 0.05, 25 patients will be needed per group. A planned interim analysis was performed to substantiate preparation of further study protocols using CEDI, and results are reported in this paper.

Randomization

A table was created by a web based randomization system to allocate treatments, with an allocation ratio of 1:1. Stratified block randomization using random block size (2, 4 and 6) was conducted to allocate patients to standard care and to intervention with CEDI. Stratification was performed according to disease location. Patients eligible to enter the study were referred by Oncologists, and after obtaining consent, patients were enrolled in the study by researcher (SV), which was responsible for allocation consignment.

Procedures

Clinical data

Demographic and clinical data as age, gender, tumor site, histological type, TNM staging, ChT toxicity, overall survival were prospectively recorded and retrieved from electronic records. ChT toxicity was graded according to National Cancer Institute Common Toxicity Criteria. Dose-limiting toxicity (DLT) was defined as any grade 3/4 toxicity associated with physician-ordered dose reduction or termination of therapy and ChT delay. This data was collected by Oncologists. The most common neoadjuvant treatments were: FLOT (5-Fluorouracil, Folinic acid, Oxaliplatin, Docetaxel) for gastric, XELOX (Oxaliplatine and Capecitabine) followed by Capecitabine plus radiotherapy for rectal, Carboplatine/ Paclitaxel and radiotherapy for esophagus and FOLFIRINOX (5-Fluorouracil, Irinotecan and Oxaliplatin) for pancreatic cancer patients. Duration of neo-adjuvant therapies varied from 8 to 12 weeks.

Anthropometric measures and nutritional assessment

Anthropometric measures (AM) such as weight and height were obtained, and Body Mass Index was calculated. All AM were performed according to previously established protocols [27]. Patient Generated Subjective Global Assessment (PG-SGA) was conducted by an experienced dietitian and patients were classified as well nourished (SGA A), moderately or suspected of being malnourished (SGA B) or severely malnourished (SGA C). Assessments were conducted before and after neo-adjuvant treatments.

Body composition assessment

Cross-sectional imaging evaluation

Body composition analysis was conducted with Computed Tomography (CT) scan image analysis [5]. Images were selected at the third lumbar vertebra (L3) using a portal venous phase. CT scans were used opportunistically, as CT is performed at diagnosis and after neo-adjuvant treatment. Image thickness was 5mm and tube voltage was 100kv. Images were processed with Slice-o-Matic (Tomovison) and ABCS module that performs automatic segmentation of tissue cross-sectional areas, whereas posterior validation of

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image processing was done by the Radiologist, with manual corrections as necessary. Segmentation of tissue cross-sectional areas was conducted according to the following Hounsfield unit thresholds: -29 to 150 for skeletal muscle, -190 to -30 for subcutaneous and intramuscular adipose tissue, and -50 to -150 for visceral adipose tissue. Cross-sectional skeletal muscle, visceral fat, and subcutaneous fat was recorded in squared centimeters and mean muscle radiation attenuation in Hounsfield units. Skeletal muscle area (SMA) was normalized for stature to calculate the skeletal muscle index (SMI) - cm^2/m^2. Sarcopenia was defined as SMI lower than 41 cm^2/m^2 in women, lower than 43 cm^2/m^2 in men with body mass index (BMI) <25 Kg/m^2 and lower than 53 in men with BMI > 25 Kg/m^2 as described by Martin et al [5]. Visceral obesity was defined as visceral fat area >130cm^2 [28]. An inter-reliability analysis was conducted and variance coefficients computed for two duplicate CT scans was 0.32%, 1.09%, 0.39% and 4.04%, for skeletal muscle, visceral adipose tissue, subcutaneous adipose tissue and intramuscular adipose tissue areas, respectively.

Dietary Intake assessment

Dietary intake was assessed with a Semi-quantitative Food frequency questionnaire to estimate dietary intake of both the intervention and control group before and after neo-adjuvant therapy and 24h recalls to assess dietary intake of patients undergoing CEDI at every 2 weeks in order to estimate compliance to established dietary goals. The Semi-quantitative Food Frequency Questionnaire (FFQ) used was developed for the Portuguese population [29] and is designed to evaluate usual dietary intake. This questionnaire includes 86 commonly-eaten food or drinks and participants were asked to estimate the amount and frequency of intake of each food/drink according to frequency and amount at baseline and before surgery. Conversion of foodstuffs to nutrients was conducted with software Food Processor Plus (ESHA Research, Salem, Oregon) which has been adapted to the Portuguese commonly-eaten food or drinks. The 24h recall using a modified USDA five-pass method consists in 5 steps where the first is to list all foods consumed on the previous 24h. On the second step the interviewer asks about possible forgotten food items. In the third step the interviewer clarifies the time and occasion of the consumed foods and on the fourth step clarifies portion size [30]. Conversion of foodstuffs to nutrients was conducted with Nutrium® software which has been developed for the Portuguese population [26].

Functional status assessment

Performance Status was assessed with Eastern Cooperative Oncology Group Performance Status scale. According to these criteria patients are classified from grade 0 (fully active) to grade 4 (bedridden). Prior to initiation and after neo-adjuvant treatment a 6 min walk test (6MWT) was conducted by cardiopulmonary technicians blinded to the intervention groups, were walking distance and percentage of predicted normal values were recorded. Handgrip strength was measured with a dynamometer (JAMAR®) and measurements were recorded in kg. Handgrip strength was measured 3 times with the non-dominant arm according to manufacturer's instructions. Mean handgrip strength was analyzed with gender specific thresholds from the revised guidelines of the European Working Group on Sarcopenia in Older People (EWGSOP) (<27kg in men and <16kg in women) [31].

Patient Reported Outcome Measures

Quality of life was assessed before and after neo-adjuvant treatment with the European Organization for Research and Treatment of Cancer (EORTC) questionnaire. This questionnaire allows determination of functional, symptoms and overall quality of life score.

Statistical analysis

Adherence to CEDI was analyzed with an intention to treat approach, whereas anthropometric measures, body composition, functional status, quality of life and dietary intake were analyzed with a per protocol approach**.** Continuous variables were described as median and inter-quartile range, while categorical variables were expressed as frequency and percentage. Chi-square test or Fisher exact test were used to assess association between categorical variables. Differences in means from continuous variables were analyzed by t-test or Mann Whitney U test as appropriate, according to variables' adjustment to a normal distribution. Shapiro-Wilk test was used to test for normality. Effect size was computed with Cohen's d for t tests and r for Mann-Whitney U tests. Paired-samples t test or Wilcoxon Signed Rank Test were used to analyze longitudinal data within the control and intervention arm. Statistical analysis was conducted with R Studio Version 1.2.5042 software.

Results

Study population

From June 2018 to November 2019, 46 patients were screened resulting in 39 patients being randomly allocated either to the intervention (n=19) or to the control arm (n=20). All patients had indication for neo-adjuvant treatment. All patients had stages II/III disease, except for one patient randomly allocated to the intervention arm with gastric cancer and a single liver metastasis (stage IV disease) who was included since the patient was eligible for neo-adjuvant treatment. Figure 1 presents the trial profile and reasons for exclusion. A total of 32 patients completed follow up evaluations.

Baseline characteristics are shown on table 1. Patients in both groups were well matched in regard to age, sex, disease site, serum C-reactive protein, albumin and total proteins,

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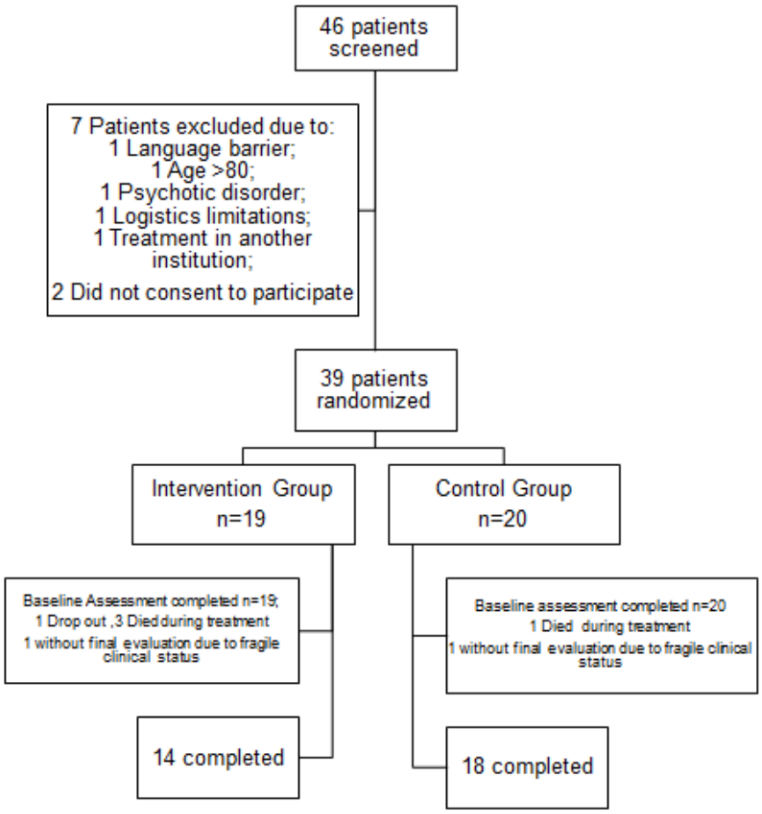

Figure 1: Trial profile

Body Mass Index (BMI), nutritional assessment (PG-SGA and CT-derived body composition), functional status (handgrip strength and 6 minute walking test), quality of life score and dietary intake. In regard to ECOG scale we found a higher proportion of patients with ECOG 0 in the control arm and a lower proportion of patients ECOG 2, than in the intervention arm (p=0.026).

Adherence analysis

Analysis was conducted for 19 patients that gave consent and completed baseline measurements. One patient dropped out on the second week of intervention because CEDI was viewed as an additional burden. During follow up 3 patients who entered CEDI, died and one refused to pursue further evaluations due to decline of performance status. In the control group 1 patient died and 1 patient refused to pursue further evaluations due to decline of performance status.

Adherence to estimated nutritional requirements

Globally, 17/19 (89.4%), 14/19 (73.6%) and 6/19 (31.5%) were able to meet a daily calorie intake above 50%, 75% and 100% of estimated total calorie daily requirements on at least one visit, respectively. In regard to protein intake, 17/19 (89.4%), 17/19 (89.4%) and 9/19 (47.3%) were able to meet a protein intake above 50%, 75% and 100% of estimated protein requirements, respectively. In regard to total fat intake, most patients were able to maintain fat intake within 25-30% of total calorie intake and 7/19 (36.8%) patients had a total fat intake exceeding 35% on at least one visit. As planned all patients had a monounsaturated fat intake above 30% of total fat intake on at least one visit. Details for each patient concerning percentage of nutritional requirements met are presented in figure S1 of supplementary material.

Adherence to oral nutritional supplements and exercise

A total of 13/19(68.4%) adhered to oral nutritional supplements and 13/19 (68.4%) to the exercise program. Patients that adhered to oral nutritional supplements (ONS) were found to have a significantly higher median daily calorie intake (ONS Adherent- 1781kcal/day, Interquartile Range (IQR)-633 vs. ONS non-Adherent- Median (Med)-1537kcal, IQR-332; p=0.022), but no difference in regard to protein intake (ONS Adherent-91g/day, IQR- 22 vs ONS non-Adherent-84g/day, IQR-25, p=0.707). Adherence to supplementation was not influenced by tumor location (esophagus-2/2(15.4%), gastric-6/8 (46.2%), pancreatic-1/2 (7.7%) and rectal-4/6 (30.8%); p=1). In regard to exercise, no differences were found in regard to daily calorie (Exercise Adherent: Med-1659kcal/day, IQR-452, Exercise non-Adherent: Med-1470kcal/day, IQR-319; p=0.208) and

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Table 1: Baseline characteristics. **Med**-Median; **IQR**-Interquartile Range; **PG-SGA**-Patient Generated Subjective Global Assessment; **ECOG**-Eastern Cooperative Oncology Group Performance Status scale; **CT**- Computed Tomography; **6MWT**-6 Minute Walking Test; **6MWT-% Predicted**-Percentage of predicted normal values; [a]Semi Quantitative Food Frequency questionnaire derived estimated daily calorie, protein, carbohydrates and fat intake for usual daily intake before disease.

	Intervention n=19				Control n=20				
	n	%	Med	IQR	n	%	Med	IQR	p
Age			64	9.5	20		64.5	19	0.978
Male	14	73.3			15	75			0.925
Disease Site									
Esophagus	2	10.5			1	5			0.899
Gastric	9	47.4			9	45			
Pancreas	2	10.5			3	15			
Rectum	6	31.6			7	35			
C-Reactive Protein			0.5	0.6			0.4	0.9	1
Albumin			4.2	0.5			4.1	0.7	0.67
Total proteins			6.8	0.8			6.7	1.1	0.665
Body Mass Index			24.9	6.5			26	5.8	0.737
Body Mass Index Categories									
Underweight	3	15.8				2	10		0.927
Normal weight	7	35				7	35		
Overweight	6	31.6				8	40		
Obese	3	15.8				3	15		
PG-SGA									
Suspected Malnutrition	6	31.6			11	55			0.324
Malnourished	2	10.5			1	5			
ECOG									0.026
0	8	42.1			12	60			
1	9	47.4			2	10			
2	2	10.5			6	30			
CT Body Composition									
Skeletal Muscle Area									
Male			158.5	32.5			166.1	20.3	0.679
Female			99.8	11.8			101	22	0.739
Skeletal Muscle Index									
Male			54.2	13.4			56.5	8.4	0.431
Female			41.5	7.8			41.6	8.9	0.828
Visceral Adipose Tissue									
Male			133.4	102.4			175.4	153.9	0.2
Female			83.1	65.8			91.9	64.8	0.904
Subcutaneous Adipose Tissue									
Male			98.6	113.2			112.5	81.3	0.538
Female			137.3	50.5			249.2	60.4	0.246
Total Adipose Tissue									
Male			274.7	200.9			342.5	182.9	0.238
Female			248.7	67.8			362.4	145.4	0.433
Intramuscle Adipose Tissue									
Male			9.1	5.6			9.7	5.7	0.92

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Female			9	6.7			16.2	8.3	0.109
Sarcopenia	4	23.5			3	21.4			0.889
Low Muscle Attenuation	8	47.1			6	42.9			0.815
Visceral Obesity	7	41.2			8	57.1			0.376
Sarcopenic Obesity	1	5.26			0	0			0.31
HandGrip Strength			33	18.5			29	14	0.713
Low HandGrip Strength	5	27.8			5	25			0.846
6MWT-Distance (m)			400	127.5			444	182	0.183
6MWT-% Predicted			76	21.2			81	24.9	0.326
Low 6MWT-Distance (m)	9	47.4			7	41.2			0.708
Quality of life Global			66.7	37.5			58.3	29.2	0.997
Calorie Intake (kcal)[a]			3847	1278			3208	1308	0.517
Calorie Intake (kcal/kg)[a]			55	26			47	25	0.158
Protein (g)[a]			159	59			131	59	0.515
Protein (g/kg)[a]			2.2	0.7			1.7	1.1	0.376
Carbohydrates (g)[a]			369	167			334	144	0.275
Carbohydrates (g/kg)[a]			5.3	1.5			4.9	1.5	0.289
Fat (g)[a]			172	71			131	60	0.463
Fat (g/kg)[a]			2.3	1.1			1.9	1.3	0.239

protein (Exercise Adherent: Med-91g/day, IQR-19, Exercise non-Adherent: Med-81g/day, IQR-25; p=0.593) intake. In respect to tumor location we found that all patients with gastric cancer adhered to exercise (1/2(7.7%) esophagus, gastric-8/8 (61.5%), pancreatic-0/2 (0.0%) and rectal-4/6 (30.8%) (p=0.02)).

Adherence to Combined Exercise and Dietary Intervention (CEDI)

At the second visit, approximately one month after CEDI initiation, 13/19 (68.4%) were able to meet more than 75% of their calorie and protein estimated requirements or maintained oral nutritional supplement intake and exercise for 1 month and thus were considered fully adherent to CEDI. Adhesion to all studied criteria is presented on figures 2 and 3.

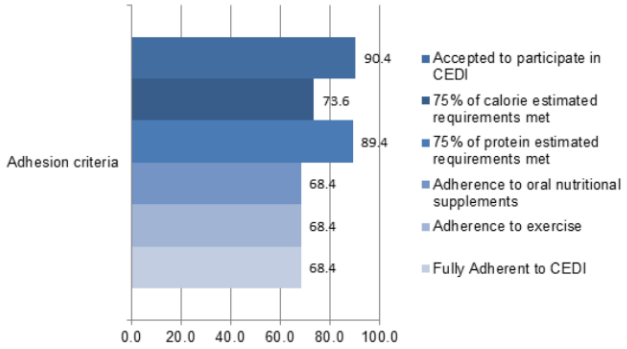

Figure 2: Adherence to Combined Exercise and Dietary Intervention: percentage of patients that accepted to participate in CEDI and patients who adhered to individual components such as 75% of estimated calories and protein requirements, oral nutritional supplements, exercise and fully adherent patients with 75% of calorie and protein estimated requirements met /maintained oral supplement intake and exercise after 1 month follow up.

Longitudinal analysis

CEDI vs. Control

Anthropometric, bioelectrical impedance, CT scan body composition measures, as well as grip strength, 5 minute walking distance, percentage of predicted normal values and quality of life score at baseline (before neo-adjuvant treatment) and at follow up (after neo-adjuvant treatment) are presented per trial arm on table 2. Further information regarding weight and CT-derived body composition change is available in figure S2 of supplementary material. Patients in the intervention arm were able to maintain weight during neo-adjuvant therapy, in contrast to patients in the control arm who lost a median weight of 3.34kg, which represents 5.10% of their initial weight. Similarly, patients in the intervention arm maintained waist circumference, whereas patients in the control arm lost a median 2.5 cm. In regard to CT scan derived body composition a near significant difference was found for skeletal muscle area, where patients in the control arm had a higher median loss of skeletal muscle area when compared with the intervention arm. In respect to visceral adipose tissue, we observed a significantly higher loss in the control group. There were no differences between study groups in bioelectrical impedance measurements. In regard to functional status, patients in the intervention group improved median walking distance and median percentage of predicted normal values from the 6 minute walking test. Also,

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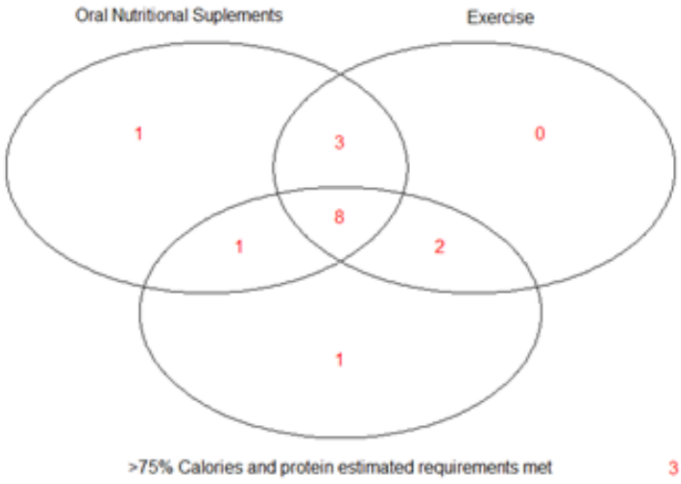

Figure 3: Venn diagram for the adherence to oral nutritional supplements, exercise and more than 75% of calorie and proteins estimated requirements met after 1 month of Combined Exercise and Dietary Intervention (CEDI) prescription.

Table 2: Anthropometric measures, bioelectrical impedance, computed tomography (CT) derived body composition, functional status and quality of life at baseline (before neoadjuvant treatment) and follow up (after neoadjuvant treatment). [a]Between group differences- 2-sample t test or Mann-Whitney U test; [b] Effect size computed with Cohen's d for t tests and r for Mann-Whitney U tests; **6MWT**-6 Minute Walking Test; **6MWT-% Predicted**-Percentage of predicted normal values.

		Intervention arm Median (IQR) n=19	Control arm Median (IQR) n=20	P[a]	Effect Size[b]
Anthropometric Measures					
Weight (kg)		n=14	n=18		
	Baseline	67.0 (18.4)	68.7(21.9)		
	Follow Up	72.5(17.0)	61.2(25.5)		
	Difference	0.05 (2.9)	-3.4 (6.3)		
	%Difference	0.062(4.5)	5.1(10.7)	**0.008**	**0.457**
Waist Circumference (cm)		n=14	n=18		**[0.44,0.46]**
	Baseline	91.0(14.5)	94.5(13.5)		
	Follow Up	96.0(11.5)	89.5(16.7)		
	Difference	0(4.5)	-2.5(9.5)	**0.028**	**-0.56** **[-1.08, -0.034]**
Bioelectrical impedance					
Fat Free Mass (kg)		n=13	n=16		
	Baseline	52.6(16.5)	53.9(23.4)		
	Follow Up	56.5(18.9)	49.8(21.7)		
	Difference	0.1 (1.8)	-0.70(3.9)	0.455	
Fat Mass (kg)		n=14	n=16		
	Baseline	17.10(6.0)	16.30(7.4)		
	Follow Up	15.20(7.2)	15.15(6.8)		
	Difference	1.80(5.2)	-0.75(4.9)	0.58	
Phase angle		n=13	n=16		
	Baseline	6.00(1.3)	6.30(1.1)		
	Follow Up	5.80(0.8)	5.25(1.8)		
	Difference	-0.60(1.1)	-0.6(0.8)	0.126	

Citation: Velho S, Moço S, Capitão C, Branco M, Costa L, Rodrigues S, Abreu C, Alves R, Pires F, Sousa P, Agostinho L, Cruz R, Clemente S, Borges A, Lopes F, Godinho J, Faria A, Teixeira JA, Passos Coelho JL, Maio R, Baracos VE, Cravo M. Adherence to Combined Exercise and Dietary Intervention in Patients with Gastrointestinal Cancer Undergoing Neo-Adjuvant Therapy: An Open-Label, Pilot, Randomized Controlled Trial. Journal of Food Science and Nutrition Research 5 (2022): 669-681.

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CT scan image analysis					
Skeletal Muscle tissue area (cm^2)		n=11	n=14		
	Baseline	151.3(56.0)	147.25(51.3)		
	Follow Up	153.6(32.4)	128.15(45.4)		
	Difference	-8.2(16.2)	-12.15(15.7)	**0.09**	**-0.79 [-1.77;0.18]**
Visceral adipose tissue area (cm^2)		n=11	n=14		
	Baseline	115.4(132.1)	141.50(136.7)		
	Follow Up	108.1(103.3)	107.(130.0)		
	Difference	-4.0(38.6)	-57.9(102.1)	**0.027**	**-1.1 [-2.10;-0.09]**
Subcutaneous adipose tissue area (cm^2)		n=11	n=14		
	Baseline	115.0(83.4)	123.0(83.4)		
	Follow Up	77.41(91.6)	141.85(150.3)		
	Difference	9.40(41.1)	-20.93(23.4)	0.5192	
Intra Muscular Adipose Tissue area (cm^2)		n=11	n=14		
	Baseline	9.0(4.0)	10.6(6.9)		
	Follow Up	11.3(4.3)	9.6(10.0)		
	Difference	1.5(3.1)	-0.5(4.6)	0.311	
Muscle Attenuation		n=11	n=14		
	Baseline	39.6(8.5)	37.6(10.3)		
	Follow Up	37.4(5.6)	37.4(13.9)		
	Difference	1.5(1.7)	0.12(3.2)	0.725	

functional score from quality of life questionnaire differed significantly between groups with a significant improvement for the intervention group. In respect to daily caloric and protein intake estimated with food frequency questionnaire, no differences were found between control and intervention arm in regard to the median difference before and after neo-adjuvant treatment (Calories-Intervention: Med:-1243, IQR: 1159 vs. Control: Med:-478, IQR:1216, p=0.483; Protein-Intervention: Med:-11, IQR: 69 vs. Control:Med:17, IQR:44, p=0.91).

Pairwise analysis-CEDI group

Patients in the intervention arm had a near significant skeletal muscle area loss (Baseline: Med: 151.30, IQR:56.0 vs. follow up: Med: 153.60, IQR:32.40, p=0.052), but probably clinically negligent, since they were able to improve significantly their 6MWT distance (Baseline:Med-400.0, IQR: 127.5; follow up: Med: 486.00, IQR:151.75, p=0.02), percentage of predicted normal value of 6MWT (Baseline:75.97, IQR: 21.24; follow up: Med: 89.54, IQR:23.07, p=0.08) and median functional score from quality of life questionnaire (Baseline:82.35, IQR:21.56; follow up: Med: 88.24, IQR:13.73, p=0.009). Improvement in symptoms was observed (intervention-Baseline: 18.8, IQR:30.3 ; follow up: Med: 9.09, IQR:12.12, p= 0.035).

Pairwise analysis-control group

Patients in the control arm had a significant reduction in in their median weight (Baseline:Med:68.7 (21.87), follow up: Med: 61.20 (25.55), p=0.017), waist circumference (Baseline: Med:94.5(13.5), follow up: Med:89.5, p=0.017), median skeletal muscle area (Baseline: Med: 147.25, IQR: 51.30 vs. follow up: Med: 128.15, IQR:51.30, p=0.0008) and visceral adipose tissue (Baseline: Med: 141.5, IQR: 136.67 vs. follow up: Med: 107.05, IQR:130.0, p=0.0097), as well as a near significant reduction in 6MWT distance (Baseline:444.0, IQR: 182.0; follow up: Med: 451.00, IQR:163.00, p=0.09). Also, there was a significant reduction in phase angle (baseline: Med: 6.30, IQR: 1.15 vs. follow up: Med: 5.29, IQR: 0.85, p=0.003). Improvement in symptoms was observed (Baseline:27.27, IQR:30.3; follow up: Med:18.18, IQR:18.18, p=0.010).

Chemotherapy toxicity and adverse events

A total of 20/39 (51.28%) experienced toxicity to neo-adjuvant treatment with no differences between groups (CEDI-8/19 (42.1%) vs. control-12/20 (60.0%); p=0.33). No between groups differences were found in regard to the percentage of patients that had to reduce dosage (CEDI-4/7 (57.1%); control-3/7 (42.9%), p=0.56), dose limiting toxicity

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DOI:10.26502/jfsnr.2642-110000113

(CEDI-2/4 (50.0%); control 2/4 (50.0%), p=0.92) or delay treatment (CEDI-1 (100%); control-0 (0%), p=0.28). There were 4 serious adverse events, 3 in the intervention and 1 in the control arm but none related to the intervention. Details regarding neo-adjuvant treatment can be found in table S1 of supplemental material.

Discussion

This open label randomized controlled trial demonstrated that a Combined Exercise and Dietary Intervention (CEDI) in patients with gastrointestinal cancer under neo-adjuvant treatment is feasible and has a reasonably high adherence. Also, CEDI patients were able to maintain their pre-treatment nutritional status and improve functional status. To our knowledge this is the first combined exercise and nutritional intervention program performed in cancer GI patients during neo-adjuvant treatment.

Recent studies have reported that adherence to behavioural interventions varies substantially, from 8 to 93% [23,32-34]. It is noteworthy that this high adhesion variability, may be attributed to heterogeneity in the type of intervention, namely the time of implementation (pre-treatment, post-treatment, survivors), aim (ex: weight loss in overweight survivors, nutritional status optimization preoperatively, implementation of specific dietary recommendations as high fiber diet, etc), duration, type (dietary intervention, supplements and exercise), disease stage, site and treatment, etc. Another challenge that further adds to the complexity of studying adherence rates is the inexistence of specific criteria to define optimal adherence, although some studies have defined an adherence equal or higher to 50% as acceptable [23]. In our study 68.4% of patients were fully adhered to CEDI, which we consider as reasonably high, comparing with previously reported adherence rates as low as 48% for oral nutritional supplements and 60% for exercise [23], and bearing in mind that these patients had locally advanced disease, were under neo-adjuvant treatment and therefore may be more symptomatic. This adhesion study was deemed by us as crucial, since adhesion rates are variable and we are aiming to pursue further studies to explore the influence of CEDI in patients under neo-adjuvant treatments, and thus it would be imprudent to tackle this issue before knowing if these patients were willing to participate in CEDI. Although cancer cachexia is known to impair anti-cancer treatments, cause distress in patients and families and decreased survival, it remains to date without standard care, and therefore strategies to deal with this condition are highly warranted [35]. During the past decades a multimodal intervention has been advocated, due to the existing knowledge that cancer cachexia is a multidimensional condition [22,36,37]. Still, further increasing the complexity is the uncertainty of the most appropriate endpoint regarding cancer cachexia, were besides weight, muscle mass quantity and quality, measures of function such as 6MWT, hand grip strength, quality of life and activities of daily living are at present considered equally or even more relevant [35]. When addressing multimodal interventions in cancer patients the MENAC study clearly stands out. Solheim T et al. [23] have reported on an intervention Exercise, Nutrition and Anti-Inflammatory medication in cachexia (pre-MENAC) versus standard care, conducted with patients with stage III/IV small cell lung cancer or inoperable pancreatic cancer with indication for ChT, showing a positive effect on weight. Indeed our results are consistent with those of MENAC, since patients in CEDI group were also able to maintain weight, and in addition we were able to show that these patients loose less muscle mass and improve functional status. In contrast, patients in the control arm lost skeletal muscle, visceral adipose tissue and worsened functional status. Visceral adipose tissue loss could seem like a positive characteristic of the control group, however it is important to note that 1) concomitant reduction of skeletal muscle and visceral adipose tissue is inherent to dietary restriction [38], meaning that these patients probably did not meet their nutritional requirements during treatment; 2) evidence supports a survival advantage for patients with higher content in skeletal muscle mass in obese patients with cancer [39], showing that muscle mass is presumably a key component. Still, this finding further supports the use of sophisticated and reliable body composition techniques for the optimization of dietary intervention, since besides calculating nutritional requirements with established calories and macronutrients per kg, body composition should also be considered in the estimation of nutritional requirements. Indeed we are aware that sample size is one of the limiting aspects of generalizability of results and cautious interpretation is therefore needed. The open label nature of our study design is also a limitation, but we did address this issue providing an intervention individualized for each patient, that would be difficult to mimic and all professionals involved except for Nutritionists and Physiotherapist were blinded to the study intervention.

Conclusions

Our study has allowed us to understand that CEDI is feasible, and that most patients are willing to participate even under neo-adjuvant ChT, resulting in potential benefits regarding nutritional and functional status. To our knowledge there are no studies evaluating intervention programs with the characteristics of CEDI in patients with gastrointestinal cancer undergoing neo-adjuvant treatment. We are aware that due to sample size interpretation of results should be conscious, however we feel that the encouraging results of this study are a starting point to pursue further well powered studies namely to investigate the role of CEDI in post-operatory complications, cancer cachexia and inflammation.

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Abbreviations

AM- Anthropometric measures

CEDI- Combined Exercise and Dietary Intervention

ChT- neo-adjuvant chemo/radiotherapy

CT- Computed Tomography

DLT- Dose-limiting toxicity

EF- Effect size

EORTC- European Organization for Research and Treatment of Cancer

EWGSOP- European Working Group on Sarcopenia in Older People

FFQ- Food Frequency Questionnaire

GI-Gastrointestinal

PG-SGA- Patient Generated Subjective Global Assessment

6MWT-6 min walk test

SMA- Skeletal muscle area

SMI- skeletal muscle index

Declarations

Ethics approval

Approval was obtained from the Scientific and Ethics Committee of Hospital de Santa Maria and Hospital Beatriz Ângelo, Portugal. The procedures used in the study adhere to the tenets of Declaration of Helsinki. Informed written consent was obtained from all individual participants included in the study. Clinical data was prospectively collected from electronic charts, however data was coded in order to maintain anonymity.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

Funding sources

No funds, grants, or other support was received.

Authors' contributions

MC,VB study conceptualization; SM, CC, MB, LC, FL, JG, AF collected data and created the study database; CA, FP, AB, SC, SR exercise intervention conceptualization and implementation; PS, LA, RC validation of computed tomography image analysis for body composition; SV nutritional intervention conceptualization and implementation; data analysis, original draft preparation; JAT, JLPC resources and review; RM, MC, VB supervision, review and editing.

Acknowledgements

The authors would like to thank Andre Santos, CEO of Nutrium, who provided access to Nutrium free of charge. The Oral Nutritional Supplements (Forticare®) were provided from Nutricia free of charge.

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Lower skeletal muscle attenuation and high visceral fat index are associated with complicated disease in patients with Crohn's disease: An exploratory study

Clinical Nutrition ESPEN xxx (2017) e1–e7

Contents lists available at ScienceDirect

Clinical Nutrition ESPEN

journal homepage: http://www.clinicalnutritionespen.com

Original article

Lower skeletal muscle attenuation and high visceral fat index are associated with complicated disease in patients with Crohn's disease: An exploratory study

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ARTICLE INFO

Article history:
Received 13 September 2016
Accepted 9 April 2017

SUMMARY

Background and aims: The prognostic value of body composition analysis in patients with Crohn's disease (CD) is poorly explored. The aims of the present study were to assess fat and skeletal muscle compartments including muscle radiation attenuation (MA) in patients with CD, and to analyze its predictive value to identify complicated phenotypes.

Methods: Seventy one patients with CD who have had an abdominal CT within one month of clinical, laboratory, and endoscopic evaluation were included. Skeletal muscle area (SMA) and index (SMI), visceral fat area (VFA) and index (VFI), subcutaneous fat area (SFA), and mean MA were measured using appropriate software. Sarcopenia, as defined by Martin's criteria was assessed. Montreal classification was used to characterize disease phenotype.

Results: Mean MA was lower in patients >40 years ($p = 0.001$), L2 ($p = 0.09$) and stricturing/penetrating disease ($p = 0.03$) whereas SMA and SMI were significantly lower in patients with positive C-reactive protein and previous hospital admissions ($p < 0.01$). On multivariate analysis, higher MA was protective against the complicated disease phenotype (stricturing/penetrating disease and/or previous surgeries) (OR 0.81; $p = 0.002$) whereas a high visceral fat index increased such risk (OR 26.1; $p = 0.02$). A ROC curve showed a 82.4% sensibility, 90.3% specificity, 17.6% positive predictive value, 9.7% negative predictive value and an area under the curve (AUC) of 0.91 for body composition analysis to predict complicated disease.

Conclusions: A lower muscle attenuation and a high visceral fat index seem to be associated with more severe phenotypes in patients with CD.

1. Introduction

In recent years, the relationships between body composition and clinical outcomes have been extensively studied in the field of oncology, facilitated by the advent of appropriate software applied to diagnostic imaging technologies such as computed tomography (CT). Body composition parameters such as sarcopenia, visceral obesity, and muscle infiltration by fat are now recognized as important prognostic factors predicting toxicity and response to chemotherapy, postoperative complications and even survival, more accurately than other variables classically associated to a better prognosis such as TNM stage [1–5].

Changes in body composition evaluated by various methods such as computed tomography, magnetic resonance or abdominal ultrasound, have also been described in Crohn's disease (CD), but their clinical significance and predictive value remain unclear [6,7]. Changes in mesenteric fat, also known as fat wrapping, have been recognized in patients with CD since its initial description [8].

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http://dx.doi.org/10.1016/j.clnesp.2017.04.005

Studies performed during the last decade show that increased body mass index in CD patients is associated with poorer prognosis, early need for surgery, higher risk of active disease and earlier loss of response to therapy [9–11]. Further supporting the active role of mesenteric fat in promoting intestinal inflammation, recent studies showed that visceral fat in patients with CD undergoing intestinal resection was associated with higher risk of postoperative complications and postoperative recurrence [6,12]. However, whether visceral fat accumulation is a consequence of long standing disease or a primary event involved in the pathogenesis of the disease is still unclear [13,14]. Sarcopenia (severe muscle depletion) has been shown to be highly prevalent in CD, possibly as a result of poor nutrition, uncontrolled inflammation, and physical inactivity among others [15], and to be associated with major postoperative complications. Treatment with anti-TNF was shown to reverse sarcopenia, further supporting the concept that it may represent a biomarker of chronic inflammation and wasting [16]. Finally, skeletal muscle radiation attenuation (MA) is a radiologic metric inversely related to muscle fat content [1]. A reduction in MA, mirroring excess fat deposition in the muscle tissue, has been described in several chronic inflammatory conditions such as obesity, type 2 diabetes, and in cancer patients [1], in whom it is associated with a poorer prognosis [2]. The value of these body composition variations, as markers of chronic inflammation and in predicting more severe phenotypes in patients with CD has not been previously tested. The aims of the present study were to perform a comprehensive description of the skeletal muscle and fat compartments in patients with CD, to analyze the recently described variable MA, and to explore possible associations of these body composition measurements with complicated phenotypes with the aim of assessing its potential use as early predictors of severe disease.

2. Materials and methods

2.1. Study population

The study protocol was approved by the Scientific and Ethics Committee of Hospital Beatriz Ângelo in Loures, Portugal. We retrospectively reviewed all the clinical records of CD patients followed in our clinic between 2012 and 2015. Patients were included if they had a computed tomography enterography (CTE) or computed tomography ordered as part of clinical workup within one month of full clinical, laboratorial and, whenever possible, endoscopic evaluation. Phenotypic characteristics retrospectively collected from charts included demographic data, age of disease onset, disease extension, and behavior according to Montreal classification [17], and previous therapies including surgery. Patients with a history of a stricturing (B2) or penetrating (B3) complication and/or previous resection surgery at any time point during their clinical course were considered as having a complicated phenotype. Laboratory values were abstracted from electronic charts. Anemia defined as a hemoglobin value lower than 12 g/dl for women or 13 g/dl in men. C-Reactive protein (CRP) was considered positive when higher than 0.5 mg/dl.

2.2. Cross-sectional imaging evaluation

CT scans were obtained and evaluated for body composition data by two investigators who were blinded to clinical and endoscopic data to ensure objective interpretation of image findings. Skeletal muscle and fat tissue cross-sectional areas were measured on CT images, at the level of the third lumbar vertebrae (L3) with the patient lying supine as shown in Fig. 1. Skeletal muscle area (SMA), visceral fat area (VFA) and subcutaneous fat area (SFA) were measured in square centimeters on the basis of the pixel count using appropriate software [2]. Briefly, muscle is annotated and is quantified within a Hounsfield unit (HU) ranging from −29 to 150; visceral fat ranges from −150 to −50 HU, and subcutaneous fat from −190 to −30 HU. Muscle radiation attenuation was calculated for muscle area from −190 to −30 HU. Skeletal muscle area (SMA) was normalized for stature to calculate the skeletal muscle index (SMI) – cm^2/m^2. Visceral Fat Index (VFI) was defined as the ratio of areas of visceral to subcutaneous fat. Sarcopenia was defined as SMI lower than 41 cm^2/m^2 in women, lower than 43 cm^2/m^2 in men with body mass index (BMI) < 25 kg/m^2 and <53 in men with BMI ≥ 25 kg/m^2 as described by Martin et al. [2] based on the International Consensus of Sarcopenia [18]. Visceral obesity was defined as visceral fat area > 130 cm^2 [19].

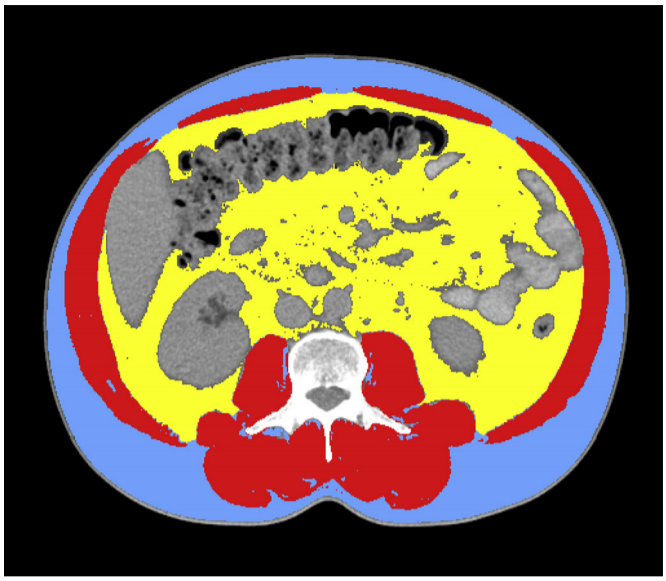

Fig. 1. Axial computed tomography (CT) images at the level of the third lumbar vertebrae were analyzed for muscle and fat tissue cross sectional areas and analyzed using an appropriate software. Muscle mass is shown in red and was quantified within a Hounsfield unit (HU) range of −29 to 150, visceral fat shown in yellow, range from −150 to −50 and subcutaneous fat shown in blue range from −190 to 30. Muscle radiation attenuation was calculated for muscle area.

2.3. Statistical analysis

Continuous variables were described as mean, median and range, while categorical variables were expressed as frequency and percentage. Differences in mean continuous variables and dichotomous variables were analyzed by *t*-test or Mann Whitney *U* test as appropriate, according to variable's adjustment to a normal distribution. Difference in mean continuous variables and categorical variables with more than two levels was conducted with One-way analysis of variance (ANOVA) or Kruskal–Wallis test, as appropriate. Chi-squared test and Fisher's Exact Test were used to explore associations between categorical variables. A p-value < 0.05 was considered statistically significant. Univariate logistic regression was first performed using complicated behavior (B1 vs B2 or B3 and/or previous resection surgery) as the dependent variable and clinically relevant factors as independent variables namely gender, age, disease duration and location, weight and BMI, skeletal muscle area, subcutaneous and visceral fat area, visceral obesity, mesenteric fat index, MA and sarcopenia, anemia and CRP positivity.

On multivariate analysis both manual and automatic variable selection methods were preformed. Hosmer and Lemeshow (HL) method was used for manual variable selection, and, as part of this method, a p-value cut-off of 0.25 on univariate analysis was used.

Please cite this article in press as: Cravo ML, et al., Lower skeletal muscle attenuation and high visceral fat index are associated with complicated disease in patients with Crohn's disease: An exploratory study, Clinical Nutrition ESPEN (2017), http://dx.doi.org/10.1016/j.clnesp.2017.04.005

Also an automatic variable selection with backward, forward and both stepwise regression was performed. In this analysis all predictors that were significant or clinically relevant were included. Three possible models were obtained: HL model, both stepwise (backward stepwise was identical to both stepwise) and forward stepwise. Finally, models were compared using Akaike Information Criteria (AIC), and the selected model had lowest AIC, which was the model obtained through both stepwise analysis and is presented in this paper. Receiver Operating Characteristic (ROC) curve was plotted for the selected model; sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and area under the curve were calculated. Statistical analysis was performed with Statistical Package for the Social Sciences (SPSS, IBM) and R software.

3. Results

3.1. Demographics and clinical features

Overall 71 patients fulfilled inclusion criteria and were reviewed. 18/89 CD patients were excluded because they did not have a CT scan with one month of clinical, laboratorial and endoscopic evaluation. Clinical and demographic data are shown in Table 1. CTE was ordered to evaluate disease extension in 37% patients with recently diagnosed disease, to rule out disease complications in 52%, and to evaluate response to therapy in the remaining 11% patients. Body composition data did not differ according to reason for performing CTE (data not shown).

3.2. Body composition

3.2.1. BMI, sarcopenia and visceral obesity

According to BMI, 11.3% of patients were underweight (BMI < 18.5 kg/m^2), 49.3% had a normal BMI, 28.2% were overweight and 11.3% were obese with a BMI equal or greater than 30 kg/m^2. Sarcopenia was observed in 31% patients, whereas visceral obesity was present in 28.2% of the total population. Sarcopenia was more frequently observed in patients with a BMI lower than 25 kg/m^2 (39%) as compared to those with BMI higher than 25 kg/m^2 (13.5%) ($p = 0.05$). Previously hospitalized patients were more frequently sarcopenic (39% vs 9%, $p = 0.014$). As expected, visceral obesity was more frequent in patients with BMI higher than 25 kg/m^2 (64.3% vs 4.7%, $p < 0.001$); also mean subcutaneous fat area (84.2 ± 57.3 vs 233.6 ± 100.6 cm^2; $p < 0.001$) and mean total fat area (127.3 ± 97.0 vs 396.8 ± 150.7 cm^2, $p < 0.001$) were higher in patients with BMI over 25 kg/m^2

Table 1
Clinical characteristics of patients included in the study.

N	71
Median age (years)	43
Male/female	36/35
Montreal classification	
A1/A2/A3	5/47/19
L2/L3/L3/+L4	27/7/37/3
B1/B2/B3/p	36/24/11/25
Duration of disease (years)	9.7 (0–32)
Smoking habits	
Yes/no/unknown	36/31/5
Previous surgery	
Yes/no	26/45
Previous hospital admission	
Yes/No	51/20
Recent corticosteroids	
Yes/no	8/63
Current medication	
5-ASA	22
Azathioprine	21
Biologics	2
Biologics + Azathioprine	5
Harvey-Bradshaw Index	
Remission	25
Mild disease	24
Moderate disease	21
Severe disease	1
Mean C-reactive protein (mg/dL)	4.0 ± 6.0
C-reactive protein	
Positive/negative	47/20
Mean hemoglobin (mg/dL)	12.5 ± 2.3
Anemia	
Yes/no	30/36
Endoscopic activity	
Yes/no	39/23

3.2.2. Sarcopenia and visceral obesity

Table 2 shows the associations between body composition parameters as measured by CT which evaluate skeletal muscle and visceral fat. SMA and SMI were significantly higher in patients with visceral obesity. In contrast, MA which is a negative prognostic factor, was lower in patients with visceral obesity (34.1 ± 9.0 vs 44.7 ± 9.2 HU; $p < 0.001$).

Table 3 shows values for body composition data according to demographics, clinical and biological variables. We observed significant direct correlation between fat areas and visceral fat index with aging, both for subcutaneous and visceral fat, as opposed to MA which decreased with age. SMA and SMI were not influenced by age, as opposed to gender with females exhibiting significantly lower skeletal muscle values. No significant associations were observed with duration of disease except for subcutaneous fat area for which a positive correlation was found. When we explored whether there were any associations with Montreal classification, we observed that patients diagnosed >40 years of age (A3) had a higher value for visceral fat area and visceral fat index whereas MA was significantly lower. In regards to disease location we also observed significant associations, with L2 patients exhibiting a distinct pattern of visceral fat distribution with higher VFI and lower MA although the latter did not reach statistical significance ($p = 0.09$). Patients with complicated phenotype (B2 or B3, and/or history of surgery), presented lower MA − 39.5 ± 9.4 vs 44 ± 10 HU, $p = 0.02$. Visceral obesity was more prevalent in patients with L2 disease (62.5% vs 27% in L1 and 21% in L3 patients − $p = 0.06$). We then used positive CRP and previous hospital admission as surrogate markers for disease activity and severity, respectively. When we compared patients with a positive CRP or with previous hospital admission, we observed that SMA and SMI were significantly lower (127 ± 33 vs 155 ± 35 cm^2, $p = 0.003$; 52 ± 8.6 vs 45.2 ± 9.9 cm^2/m^2, $p = 0.008$, respectively), as well as MA in previous hospitalized patients (45 ± 9.4 vs 40 ± 10 HU, $p = 0.047$). Visceral fat area, subcutaneous fat area and total fat area weren't associated to CRP or previous hospital admission. Also, no significant associations were observed between MA and endoscopic activity, Harvey Bradshaw index, or current medical treatment. However, patients on recent (one month or less) corticosteroid therapy had a lower MA as compared to non-steroid treated patients (33.8 ± 13.6 vs 42.7 ± 9.5 HU, $p = 0.056$), and more frequent visceral obesity (62.5% vs 23.8%, $p = 0.035$). Mean total fat area (217.9 ± 167.3 vs 356.8 ± 229.1 cm^2, $p = 0.098$) and mean subcutaneous fat area (220.5 ± 148.7 vs 133.3 ± 96.8 cm^2, $p = 0.1$) were higher for patients on recent corticosteroid therapy, although not statistically significant.

3.3. Model for complicated disease incorporating body composition parameters

We performed multiple logistic regression analysis to assess the prognostic value of these body composition variables in predicting our primary outcome – complicated disease: B2 or B3 disease and/

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Table 2
Associations between sarcopenia and visceral obesity and parameters of body composition as measured by CT.

	Sarcopenia			Visceral obesity		
	No ($n = 49$)	Yes ($n = 22$)	p-Value	No ($n = 51$)	Yes ($n = 20$)	p-Value
Skeletal muscle area (cm^2)	150.1 ± 32.0	102.5 ± 101.2	<0.001	127.7 ± 29.2	154.9 ± 44.7	0.019
Skeletal muscle index (cm^2/m^2)	51.9 ± 7.9	36.6 ± 4.8	<0.001	44.8 ± 8.8	53.1 ± 10.7	<0.001
Subcutaneous fat area (cm^2)	153.3 ± 104.4	120.4 ± 109.0	0.132	105.4 ± 79.0	239.4 ± 107.5	<0.001
Visceral fat area (cm^2)	105.0 ± 101.1	58 ± 72.9	0.055	37.2 ± 35.0	226.4 ± 57.1	<0.001
Visceral fat index	0.66 ± 0.53	0.47 ± 0.48	0.896	0.40 ± 0.33	1.1 ± 0.54	<0.001
Muscle attenuation (HU)	42.35 ± 9.1	40.3 ± 12.6	0.105	44.7 ± 9.2	34.1 ± 9.0	<0.001

HU – Hounsfield unit.

Table 3
Association between body composition data and demographics, clinical and biological variables.[a]

	Skeletal muscle area	Skeletal muscle index	Subcutaneous fat area	Visceral fat area	Visceral fat index	Muscle attenuation
Age (years)	NS	NS	$R = 0.46$; $p = 0.000$	$R = 0.58$; $p = 0.000$	$R = 0.44$; $p = 0.000$	$R = -0.67$; $p = 0.000$
Gender						
Female	107.8 ± 16.4	41.1 ± 6.6	NS	NS	NS	NS
Male	162.1 ± 29	53.0 ± 9.2				
	$p = 0.000$	$p = 0.000$				
Duration of disease (years)	NS	NS	$R = 0.36$	NS	NS	NS
			$p = 0.002$			
Age of onset						
A1 (<16)	NS	NS	NS	89 ± 85	0.56 ± 0.60	46 ± 5
A2 (17–40)				64 ± 85	0.46 ± 0.45	44 ± 9.7
A3 (>40)				156 ± 92	0.96 ± 0.50	34 ± 9.2
				$p = 0.001$	$p = 0.002$	$p = 0.001$
Location						
L1	NS	NS	NS	154 ± 72	0.71 ± 0.51	43.3 ± 8.3
L2				70 ± 90	1.02 ± 0.66	32.1 ± 14.4
L3				130 ± 69	0.44 ± 0.43	42.6 ± 9.6
				$p = 0.02$	$p = 0.009$	$p = 0.09$
C-reactive protein (mg/dL)						
<0.5	151.9 ± 39	52.6 ± 11.1	NS	NS	NS	NS
≥0.5	127 ± 30	44.3 ± 8.1				
	$p = 0.007$	$p = 0.001$				
Previous hospitalization						
No	155 ± 35	52 ± 8.6	NS	NS	NS	45 ± 9.4
Yes	127 ± 33	45.2 ± 9.9				40 ± 10
	$p = 0.003$	$p = 0.008$				$p = 0.047$

[a] Association between body composition measurements and age and disease duration are presented as coefficient of correlation and p-value, whereas age of onset and location variables, CRP lower or higher than 0.5 mg/dL and previous hospitalizations are presented as mean ± standard deviation and p-value; NS – non-significant.

or previous resection surgeries. As shown in Table 4, on univariate analysis we observed that anemia was associated with complicated phenotypes (OR 5.2; 95% CI 1.7–18.3; $p = 0.0005$). On multivariate analysis the selected model included MA, disease location, visceral fat index and anemia. We observed that a higher MA (continuous variable) was a protective factor for complicated phenotypes (OR 0.81; 95% CI 0.70–0.91; $p = 0.002$). Isolated colonic disease was associated with a decreased risk of complicated disease (OR 0.03; 95% CI 0.001–0.45; $p = 0.02$). A high visceral fat index was associated with increased risk of complicated phenotype (OR 26.1; 95% CI 2.0–754; $p = 0.02$). Anemia remained as a significant risk factor for complicated phenotype (OR 36; 95% CI 5.6–418.3; $p = 0.0007$) after adjusting for MA, disease site, and visceral obesity and CRP. Positive CRP was associated with a reduced risk of complicated phenotypes (OR 0.075; 95% CI 0.006–0.49; $p = 0.015$). The reason for this protective effect is not apparent but we may hypothesize that when a complication like stricture or fistula is present there is no longer active inflammation but mostly fibrosis which is not associated with increased CPR. A ROC curve was plotted for the previous model showing a 82.4% sensibility, 90.3% specificity, 17.6 PPV, 9.7% NPV and an AUC of 0.91 (Fig. 2) for predicting complicated disease.

4. Discussion

Herein we have assessed the prevalence of sarcopenia, visceral obesity and muscle attenuation in patients with CD, and its associations with complicated phenotypes. Changes in body composition have been reported in patients with Crohn's disease as compared to controls, but the methods used are various and the clinical significance of these changes remains unclear. A recently published study [20] showed that body composition evaluation using CT imaging correlates strongly with DXA analysis which is the gold standard method to evaluate body composition. Also, the recently described MA can only be assessed in CT scans. In the present study, we observed that 1) sarcopenia was highly prevalent even in overweight CD patients, 2) and more prevalent in patients with prior history of hospitalization, 3) and that a reduction in MA (reflecting increased deposition of fat in the skeletal muscle) and an increase in VFI were positively associated with more complicated phenotypes. A model using these body composition parameters showed a AUC value of 0.91 to predict complicated disease (B2/B3 phenotypes and/or previous surgery). These results are in line with those obtained by Erhayiem et al. [21] although the latter did not

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Table 4
Univariate and multivariate logistic analysis with disease behavior as dependent variable.[a]

Disease behavior, B2 + B3 vs B1	Univariate analysis			Multivariate analysis		
	OR	95% CI	*p*-Value	OR	95% CI	*p*-Value
Age	1.02	0.99–1.06	0.089	Excl.		
Gender						
Female	1.00			Excl		
Male	1.05	0.41–2.69	0.904	Excl		
Weight	0.98	0.94–1.01	0.229	Excl.		
Body mass index (kg/m^2)	0.96	0.86–1.06	0.434	Excl		
Disease duration	1.03	0.98–1.09	0.166	1.2	1.07–1.40	0.004
Disease localization						
L1	1.00		0.134	1.00		
L2	0.45	0.06–2.42		0.03	0.001–0.45	0.023
L3 + L4	2.0	0.72–5.65		1.86	0.33–8.72	0.53
Skeletal muscle area	0.99	0.97–1.00	0.304	Excl		
Skeletal muscle index	0.99	0.94–1.03	0.623	Excl		
Visceral fat area	0.99	0.99–1.00	0.508	0.97	0.94–0.98	0.005
Visceral fat index	1.28	0.52–3.25	0.583	26.1	2.0–754.0	0.026
Subcutaneous fat area	0.99	0.99–1.00	0.477	Excl		
Muscle attenuation	0.96	0.91–1.00	0.081	0.81	0.70–0.91	0.002
Visceral obesity			0.129	Excl		
No	1.00					
Yes	0.44	0.14–1.2				
Sarcopenia			0.553	Excl		
No	1.00					
Yes	1.35	0.49–3.78				
Anemia			0.027			
No	1.00			1.00		
Yes	3.2	1.13–10.1		36.3	5.6–418.3	0.007
C-reactive protein			0.282			
Negative	1.00			1.00		
Positive	0.56	0.18–1.60		0.08	0.006–0.49	0.01

[a] OR – odds ratio; 95% CI – 95% confidence interval; Excl – excluded; NI – not included.

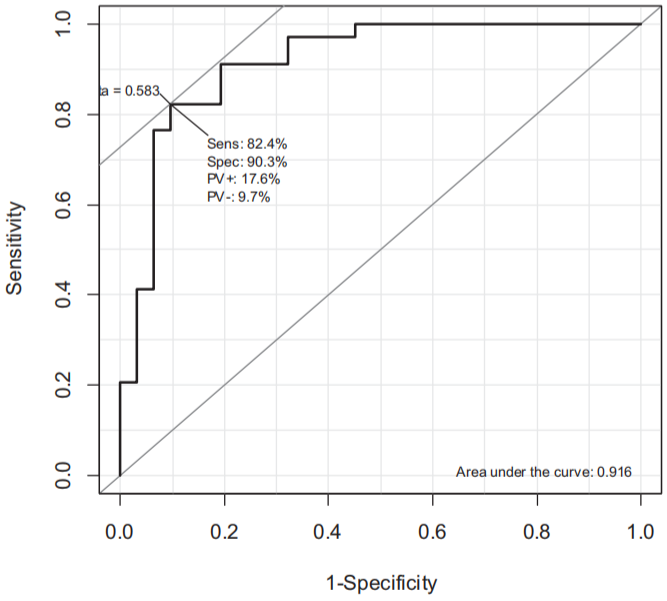

Fig. 2. Receiver operating characteristic (ROC) curve for model assessment. Multivariate logistic regression model; dependent variable: B2 or B3 phenotype and/or previous resection surgery; independent variables: disease duration and location, muscle attenuation, visceral fat area, visceral fat index, anemia and positive C-reactive protein. Sens – Sensitivity; Spec – Specificity; PV+ – Positive predictive value; PV– – Negative predictive value.

measure skeletal muscle area or index nor did they measure muscle attenuation. In our study we found that SMA and SMI were significantly lower in patients with positive CRP and previous hospital admissions reflecting patients with a more chronic and protracted course of disease.

Although we used the cutoff points to identify sarcopenia [2] validated in cancer patients, which might not be adequate to estimate sarcopenia in CD patients [22], we believe our findings strengthen the concept that in the era of obesity we cannot draw any conclusions about the nutritional status of CD patients based on weight only. More importantly, we also observed that patients with visceral obesity were the ones who had higher SMA and SMI but lower MA. This is different from the sarcopenic obesity described in certain cancer sub-populations [2] where expansion of visceral fat is associated with depletion of skeletal muscle, both reflecting a more inflammatory and catabolic setting. Our observations are consistent with the hypothesis that, by contrast to cancer patients, in CD, excess of visceral fat may not be the result of a chronic inflammatory process as it is not associated to depletion of skeletal muscle, but rather constitute a primary process in disease pathogenesis. This is further supported by the lack of association found between visceral fat or MA and disease duration. Furthermore, in our multivariate model, adjusted for age, MA was still predictive of complicated phenotypes. The only fat compartment which was found to increase with duration of disease was subcutaneous fat which plays no specific role in chronic inflammation as cytokine production profiles differ between subcutaneous and visceral fat [23].

Interestingly, we also observed significant associations between visceral fat area, visceral fat index and MA and Montreal characteristics such as age of disease onset, disease location and behavior. Specifically, lower MA, reflecting infiltration of muscle by fat, was associated with complicated disease, raising the possibility whether this parameter could be used to predict disease severity and progression. As opposed to visceral fat parameters which correlated with disease characteristics, SMA and SMI and index were significantly lower in patients with positive CRP and previous hospital admissions which certainly reflect patients with

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a more chronic and protracted course of disease. MA was also lower in previous hospitalized patients probably identifying more wasted patients.

Previous studies in CD patients found that mesenteric fat hypertrophy could be present at disease presentation and be a primary event involved in disease pathogenesis [24,25]. Most available data suggest that mesenteric fat promotes intestinal inflammation, with some studies linking expansion of visceral fat with more aggressive phenotypes, earlier need of surgery and poor response to therapy [6,9–11]. These observations are not consistent across all studies with some observations favoring the hypothesis that mesenteric fat may constitute a host response, a mean of containing inflammation and decreasing the risk of fistula formation [26]. Simultaneously, decrease of skeletal muscle mass has been shown to exist in the majority of patients with CD [15] but to our knowledge, no previous study has simultaneously evaluated both body compartments. These changes in body composition are most probably related to each other and the stimuli responsible for expansion of mesenteric fat could be the ones which promote wasting of skeletal muscle and/or increased infiltration of skeletal muscle by fat tissue – muscle attenuation .

Lower MA has been shown to be an important prognostic factor in cancer patients [1] although the mechanism whereby this contributes to worsen the prognosis remains to be clarified. To our knowledge this is the first study showing that a lower MA might also represent a negative prognostic factor in CD. In contrast to disease location which tends to remain quite stable over years, disease behavior changes over the years with the majority of patients being diagnosed as an inflammatory phenotype (B1) but some of these moving into more complicated phenotypes such as B2/B3. Numerous attempts have been made to identify early predictors of complicated phenotypes in order to select patients who could benefit from early aggressive therapy. Although our data needs to be confirmed in future prospective and longitudinal studies, low MA in patients with a recent diagnosis of CD could be a predictive biomarker of increased risk to progress into complicated phenotypes, which could benefit from the early institution of more effective therapies. In our institution, CT is often performed as the first cross-sectional imaging investigation to map disease extent in adult patients, since it is prone to less artifacts and more accessible, and therefore this could be a tool used to predict disease behavior in CD at diagnosis. Due to radiation exposure, there is a tendency to replace it by MRI but, with the available technology, it is not possible to measure MA using MRI.

This study has several limitations namely the heterogeneity of the study population and the fact that CT was not performed in all patients upon diagnosis. Although in the present study we did not find any association with current medical therapy, except for recent corticosteroid intake, we cannot exclude that changes in body composition observed were not primary but secondary to disease evolution and/or therapies performed. However, if we only included patients with recently diagnosed CD where CT was being performed as part of the initial staging process, we could not explore possible associations with complicated phenotypes which, in most patients, develop with 5–10 years. Another limitation is the small number of patients included in the present study. However, this exploratory study enabled us to identify possible biomarkers of body composition with a potential prognostic value.

In conclusion, this is the first study where a significant association between fat and fat-free compartments and Cohn's disease phenotype according to Montreal classification was found. We identified that body composition, namely lower MA and increased visceral obesity were associated with complicated disease. We believe that these findings together indicate that the systematic assessment of body composition parameters may have a predictive value in identifying patients who will develop complicated phenotypes. Body composition analysis can be made using CT scans ordered as part of routine clinical care in patients with Crohn's disease. Prospective multicenter studies are needed to confirm the findings of this study and assess the utility of these parameters to predict disease behavior and act as a prognostic tool for patients with CD.

Statement of authorship

Marília Cravo participated in the study design, execution of study, interpretation of data and drafting of manuscript; Sónia Velho participated in the study design, collected nutrition data, performed body composition and statistical analysis; Joana Torres performed critical review of the final version; Maria Pia Costa Santos and Carolina Palmela were responsible for reviewing electronic charts and collecting all clinical data; Rita Cruz and João Strecht selected CT scans images for body composition analysis; Rui Maio participated in the study design and critical review of manuscript; Vickie Baracos participated in the study design, supplied software to analyze body composition, critical review and approval of final version.

Conflict of interest statement

The authors report no conflict of interest.

Funding sources

No funding was needed.

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BODY COMPOSITION AND CROHN'S DISEASE BEHAVIOR: IS ADIPOSITY THE MAIN GAME CHANGER?

Nutrition 108 (2023) 111959

Contents lists available at ScienceDirect

Nutrition

journal homepage: www.nutritionjrnl.com

Applied nutritional investigation

Body composition and Crohn's disease behavior: Is adiposity the main game changer?

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ARTICLE INFO

Article History:
Received 10 June 2022
Received in revised form 17 December 2022
Accepted 24 December 2022

Keywords:
Body composition
Total fat
Visceral obesity
Crohn disease behavior
Abdominal surgery

ABSTRACT

Objective: We investigated the association between body composition upon diagnosis and complicated phenotypes and time until surgery in patients with Crohn's disease (CD).
Methods: We conducted a retrospective cohort study including patients with CD who had a computed tomography enterography or a magnetic resonance enterography performed ≤6 mo of diagnosis. Skeletal muscle and visceral and subcutaneous adipose tissue cross-sectional areas were determined with computed tomography or magnetic resonance images at the third lumbar vertebral level, processed with the sliceOmatic (TomoVison, Magog, QC, Canada) and ABACS plugin.
Results: We included 63 patients: 33 (52%) men, median age 35 y. Disease location (L) and behavior (B) according to the Montreal classification were L1 (ileal disease) = 28 (44%), L2 (colonic disease) = 13 (21%), L3 (ileocolonic disease) = 18 (28%), L1 + L4 (ileal and isolated upper disease) = 1 (2%), L3 + L4 (ileocolonic and isolated upper disease) = 3 (5%), B1 (non-stricturing) = 39 (62%), B2 (stricturing) = 11 (17%), and B3 (penetrating)= 13 (21%); 20 (32%) patients had perianal disease. Visceral obesity was present in 12 (19%) patients and was associated with higher age of CD onset (median 60 versus 34 y; $P = 0.002$) and complicated disease behavior (B2 and B3) (66.7% versus 31.7%; $P = 0.021$). After adjusting for age and perianal disease, total adipose tissue was associated with a 4% increase in the odds of complicated behavior per 10 cm^2 of total adipose tissue (odds ratio [OR] = 1.004; 95% confidence interval [CI], 1.00–1.008; $P = 0.043$). Median follow-up time was 3.35 y, during which 15 (24%) of patients underwent abdominal surgery. Visceral obesity was associated with 5.10-times higher risk of abdominal surgery (95% CI, 1.52–17.09; $P = 0.008$); after adjusting for disease behavior, visceral obesity maintained a near-significant association with a 2.90-times higher risk of surgery (95% CI, 0.83–10.08; $P = 0.09$).
Conclusion: Total fat was associated with complicated disease phenotype and visceral obesity, with higher risk of abdominal surgery and shorter time until surgery.

Introduction

Crohn's disease (CD) is a chronic and relapsing disease, characterized by a discontinuous and transmural inflammatory process, affecting the entire gastrointestinal tract [1] with extraintestinal manifestations and associated immune disorders [2]. Mesenteric fat wrapping is considered a hallmark of CD and has been recognized as a key feature since its initial description. Recent research has suggested that obesity, visceral fat, and in particular mesenteric fat may be involved in the pathogenesis and course of CD [1].

Body composition analysis with computed tomography (CT) has been recently validated in CD patients, and this technique has accurately predicted fat mass, fat-free mass, and appendicular skeletal muscle by processing a single CT slice [3]. Magnetic resonance

Sónia Velho and Bárbara Morão contributed to this work equally.

This research was partially co-financed by Hospital da Luz Lisboa under the initiative "Luz Investigação" in the context of the Group GENIUS (reference: LH.INV. F2019015).

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https://doi.org/10.1016/j.nut.2022.111959
0899-9007/

imaging (MRI) has also been validated using dual-energy x-ray absorptiometry as the gold standard and had a high correlation with CT scan–derived measurements [4]. Body composition assessment with these sophisticated techniques is highly warranted, because these are more informative than commonly used anthropometric measures, such as body mass index (BMI), which is known to be a poor predictor of body composition abnormalities, such as sarcopenia [5,6], visceral obesity [7], and sarcopenic obesity [8].

Noticeably, compared with BMI, visceral adiposity derived from imaging techniques, such as CT scan and MRI, has been more constantly related to intestinal bowel disease (IBD) outcomes. Indeed, in CD, visceral fat or its mesenteric fat component has been associated with unfavorable therapeutic outcomes, such as complicated disease [9,10], increased risk of postoperative complications after elective ileocolectomy [11], higher postoperative recurrence after ileocolic resection [12], and higher risk of surgery and penetrating disease [13] and has been determined as an independent risk factor for endoscopic recurrence [14].

Although the link between excess adiposity and CD is still not completely understood, several plausible biological mechanisms have been proposed. Adipose tissue is both a storage and an endocrine organ that is able to release a number of adipokines, such as adiponectin, interleukin (IL)-1, IL-6, IL-8, interferon-γ, tumor necrosis factor α, leptin, apelin, chemerin, and resistin [1]. The expanding adipose tissue is known to release proinflammatory cytokines, such as tumor necrosis factor α, IL-6, and IL-8 (CXCL8), and inflammatory ligands like lipopolysaccharide, which activate Toll-like receptors and consequently nuclear factor κB, further fueling inflammation [15].

In a previous study [10], we observed that excess of visceral fat was associated with structuring and penetrating phenotypes. Whether this excess of fat was previous to or a consequence of chronic inflammation could not be clarified, because body composition measures were not performed on diagnosis. In the present study, all measurements of body composition were made ≤6 month of diagnosis, and we sought to analyze the association between body composition and outcome, namely disease phenotype and time, until abdominal surgery. Furthermore, we compared longitudinal body composition evolution between baseline matched patients with favorable outcomes (Fos) and unfavorable outcomes (Uos).

Materials and methods

Study population

The study protocol was approved by the scientific and ethics committee of the Hospital Beatriz Ângelo in Loures, Portugal. Clinical records of patients with an incident diagnosis of CD in our clinic between January 2012 and June 2017 were retrospectively reviewed. Patients were included if they had either CT enterography or magnetic resonance enterography as part of a clinical workup ≤6 mo of diagnosis, which included clinical, laboratory, and endoscopic evaluation. Phenotypic characteristics were retrospectively collected from charts, including demographic data, age of disease onset, disease extension, and behavior (B), according to the Montreal classification [16]. Complicated disease phenotype was defined as B2 (stricturing) or B3 (penetrating) phenotype, according to the Montreal classification. Time until abdominal surgery was defined in years between diagnosis and abdominal surgery. Therapies prescribed, response and disease evolution, hospital admission, surgery, and postoperative complications were also recorded. Laboratory values were abstracted from electronic charts. Anemia was defined as a hemoglobin value <12 g/dL for women or <13 g/dL in men. C-reactive protein values were also registered.

Cross-sectional imaging evaluation

CT scans or MRIs at diagnosis and follow-up were obtained and processed for body composition analysis by one investigator blinded to clinical and endoscopic data to ensure objective interpretation of image findings. Images were selected by radiologists at the third lumbar vertebra using a portal venous phase and processed with the sliceOmatic (TomoVison, Magog, QC, Canada) and ABACS plugin that perform an automatic segmentation of tissue cross-sectional areas of CT scans; MRIs were segmented manually. Posterior validation of image processing was done by a nutritionist and radiologist, with manual corrections as necessary. Image thickness was 5 mm and tube voltage was 100 kV. Segmentation of tissue cross-sectional areas was conducted according to the following Hounsfield unit thresholds: −29 to 150 for skeletal muscle, −190 to −30 for subcutaneous and intramuscular adipose tissue, and −50 to −150 for visceral adipose tissue. Cross-sectional skeletal muscle, visceral fat, and subcutaneous fat were recorded in square centimeters and mean muscle radiation attenuation in Hounsfield units. Skeletal muscle area was normalized for stature to calculate the skeletal muscle index (SMI) in square centimeters per square meters. Sarcopenia was defined as SMI <41 cm^2/m^2 in women and as <43 cm^2/m^2 in men with BMI <25 kg/m^2 and as <53 kg/m^2 in men with BMI ≥25 kg/m^2, as described by Martin et al [5] based on an international consensus of sarcopenia [17]. Visceral obesity was defined as visceral fat area ≥80.1 cm^2 for women and ≥163.8 cm^2 for men [18]. An inter-reliability analysis was conducted, and variance coefficients computed for two duplicate CT scans were 1.2%, 1.9%, and 4.2%, for skeletal muscle, visceral adipose tissue, and subcutaneous adipose tissue, respectively.

Statistical analysis

Continuous variables were described as mean, median, and interquartile range (IQR), while categorical variables are expressed as frequency and percentage. Differences in mean continuous variables and dichotomous variables were analyzed by *t* test or Mann-Whitney *U* test as appropriate, according to variable's adjustment to a normal distribution. A χ^2 test and Fisher exact test were used to explore associations between categorical variables. $P < 0.05$ was set as statistically significant.

Simple logistic regression was be performed do analyze the relationship between dependent variables, such as complicated behavior (B1, non-stricturing versus B2, stricturing or B3, penetrating) and relevant clinical and body composition variables. Multiple logistic regression was performed using variables clinically relevant and/or with $P < 0.25$ in simple logistic regression. Time until abdominal surgery was analyzed with Kaplan-Meier survival curves, and a multiple proportional hazards Cox model was also adjusted.

In the longitudinal analysis of body composition and its association with clinical outcome, a composite end point was used to define Favorable Outcomes (FO) or Unfavorable Outcomes (UO), which comprised the following components: abdominal surgery, therapy intensification, and complicated disease phenotype at follow-up. The differences between baseline and follow-up body composition cross-sectional areas were computed and outcome group comparisons were performed. Statistical analysis was performed with Posit software.

Results

Demographic characteristics and clinical features

Overall, 72 patients fulfilled inclusion criteria and were reviewed; 9 of 72 patients were excluded because of a missing CT scan (6 patients) or MRIs with artifact (3 patients). Clinical and demographic data are listed in Table 1.

Body mass index and body composition

According to BMI classification, 17 of 63 (26.9%) were underweight (BMI <20 kg/m^2), 31 of 63 (49.2%) had normal weight, and 15 of 63 (23.8%) were overweight or obese; 12 of 63 (19%) presented with visceral obesity; 32 of 63 (50.8%) were sarcopenic; and 5 of 63 (7.9%) had sarcopenic obesity. A Venn diagram presenting body composition phenotypes can be viewed in Figure 1. Results from the analysis of the association between BMI, body composition, and sex are presented in Table 2. Sarcopenia was more prevalent among women (22 of 30 [73.3%] versus 10 of 33 [30.3%] men; $P < 0.001$); accordingly, median SMI was higher for men (median = 48.07 [IQR = 12.46] versus median for women = 37.50 [IQR = 9.63]; $P < 0.001$). No other significant associations were found between sex and body composition.

Associations between disease characteristics and body composition are presented in Table 3. Sarcopenia was found significantly

Table 1
Clinical characteristics of patients included in the study

N	63
Median age /IQR	35/22.5
Male/female	33/30
Montreal classification	
A1/A2/A3	5/34/24
L1/L2/L3/ L1 + L4/L3 + L4	29/13/21/1/3
B1/B2/B3	39/11/13
Perianal disease	
Yes/no	20/43
Median duration of disease /IQR	3.35/4.19
Smoking habits	
Yes/no/ex-smoker	21/36/6
Surgery after diagnosis	
Yes/no	25/38
Corticosteroids	
Yes/no	17/46
Medication	
Azathioprine	42
Biologics	31
C-reactive protein	
Positive/negative	45/8
Median hemoglobin /IQR	13.4/2.8
Anemia	
Yes/no	18/38
Endoscopic activity	
Yes/no	10/45

IQR, interquartile range;A, Age at diagnosis; A1,< OR=16; A2, 17-19; A3> or=40; L, Location; L1, ileal; L2, colonic, L3, ileocolonic, L4, isolated upper disease; B, Behavior; B1, non-stricturing, B2, stricturing, B3, penetrating.

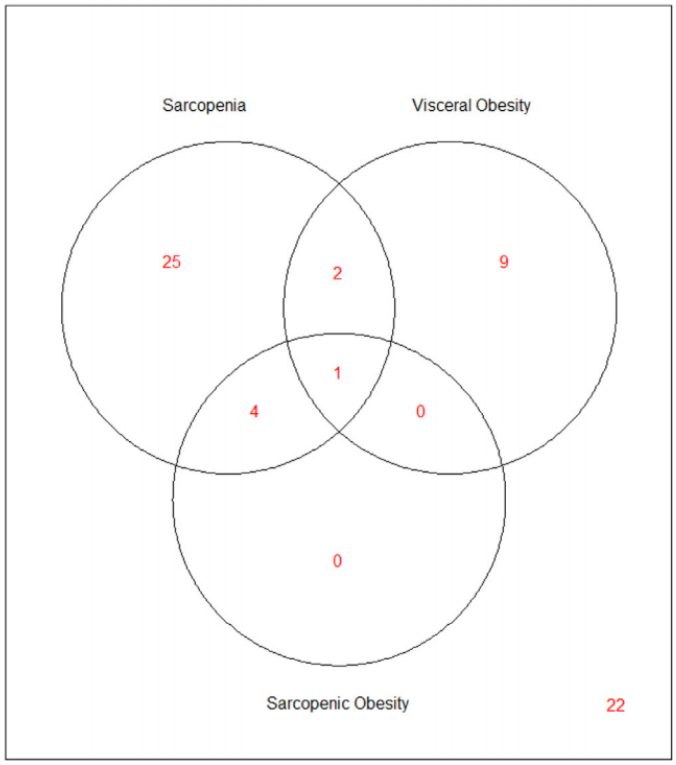

Fig. 1. Venn diagram of body composition phenotypes: sarcopenia, visceral obesity, and sarcopenic obesity.

associated with ileocolonic disease location (14 sarcopenic [66.6%] versus 7 non sarcopenic [33.4%] of 21 patients with ileocolonic disease location; $P = 0.054$) and anemia, because the number of sarcopenic patients with anemia was almost three-fold the number of non-sarcopenic patients with anemia (13 sarcopenic [72.2%] versus 5 non-sarcopenic [22.8%] of 18 patients with anemia; $P = 0.035$). Visceral obesity was associated with older age of onset in both continuous (median = 59.5 [IQR = 16.5] versus median = 34.0 [IQR = 21.0]; $P = 0.002$) and categorized form (9 of 12 [75%] patients with visceral obesity were age >40; $P = 0.021$) and also with complicated disease phenotype, where 8 of 12 (66.7%) patients with visceral obesity and 16 of 51 (31.7%) patients without visceral obesity had complicated disease phenotype ($P = 0.021$).

Clinical and body composition features associated with complicated phenotype at diagnosis

According to results obtained with simple logistic regression, age at diagnosis was associated with a 3% increase in the odds of complicated disease per year (OR = 1.03; 95% confidence interval [CI], 1.00–1.06; $P = 0.05$). In regard to body composition, visceral obesity was associated with a ~4-times higher risk of complicated phenotype compared with patients without visceral obesity (OR = 4.37; 95% CI, 1.19–18.44; $P = 0.03$). Likewise, total adipose tissue was associated with a 4% increase in the odds of complicated disease per 10 units of total adipose tissue (OR = 1.004; 95% CI,

Table 2
Body mass index and body composition at diagnosis

Body Mass Index and Body Composition Variables	Total	Values* (*N* = 63)		
		Women *n* = 30	Men *n* = 33	*P* value
Body mass index (kg/m^2)	21.97 (5.07)	22.66 (5.08)	21.80 (4.63)	0.316
Body mass index categories				
<20.0	17 (26.9)	7 (23.3)	10 (30.3)	0.288
20.0–24.9	31 (49.2)	15 (50.0)	16 (48.5)	
25.0–29.9	12 (19.0)	5 (16.7)	7 (21.2)	
≥30	3 (4.8)	3 (10.0)	0	
SMI (cm^2/m^2)	42.9 (13.5)	37.50 (9.63)	48.07 (12.46)	< 0.001
Visceral fat index (cm^2/m^2)	12.11 (33.49)	11.07 (17.19)	18.36 (42.25)	0.270
Subcutaneous fat index (cm^2/m^2)	38.72 (41.15)	61.12 (61.21)	30.44 (26.84)	0.0008
Total fat (cm^2)	168.58 (227.24)	176.86 (243.89)	157.21 (219.71)	0.362
Muscle radiation attenuation (HU)	46.88 (17.72)	44.64 (14.53)	49.99 (19.91)	0.640
VFA:SMA ratio	0.31 (0.62)	0.31 (0.51)	0.46 (0.83)	0.656
Visceral obesity	12 (19.0)	5 (16.7)	7 (21.2)	0.646
Sarcopenia	32 (50.8)	22 (73.3)	10 (30.3)	< 0.001
Sarcopenic obesity	5 (7.9)	4 (13.3)	1 (3)	0.130

HU, Hounsfield units; SMI, skeletal muscle index; VFA:SMA, visceral fat area–to–skeletal muscle area
*Results are expressed as number (percentage) or median (interquartile range).

Table 3
Association between body composition phenotypes and demographic characteristics and clinical and biological variables

Variables	Sarcopenia Yes (n = 32)	No (n = 31)	P	Visceral obesity Yes (n = 12)	No (n = 51)	P
Age (y)	34 (22.75)	39 (30.0)	0.119	59.5 (16.5)	34.0 (21.0)	0.0002
Age of onset (y)						
A1 (<16)	3 (9.4)	2 (6.5)	0.51	0 (0)	5 (9.8)	0.012
A2 (17–40)	19 (59.4)	15 (48.4)		3 (25.0)	31 (60.8)	
A3 (>40)	10 (31.2)	14 (45.2)		9 (75.0)	15 (29.4)	
Location						
L1	10 (31.2)	19 (61.3)	0.054	7 (58.3)	22 (43.1)	0.634
L2	8 (25.0)	5 (16.1)		2 (16.7)	11 (21.6)	
L3	14 (43.8)	7 (22.6)		3 (25.0)	18 (35.3)	
Phenotype						
B1	19 (59.4)	20 (64.4)	0.672	4 (33.3)	35 (68.6)	0.029
B2	5 (15.6)	6 (19.4)		5 (41.7)	6 (11.8)	
B3	8 (25.0)	5 (16.1)		3 (25.0)	10 (19.6)	
Perianal disease						
No	22 (68.8)	21 (67.7)	0.931	9 (75.0)	34 (66.7)	0.57
Yes	10 (31.2)	10 (32.3)		3 (25.0)	17 (33.3)	
C-reactive protein (mg/dL)						
<0.5	4 (14.3)	4 (16.0)	0.51	1 (12.5)	7 (15.6)	0.82
≥0.5	24 (85.7)	21 (84.0)		7 (87.5)	38 (84.4)	
Anemia						
No	16 (55.2)	22 (81.5)	0.035	9 (81.8)	16 (35.4)	0.268
Yes	13 (44.8)	5 (18.5)		2 (18.2)	29 (64.4)	
Hospitalization after diagnosis						
No	15(46.9)	17 (54.8)	0.527	5 (41.7)	27 (52.9)	0.482
Yes	17 (53.1)	14 (45.2)		7 (58.3)	24 (47.1)	

Results expressed as number(percentage) or median (IQR); A, Age at diagnosis; A1,< OR=16; A2, 17-19; A3> or=40; B, Behavior; B1, non-stricturing, B2, stricturing, B3, penetrating.L1, ileal; L2, colonic; L3, ileocolonic,

1.001–1.008; P = 0.006). It is noteworthy that other significant associations were found for other continuous variables concerning body composition, such as visceral adipose tissue area (OR = 1.007; 95% CI, 1.00–1.014; P = 0.0242) and index (OR = 1.02; 95% CI, 1.00–1.04; P = 0.0244), subcutaneous adipose tissue area (OR = 1.006; 95% CI, 1.00–1.01; P = 0.0247), and total fat–to–skeletal muscle ratio (OR = 1.67; 95% CI, 1.27–2.66; P = 0.016). On the other hand, non-significant associations were found for sex (women: OR = 0.28; 95% CI, 0.06–1.03; P = 0.075), disease location (L) (L2: OR = 0.37; 95% CI, 0.07–1.50; P = 0.188 and L3: OR = 0.75; 95% CI, 0.24–2.36; P = 0.634), corticosteroid therapy (OR = 0.59; 95% CI, 0.16–1.88; P = 0.391) sarcopenia (OR = 1.24; 95% CI, 0.44–3.49; P = 0.675), and skeletal muscle area (OR = 1.00, 95% CI, 0.98–1.01; P = 0.95) and SMI (OR = 1.00; 95% CI, 0.94–1.05; P = 0.988).

On multiple logistic regression (Table 4), we included all variables with $P \leq 0.05$ and limited the number of variables selected to avoid model overfiting. Thus, regarding body composition, we decided to use only total fat in the final model, because all other significant variables are accounted for in total fat, which means that including others would be redundant, and also because total fat was substantially more significant. In order to account for between biological sex variability, we mean-centered total fat per sex. After adjusting for age and perianal disease, total fat remained statistically significant and was associated with a 4% increase in the odds of complicated disease per 10 units of total adipose tissue (OR = 1.004; 95% CI, 1.00–1.008; P = 0.043). According to the receiver operating characteristic curve analysis, this model had a fair ability of discriminating complicated disease phenotype, with an area under the curve of 0.728, sensitivity of 70.8, specificity of 69.2, positive predicted value of 20.6, and negative predictive value of 41.4 (Fig. 2).

Time until surgery and body composition

Estimated mean time until surgery was 2.57 y. According to Kaplan-Meier curve comparison, disease phenotype (B1,non-stricturing = 7.49, B2,stricturing = 3.16, and B3, penetrating = 4.00; $P <$ 0.0001) and visceral obesity (yes = 4.13 versus no = 6.16; P = 0.0035) were associated with time until abdominal surgery (Figs. 3 and 4). Non-significant variables included Montreal age of onset (A) (A1, ages $\leq$ 16 = 6.91, A2, 17-19 = 6.34, and A3≥40y = 5.32; P = 0.22), Montreal L (L1 (ileal disease) = 5.62, L2 (colonic disease) = 7.10, and L3 (ileocolonic) = 5.99; P = 0.4), corticosteroids (yes = 6.41 and no = 5.93; P = 0.58), and sarcopenia (yes = 6.09 and no = 5.83; P = 0.79), whereas a near-significant association was found for perianal disease (yes = 7.20 and no = 5.35; P = 0.05) and sarcopenic obesity (yes = 4.13 and no = 6.16; P = 0.09). Table 5 presents restricted mean time to abdominal surgery and results from simple and multiple proportional hazards Cox models. For a matter of simplicity, only statistically significant results are presented in Table 5; non-significant variables included Montreal A (A2: hazard ratio [HR] = 1.50; 95% CI, 0.18–12.39; P = 0.70 and A3: HR = 3.55; 95% CI, 0.41–30.68; P = 0.24), Montreal L (L2: HR = 0.25; 95% CI, 0.03–2.07; P = 0.202 and L3: HR = 0.85; 95% CI, 0.29–2.4; P = 0.77), corticosteroids (HR = 0.71; 95% CI, 0.218–2.32; P = 0.575), sarcopenia (HR = 0.87; 95% CI, 0.31–2.42; P = 0.787), and sarcopenic obesity (HR = 2.91; 95% CI, 0.80–10.53; P = 0.103); and a near-significant association was found for perianal disease (HR = 0.25; 95% CI, 0.05–1.12; P = 0.07). Patients with B2 and B3 phenotype had 18- and 12-times higher risk of abdominal surgery compared with B1, respectively. In regard to body composition, patients with visceral obesity presented with a 5-times higher risk of abdominal surgery compared with patients without visceral obesity.

Table 4
Results from simple and multiple logistic regression form the analysis of predictive factors associated with disease phenotype

	Disease phenotype		Simple logistic regression			Multiple logistic regression		
Variables	B1 (n = 39)	B2/B3 (n = 24)	OR	95% CI	P	OR	95% CI	P
Age at diagnosis (y)	34 (24)	41.5 (31.25)	1.03	1.00–1.06	0.05	1.004	0.11–3.49	0.576
Age (y)								
≥25	26	21	1.00					
<25	13	3	0.28	0.06–1.03	0.075			
Sex								
Male	20	13	1.00					
Female	19	11	1.12	0.40–3.41	0.824			
Disease location								
L1	16	13	1.00					
L2	10	3	0.37	0.07–1.50	0.188			
L3/L4	13	8	0.75	0.24–2.36	0.634			
Perianal disease								
Yes	23	20	1.00			1.00		
No	16	4	0.28	0.07–0.93	0.05	0.40	0.09–1.52	0.195
Body composition								
Sarcopenia								
No	20	11	1.00					
Yes	19	13	1.24	0.44–3.49	0.675			
Low muscle radiation attenuation								
No	28	13	1.00					
Yes	4	5	2.69	0.62–12.53	0.1867			
Visceral obesity								
No	35	16	1.00					
Yes	4	8	4.37	1.19–18.44	0.030			
Total adipose tissue	129.06 (156.95)	261.31 (295.05)	1.004	1.001–1.008	0.0066	1.004	1.00–1.008	0.043

Results expressed as number or median (IQR). L, Location; L1, ileal; L2, colonic, L3, ileocolonic, L4, isolated upper disease; CI, confidence interval; OR, odds ratio

Furthermore, a proportional hazards Cox model was defined, including variables with $P < 0.25$ in simple analysis or deemed as clinically relevant, namely perianal disease, disease phenotype, and visceral obesity. However, after stepwise variable selection, only disease phenotype and visceral obesity remained in the final model. In this model, visceral obesity maintained a near-significant association with a risk of surgery 2.90-times higher in patients with visceral obesity compared with patients without visceral obesity, after adjusting for disease phenotype.

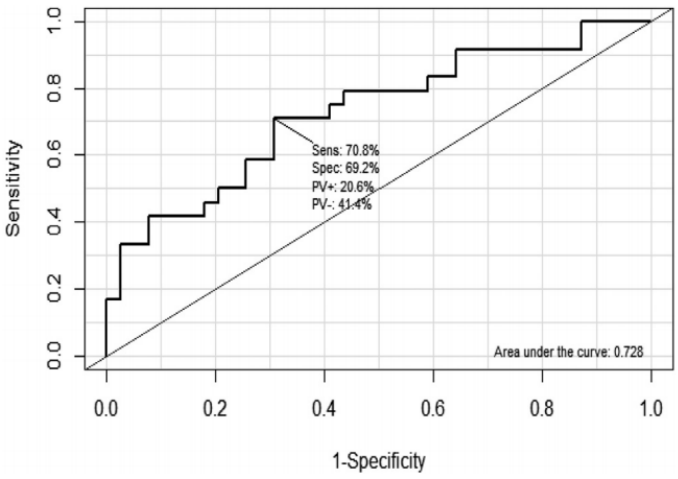

Fig. 2. Receiver operating characteristic curve for complicated disease phenotype as the dependent variable and age at diagnosis, perianal disease, and mean centered total adipose tissue per sex (n = 63). Sens, sensitivity; Spec, specificity; PV+, positive predictive value; PV−, negative predictive value.

Body composition evolution and outcome

In a subset of 30 patients, we were able to obtain information regarding body composition at follow-up, with a median follow-up of 3.29 y. FOs and UO was defined with a composite end point, which included the following components: abdominal surgery, treatment intensification, and complicated disease phenotype at follow-up; 19 of 30 were categorized as having an UO and were compared with 11 of 30 who had an FO. At baseline, patients with FO and UO were well matched in regard to Montreal classification, perianal disease, age and sex, and corticosteroid therapy (data not shown). In regard to treatment during follow-up period, the UO group had more frequently azathioprine medication (FO = 5 [22.7%] versus OU = 17 [77.3%]; P = 0.008) and biological therapy (FO = 4 [23.5%] versus UO = 13 [76.5%]; P = 0.09).

Patients with UO had a significantly higher increase of skeletal muscle (median difference = 12.20; IQR = 16.45 versus median = 7.9; IQR = 10.8; P = 0.0005), subcutaneous adipose tissue (median = 47.48; IQR = 108.10 versus median = 24.80; IQR = 57.71; P = 0.005) and total adipose tissue (median = 114.03; IQR = 154.40 versus median = 27.57; IQR = 136.21; P = 0.034), whereas a near-significant P value was obtained for visceral adipose tissue (median = 23.84; IQR = 64.77 versus median = 1.16; IQR = 42.87; P = 0.1) compared with patients with FO.

Discussion

Herein, we have assessed the association between body composition on diagnosis in patients with CD and disease outcome, such as complicated phenotypes and time until abdominal surgery. We found that total fat is independently associated with complicated disease phenotypes (B2, stricturing and B3 penetrating) independently of age

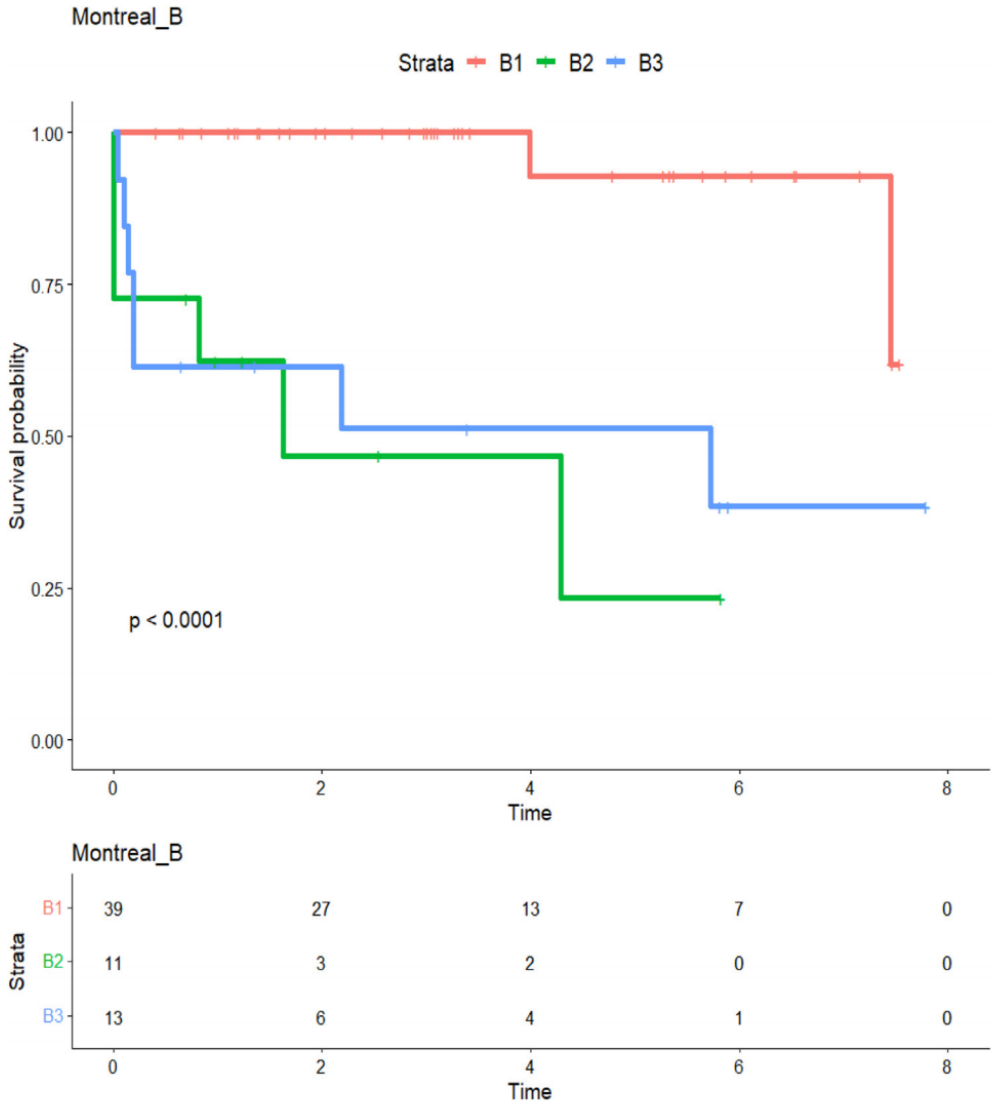

Fig. 3. Kapla-Meier curves for time until abdominal surgery and disease phenotype.

and perianal disease; visceral fat seems to be present at diagnosis and is the only body composition compartment that comes near to a significant association with time until abdominal surgery, when adjusted for disease phenotype. Moreover, patients with UO had an almost 4-times increase in the amount of total body fat from baseline until follow-up, compared with patients with FO.

The association between body composition and disease phenotype is in line with the results from a previous study conducted by our group, in which lower muscle attenuation and high visceral fat index were associated with more severe phenotypes in patients with CD. However, in our previous study, body composition was not measured on diagnosis, which did not allow drawing conclusions on whether these changes were causes or consequences of these complicated phenotypes. In the present study, we found that visceral obesity and more significantly total fat area were associated with complicated disease phenotype. In the present study, we were not able to explore muscle radiation attenuation, because, besides CT scans, we also used MRIs and, in these images, muscle radiation attenuation cannot be measured. Nevertheless, we included total fat, which may in fact be even more important. Previous studies focused on the association between the visceral fat–to–subcutaneous fat ratio and disease phenotype with contradictory results [9,19]. These were smaller studies and did not assess the association between total fat and disease phenotype. To our knowledge this is the first study analyzing the association between total fat derived from sophisticated body composition techniques, such as CT or MRI, and disease phenotype.

In our study, a near-significant association was found for visceral obesity and time until abdominal surgery, which means patients with visceral obesity may need earlier surgery. This result is concordant with a recent study, where patients with both high visceral fat–to–subcutaneous fat and sarcopenia had the highest probability of surgery [20] and, in another study, where both sarcopenia and visceral obesity were associated with the occurrence of abdominal surgery [21]. It is worth pointing out that in our study population, only 3 patients presented both visceral obesity and sarcopenia and were all included in the visceral obesity group.

Furthermore, in longitudinal analysis of body composition, patients with UO had a significantly higher increase in skeletal muscle, visceral adipose tissue, subcutaneous adipose tissue, and total adipose tissue. Although this may seem a paradox, because skeletal muscle did increase in patients with UO, interpretation of this result should be done, considering that in these patients we also observed a significant and concomitant increase in adipose tissue. Patients with UO had an increase of total body fat >4-times the increase of body fat in patients with FO, whereas we observed

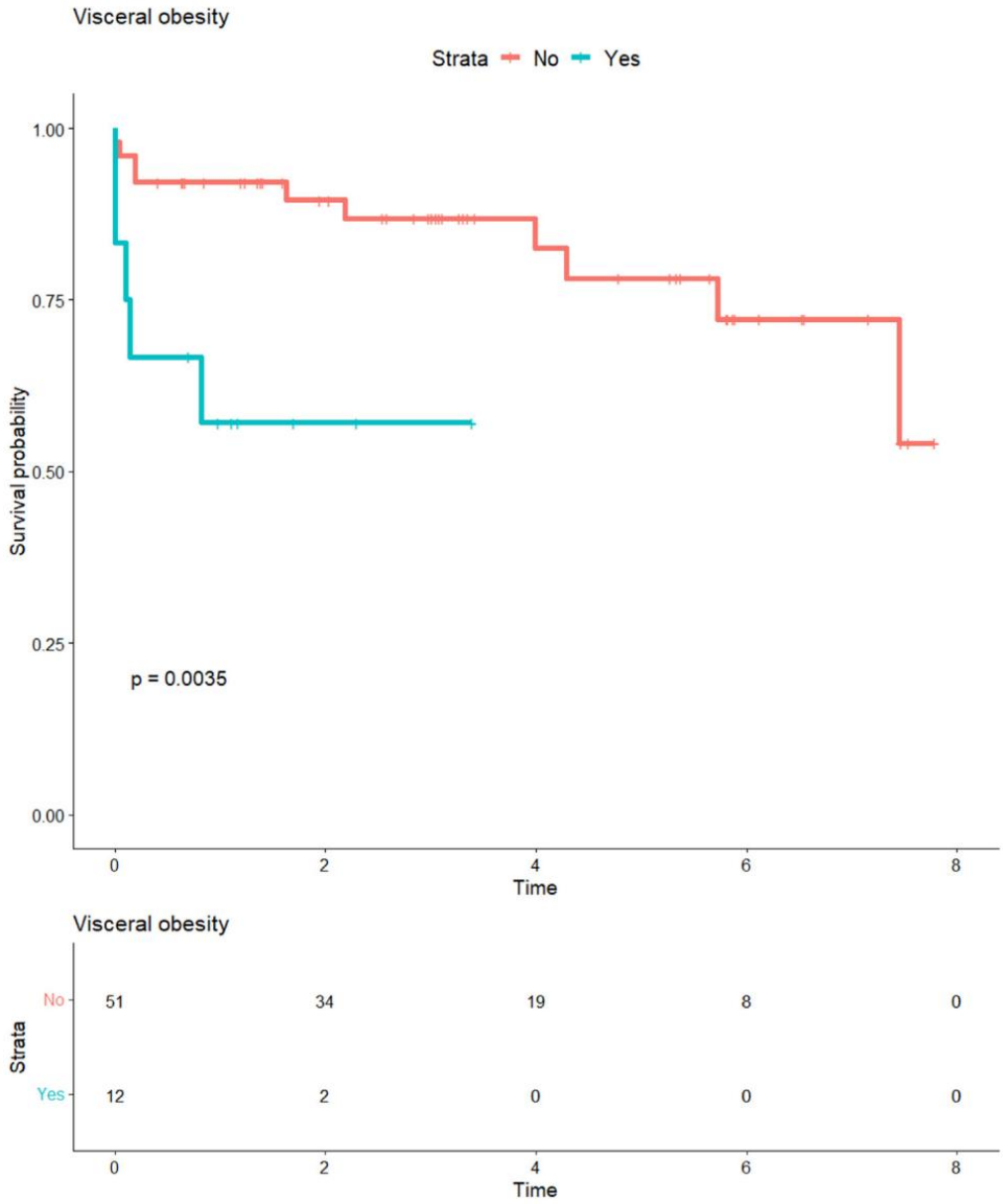

Fig. 4. Kaplan-Meier curves for time until abdominal surgery and visceral obesity.

a more modest increase in skeletal muscle. In the natural process of weight gain, skeletal muscle development may occur to support extra weight resulting from the expanding fat mass [22]. However, we believe that the proinflammatory environment, because of an increase in adipokines released by the expanding adipose tissue, may hinder the supposed beneficial effect of skeletal muscle

Table 5
Mean time to abdominal surgery and simple and multiple proportional hazards Cox model

Variables	*n*	Abdominal surgery	Restricted Mean time to surgery (y)	Simple analysis					Multiple analysis				
				Coef	SE	HR	95% CI	*P*	Coef	SE	HR	95% CI	*P*
Perianal disease													
No	43	13	5.35			1.00			Excluded				
Yes	20	2	7.20	−1.37	0.76	0.52	0.05–1.12	0.07					
Montreal classification													
B1	39	2	7.41			1.00					1.00		
B2	11	6	3.16	2.89	0.82	18.04	3.50–91.10	0.0005	2.67	0.84	14.50	2.76–76.02	0.001
B3	13	7	4.00	2.48	0.80	12.01	2.48–58.12	0.002	2.39	0.80	10.99	2.26–53.46	0.003
Visceral obesity													
No	51	10	6.37			1.00					1.00		
Yes	12	5	4.35	1.62	0.61	5.10	1.52–17.09	0.008	1.06	0.63	290	0.83–10.08	0.09
C statistics									0.865				

CI, confidence interval; Coef, coefficient; HR, hazard ratio; B, Behavior; B1, non-stricturing, B2, stricturing, B3, penetrating.

increase. Indeed, the prevalence of obesity and overweight measured with BMI has increased in CD patients and has been associated with both CD etiology and worse disease course [1], thus supporting the hypothesis that total body fat may have an effect on CD outcome.

There are two major types of adipose tissue, white adipose tissue and brown adipose tissue. Beige adipose tissue may be considered a third type, identified in recent years. Brown adipose tissue is located in the neck and interscapular region and has been considered a heat-producing tissue mostly associated with maintaining body temperature of newborns; however, brown adipose tissue has also been recognized in adults, and its role in obesity treatment through energy dissipation as heat has been hypothesized [23]. Beige adipose tissue may be present within white adipose tissue and supraclavicular location and consists of adipocytes with thermogenic proprieties, because like brown adipose tissue, beige adipose tissue has numerous mitochondria [23]. White adipose tissue comprises visceral adipose tissue and subcutaneous adipose tissue, which are known to have distinct metabolic and immunologic profiles. In particular, visceral obesity has been associated with higher inflammatory potential. In particular, mesenteric fat deposition leads to the disturbance of homeostasis of the intestine, participating directly or indirectly in low-grade inflammation, imbalance between the leptin-to-adiponectin ratio, disruption of the intestinal mucosa, and intestinal permeability, which again favors adipokine release, bacterial translocation, and T-cell infiltration, all of which are involved in the pathogenesis of IBD [1]. On the other hand, although inconsistently, subcutaneous adipose tissue has been associated with altered pharmacokinetics of drugs. Increased subcutaneous adipose tissue has been associated with decreasing levels of 6-thioguanine and adalimumab and speeded loss of response to infliximab [24]. All these observations support the findings of the present study, because total body fat may be implicated in CD etiology and behavior and may also influence response to therapy.

Besides the previously stated physiologic effect of body fat, increasing body fat is a result of excess nutrition, in which the ingestion of dietary components (e.g., xenobiotics and food additives) that may alter gut microbiota is highly likely and has been previously reported [25,26] to have an effect on CD pathogenesis and behavior. Indeed, diet seems to play a leading role in the pathogenesis of IBD along with sedentary lifestyle and genetic susceptibility, because it is involved in gut homeostasis. In particular, diet has been associated with the composition and functioning of gut microbiota, gut barrier host immunity, and hormone release [27]. The adoption of western nutritional habits is known to shift traditionally plant-based diets to animal-sourced food, supporting a substantial change in microbiota and microbiome [28], with reduction of bacteria, such as *Prevotella* and *Treponema,* which are involved in fiber degradation [28]. The western dietary pattern is characterized by an overall higher calorie intake, mostly derived from sugar, refined carbohydrates, animal proteins, and ultraprocessed foods and has been associated with higher risk of obesity, type 2 diabetes mellitus, cardiovascular disease [29], and apparently IBD.

Conclusion

This study has allowed us to confirm the relationship between body composition, specifically total fat and visceral obesity upon diagnosis, and CD outcome, namely, disease phenotype and time until abdominal surgery. Also, this study further clarified that patients exhibiting worse outcome do actually change body composition with time, indicating a significant increase in all body composition compartments, but the greatest one is in total fat. We are aware that sample size is one of the limiting aspects of generalizability of our results, and cautious interpretation is therefore needed. Well-powered intervention studies focusing on body composition in CD are mandatory, because confirming the link between body composition and outcome may have an effect on treatment by including body composition changing interventions, such as diet and exercise in standard treatment of patients with CD.

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