Universidade do Estado do Rio de Janeiro
Centro Biomédico
Instituto de Nutrição

Nilian Carla Silva Souza

Estudo da massa e qualidade muscular por tomografia computadorizada em pacientes com câncer colorretal

Rio de Janeiro
2018

Nilian Carla Silva Souza

Estudo da massa e qualidade muscular por tomografia computadorizada em pacientes com câncer colorretal

Tese apresentada, como requisito parcial para obtenção do título de Doutor, ao Programa de Pós-Graduação em Alimentação, Nutrição e Saúde, da Universidade do Estado do Rio de Janeiro.

Orientador (a): Prof.ª Dra. Carla Maria Avesani

Coorientador (a): Prof.ª Dra. Maria Cristina Gonzalez

Rio de Janeiro

2018

CATALOGAÇÃO NA FONTE
UERJ / REDE SIRIUS / BIBLIOTECA CEH/A

S729 Souza, Nilian Carla Silva.
Estudo da massa e qualidade muscular por tomografia computadorizada em pacientes com câncer colorretal / Nilian Carla Silva Souza. – 2018.
125 f.

Orientadora: Carla Maria Avesani.
Coorientadora: Maria Cristina Gonzalez.
Tese (Doutorado) – Universidade do Estado do Rio de Janeiro. Instituto de Nutrição.

1. Nutrição – Teses. 2. Câncer colorretal – Teses. 3. Massa muscular – Teses. I. Avesani, Carla Maria.II. Gonzalez, Maria Cristina. III. Universidade do Estado do Rio de Janeiro. Instituto de Nutrição. IV. Título.

es CDU 612.3

_____ _____
Assinatura Data

Nilian Carla Silva Souza

Estudo da massa e qualidade muscular por tomografia computadorizada em pacientes com câncer colorretal

Tese apresentada, como requisito parcial para obtenção do título de Doutor, ao Programa de Pós-Graduação em Alimentação, Nutrição e Saúde, da Universidade do Estado do Rio de Janeiro.

Aprovada em 26 de novembro de 2018.

Banca Examinadora:

_____
Prof. Dr. Julio Beltrame Daleprane (Presidente da banca)
Instituto de Nutrição - UERJ

_____
Prof.ª Dra. Danielly Cristiny Ferraz da Costa
Instituto de Nutrição - UERJ

_____
Prof.ª Dra. Josely Correa Koury
Instituto de Nutrição – UERJ

_____
Prof.ª Dra. Vivian Wahrlich
Universidade Federal Fluminense - UFF

_____
Prof.ª Dra. Anke Bergmann
Instituto Nacional de Câncer - INCA

Rio de Janeiro
2018

DEDICATÓRIA

À minha mãe Neyla, minha maior incentivadora, pelo apoio incondicional em todos os momentos. Esta conquista não é só minha, mas sua também.

AGRADECIMENTOS

Agradeço primeiramente a Deus por abençoar minha vida e dar forças para seguir em frente.

À minha mãe por todo incentivo ao estudo desde o início da minha vida acadêmica. De lá pra cá muitos caminhos foram percorridos e hoje, ao ver finalizado o Doutorado, imagino e sinto a felicidade de você ao ver concluída esta etapa.

À minha família, minha maior referência, pelo apoio de sempre, mesmo distante.

Não posso deixar de agradecer aos pacientes e suas famílias pela participação neste estudo. Sem eles este estudo não seria possível.

À minha orientadora Carla Avesani que sempre me incentivou e auxiliou em todas as etapas desta tese. Pessoa de grande talento e coração. Agradeço não somente pelo exemplo de professora e orientadora dedicada e compromissada com a tarefa, mas também pela amizade, carinho e afeto que dedica a mim e a todos os seus alunos e orientandos. Muito obrigada por esses anos de trabalho, estudo, viagens e momentos de confraternização que podemos compartilhar.

À minha coorientadora Maria Cristina Gonzalez pelo incansável entusiasmo pela ciência, pelo comprometimento com a realização do projeto, colaboração, ensinamentos e amizade.

À UERJ, instituição de referência no ensino da graduação e pós-graduação, que por quatro anos me acolheu. Quantas amizades feitas, quantos momentos inspiradores de estudo e trabalho.

À toda equipe do PPG-ANS, professores e funcionários administrativos, agradeço por terem contribuído na minha formação, pela eficiência e disponibilidade sempre.

À Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES) pelo apoio financeiro.

Agradeço aos amigos que fiz na UERJ, ao nosso grupo Rim-UERJ, às amigas Fernanda, Juliana Cordeiro, Juliana Giglio, Jéssica e Larissa.

À minha amiga de sempre e que nesta fase se manteve presente, Gabriela Salim.

À família INCA, sem a qual esse trabalho não seria possível. Obrigada Nivaldo e Viviane por permitirem a execução desse trabalho. À Renata por me auxiliar nas etapas da pesquisa desde o início. À toda a equipe da Sessão de Nutrição e Dietética que de alguma forma colaborou com este trabalho, agradeço pela parceria e amizade. Ao Serviço de Radiologia do INCA, em especial ao Dr. Carlos Eduardo Lassance Cabral, enfermeiras Nely,

Márcia e Cláudia pela colaboração fundamental e a todos os funcionários que auxiliaram no projeto.

Ao Professor Antônio Ponce de León e à Abdul Rashid Qureshi pelo auxílio nas análises estatísticas.

Ao querido grupo da Professora Carla Prado pela excelente recepção na Universidade de Alberta. Em especial à Professora Carla Prado pelo acolhimento, apoio e idealização dos manuscritos, e à amiga Jingjie Xiao, companheira de todas as horas durante minha estadia no Canadá, pela amizade e auxílio nas análises de tomografia computadorizada. Não poderia deixar de agradecer à Camila, Claire, Sherin, Sarah, Letícia, Stephanie, Maha e Taiwo pela parceria e momentos especiais.

RESUMO

SOUZA, N. C. S. *Estudo da massa e qualidade muscular por tomografia computadorizada em pacientes com câncer colorretal.* 2018. 125 f. Tese (Doutorado em Alimentação, Nutrição e Saúde) – Instituto de Nutrição, Universidade do Estado do Rio de Janeiro, Rio de Janeiro, 2018.

A sarcopenia consiste em uma síndrome caracterizada pela redução de massa muscular e da capacidade funcional e está presente em enfermidades crônicas inflamatórias, como o câncer, independente da faixa etária. A prevalência de redução de massa muscular em pacientes oncológicos é elevada e pode variar entre 20 a 70%. Desta forma, o presente estudo teve como objetivo avaliar a validade dos métodos de avaliação da massa muscular em pacientes com câncer colorretal. O primeiro artigo gerado a partir desta tese teve como objetivo explorar os determinantes da mioesteatose e sua associação com os componentes da fragilidade em pacientes com câncer colorretal. Esse estudo apresentou como principais achados que a gordura corporal e a velocidade da marcha foram os determinantes significantes e independentes da mioesteatose e que a mioesteatose estava associada à fragilidade em pacientes obesos. No segundo artigo, o objetivo foi avaliar a massa muscular de pacientes com câncer colorretal através da técnica da tomografia computadorizada (TC) na região da terceira vértebra lombar e também por métodos com alta aplicabilidade clínica, sendo que a TC foi considerada o método de referência. Ademais, estabeleceu-se como objetivos específicos avaliar: 1) a validade dos métodos utilizados na prática clínica para avaliação da massa muscular (área muscular do braço corrigida, circunferência da panturrilha, massa muscular esquelética obtida pela impedância bioelétrica e exame físico de massa muscular obtido a partir da avaliação subjetiva global produzida pelo paciente) em comparação com a TC; 2) a associação entre a redução da massa muscular, avaliada por diferentes métodos, e os parâmetros clínicos e de estado nutricional; 3) identificar qual método substitutivo apresenta maior valor prognóstico para mortalidade no diagnóstico de redução de massa muscular. Os principais achados mostram que o exame físico foi o método com maior concordância com a TC para avaliar a massa muscular. O grupo com redução de massa muscular avaliada por diferentes métodos apresentou maior prevalência de desnutrição e menores valores de índice de massa corporal, gordura corporal e ângulo de fase. O modelo de regressão de Cox ajustado para idade, sexo e estadiamento mostrou que o exame físico apresentou maior valor preditivo para mortalidade entre os métodos investigados. Ademais, notou-se que a prevalência de redução de massa muscular variou de 9,6 a 54,3%, a depender do método utilizado para avaliar a massa muscular. Esses estudos sugerem a importância de se avaliar a massa e a qualidade muscular em pacientes com câncer, considerando sua necessidade para o diagnóstico da sarcopenia, na prevenção de alterações do estado nutricional e pela possibilidade de iniciar intervenções terapêuticas mais precoces. Além disso, métodos mais acessíveis na prática clínica, como o exame físico, apresentaram boa concordância com método ouro (TC) para a avaliação da massa muscular em pacientes com câncer colorretal.

Palavras-chave: Câncer colorretal. Massa muscular. Mioesteatose. Sarcopenia. Tomografia computadorizada.

ABSTRACT

SOUZA, N. C. S. *Study of muscle mass and muscle quality assessed by computed tomography in patients with colorectal cancer.* 2018. 125 f. Tese (Doutorado em Alimentação, Nutrição e Saúde) – Instituto de Nutrição, Universidade do Estado do Rio de Janeiro, Rio de Janeiro, 2018.

Sarcopenia is a syndrome defined as the concomitant condition of low muscle mass and low muscle function that occurs with aging, as well as in chronic diseases, such as cancer. Low muscularity is often observed in patients with cancer and its prevalence varies from 20 to 70%. The present study aimed to evaluate the validity of methods to measure muscle mass in patients with colorectal cancer. The first study of this thesis aimed to explore the determinants of myosteatosis and to investigate whether myosteatosis is associated with frailty components in patients with colorectal cancer. This study showed that body fat and gait speed were the significant and independent determinants of myosteatosis and that myostetatosis was associated with frailty in obese patients. Considering computed tomography (CT) as a reference method, the aim of the second study was to evaluate the muscle mass in patients with colorectal cancer at the third lumbar vertebra region as well as by surrogate methods that are suitable for clinical practice. In addition, this study also sought to investigate: 1) the validity of methods used in clinical practice to evaluate muscle mass (mid-upper arm muscle area, calf circumference, skeletal muscle mass assessed by bioelectrical impedance analysis and muscle deficit by the physical examination from the patient-generated subjective global assessment) compared with CT; 2) the association between different muscle measurements with clinical parameters and nutritional status 3) to identify which substitute method shows the highest prognostic value of low muscularity. The main findings of the second study showed that physical exam was the method with higher agreement with CT to assess muscle mass. Low Muscularity groups had higher proportion of malnourished individuals and lower values of body mass index, body fat percentage and phase angle. The Cox regression models adjusted for age, sex and tumor stage showed that physical exam had the highest hazard ratio and C-statistic value among all methods investigated. In addition, the prevalence of low muscle mass varied from 9.6 to 54.3%, depending on the method applied to evaluate muscle mass. These studies corroborate the importance of assessing muscle mass and muscle quality in patients with cancer, considering the relevance for the diagnosis of sarcopenia, the prevention of nutritional disturbances and the possibility to apply early therapeutic interventions. In addition, methods accessible for use in clinical practice, such as physical exam, showed a good agreement with the gold standard method (CT) for the evaluation of muscle mass in colorectal cancer patients.

Keywords: Colorectal cancer. Muscle mass. Myosteatosis. Sarcopenia. Computed tomography.

RESUMEN

SOUZA, N. C. S. *Estudio de la masa y calidad muscular por tomografía computarizada en pacientes con cáncer colorrectal.* 2018. 125 f. Tese (Doutorado em Alimentação, Nutrição e Saúde) – Instituto de Nutrição, Universidade do Estado do Rio de Janeiro, Rio de Janeiro, 2018.

La sarcopenia es un síndrome caracterizado por la pérdida de masa muscular y capacidad funcional. Aparece en pacientes con enfermedades inflamatorias crónicas, como el cáncer, independientemente de la edad. La prevalencia de pérdida de masa muscular en pacientes con cáncer es elevada y oscila entre 20 a 70%. De esta forma, el presente estudio tuvo como objetivo analizar la validez de los métodos de evaluación de la masa muscular en pacientes con cáncer colorrectal. El primer artículo de esta tesis tuvo como objetivo explorar los factores associados con la mioesteatosis y la asociación entre la miosteatosis y los componentes de la fragilidad en pacientes con cáncer colorrectal. Este estudio presentó como principal conclusión que la gordura corporal y la velocidad de marcha estaban asociadas con la mioesteatosis y que la misma estaba asociada con la fragilidade en obesos. Teniendo en cuenta la tomografia computarizada (TC) como método de referencia, el segundo artículo tuvo como objetivo estudiar la masa muscular en pacientes con cáncer colorrectal a través de la técnica de TC en la región de la tercera vértebra lumbar. Además, se estableció como objetivos específicos evaluar: 1) la validez de los métodos utilizados en la práctica clínica para la evaluación de la masa muscular (área muscular del brazo corregida, circunferencia de la pantorrilla, masa muscular esquelética por impedancia bioeléctrica y la pérdida de masa muscular obtenida a partir del examen físico en la valoración global subjetiva generada por el paciente) en comparación con la TC; 2) la asociación entre la pérdida de masa muscular, evaluada por diferentes métodos, y los parámetros clínicos y de estado nutricional; 3) identificar qué método sustitutivo presenta mayor valor pronóstico de mortalidad para el diagnóstico de la pérdida de masa muscular. Las principales conclusiones del segundo estudio muestran que el examen físico fue el método con mayor concordancia con la TC para evaluar la masa muscular. El grupo con reducción de masa muscular presentó mayor prevalencia de desnutrición y menor índice de masa corporal, gordura corporal y ángulo de fase. El modelo de regresión de Cox ajustado por edad, sexo y el grado de la enfermedad mostró que el examen físico presentó mayor valor predictivo de mortalidad entre los métodos investigados. Además, se notó que la prevalencia de pérdida de masa muscular varió entre 9,6 y 54,3%, dependiendo del método utilizado para evaluar la masa muscular. Estos estudios demuestran la importancia de estudiar la masa y la calidad muscular en pacientes con cáncer para el diagnóstico de la sarcopenia, para prevenir alteraciones del estado nutricional y para iniciar intervenciones terapéuticas de forma rápida y efectiva. Finalmente, métodos más accesibles en la práctica clínica, como el examen físico, presentaron buena concordancia con el método oro (TC) para la evaluación de la masa muscular en pacientes con cáncer colorrectal.

Palabras clave: Cáncer colorrectal. Masa muscular. Mioesteatosis. Sarcopenia. Tomografía computarizada.

LISTA DE ILUSTRAÇÕES

Revisão da literatura

Artigo 1

Artigo 2

LISTA DE TABELAS

Revisão da literatura

Artigo 1

Artigo 2

LISTA DE ABREVIATURAS E SIGLAS

Português

AMBc	Área muscular do braço corrigida
ASG-PPP	Avaliação subjetiva global produzida pelo paciente
BIA	Impedância bioelétrica
CB	Circunferência do braço
DXA	Absorciometria de duplo feixe de raios X
IMC	Índice de massa corporal
IMME	Índice de massa muscular esquelética
IMMEL	Índice de massa muscular esquelética lombar
INCA	Instituto Nacional de Câncer José Alencar Gomes da Silva
INCA I	Hospital do Câncer I
L3	Terceira vértebra lombar
MME	Massa muscular esquelética
PCR-us	Proteína C-reativa ultrassensível
PCT	Prega cutânea tricipital
RM	Ressonância magnética
TC	Tomografia computadorizada
TCLE	Termo de Consentimento Livre e Esclarecido

LISTA DE ABREVIATURAS E SIGLAS

Inglês

AMAc	*Corrected mid-upper arm muscle area*
BIA	*Bioelectrical impedance analysis*
% BF	*Body fat percentage*
BMI	*Body mass index*
CRC	*Colorectal cancer*
CRP	*High-sensitivity C-reactive protein*
CT	*Computed tomography*
ECOG	*Eastern Cooperative Oncology Group*
EWGSOP	*European Working Group on Sarcopenia in Older People*
HU	*Hounsfield unit*
L3	*Third lumbar vertebra*
% MFI	*Muscle fat infiltration percentage*
MRI	*Magnetic resonance imaging*
PG-SGA	*Patient-generated subjective global assessment*
SMM	*Skeletal muscle mass*
SMI	*Skeletal muscle index*

SUMÁRIO

INTRODUÇÃO

O câncer é uma enfermidade crônica que pode levar à redução da massa muscular, decorrente tanto da diminuição da ingestão alimentar, quanto do concomitante estado pró-inflamatório que leva à diminuição da síntese proteica e ao aumento do catabolismo proteico e do gasto energético. Ademais, os sintomas e efeitos colaterais provenientes do tratamento instituído (como a cirurgia, a quimioterapia e a radioterapia) também contribuem tanto para a redução da ingestão alimentar quanto para o desenvolvimento do quadro pró-inflamatório (1, 2). Esse quadro se manifesta de forma exacerbada nas neoplasias de intestino, como o câncer colorretal, que por cursarem com obstrução intestinal, adicionam a esse conjunto a má absorção de nutrientes (3).

Como consequência, a desnutrição constitui uma das comorbidades mais frequentes em pacientes com câncer colorretal, podendo ser maior do que nos demais tipos de câncer (4). Estima-se que a prevalência de desnutrição no câncer colorretal seja de 20 a 50% a depender do método empregado para se fazer o diagnóstico e do estadiamento da doença (4-6). Chama atenção que parte desses estudos mostra que o compartimento de massa muscular seja aquele com maior comprometimento, mesmo nos estágios mais avançados da doença, quando se observa que uma parcela dos pacientes cursa com sobrepeso ou obesidade (7-10). A redução de massa muscular foi inicialmente chamada de sarcopenia, a qual estaria associada ao envelhecimento (11). Contudo, desde a publicação de quatro consensos direcionados à definição, etiologia e critérios diagnósticos de sarcopenia no ano de 2010 (12-15), a definição dessa síndrome foi revisada, sendo a sarcopenia estabelecida como uma síndrome caracterizada pela redução concomitante de massa e de função muscular, que ocorre com o envelhecimento, mas que também pode ser secundária às enfermidades consumptivas como o câncer, independente da faixa etária (12-15). Esses consensos alertam ao prognóstico desfavorável da sarcopenia, que inclui piora da qualidade de vida, maior toxicidade à terapia antineoplásica e aumento da mortalidade (7, 16, 17). No entanto, uma vez que a força muscular tem mostrado maior associação com a funcionalidade quando comparada à massa muscular (18, 19), a comunidade científica despertou seu interesse para a avaliação da qualidade muscular, que engloba a mioesteatose, em diversos grupos, incluindo aqueles com enfermidades como o câncer (10, 20, 21). Neste contexto, a revisão do consenso de sarcopenia do *European Working Group on Sarcopenia in Older People* (EWGSOP) publicado em 2018 passa a priorizar a avaliação da força muscular como primeira etapa do processo de diagnóstico da sarcopenia, sendo que a avaliação da massa e da qualidade

muscular deve ser realizada com intuito de se confirmar o diagnóstico de sarcopenia (22). Vale salientar que na revisão desse consenso, o grupo de trabalho do EWGSOP (22) passou a valorizar a redução da força e funcionalidade muscular e trouxe à tona a discussão da qualidade muscular, assunto esse não abordado no consenso anterior.

Sendo assim, considerando que a avaliação da massa muscular faz parte do critério diagnóstico da sarcopenia e que a massa muscular é um importante fator prognóstico de sobrevida em pacientes oncológicos, faz-se necessário o estudo dos métodos para sua avaliação. Os métodos de imagem considerados padrão ouro na avaliação da composição corporal, como a ressonância magnética (RM) e a tomografia computadorizada (TC), apesar de permitirem a avaliação da massa muscular e da mioesteatose, apresentam maior custo, acesso limitado e necessidade de técnico especializado para operação dos exames, além de expor o paciente à radiação, no caso da TC. Esse conjunto de fatores limita o emprego da RM e da TC na prática clínica (23). Em contrapartida, os métodos de menor precisão como a impedância bioelétrica (BIA), a antropometria e o exame físico inserido na avaliação subjetiva global produzida pelo paciente (ASG-PPP), agregam características de maior aplicabilidade na prática clínica, de forma que o seu desempenho em relação aos métodos de maior precisão devam ser investigados antes que os mesmos sejam adotados no ambiente ambulatorial e hospitalar.

1 **REVISÃO DE LITERATURA**

1.1 **Definição e epidemiologia do câncer colorretal**

Câncer é o nome dado a um conjunto de mais de 100 doenças que têm em comum o crescimento descontrolado de células que podem invadir tecidos e órgãos, podendo expandir-se para outras regiões do corpo (24). Do grego *karkínos* ou caranguejo, a palavra foi utilizada por Hipócrates, que viveu entre 460 e 377 a.C, para descrever essa enfermidade caracterizada pelo desenvolvimento de tumores malignos (24).

Atualmente, o câncer constitui uma das principais causas de morte. Para o ano de 2030 são estimados 21,6 milhões de casos novos de câncer e 13 milhões de mortes, com maior impacto nos países em desenvolvimento (25). Em países desenvolvidos, predominam os cânceres de pulmão, mama, cólon e reto, próstata e estômago (26). Devido à urbanização e mudança no estilo de vida de países em desenvolvimento, o padrão está mudando rapidamente, e vem-se observando um aumento progressivo nos cânceres de pulmão, mama, cólon e reto (27). No entanto, ainda persistem os cânceres relacionados às condições socioeconômicas menos favoráveis, como colo do útero, estômago, fígado e esôfago (27), sendo os cânceres de mama, colo de útero, pulmão, cólon e reto e próstata os mais frequentes (26).

No Brasil, segundo estimativas do Instituto Nacional de Câncer José Alencar Gomes da Silva (INCA), espera-se para o biênio de 2018-2019 a ocorrência de 600 mil casos novos de câncer (28). Ademais, o câncer de pele do tipo não melanoma será o mais incidente na população brasileira, seguido pelos tumores de próstata, mama, cólon e reto, pulmão e estômago (28). Ao avaliar a incidência dos tipos de câncer por sexo, os mais frequentes após o câncer de pele do tipo não melanoma serão próstata (31,7%), pulmão (8,7%), cólon e reto (8,1%), estômago (6,3%) e cavidade oral (5,2%) em homens e mama (29,5%), cólon e reto (9,4%), colo do útero (8,1%), pulmão (6,2%) e tireoide (4,0%) em mulheres (28).

Dentre os tipos de câncer mais incidentes, o câncer colorretal refere-se àqueles localizados no intestino grosso (o cólon) e no reto (29) e se sobressaem por estarem fortemente relacionados ao estilo de vida e ao hábito alimentar, caracterizado pela elevada ingestão de carnes vermelhas e carnes processadas e baixa ingestão de frutas, legumes e verduras (25). Ademais, associa-se com a ocorrência de sobrepeso e obesidade, inatividade física, consumo de álcool e tabagismo (25). A história familiar, a predisposição genética ao desenvolvimento de doenças crônicas do intestino e a idade também são fatores de risco para o desenvolvimento desse tipo de câncer (25).

Com relação ao tratamento e a sobrevida do câncer colorretal, os mesmos são dependentes do estágio da doença (25). A cirurgia é a primeira opção de tratamento em estágios iniciais (25). A radioterapia e a quimioterapia podem ser usadas como terapia neoadjuvante, com intuito de redução da massa tumoral, ou como terapia adjuvante, com a finalidade de redução das células tumorais residuais (25). Para pacientes com doença avançada, podem ser utilizadas a quimioterapia, terapia-alvo, ablação ou embolização (25). As taxa de sobrevida em cinco anos é variável de acordo com a região do globo (20% - 60%) (30), sendo que em estágios iniciais da doença a sobrevida pode chegar a 90% (25). No entanto, mesmo em países desenvolvidos, menos da metade dos casos são diagnosticados nesta fase devido à subutilização dos métodos de rastreamento (30).

Os sintomas decorrentes do tratamento instituído, assim como dos efeitos diretos da obstrução intestinal e da má absorção podem levar ao desenvolvimento da desnutrição (3). Segundo dados obtidos de 42 mil pacientes do programa nacional de melhoria da qualidade cirúrgica do colégio americano de cirurgiões, a desnutrição no câncer colorretal é frequente, sendo maior do que nos demais tipos de câncer (4). Dessa forma, ferramentas de diagnóstico relacionadas ao desenvolvimento de desnutrição são importantes tanto para reversão deste quadro, quanto para fazer acompanhamento após início da intervenção nutricional e do tratamento da doença.

1.2 **Desnutrição, caquexia e sarcopenia no câncer**

A prevalência de desnutrição no paciente oncológico é elevada e pode variar entre 10 a 80% de acordo com os fatores relacionados à doença (tipo, localização e estágio do tumor), ao tratamento (clínico ou cirúrgico) e ao tipo de ferramenta utilizada na avaliação (5, 31-33). O comprometimento do estado nutricional está associado à menor resposta ao tratamento, à piora da qualidade de vida, ao aumento do risco de complicações pós-operatórias, ao tempo de internação e à mortalidade (5, 34-36).

As causas dos distúrbios nutricionais como a desnutrição nesta população são diversas, estando associadas à redução da ingestão alimentar devido à anorexia, constipação intestinal, náusea, xerostomia, disfagia, odinofagia, alterações do paladar e saciedade precoce. Concomitante a esse quadro, observa-se causas não relacionadas à redução da ingestão alimentar como a má absorção de nutrientes devido ao aumento das perdas nutricionais por vômitos e diarreia (37-39), ocorrência de estado pró-inflamatório com aumento no gasto energético e proteico decorrentes do próprio tumor, os quais suscetibilizam ainda mais o desenvolvimento de desnutrição (Figura 1) (40). Sendo assim, como a atividade inflamatória

faz parte da etiologia da desnutrição no câncer, o termo caquexia define com maior precisão o tipo de "desnutrição" presente neste grupo de pacientes (13, 41). Apesar da caquexia constituir causa direta de mortalidade em mais de 30% dos pacientes oncológicos (42), esta síndrome ainda é pouco identificada, devido à ausência de uma definição padrão que permita o seu diagnóstico (43-45).

Fearon et al. (2011) (46) definiram a caquexia neoplásica como uma síndrome multifatorial caracterizada pela perda contínua de massa muscular, associada ou não à perda de gordura corporal. Contudo, a terapia nutricional convencional de forma isolada pode não ser efetiva para reverter o quadro de caquexia, o que pode levar ao comprometimento progressivo da capacidade funcional. Os critérios diagnósticos estabelecidos para a caquexia incluem: perda de peso superior a 5% nos últimos seis meses, ou perda de peso superior a 2% associada ao índice de massa corporal (IMC) inferior a 20 kg/m^2 ou à presença de sarcopenia (46).

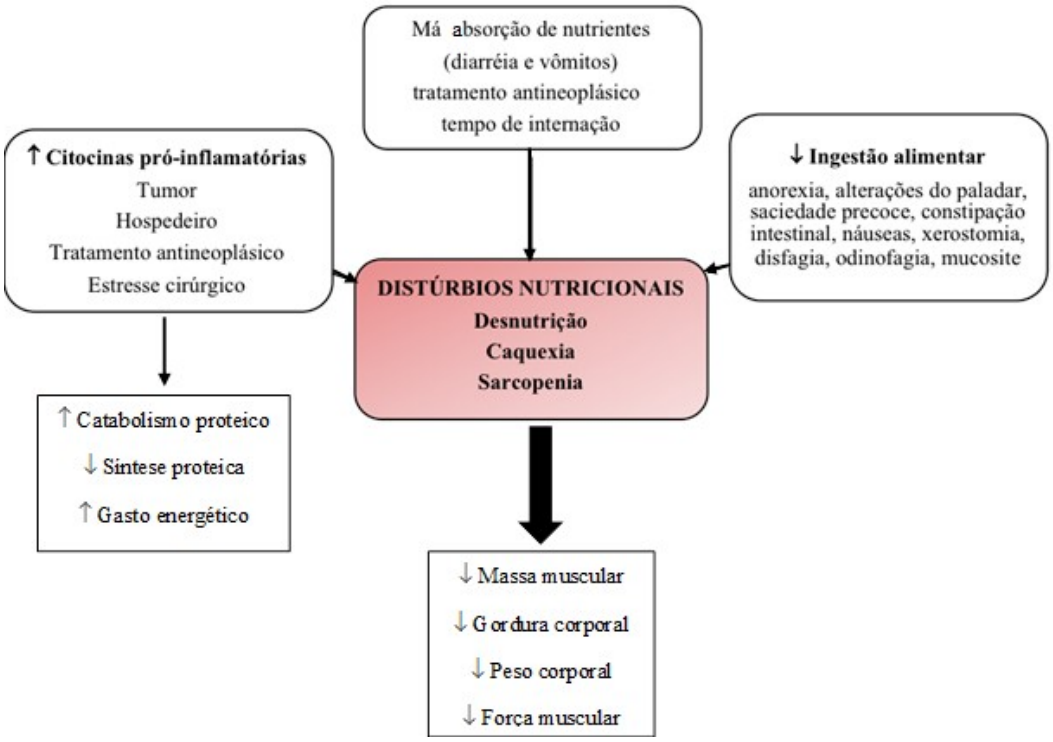
O processo de caquexia neoplásica pode ser classificado em três estágios: *pré-caquexia*, *caquexia* e *caquexia refratária*. O risco de desenvolvimento da caquexia é variável e depende do tipo e do estágio do tumor, da presença de inflamação sistêmica e de anorexia, além da falta de resposta à terapia antineoplásica. O estágio de *pré-caquexia* é caracterizado pela presença de anorexia, de alterações metabólicas e dos primeiros sinais clínicos, tais como a perda de peso inferior a 5%. No estágio da *caquexia* ocorre perda de peso contínua associada à redução importante da ingestão alimentar e ao estado pró-inflamatório. No estágio de *caquexia refratária* adiciona-se o catabolismo intenso, falha da resposta ao tratamento, baixo *escore* de desempenho e expectativa de vida inferior a três meses (46).

Atualmente observa-se que os conceitos em torno do processo de desnutrição estão sendo discutidos (41, 47). O desafio está em definir com mais clareza a nomenclatura, bem como os critérios para a distinção da desnutrição proteico-energética da caquexia. Isto tornaria possível um planejamento adequado da intervenção nutricional, visando à recuperação do estado nutricional, à redução dos efeitos adversos decorrentes da doença e do tratamento e à melhoria da qualidade de vida (48, 49).

Em paralelo, a sarcopenia, inicialmente definida como a perda de massa muscular associada ao envelhecimento (11), também merece ser discutida em pacientes oncológicos. Segundo Biolo et al. (2014) (2), enfermidades crônicas inflamatórias, como o câncer, podem levar ao desenvolvimento da sarcopenia, independente da faixa etária. De fato, a prevalência de sarcopenia, definida como a redução de massa muscular avaliada por TC na região localizada no nível da terceira vértebra lombar (L3) é elevada em pacientes oncológicos e pode variar entre 20 a 70% a depender do tipo de tumor, estadiamento da doença e do ponto

de corte utilizado para diagnosticar redução de massa muscular (3). Um diferencial desta síndrome está no fato da mesma se fazer presente de maneira associada ou não à desnutrição proteico-energética ou à caquexia e até mesmo com o sobrepeso/obesidade (7-10). Dessa forma, a sarcopenia deve ser entendida como um distúrbio nutricional, mas também como uma síndrome de redução importante de massa e força muscular com efeitos adversos sobre a qualidade de vida (47). Este conceito está alinhado ao consenso de 2010, proposto pelo EWGSOP onde a sarcopenia associada ao envelhecimento é definida como a perda de massa muscular, encontrada em idosos, associada à redução da força muscular ou do desempenho físico (12). Nesse consenso, é reconhecido que a sarcopenia está relacionada aos fatores causados pelo envelhecimento (sarcopenia primária), e também aos fatores secundários como à redução da atividade física, às doenças relacionadas à falência de órgãos, doenças inflamatórias e endócrinas, neoplasias e à ingestão inadequada de energia e proteína (12). Dentre os pacientes oncológicos, a prevalência de sarcopenia empregando o conceito que integra a redução de massa muscular e de funcionalidade é pouco descrita na literatura e varia de 10 a 30% a depender do tipo de tumor e faixa etária (50-54).

Figura 1 – Etiologia dos distúrbios nutricionais em pacientes oncológicos



Fonte : O autor, 2018.

Em 2018 foi publicado a atualização do consenso de sarcopenia de 2010 do grupo de trabalho do EWGSOP (22). Nesta revisão, a redução da força muscular é considerada como característica chave da sarcopenia, uma vez que estudos têm mostrado uma maior associação entre a força muscular e eventos adversos relacionados à funcionalidade (18, 19), e prioriza a avaliação da força muscular como primeira etapa do processo de diagnóstico da sarcopenia. A avaliação da massa muscular é recomendada em caso de redução da força muscular, com intuito de confirmar o diagnóstico de sarcopenia e, por fim, a avaliação do desempenho físico é indicada para a detecção da sarcopenia grave (22). Além disso, o EWGSOP considera a avaliação da qualidade muscular como critério a ser incluído na etapa de diagnóstico da sarcopenia (22). A qualidade muscular se refere a um conceito relativamente novo e está associada às alterações micro e macroscópicas na arquitetura e composição muscular, ao aumento da infiltração de gordura no músculo, conhecida como mioesteatose, às alterações no metabolismo muscular, à fibrose e à ativação neuronal, que interferem na função muscular (55). Até o momento, não há consenso sobre a utilização de métodos de avaliação da qualidade muscular na prática clínica (22).

Em relação aos pontos de corte utilizados na determinação de redução da massa muscular, os consensos recomendam a utilização do valor abaixo de dois desvios-padrão da média para adultos jovens de uma população de referência (12, 13, 15, 22). No entanto, a validade de se empregar pontos de corte estipulados para uma população diferente daquela estudada é questionável. Além disso, a maioria dos pontos de corte descritos nos consensos foram desenvolvidos para população idosa (12-15). Assim, considerando que a redução da massa muscular pode estar presente em adultos, os pontos de corte utilizados para idosos podem ser inadequados para o grupo de pacientes oncológicos. Dessa forma, não há consenso na literatura sobre qual o ponto de corte a ser empregado na avaliação da redução de massa muscular em pacientes oncológicos pela TC, bem como por outros métodos.

Os critérios de diagnóstico da sarcopenia incluem marcadores de funcionalidade, que abrangem força muscular e desempenho físico, e marcadores de massa e qualidade muscular. Considerando que a avaliação da massa muscular constitui um dos componentes para o diagnóstico de sarcopenia, e que não há um consenso sobre qual o ponto de corte deve ser utilizado nesta população, vale discutir o comportamento de métodos com essa finalidade, bem como os diferentes pontos de corte encontrados na literatura.

Em resumo, a desnutrição, caquexia e sarcopenia referem-se a distúrbios nutricionais distintos, porém com grande intersecção de critérios diagnósticos como mostra a Tabela 1. Além disso, também dividem desfechos comuns como a piora da qualidade de vida, o

aumento do tempo de internação hospitalar, o aumento do risco de complicações pós-operatórias, a menor resposta ao tratamento, a maior toxicidade à terapia antineoplásica e o aumento das taxas de mortalidade (5, 7, 16, 17, 34-36). Dessa forma, fica claro a necessidade de investigar métodos que permitam seu diagnóstico precoce e sejam capazes de avaliar o efeito de intervenções nutricionais e médicas.

Tabela 1 - Critérios para o diagnóstico de desnutrição, caquexia e sarcopenia

Critérios diagnósticos	**Desnutrição**	**Caquexia**	**Sarcopenia**
Redução de gordura corporal	x		
Redução de massa muscular	x	x	x
Redução de força muscular			x
Redução de qualidade muscular e funcionalidade muscular			x

Fonte: o autor, 2018.

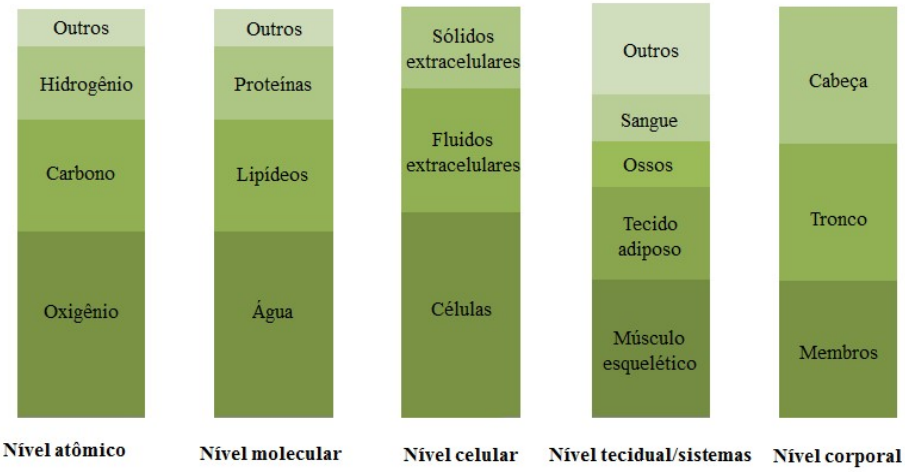
1.3 **Métodos de avaliação de massa muscular**

Conforme descrito anteriormente, a avaliação da composição corporal em pacientes oncológicos é de grande importância para o diagnóstico de desnutrição, sarcopenia e caquexia, que além de frequentes, associam-se com pior prognóstico (56, 57).

O estudo dos modelos teóricos de composição corporal pode ser feito conforme proposto por Wang et al. (1992) (58), o qual é organizado em cinco níveis de complexidade crescente: nível atômico (refere-se aos elementos e átomos que formam o corpo humano como o oxigênio, hidrogênio, nitrogênio, carbono, cálcio e fósforo), nível molecular (junção dos elementos formando compostos químicos como a água, lipídios, proteínas, minerais e glicogênio), nível celular (configuração dos compostos químicos em células, fluídos e sólidos extracelulares), nível tecidual/sistemas (organização dos componentes celulares em tecido adiposo, músculo esquelético, sangue, ossos, órgãos e sistemas) e nível corporal (compreende o tamanho, a forma e as características físico corporais tais como estatura e peso corporal) (58) (Figura 2). Segundo este modelo, o peso corporal equivale à soma de todos os componentes de cada nível e, durante períodos de estabilidade (manutenção do peso corporal) observam-se proporções estáveis entre os componentes corporais (58). A forma mais usual de proceder à quantificação é com o uso de expressões matemáticas as quais relacionam os compartimentos corporais entre si no mesmo nível ou em níveis diferentes. Assim, cada nível

de composição corporal pode ser caracterizado por uma equação algébrica, as quais servem de base para formar os modelos de multicompartimentos corporais (59).

Figura 2- Níveis de composição corporal

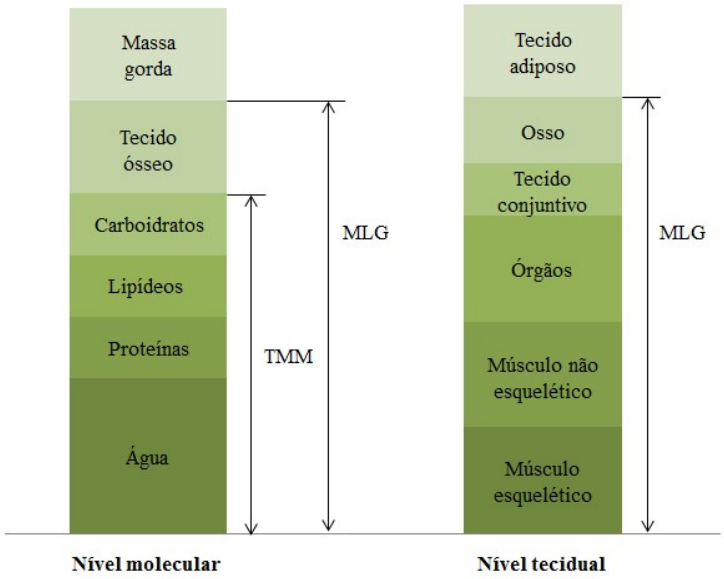


Fonte: adaptado de Wang et al., 1992 (58).

Os elementos do nível atômico são mensuráveis por técnicas como a análise de ativação de nêutrons. O princípio que fundamenta o nível atômico para mensuração da composição corporal se baseia na estreita relação entre os componentes químicos e os tecidos corporais. A medida de nitrogênio permite fazer o balanço de nitrogênio que é um indicador do *turnover* proteico e a dosagem de cálcio total é um indicativo do conteúdo mineral. O nível molecular pode ser avaliado por meio da dosagem de água corporal total, BIA e absorciometria de duplo feixe de raios X (DXA). O nível celular pode ser avaliado através da diluição de isótopos estáveis como a água duplamente marcada. O nível tecidual/sistemas é avaliado por meio de técnicas de imagem como a RM e a TC. Já o nível corporal é avaliado por métodos como a antropometria (dobras cutâneas e circunferências) (58, 60). Dessa forma, a organização por níveis de composição corporal proposta por Wang et al. (1992) (58) permitiu a leitura da composição corporal por modelos multicompartimentais, o que adicionou maior precisão em sua aferição. Para tanto, é importante trazer a definição quanto à sua terminologia. Outro ponto conceitual que merece atenção refere-se aos termos massa magra e massa livre de gordura, por muitas vezes empregados erroneamente como sinônimos. A massa magra, mais corretamente denominada tecido mole magro, se refere à soma da água e proteína corporal, carboidratos, lipídios da membana celular, e tecido mineral mole, excluindo-se os compartimentos de gordura e conteúdo mineral ósseo (Figura 3). A soma do tecido mole magro e osso correspondem à massa livre de gordura. Pelo nível tecidual, a massa livre de gordura é formada pelo músculo esquelético e não esquelético, órgãos, tecido

conjuntivo e ósseo (Figura 3). A massa gorda e tecido adiposo são denominações similares, uma em nível molecular e a outra em nível tecidual, respectivamente. O tecido adiposo é um tecido conjuntivo formado pelos adipócitos, fibras de colágeno e elastina, fibroblastos e capilares. Já a massa gorda é constituída por triglicerídeos e compõe aproximadamente 80% de tecido adiposo (23).

Figura 3 - Compartimentos corporais descritos pelo nível molecular e tecidual



Legenda: MLG - massa livre de gordura; TMM - tecido mole magro.
Fonte: adaptado de Prado e Heymsfield, 2014 (23).

Dentre os métodos de referência utilizados na avaliação da massa muscular, a RM e a TC são considerados métodos precisos e acurados por apresentar elevado grau de especificidade na discriminação dos componentes da massa livre de gordura (músculo esquelético e não esquelético, órgãos viscerais e osso) e o tecido adiposo (subcutâneo, visceral e intramuscular) (60, 61). Além disso, a avaliação do conteúdo de gordura intramuscular fornece informações adicionais a respeito da qualidade muscular (10). A RM tem como princípio a emissão de ondas de rádio que incidem sobre os núcleos de hidrogênio corporais, submetidos a um campo magnético, o que geram imagens do tecido (60). Esta técnica tem a vantagem de não utilizar radiação. No entanto, o alto custo, o acesso limitado e a dificuldade técnica limitam seu uso (23). A técnica da TC consiste na atenuação dos raios X, de acordo com as diferentes densidades de cada tecido (60). Semelhante à RM, essa técnica se caracteriza por elevado custo, acesso limitado e dificuldade técnica, o que limita o seu emprego para avaliação exclusiva da composição corporal (23).

Particularmente nos pacientes oncológicos, os exames de TC são realizados com a finalidade de estadiamento tumoral e de monitoramento da resposta ao tratamento, o que torna conveniente a sua utilização também para a avaliação da composição corporal. No entanto, a maioria dos exames de TC realizados nesse grupo de pacientes contemplam regiões corporais específicas. Em um estudo com indivíduos saudáveis, Shen et al. (2004) (62) encontraram boa correlação dos valores de massa muscular e adiposa da região lombar, obtidos através dos exames de RM, com as respectivas reservas corporais (62). Em 2008, Mourtzakis et al. (63) demonstraram em pacientes com tumor de cólon e pulmão avançado que a massa muscular e adiposa quantificada na região localizada ao nível de L3, através do exame TC, apresentou forte correlação com os valores de massa livre de gordura e de gordura corporal avaliados pelo DXA (63). Em razão desses achados, alguns trabalhos em pacientes oncológicos têm empregado a TC na avaliação da massa muscular (7-9), o que tem permitido o emprego da TC para avaliação de sarcopenia na área da pesquisa clínica. Neste contexto, o EWGSOP reconhece avaliação da massa muscular através da TC ao nível de L3 como um dos métodos de avaliação da massa muscular em pacientes oncológicos (22). Contudo, conforme exposto acima, não é possível expandir o emprego da TC para o âmbito da prática clínica, uma vez que esse equipamento apresenta elevado custo, requer técnico especializado, além de expor o paciente à radiação (23). Dessa forma, faz-se importante explorar métodos de avaliação de massa muscular que possam ser expandidos para uso ambulatorial e hospitalar.

A DXA constitui outro método de avaliação de imagem corporal que tem como vantagem à TC a exposição a menor radiação, menor custo, maior rapidez, além de permitir avaliação da composição corporal de corpo inteiro com análise segmentar (braços, pernas e tronco) dos compartimentos corporais (23). Através de tecnologia da avaliação da atenuação de duplo feixe de raios X, o aparelho é capaz de determinar a densidade óssea e as quantidades de tecido mole magro e gordo com acurácia adequada (60). Apesar de suas vantagens em relação à TC, a DXA não é um equipamento portátil, além de ter alto custo operacional, o que inviabiliza o seu uso em estudos epidemiológicos e na prática clínica (12).

Dentre os métodos de avaliação da composição corporal mais utilizados na prática clínica, destaca-se a BIA. O princípio dessa técnica baseia-se nos diferentes níveis de condução elétrica dos tecidos biológicos expostos a uma corrente elétrica de baixa intensidade. Nesse caso, pode-se comparar o corpo humano a um circuito elétrico composto por uma resistência (água e massa livre de gordura) em série com um condensador (membranas celulares e gordura). Os fluidos intra e extracelulares comportam-se como condutores, enquanto as membranas celulares atuam como elementos capacitantes (64). Dessa

forma, pode-se estimar a quantidade de água corporal, e, admitindo valores constantes, a proporção de massa livre de gordura e gordura corporal (60). A BIA é considerada um método de composição corporal rápido, prático e de baixo custo. No entanto, o estado de hidratação, indivíduos com valores de IMC extremos (IMC < 16 kg/m^2 ou > 34 kg/m^2), a equação empregada, bem como o protocolo e equipamento utilizados podem influenciar em seus resultados (65, 66). Além disso, Mourtzakis et al. (2008) (63) mostraram baixa precisão na avaliação da massa livre de gordura em pacientes oncológicos comparado ao DXA (63). Por esse motivo é importante investigar equações que apresentem bom desempenho para avaliação de massa muscular em comparação aos métodos de referência. O EWGSOP publicado em 2010 (12) propõe o emprego da avaliação da massa muscular esquelética (MME) a partir de uma equação que emprega os valores de resistência, aferidos diretamente pela BIA, além de variáveis como estatura, gênero e idade (67). Desconhecemos até o momento estudos que tenham testado o uso dessa equação em pacientes oncológicos em relação a um método de referência. Giglio et al. (2018) (68) mostrou que a massa muscular esquelética estimada através da equação de Janssen (67) apresentou concordância moderada com a massa muscular avaliada pela TC ao nível de L3 em pacientes com doença renal crônica em tratamento não dialítico (coeficiente kappa: 0.41, sensibilidade: 57,1%, especificidade: 85,1% para homens; coeficiente kappa: 0,39, sensibilidade: 55%, especificidade: 84,4% para mulheres).

As medidas antropométricas também constituem outra alternativa de baixo custo e de fácil aplicação na rotina clínica. Para a mensuração de massa muscular diversas medidas foram avaliadas como, por exemplo, a área muscular do braço corrigida (AMBc), a circunferência da panturrilha e a espessura do músculo adutor do polegar (2, 12, 69). Segundo o EWGSOP publicado em 2010, a circunferência da panturrilha constitui a medida com melhor correlação com a massa muscular em idosos (12). Em mulheres com câncer ginecológico, Laky et al. (2008) (70) relataram forte correlação entre a AMBc com o conteúdo de potássio corporal total. Contudo, as medidas antropométricas podem sofrer influência de fatores não nutricionais, como o desequilíbrio de fluidos e da massa tumoral e, por isto, sua utilização tem sido questionada (66). Ademais, a variabilidade inter e intra-avaliadores pode reduzir a precisão das medidas e, portanto, é de grande importância a padronização da técnica, bem como o treinamento dos avaliadores, buscando, assim, maior precisão das medidas. Outra medida de alta aplicabilidade na prática clínica, mas que tem sido pouco explorada como uma alternativa para avaliação da massa muscular em pacientes oncológicos é o exame físico de déficit de massa muscular inserido na ASG-PPP (71). Por se

tratar de um método subjetivo, a avaliação do exame físico da massa muscular tem sua precisão dependente da experiência do avaliador. Essa limitação, contudo, pode ser parcialmente contornada pelo treinamento adequado e cuidadoso do avaliador com pareamento das medidas para avaliação da concordância inter e intra-avaliadores. Em pacientes oncológicos, nenhum estudo até o momento comparou o desempenho do exame físico de massa muscular com outros métodos de maior precisão para esse fim. Ao nosso conhecimento, há trabalhos que compararam a classificação global da ASG-PPP com a avaliação da massa muscular pela TC para o diagnóstico de desnutrição em pacientes oncológicos (56), mas que difere da avaliação do desempenho do exame físico de massa muscular da ASG-PPP. Raeder et al. (2018) (72) em um estudo com 97 pacientes com câncer colorretal não metastático identificaram 64% de sensibilidade e 78% de especificidade do exame físico contido na ASG-PPP em relação à massa livre de gordura estimada pela BIA (72). Em pacientes com doença renal crônica em tratamento não dialítico, o exame físico não apresentou boa concordância com a massa muscular avaliada pela TC ao nível de L3 (68). Este resultado pode ser atribuído à possível influência do edema na avaliação do déficit muscular neste grupo de pacientes (73). Considerando a praticidade da avaliação do exame físico, investigações que foquem na avaliação do seu desempenho para avaliação da massa muscular certamente adicionariam importante conhecimento para a rotina clínica do nutricionista.

1.4 **Mioesteatose e capacidade funcional**

A qualidade muscular está associada à alterações musculares que incluem a infiltração de gordura no músculo, conhecida como mioesteatose, a qual se refere ao depósito de gordura localizado no interior do músculo, sob a fáscia e entre as fibras musculares (55). Nos últimos anos, a mioesteatose emergiu como um importante fator relacionado à capacidade funcional em idosos (74-76). Ao contrário do que se acreditava à respeito da relação positiva entre a massa e função muscular, estudos recentes mostram que a mioesteatose está fortemente associada à capacidade funcional, independentemente da área muscular (20, 74, 75, 77). Tal achado pode ser explicado pelo fato da mioesteatose diminuir a área contrátil do músculo e influenciar negativamente o desempenho muscular (77).

A mioesteatose também têm sido descrita em condições clínicas como diabetes, obesidade, doença pulmonar obstrutiva crônica, cirrose, doença renal crônica e câncer (10, 78-81) e está associada ao aumento de complicações pós-operatórias e diminuição da

sobrevida em pacientes oncológicos (10, 82-84). Apesar dos mecanismos moleculares envolvidos na redução de massa muscular relacionada ao câncer não estarem totalmente elucidados, evidências sugerem o papel crucial do aumento da degradação proteica e inibição da síntese proteica, levando a um balanço proteico negativo (1), além da infiltração patológica de gordura intramuscular (10). No entanto, estudos demonstram que a redução de massa muscular e a miosteatose representam fenótipos clínicos distintos (21). Embora pouco conhecida, a mioesteatose reflete o comprometimento da síntese e eliminação de triglicerídeos e pode estar associada a resposta inflamatória sistêmica em pacientes com câncer (85). Na obesidade, os mecanismos fisiológicos relacionados a mioesteatose incluem alterações na estrutura e na função mitocondrial, alteração no metabolismo de ácidos graxos, regulação positiva da atividade de macrofágos e células T e secreção de citocinas pró-inflamatórias que induzem inflamação muscular com consequente acúmulo de gordura no músculo (86, 87). Apesar de serem entidades distintas, a redução de massa muscular e a mioesteatose quando ocorrem concomitantemente podem conferir efeito adicional no prognóstico clínico do paciente oncológico (21).

A biópsia muscular pode ser considerada um método direto de avaliação do conteúdo de triglicérides musculares, porém por ser um método invasivo, seu emprego, mesmo no âmbito da pesquisa clínica, é dificultado. Já os métodos de imagem, como a TC e a RM, emergem como opção mais viável em diversas pesquisas clínicas como câncer. Ambos têm sido empregados na avaliação da mioesteatose através da quantificação da gordura intramuscular e do cálculo da atenuação muscular (23), o qual se refere ao valor médio de radiodensidade do tecido muscular e está associada à infiltração de gordura no músculo (78).

Em suma, o câncer é uma enfermidade caracterizada pelo aumento da produção de citocinas pró-inflamatórias que podem levar à redução da massa muscular, à mioesteatose e ao desenvolvimento da sarcopenia. Levando em consideração a alta prevalência de distúrbios nutricionais caracterizados pela perda de massa muscular, o comprometimento da força e funcionalidade do músculo e piora da qualidade muscular, e também pelo importante papel no pior prognóstico de sobrevida do paciente oncológico com tais distúrbios nutricionais, torna-se imprescindível a investigação de métodos de avaliação composição corporal, com ênfase em massa muscular, em pacientes com câncer colorretal.

2 **OBJETIVOS**

2.1 **Objetivo geral**

Avaliar a validade dos métodos de avaliação da massa muscular utilizados na prática clínica em comparação com a tomografia computadorizada em pacientes com câncer colorretal.

2.2 **Objetivos específicos**

- Descrever a massa muscular, a infiltração de gordura intramuscular e atenuação muscular pela técnica de tomografia computadorizada na região da terceira vértebra lombar;
- Avaliar a validade dos métodos de avaliação da massa muscular aplicados na prática clínica (área muscular do braço corrigida, circunferência da panturrilha, impedância bioelétrica e exame físico de massa muscular contido na avaliação subjetiva global produzida pelo paciente) em comparação com a massa muscular avaliada pela tomografia computadorizada;
- Avaliar a associação entre os diferentes métodos de avaliação da massa muscular com parâmetros clínicos e de estado nutricional;
- Identificar qual o método de avaliação da massa muscular apresenta maior valor prognóstico para mortalidade no diagnóstico de redução da massa muscular;
- Avaliar a prevalência de redução da massa muscular pela técnica de tomografia computadorizada e pelos métodos substitutos de avaliação da massa muscular;
- Explorar os determinantes da mioesteatose;
- Avaliar a associação entre a capacidade funcional e a fragilidade com os parâmetros de qualidade muscular (gordura intramuscular e atenuação muscular).

3 **CASUÍSTICA E MÉTODOS**

3.1 **Delineamento, indivíduos e local do estudo**

O trabalho consiste em um estudo de desenho observacional e longitudinal com uma amostra de conveniência composta por pacientes com diagnóstico de tumor colorretal atendidos no Hospital do Câncer I (INCA I) durante o período entre Abril de 2015 a Junho de 2016.

3.1.1 Critérios de inclusão

Indivíduos de ambos os sexos, idade igual ou superior à 18 anos, com diagnóstico de neoplasia colorretal, independente do estadiamento da doença, com exame de TC ao nível da região de L3, que aceitaram participar do estudo e assinaram o Termo de Consentimento Livre e Esclarecido (TCLE) (Apêndice A).

3.1.2 Critérios de exclusão

Indivíduos portadores de marca-passo, com *performance status* superior a três, segundo a escala do *Eastern Cooperative Oncology Group* (88), com diagnóstico de câncer de canal anal, tumor sincrônico, com mais de um tipo de tumor primário, doença renal crônica, insuficiência cardíaca congestiva ou cirrose hepática descompensada, cadeirantes e que apresentavam amputação de algum membro.

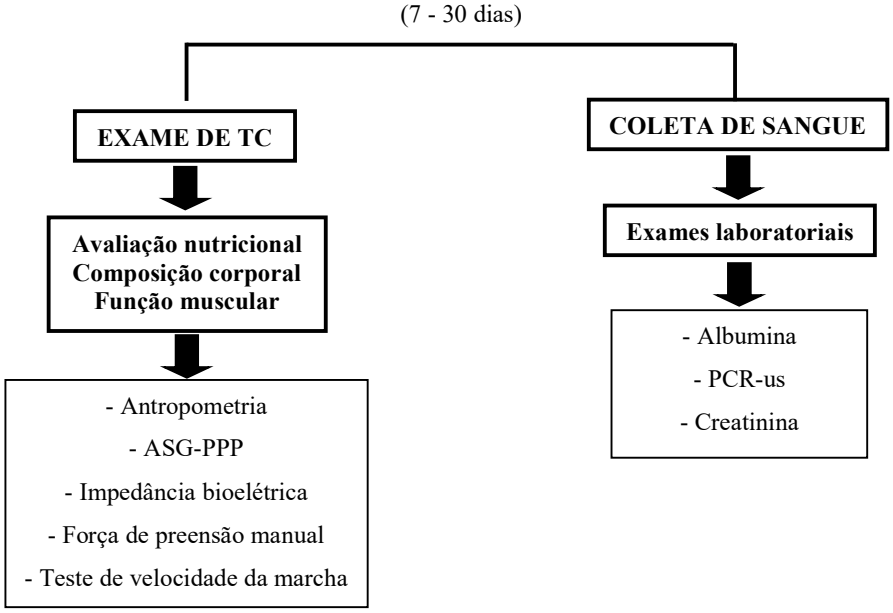
Dos 204 pacientes incluídos no estudo, 5 pacientes com diagnóstico de câncer de canal anal, 3 com tumor sincrônico e 2 com mais de um tipo de tumor primário foram excluídos totalizando 194 pacientes com diagnóstico de neoplasia colorretal.

3.2 **Protocolo do estudo**

Os pacientes com neoplasia colorretal agendados para realização do exame de TC ao nível da região de L3 no INCA I entre Abril de 2015 a Junho de 2016 foram selecionados para parcipar do estudo. No dia do exame, os pacientes selecionados foram convidados a participar do estudo e aqueles que consentiam, assinavam o TCLE (Apêndice A). Os pacientes chegavam ao local do exame em jejum de 8 horas (água e medicação eram

mantidos) e após o exame de TC era realizada a avaliação do estado nutricional, da composição corporal e da função muscular. As variáveis foram coletadas por meio de uma ficha de coletas de dados (Apêndice B). Entre 7 a 30 dias após o exame de TC, conforme data de agendamento da consulta médica, o paciente retornava em jejum de 8 horas para coleta de sangue e análises laboratoriais (Figura 4). Os primeiros 200 pacientes que aceitaram a participar do estudo e atendiam aos critérios de elegibilidade foram incluídos no estudo.

Figura 4 - Desenho experimental para a coleta de dados



Legenda: ASG-PPP: Avaliação subjetiva global produzida pelo paciente; TC: Tomografia computadorizada; PCR-us: proteína C-reativa ultrassensível.
Fonte : O autor, 2016.

Na história clínica foram coletados dados de anamnese, como idade, gênero, tempo de doença, tratamento prévio e atual, estadiamento clínico, *performance status,* comorbidades, uso de medicamentos, história familiar de câncer em formulário próprio (Apêndice B) através das informações obtidas em prontuário. Em relação à história social foram realizadas perguntas a respeito da renda familiar, escolaridade, estado civil e raça.

3.3 **Avaliação nutricional**

3.3.1 Avaliação antropométrica

O peso corporal foi aferido em balança digital da marca Filizola® (Filizola, Brasil) com capacidade máxima de 180 kg, em escala de 0,1 kg, com o paciente em pé, posicionado no centro da plataforma da balança, vestindo roupas leves e sem calçados. A estatura foi verificada utilizando-se o estadiômetro anexado à balança, com capacidade de 2 m e escala em centímetros, com o paciente descalço, em posição ereta e calcanhares juntos. A partir dos dados de peso e estatura, o IMC foi calculado através da fórmula peso/estatura^2 (kg/m^2) e classificado segundo o intervalo de referência estipulado pela Organização Mundial de Saúde (89).

A circunferência do braço (CB) foi medida com fita métrica inextensiva e inelástica, com comprimento de 150,0 cm e precisão de 0,10 cm, com o braço não dominante relaxado e voltado para a coxa, entre o ponto médio entre o processo acromial da escápula e a articulação úmero radial. A prega cutânea tricipital (PCT) foi aferida com adipômetro (Lange®, EUA), com leitura de 1,0 mm, na região anterior do braço, no mesmo ponto da CB. As medidas foram feitas em triplicata para o cálculo da média. Os valores de CB e PCT foram utilizados no cálculo da AMBc por meio das fórmulas: AMBc (cm^2): $[CB\ (cm) - (\pi \times PCT\ (cm))]^2/4\pi$ - 10cm^2 para homens e AMBc (cm^2): $[CB\ (cm) - (\pi \times PCT\ (cm))]^2/4\pi$ - 6,5cm^2 para mulheres (90). A medida da circunferência da panturrilha foi aferida na área de maior diâmetro da panturrilha com o indivíduo sentado em uma cadeira com a perna flexionada a 90° com o auxílio de fita métrica inelástica.

3.3.2 Avaliação subjetiva global produzida pelo paciente (ASG-PPP)

O instrumento foi aplicado por um único avaliador o qual passou por treinamento prévio. O instrumento é dividido em duas partes (Anexo A). A primeira é respondida pelo paciente ou cuidador e envolve questões sobre perda de peso, alterações na ingestão alimentar e na capacidade funcional e sintomas que possam interferir no consumo alimentar como perda de apetite, alterações do paladar, náuseas e vômitos. Na segunda parte, o avaliador atribui pontos às comorbidades associadas, aos fatores relacionados ao diagnóstico e ao tratamento que aumentam a demanda metabólica. O exame físico é direcionado à avaliação da reserva muscular e adiposa e à presença de edema e ascite. Ao final da avaliação, os indivíduos são

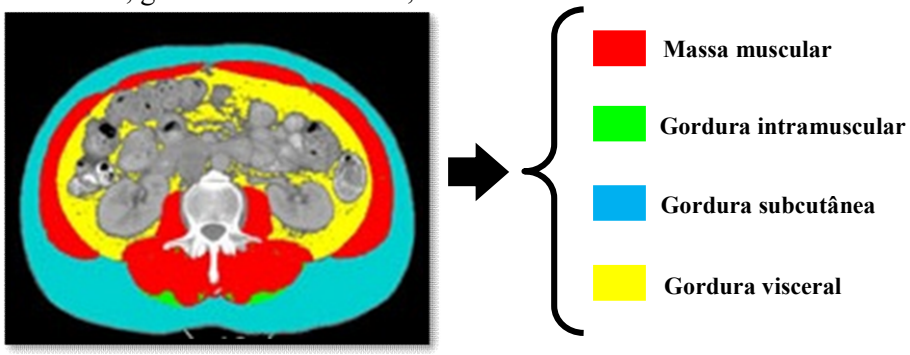
classificados em A - bem nutrido; B – risco nutricional ou desnutrição moderada e C – desnutrição grave e é calculada a pontuação (71). Na avaliação do exame físico da massa muscular foi considerado como déficit de massa muscular a depleção leve, moderada ou grave (pontuação +1, +2 e +3 do exame físico, respectivamente). A pontuação "0" foi considerada como ausência de depleção de massa muscular.

3.4 **Avaliação da composição corporal**

3.4.1 Tomografia computadorizada (TC)

Em relação ao exame de TC, a massa muscular (músculos psoas, sacroileolombar, quadrado lombar, transverso abdominal, oblíquo interno e externo e reto abdominal) e adiposa (gordura subcutânea, visceral e intramuscular) foram avaliadas através das imagens localizadas ao nível da região L3. O *software* Slice-O-Matic, versão 5,0, (Tomovision, Montreal, Canadá) foi utilizado no cálculo das áreas correspondentes de acordo com os valores de atenuação de cada tecido estimada pela escala de Hounsfield (de -29HU a +150HU para músculo, de -190HU a -30HU para gordura subcutânea e intramuscular e de -150HU a -50HU para gordura visceral) (63) (Figura 5). A área muscular foi normalizada pelo estatura ao quadrado (m^2) e relatada como índice de massa muscular esquelético lombar (IMMEL) (cm^2/m^2). A atenuação muscular também foi avaliada através do cálculo do valor médio da radiodensidade do músculo esquelético.

Figura 5 – Imagem do corte da terceira vértebra lombar pela técnica da tomografia computadorizada com a descrição dos tecidos de massa muscular, gordura intramuscular, subcutânea e visceral



Fonte: O autor, 2018.

3.4.2 Impedância bioelétrica (BIA)

A BIA foi realizada pelo aparelho tetrapolar de frequência única RJL®, modelo Quantum II, (RJL Systems®, EUA) com aplicação de corrente elétrica de 800 μA e freqüência de 50 kHz. As medidas foram feitas com o indivíduo deitado na posição supina, com os braços e as pernas afastados a 30º em relação ao tronco. Um eletrodo foi fixado no dorso da mão direita, próximo à articulação metacarpofalangeana, e, o outro, no pulso entre as proeminências distais do rádio e da ulna. Os outros dois eletrodos foram colocados no dorso do pé direito próximo ao arco transverso e entre os maléolos medial e lateral do tornozelo. O valor da estatura (cm) e da resistência (ohms) foram utilizados na estimativa da MME por meio do modelo de regressão proposto por Janssen et al. (2000) (37), ajustada por sexo (0 = feminino; 1 = masculino) e idade (anos): MME (kg) = [(estatura^2/resistência x 0,401) + (sexo x 3,825) + (idade x – 0,071)] + 5,102. A MME foi normalizada pelo estatura ao quadrado (m^2) e relatada como índice de massa muscular esquelétic (IMME) (kg/m^2).

3.5 **Avaliação da capacidade funcional**

3.5.1 Avaliação da força muscular

A avaliação da força muscular foi realizada através da avaliação da força de preensão manual utilizando o dinamômetro hidráulico da marca Jamar® (Sammons Preston®, EUA). Os pacientes executaram o teste em posição sentada, com o cotovelo flexionado em angulo de 90º, antebraço e pulso em posição neutra. A manopla do dinamômetro foi ajustada individualmente de acordo com o tamanho das mãos de forma que a haste mais próxima do corpo do dinamômetro fosse posicionada sobre as falanges médias dos dedos indicador, médio e anular. Os indivíduos foram orientados a realizar três contrações isométricas máximas, com um intervalo de aproximadamente um minuto entre as medidas. Foram obtidas três medidas de cada mão (dominante e não dominante) e utilizada a maior medida obtida para cada uma das mãos (91).

3.5.2 Avaliação do desempenho físico

O desempenho físico foi avaliado através do teste de velocidade da marcha. Era solicitado ao paciente que caminhasse em seu passo habitual uma distância de 4,6 metros.

Eram cronometrados os tempos das duas caminhadas (ida e volta), com intervalo de aproximadamente 15 segundos cada uma, e considerado o menor tempo de caminhada (91).

3.6 **Exames laboratoriais**

Consistiu nas dosagens séricas de proteína C-reativa ultrassensível (PCR-us), albumina e creatinina. A PCR-us foi avaliada através do método turbidimétrico, a albumina pelo método verde de bromocresol e a creatinina pelo método colorimétrico de Jaffé modificado. Os exames laboratoriais em questão foram realizados na rotina do acompanhamento clínico do paciente, usando kits específicos, segundo padronização do laboratório de patologia clínica do INCA I.

3.7 **Critérios de avaliação de redução de massa muscular**

A redução de massa muscular foi avaliada por meio da AMBc, circunferência da panturrilha, BIA, e TC e exame físico de massa muscular contida na ASG-PPP. Os pontos de corte utilizados para definir redução de massa muscular a partir dos métodos acima seguem descritos na Tabela 2.

Tabela 2 - Métodos e pontos de corte para definir redução de massa muscular

Métodos	Pontos de corte	Referência
Tomografia computadorizada		
Homem	IMMEL < 44,7 cm^2/m^2	(92)
Mulher	IMMEL < 32,8 cm^2/m^2	
Impedância bioelétrica		
Homem	IMME < 10,76 kg/m^2	(12)
Mulher	IMME < 6,76 kg/m^2	
Área muscular do braço corrigida		
Homem	< 21,4 cm^2	(93)
Mulher	< 21,6 cm^2	
Circunferência da panturrilha		(94)
Homem	< 34 cm	
Mulher	< 33 cm	
Exame físico ASG-PPP	Déficit massa muscular: +1, +2 ou +3	(71)

Legenda: IMMEL: Índice de massa muscular esquelético lombar; IMME: Índice de massa muscular esquelético; IMC: Índice de massa corporal; ASG-PPP: Avaliação subjetiva global produzida pelo paciente.
* Os pontos de corte para massa muscular ao nível da terceira vértebra lombar estipulados baseiam-se nos valores de IMMEL no percentil 10 de uma população caucasiana saudável (92)

3.8 **Critérios para definição de sarcopenia**

Foram empregados os critérios propostos pelo EWGSOP publicado em 2010 (12), o qual define sarcopenia como a redução concomitante de massa muscular e capacidade funcional. De acordo com esse consenso, a sarcopenia é definida como redução da massa muscular associada à diminuição da força muscular ou do desempenho físico. (12). Foram utilizados como pontos de corte indicativos de redução de massa muscular, os valores de índice de massa muscular esquelético lombar propostos por Martin et al. (2013) (10) (homens: < 43 cm^2/m^2 para IMC $\leq 24{,}99$ kg/m^2 e < 53 cm^2/m^2 para IMC ≥ 25 kg/m^2; mulheres: < 41 cm^2/m^2). A redução força de preensão manual foi definida como inferior a 30 kg para os homens e inferior a 20 kg para as mulheres. A redução de velocidade da marcha foi definida como inferior a 0,8 m/s (12). Vale ressaltar que não foram empregados os critério propostos pelo EWGSOP revisado e publicado em 12 de outubro de 2018 (22), pelo fato das análises terem sido feitas a partir de Abril do ano corrente e a submissão à publicação do manuscrito em Agosto.

3.9 **Fenótipo de fragilidade**

Foi utilizado o fenótipo de fragilidade definido por Fried et al. (95) como a presença de pelo menos três dos seguintes critérios: 1. perda de peso não intencional (> 3 kg no ano último ano); 2. diminuição da força de preensão manual (20% dos valores mais baixos de força de preensão manual da amostra, ajustados por sexo e IMC); 3. diminuição da velocidade de marcha (20% dos valores mais baixos de velocidade de marcha da amostra, ajustado para sexo e altura); 4. baixo nível de atividade física (definido como o mais baixo quintil de atividade física avaliada pelo questionário internacional de atividade física versão reduzida (96), de acordo com o sexo,); 5. Fadiga autorelatada (identificado por duas questões da escala de depressão do Centro de Estudos Epidemiológicos) (97).

3.10 **Sobrevida**

O acompanhamento de sobrevida foi obtido a partir dos dados do prontuário eletrônico após um ano da inclusão do último paciente (tempo de acompanhamento - mediana: 17 meses; intervalo interquartil: 12 a 23 meses). O tempo de sobrevida foi definido como tempo desde a inclusão no estudo até a morte e registrado em número de meses. Pacientes que ainda

estavam vivos e os casos de perda de acompanhamento, mudança de cidade ou de centro de tratamento e alta foram censurados na data da última consulta no hospital.

3.11 **Aspectos éticos**

O projeto de pesquisa foi aprovado pelo comitê de ética em pesquisa (Número CAAE: 38992014.5.0000.5274) (Anexo B). Os voluntários foram incluídos após serem esclarecidos dos procedimentos experimentais e dos possíveis eventos adversos, segundo determinações da Resolução nº 466/12 do Conselho Nacional de Saúde. Aqueles que concordaram, assinaram o TCLE (Apêndice A).

Os participantes classificados com desnutrição ou em risco nutricional segundo a ASG-PPP foram orientados quanto à terapia nutricional e encaminhados ao ambulatório de nutrição para acompanhamento.

3.12 **Análise estatística**

Será descrita nos artigos científicos, uma vez que a análise estatística diferiu a depender do estudo e seus respetivos objetivos. Para todas as análises foram considerados intervalo de confiança de 95% e $p<0,05$. O programa SPSS versão 20 ou Stata versão 15 foram utilizados para análise estatística.

4 **RESULTADOS**

Os resultados desta tese serão apresentados nesta seção, por meio de dois artigos científicos. Ambos têm como eixo central o estudo da avaliação da massa muscular e da qualidade muscular em pacientes com câncer colorretal.

4.1 **Artigo 1: Frailty is associated with myosteatosis in obese patients with colorectal cancer**

Este trabalho procurou responder o segundo objetivo específico da tese: explorar os determinantes da mioesteatose e a associação entre a capacidade funcional e a fragilidade com os parâmetros de qualidade muscular (gordura intramuscular e atenuação muscular) em pacientes com câncer colorretal.

O mesmo foi submetido ao *Clinical Nutrition* (fator de impacto 5,496) em 10 de agosto de 2018. A confirmação da submissão do trabalho encontra-se no Anexo C. O parecer da primeira revisão da revista foi recebido em 06/11/18 (Anexo D). Os revisores solicitaram mudanças para nova submissão, as quais serão respondidas em breve.

Frailty is associated with myosteatosis in obese patients with colorectal cancer

Nilian Carla Silva Souza [a,f], Maria Cristina Gonzalez [b], Renata Brum Martucci [a, e], Viviane Dias Rodrigues [a], Nivaldo Barroso de Pinho [c], Antonio Ponce de Leon [d], Carla Maria Avesani [e, f]

[a] Nutrition and Dietetic Service, Cancer Hospital Unit I, National Cancer Institute José Alencar Gomes da Silva, Rio de Janeiro, Brazil.

[b] Post-graduate Program in Health and Behavior, Catholic University of Pelotas, Pelotas, Brazil.

[c] Technical Support Division, Cancer Hospital Unit I, National Cancer Institute José Alencar Gomes da Silva, Rio de Janeiro, Brazil.

[d] Institute of Social Medicine, Rio de Janeiro State University, Rio de Janeiro, Brazil; Centre of Epidemiology and Community Health (CES), Stockholm County Council, SLSO, Stockholm, Sweden.

[e] Department of Applied Nutrition, Nutrition Institute, Rio de Janeiro State University, Rio de Janeiro, Brazil.

[f] Graduation Program in Nutrition, Food and Health. Nutrition Institute, Rio de Janeiro State University, Rio de Janeiro, Brazil.

Corresponding author:
Nilian Carla Silva Souza
Praça da Cruz Vermelha, 23, 5˚ andar, Centro, Rio de Janeiro, RJ, 20230-130, Brazil. Fax: +55 21 3207-1665.
Email: niliansouza@yahoo.com.br

ABSTRACT

Background & Aims: We aimed to explore the determinants of muscle fat infiltration and to investigate whether myosteatosis, assessed as muscle fat infiltration percentage (% MFI) and muscle attenuation from computed tomography (CT), is associated with frailty in a group of patients with colorectal cancer (CRC). **Methods:** Cross sectional study including CRC patients. CT scan of the third lumbar vertebra was used to quantify body composition and the degree of % MFI (reported as percentage of fat within muscle area). Frailty was defined by Fried et al. (2001) as the presence of more than 3 criteria: unintentional weight loss, self-reported exhaustion, weakness (low handgrip strength), slow walking speed (gait speed) and low physical activity. Obesity was defined according to sex-and-age-specific body fat percentage (% BF) cutoff. **Results:** A sample of 184 patients (age 60 ± 11 years; 58% men; 29% of patients with frailty) was studied. The sample was divided according to tertiles of % MFI (1st tertile 0 to 2.89, n=60; 2nd tertile ≥ 3.9 to 8.19%, n=64; 3rd tertile ≥ 8.2 to 26%, n=60). Age, females, body mass index, % BF, subcutaneous and visceral adipose tissue and the proportion of patients with frailty were significantly higher in the 3rd % MFI tertile. Phase angle and muscle attenuation were significantly lower in the 3rd % MFI tertile. The determinants of % MFI (r^2=0.49), which was log transformed due to its normal distribution, were % BF (ß=0.54; e^{β}=1.72; 95% CI: 0.032 to 0.051; P<0.01), age (ß=0.34; e^{β}=1.40; 95% CI: 0.016 to 0.032; P<0.01) and gait speed (ß=-0.12; e^{β}=0.87; 95% CI: -0.84 to -0.001; P=0.049). In addition, in obese patients (n=74) presenting 4 or 5 frailty criteria increased the chance of having higher % MFI and lower muscle attenuation, after adjustment for sex and age, when compared to none or 1 criteria. **Conclusions:** In a sample of CRC patients, % BF and gait speed were the determinants of % MFI. In addition, markers of myostetatosis were associated with frailty in obese patients.

Keywords: frailty, myosteatosis, obesity, cancer.

4.1.1 Introduction

With an increasingly aging population, the prevalence of age-related cancers such as colorectal cancer (CRC) is rising, especially in the less developed regions (1). CRC is amongst the types of cancer with the highest incidence rates and in fact, CRC is the third in world incidence and fourth in the mortality rates (2). In the context where cancer and aging are present, other comorbidities might occur. Frailty is defined as an age-associated syndrome of decreased physiologic reserves and function, leading to increased vulnerability for adverse events. In oncology, frailty is highly prevalent in young and older cancer patients (3, 4) and has been associated with increased chemotherapy toxicity, surgical complications and mortality (3-5).

In general, the decline in function is commonly attributable to a decrease in muscle size, but emerging evidence suggests that intramuscular fat infiltration, known as myosteatosis, is associated with lower muscle strength and mobility independently of muscle size (6-9). Increased intramuscular fat infiltration is present in aging, in conditions of physical inactivity (7, 8, 10, 11) and in multiple disease states including diabetes, obesity, chronic obstructive pulmonary disease, cirrhosis and cancer (12-17). The importance of such condition lies on its association with poor outcomes, including increased postoperative complications and higher mortality rates (14-16, 18, 19).

However, the assessment of myosteatosis requires the use of images techniques not available for daily clinical use, such as computed tomography (CT) and magnetic resonance imaging (MRI) (20). CT and MRI are considered gold-standard imaging methods for evaluating body composition, especially muscle mass, and have been used to assess intramuscular adipose tissue and muscle attenuation, markers of myosteatosis. In the setting of oncology, TC and MRI are applied for medical diagnosis and for follow-up purposes and could also be opportunistically used to assess body composition. The CT scan of the abdomen normally used for CRC diagnosis include the level of the third lumbar vertebra (L3). This set has recently been validated as the standard landmark for muscle mass analysis and can be also used to assess myosteatosis in cancer patients (21).

As frailty and muscle mass abnormalities are prevalent in patients with cancer and are associated with adverse outcomes, we sought to better understand their relationship. Therefore, our goal is to explore the determinants of muscle fat infiltration and to investigate whether skeletal muscle measurements, especially myosteatosis, is associated with frailty in patients with CRC.

4.1.2 Materials and methods

4.1.2.1 Subjects and study design

This study included patients with CRC recruited between April 2015 and June 2016 at the outpatient clinic of the Cancer Hospital Unit I of the National Cancer Institute José Alencar Gomes da Silva (INCA, Rio de Janeiro, Brazil). Those that were scheduled for abdominal CT scan at the L3 region as part of routine care and that met study eligibility criteria were invited to participate. Inclusion criteria comprised age higher than 18 years old and Eastern Cooperative Oncology Group (ECOG) performance score below 3. In addition, those with physical deformity unable to carry out tests for muscle strength or physical performance, with pacemaker, congestive heart failure, chronic kidney disease and liver cirrhosis were not included in the study. From 194 patients initially included in the study, 10 were excluded due to lack of CT scans (n=1), lack of bioelectrical impedance analysis (BIA) (n=1), CT scan with no images from the third lumbar vertebra (n=1) and not having data on the frailty phenotype (n=7). Therefore, 184 patients were included as depicted in **Figure 1**. The local Research Ethical Committee from National Cancer Institute José Alencar Gomes da Silva approved the study (protocol number 38992014.5.0000.5274) and informed consent was obtained from each subject before their inclusion.

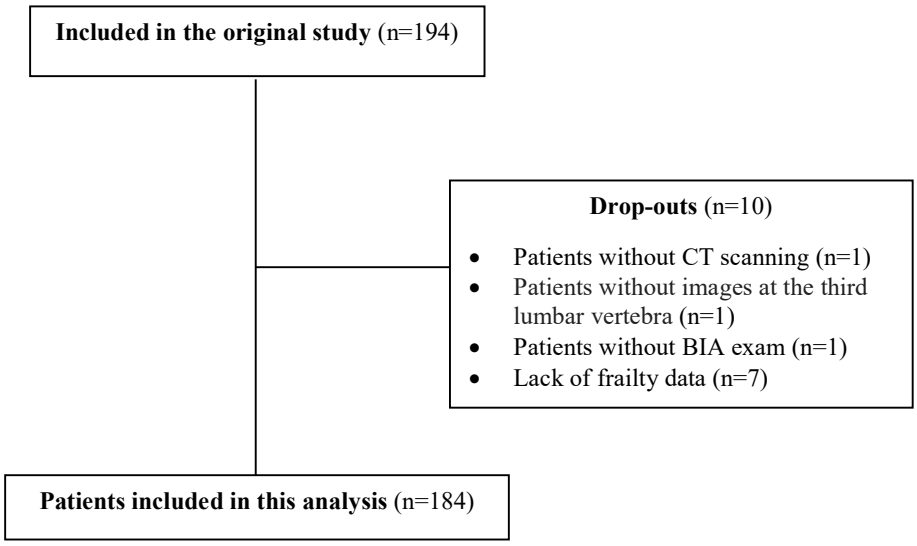


Figure 1- Flow chart of study inclusion and exclusion.
CT: Computed tomography; BIA: Bioelectrical impedance analysis.

4.1.2.2 Study protocol

After consenting to participate, patients received instructions to fast for 6 h before the CT scan (water-soluble oral contrast and medication were allowed). After CT scan, all participants had the nutritional status, body composition, and muscle function assessed. Blood samples were then scheduled to be collected under fasting conditions not later than 30 days after the CT scan. Clinical data were collected from medical records such as age, sex, previous and current treatment, comorbidities, ECOG performance score, tumor site and stage.

4.1.2.3 Nutritional assessment

Body weight (kg) was assessed using a platform-type mechanical scale (Filizola, São Paulo, Brazil) with a maximum capacity of 150 kg and variation 0.1 kg and height (cm) by a vertical stadiometer 200 cm long and with a 0.1 cm precision. Body mass index (BMI) was calculated as body weight in kilograms divided by squared height. The scored Patient-generated Subjective Global Assessment (PG-SGA) was carried out by a trained dietitian. The scored PG-SGA includes two sections: (1) history of weight loss over the previous six months, dietary intake, gastro-intestinal symptoms and functional capacity; (2) clinical condition, metabolic stress, and physical examination assessing muscle wasting, loss of subcutaneous fat mass and presence of edema/ascites. Each patient was classified as well nourished (PG-SGA A), mild to moderately malnourished (PG-SGA B), or severely malnourished (PG-SGA C) (22).

4.1.2.4 Body composition

Body composition was assessed by BIA and CT. BIA was performed with a tetrapolar device model Quantum II (RJL Systems, Detroit, MI, USA), with one electrical current of 800 μA at 50 kHz. The BIA device provides resistance and reactance values in Ohms (Ω). Phase angle was calculated with the following equation: phase angle (°) = arc tangent (reactance Ω /resistance Ω) x (180/π). The resistance was used to calculate skeletal muscle mass (SMM) obtained through the equation proposed by Janssen et al. (23) and SMM was normalized by height square (m^2) and reported as skeletal muscle index (SMI) (kg/m^2).

The SMM (kg) equation follows: [((height centimeter)^2 / resistance × 0.401) + (sex (0 for female and 1 for male) × 3.825) + (age years × (-0.071))] + 5.102. The percentage of total body fat (% BF) was assessed by BIA based on the predictive equation provided from the manufacturer's software. Obesity was defined according to sex-and-age-specific % BF cutoff points for the healthy population (24).

The CT images were acquired for medical diagnosis/follow-up purposes and were digitally stored in the patient's medical record, which are useful for the assessment of body composition as well. CT images were analyzed for tissue cross sectional area (cm^2) at L3 using the Slice-O-Matic software, version 5.0 (Tomovision, Montreal, Quebec, Canada). One image extending from the L3 was assessed for skeletal muscle (psoas, erector spinae, quadratus lumborum, transversus abdominus, external and internal obliques, and rectus abdominus), and adipose tissue (visceral, subcutaneous, and intramuscular). CT Hounsfield unit (HU) thresholds for each tissue were -29HU to +150HU for skeletal muscle, -190HU to -30HU for subcutaneous and intramuscular adipose tissue and -150HU to -50HU for visceral adipose tissue (21). The same trained dietitian read all the CT images. Skeletal muscle area was normalized by height square (m^2) and reported as lumbar skeletal muscle index (SMI) (cm^2/m^2). Muscle attenuation was also evaluated from CT and was derived by averaging the Hounsfield unit of skeletal muscle. The attenuation of skeletal muscle is inversely related to muscle fat content (12). In addition, the percentage of muscle fat infiltration (% MFI) in relation to the skeletal muscle mass in the slice L3 was calculated using the following formula (17):

% MFI = IAT (cm^2)/[IAT (cm^2) + SMM(cm^2)] x 100. Where, MFI: muscle fat infiltration; IAT: intramuscular adipose tissue; SMM: skeletal muscle mass.

4.1.2.5 Measurement of muscle strength and physical performance

Muscle strength was measured using a Jamar® hydraulic hand dynamometer (Sammons Preston, Chicago, IL). Each individual sat in a chair with armrests, without rings, watches, or other objects on their hands or wrists. The upper limb to be evaluated was placed alongside the body with the elbow at a 90˚ angle; the contralateral limb was relaxed on the thigh. During the exam, the patient was instructed to use the maximum strength in each measurement. Three measurements were determined for each hand in an alternating manner, and the maximum strength was defined as the greatest of the six measurements.

Physical performance was assessed by 4.6 m gait speed test. The subject was instructed to walk as fast as possible, but not running, through a predetermined 4.6 m straight path with no obstacles while the time to complete the course was measured. The test was applied twice, with an interval of approximately 30 seconds between applications and the lower of the two measurements was considered.

4.1.2.6 Definition of sarcopenia

Sarcopenia was defined as low skeletal muscle mass plus low muscle strength and/or low physical performance according to the European Working Group on Sarcopenia in Older People (EWGSOP) (25). Individuals who did not meet these criteria were considered normal for the outcome studied. Low SMI assessed by CT were classified according to Martin et al. cutoff points (15) (men: <43 cm^2/m^2 for BMI <25 kg/m^2 and <53 cm^2/m^2 for BMI ≥25 kg/m^2; women: <41 cm^2/m^2). Low handgrip strength were defined as less than 30 kg for men and less than 20 kg for women and for gait speed was less than 0.8 m/s (25).

4.1.2.7 Frailty phenotype

Frailty phenotype was defined by Fried et al. (26) as the presence of at least 3 of the following criteria: 1. unintentional weight loss (> 3 kg in past year); 2. low handgrip strength (the lowest 20% of the population adjusted for sex and body mass index); 3. slow walking speed (the slowest 20% of the population based on time to walk 4.6 m, adjusting for sex and height); 4. low physical activity level (defined as the lowest quintile of physical activity according to sex. Physical activity was evaluated by the International Physical Activity Questionnaire Short Form) (27); 5. self-reported of exhaustion (identified by two questions from the Center for Epidemiological Studies Depression scale) (28).

4.1.2.8 Laboratorial measurements

Serum dosages of albumin (green bromocresol) was evaluated in the laboratory of the National Cancer Institute José Alencar Gomes da Silva hospital.

4.1.2.9 Statistical analyses

Continuous variables were summarized as mean ± standard deviation or median and interquartile range, depending on its normality distribution (assessed by Shapiro-Wilk test). Categorical variables were summarized as the absolute frequencies and their corresponding percentages. The % MFI was divided in tertiles. The comparisons among the groups of % MFI tertiles were performed by the χ^2 test for categorical covariates, by ANOVA test with post-hoc test of Bonferroni for continuous covariates with normal distribution and by the Kruskal-Wallis test for non-normally distributed continuous covariates. The crude association between % MFI and body fat was assessed by Spearman's correlation coefficient test. In order to evaluate the determinants of % MFI as well as to investigate the association between % MFI and frailty, multiple linear regression models were used after adjustments for sex and age. The % MFI, as the dependent variable, was log-transformed to normalize its conditional distribution in the multiple linear regression analysis. Hence, the inverse function was applied to the estimated coefficients, i.e., e^{β}. The respective 95% confidence interval was obtained likewise. Under the linear regression model for the log transformed dependent variable, 100 (e^{β} - 1) is interpreted as the percent increase (if β is positive) or 100 (1 - e^{β}) as the percent decrease (if β is negative) in the expected value of the dependent variable for a unit increase in the respective covariate. As sensitivity analysis, muscle attenuation was used as proxy of muscle quality and muscle attenuation determinants was also tested in a different model, adjusted for sex and age. Statistical significance was defined as P values below 0.05. The Statistical Package for the Social Sciences (SPSS) version 20.0 (SPSS, Inc., Chicago, IL, USA) was used for the statistical analyses.

4.1.3 Results

This study included 184 patients, mostly males (n=107; 58%) and with a mean age of 60.4 ± 11.4 years. Hypertension was observed in 46% of the patients (n=86) whilst 23% (n=42) had cancer stage 0 to II and 77% (n=142) cancer stage III to IV. **Table 1** describes demographic, clinical, nutritional, body composition and muscle function parameters according to the tertiles of muscle fat infiltration percentage (% MFI). Age and the proportion of females increased with the % MFI tertiles. Also of note, BMI, % BF, abdominal subcutaneous adipose tissue and visceral adipose tissue were significantly higher in the 3rd %

MFI tertile, while the lumbar skeletal muscle index tended to decrease in the 3rd % MFI tertile. Moreover, phase angle and muscle attenuation, markers of muscle integrity were significantly lower in the 3rd tertile. When stratified by sex, no differences were observed for HGS and gait speed among the tertiles groups. The number of patients with sarcopenia, that is, low muscle mass by lumbar skeletal muscle index and low muscle strength or gait speed, although not significant, tended to increase across the % MFI tertiles. The determinants of % MFI were assessed by multiple linear regression analysis, where log of % MFI was the dependent variable and age, sex, % BF, HGS and gait speed were listed as possible independent variables. After running a few model specification choices, the variables that remained significant in the model (r^2=0.49) were % BF (ß=0.54; e^{β}=1.72; 95% CI: 0.032 to 0.051; P<0.01), age (ß=0.34; e^{β}=1.40; 95% CI: 0.016 to 0.032; P<0.01) and gait speed (ß=-0.12; e^{β}=0.87; 95% CI: -0.84 to -0.001; P=0.049).

Table 1- Demographic, clinic, nutritional status, body composition and muscle function parameters according to tertiles of muscle fat infiltration percentage (n=184)

	1st % MFI Tertile (n=60)	2nd % MFI Tertile (n=64)	3rd % MFI Tertile (n=60)	
	0 to 3.89	**≥3.9 to 8.19%**	**≥8.2 to 26%**	***P***
Age (years)[1]	55.2±11.1 [a]	61.9±10.7 [b]	64±10.8 [b]	**<0.001** [†]
Sex				
Male [n (%)]	51 (85%) [a]	31 (48%) [a]	25 (42%) [a]	**<0.001** [*]
Female [n (%)]	9 (15%) [b]	33 (52%) [a]	35 (58%) [b]	
Cancer stage [n (%)]				
0-II	9 (15%)	17 (27%)	16 (27%)	0.21 [*]
III-IV	51 (85%)	47 (73%)	44 (73%)	
ECOG performance score [†] [n (%)]				
0	26 (43%)	24 (38%)	28 (47%)	0.27 [*]
1-2	34 (57%)	40 (62%)	31 (53%)	
BMI (kg/m²)[1]	25.4±5.2 [a]	26.9±4.2 [a]	29.3±6.0 [b]	**<0.001** [†]
PG-SGA [†] [n (%)]				
PG-SGA A	36 (60%)	46 (73%)	43 (72%)	0.30 [*]
PG-SGA B/C	24 (40%)	17 (27%)	17 (28%)	
Albumin [¶] (g/dL)[1]	4.4 ± 0.4	4.4 ± 0.4	4.3 ± 0.4	0.74 [†]
Lumbar skeletal muscle index (cm²/m²)[1]				
Male	52.4 ± 9.9	49.6 ± 7.3	47.6 ± 8.8	0.08 [†]
Female	44.5 ± 9.9	43.4 ± 5.7	42.2 ± 7.7	0.64 [†]
Muscle attenuation (HU)[1]				
Male	42.2 ± 4.4 [a]	35.8 ± 4.8 [b]	28.5 ± 5.5 [c]	**<0.001** [†]
Female	40.1 ± 8.6 [a]	33.4 ± 5.6 [b]	26 ± 4.8 [c]	**<0.001** [†]
Subcutaneous adipose tissue (cm²)[2]				
Male	113.8 (70.5;184.4) [a]	161.2 (138;196) [b]	161.6 (135.1;226.3) [b]	**0.003** [#]
Female	108.2 (40.3;214.1) [a]	184.5 (122.5;274.1) [a,b]	285 (180.1;348.5) [b]	**0.003** [#]
Visceral adipose tissue (cm²)[2]				
Male	97 (53.4;166) [a]	169.3 (120.5;226.7) [b]	192.8 (132.4;239.4) [b]	**<0.001** [#]
Female	33.7 (11.1;75) [a]	74.7 (41.8;143.9) [a,b]	114.9 (61.8;168.3) [b]	**0.003** [#]
Body fat [%][2]				
Male	25.6 (19.7;33.7) [a]	31 (26.9;36) [a,b]	33 (29.4;38) [b]	**0.003** [#]
Female	33.7 (19.8;41.9) [a]	40.4 (35;47.1) [a]	47 (39.6;52.6) [b]	**< 0.001** [#]
Skeletal muscle index (BIA) (kg/m²)[1]				
Male	10 ± 1.1	9.9 ± 1	10 ± 1.4	0.98 [†]
Female	7.5 ± 1.1	7.4 ± 0.9	7.6 ± 1.4	0.87 [†]
Phase angle (°)[1]				
Male	6.0 ± 1 [a]	5.8 ± 0.9 [a,b]	5.3 ± 0.9 [b]	**0.005** [†]
Female	5.7 ± 0.6	5.3 ± 0.8	5.2 ± 0.9	0.36 [†]
Handgrip strength (kg)[2]				
Male	36 (31;43)	36 (31;40)	35 (29;38)	0.43 [#]
Female	18 (17;27.5)	22 (20;26.7)	22 (18;27)	0.73 [#]
Gait speed (m/s)[1]				
Male	1.20 ± 0.3	1.13 ± 0.2	1.08 ± 0.3	0.13 [†]
Female	0.96 ± 0.2	1.01 ± 0.2	0.97 ± 0.2	0.57 [†]
Sarcopenia [n (%)]	7 (12%)	8 (13%)	14 (23%)	0.14 [*]

ECOG: Eastern Cooperative Oncology Group; BMI: Body mass index; PG-SGA: Patient-generated subjective global assessment; BIA: Bioelectrical impedance analysis; MFI: Muscle fat infiltration.
[1] Mean and standard deviation; [2] Median and interquartile range; [†] ANOVA test; [*]Chi-square test; [#] Kruskal-Wallis test; [†] N=183; [¶] N=163; Different letters [(a,b,c)] indicate statistically significant differences among the groups ($p<0.05$).

The prevalence of frailty phenotype components according to tertiles of % MFI is shown in **Table 2**. Although a significantly higher proportion of patients had spontaneous weight loss in the 3rd tertile, it was also largely present in the 1st and 2nd tertiles, a finding

similar to exhaustion, which was seen in about 70% of the % MFI groups. The remaining frailty components, though not significant, tended to show higher prevalence in the 3rd tertile. In fact, **Figure 2** shows that the prevalence of frailty, that it is, the concomitance of 3 or more components, was significantly higher in the 3rd tertile of % MFI (1st tertile n=11, 18%; 2nd tertile n=18, 28% and 3rd tertile, n=25, 42%; P=0.02). In the entire group, frailty was present in 29% (n=54) of the patients.

Table 2- Prevalence of frailty phenotype components by muscle fat infiltration tertiles (n=184)

	1st % MFI Tertile (n=60)	**2nd % MFI Tertile (n=64)**	**3rd % MFI Tertile (n=60)**	
	0 to 3.89%	**≥3.9 to 8.19%**	**≥8.2 to 26%**	***P*** *
Frequency of frailty components [n (%)]				
Unintentional weight loss	40 (67%) [a]	45 (70%) [a]	52 (87%) [b]	**0.02**
Exhaustion	47 (78%)	49 (77%)	46 (77%)	0.96
Low handgrip strength	15 (25%)	14 (22%)	19 (32%)	0.45
Low gait speed	9 (15%)	14 (22%)	15 (25%)	0.38
Low physical activity	7 (12%)	15 (23%)	13 (22%)	0.20

* Chi-square test. Different letters [(a,b,c)] indicate statistically significant differences between groups (p<0.05).

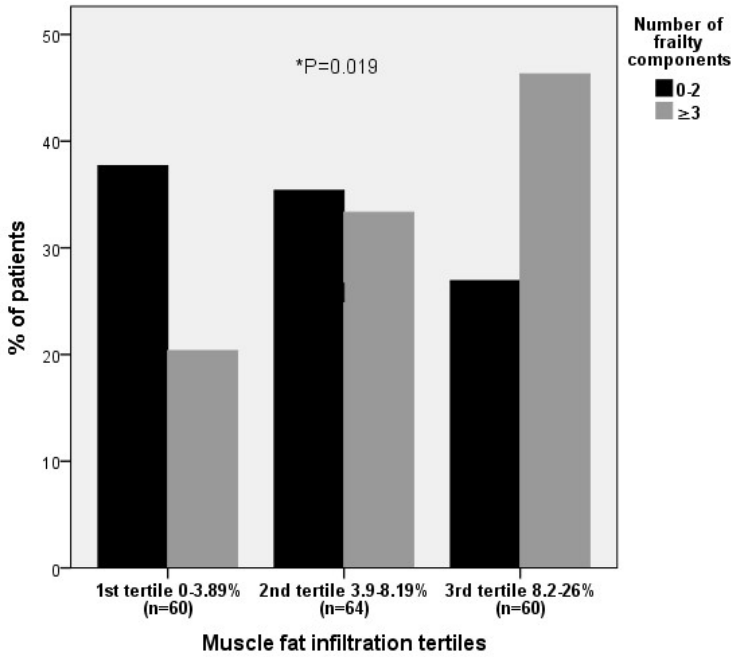


Figure 2 - Number of frailty components according to muscle fat infiltration percentage tertiles (n=184).
* Chi-square test.

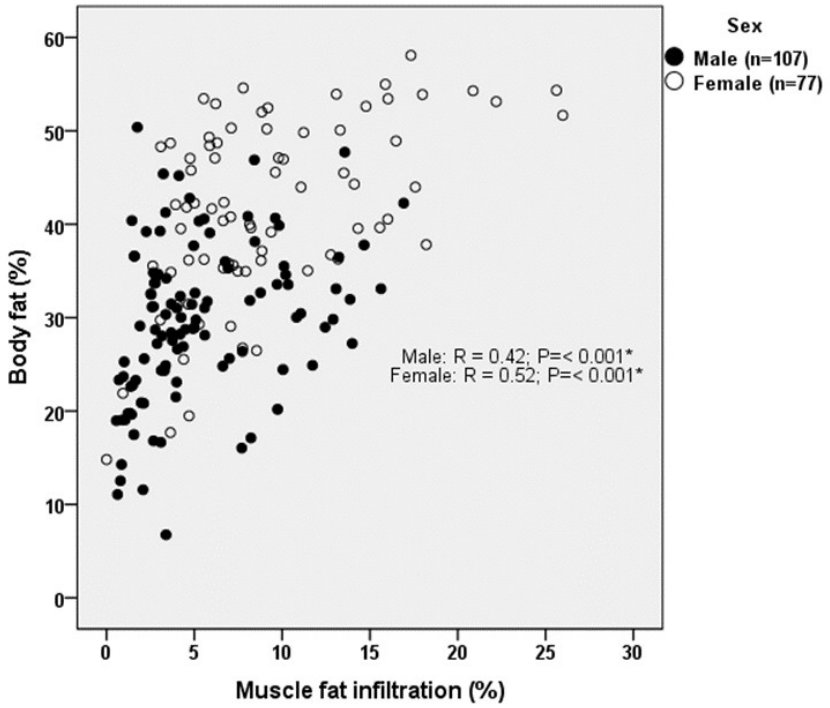


Figure 3 – Correlation between muscle fat infiltration and body fat (n=184).
*Spearman's test.

Considering that % BF was highly correlated with % MFI in both males and females (males: r=0.42, P<0.001; females: r=0.52, P<0.001) (**Figure 3**), two linear regression models were tested to investigate whether the correlation between % MFI and frailty differed in obese (n=74) and non-obese patients (n=110). In the multiple linear regression analysis adjusted by sex and age, in the obese group, but not in the non-obese group, presenting 4 or 5 criteria augments in 174% (Exp (β) = 2.74) the expected value of % MFI as compared to the none or 1 criteria of frailty (reference group) (**Table 3)**. Similarly, in a sensitivity analysis, muscle attenuation was used a proxy of myosteatosis and was used as dependent variable, adjusted for sex and age. Compared with none or 1 frailty criteria, presenting 4 or 5 criteria in the obese group, but not in the non-obese group, diminished almost 9 units of muscle attenuation in the multiple linear regression analysis adjusted for sex and age (**Supplementary Table 1**). As lower muscle attenuation indicates higher myosteatosis, the later result indicates that presenting 4 or 5 frailty criteria was correlated with myosteatosis.

Table 3 – Association between percentage of muscle fat infiltration (log) and frailty phenotype adjusted for sex and age in obese and non-obese patients (n=184)*

	Obese (n=74)			Non-obese (n=110)		
	Exp (β)	95% CI	*P*	Exp (β)	95% CI	*P*
Number of frailty components						
0-1 (reference)						
2	1.33	0.83; 2.12	0.231	1.31	0.98; 1.76	0.07
3	1.49	0.9; 2.46	0.120	1.37	0.95; 1.98	0.09
4-5	2.74	1.37; 5.47	**0.004**	1.25	0.74; 2.12	0.39
Sex (male)	0.51	0.39; 0.66	**<0.001**	0.55	0.43; 0.71	**<0.001**
Age (y)	1.01	0.99; 1.02	0.078	1.03	1.02; 1.04	**<0.001**

* Multiple linear regression analysis; Exp (β): Exponential beta; 95% CI: 95% confidence interval.

Supplementary Table 1– Association between muscle attenuation and frailty phenotype adjusted for sex and age in obese and non-obese patients (n=184)*

	Obese (n=74)				Non-obese (n=110)			
	β	95% CI	SE	*P*	β	95% CI	SE	*P*
Number of frailty components								
0-1 (reference)								
2	-0.86	-5.37; 3.64	2.30	0.707	-1.54	-4.36; 1.27	1.43	0.28
3	-2.56	-7.4; 2.27	2.46	0.299	-4.95	-8.47; -1.44	1.79	**0.006**
4-5	-8.66	-15.34; -1.99	3.4	**0.011**	-1.59	-6.66; 3.47	2.58	0.53
Sex (male)	5.97	3.43; 8.5	1.29	**<0.001**	5.49	3.11; 7.86	1.21	**<0.001**
Age (y)	-0.24	-0.35; -0.14	0.05	**<0.001**	-0.3	-0.41; -0.19	0.05	**<0.001**

* Multiple linear regression analysis; SE: Standard error; 95% CI: 95% confidence interval.

4.1.4 Discussion

This study aimed to explore the determinants of % MFI and to investigate whether muscle fat content, known as myosteatosis, was associated with frailty in a representative group of 194 well characterized CRC patients with measurements of body composition. By using CT images available for diagnostic purposes, we assessed body composition with high precision and no harm for the patient. Our main finding was that body fat and gait speed were independent determinants of % MFI in a model adjusted for sex and age. Moreover, we also found that in obese CRC patients, presenting 4 or more components of frailty were positively associated with % MFI and inversely associated with muscle attenuation. This finding indicates that myosteatosis was associated with frailty in obese patients. Overall, these

findings suggest that body fat and gait speed were the determinants of % MFI and highlight the importance of % MFI as a contributor of frailty in CRC obese patients.

Of note, we found positive associations between % MFI and body fat measurements, including BMI, total body fat, abdominal subcutaneous adipose tissue and visceral adipose tissue, all of which were significantly higher in the 3rd tertile of % MFI. Therefore, obesity plays an important role in % MFI and subsequently in increased myosteatosis, a finding previously shown in studies including individuals with and without cancer (12, 29, 30). The alterations inherent to the increased body fat accumulation (i.e. obesity), such as the changes in mitochondrial function, the impaired fatty acid metabolism, the defect in the ability of subcutaneous fat to store excess fatty acids and the accumulation of macrophage and T-cell, which induce muscle inflammation with consequent fat accumulation in the skeletal muscle (31, 32) are likely to explain the role of obesity in increasing % MFI. The consequence of myosteatosis is a worse muscle quality and diminished muscle contractile area, which has been claimed to be associated with lower muscle function in the elderly (7-9, 33), due to a change in activation, proliferation and differentiation of skeletal muscle stem cells into adipocytes (31). Aligned with this speculation, in the present study, patients in the 3rd tertile of % MFI were significantly older than that those in the 1st tertile of % MFI, reinforcing the notion that aging is related to myosteatosis, even in CRC patients. Regarding muscle mass, we found that lumbar SMI assessed by CT and total SMI assessed by BIA were not significantly different among the tertiles. We hypothesize that this result is justified by the inability of the muscle mass measurements to discriminate the amount of fat within the muscle. In fact, a previous study including patients with cancer could not find a variation in the skeletal muscle mass area, although muscle attenuation (a marker of myosteatosis) varied across the individuals (15). Surprisingly, phase angle, considered a marker of the amount and quality of soft tissue mass (34), was able to follow the differences between the % MFI tertiles in males, signifying phase angle as a potential superior marker to discriminate for myosteatosis. Finally, although muscle function measurements were not different among the tertiles, gait speed was inversely associated with % MFI, by diminishing in 13% the expected value of % MFI, in a model adjusted for sex and age. This finding is in accordance with a previous study in patients with cancer showing that muscle attenuation was more strongly associated with physical function than with skeletal muscle mass (6). Such finding can be explained by the fact that higher MFI diminishes the muscle contractile area and impact negatively in muscle function (9). Overall, body fat and gait speed, representing obesity and muscle function respectively, were determinants of % MFI in a sample of CRC patients.

Frailty is an age-associated syndrome well described in the geriatric population that can also be associated with myosteatosis and therefore, higher % MFI. According to the definition conceptualized by Fried et al. (26), frailty involves the decline in many physiological domains including muscle mass, strength, loss of body weight, weakness and poor balance (35), which in turn leads to vulnerability to adverse events and worse outcome, such as increased susceptibility to falls, worse quality of life, higher mortality rate, increased risk of postoperative complications, admissions and chemotherapy intolerance (3, 4, 36). More recently, frailty also became a subject of interest in patients with cancer with prevalence raging from depending on the type of cancer, the instrument and cut-point used to diagnose frailty (3). In the present study, 29% (n=54) of the patients fulfilled the criteria of frailty phenotype defined by Fried et al. (26) with a higher prevalence in the 3rd tertile of % MFI. Our finding agrees with those from Williams et al. (37) in which skeletal muscle density and skeletal muscle gauge, both assessed by CT and markers of myosteatosis, were related to frailty index even after adjusting by sex and age, in a sample of 162 older cancer patients. Moreover, since we found that body fat was an important determinant of % MFI, we furthered our analysis, by speculating that the correlation between frailty and % MFI could be more pronounced in obese patients. In fact, we found that in obese, but not in the non-obese, presenting 4 or more criteria augmented 174% the expected value of % MFI as compared to the none or 1 criteria of frailty (reference group). Moreover, these findings were confirmed in a sensitivity analysis using muscle attenuation, a proxy of % MFI. In this analysis, presenting 4 or more criteria of frailty was associated with almost 9 units decrease of muscle attenuation in obese, but not in non-obese patients. Although our study design does not allow to stablish a cause-effect relation, these results clearly shows that myosteatosis is associated with frailty and therefore, should be a target of treatment.

Lastly, the clinical implication of our findings deserves attentions. As far as we know, myosteatosis has not yet been a body compartment of target in interventional studies conducted in patients with cancer, since reversing wasting and cachexia were the focus of attention in nutritional interventions. With the findings from present study we instigate researchers to shift focus toward the other side of the coin that is, the adverse outcomes of obesity in CRC patients, such as myosteatosis and frailty. As obesity in the present study was present in 40.8% of the patients, targeting interventions of enhancing physical activity (38) and dietary omega-3 fatty acid supplementation (39, 40) to reverse frailty and myosteatosis will likely improve quality of life, an outcome understood of high value in ill patients such as those from this study.

The limitations and strength of the present study should be addressed. As limitations, because this was a convenient sample across various time points in the cancer care continuum, we cannot draw conclusions regarding the treatment impact on skeletal muscle, % MFI and physical function. In addition, since this an observational and a cross-sectional study, a causal-effect relationship between % MFI and frailty cannot be stablished. The strengths include a representative and relatively large sample of CRC patients with body composition assessed by CT, which provides an accurate and precise assessment, enabling to identify muscle abnormalities, especially muscle fat infiltration, a subject not yet largely investigated in cancer patients. Also, it is one of the few studies that use CT scans to investigate the association between body composition parameters and frailty among patients with cancer.

In conclusion, body fat and gait speed were determinants of % MFI and presenting 4 or more criteria of frailty was associated with intramuscular fat infiltration and muscle attenuation in obese patients with CRC, suggesting the role of myosteatosis in frailty. Finally, clinicians should be aware of the clinical relevance of assessing body composition, particularly myosteatosis, in future studies in order to propose individualized interventions.

4.1.5 Acknowledgments

We would like to thank Bianca Umbelino and Ana Clara Lopes who participated in the data collection of the study.

4.1.6 Conflict of Interest

The authors declare no conflicts of interest.

4.1.7 Funding Sources

This study was financed in part by the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior – Brasil (CAPES) – Finance Code 001.

4.1.8 References

1 Pilleron S, Sarfati D, Janssen-Heijnen M, Vignat J, Ferlay J, Bray F, et al. Global cancer incidence in older adults, 2012 and 2035: A population-based study. Int J Cancer. 2019;144(1):49-58.

2. Fitzmaurice C, Dicker D, Pain A, Hamavid H, Moradi-Lakeh M, MacIntyre MF, et al. The Global Burden of Cancer 2013. JAMA Oncol. 2015;1(4):505-27.

3. Handforth C, Clegg A, Young C, Simpkins S, Seymour MT, Selby PJ, et al. The prevalence and outcomes of frailty in older cancer patients: a systematic review. Ann Oncol. 2015;26(6):1091-101.

4. Kumar A, Langstraat CL, DeJong SR, McGree ME, Bakkum-Gamez JN, Weaver AL, et al. Functional not chronologic age: Frailty index predicts outcomes in advanced ovarian cancer. Gynecol Oncol. 2017;147(1):104-9.

5. Tan KY, Kawamura YJ, Tokomitsu A, Tang T. Assessment for frailty is useful for predicting morbidity in elderly patients undergoing colorectal cancer resection whose comorbidities are already optimized. Am J Surg. 2012;204(2):139-43.

6. Williams GR, Deal AM, Muss HB, Weinberg MS, Sanoff HK, Nyrop KA, et al. Skeletal muscle measures and physical function in older adults with cancer: sarcopenia or myopenia? Oncotarget. 2017;8(20):33658-65.

7. Goodpaster BH, Carlson CL, Visser M, Kelley DE, Scherzinger A, Harris TB, et al. Attenuation of skeletal muscle and strength in the elderly: The Health ABC Study. J Appl Physiol (1985). 2001;90(6):2157-65.

8. Visser M, Kritchevsky SB, Goodpaster BH, Newman AB, Nevitt M, Stamm E, et al. Leg muscle mass and composition in relation to lower extremity performance in men and women aged 70 to 79: the health, aging and body composition study. J Am Geriatr Soc. 2002;50(5):897-904.

9. Delmonico MJ, Harris TB, Visser M, Park SW, Conroy MB, Velasquez-Mieyer P, et al. Longitudinal study of muscle strength, quality, and adipose tissue infiltration. Am J Clin Nutr. 2009;90(6):1579-85.

10. Pagano AF, Brioche T, Arc-Chagnaud C, Demangel R, Chopard A, Py G. Short-term disuse promotes fatty acid infiltration into skeletal muscle. J Cachexia Sarcopenia Muscle. 2018;9(2):335-47.

11. Lang T, Cauley JA, Tylavsky F, Bauer D, Cummings S, Harris TB. Computed tomographic measurements of thigh muscle cross-sectional area and attenuation

coefficient predict hip fracture: the health, aging, and body composition study. J Bone Miner Res. 2010;25(3):513-9.

12. Goodpaster BH, Kelley DE, Thaete FL, He J, Ross R. Skeletal muscle attenuation determined by computed tomography is associated with skeletal muscle lipid content. J Appl Physiol (1985). 2000;89(1):104-10.
13. Robles PG, Sussman MS, Naraghi A, Brooks D, Goldstein RS, White LM, et al. Intramuscular Fat Infiltration Contributes to Impaired Muscle Function in COPD. Med Sci Sports Exerc. 2015;47(7):1334-41.
14. Montano-Loza AJ, Angulo P, Meza-Junco J, Prado CMM, Sawyer MB, Beaumont C, et al. Sarcopenic obesity and myosteatosis are associated with higher mortality in patients with cirrhosis. J Cachexia Sarcopenia Muscle. 2016;7(2):126-35.
15. Martin L, Birdsell L, Macdonald N, Reiman T, Clandinin MT, McCargar LJ, et al. Cancer cachexia in the age of obesity: skeletal muscle depletion is a powerful prognostic factor, independent of body mass index. J Clin Oncol. 2013;31(12):1539-47.
16. Kumar A, Moynagh MR, Multinu F, Cliby WA, McGree ME, Weaver AL, et al. Muscle composition measured by CT scan is a measurable predictor of overall survival in advanced ovarian cancer. Gynecol Oncol. 2016;142(2):311-6.
17. Vivodtzev I, Moncharmont L, Tamisier R, Borel JC, Arbib F, Wuyam B, et al. Quadriceps muscle fat infiltration is associated with cardiometabolic risk in COPD. Clin Physiol Funct Imaging. 2018;38(5):788-97.
18. Boer BC, de Graaff F, Brusse-Keizer M, Bouman DE, Slump CH, Slee-Valentijn M, et al. Skeletal muscle mass and quality as risk factors for postoperative outcome after open colon resection for cancer. Int J Colorectal Dis. 2016;31(6):1117-24.
19. Berkel AEM, Klaase JM, de Graaff F, Brusse-Keizer MGJ, Bongers BC, van Meeteren NLU. Patient's Skeletal Muscle Radiation Attenuation and Sarcopenic Obesity are Associated with Postoperative Morbidity after Neoadjuvant Chemoradiation and Resection for Rectal Cancer. Dig Surg. In press 2018.
20. Prado CM, Heymsfield SB. Lean tissue imaging: a new era for nutritional assessment and intervention. JPEN J Parenter Enteral Nutr. 2014;38(8):940-53.
21. Mourtzakis M, Prado CM, Lieffers JR, Reiman T, McCargar LJ, Baracos VE. A practical and precise approach to quantification of body composition in cancer patients using computed tomography images acquired during routine care. Appl Physiol Nutr Metab. 2008;33(5):997-1006.

22. Ottery FD. Definition of standardized nutritional assessment and interventional pathways in oncology. Nutrition. 1996;12(1 Suppl):S15-9.
23. Janssen I, Heymsfield SB, Baumgartner RN, Ross R. Estimation of skeletal muscle mass by bioelectrical impedance analysis. J Appl Physiol (1985). 2000;89(2):465-71.
24. Heo M, Faith MS, Pietrobelli A, Heymsfield SB. Percentage of body fat cutoffs by sex, age, and race-ethnicity in the US adult population from NHANES 1999-2004. Am J Clin Nutr. 2012;95(3):594-602.
25. Cruz-Jentoft AJ, Baeyens JP, Bauer JM, Boirie Y, Cederholm T, Landi F, et al. Sarcopenia: European consensus on definition and diagnosis: Report of the European Working Group on Sarcopenia in Older People. Age Ageing. 2010;39(4):412-23.
26. Fried LP, Tangen CM, Walston J, Newman AB, Hirsch C, Gottdiener J, et al. Frailty in older adults: evidence for a phenotype. J Gerontol A Biol Sci Med Sci. 2001;56(3):M146-56.
27. Craig CL, Marshall AL, Sjostrom M, Bauman AE, Booth ML, Ainsworth BE, et al. International physical activity questionnaire: 12-country reliability and validity. Med Sci Sports Exerc. 2003;35(8):1381-95.
28. Orme JG, Reis J, Herz EJ. Factorial and discriminant validity of the Center for Epidemiological Studies Depression (CES-D) scale. J Clin Psychol. 1986;42(1):28-33.
29. Xiao J, Caan BJ, Weltzien E, Cespedes Feliciano EM, Kroenke CH, Meyerhardt JA, et al. Associations of pre-existing co-morbidities with skeletal muscle mass and radiodensity in patients with non-metastatic colorectal cancer. J Cachexia Sarcopenia Muscle. 2018;9(4):654-63.
30. Esfandiari N, Ghosh S, Prado CM, Martin L, Mazurak V, Baracos VE. Age, Obesity, Sarcopenia, and Proximity to Death Explain Reduced Mean Muscle Attenuation in Patients with Advanced Cancer. J Frailty Aging. 2014;3(1):3-8.
31. Miljkovic I, Zmuda JM. Epidemiology of myosteatosis. Curr Opin Clin Nutr Metab Care. 2010;13(3):260-4.
32. Khan IM, Perrard XY, Brunner G, Lui H, Sparks LM, Smith SR, et al. Intermuscular and perimuscular fat expansion in obesity correlates with skeletal muscle T cell and macrophage infiltration and insulin resistance. Int J Obes (Lond). 2015;39(11):1607-18.
33. Visser M, Goodpaster BH, Kritchevsky SB, Newman AB, Nevitt M, Rubin SM, et al. Muscle mass, muscle strength, and muscle fat infiltration as predictors of incident

mobility limitations in well-functioning older persons. J Gerontol A Biol Sci Med Sci. 2005;60(3):324-33.

34. Norman K, Stobaus N, Pirlich M, Bosy-Westphal A. Bioelectrical phase angle and impedance vector analysis--clinical relevance and applicability of impedance parameters. Clin Nutr. 2012;31(6):854-61.
35. Fried LP, Hadley EC, Walston JD, Newman AB, Newman A, Guralnik JM, et al. From bedside to bench: research agenda for frailty. Sci Aging Knowledge Environ. 2005;2005(31):pe24.
36. Sánchez-García S, García-Peña C, Salvà A, Sánchez-Arenas R, Granados-García V, Cuadros-Moreno J, et al. Frailty in community-dwelling older adults: association with adverse outcomes. Clin Interv Aging. 2017;12:1003-11.
37. Williams GR, Deal AM, Muss HB, Weinberg MS, Sanoff HK, Guerard EJ, et al. Frailty and skeletal muscle in older adults with cancer. J Geriatr Oncol. 2018;9(1):68-73.
38. Strasser B, Steindorf K, Wiskemann J, Ulrich CM. Impact of resistance training in cancer survivors: a meta-analysis. Med Sci Sports Exerc. 2013;45(11):2080-90.
39. Murphy RA, Mourtzakis M, Chu QS, Baracos VE, Reiman T, Mazurak VC. Nutritional intervention with fish oil provides a benefit over standard of care for weight and skeletal muscle mass in patients with nonsmall cell lung cancer receiving chemotherapy. Cancer. 2011;117(8):1775-82.
40. Ewaschuk JB, Almasud A, Mazurak VC. Role of n-3 fatty acids in muscle loss and myosteatosis. Appl Physiol Nutr Metab. 2014;39(6):654-62.

4.2 **Artigo 2: Diagnosis of muscle wasting in colorectal cancer patients by computed tomography and surrogate methods: which one can better identify low muscularity and predict poor outcome?**

Este trabalho procurou responder ao primeiro objetivo específico da tese: avaliar a validade dos métodos de avaliação da massa muscular utilizados na prática clínica em comparação com a tomografia computadorizada; avaliar a associação entre a redução da massa muscular, avaliada por diferentes métodos, e os parâmetros clínicos e de estado nutricional; e identificar qual método substitutivo apresenta maior valor prognóstico para mortalidade no diagnóstico de redução de massa muscular.

O artigo será submetido à publicação após a defesa da tese e após ouvir as considerações da banca.

Diagnosis of muscle wasting in colorectal cancer patients by computed tomography and surrogate methods: which one can better identify low muscularity and predict poor outcome?

Nilian Carla Silva Souza [a,f], Maria Cristina Gonzalez [b], Renata Brum Martucci [a, e], Viviane Dias Rodrigues [a], Nivaldo Barroso de Pinho [c], Abdul Rashid Qureshi [d], Carla Maria Avesani [d, e, f]

[a] Nutrition and Dietetic Service, Cancer Hospital Unit I, National Cancer Institute José Alencar Gomes da Silva, Rio de Janeiro, Brazil.

[b] Post-graduate Program in Health and Behavior, Catholic University of Pelotas, Pelotas, Brazil.

[c] Technical Support Division, Cancer Hospital Unit I, National Cancer Institute José Alencar Gomes da Silva, Rio de Janeiro, Brazil.

[d] Divisions of Renal Medicine and Baxter Novum, Department of Clinical Science, Intervention and Technology, Karolinska Institutet, Stockholm, Sweden.

[e] Department of Applied Nutrition, Nutrition Institute, Rio de Janeiro State University, Rio de Janeiro, Brazil.

[f] Graduation Program in Nutrition, Food and Health. Nutrition Institute, Rio de Janeiro State University, Rio de Janeiro, Brazil.

Corresponding author:

Nilian Carla Silva Souza

Praça da Cruz Vermelha, 23, 5˚ andar, Centro, Rio de Janeiro, RJ, 20230-130, Brazil. Fax: +55 21 3207-1665.

Email: niliansouza@yahoo.com.br

ABSTRACT

Background & Aims: Considering the importance of assessing muscle mass in patients with cancer, we aimed to evaluate the agreement between computed tomography (CT) with surrogate methods commonly applied in clinical practice for the assessment of low muscularity, the association between different muscle measurements with clinical parameters and nutritional status and the prognostic value of low muscle mass with survival for all muscle measurements studied in patients with colorectal cancer (CRC). **Methods:** Cohort study including CRC patients with 17 months follow-up (interquartile range 12-23) for mortality. Low muscle mass was evaluated by corrected mid-upper arm muscle area (AMAc), calf circumference, skeletal muscle mass by bioelectrical impedance analysis (BIA), muscle deficit by the physical examination from the Patient-generated Subjective Global Assessment (PG-SGA) and lumbar muscle cross-sectional area by CT, which was used as the reference method. For CT, the skeletal muscle mass index (SMI) was calculated as muscle cross-sectional area (cm^2)/height^2 (m^2) at third lumbar vertebra with cutoff points: men < 44.7 cm^2/m^2, women < 32.8 cm^2/m^2; AMAc: men < 21.4 cm^2, women: < 21.6 cm^2; SMI from BIA: men < 10.76 kg/m^2, women: < 6.76 kg/m^2; calf circumference: men < 34 cm, women < 33 cm; and deficit of muscle scored as +1, +2 or +3 from physical exam. **Results:** This study included 188 patients (age 61 ±11.4 years; 57% men, 32% with malnutrition by the PG-SGA). The prevalence of low muscle mass was 9.6% for AMAc, 20.2% for calf circumference, 54.3% for BIA, 29.3% for physical exam and 17.6% for CT. Among the methods tested, the physical exam had the highest kappa coefficient compared to CT (kappa coefficient: 0.48; sensitivity: 47.3%, specificity: 94.7%). Low Muscularity groups had higher proportion of malnourished individuals and lower values of body mass index, body fat percentage (% BF) and phase angle. The Cox regression models adjusted for age, sex and tumor stage showed that, except for low muscle mass assessed by BIA, the Low Muscularity groups predicted higher mortality rates than the Normal Muscularity group. However, physical exam had the highest hazard ratio and C-statistic value among all methods investigated (HR: 2.58; 95%IC: 1.47-4.53; C-statistic: 0.69). **Conclusions:** Compared with CT, physical exam had the best agreement to assess low muscle mass in CRC patients. The Low Muscularity groups had higher proportion of malnourished individuals and lower % BF. In addition, physical exam showed the strongest predictive results in the survival analysis among all methods investigated.

Keywords: Low muscle mass, computed tomography, cancer.

4.2.1 Introduction

Low muscle mass is a common feature of patients with cancer with an estimated prevalence varying from 5 to 89% depending on the method and cutoff applied for its diagnose (1, 2). The etiology of low muscle mass in patients with cancer is multifactorial and mainly involves an inhibition of protein synthesis and an increase in protein degradation, leading to a negative protein balance (3). The factors contributing to low muscle mass include tumor-related mechanisms, host response to tumor, anticancer treatment, reduced protein intake and physical inactivity (3). Of note, as shown in recent studies, low muscle mass can also occur in overweight and obese people (4-7) and it is associated with shorter survival, chemotherapy toxicity, tumor progression, adverse postoperative outcomes and poor quality of life in patients with cancer (4-6, 8-10).

Although muscle mass assessment appears to be mandatory for patients with cancer, it is not routinely performed in clinical practice. Among the methods that yields muscle mass assessments by suitable tools for clinical practice, the anthropometric measurements (mid-upper arm muscle circumference, calf circumference and adductor pollicis muscle thickness) and Bioelectrical Impedance Analysis (BIA) emerge due to its characteristics of being portable, noninvasive and inexpensive. However, these methods have limited applicability in obese patients and when edema is present (11). Another method currently performed to assess nutritional status in patients with cancer is the Patient-generated Subjective Global Assessment (PG-SGA) (12). This method is rapid, cost effective and feasible, and therefore can be easily implemented in clinical settings to assess muscle mass as it includes the assessment of muscle deficit in the physical exam.

In parallel, Computed Tomography (CT) is considered a gold-standard method for evaluating body composition (13). Recently, the level of the third lumbar vertebra (L3) from CT scan has been validated as the standard landmark for assess body composition in patients with cancer (14) and has been opportunistically used to assess muscle mass in some studies in oncologic and non-oncologic individuals (15-18). Although CT scan of the abdomen include L3 and it is routinely used for diagnosis and follow-up in colorectal cancer (CRC) patients, its high cost, the need of training and the exposition to radiation dose limit the use of CT to research purposes and highlight the importance of testing other methods to assess muscle mass in clinical practice. Therefore, considering the importance of assessing muscle mass in patients with cancer, we aimed to evaluate in a sample of patients with CRC the agreement, sensibility and specificity between CT and surrogate methods highly applied in the clinical setting to diagnose low muscle mass, to explore the association between different muscle mass measurements for the diagnosis of low muscle mass with clinical parameters and

nutritional status, and to test which low muscle mass assessment method has the best prognostic value to predict overall survival.

4.2.2 Materials and methods

4.2.2.1 Subjects and study design

This study included patients with CRC recruited between April 2015 and June 2016 at the outpatient clinic of the Cancer Hospital Unit I of the National Cancer Institute José Alencar Gomes da Silva (INCA, Rio de Janeiro, Brazil). Those who met eligibility criteria and were scheduled for abdominal CT scan at the L3 region, as part of routine care, were invited to participate. Inclusion criteria comprised age higher than 18 years old and Eastern Cooperative Oncology Group performance status below 3. In addition, those with physical deformity unable to carry out tests for muscle strength or physical performance, with pacemaker, congestive heart failure, chronic kidney disease, liver cirrhosis, anal canal cancer, synchronous colorectal cancer and with more than one cancer type were not included in the study. From 204 patients initially invited to participate in the study 188 were eligible to participate. The reasons for dropout are depicted in **Figure 1**. The local Research Ethical Committee from National Cancer Institute José Alencar Gomes da Silva approved the study (protocol number 38992014.5.0000.5274) and a written informed consent was obtained from each subject before their inclusion.

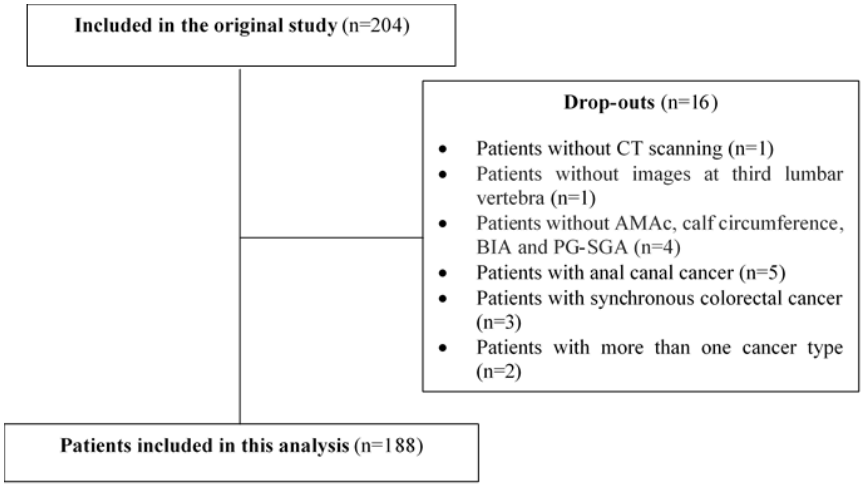


Figure 1- Flow chart of study inclusion and exclusion.
CT: Computed tomography; AMAc: Corrected mid-upper arm muscle circumference; BIA: Bioelectrical impedance analysis; PG-SGA: Patient-generated subjective global assessment.

4.2.2.2 Study protocol

After consenting to participate, patients received instructions to fast for 6 h before the CT scan (water-soluble oral contrast and medication were allowed). After CT scan, all participants had the nutritional status, body composition, and muscle function assessed. Blood samples were then scheduled to be collected under fasting conditions not later than 30 days after the CT scan. Clinical data were collected from medical records such as age, sex, previous and current treatment, comorbidities, performance status, tumor site and stage.

4.2.2.3 Muscle mass assessment

Five different muscle mass measurements were used to diagnose low muscle mass according to the cutoffs shown in Table 1: corrected mid-upper arm muscle area (AMAc), calf circumference, skeletal muscle mass (SMM) from BIA (19), physical exam of muscle mass deficit from PG-SGA and muscle cross-sectional area from CT scans. According to each of these measurements and cutoffs described in Table 1, patients were classified as Low Muscularity group and Normal Muscularity group.

Corrected mid-upper arm muscle area (AMAc): AMAc was calculated according to the equation AMAc (cm^2) = [Mid upper arm circumference (cm) - 0.314 × triceps skinfold thickness (mm)]$^2 / 4\pi$, corrected by sex (- 10 for men and– 6.5 for women, respectively) (20). Mid-upper arm circumference was measured three times by a trained dietitian at the midpoint of the non-dominant upper arm between the acromion process and the tip of the olecranon process, using a non-elastic, flexible measuring tape. The triceps skin fold (TSF) was measured three times at the same point using a Lange® caliper (Cambridge Scientific Industries, Inc.). The mean value of these measurements was recorded.

Calf circumference: It was assessed by using an inextensible tape with the subject in the sitting position, feet 20 cm apart. The measurement was taken on both sides at the point of greatest circumference. The mean of the three measurements was calculated.

Bioelectrical impedance analysis (BIA) for Skeletal muscle mass (SMM) : It was determined using the Janssen's equation as follows (19):

SMM (kg)= [((height centimeter)^2 / resistance × 0.401) + (sex (0 for female and 1 for male) × 3.825) + (age years × (-0.071))] + 5.102.

A bioelectrical impedance analyzer, tetrapolar device model Quantum II (RJL Systems, Detroit, MI, USA), with an electrical current of 800 μA at 50 kHz was used to assess resistance and reactance values in Ohms (Ω). SMM was normalized by height squared (m^2) and reported as skeletal muscle index (SMI) (kg/m^2). In addition, phase angle was calculated with the following equation: phase angle (degrees) = arctan (Xc/R) x (180/Π).

Physical examination of muscle mass deficit: It is part of the PG-SGA form (12). Muscle wasting was investigated by a trained dietitian through visual inspection and palpation of muscles with loss of bulk and tone in the sites of temple, clavicle, shoulder, scapula, thigh, calf and interosseous muscle indicating muscle depletion. The degree of muscle depletion was evaluated and rated as 0 (normal), +1 (mild), +2 (moderate) and +3 (severe). The assessment was carried out by trained dietitian.

Computed tomography (CT) for skeletal muscle area (cm^2): It was assessed with the Slice-O-matic software, version 5.0 (Tomovision, Montreal, Quebec, Canada) using routine CT scans conducted for diagnostic/follow-up purposes and were digitally stored in the patient's medical record. One image extending from L3 was assessed for skeletal muscle (psoas, erector spinae, quadratus lumborum, transversus abdominus, external and internal obliques, and rectus abdominus). CT Hounsfield unit (HU) thresholds -29HU to +150HU were used for skeletal muscle, -190HU to -30HU for subcutaneous adipose tissue and intramuscular adipose tissue and -150HU to -50HU for visceral adipose tissue (14). The same trained dietitian read all the CT images. Skeletal muscle area was normalized by height squared (m^2) and reported as lumbar skeletal muscle index (SMI) (cm^2/m^2). Muscle attenuation was also evaluated from CT and was derived by averaging the Hounsfield unit of skeletal muscle. The percentage of muscle fat infiltration (% MFI) in relation to the skeletal muscle mass at the L3 slice was also calculated using the following formula (21):

% MFI = IAT (cm^2)/[IAT (cm^2) + SMM(cm^2)] x 100, where MFI: muscle fat infiltration; IAT: intramuscular adipose tissue; SMM: skeletal muscle mass.

Table 1- Low muscle mass according to different methods and cut-offs

Methods	Cut-off	Reference
AMAc		
Male	< 21.4 cm^2	(22)
Female	< 21.6 cm^2	
Calf Circumference		(23)
Male	< 34 cm	
Female	< 33 cm	
SMI - BIA		
Male	SMI < 10.7 6 kg/m^2	(24)
Female	SMI < 6.76 kg/m^2	
MM physical exam from PG-SGA	Muscle mass deficit: +1, +2 ou +3	(12)
SMI - CT		
Male	SMI < 44.7 cm^2/m^{2a}	(25)
Female	SMI < 32.8 cm^2/m^{2a}	

AMAc: Corrected mid-upper arm muscle circumference; MM: Muscle mass; PG-SGA: Patient-generated subjective global assessment; SMI: Skeletal muscle index; BIA: Bioelectrical impedance analysis; CT: Computed tomography.
[a]Cut-off values of muscle mass at L3 level for CT scans are based on SMI 10th percentile values of a healthy Caucasian population (25).

4.2.2.4 Measurement of muscle strength and physical performance

Muscle strength was measured using a Jamar® hydraulic hand dynamometer (Sammons Preston, Chicago, IL). Each individual sat in a chair and the upper limb was placed alongside the body with the elbow at a 90˚ angle; the contralateral limb was relaxed on the thigh. During the exam, the patient was instructed to use the maximum strength in each measurement. Three measurements were determined for each hand in an alternating manner, and the maximum strength was defined as the greatest of the six measurements.

Physical performance was assessed by 4.6 m gait speed test. The subject was instructed to walk as fast as possible, but not running, through a predetermined 4.6 m straight path with no obstacles while the time to complete the course was measured. The test was applied twice, with an interval of approximately 30 seconds between applications, and the lower of the two measurements was considered for use.

4.2.2.5 Nutritional assessment

Body weight (kg) was assessed using a platform-type mechanical scale (Filizola, São Paulo, Brazil) with a maximum capacity of 150 kg and variation 0.1 kg and height (cm) by a vertical stadiometer 200 cm long and with a 0.1 cm precision. Body mass index (BMI) was calculated as body weight in kilograms divided by squared height. The percentage of total body fat (% BF) was assessed by BIA based on the predictive equation provided from the manufacturer's software. Obesity was defined according to sex-and-age-specific % BF cutoff points for the healthy population (26). In addition, the PG-SGA was also used to assess nutritional status. It includes two sections: (1) history of weight loss over the previous six months, dietary intake, gastro-intestinal symptoms and functional capacity; (2) clinical condition, metabolic stress, and physical examination assessing muscle wasting, loss of subcutaneous fat mass and presence of edema/ascites. In order to evaluate nutritional status, each patient is classified as well nourished (PG-SGA A) and malnourished (PG-SGA B and C) (12).

4.2.2.6 Laboratorial measurements

Serum dosages of albumin (green bromocresol) and high-sensitivity C-reactive protein (CRP) (turbidimetric method) was measured by specific kits from Roche® using a COBAS 311 analyzer (Roche Diagnostics®, Mannheim, German) in the laboratory of the Cancer Hospital Unit I of the National Cancer Institute José Alencar Gomes da Silva.

4.2.2.7 Overall survival

Survival data were obtained from the electronic medical record of each patient after one year the last patient had been included (median: 17 months; interquartile range: 12-23 months). Survival time was defined as time from inclusion in the study until death and recorded as number of months. Patient who were still alive were censored at date of last consultation in the hospital.

4.2.2.8 Statistical analyses

Continuous variables were summarized as mean ± standard deviation or median and interquartile range, depending on its normality distribution (assessed by Shapiro-Wilk test). Categorical variables were summarized as the absolute frequencies and their corresponding percentages. To assess differences or association among clinical parameters, nutritional status, body composition, and physical function according to the presence of low muscle mass based on different muscle measurements, t-tests were used for normal distributed variables, Mann Whitney test for not normal distributed variables and Chi-square test for categorical variables. The agreement between CT and the surrogate methods for the assessment of muscle mass (AMAc, calf circumference, SMI from BIA, muscle mass deficit from PG-SGA physical exam) was evaluated by kappa test. The kappa value of agreement can be interpreted as follows: 0.20 poor, 0.21 to 0.60 moderate, 0.61 to 0.80 good and 0.81 to 1.00 very good (27). The sensitivity and specificity of the methods were assessed through a cross-reference table. Kaplan Meier survival curves for different muscle mass measurements were also performed. Multiple Cox regression analysis were performed to test associations between overall survival and Low Muscularity groups assessed by different muscle mass measurements adjusted for age, sex and tumor stage. Harrell's C statistic (C-statistic) test was calculated for all measurements to assess which muscle mass method showed the best predictive accuracy for survival. In this test, the higher C-statistic value, the better the model's accuracy. Statistical significance was defined as p values below 0.05. The Statistical Package for the Social Sciences (SPSS) version 20.0 (SPSS, Inc., Chicago, IL, USA) was used for the statistical analyses, except for C-statistics, in which STATA 15.0 was used.

4.2.3 Results

This study included 188 patients, mostly males (n=108; 57%) with a mean age of 61 ± 11.4 years, mean BMI of 27.1 ± 5.4 kg⁄m^2 and with 32% (n=60) of the patients with malnutrition according to PG-SGA. Moreover, the majority had cancer on stage III to IV (n=147; 78%) and 58% (n=108) had performance status 1 and 2. The prevalence of low muscle varied from 9.6% to 54.3% depending on the method applied to assess muscle mass (**Figure 2**).

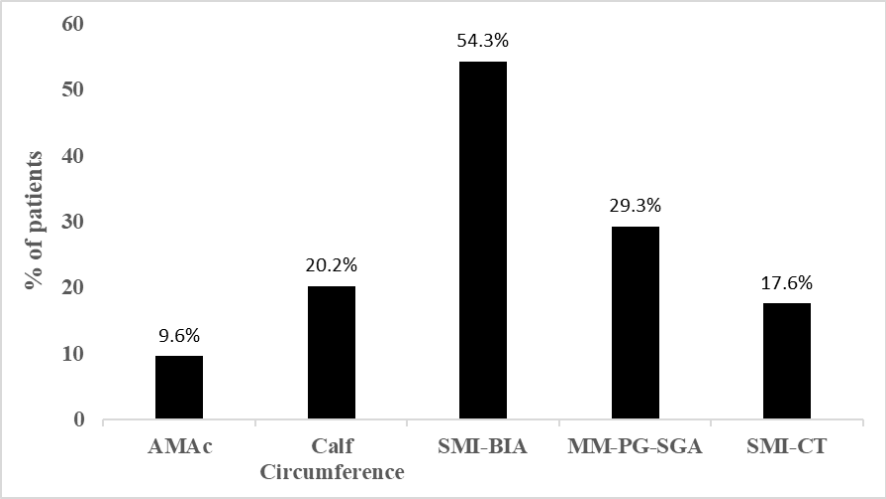


Figure 2- Low muscle mass prevalence according to different muscle mass measurements techniques (n=188).
AMAc: Corrected mid-upper arm muscle circumference; SMI: Skeletal muscle index; BIA: Bioelectrical impedance analysis; MM-PG-SGA: Muscle mass assessed by patient-generated subjective global assessment; CT: Computed tomography.

The agreement between CT and the surrogate methods for the assessment of low muscle mass is shown in **Table 2**. As can be seen, the kappa coefficients were indicative of moderate agreement and the specificity was higher than the sensibility. Although showing low sensibility, the physical exam had the highest kappa coefficient among all methods tested.

Table 2- Agreement between muscle mass evaluated by computed tomography and methods applied in clinical practice (n = 188)

	Kappa test (r;*p*)	**Sensibility (%)**	**Specificity (%)**
CT *vs* AMAc	0.26 (<0.01)	50	85.9
CT *vs* Calf Circumference	0.32 (<0.01)	42.1	88.7
CT *vs* SMI-BIA	0.26 (<0.01)	30.4	97.7
CT *vs* MM-PG-SGA	0.48 (<0.01)	47.3	94.7

CT: Computed tomography; AMAc: Corrected mid-upper arm muscle circumference SMI: Skeletal muscle index; BIA: Bioelectrical impedance analysis; MM-PG-SGA: Muscle mass assessed by patient-generated subjective global assessment.

Table 3 and **Table 4** describe clinical parameters, nutritional status, body composition and physical function according to Low Muscularity groups defined by different muscle mass methods. Differences between Low Muscularity and Normal Muscularity groups were observed for sex when muscle mass was assessed by BIA and CT; for age when assessed by

BIA; for performance status when assessed by calf circumference and physical exam (**Table 3**). These differences showed that the Low Muscularity group had higher proportion of males, older patients and worse performance status. For all methods applied to assess muscle mass, the patients in the Low Muscularity group had significantly lower BMI, higher prevalence of malnutrition and lower values of phase angle, subcutaneous adipose tissue, % BF and visceral adipose tissue (except for BIA) (**Table 4**). Moreover, handgrip strength was lower in Low Muscularity group when assessed by AMAc, calf circumference and BIA and gait speed was lower when assessed by AMAc, calf circumference and physical exam. Interestingly, in the Low Muscularity groups, % BF was within the normal values and not indicating malnutrition. Similarly, serum albumin was within the normal range (>3.5 g/dL) in both groups (**Table 4**).

Table 3- Differences in clinical parameters between Low Muscularity groups defined by different muscle mass measurements (n=188)

	AMAc			**Calf Circumference**			**SMI – BIA**			**MM-PG-SGA**			**SMI – CT**		
	Low muscularity (n=18)	Normal muscularity (n=170)	***P***	Low muscularity (n=38)	Normal muscularity (n=150)	***P***	Low muscularity (n=102)	Normal muscularity (n=86)	***P***	Low muscularity (n=55)	Normal muscularity (n=133)	***P***	Low muscularity (n=33)	Normal muscularity (n=155)	***P***
Male [n (%)] [a]	7 (39%)	101 (59%)	0.09	20 (53%)	88 (59%)	0.50	81 (79%)	27 (31%)	**<0.01**	36 (66%)	72 (54%)	0.15	28 (85%)	80 (52%)	**<0.01**
Age (years) [b]	57.6±12.5	60.8±11.3	0.31	64±13.2	59.6±10.7	0.06	62±11.8	58.6±10.6	**0.03**	62.6±11.4	59.6±11.3	0.10	62.4±11.3	60.1±11.4	0.27
PS [n (%)] [a, †]															
0	5 (28%)	73 (43%)	0.43	10 (26%)	68 (46%)	**0.03**	43 (42%)	35 (42%)	0.99	15 (27%)	63 (48%)	**0.02**	12 (36%)	66 (43%)	0.75
1-2	13 (72%)	95 (57%)		28 (74%)	80 (54%)		59 (58%)	49 (58%)		40 (73%)	68 (52%)		21 (64%)	87 (57%)	
Tumor Stage [n (%)][a]	2 (11%)	39 (23%)	0.24	8 (21%)	33 (22%)	0.89	19 (19%)	22 (26%)	0.25	10 (18%)	31 (23%)	0.43	5 (15%)	36 (23%)	0.30
0-II	16 (89%)	131 (77%)		30 (79%)	117 (78%)		83 (81%)	64 (74%)		45 (82%)	102 (77%)		28 (85%)	119 (77%)	
III-IV															

Results are shown as n (%), mean ± standard deviation or median (IQR Q1-Q3). AMAc: Corrected mid-upper arm muscle circumference; SMI: Skeletal muscle index; BIA: Bioelectrical impedance analysis; MM-PG-SGA: Muscle mass assessed by patient-generated subjective global assessment; CT: Computed tomography; PS: Performance status; [a] Chi-square test; [b] t test; [†] N=186.

Table 4- Differences in nutritional status and body composition between Low Muscularity groups defined by different muscle mass measurements (n=188)

	AMAc			Calf Circumference			SMI – BIA			MM-PG-SGA			SMI - CT		
	Low muscularity (n=18)	Normal muscularity (n=170)	***P***	Low muscularity (n=38)	Normal muscularity (n=150)	***P***	Low muscularity (n=102)	Normal muscularity (n=86)	***P***	Low muscularity (n=55)	Normal muscularity (n=133)	***P***	Low muscularity (n=33)	Normal muscularity (n=155)	***P***
BMI (kg/m²) [a]	21.7±4.9	27.9±5.1	**<0.01**	21.8±3.2	28.7±4.9	**<0.01**	24.8±4.1	30.3±5.2	**<0.01**	21.7±2.4	29.6±4.5	**<0.01**	22.3±3	28.4±5.2	**<0.01**
PG-SGA B/C [n (%)] [b]	14 (78%)	46 (27%)	**<0.01**	25 (66%)	35 (23%)	**<0.01**	43 (42%)	17 (20%)	**<0.01**	47 (85%)	13 (10%)	**<0.01**	26 (79%)	34 (22%)	**<0.01**
Albumin (g/dL) [a, †]	4.1±0.5	4.4±0.4	0.07	4.1±0.5	4.4±0.3	**<0.01**	4.4±0.4	4.3±0.4	0.70	4.1±0.4	4.4±0.3	**<0.01**	4.2±0.3	4.4±0.4	**0.03**
CRP (mg/dL) [c, □]	0.5 (0.3-1.4)	0.4 (0.2 – 0.9)	0.67	0.4 (0.2-1.7)	0.4 (0.3-0.9)	0.95	0.4 (0.2-1)	0.5 (0.3-0.9)	0.84	0.4 (0.2-1.4)	0.4 (0.3 – 0.9)	0.53	0.4 (0.3-1.6)	0.4 (0.2-0.9)	0.38
PA (°) [a]	4.9±0.8	5.7±0.9	**<0.01**	4.9±0.9	5.8±0.9	**<0.01**	5.5±1	5.8±0.9	**0.04**	4.9±0.8	5.9±0.8	**<0.01**	4.9±0.7	5.8±0.9	**<0.01**
MA (HU) [a]	33.8±11	34.5±7.6	0.72	34.1±9.6	34.5±7.5	0.80	35.5±7.6	33±8.1	**0.03**	35.5±9.1	33.9±7.4	0.22	35.2±8.6	34.2±7.8	0.52
MFI (%) [c]	7.7 (5.2-11.6)	5.3 (3.1-9.6)	0.07	6.5 (4.2-10.6)	5.5 (3.1-9.2)	0.15	5.6 (3.4-10.4)	5.5 (3-8.6)	0.31	8 (4.7-11.7)	4.9 (2.8-8.5)	**<0.01**	7.1 (3.6-12.7)	5.3 (3.2-9.4)	0.15
SAT (cm²) [c]	95 (52-153)	170 (121-242)	**<0.01**	99 (65-148)	182 (134-282)	**<0.01**	135 (96-171)	224 (158-334)	**<0.01**	96 (55-134)	206 (152-290)	**<0.01**	103 (74-149)	182 (127-281)	**<0.01**
VAT (cm²) [c]	53 (31-87)	134 (75-187)	**<0.01**	58 (31-110)	142 (80-193)	**<0.01**	115 (54-183)	139 (72-182)	0.27	54 (31-127)	143 (89-198)	**<0.01**	78 (48-167)	134 (75-183)	**0.02**
Body fat (%) [c]	27 (17-36)	35 (28-42)	**0.02**	27 (17-36)	35 (28-42)	**<0.01**	30 (23-35)	41 (34-49)	**<0.01**	26 (19-33)	38 (31-47)	**<0.01**	26 (20-33)	36 (30-45)	**<0.01**
HGS (kg) [c]	22 (18-29)	30 (24-37)	**<0.01**	25 (18-29)	32 (24-38)	**<0.01**	34 (26-37)	27 (22-32)	**<0.01**	28 (20-35)	30 (24-38)	0.07	32 (26-36)	29 (22-37)	0.50
GS (m/s) [a]	0.98±0.18	1.09±0.24	**0.02**	0.97±0.18	1.11±0.24	**<0.01**	1.11±0,24	1.05±0.24	0.09	1.03±0.24	1.11±0.24	**0.04**	1.09±0.25	1.08±0.24	0.97

Results are shown as n (%), mean ± standard deviation or median (IQR Q1-Q3). AMAc: Corrected mid-upper arm muscle circumference; SMI: Skeletal muscle index; BIA: Bioelectrical impedance analysis; MM-PG-SGA: Muscle mass assessed by patient-generated subjective global assessment; CT: Computed tomography; BMI: Body mass index; PG-SGA: Patient-generated subjective global assessment; CRP: C-reactive protein; PA: Phase angle; MA: Muscle attenuation; MFI: Muscle fat infiltration; SAT: Subcutaneous adipose tissue; VAT: Visceral adipose tissue; HGS: Handgrip strength; GS: Gait speed; [a] t test; [b] Chi-square test; [c] Mann-Whitney test; [†] N=168; [□] N=157.

After 17 months (interquartile range 12-23 months) of follow-up, there were 52 deaths. The number of deceased patients in the groups of low muscle mass were 8 when assessed by AMAc, 16 by calf circumference, 32 by BIA, 25 by physical exam and 16 by CT, representing 44%, 42%, 31%, 45% and 48% in each group respectively. **Figure 3** shows the survival plots by the different methods assessing low muscle mass. Of note, except for the group of low muscle mass assessed by BIA, patients with low muscle mass had significantly lower survival. The Cox model adjusted by sex, age and tumor stage (**Table 5**) showed that the Low Muscularity group had an increased hazard ratio for mortality when muscle mass was assessed by calf circumference, physical exam and CT, but not by AMAc and BIA. Of note, muscle wasting assessed by the physical exam had the highest hazard ratio (HR: 2.58; 95%IC: 1.47-4.53) and C-statistic value (0.69) among all methods investigated.

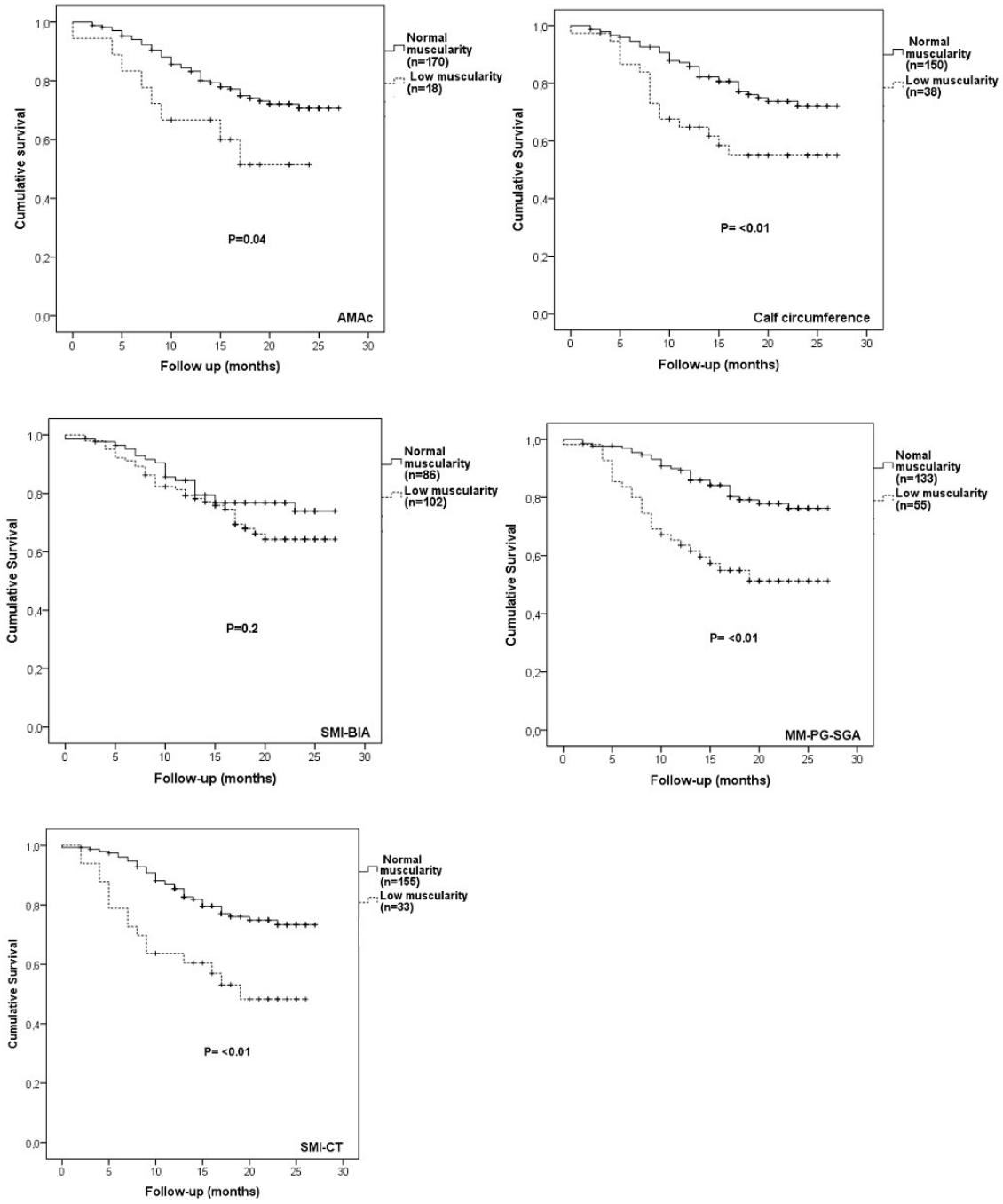


Figure 3- Kaplan Meier survival curves of different muscle mass measurements (n=188). AMAc: Corrected mid-upper arm muscle circumference; SMI: Skeletal muscle index; BIA: Bioelectrical impedance analysis, MM-PG-SGA: Muscle mass assessed by patient-generated subjective global assessment; CT: Computed tomography.

Table 5- Multiple Cox regression analysis of different muscle mass measurements (n=188)

Variable	HR	95% CI	*P*	C-statistic
Model 1[a]				
Low muscle mass- AMAc	1.93	0.85; 4.36	0.11	0.63
Model 2 [a]				
Low muscle mass- Calf circumference	2.04	1.10; 3.75	**0.02**	0.65
Model 3 [a]				
Low muscle mass- SMI-BIA	1.17	0.61; 2.25	0.62	0.63
Model 4 [a]				
Low muscle mass- MM-PG-SGA	2.58	1.47; 4.53	**<0.01**	0.69
Model 5 [a]				
Low muscle mass- SMI-CT	2.31	1.24; 4.29	**<0.01**	0.65

AMAc: Corrected mid-upper arm muscle circumference; SMI: Skeletal muscle index; BIA: Bioelectrical impedance analysis; MM-PG-SGA: Muscle mass assessed by patient-generated subjective global assessment; CT: Computed tomography; HR, Hazard ratio; CI: Confidence interval; [a] Adjusted for age, sex and tumor stage. The group with normal muscularity was taken as reference for the analysis.

4.2.4 Discussion

This study aimed to evaluate the agreement between CT with surrogate methods highly applied in the clinical setting for the assessment of muscle mass and to assess the prognostic value of low muscle mass with survival in a follow-up of 17 months in a representative group of 188 well characterized CRC patients. Our main finding was that among all methods tested, muscle wasting assessed by the physical exam from PG-SGA showed the highest kappa coefficient and the best agreement with CT, which was taken as the reference method. In addition, as expected, the Low Muscularity groups had higher proportion of malnourished individuals and lower % BF. Depending on the method applied to assess muscle mass, the Low Muscularity groups had lower handgrip strength and gait speed, denoting lower strength and muscle function. Finally, the Cox regression models adjusted for age, sex and tumor stage showed that, except for low muscle mass assessed by AMAc and BIA, the Low Muscularity groups predicted higher mortality rates than the Normal Muscularity group. Moreover, the method of the physical exam had the highest hazard ratio and C-statistic value among all methods investigated. These results are aligned with the notion that low muscle mass has a negative impact on outcome, which emphasizes the importance of implementing its assessment by a method that can be easily used in the routine care of cancer patients.

In addition, we observed a wide variation on the prevalence of low muscle mass (9.6% to 54.3%) depending on the method applied, which was similar to the reported findings in two studies carried on patients with varying types of cancer (1, 2) . This large variability may be explained not only by different methods applied, but also by distinct thresholds to screen for low muscle mass. Although the European Working Group on Sarcopenia in Older People recommends using normative data of the study population (24), researchers have used different cutoff points of the distinct populations to assess low muscle mass and the results may be difficult to interpret. Therefore, our findings together with those previous reported highlights the importance of exploring which method has the best agreement with a reference method. In this regard, we showed that the muscle deficit assessed by the physical exam from the PG-SGA had the best agreement with CT, the later considered a gold standard method for this end (28) and in an area that was shown to reflect the muscle mass of the whole body in healthy individuals (17) and in patients with cancer (14). We speculate that the good performance of physical exam may result from the fact that it includes the assessment of seven sites of the body (temple, clavicle, shoulder, scapula, thigh, calf and interosseous muscle), which will be rated according to the clinical judgement of the examiner in +1 (mild), + 2 (moderate) and +3 (severe) of muscle deficit. Hence, we hypothesize that it can yield a better overall condition of muscle depletion than the other methods, such as calf circumference and AMAc, that restricts the assessment to one site of muscle area. Preferably, the physical exam should be performed by a trained dietitian, but other health care professionals (nurses, physicians, physiotherapist) can also be trained for that. As there is no need of equipment and the exam takes less than 10 minutes to be completed, it can be easily implemented in the clinical setting, such as in outpatient clinics and hospitals. However, it should be acknowledged that the physical exam has the disadvantage of not being an objective measurement and therefore, can be subjected to a large inter and intra examiner variability, which requires further investigation. In agreement with our results, Raeder et al. in a study with 97 non-metastatic CRC patients identified 64% of sensitivity and 78% of specificity of the physical exam from PG-SGA when compared with fat free mass estimated by BIA (29). On the other hand, in a study from our group carried in non-dialyzed chronic kidney disease patients, we failed to show a good agreement between CT and the physical exam from Subjective Global Assessment (kappa coefficient in male: 0.32; sensitivity: 40%; specificity: 88%; kappa coefficient in female: -0.12; sensitivity: 9%; specificity: 79%) (18). The difference in the results between oncologic and chronic kidney disease patients may be attributed to the characteristics related to the group itself. Chronic kidney disease patients are

known to show fluctuation in the hydration status that is likely not to be visualized by the physical exam (30), unless it comes as a pronounced edema. It indicates that the performance of methods assessing body composition and therefore, low muscle mass, should be carefully investigated in different clinical settings. In addition, it should also be kept in mind that the results from our study, as well from the previous one in patients with cancer showed a better specificity than sensibility of the physical exam to diagnose muscle wasting, suggesting a limited capacity to detect the true cases of low muscle mass. Despite of these findings, the physical exam was able to differentiate nutritional status between patients with and without muscle wasting.

Also of note, in our findings the Low Muscularity group had worse nutritional status than the Normal Muscularity group, as depicted by higher prevalence of malnutrition by PG-SGA, lower values of phase angle, BMI, abdominal subcutaneous adipose tissue and % BF. However, in all groups of low muscle mass, the mean % BF was not indicative of low values, suggesting that overweight and obesity can occur together with low muscle mass, which is known as sarcopenia obesity (4-7). Similarly, for all methods applied, serum albumin was indicative of normal values, that is above 3.5 g⁄dL, even in the Low Muscularity group, which is aligned with the median CRP levels denoting low degree of inflammation, suggesting that serum albumin is not a marker of low muscle mass, but most likely, a response of an inflammatory condition. Finally, phase angle, considered a marker of the amount and quality of soft tissue mass (31), was able to detect the differences between the group with and without muscle loss.

Finally, we furthered our analysis by investigating the prognostic outcome on overall mortality of low muscle mass diagnosed by different methods. Except for AMAc and BIA, low muscle mass diagnosed by the remaining methods were able to predict overall mortality in the models adjusted for sex, age and cancer stage. Our findings are not in accordance with a previous study (32) in which among the methods applied to diagnose for cachexia in patients with cancer, AMAc had the higher hazard ratio compared to the other methods investigated (HR: 2.00 (95% CI: 1.42; 2.83) for AMAc; HR: 1.64 (95% CI: 1.15; 2.34) for CT and 1.50 (1.05; 2.14) for BIA). The lack of agreement with our results is likely to be explained by the fact that Blauwhoff-Buskermolen et al. (32) applied different cutoffs for AMAc, BIA and CT and assessed muscle mass by CT in L3 and in fourth thoracic vertebra, while we assessed at L3. Moreover, in our study, the physical exam had the highest hazard ratio for mortality (HR: 2.58; 95%IC: 1.47-4.53) and the higher C-statistics (0.69). We are not aware of studies in patients with cancer testing the prognostic effect of muscle wasting assessed by the physical

exam on overall mortality. But in nondialyzed and dialyzed patients, Carrero et al. (33) also showed that mortality was significantly higher in patients having muscle depletion by physical exam, which is in agreement with our results. Altogether, muscle wasting assessed from the physical exam had the best agreement with CT, was able to differentiate nutritional status measured by objective measurements and had the best predictive results in the survival analysis.

The strengths of the present study include the measurement of muscle mass by four surrogate methods and one reference method, all performed by the same trained researcher and in a representative and relatively large sample of CRC patients. Moreover, our findings showing the reliability of the physical exam for the assessment of muscle wasting has important clinical application allowing its implementation in the routine when screening patient with high need of nutritional care. The limitations include the lack of a long-term follow up, the use of a convenient sample and the lack of reference values for low muscle mass from Brazilian normative tables, except for calf circumference. Therefore, future prospective studies are warranted to confirm our findings.

In conclusion, physical exam showed the highest kappa coefficient and the best agreement with CT. Low Muscularity groups had higher proportion of malnourished individuals and lower values of % BF and phase angle. Although calf circumference, physical exam and CT were independent factors of mortality in patients with CRC, physical exam showed the strongest predictive results in the survival analysis among all methods investigated.

4.2.5 References

1. Ryan AM, Power DG, Daly L, Cushen SJ, Ní Bhuachalla Ē, Prado CM. Cancer-associated malnutrition, cachexia and sarcopenia: the skeleton in the hospital closet 40 years later. Proc Nutr Soc. 2016;75(2):199-211.
2. Rier HN, Jager A, Sleijfer S, Maier AB, Levin MD. The Prevalence and Prognostic Value of Low Muscle Mass in Cancer Patients: A Review of the Literature. Oncologist. 2016;21(11):1396-409.
3. Johns N, Stephens NA, Fearon KC. Muscle wasting in cancer. Int J Biochem Cell Biol. 2013;45(10):2215-29.
4. Prado CM, Lieffers JR, McCargar LJ, Reiman T, Sawyer MB, Martin L, et al. Prevalence and clinical implications of sarcopenic obesity in patients with solid

tumours of the respiratory and gastrointestinal tracts: a population-based study. Lancet Oncol. 2008;9(7):629-35.

5. Martin L, Birdsell L, Macdonald N, Reiman T, Clandinin MT, McCargar LJ, et al. Cancer cachexia in the age of obesity: skeletal muscle depletion is a powerful prognostic factor, independent of body mass index. J Clin Oncol. 2013;31(12):1539-47.
6. Tan BH, Birdsell LA, Martin L, Baracos VE, Fearon KC. Sarcopenia in an overweight or obese patient is an adverse prognostic factor in pancreatic cancer. Clin Cancer Res. 2009;15(22):6973-9.
7. Caan BJ, Meyerhardt JA, Kroenke CH, Alexeeff S, Xiao J, Weltzien E, et al. Explaining the Obesity Paradox: The Association between Body Composition and Colorectal Cancer Survival (C-SCANS Study). Cancer Epidemiol Biomarkers Prev. 2017;26(7):1008-15.
8. Prado CM, Baracos VE, McCargar LJ, Reiman T, Mourtzakis M, Tonkin K, et al. Sarcopenia as a determinant of chemotherapy toxicity and time to tumor progression in metastatic breast cancer patients receiving capecitabine treatment. Clin Cancer Res. 2009;15(8):2920-6.
9. Lieffers JR, Bathe OF, Fassbender K, Winget M, Baracos VE. Sarcopenia is associated with postoperative infection and delayed recovery from colorectal cancer resection surgery. Br J Cancer. 2012;107(6):931-6.
10. Morishita S, Kaida K, Tanaka T, Itani Y, Ikegame K, Okada M, et al. Prevalence of sarcopenia and relevance of body composition, physiological function, fatigue, and health-related quality of life in patients before allogeneic hematopoietic stem cell transplantation. Support Care Cancer. 2012;20(12):3161-8.
11. Davies M. Nutritional screening and assessment in cancer-associated malnutrition. Eur J Oncol Nurs. 2005;9 Suppl 2:S64-73.
12. Ottery FD. Definition of standardized nutritional assessment and interventional pathways in oncology. Nutrition. 1996;12(1 Suppl):S15-9.
13. Heymsfield SB, Wang Z, Baumgartner RN, Ross R. Human body composition: advances in models and methods. Annu Rev Nutr. 1997;17:527-58.
14. Mourtzakis M, Prado CM, Lieffers JR, Reiman T, McCargar LJ, Baracos VE. A practical and precise approach to quantification of body composition in cancer patients using computed tomography images acquired during routine care. Appl Physiol Nutr Metab. 2008;33(5):997-1006.

15. Mauricio SF, Xiao J, Prado CM, Gonzalez MC, Correia M. Different nutritional assessment tools as predictors of postoperative complications in patients undergoing colorectal cancer resection. Clin Nutr. 2018;37(5):1505-11.
16. Feliciano EMC, Kroenke CH, Meyerhardt JA, Prado CM, Bradshaw PT, Kwan ML, et al. Association of Systemic Inflammation and Sarcopenia With Survival in Nonmetastatic Colorectal Cancer: Results From the C SCANS Study. JAMA Oncol. 2017;3(12):e172319.
17. Shen W, Punyanitya M, Wang Z, Gallagher D, St-Onge MP, Albu J, et al. Total body skeletal muscle and adipose tissue volumes: estimation from a single abdominal cross-sectional image. J Appl Physiol (1985). 2004;97(6):2333-8.
18. Giglio J, Kamimura MA, Souza NC, Bichels AV, Cordeiro AC, Pinho N, et al. Muscle mass assessment by computed tomography in chronic kidney disease patients: agreement with surrogate methods. Eur J Clin Nutr. In press 2018.
19. Janssen I, Heymsfield SB, Baumgartner RN, Ross R. Estimation of skeletal muscle mass by bioelectrical impedance analysis. J Appl Physiol (1985). 2000;89(2):465-71.
20. Heymsfield SB, McManus C, Smith J, Stevens V, Nixon DW. Anthropometric measurement of muscle mass: revised equations for calculating bone-free arm muscle area. Am J Clin Nutr. 1982;36(4):680-90.
21. Vivodtzev I, Moncharmont L, Tamisier R, Borel JC, Arbib F, Wuyam B, et al. Quadriceps muscle fat infiltration is associated with cardiometabolic risk in COPD. Clin Physiol Funct Imaging. 2018;38(5):788-97.
22. Miller MD, Crotty M, Giles LC, Bannerman E, Whitehead C, Cobiac L, et al. Corrected arm muscle area: an independent predictor of long-term mortality in community-dwelling older adults? J Am Geriatr Soc. 2002;50(7):1272-7.
23. Barbosa-Silva TG, Bielemann RM, Gonzalez MC, Menezes AM. Prevalence of sarcopenia among community-dwelling elderly of a medium-sized South American city: results of the COMO VAI? study. J Cachexia Sarcopenia Muscle. 2016;7(2):136-43.
24. Cruz-Jentoft AJ, Baeyens JP, Bauer JM, Boirie Y, Cederholm T, Landi F, et al. Sarcopenia: European consensus on definition and diagnosis: Report of the European Working Group on Sarcopenia in Older People. Age Ageing. 2010;39(4):412-23.
25. van der Werf A, Langius JAE, de van der Schueren MAE, Nurmohamed SA, van der Pant KAMI, Blauwhoff-Buskermolen S, et al. Percentiles for skeletal muscle index,

area and radiation attenuation based on computed tomography imaging in a healthy Caucasian population. Eur J Clin Nutr. 2018;72(2):288-96.

26. Heo M, Faith MS, Pietrobelli A, Heymsfield SB. Percentage of body fat cutoffs by sex, age, and race-ethnicity in the US adult population from NHANES 1999-2004. Am J Clin Nutr. 2012;95(3):594-602.
27. Fleiss J. The design and analysis of clinical experiments. New York, USA, 1986.
28. Prado CM, Heymsfield SB. Lean tissue imaging: a new era for nutritional assessment and intervention. JPEN J Parenter Enteral Nutr. 2014;38(8):940-53.
29. Raeder H, Henriksen C, Bohn SK, AR OdFV, Henriksen HB, Kvaerner AS, et al. Agreement between PG-SGA category and fat-free mass in colorectal cancer patients. Clin Nutr ESPEN. 2018;27:24-31.
30. Carrero JJ, Johansen KL, Lindholm B, Stenvinkel P, Cuppari L, Avesani CM. Screening for muscle wasting and dysfunction in patients with chronic kidney disease. Kidney Int. 2016;90(1):53-66.
31. Norman K, Stobaus N, Pirlich M, Bosy-Westphal A. Bioelectrical phase angle and impedance vector analysis--clinical relevance and applicability of impedance parameters. Clin Nutr. 2012;31(6):854-61.
32. Blauwhoff-Buskermolen S, Langius JAE, Becker A, Verheul HMW, de van der Schueren MAE. The influence of different muscle mass measurements on the diagnosis of cancer cachexia. J Cachexia Sarcopenia Muscle. 2017;8(4):615-22.
33. Carrero JJ, Chmielewski M, Axelsson J, Snaedal S, Heimburger O, Barany P, et al. Muscle atrophy, inflammation and clinical outcome in incident and prevalent dialysis patients. Clin Nutr. 2008;27(4):557-64.

CONSIDERAÇÕES FINAIS

Condições clínicas que apresentam como característica comum o estado pró-inflamatório e o aumento do catabolismo proteico podem predispor à perda de massa muscular, à mioesteatose e ao desenvolvimento de sarcopenia (98, 99). A perda de massa muscular e a mioesteatose são frequentes em pacientes com câncer e podem estar presentes tanto em indivíduos com caquexia quanto em indivíduos com sobrepeso e obesidade (98, 100-102). Além disso, a mioesteatose está fortemente associada com a função muscular independente de massa muscular (103-106). O desfecho negativo de ambas as condições está no desenvolvimento da síndrome da fragilidade, piora da qualidade de vida e aumento na taxa de morbimortalidade (98, 107-111).

Na atualização no consenso de 2010 publicado em 2018, o EWGSOP recomenda a avaliação da massa e qualidade muscular no intuito de se confirmar o diagnóstico de sarcopenia (112). Diferentes métodos e pontos de corte podem ser empregados para o diagnóstico de redução de massa muscular (113). Contudo, são escassos os estudos que comparam os métodos de avaliação da massa muscular disponíveis na prática clínica com um método de referência.

A partir de uma amostra de pacientes com câncer colorretal, foram desenvolvidos dois estudos com objetivos diferentes, mas que convergiam na avaliação da massa e qualidade muscular. No primeiro estudo, que teve como objetivo explorar os determinantes da mioesteatose e sua associação com os componentes da fragilidade, observou-se que a gordura corporal e a velocidade da marcha foram fatores determinantes da mioesteatose e que a mioesteatose estava associada à fragilidade em pacientes obesos com câncer colorretal. No segundo estudo, que buscou avaliar a validade dos métodos de avaliação da massa muscular utilizados na prática clínica em comparação com a TC, considerada padrão ouro para esse fim, observou-se que o exame físico foi o método com melhor concordância com a TC além de apresentar maior valor preditivo para mortalidade em relação aos demais métodos avaliados. O grupo com redução de massa muscular avaliada por diferentes métodos apresentou maior prevalência de desnutrição e menor valor de IMC, gordura corporal e ângulo de fase. Ademais, a prevalência de redução de massa muscular encontrada variou de 9,6 a 54,3% a depender do método aplicado para avaliação de massa muscular. Adicionalmente, a gordura corporal não se apresentou reduzida, mesmo nos grupos classificados com redução de massa muscular, o que enaltece a importância do rastreamento para redução de massa muscular mesmo em indivíduos com sobrepeso. O pior prognóstico de

sobrevida notado nos grupos de redução de massa muscular corroboram a importância do rastreamento para redução de massa muscular.

A partir desses achados, é possível destacar a importância de se avaliar a massa e a qualidade muscular em pacientes com câncer. Apesar da avaliação da massa e qualidade muscular serem uma etapa necessária para o diagnóstico de sarcopenia, os métodos disponíveis para a avaliação da qualidade muscular não estão disponíveis na prática clínica. No entanto, a detecção da redução de massa muscular possibilita o início de intervenções terapêuticas precoces e possivelmente com maior chance de êxito. Do mesmo modo, na inviabilidade de se utilizar um método padrão ouro para avaliação da massa muscular, foi observado que técnicas simples e de baixo custo, como o exame físico, apresentaram boa correlação com a TC no grupo de pacientes com câncer colorretal. Dessa forma, este trabalho aponta para medidas que permitam o uso corrente na prática clínica de avaliação desse compartimento da composição corporal. Os pontos de corte capazes de diagnosticar redução de massa muscular e que se associam com pior desfecho de morbimortalidade em pacientes com câncer se mantém ainda a serem investigados, sendo esse, um importante objeto de investigação para pesquisas futuras.

REFERÊNCIAS

1. Johns N, Stephens NA, Fearon KC. Muscle wasting in cancer. Int J Biochem Cell Biol. 2013;45(10):2215-29.

2. Biolo G, Cederholm T, Muscaritoli M. Muscle contractile and metabolic dysfunction is a common feature of sarcopenia of aging and chronic diseases: from sarcopenic obesity to cachexia. Clin Nutr. 2014;33(5):737-48.

3. Ryan AM, Power DG, Daly L, Cushen SJ, Ní Bhuachalla Ē, Prado CM. Cancer-associated malnutrition, cachexia and sarcopenia: the skeleton in the hospital closet 40 years later. Proc Nutr Soc. 2016;75(2):199-211.

4. Hu WH, Cajas-Monson LC, Eisenstein S, Parry L, Cosman B, Ramamoorthy S. Preoperative malnutrition assessments as predictors of postoperative mortality and morbidity in colorectal cancer: an analysis of ACS-NSQIP. Nutr J. 2015;14:91.

5. Pressoir M, Desné S, Berchery D, Rossignol G, Poiree B, Meslier M, et al. Prevalence, risk factors and clinical implications of malnutrition in French Comprehensive Cancer Centres. Br J Cancer. 2010;102(6):966-71.

6. Yamano T, Yoshimura M, Kobayashi M, Beppu N, Hamanaka M, Babaya A, et al. Malnutrition in rectal cancer patients receiving preoperative chemoradiotherapy is common and associated with treatment tolerability and anastomotic leakage. Int J Colorectal Dis. 2016;31(4):877-84.

7. Prado CM, Lieffers JR, McCargar LJ, Reiman T, Sawyer MB, Martin L, et al. Prevalence and clinical implications of sarcopenic obesity in patients with solid tumours of the respiratory and gastrointestinal tracts: a population-based study. Lancet Oncol. 2008;9(7):629-35.

8. Tan BH, Birdsell LA, Martin L, Baracos VE, Fearon KC. Sarcopenia in an overweight or obese patient is an adverse prognostic factor in pancreatic cancer. Clin Cancer Res. 2009;15(22):6973-9.

9. Baracos VE, Reiman T, Mourtzakis M, Gioulbasanis I, Antoun S. Body composition in patients with non-small cell lung cancer: a contemporary view of cancer cachexia with the use of computed tomography image analysis. Am J Clin Nutr. 2010;91(4):1133S-7S.

10. Martin L, Birdsell L, Macdonald N, Reiman T, Clandinin MT, McCargar LJ, et al. Cancer cachexia in the age of obesity: skeletal muscle depletion is a powerful prognostic factor, independent of body mass index. J Clin Oncol. 2013;31(12):1539-47.

11. Rosenberg I. Summary comments: epidemiological and methodological problems in determining nutritional status of older persons. Am J Clin Nutr. 1989; 50:1231-3.

12. Cruz-Jentoft AJ, Baeyens JP, Bauer JM, Boirie Y, Cederholm T, Landi F, et al. Sarcopenia: European consensus on definition and diagnosis: Report of the European Working Group on Sarcopenia in Older People. Age Ageing. 2010;39(4):412-23.

13. Muscaritoli M, Anker SD, Argilés J, Aversa Z, Bauer JM, Biolo G, et al. Consensus definition of sarcopenia, cachexia and pre-cachexia: joint document elaborated by Special Interest Groups (SIG) "cachexia-anorexia in chronic wasting diseases" and "nutrition in geriatrics". Clin Nutr. 2010;29(2):154-9.

14. Fielding RA, Vellas B, Evans WJ, Bhasin S, Morley JE, Newman AB, et al. Sarcopenia: an undiagnosed condition in older adults. Current consensus definition: prevalence, etiology, and consequences. International working group on sarcopenia. J Am Med Dir Assoc. 2011;12(4):249-56.

15. Morley JE, Abbatecola AM, Argiles JM, Baracos V, Bauer J, Bhasin S, et al. Sarcopenia with limited mobility: an international consensus. J Am Med Dir Assoc. 2011;12(6):403-9.

16. Prado CM, Baracos VE, McCargar LJ, Reiman T, Mourtzakis M, Tonkin K, et al. Sarcopenia as a determinant of chemotherapy toxicity and time to tumor progression in metastatic breast cancer patients receiving capecitabine treatment. Clin Cancer Res. 2009;15(8):2920-6.

17. Morishita S, Kaida K, Tanaka T, Itani Y, Ikegame K, Okada M, et al. Prevalence of sarcopenia and relevance of body composition, physiological function, fatigue, and health-related quality of life in patients before allogeneic hematopoietic stem cell transplantation. Support Care Cancer. 2012;20(12):3161-8.

18. Schaap LA, Koster A, Visser M. Adiposity, muscle mass, and muscle strength in relation to functional decline in older persons. Epidemiol Rev. 2013;35:51-65.

19. Schaap LA, van Schoor NM, Lips P, Visser M. Associations of Sarcopenia Definitions, and Their Components, With the Incidence of Recurrent Falling and Fractures: The Longitudinal Aging Study Amsterdam. J Gerontol A Biol Sci Med Sci. 2018;73(9):1199-204.

20. Williams GR, Deal AM, Muss HB, Weinberg MS, Sanoff HK, Nyrop KA, et al. Skeletal muscle measures and physical function in older adults with cancer: sarcopenia or myopenia? Oncotarget. 2017;8(20):33658-65.

21. Stretch C, Aubin JM, Mickiewicz B, Leugner D, Al-Manasra T, Tobola E, et al. Sarcopenia and myosteatosis are accompanied by distinct biological profiles in patients with pancreatic and periampullary adenocarcinomas. PLoS One. 2018;13(5):e0196235.

22. Cruz-Jentoft AJ, Bahat G, Bauer J, Boirie Y, Bruyere O, Cederholm T, et al. Sarcopenia: revised European consensus on definition and diagnosis. Age Ageing. In press 2018.

23. Prado CM, Heymsfield SB. Lean tissue imaging: a new era for nutritional assessment and intervention. JPEN J Parenter Enteral Nutr. 2014;38(8):940-53.

24. Ministério da Saúde. Instituto Nacional de Câncer José Alencar Gomes da Silva; Thuler LCS (org.). ABC do câncer: abordagens básicas para o controle do câncer. 3.ed. Rio de Janeiro: Inca, 2017.

25. American Cancer Society. Cancer Facts & Figures 2018. Atlanta: American Cancer Society, 2018.

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

27. World Health Organization, Stewart BW, Wild CP, editors. World Cancer Report 2014. Lyon, France: International Agency for Research on Cancer, 2014.

28. Mistério da Saúde. Instituto Nacional de Câncer José Alencar Gomes da Silva. Estimativa 2018: incidência de câncer no Brasil. Rio de Janeiro: Inca, 2017.

29. Instituto Nacional de Câncer [homepage na internet]. Câncer colorretal. [Acesso em 22 out 2018]. Disponível em: http://www2.inca.gov.br/wps/wcm/connect/tiposdecancer/site/home/colorretal

30. American Cancer Society. Global Cancer Facts & Figures 3rd Edition. Atlanta: American Cancer Society, 2015.

31. Bozzetti F, Group SW. Screening the nutritional status in oncology: a preliminary report on 1,000 outpatients. Support Care Cancer. 2009;17(3):279-84.

32. Ramos Chaves M, Boléo-Tomé C, Monteiro-Grillo I, Camilo M, Ravasco P. The diversity of nutritional status in cancer: new insights. Oncologist. 2010;15(5):523-30.

33. Wie GA, Cho YA, Kim SY, Kim SM, Bae JM, Joung H. Prevalence and risk factors of malnutrition among cancer patients according to tumor location and stage in the National Cancer Center in Korea. Nutrition. 2010;26(3):263-8.

34. Bozzetti F, Gianotti L, Braga M, Di Carlo V, Mariani L. Postoperative complications in gastrointestinal cancer patients: the joint role of the nutritional status and the nutritional support. Clin Nutr. 2007;26(6):698-709.

35. Di Fiore F, Lecleire S, Pop D, Rigal O, Hamidou H, Paillot B, et al. Baseline nutritional status is predictive of response to treatment and survival in patients treated by definitive chemoradiotherapy for a locally advanced esophageal cancer. Am J Gastroenterol. 2007;102(11):2557-63.

36. van den Berg MG, Rasmussen-Conrad EL, van Nispen L, van Binsbergen JJ, Merkx MA. A prospective study on malnutrition and quality of life in patients with head and neck cancer. Oral Oncol. 2008;44(9):830-7.

37. Volpato LE, Silva TC, Oliveira TM, Sakai VT, Machado MA. Radiation therapy and chemotherapy-induced oral mucositis. Braz J Otorhinolaryngol. 2007;73(4):562-8.

38. Davila M, Bresalier RS. Gastrointestinal complications of oncologic therapy. Nat Clin Pract Gastroenterol Hepatol. 2008;5(12):682-96.

39. Melichar B, Dvorák J, Krcmová L, Hyspler R, Urbánek L, Solichová D. Intestinal permeability and vitamin A absorption in patients with chemotherapy-induced diarrhea. Am J Clin Oncol. 2008;31(6):580-4.

40. Baracos VE, Martin L, Korc M, Guttridge DC, Fearon KCH. Cancer-associated cachexia. Nat Rev Dis Primers. 2018;4:17105.

41. Cederholm T, Barazzoni R, Austin P, Ballmer P, Biolo G, Bischoff SC, et al. ESPEN guidelines on definitions and terminology of clinical nutrition. Clin Nutr. 2017;36(1):49-64.

42. von Haehling S, Anker SD. Cachexia as a major underestimated and unmet medical need: facts and numbers. J Cachexia Sarcopenia Muscle. 2010;1(1):1-5.

43. Springer J, von Haehling S, Anker SD. The need for a standardized definition for cachexia in chronic illness. Nat Clin Pract Endocrinol Metab. 2006;2(8):416-7.

44. Evans WJ, Morley JE, Argilés J, Bales C, Baracos V, Guttridge D, et al. Cachexia: a new definition. Clin Nutr. 2008;27(6):793-9.

45. Fox KM, Brooks JM, Gandra SR, Markus R, Chiou CF. Estimation of Cachexia among Cancer Patients Based on Four Definitions. J Oncol. 2009;2009:693458.

46. Fearon K, Strasser F, Anker SD, Bosaeus I, Bruera E, Fainsinger RL, et al. Definition and classification of cancer cachexia: an international consensus. Lancet Oncol. 2011;12(5):489-95.

47. Cederholm T, Jensen GL, Correia M, Gonzalez MC, Fukushima R, Higashiguchi T, et al. GLIM criteria for the diagnosis of malnutrition - A consensus report from the global clinical nutrition community. Clin Nutr. In press 2018.

48. Arends J, Bodoky G, Bozzetti F, Fearon K, Muscaritoli M, Selga G, et al. ESPEN Guidelines on Enteral Nutrition: Non-surgical oncology. Clin Nutr. 2006;25(2):245-59.

49. Rock CL, Doyle C, Demark-Wahnefried W, Meyerhardt J, Courneya KS, Schwartz AL, et al. Nutrition and physical activity guidelines for cancer survivors. CA Cancer J Clin. 2012;62(4):243-74.

50. Fukuda Y, Yamamoto K, Hirao M, Nishikawa K, Nagatsuma Y, Nakayama T, et al. Sarcopenia is associated with severe postoperative complications in elderly gastric cancer patients undergoing gastrectomy. Gastric Cancer. 2016;19(3):986-93.

51. Huang DD, Wang SL, Zhuang CL, Zheng BS, Lu JX, Chen FF, et al. Sarcopenia, as defined by low muscle mass, strength and physical performance, predicts complications after surgery for colorectal cancer. Colorectal Dis. 2015;17(11):O256-64.

52. Wang SL, Zhuang CL, Huang DD, Pang WY, Lou N, Chen FF, et al. Sarcopenia Adversely Impacts Postoperative Clinical Outcomes Following Gastrectomy in Patients with Gastric Cancer: A Prospective Study. Ann Surg Oncol. 2016;23(2):556-64.

53. Huang DD, Chen XX, Chen XY, Wang SL, Shen X, Chen XL, et al. Sarcopenia predicts 1-year mortality in elderly patients undergoing curative gastrectomy for gastric cancer: a prospective study. J Cancer Res Clin Oncol. 2016;142(11):2347-56.

54. Makiura D, Ono R, Inoue J, Kashiwa M, Oshikiri T, Nakamura T, et al. Preoperative sarcopenia is a predictor of postoperative pulmonary complications in esophageal cancer following esophagectomy: A retrospective cohort study. J Geriatr Oncol. 2016;7(6):430-6.

55. McGregor RA, Cameron-Smith D, Poppitt SD. It is not just muscle mass: a review of muscle quality, composition and metabolism during ageing as determinants of muscle function and mobility in later life. Longev Healthspan. 2014;3(1):9.

56. Thoresen L, Frykholm G, Lydersen S, Ulveland H, Baracos V, Prado CM, et al. Nutritional status, cachexia and survival in patients with advanced colorectal carcinoma. Different assessment criteria for nutritional status provide unequal results. Clin Nutr. 2013;32(1):65-72.

57. Ozola Zalite I, Zykus R, Francisco Gonzalez M, Saygili F, Pukitis A, Gaujoux S, et al. Influence of cachexia and sarcopenia on survival in pancreatic ductal adenocarcinoma: a systematic review. Pancreatology. 2015;15(1):19-24.

58. Wang ZM, Pierson RN, Heymsfield SB. The five-level model: a new approach to organizing body-composition research. Am J Clin Nutr. 1992;56(1):19-28.

59. Wang ZM, Heshka S, Pierson RN, Heymsfield SB. Systematic organization of body-composition methodology: an overview with emphasis on component-based methods. Am J Clin Nutr. 1995;61(3):457-65.

60. Heymsfield SB, Wang Z, Baumgartner RN, Ross R. Human body composition: advances in models and methods. Annu Rev Nutr. 1997;17:527-58.

61. Mitsiopoulos N, Baumgartner RN, Heymsfield SB, Lyons W, Gallagher D, Ross R. Cadaver validation of skeletal muscle measurement by magnetic resonance imaging and computerized tomography. J Appl Physiol (1985). 1998;85(1):115-22.

62. Shen W, Punyanitya M, Wang Z, Gallagher D, St-Onge MP, Albu J, et al. Total body skeletal muscle and adipose tissue volumes: estimation from a single abdominal cross-sectional image. J Appl Physiol (1985). 2004;97(6):2333-8.

63. Mourtzakis M, Prado CM, Lieffers JR, Reiman T, McCargar LJ, Baracos VE. A practical and precise approach to quantification of body composition in cancer patients using computed tomography images acquired during routine care. Appl Physiol Nutr Metab. 2008;33(5):997-1006.

64. Ellis KJ. Human body composition: in vivo methods. Physiol Rev. 2000;80(2):649-80.

65. Kyle UG, Bosaeus I, De Lorenzo AD, Deurenberg P, Elia M, Manuel Gómez J, et al. Bioelectrical impedance analysis-part II: utilization in clinical practice. Clin Nutr. 2004;23(6):1430-53.

66. Davies M. Nutritional screening and assessment in cancer-associated malnutrition. Eur J Oncol Nurs. 2005;9 Suppl 2:S64-73.

67. Janssen I, Heymsfield SB, Baumgartner RN, Ross R. Estimation of skeletal muscle mass by bioelectrical impedance analysis. J Appl Physiol (1985). 2000;89(2):465-71.

68. Giglio J, Kamimura MA, Souza NC, Bichels AV, Cordeiro AC, Pinho N, et al. Muscle mass assessment by computed tomography in chronic kidney disease patients: agreement with surrogate methods. Eur J Clin Nutr. In press 2018.

69. Melo CY, Silva SA. Adductor pollicis muscle as predictor of malnutrition in surgical patients. Arq Bras Cir Dig. 2014;27(1):13-7.

70. Laky B, Janda M, Cleghorn G, Obermair A. Comparison of different nutritional assessments and body-composition measurements in detecting malnutrition among gynecologic cancer patients. Am J Clin Nutr. 2008;87(6):1678-85.

71. Ottery FD. Definition of standardized nutritional assessment and interventional pathways in oncology. Nutrition. 1996;12(1 Suppl):S15-9.

72. Raeder H, Henriksen C, Bohn SK, AR OdFV, Henriksen HB, Kvaerner AS, et al. Agreement between PG-SGA category and fat-free mass in colorectal cancer patients. Clin Nutr ESPEN. 2018;27:24-31.

73. Carrero JJ, Johansen KL, Lindholm B, Stenvinkel P, Cuppari L, Avesani CM. Screening for muscle wasting and dysfunction in patients with chronic kidney disease. Kidney Int. 2016;90(1):53-66.

74. Goodpaster BH, Carlson CL, Visser M, Kelley DE, Scherzinger A, Harris TB, et al. Attenuation of skeletal muscle and strength in the elderly: The Health ABC Study. J Appl Physiol (1985). 2001;90(6):2157-65.

75. Visser M, Kritchevsky SB, Goodpaster BH, Newman AB, Nevitt M, Stamm E, et al. Leg muscle mass and composition in relation to lower extremity performance in men and women aged 70 to 79: the health, aging and body composition study. J Am Geriatr Soc. 2002;50(5):897-904.

76. Visser M, Goodpaster BH, Kritchevsky SB, Newman AB, Nevitt M, Rubin SM, et al. Muscle mass, muscle strength, and muscle fat infiltration as predictors of incident mobility limitations in well-functioning older persons. J Gerontol A Biol Sci Med Sci. 2005;60(3):324-33.

77. Delmonico MJ, Harris TB, Visser M, Park SW, Conroy MB, Velasquez-Mieyer P, et al. Longitudinal study of muscle strength, quality, and adipose tissue infiltration. Am J Clin Nutr. 2009;90(6):1579-85.

78. Goodpaster BH, Kelley DE, Thaete FL, He J, Ross R. Skeletal muscle attenuation determined by computed tomography is associated with skeletal muscle lipid content. J Appl Physiol (1985). 2000;89(1):104-10.

79. Robles PG, Sussman MS, Naraghi A, Brooks D, Goldstein RS, White LM, et al. Intramuscular Fat Infiltration Contributes to Impaired Muscle Function in COPD. Med Sci Sports Exerc. 2015;47(7):1334-41.

80. Montano-Loza AJ, Angulo P, Meza-Junco J, Prado CMM, Sawyer MB, Beaumont C, et al. Sarcopenic obesity and myosteatosis are associated with higher mortality in patients with cirrhosis. J Cachexia Sarcopenia Muscle. 2016;7(2):126-35.

81. Wilkinson TJ, Gould DW, Nixon DGD, Watson EL, Smith AC. Quality over quantity? Association of skeletal muscle myosteatosis and myofibrosis on physical function in chronic kidney disease. Nephrol Dial Transplant. In press 2018.

82. Kumar A, Moynagh MR, Multinu F, Cliby WA, McGree ME, Weaver AL, et al. Muscle composition measured by CT scan is a measurable predictor of overall survival in advanced ovarian cancer. Gynecol Oncol. 2016;142(2):311-6.

83. Boer BC, de Graaff F, Brusse-Keizer M, Bouman DE, Slump CH, Slee-Valentijn M, et al. Skeletal muscle mass and quality as risk factors for postoperative outcome after open colon resection for cancer. Int J Colorectal Dis. 2016;31(6):1117-24.

84. Berkel AEM, Klaase JM, de Graaff F, Brusse-Keizer MGJ, Bongers BC, van Meeteren NLU. Patient's Skeletal Muscle Radiation Attenuation and Sarcopenic Obesity are Associated with Postoperative Morbidity after Neoadjuvant Chemoradiation and Resection for Rectal Cancer. Dig Surg. In press 2018.

85. Malietzis G, Johns N, Al-Hassi HO, Knight SC, Kennedy RH, Fearon KC, et al. Low Muscularity and Myosteatosis Is Related to the Host Systemic Inflammatory Response in Patients Undergoing Surgery for Colorectal Cancer. Ann Surg. 2016;263(2):320-5.

86. Miljkovic I, Zmuda JM. Epidemiology of myosteatosis. Curr Opin Clin Nutr Metab Care. 2010;13(3):260-4.

87. Khan IM, Perrard XY, Brunner G, Lui H, Sparks LM, Smith SR, et al. Intermuscular and perimuscular fat expansion in obesity correlates with skeletal muscle T cell and macrophage infiltration and insulin resistance. Int J Obes (Lond). 2015;39(11):1607-18.

88. Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982;5(6):649-55.

89. World Health Organization. Physical status: the use and interpretation of anthropometry. Geneva: Technical Report Series, n. 854, 1995.

90. Heymsfield SB, McManus C, Smith J, Stevens V, Nixon DW. Anthropometric measurement of muscle mass: revised equations for calculating bone-free arm muscle area. Am J Clin Nutr. 1982;36(4):680-90.

91. Barbosa-Silva TG. Prevalência de sarcopenia em idosos não institucionalizados de uma cidade brasileira de médio porte. Rio Grande do Sul. Dissertação [Mestrado em Epidemiologia] – Universidade Federal de Pelotas, 2013.

92. van der Werf A, Langius JAE, de van der Schueren MAE, Nurmohamed SA, van der Pant KAMI, Blauwhoff-Buskermolen S, et al. Percentiles for skeletal muscle index, area and radiation attenuation based on computed tomography imaging in a healthy Caucasian population. Eur J Clin Nutr. 2018;72(2):288-96.

93. Miller MD, Crotty M, Giles LC, Bannerman E, Whitehead C, Cobiac L, et al. Corrected arm muscle area: an independent predictor of long-term mortality in community-dwelling older adults? J Am Geriatr Soc. 2002;50(7):1272-7.

94. Barbosa-Silva TG, Bielemann RM, Gonzalez MC, Menezes AM. Prevalence of sarcopenia among community-dwelling elderly of a medium-sized South American city: results of the COMO VAI? study. J Cachexia Sarcopenia Muscle. 2016;7(2):136-43.

95. Fried LP, Tangen CM, Walston J, Newman AB, Hirsch C, Gottdiener J, et al. Frailty in older adults: evidence for a phenotype. J Gerontol A Biol Sci Med Sci. 2001;56(3):M146-56.

96. Craig CL, Marshall AL, Sjostrom M, Bauman AE, Booth ML, Ainsworth BE, et al. International physical activity questionnaire: 12-country reliability and validity. Med Sci Sports Exerc. 2003;35(8):1381-95.

97. Orme JG, Reis J, Herz EJ. Factorial and discriminant validity of the Center for Epidemiological Studies Depression (CES-D) scale. J Clin Psychol. 1986;42(1):28-33.

98. Martin L, Birdsell L, Macdonald N, Reiman T, Clandinin MT, McCargar LJ, et al. Cancer cachexia in the age of obesity: skeletal muscle depletion is a powerful prognostic factor, independent of body mass index. J Clin Oncol. 2013;31(12):1539-47.

99. Johns N, Stephens NA, Fearon KC. Muscle wasting in cancer. Int J Biochem Cell Biol. 2013;45(10):2215-29.

100. Prado CM, Lieffers JR, McCargar LJ, Reiman T, Sawyer MB, Martin L, et al. Prevalence and clinical implications of sarcopenic obesity in patients with solid tumours of the respiratory and gastrointestinal tracts: a population-based study. Lancet Oncol. 2008;9(7):629-35.

101. Tan BH, Birdsell LA, Martin L, Baracos VE, Fearon KC. Sarcopenia in an overweight or obese patient is an adverse prognostic factor in pancreatic cancer. Clin Cancer Res. 2009;15(22):6973-9.

102. Baracos VE, Reiman T, Mourtzakis M, Gioulbasanis I, Antoun S. Body composition in patients with non-small cell lung cancer: a contemporary view of cancer cachexia with the use of computed tomography image analysis. Am J Clin Nutr. 2010;91(4):1133S-7S.

103. Williams GR, Deal AM, Muss HB, Weinberg MS, Sanoff HK, Nyrop KA, et al. Skeletal muscle measures and physical function in older adults with cancer: sarcopenia or myopenia? Oncotarget. 2017;8(20):33658-65.

104. Visser M, Kritchevsky SB, Goodpaster BH, Newman AB, Nevitt M, Stamm E, et al. Leg muscle mass and composition in relation to lower extremity performance in men and women aged 70 to 79: the health, aging and body composition study. J Am Geriatr Soc. 2002;50(5):897-904.

105. Goodpaster BH, Carlson CL, Visser M, Kelley DE, Scherzinger A, Harris TB, et al. Attenuation of skeletal muscle and strength in the elderly: The Health ABC Study. J Appl Physiol (1985). 2001;90(6):2157-65.

106. Delmonico MJ, Harris TB, Visser M, Park SW, Conroy MB, Velasquez-Mieyer P, et al. Longitudinal study of muscle strength, quality, and adipose tissue infiltration. Am J Clin Nutr. 2009;90(6):1579-85.

107. Stretch C, Aubin JM, Mickiewicz B, Leugner D, Al-Manasra T, Tobola E, et al. Sarcopenia and myosteatosis are accompanied by distinct biological profiles in patients with pancreatic and periampullary adenocarcinomas. PLoS One. 2018;13(5):e0196235.

108. Boer BC, de Graaff F, Brusse-Keizer M, Bouman DE, Slump CH, Slee-Valentijn M, et al. Skeletal muscle mass and quality as risk factors for postoperative outcome after open colon resection for cancer. Int J Colorectal Dis. 2016;31(6):1117-24.

109. Berkel AEM, Klaase JM, de Graaff F, Brusse-Keizer MGJ, Bongers BC, van Meeteren NLU. Patient's Skeletal Muscle Radiation Attenuation and Sarcopenic Obesity are Associated with Postoperative Morbidity after Neoadjuvant Chemoradiation and Resection for Rectal Cancer. Dig Surg. 2018;13:1-8.

110. Williams GR, Deal AM, Muss HB, Weinberg MS, Sanoff HK, Guerard EJ, et al. Frailty and skeletal muscle in older adults with cancer. J Geriatr Oncol. 2018;9(1):68-73.

111. Morishita S, Kaida K, Tanaka T, Itani Y, Ikegame K, Okada M, et al. Prevalence of sarcopenia and relevance of body composition, physiological function, fatigue, and health-related quality of life in patients before allogeneic hematopoietic stem cell transplantation. Support Care Cancer. 2012;20(12):3161-8.

112. Cruz-Jentoft AJ, Bahat G, Bauer J, Boirie Y, Bruyere O, Cederholm T, et al. Sarcopenia: revised European consensus on definition and diagnosis. Age Ageing. In press 2018.

113. Cruz-Jentoft AJ, Baeyens JP, Bauer JM, Boirie Y, Cederholm T, Landi F, et al. Sarcopenia: European consensus on definition and diagnosis: Report of the European Working Group on Sarcopenia in Older People. Age Ageing. 2010;39(4):412-23.

APÊNDICE A– Termo de Consentimento Livre e Esclarecido

TERMO DE CONSENTIMENTO LIVRE E ESCLARECIDO

Título do Projeto: **VALIDAÇÃO DOS DIFERENTES MÉTODOS DE AVALIAÇÃO DA MASSA MUSCULAR UTILIZADOS NA PRÁTICA CLÍNICA NA AVALIAÇÃO DA SARCOPENIA EM PACIENTES COM NEOPLASIA COLORRETAL**

Nome do voluntário: _____

Você está sendo convidado (a) a participar de um estudo que irá comparar diferentes métodos utilizados para avaliar a quantidade de músculo distribuído no corpo em pacientes com câncer de intestino atendidos no Hospital do Câncer I (HCI) no Instituto Nacional de Câncer (INCA). Este estudo é coordenado pela professora Drª Carla Maria Avesani (Universidade Estadual do Rio de Janeiro) e pela pesquisadora Nilian Souza (nutricionista do INCA).

JUSTIFICATIVA

O câncer é uma doença que pode causar má nutrição, perda de peso e de músculo podendo interferir negativamente na resposta ao tratamento e na qualidade de vida. A tomografia computadorizada é considerada um dos métodos para avaliação da quantidade de músculo distribuída no corpo. Considerando que os exames de tomografia computadorizada são pedidos pelo médico durante o período de tratamento do câncer, as imagens podem ser aproveitadas para esta avaliação.

Para que você possa decidir se quer participar ou não deste estudo, precisa conhecer seus benefícios, riscos e implicações.

OBJETIVO DO ESTUDO

Neste estudo vamos comparar alguns métodos utilizados para avaliação da quantidade de músculo, como a impedância bioelétrica, a antropometria e avaliação subjetiva global produzida pelo paciente (ASG-PPP) (explicados a seguir), com o exame de tomografia computadorizada em pacientes com câncer de intestino.

PROCEDIMENTOS DO ESTUDO

Aceitando participar do estudo e após a assinatura desse Termo de Consentimento Livre e Esclarecido, você participará de uma avaliação e passará por uma coleta de sangue que serão realizadas no mesmo dia que está marcado o exame de tomografia computadoriza solicitado pelo médico responsável pelo seu tratamento. A avaliação será realizada nas dependências da radiologia, localizada no 2º andar, antes da realização da tomografia computadorizada, e terá duração de 60 a 90 minutos.

Coleta de sangue: serão coletados 1 (um) tubo de 10ml, correspondente a uma colher de sopa, por um profissional capacitado, para dosagem de proteínas e glicose do sangue e avaliação da função renal.

Antropometria: serão aferidos (medidos) seu peso, altura, circunferência do braço**,** panturrilha e cintura (com fita métrica), e dobra cutânea na parte de trás do seu braço (com uma pinça especial chamada adipômetro).

Impedância bioelétrica: será solicitado que você deite na maca de barriga para cima com os braços e as pernas afastados do corpo. Serão colocados adesivos (como os usados no

eletrocardiograma) nas mãos e nos pés e nestes adesivos serão conectados fios que serão ligados ao aparelho. Os dados obtidos serão registrados e usados para as análises do estudo. Estas medidas são rápidas e não causarão dor nem desconforto.

Os dados do exame de tomografia computadorizada serão aproveitados para avaliar a quantidade de músculo do corpo.

Você deverá estar em jejum de 8 (oito) horas para que sejam feitas a coleta de sangue, a impedância bioelétrica e a tomografia computadorizada.

Avaliação subjetiva global produzida pelo paciente (ASG-PPP): é um questionário autoexplicativo dividido em 3 (três) partes com duração de aproximadamente 10 (dez) a 15 (quinze) minutos. Na primeira parte você responderá perguntas sobre peso, altura, tipo e quantidade de alimentação ingerida, sintomas que podem interferir na sua alimentação e atividade física. Na segunda parte, serão registrados dados da sua ficha de acompanhamento, como tipo e localização da doença, idade, outras doenças, tratamentos já realizados e a presença de febre e/ou uso de remédios. Na terceira parte será realizado o exame físico. Nessa etapa você deverá estar deitado na maca onde o pesquisador verificará se você tem sinais de má nutrição como perda de músculo e de gordura e inchaço.

Você também será avaliado pelo teste da força de preensão manual (força do aperto de mão) na mão esquerda e direita utilizando um aparelho chamado dinamômetro. A medida será realizada em três momentos com um intervalo de um minuto entre as medidas. Você também realizará um teste que avalia sua velocidade de caminhar. Será solicitado que você caminhe uma distância de 4 (quatro) metros. Serão cronometrados os tempos das duas caminhadas (ida e volta), com intervalo de aproximadamente 15 segundos cada uma. Além disso, será aplicado um questionário que avalia seu nível de atividade física e cansaço.

RISCOS

O seu tratamento será exatamente o mesmo caso você participe ou não deste estudo. Toda pesquisa possui um risco e no caso de participar deste estudo serei submetido a um questionário onde meu maior desconforto será respondê-lo. As medidas de peso, altura, circunferências (braço, panturrilha e cintura), dobra cutânea do braço e o exame de impedância bioelétrica não trarão desconforto. O exame físico poderá lhe causar uma sensação de cócegas, porém não será doloroso. A coleta de sangue pode ocasionar leve dor no local ou manchas roxas passageiras. Os testes que avaliam sua velocidade de caminhar e a força do aperto de mão podem ocasionar cansaço e queda. Caso você apresente algum sintoma de cansaço os testes não serão realizados. O risco relacionado à realização do exame de tomografia computadorizada é a sua exposição à radiação.

BENEFÍCIOS

A participação no estudo não trará benefícios diretos a você. No entanto, com o resultado dessa pesquisa poderemos encontrar um método de avaliação da quantidade de músculo mais prático e simples e, desta maneira, tentar prevenir e recuperar a perda de músculo, o que pode melhorar a resposta ao tratamento e a qualidade de vida do paciente com câncer.

ACOMPANHAMENTO, ASSISTÊNCIA E RESPONSÁVEIS.

Durante a participação no estudo você será acompanhado pela nutricionista Nilian Souza que faz parte da equipe de nutricionistas do hospital (INCA) e tem o direito de ser mantido atualizado sobre os resultados parciais e finais da pesquisa.

CARÁTER CONFIDENCIAL DOS REGISTROS

Seus registros médicos poderão ser consultados pela equipe que participará do estudo e pelo Comitê de Ética em Pesquisa do Instituto Nacional de Câncer (CEP-INCA). Seu nome não será revelado em hipótese alguma. Antes de processar os resultados, seus dados pessoais serão totalmente transformados em números que não permitirão a sua identificação. Assim, as informações de seu registro médico serão utilizadas para propósitos de publicação, que ocorrerão independentemente dos resultados obtidos.

TRATAMENTO MÉDICO EM CASO DE DANOS

Todo e qualquer dano decorrente do desenvolvimento deste projeto de pesquisa, e que necessite de atendimento médico, ficará a cargo da instituição (INCA). Seu tratamento e acompanhamento médico não dependem de sua participação neste estudo.

CUSTOS

Não haverá qualquer custo ou forma de pagamento a você pela sua participação no estudo. Todos os procedimentos referentes ao estudo serão realizados no mesmo dia que está marcado o exame de tomografia computadoriza solicitado pelo médico responsável pelo seu tratamento. Não será necessário comparecer ao hospital fora deste dia, assim, não há necessidade de gastos extras.

BASES DA PARTICIPAÇÃO

É importante que você saiba que a sua participação neste estudo é completamente voluntária e que você pode se recusar a participar ou interromper sua participação a qualquer momento, sem penalidades ou perda de benefícios aos quais você tem direito. Se você decidir interromper sua participação, a equipe participante do estudo deverá ser informada.

GARANTIA DE ESCLARECIMENTOS

A qualquer momento você e seus familiares poderão fazer perguntas sobre o estudo. Quando isto for necessário, ligue para a nutricionista Nilian Souza no telefone (21) 98530-0149. Se você quiser saber seus direitos como participante do estudo, também poderá entrar em contato com o **Comitê de Ética em Pesquisa (CEP) do INCA**, situado à Rua do Resende, 128 , sala 203, Centro, Rio de Janeiro, telefones (21) 3207- 4550 ou (21) 3207-4556 (horário de atendimento: de 9 às 12h e de 14 às 16h), ou também pelo e-mail: cep@inca.gov.br. O CEP é formado por profissionais de diferentes áreas, que revisam os projetos de pesquisa que envolvem seres humanos, para garantir os direitos, a segurança e o bem-estar de todos as pessoas que se voluntariam à participar destes.

Li as informações acima e entendi o propósito, benefícios e riscos deste estudo. Tive a oportunidade de fazer perguntas e todas foram respondidas. Entendo que não receberei compensação monetária para minha participação neste estudo. Eu, por intermédio deste, dou livremente meu consentimento para participar neste estudo.

Eu recebi uma via assinada deste formulário de consentimento.

_____ ____ / _____ / _____

(Assinatura do Paciente) dia mês ano

_____

(Nome do Paciente – letra de forma)

_____ ____ / ____ / _____

(Assinatura de Testemunha, se necessário) dia mês ano

Eu, abaixo assinado, expliquei completamente os detalhes relevantes deste estudo ao paciente indicado acima e/ou pessoa autorizada para consentir pelo paciente.

_____ ____ / ____ / ____

(Assinatura da pessoa que obteve o consentimento) dia mês ano

APÊNDICE B – Formulário de coleta de dados

I - Identificação
N° Identificação (ID): _____
Data da realização TC (DATA_TC): _____/_____/_____
1ª consulta (DATA_PRONT): _____/_____/_____
Tempo de tratamento (MESES_INCA): _____ meses
Inicio tratamento (INICIO_INCA): (0) Outros hospitais (1) INCA
Data de nascimento (DAT_NASC): _____/_____/_____
Idade (IDADE): _____ anos
Faixa Etária (F_ETARIA): (0) Adulto (1) Idoso (> 65 anos)
Sexo (SEXO): (0) Feminino (1) Masculino
Performance Status (PS): (0) (1) (2) (3) (4)

II – História da Doença Atual
Localização do tumor (LOC_TUM):
(1) cólon (2) retossigmóide (3) reto (4) canal anal
Classificação Internacional de Doenças (CID): _____
CID de matrícula (CID_MAT): _____
Estadiamento (ESTAD): (0) 0 (1) I (2) II (3) III (4) IV
Estadiamento TNM (ESTAD_TNM):_____
Metástase à distância (MTX): (0) Sim (1) Não
Local (LOCAL_MTX):
(0)fígado (1)pulmão (2)LFN à distância (3)peritônio (4)osso (5)SNC (6)ovário
(7) útero (8) ≥ 2 locais (9) NA (10) Outros
Momento do tratamento (MOM_TRAT): (0) Pré (1) Durante (2) Pós
Fim do tratamento (FIM_TRAT): _____/_____/_____
Duração tratamento (MESES_TRAT_CONT):_____ meses
Tratamento atual (TRAT_AT): (0) QT (1) RxT (2) QT e RxT (3) Pré OP (4) Pós OP (5) Outros (6) NA
Medicamentos (MED_QT): (0)5FU+LV (1)FOLFOX (2)FLOX (3)FOLFIRI (4)Xeloda (5)Xelox (6)Cetuximabe (7)Bevacizumabe (8)Outros (9)NA
Dose RT (DOSE_RTX):_____
Tipo cirurgia (TIPO_CIR): (0) RAR (1) RAP (2) colectomia (3) hepatectomia (4) lobectomia (5)Outros (6) NA
Finalidade do tratamento (FINA_TRAT): (0) Curativo (1) Neoadjuvante (2) Adjuvante
(3) Paliativo (4) Não definido
Tratamento prévio (TRAT_PREVIO): (0) QT (1) RxT (2) QT e RxT (3) CIR (4) QT e CIR (5) RxT e CIR (6) QT, RxT e CIR (7) Outros (8) NA
Medicamentos (MED_QT_PREV): (0)5FU+LV (1)FOLFOX (2)FLOX (3)FOLFIRI (4)Xeloda (5)Xelox (6)Cetuximabe (7)Bevacizumabe (8)Outros (9)NA
Dose RT (DOSE_RTX_PREV):_____
Tipo cirurgia (TIPO_CIR_PREV): (0) RAR (1) RAP (2) colectomia (3) hepatectomia
(4) lobectomia (5) Outros (6) NA
História de neoplasia pregressa - há mais de 5 anos (HNP): (0) Sim (1) Não

III – História Social
Co-morbidades* (COMORB): (1) Não (2) HAS (3) DM (4) HAS e DM (5) ICC (6) IRC (7) IR (8) Outras (9) HAS e outras (10) DM e outras
Uso de medicamentos (USO_MEDIC): (0) Sim (1) Não
Medicamentos (MEDIC):_____

Estado civil (EST_CIV): (0) Solteiro (1) Casado/amasiado (2) Viúvo (3) Divorciado/Separado

Raça (RACA): (0) Negra (1) Parda (2) Branca (3) Amarela (4) Indígena
Renda familiar (RF_SALMIN): (1) <1 sal (2) 1-2 sal (3) 2-3 sal (4) 3-4 sal (5) 4-5 sal (6) >5 sal (7) Não sabe
Principal provedor (PRINC_PROV): (0) Próprio (1) Outro (3) Ambos
N° pessoas que contribuem com a renda (PES_REND): _____
N° pessoas na moradia (PES_MOR): _____
Anos de estudo (AN_EST): _____ anos
Sabe ler (LE): (0) Sim (1) Não
Sabe escrever (ESCREV): (0) Sim (1) Não
Ocupação atual (OCUP_AT): (0) Sim (1) Não
Aposentado (APOS): (0) Sim (1) Não

IV – Informações Nutricionais
Terapia Nutricional (TN): (0) Sim (1) Não
Via (VIA_TN): (0) Oral (1) Enteral (2) Oral e Enteral (3) NA
Momento (MOM_TN): (0) Atual (1) Pregressa (2) NA

Peso atual (PESO_AT): ____ kg, Peso relatado (PESO_RELAT):____ kg
Altura (ALT): _____m, Índice de massa coporal (IMC): _____ kg/m^2
Peso relatado 6 meses (PESO_6M):___kg, Percentual perda de peso 6m (PPP_6M): ___ %
Peso relatado 1 ano (PESO_1A):____ kg, Percentual perda de peso 1 ano (PPP_1A:____ %,
Circunferência do braço (CB): _____ cm, Prega cutânea tricipital (PCT):_____ cm
Circunferência muscular do Braço (CMB):____cm
Área muscular do braço corrigida (AMBc)____cm
Circunferência panturrilha (CPANT): _____cm
Circunferência cintura (CCINT): _____cm, Circunferência quadril (CQUADRIL): _____cm

BIA
Resistência (RES):_____, Reactância (REAC):_____,

	Resistência	Reactância
1ª aferição		
2ª aferição		
3ª aferição		

TC
Área Muscular (MM_L3):_____cm^2, Atenuação Muscular (MA):_____HU
Índice Muscular Esquelético lombar (SMI_L3)*: _____cm^2/m^2, Gordura subcutânea (SAT_TC):_____cm^2,
Gordura visceral (VAT_TC):_____cm^2, Gordura intramuscular (IAT_TC):_____cm^2

Bioquímica:
Albumina (ALB):____g/dl, Pré-albumina (PRE_ALB):____g/dl, Glicemia(GLI):____mg/dl, Proteína C-Reativa(PCR):____mg/dl, Creatinina (CREAT): ____mg/dl

ASG-PPP
Escore (ESCORE_ASG) = _____, Classificação (CLASS_ASG): (0) A (1) B (2) C
Exame físico: Reserva muscular (ESCORE_.MÚSCULO) (0) 0 (1) +1 (2) +2 (3) +3
Reserva adiposa (ESCORE_GORDURA) (0) 0 (1) +1 (2) +2 (3) +3
Estado de hidratação (ESCORE_HIDRATAÇÃO) (0) 0 (1) +1 (2) +2 (3) +3

Fenótipo de Fragilidade:
1-Perda de peso não intencional igual ou superior a 3 kg no último ano*:*
Perda de peso real = peso obtido na avaliação – peso registrado em prontuário 1 ano antes
_____ = _____ – _____

2-Força de preensão manual:
*Marcar um "X" na mão dominante

	Mão Direita ( )	Mão Esquerda ( )
1º medida		
2º medida		
3º medida		

Maior força de preensão manual (FORÇA_PREENSÃO): _____kg

3-Fadiga relatada (FADIGA):
(a) "*Com que freqüência, na última semana, o (a) Sr (a) sentiu que tudo que fez exigiu um grande esforço/foi muito custoso?*" 0 ( ) 1 ( ) 2 ( ) 3 ( )
(b) "*Com que freqüência, na última semana, o (a) Sr (a) sentiu que não conseguia levar adiante as suas coisas (iniciava alguma coisa mas não conseguia terminar?*"
0 ( ) 1 ( ) 2 ( ) 3 ( )
As respostas para ambas as questões serão:
0= nunca ou raramente (< 1 dia),
1= Poucas vezes (1-2 dias),
2= Algumas vezes (3-4 dias) ou,
3= A maior parte do tempo

4- Velocidade de caminhada:

Teste da marcha com 4,6m	Tempo (segundos)	m/s
Ida		
Volta		

Menor tempo no teste de velocidade de caminhada: _____segundos
Velocidade de caminhada (VEL_CAMINHADA): _____m/s
*Utilizou algum auxiliar de marcha (AUXILIAR_MARCHA)? (1) Não (2) Andador (3) Bengala (4) Muletas (5) Outro
*Registrar motivo da não realização de alguma etapa:
_____

5-Atividade física - **Questionário Internacional de Atividade Física - IPAQ - versão curta**

1a. Em quantos dias da última semana você **CAMINHOU** por pelo menos 10 minutos contínuos em casa ou no trabalho, como forma de transporte para ir de um lugar para outro, por lazer, por prazer ou como forma de exercício?
_____ dias por **SEMANA** ( ) Nenhum

1b. Nos dias em que você caminhou por pelo menos 10 minutos contínuos, quanto tempo no total você gastou caminhando **por dia**?

Segunda	Terça	Quarta	Quinta	Sexta	Sábado	Domingo

Total: _____ horas _____ minutos

2a. Em quantos dias da última semana, você realizou atividades **MODERADAS (**precisam de algum esforço físico) por pelo menos 10 minutos contínuos, como, pedalar leve na bicicleta, nadar, dançar, fazer ginástica aeróbica leve, jogar vôlei recreativo, carregar pesos leves, fazer serviços domésticos na casa, no quintal ou no jardim como varrer, aspirar, cuidar do jardim, ou qualquer atividade que fez aumentar **moderadamente** sua respiração ou batimentos do coração **(POR FAVOR NÃO INCLUA CAMINHADA).**
_____ dias por **SEMANA** ( ) Nenhum

2b. Nos dias em que você fez essas atividades moderadas por pelo menos 10 minutos contínuos, quanto tempo no total você gastou fazendo essas atividades **por dia**?

Segunda	Terça	Quarta	Quinta	Sexta	Sábado	Domingo

Total: _____ horas _____ minutos

3a Em quantos dias da última semana, você realizou atividades **VIGOROSAS (**precisam de um grande esforço físico) por pelo menos 10 minutos contínuos, como, correr, fazer ginástica aeróbica, jogar futebol, pedalar rápido na bicicleta, jogar basquete, fazer serviços domésticos pesados em casa, no quintal ou cavoucar no jardim, carregar pesos elevados ou qualquer atividade que fez aumentar **MUITO** sua respiração ou batimentos do coração.

_____ dias por **SEMANA** ( ) Nenhum

3b Nos dias em que você fez essas atividades vigorosas por pelo menos 10 minutos contínuos quanto tempo no total você gastou fazendo essas atividades **por dia**?

Segunda	Terça	Quarta	Quinta	Sexta	Sábado	Domingo

Total: _____ horas _____ minutos

As últimas questões são sobre o tempo gasto sentado todo dia, no trabalho, em casa e durante o tempo livre. Não incluir o tempo gasto sentando durante o transporte em ônibus, trem, metrô ou carro.

4a. Quanto tempo no total você gasta sentado durante um dia de semana (TSENT_SEMANA)? _____ horas _____ min

4b. Quanto tempo no total você gasta sentado durante um dia de final de semana (TSENT_FSEMANA)? _____ horas _____ m

ANEXO A - Avaliação subjetiva global produzida pelo paciente

Identificação Nº:_____ Sexo:_____

1. PESO *(veja anexo 1)*
Resumo do meu peso atual e recente:
Eu atualmente peso aproximadamente:____,___Kg
Eu tenho aproximadamente 1 metro e _____cm
Há um mês atrás eu pesava aproximadamente:____,___Kg
Há seis meses atrás eu pesava aproximadamente:____,___Kg

Durante as 2 últimas semanas meu peso:
☐ *Diminuiu (1)* ☐ *ficou igual (0)* ☐ *Aumentou (0)*

Caixa 1 ☐

2. INGESTÃO ALIMENTAR: *Em comparação a minha alimentação normal, eu poderia considerar minha ingestão alimentar durante o último mês como:*

☐ *sem mudanças (0)*
☐ *mais que o normal (0)*
☐ *menos que o normal (1)*

Atualmente, eu estou comendo:
☐ *comida normal (alimentos sólidos) em menor quantidade (1)*
☐ *comida normal (alimentos sólidos) em pouca quantidade (2)*
☐ *apenas líquidos (3)*
☐ *apenas suplementos nutricionais (3)*
☐ *muito pouco de qualquer comida (4)*
☐ *apenas alimentos por sonda ou pela veia (0)*

Caixa 2 ☐

3. SINTOMAS: *Durante as 2 últimas semanas, eu tenho tido os seguintes problemas que me impedem de comer o suficiente (marque todos os que estiver sentindo):*
☐ *sem problemas para se alimentar (0)*
☐ *sem apetite, apenas sem vontade de comer (3)*
☐ *náusea (1)* ☐ *vômito (3)*
☐ *constipação (1)* ☐ *diarréia (3)*
☐ *feridas na boca (2)* ☐ *boca seca (1)*
☐ *alimentos têm gosto estranho ou não têm gosto (1)*
☐ *os cheiros me enjoam (1)*
☐ *problemas para engolir (2)*
☐ *rapidamente me sinto satisfeito (1)*
☐ *dor; onde? (3) _____*
☐ *outros**: (1) _____*
*** ex. depressão, problemas dentários ou financeiros*

Caixa 3 ☐

4. ATIVIDADES E FUNÇÃO: *No último mês, eu consideraria minha atividade como:*
☐ *Normal, sem nenhuma limitação (0)*
☐ *Não totalmente normal, mas capaz de manter quase todas as atividades normais (1)*
☐ *Não me sentindo bem para a maioria das coisas, mas ficando na cama ou na cadeira menos da metade do dia (2)*
☐ *capaz de fazer pouca atividade, e passando a maior parte do tempo na cadeira ou na cama (3)*
☐ *bastante tempo acamado, raramente fora da cama (3)*

Caixa 4 ☐

Somatório dos escores das caixas 1 a 4 ☐ *A*

O restante do questionário será preenchido pelo seu médico, enfermeira ou nutricionista. Obrigada.

5. DOENÇA E SUA RELAÇÃO COM REQUERIMENTOS NUTRICIONAIS (Veja anexo 2)
Todos os diagnósticos relevantes (especifique): _____
Estadiamento da doença primária (circule se conhecido ou apropriado) I II III IV Outro: _____
Idade: _____ *Escore numérico do anexo 2* ☐ *B*

6. DEMANDA METABÓLICA (Veja anexo 3) *Escore numérico do anexo 3* ☐ *C*

7. EXAME FÍSICO (Veja anexo 4) *Escore numérico do anexo 4* ☐ *D*

AVALIAÇÃO GLOBAL *(Veja anexo 5)*
☐ *Bem Nutrido ou anabólico (ASG-A)*
☐ *Desnutrição moderada ou suspeita (ASG-B)*
☐ *Gravemente desnutrido (ASG-C)*

Escore Total da ASG produzida pelo paciente:
Escore numérico total de A+B+C+D acima
(Siga as orientações de triagem abaixo) ☐

Recomendações de triagem nutricional: a somatória dos escores é utilizada para definir intervenções nutricionais específicas, incluindo a orientação do paciente e seus familiares, manuseio dos sintomas incluindo intervenções farmacológicas e intervenção nutricional adequada (alimentos, suplementos nutricionais, nutrição enteral ou parenteral). A primeira fase da intervenção nutricional inclui o manuseio adequado dos sintomas.
0 — 1: Não há necessidade de intervenção neste momento. Reavaliar de forma rotineira durante o tratamento.
2 — 3: Educação do paciente e seus familiares pelo nutricionista, enfermeira ou outro profissional, com intervenção farmacológica de acordo com o inquérito dos sintomas (caixa 3) e exames laboratoriais se adequado.
4 — 8: Necessita intervenção pela nutricionista, juntamente com a enfermeira ou médico como indicado pelo inquérito dos sintomas (caixa 3).
≥ 9: Indica necessidade crítica de melhora no manuseio dos sintomas e/ou opções de intervenção nutricional.

Regras para pontuação da Avaliação Subjetiva Global produzida pelo paciente (ASG-PPP)

As caixas de 1 a 4 da ASG-PPP foram feitas para serem preenchidas pelo paciente. O escore numérico da ASG-PPP é determinado usando: **1)** os pontos entre parênteses anotados nas caixas 1 a 4 e **2)** na folha abaixo para itens não pontuados entre parênteses. Os escores para as caixas 1 e 3 são aditivos dentro de cada caixa e os escores das caixas 2 e 4 são baseados no escore mais alto marcado pelo paciente.

Anexo 1 - *Escore da perda de peso*

Para determinar o escore, use o peso de 1 mês atrás se disponivel. Use o peso de 6 meses atrás apenas se não tiver dados do peso do mês passado. Use os pontos abaixo para pontuar as mudanças do peso e acrescente pontos extras se o paciente perdeu peso nas 2 últimas semanas. Coloque a pontuação total na caixa 1 da ASG-PPP.

Perda de peso em 1 mês	Pontos	Perda de peso em 6 meses
10% ou mais	4	20% ou mais
5 - 9,9%	3	10 - 19,9%
3 - 4,9%	2	6 - 9,9%
2 - 2,9%	1	2 - 5,9%
0 - 1,9%	0	0 - 1,9%

Pontuação para o anexo 1
Anote na caixa A ☐

Anexo 2 - *Critério de pontuação para condição*

A pontuação é obtida pela adição de 1 ponto para cada condição listada abaixo que o paciente apresente.

Categoria	Pontos
Câncer	1
AIDS	1
Caquexia pulmonar ou cardíaca	1
Úlcera de decúbito, ferida aberta ou fístula	1
Presença de trauma	1
Idade maior que 65 anos	1

Pontuação para o anexo 2
Anote na caixa B ☐

Anexo 3 - *Pontuação do estresse metabólico*

O escore para o estresse metabólico é determinado pelo número de variáveis conhecidas que aumentam as necessidades calóricas e protéicas. O escore é aditivo sendo que se o paciente tem febre > 38.9ºC (3 pontos) e toma 10mg de prednisona cronicamente (2 pontos) teria uma pontuação de 5 pontos para esta seção.

Estresse	Nenhum (0)	Baixo (1)	Moderado (2)	Alto (3)
Febre	Sem febre	> 37,2 e < 38,3ºC	≥ 38,3 e < 38,9ºC	≥ 38,9ºC
Duração da Febre	Sem febre	< 72 horas	72 horas	> 72 horas
Corticosteróides	Sem corticosteróides	dose baixa (< 10mg prednisona/dia)	dose moderada (≥ 10 a < 30 mg prednisona)	dose alta (≥ 30 mg prednisolona)

Pontuação para o anexo 3
Anote na caixa C ☐

Anexo 4 - *Exame físico*

O exame físico indui a avaliação subjetiva de 3 aspectos da composição corporal: gordura, músculo e estado de hidratação. Como é subjetiva, cada aspecto do exame é graduado pelo grau de déficit. O déficit muscular tem maior impacto no escore do que o déficit de gordura. Definição das categorias: 0 = sem déficit, 1+ = déficit leve, 2+ = déficit moderado, 3+ = déficit grave. A avaliação dos déficit nestas categorias não devem ser somadas, mas são usadas para avaliar clinicamente o grau de déficit (ou a presença de líquidos em excesso).

Reservas de gordura:		Estado de hidratação:	
Região peri-orbital	0 +1 + 2 + 3	Edema no tornozelo	0 + 1 + 2 + 3
Prega de triceps	0 +1 + 2 + 3	Edema sacral	0 + 1 + 2 + 3
Gordura sobre as últimas costelas	0 +1 + 2 + 3	Ascite	0 + 1 + 2 + 3
Avaliação geral do déficit de gordura	**0 + 1 + 2 + 3**	**Avaliação geral do estado de hidratação**	**0 + 1 + 2 + 3**

Estado muscular:	
Têmporas (músc. temporal)	0 +1 + 2 + 3
Clavículas (peitorais e deltóides)	0 +1 + 2 + 3
Ombros (deltóides)	0 + 1 + 2 + 3
Músculatura inter-óssea	0 +1 +2 + 3
Escápula (dorsal maior, trapézio, deltóide)	0 +1 + 2 + 3
Coxa (quadriceps)	0 + 1 + 2 + 3
Panturrilha (gastrocnêmius)	0 +1 + 2 + 3
Avaliação geral do estado muscular	**0 + 1 + 2 + 3**

A pontuação do exame físico é determinado pela avaliação subjetiva geral do déficit corporal total.

Sem déficit	escore = 0 pontos
Déficit leve	escore = 1 ponto
Déficit moderado	escore = 2 pontos
Déficit grave	escore = 3 pontos

Pontuação para o anexo 4
Anote na caixa D ☐

Anexo 5 - *Categorias da avaliação global da ASG-PPP*

	Estágio A	Estágio B	Estágio C
Categoria	Bem Nutrido	Moderada desnutrido ou suspeito de desnutrição	Gravemente desnutrido
Peso	Sem perda **OU** ganho recente não hídrico	~ 5% PP em 1 mês (ou 10% em 6 meses) OU Sem estabilização ou ganho de peso (continua perdendo)	> 5% PP em 1 mês (ou 10% em 6 meses) OU Sem estabilização ou ganho de peso (continua perdendo)
Ingestão nutrientes	Sem déficit **OU** melhora significativa recente	Diminuição definitiva na ingestão	Déficit grave de ingestão
Sintomas com impacto nutricional	Nenhum **OU** melhora significativa recente permitindo ingestão adequada	Presença de sintomas de impacto nutricional (caixa 3 da ASG-PPP)	Presença de sintomas de impacto nutricional (caixa 3 da ASG-PPP)
Função	Sem déficit **OU** melhora significativa recente	Déficit funcional moderado OU piora recente	Déficit funcional grave OU piora recente significativa
Exame físico	Sem deficit OU deficit crônico porém com recente melhora clinica	Evidência de perda leve a moderada de gordura e/ ou massa muscular e/ou tônus muscular à palpação	Sinais óbvios de desnutrição (ex. perda importante dos tecidos sub-cutâneos, possivel edema)
	Categorias Globais da ASG-PPP (A,B ou C) = ☐		

ANEXO B – Aprovação do Comitê de Ética em Pesquisa

INSTITUTO NACIONAL DE CÂNCER/ INCA/ RJ

PARECER CONSUBSTANCIADO DO CEP

DADOS DO PROJETO DE PESQUISA

Título da Pesquisa: Validação dos Diferentes Métodos de Avaliação da Massa Muscular Utilizados na Prática Clínica na Avaliação da Sarcopenia em Pacientes com Neoplasia Colorretal

Pesquisador: Nilian Carla Silva Souza
Área Temática:
Versão: 3
CAAE: 38992014.5.0000.5274
Instituição Proponente: Hospital do Câncer I
Patrocinador Principal: Financiamento Próprio

DADOS DO PARECER

Número do Parecer: 942.022
Data da Relatoria: 08/02/2015

Apresentação do Projeto:
Conforme descrito no Parecer Consubstanciado CEP/INCA Nº 916.021 de 16/12/14.

Objetivo da Pesquisa:
Conforme descrito no Parecer Consubstanciado CEP/INCA Nº 916.021 de 16/12/14.

Avaliação dos Riscos e Benefícios:
Conforme descrito no Parecer Consubstanciado CEP/INCA Nº 916.021 de 16/12/14.

Comentários e Considerações sobre a Pesquisa:
Conforme descrito no Parecer Consubstanciado CEP/INCA Nº 916.021 de 16/12/14.

Considerações sobre os Termos de apresentação obrigatória:
Conforme descrito no Parecer Consubstanciado CEP/INCA Nº 916.021 de 16/12/14.

Endereço: RUA DO RESENDE, 128 - SALA 203
Bairro: CENTRO **CEP:** 20.231-092
UF: RJ **Município:** RIO DE JANEIRO
Telefone: (21)3207-4550 **Fax:** (21)3207-4556 **E-mail:** cep@inca.gov.br

Recomendações:

Não se aplica.

Conclusões ou Pendências e Lista de Inadequações:

Trata-se da análise das respostas às pendências apontadas no Parecer Consubstanciado CEP/INCA Nº 934.408 de 25/01/2015:

2: Quanto ao projeto de pesquisa:

2.5 - Na página 18 de 23, no item "Análises estatísticas" solicita-se informar:
c) todas as variáveis que serão coletadas e a forma em que os dados serão coletados.

RESPOSTA 1: Na página 18 de 23, no item "Análises estatísticas": c) As variáveis serão coletadas através de uma ficha de coleta de dados inserida no projeto e na Plataforma Brasil como "Ficha de Coleta de Dados".

ANÁLISE 1: PENDÊNCIA PARCIALMENTE ATENDIDA. Em relação à Ficha de Coleta de Dados, é importante ressaltar que sob nenhuma circunstancia poderá constar qualquer informação (nome, registro médico, endereço etc.) que permita a identificação dos participantes de pesquisa. O pesquisador principal deverá garantir a anonimização dos dados através do uso de formulários específicos. Adequar.

RESPOSTA 2: Na página 18 de 23, no item "Análises estatísticas": c) As informações referentes ao nome e ao registro médico foram retiradas do formulário e o mesmo foi modificado no projeto de pesquisa e anexado na Plataforma Brasil como "Ficha de Coleta de Dados".

ANÁLISE 2: PENDÊNCIA ATENDIDA.

2.8 – Na página 15 de 23 lê-se "A ASG-PPP será aplicada por um único avaliador bem treinado. Oquestionário é dividido em duas partes. A primeira será respondida pelo paciente ou cuidador e envolve questões sobre perda de peso, alterações na ingestão alimentar e na capacidade funcional e sintomas que possam interferir no consumo alimentar como perda de apetite, alterações do paladar, náuseas e vômitos [...]". Não foi apresentado o instrumento de coleta. Solicita-se adequação.

RESPOSTA 1: O instrumento de coleta (formulário da ASG-PPP) foi incluído no projeto e na Plataforma Brasil como “Formulário da ASG-PPP”.

ANÁLISE 1: PENDÊNCIA ATENDIDA. Caso esse formulário seja retirado do prontuário e armazenado em arquivo da pesquisadora, por favor considerar necessária a adequação indicada na análise da pendência 6 (vide acima).

RESPOSTA 2: As informações referentes ao nome e registro médico foram retiradas do formulário da ASG-PPP e o mesmo foi modificado no projeto de pesquisa e anexado na Plataforma Brasil como “Formulário da ASG-PPP”.

ANÁLISE 2: PENDÊNCIA ATENDIDA.

3 - Quanto ao documento “PB_INFORMAÇÕES_BÁSICAS_DO_PROJETO_273376.pdf” de 21/11/2014:

3.1 - No campo "desfecho primário”, o texto informado é uma justificativa, mas não esclarece qual será o desfecho primário. Solicita-se adequação.

RESPOSTA 1: O desfecho primário foi modificado para “Validar a utilização das medidas de circunferência da panturrilha, área muscular do braço corrigida, massa muscular esquelética e o exame físico da ASG-PPP para a avaliação da massa muscular e o diagnóstico da sarcopenia em pacientes com neoplasia colorretal”.

ANÁLISE 1: PENDÊNCIA ATENDIDA. Como recomendação, sugerimos redigir "validação" ao invés de "validar" nesse campo.

RESPOSTA 2: No campo “desfecho primário” a palavra “validar” foi trocada por “validação”.

ANÁLISE 2: PENDÊNCIA ATENDIDA.

3.2 – No item “Riscos e Benefícios”, os riscos devem contemplar as outras avaliações previstas no projetode pesquisa (não só a coleta de sangue), mencionando outros riscos, como queda, cansaço,

etc. (o paciente será submetido a várias avaliações exclusivas para o estudo em jejum, não somente a TC para estadiamento). Sobre os benefícios, esclarecer que não haverá benefício direto aos pacientes.

RESPOSTA 1: No item “Riscos e Benefícios” foram contemplados os riscos de queda e cansaço e foi mencionado que o paciente não terá benefício direto com o estudo em questão.

ANÁLISE 1: PENDÊNCIA PARCIALMENTE ATENDIDA. A pendência foi atendida apenas em relação à descrição do item "Benefícios". No item "Riscos", ainda não estão contemplados os riscos de todas as avaliações da pesquisa, como a aplicação do formulário. Conforme exposto pela pesquisadora: "não haverá outros riscos maiores". No entanto, os riscos considerados "pequenos" pela pesquisadora também devem ser descritos. Segundo a resolução CNS nº 466/12, risco de pesquisa é a "possibilidade de danos à dimensão física, psíquica, moral, intelectual, social, cultural ou espiritual do ser humano, em qualquer pesquisa e dela decorrente". Solicitamos adequação.

RESPOSTA 2: O campo “Riscos” foi modificado e foram contemplados os riscos de todas as avaliações incluídas na pesquisa.

ANÁLISE 2: PENDÊNCIA ATENDIDA.

4 - Quanto ao documento “TCLE doutorado.doc”:

4.4 - Os textos dos itens “RISCOS” e “BENEFÍCIOS” deverão ser adequados, citando os riscos inerentes às outras avaliações e esclarecendo que não há benefício direto ao paciente conforme pendência 3.2.

RESPOSTA 1: Na página 3 de 5 do TCLE foram contemplados os riscos de queda e cansaço e foi mencionado que o paciente não terá benefício direto com o estudo em questão.

ANÁLISE 1: PENDÊNCIA PARCIALMENTE ATENDIDA. A pendência foi atendida apenas em relação à descrição do item "Benefícios". No item "Riscos", ainda não estão contemplados os riscos de todas as avaliações da pesquisa, como a aplicação do formulário. Conforme exposto pela pesquisadora:

"não haverá outros riscos maiores". No entanto, os riscos considerados "pequenos" pela pesquisadora também devem ser descritos. Segundo a resolução CNS nº 466/12, risco de pesquisa é a "possibilidade de danos à dimensão física, psíquica, moral, intelectual, social, cultural ou espiritual do ser humano, em qualquer pesquisa e dela decorrente". Solicitamos adequação.

RESPOSTA 2: Na página 3 de 5 do TCLE o campo "Riscos" foi modificado e foram contemplados os riscos de todas as avaliações incluídas na pesquisa.

ANÁLISE 2: PENDÊNCIA ATENDIDA.

Situação do Parecer:

Aprovado

Necessita Apreciação da CONEP:

Não

Considerações Finais a critério do CEP:

Diante do exposto, o Comitê de Ética em Pesquisa do Instituto Nacional de Câncer (CEP-INCA), de acordo com as atribuições definidas na Resolução CNS 466/12 e na Norma Operacional Nº 001/2013 do CNS, manifesta-se pela aprovação do projeto de pesquisa proposto.

Ressalto o(a) pesquisador(a) responsável deverá apresentar relatórios semestrais a respeito do seu estudo.

RIO DE JANEIRO, 30 de Janeiro de 2015

Assinado por:
Carlos Henrique Debenedito Silva
(Coordenador)

ANEXO C – Confirmação da submissão do Artigo 1

Submission Confirmation for

De: Clinical Nutrition (eesserver@eesmail.elsevier.com)

Para: niliansouza@yahoo.com.br; nilian.souza@inca.gov.br

Data: sexta-feira, 10 de agosto de 2018 22:12 BRT

*** Automated email sent by the system ***

Dear Mrs. Nilian Carla S Souza,

Your submission entitled "FRAILTY IS ASSOCIATED WITH MYOSTEATOSIS IN OBESE PATIENTS WITH COLORECTAL CANCER" has been received by the Editorial office of Clinical Nutrition. Its category is Full Length Article, if this is not correct please let us know.

You will be able to check on the progress of your paper by logging on to Elsevier Editorial Systems as an author. The URL is https://ees.elsevier.com/yclnu/.

Your manuscript will be given a reference number once an Editor has been assigned.

Thank you for submitting your work to this journal.

Kind regards,

Editorial office
Clinical Nutrition

ANEXO D – Parecer da revista *Clinical Nutrition* sobre o Artigo 1

Your Submission YCLNU-D-18-00884

De: Clinical Nutrition (eesserver@eesmail.elsevier.com)

Para: niliansouza@yahoo.com.br; nilian.souza@inca.gov.br

Data: terça-feira, 6 de novembro de 2018 02:42 BRST

MS. Ref. No.: YCLNU-D-18-00884
Title: "FRAILTY IS ASSOCIATED WITH MYOSTEATOSIS IN OBESE PATIENTS WITH COLORECTAL CANCER"

Dear Mrs. Souza,

Your Full Length Article entitled "FRAILTY IS ASSOCIATED WITH MYOSTEATOSIS IN OBESE PATIENTS WITH COLORECTAL CANCER" has been sent to one or more independent reviewers and has been reviewed by the Editorial Board. I am sorry to say that it has been found unsuitable for publication in Clinical Nutrition journal in its present form. However, if you are able to address the enclosed suggestions and criticisms, we would be pleased to re-assess a revised version of your manuscript although please be aware that publication would not be guaranteed.

We request that you adjust the paper according to the Guide for Authors located at http://www.elsevier.com/journals/clinical-nutrition/0261-5614/guide-for-authors , if not already done so. Enclosed below are Comments from the Editorial Board and the Reviewers. These are appended to the end of this message.
If you decide to revise and resubmit your paper for the Clinical Nutrition journal, this should be done by Feb 04, 2019 in order to maintain the same reference number. Otherwise, it will be dealt with as a new manuscript. Your revised version should be accompanied by a letter with a point-by-point reply to the reviewers comments and explanation of the changes included in your paper. The response to the reviewers also should have continuous line numbers. Please clearly mark the changes made to the manuscript, and submit two revised versions as follows: 1) a document with track changes, and 2) a document with the changes already made.

To resubmit a revised paper, please go to https://ees.elsevier.com/yclnu/ and log in as an Author. You will see the following menu item listed "Submission Needing Revision" and you will find your submission there.

Please note that this journal offers a new, free service called AudioSlides: brief, webcast-style presentations that are shown next to published articles on ScienceDirect (see also http://www.elsevier.com/audioslides). If your paper is accepted for publication, you will automatically receive an invitation to create an AudioSlides presentation.

NOTE: Upon submitting your revised manuscript, please upload the source files for your article. For additional details regarding acceptable file formats, please refer to the Guide for Authors at: http://www.elsevier.com/journals/clinical-nutrition/0261-5614/guide-for-authors

When submitting your revised paper, we ask that you include the following items:

Manuscript and Figure Source Files (mandatory)

We cannot accommodate PDF manuscript files for production purposes. We also ask that when submitting your revision you follow the journal formatting guidelines. Figures and tables may be embedded within the source file for the submission as long as they are of sufficient resolution for Production. For any figure that cannot be embedded within the source file (such as *.PSD Photoshop files), the original figure needs to be uploaded separately. Refer to the Guide for Authors for additional information.
http://www.elsevier.com/journals/clinical-nutrition/0261-5614/guide-for-authors

Thank you for submitting your paper to Clinical Nutrition. We are looking forward to hearing from you.

Yours sincerely,

maurizio muscaritoli, MD

Associate Editor
Clinical Nutrition

Nicolaas E Deutz, MD, PhD
Editor-in-Chief
Clinical Nutrition

Comments from the Editors and Reviewers:

Reviewer #1: The manuscript provides insight on the association between muscle lipid infiltration and function in colorectal cancer patients. The association of frailty with lipid infiltration is an interesting finding (although not totally original). The fact that obesity is aggravating the scenario certainly is of clinical relevance. Nevertheless, some points deserve discussion:
- Was there control for hydration of patients, since BIA is affected by this parameter?
- handgrip may not be a good method, specially when comparing men and women, who beyond as healthy adults displaying major differences, present a different dynamic of muscle loss in ageing. Timed up and go is perhaps, a better predictor of function
-Although involuntary weight loss is reported, the patients were not classified as cachectic or not. Please comment.
- Muscle lipid infiltration could derive from obesity solely. The effect of cancer is not clear. We would suggest to measure at least plasma lipids in order to examine whether the results are a reflex of cancer (with increased lipemia), or just reflect the comprehensively described myosteatosis of obese patients.
- Albumin is not changing. Would that mean patients are not undernourished, nor cachectic?
The study presents an observational approach and mechanisms should be discussed in more depth.
- Please consider to discuss:
1: Lipina C, Hundal HS. Lipid modulation of skeletal muscle mass and function. J Cachexia Sarcopenia Muscle. 2017 Apr;8(2):190-201. doi: 10.1002/jcsm.12144. Epub 2016 Oct 8. Review. PubMed PMID: 27897400; PubMed Central PMCID: PMC5377414.

2: Xiao J, Caan BJ, Weltzien E, Cespedes Feliciano EM, Kroenke CH, Meyerhardt JA, Baracos VE, Kwan ML, Castillo AL, Prado CM. Associations of pre-existing co-morbidities with skeletal muscle mass and radiodensity in patients with non-metastatic colorectal cancer. J Cachexia Sarcopenia Muscle. 2018 Aug;9(4):654-663. doi: 10.1002/jcsm.12301. Epub 2018 Apr 19. PubMed PMID: 29675984; PubMed Central PMCID: PMC6104112.

3: Baracos VE, Arribas L. Sarcopenic obesity: hidden muscle wasting and its impact for survival and complications of cancer therapy. Ann Oncol. 2018 Feb 1;29(suppl_2):ii1-ii9. doi: 10.1093/annonc/mdx810. PubMed PMID: 29506228.

Reviewer #2: There are a couple of points of clarity that are required.
The study is not actually exploring the determinants of muscle fat infiltration but rather the functional outcomes associated with muscle fat infiltration. Body fat may be a determinant of fat infiltration (the fatter you are the more fat you have in muscles) which may also implicate frailty but a slower gait speed may be a result of having a higher level of fat in the muscles and thereby being more frail. At times, the way this is worded is confusing. In other words, is having a slow gait speed likely to contribute to myosteatosis or does a slow gait speed result from (or reflect) myosteatosis. The cause and effect are not evaluated in this study.
Methods:
For albumin, what the method used for this assessment?
Were the comorbidity conditions of the population captured? It is known that the number of comorbidities a person relates to the measure of muscle radiodensity (using CT). People with cancer commonly have 3 or more comorbidities upon presentation with cancer. If it is known, this is also part of the model.
Infiltration of fat measured by the amount of IMAT in a single slice at L3 has not been validated as a way to determine the amount of fat in muscle. IMAT distribution in muscles is highly variable and that which is present at L3 may not reflect this parameter as a whole. Further, is it know how well this measure correlates with the radiodensity

of muscle? What is the relationship between these variables in your population? Since this is the measure by which the data is categorized, this becomes important. The references cited have not validated this method at L3 in CT images.

ANEXO E – Artigo publicado em periódico como coautora

NUTRITION AND CANCER
https://doi.org/10.1080/01635581.2018.1412480

Taylor & Francis
Taylor & Francis Group

REVIEW ARTICLE

Check for updates

Factors Associated with Sarcopenia in Patients with Colorectal Cancer

Bianca Umbelino de Souza[a], Nilian Carla Silva Souza[a,c], Renata Brum Martucci[a,c], Viviane Dias Rodrigues[a], Nivaldo Barroso de Pinho[a], Maria Cristina Gonzalez[b], and Carla Maria Avesani[c]

[a]Nutrition and Dietetic Service, Cancer Hospital Unit I, Brazilian National Cancer Institute José Alencar Gomes da Silva (INCA), Rio de Janeiro, Brazil; [b]Post-graduate Program on Health and Behavior, Catholic University of Pelotas (UCPEL), Pelotas, Rio Grande do Sul, Brazil; [c]Nutrition Institute, Rio de Janeiro State University (UERJ), Rio de Janeiro, Brazil

ABSTRACT

Introduction; Sarcopenia are frequently observed in cancer patients and was associated with poor prognosis. *Objectives;* to determine the association of nutritional status, body composition, and clinic parameters with sarcopenia in patients with colorectal cancer (CRC). *Methods;* We conducted a cross-sectional study of 197 patients with CRC. The sarcopenia elements, including lumbar skeletal muscle index (SMI), handgrip strength, and gait speed were measured. The SMI was assessed by computed tomography at third lumbar vertebra. Phase angle (PA), serum albumin (SAlb), muscle attenuation (MA), and the scored patient-generated subjective global assessment (PG-SGA) were also evaluated. Univariate and multivariate analysis of factors associated with sarcopenia were performed. *Results;* Sarcopenia was present in 29 of 195 patients (15%) and was significantly correlated with advance age, lower body mass index (BMI), SAlb, PA, MA, higher PG-SGA score, and malnutrition (PG-SGA B). In univariate analysis, age, BMI, SAlb, PA, MA, PG-SGA score, and malnutrition (PG-SGA B) were associated with sarcopenia. Multivariable analysis revealed that BMI, SAlb, PA, MA, and PG-SGA score were independent predictors of sarcopenia. *Conclusion;* BMI, SAlb, PA, MA, and PG-SGA score were independent predictors of sarcopenia in patients with CRC.

ARTICLE HISTORY
Received 16 April 2017
Accepted 13 October 2017

Introduction

Colorectal cancer (CRC) is amongst the types of cancer with the highest incidence rates. In the world, CRC is third in incidence and fourth in mortality (1). In Brazil, it is the third most frequent in men and second in women, according to the Brazilian National Cancer Institute José de Alencar Gomes da Silva (INCA) (2). The etiology of CRC is associated with age, family history of CRC and genetic predisposition to the development of chronic intestinal diseases, lifestyle and eating habits (2–4).

Malnutrition is common in CRC (5–7) due to the combined effects of malignant disease progress, the host response to the tumor, anticancer treatment, and the direct effects of bowel obstruction and malabsorption (8). In severe cases, malnutrition can progress to cachexia, a specific form of malnutrition characterized by a negative protein and energy balance driven by a variable combination of reduced food intake and abnormal metabolism (9–12). Although the evidence indicates that of all cancer-related deaths more than 30% are due to cachexia (13), a lack of a definition, diagnostic criteria, and classification create difficulties to advancement in clinical practice (14,15). Fearon et al. (11) defined cancer cachexia as a multifactorial syndrome characterized by an ongoing loss of skeletal muscle mass, with or without loss of fat mass, that cannot be fully reversed by conventional nutritional support (11).

In parallel, the term sarcopenia, originally introduced to define age-related skeletal muscle decline (16), is now used to indicate any loss of muscle tissue and function due to aging, chronic diseases (including cancer), low protein–energy intake and physical inactivity (17). As a recognized malnutrition-related syndrome, sarcopenia has been confirmed that it can occur in overweight and obese people recently (18–21). Age-related sarcopenia is defined by the European Working Group on Sarcopenia in Older People (EWGSOP) as the loss of muscle and function, and has suggested a conceptual staging as presarcopenia, sarcopenia, and severe sarcopenia based on the severity of this condition (17). The prevalence of sarcopenia has been poorly studied in cancer patients and is associated with adverse postoperative outcomes, longer length of hospital stay, and poorer rehabilitation outcome (22,23).

CONTACT Bianca Umbelino de Souza bia.umbelino.20@gmail.com Nutrition and Dietetic Service, Cancer Hospital Unit I, Brazilian National Cancer Institute José Alencar Gomes da Silva, Praça da Cruz Vermelha, 23, 5° Andar, 20230-130, Rio de Janeiro, Brazil.

Current diagnostic methods for sarcopenia include measuring skeletal muscle mass and function, which includes muscular strength and physical performance. Computed tomography (CT) is a reference method used in assessing skeletal muscle mass, due to its accuracy and reliability (24,25). However, the method is expensive, requires specialized skills to operate and exposes individuals to a high radiation dose (26). The third lumbar vertebra CT has been validated as the standard landmark for body composition analysis because in this region, skeletal muscle and adipose tissue correspond to whole body tissue quantities for healthy individuals (27) and for cancer population (28).

Despite great progress, data on prevalence of sarcopenia in patients with CRC are scarce. Emerging evidence supports that sarcopenia in patients with cancer is an independent risk factor for poorer outcomes. We conducted a cross-sectional study to identify the prevalence of sarcopenia and factors associated with this syndrome in patients with CRC. We hypothesized that sarcopenia may be associated with worse clinical condition in patients with CRC.

Subjects and Methods

Subjects

From April 2015 to June 20165, all patients with CRC who underwent cancer treatment at the Cancer Hospital I of the Brazilian National Cancer Institute (INCA, Rio de Janeiro, Brazil) were included in this study. The inclusion criteria included patients who: were ≥18 years old; had abdominal CT scans at the third lumbar vertebrae level (L3) available for review; and agreed to take part in the study and signed the informed consent. Exclusion criteria included: those aged <18 years old; those with a physical deformity who were unable to be tested for muscle strength or physical performance; those with pacemaker, those with Eastern Cooperative Oncology Group (ECOG) performance score >3, and those with congestive heart failure, chronic kidney disease, and liver cirrhosis. ECOG performance score is a standard criteria for measuring the patients' level of function in terms of their ability to care for themselves, daily activity, and physical ability (30).

Study Design

Patients with CRC scheduled for abdominal CT scan at the L3 region as part of routine care, who met study eligibility criteria and those who agreed to participate and signed a consent form, were included. Patients received instructions to fast for 6 h before the CT scan (water-soluble oral contrast and medication were allowed). After CT scan, nutritional status, body composition, and muscle function were assessed. Blood samples were collected under fasting conditions 0–30 days after the CT exam.

Clinical data such as age, gender, previous and current treatment, comorbidities, ECOG performance score, tumor site and stage according to the Union for International Cancer Control (UICC) guidelines (31) were collected from medical records. Cancer staging describes the severity of an individual's cancer based on the magnitude of the primary tumor as well as on the extent cancer has spread in the body (32).

Nutritional Assessment

Body weight (kg) was assessed using a platform-type Filizola® mechanical scale (Filizola, São Paulo, Brazil) with a maximum capacity of 150 kg and variation 0.1 kg and height (cm) by a vertical stadiometer 200 cm long and with a 0.1 cm precision, according to the standardized protocols (29). Body mass index (BMI) was calculated as weight/height^2 (kg/m^2) and was classified using World Health Organization (WHO) criteria (33).

The scored patient-generated subjective global assessment (PG-SGA) was previously validated for the Portuguese language (34) and was carried out by one trained researcher. The scored PG-SGA consisted of two sections: the first included questions on weight history, food intake, nutrition impact symptoms, and functional capacity; the second contained data on clinical conditions, metabolic stress, and physical examination. Each patient was classified as well nourished (PG-SGA A), moderately malnourished or suspected of being malnourished (PG-SGA B), or severely malnourished (PG-SGA C). In addition, a total PG-SGA score was calculated (35).

Body Composition Assessment

CT images are acquired for medical diagnosis/follow-up purposes in cancer patients and have been digitally stored in the patient's medical record, which it useful in use the body composition as well. CT images were analyzed for tissue cross-sectional area (cm^2) at L3 using Slice-O-Matic software version 5.0 (Tomovision, Montreal, Quebec, Canada). One image extending from the L3 was assessed for skeletal muscle (psoas, erector spinae, quadratus lumborum, transversus abdominus, external and internal obliques, and rectus abdominus), and adipose tissue (visceral, subcutaneous, and intramuscular). CT Hounsfield unit (HU) thresholds were −29HU to +150HU for skeletal muscle, −190HU to −30HU for subcutaneous and intramuscular adipose tissue and −150HU to −50HU for visceral adipose tissue (36).

Image analysis for this study were performed by a single trained observer. Skeletal muscle area was normalized by height square (m^2) and reported as lumbar skeletal muscle index (SMI) (cm^2/m^2). Low SMI were classified according to Martin et al. (21) (men: <43 cm^2/m^2 for BMI <25 kg/m^2 and <53 cm^2/m^2 for BMI ≥25 kg/m^2; women: <41 cm^2/m^2). Muscle attenuation (MA) has also been evaluated. MA was derived by averaging the Hounsfield unit of skeletal muscle. The attenuation of skeletal muscle is inversely related to muscle fat content (21,26).

Bioelectrical impedance analysis (BIA) was performed with a tetrapolar device, single frequency (50 kHz), model Quantum II (RJL Systems, Detroit, MI, USA), according to the protocol recommended by Kyle (37). BIA provides resistance (R) and reactance (Xc) values in Ohms (Ω). Phase angle (PA) was calculated with the following equation: PA (degrees) = arc tan (Xc/R) × (180/π). The principles of PA is based on changes in resistance and reactance as alternating electric current passes through tissues. A phase shift of the current is stored in the resistive compartments of cellular membranes. PA has been interpreted as an indicator of quantity of cells, cell membrane integrity, and water distribution between the intra- and extracellular spaces (38–40).

Measurement of Muscle Strength and Physical Performance

Muscle strength was measured using a Jamar® hydraulic hand dynamometer (Sammons Preston, Chicago, IL). Each individual sat in a chair with armrests, without rings, watches, or other objects on their hands or wrists. The upper limb to be evaluated was placed alongside the body with the elbow at a 90° angle; the contralateral limb was relaxed on the thigh. During the exam, interviewers were instructed to provide verbal motivational stimulus to determine the maximum strength of the individuals for each measurement. Three measurements were determined for each hand in an alternating manner, and the maximum strength was defined as the greatest of the six measurements (41). The cut-off points for loss of handgrip strength were less than 30 kg for men and less than 20 kg for women (17).

A 4.6 m gait speed test was applied to evaluate physical performance. The subject was instructed to walk as fast as possible without running through a predetermined 4.6 m straight path with no obstacles; the time to complete the course was measured. The test was applied twice, with an interval of approximately 30 s between applications (42). To determine the loss of muscle performance, the lowest of the two measurements was considered, using the previously established cut-off point of less than 0.8 m/s (17).

Definition of Sarcopenia

Presarcopenia was defined as low skeletal muscle mass and sarcopenia was defined as low skeletal muscle mass plus low muscle strength and/or low physical performance according to the EWGSOP (15). Individuals who did not meet these criteria were considered normal for the outcome studied.

Biochemical Analysis

Albumin was quantified by the bromocresol-green method, pre-albumin by the immunoturbidimetric method, glucose by the enzymatic colorimetric method, creatinine by the modified Jaffé colorimetric method and high-sensitivity C-reactive protein (CRP) was measured by the turbidimetric method with specific kits from Roche® using a COBAS 311 analyzer (Roche Diagnostics®, Mannheim, German), according to laboratory routine.

Ethical Approval

The study was approved by the Ethics Committee of the Brazilian National Cancer Institute José Alencar Gomes da Silva (protocol number 38992014.5.0000.5274) and all participants gave written informed consent.

Statistical Analysis

The Kolmogorov–Smirnov test was used to determine the normality of continuous data. Normally distributed continuous data were presented as means and standard deviations (SD), while non-normally distributed continuous data were presented as median and interquartile range (IQR). Categorical data were compared using the χ^2 test. Normally distributed continuous data were compared using the independent samples *t*-test. Non-normally distributed continuous data and hierarchical data were compared with the Mann–Whitney *U*-test. Univariate analysis was used to identify potential risk factors for sarcopenia. Variables with a *P*-value of <0.50 were included in the multivariate logistic regression analysis adjusted for gender and age. *P*-values <0.05 were considered to be statistically significant. All data were analyzed using SPSS statistics version 20.0 (IBM, Armonk, New York, USA).

Results

From April 2015 to June 2016, 204 patients were recruited, and 7 patients with anal canal cancer were excluded. For the 197 CRC patients included in this study, mean age was 60 (standard deviation 11.4 years), 57% were male, 72% had advanced disease, 57% had already undergone cancer therapy (after treatment group), 20% had diabetes, 48% had hypertension, and 59% had an ECOG performance score of 1 or 2, as shown in Table 1.

According to BMI, most of the patients were overweight and obese (BMI $\geq$25 kg/m^2). The prevalence of obesity is higher in women and the prevalence of overweight is higher in men (Table 2). According to PG-SGA, the majority of the patients were well-nourished (PG-SGA A), and had normal albumin and pre-albumin levels. Men had a significantly higher serum creatinine than women (Table 2).

As expected, body composition and PA were significantly different between men and women (Table 3). Sarcopenia was present in 29 of 195 patients (15%) and presarcopenia in 57 of 195 patients (29%). The prevalence of sarcopenia in men was 14% and 13% in women. Although there was no statistical difference, the prevalence of presarcopenia is higher in men (33%) than in women (24%) (Table 4).

The factors associated with sarcopenia are showed in Table 5. Patients with sarcopenia were older, had lower BMI, serum albumin (SAlb), PA, MA, higher PG-SGA score and malnutrition (PG-SGA B) than those with no sarcopenia. In univariate analysis, age, BMI, SAlb, PA, MA, and malnutrition (PG-SGA B) were associated with sarcopenia ($P < 0.05$). Differences were not observed among other factors, including sex, tumor stage, ECOG performance score, CRP, and intramuscular adipose tissue. In the multivariate model after controlling for potential confounders, BMI (OR: 0.88, 95% CI: 0.80–0.97, *P*: 0.009), SAlb (OR: 0.26, 95% CI: 0.09–0.75, *P*: 0.01), PA (OR: 0.21, 95% CI: 0.11–0.41, *P*: <0.001), MA (OR: 0.91, 95% CI: 0.85–0.97, *P*: 0.004), and PG-SGA score (OR: 1.1, 95% CI: 1.02–1.2, *P*: 0.02) remained as the independent predictors for sarcopenia ($P < 0.05$).

Table 1. Clinical characteristics of all patients ($n = 197$).

	Subject
Age [years; mean (SD)]	60.5 (±11.4)
<65 years *n* (%)	128 (65%)
≥65 years *n* (%)	69 (35%)
Sex [*n* (%)]	
Male	112 (57%)
Female	85 (43%)
Tumor stage [*n* (%)]	
0–II	54 (28%)
III–IV	138 (72%)
Comorbidities [*n* (%)]	
Hypertension	94 (48%)
Diabetes	39 (20%)
ECOG performance score [*n* (%)]	
0	80 (41%)
1	105 (54%)
2	10 (5%)
Treatment phase [*n* (%)]	
Before treatment	17 (9%)
During treatment	67 (34%)
After treatment	113 (57%)

ECOG: Eastern Cooperative Oncology Group; SD: standard deviation.

Table 2. Nutritional and blood parameters of all patients by sex ($n = 197$).

	Men ($n = 112$)	Women ($n = 85$)	*P*
BMI [Kg/m^2; mean (SD)]	26.8 (±5.0)	27.6 (±6.3)	0.3[†]
BMI [*n* (%)]			0.002[‡]
BMI <18.5 Kg/m^2	1 (1%)	5 (6%)	
BMI 18.5–24.99 Kg/m^2	40 (36%)	30 (35%)	
BMI 25.0–29.99 Kg/m^2	46 (41%)	17 (20%)	
BMI ≥30.0 Kg/m^2	25 (22%)	33 (39%)	
PG-SGA [*n* (%)]			0.8[‡]
PG-SGA A	74 (67%)	59 (69%)	
PG-SGA B	33 (30%)	24 (28%)	
PG-SGA C	4 (4%)	2 (2%)	
Blood Analysis			
Albumin [g/dl; mean (SD)]	4.4 (±0.4)	4.3 (±0.4)	0.1[†]
Pre-Albumin [g/dl; mean (SD)]	0.25 (±0.10)	0.24 (±0.10)	0.5[†]
Creatinine [mg/dl; mean (SD)]	1.0 (±0.3)	0.8 (±0.2)	<0.001[†]
Glucose [mg/dl; median (IQR)]	103 (93–114)	99 (90–117)	0.4[‡§]
CRP [mg/dl; median (IQR)]	0.41 (0.26–1.40)	0.45 (0.23–0.84)	0.6[‡§]

BMI: body mass index; PG-SGA: patient-generated subjective global assessment; CRP: high-sensitivity C-reactive protein; SD: standard deviation; IQR: interquartile range;
[†]t-test; [‡]Chi-square test; [§]Non-parametric Mann–Whitney test.

Table 3. Body composition according to CT and phase angle of all patients by sex ($n = 197$).

	Men ($n = 112$)	Women ($n = 85$)	*P*
Lumbar skeletal muscle index [cm^2/m^2; mean (SD)]	50.5 (±9.0)	43.0 (±7.1)	<0.001[†]
Muscle attenuation (HU; mean (SD)]	37.0 (±7.2)	31.0 (±7.6)	<0.001[†]
Subcutaneous adipose tissue [cm^2; median (IQR)]	149.4 (102.0–195.0)	217.4 (133.4–329.0)	<0.001[‡]
Visceral adipose tissue [cm^2; median (IQR)]	153.3 (85.3–219.3)	83.4 (42.5–149.1)	<0.001[‡]
Intramuscular adipose tissue [cm^2; median (IQR)]	6.4 (3.4–10.6)	8.3 (6.0–16.0)	0.001[‡]
Phase angle [°; mean (SD)]	6.0 (±1.0)	5.3 (±1.0)	<0.001[†]

SD: standard deviation; IQR: interquartile range; CT: computed tomography;
[†]t-test; [‡]Non-parametric Mann–Whitney test.

Discussion

Most patients had advanced disease mainly due to longer waiting time to diagnosis and treatment which are associated with poorer outcomes (17,43–45). As reported to other studies, most of the patients with CRC were

Table 4. Prevalence of sarcopenia and low muscle mass in patients with colorectal cancer by sex ($n = 195$).

	Men ($n = 111$)	Women ($n = 84$)	P
Nonsarcopenia	57 (51%)	52 (62%)	0.4[1]
Presarcopenia	37 (33%)	20 (24%)	
Sarcopenia	17 (15%)	12 (14%)	

[1]Chi-square test.

overweight or obese (4) and well-nourished (44). However, some studies have shown a higher prevalence of malnutrition in patients with other types of cancer (46,47). Subjects had SAlb levels within the normal reference range. Although SAlb is an independent factor of clinical outcome (48), it can be influenced by fluid imbalance, drugs, and an acute phase response (49).

According to the body composition assessment, men had higher values of muscle mass, MA, visceral adipose tissue, and PA, while women had higher values of subcutaneous and intramuscular adipose tissue, as also reported to other studies (45,50,51). A lower MA is indicative of a greater fat infiltration into the muscle. Inflammation can increase the deposition of fat intramuscularly which then leads to reduced MA (45). In addition, low MA was a predictor of poor survival

Table 5. Factors associated with sarcopenia of patients with colorectal cancer ($n = 195$).

	Sarcopenic ($n = 29$; 15%)	Nonsarcopenic ($n = 166$; 85%)	P
Men [n (%)]	17 (59%)	94 (57%)	0.8[2]
Women [n (%)]	12 (41%)	72 (43%)	
Age [years; mean (SD)]	67.0 ± 10.0	59.5 ± 11.4	0.002[3]
Tumor stage [n (%)]			0.6[2]
0–II	7 (25%)	47 (29%)	
III–IV	21 (75%)	115 (71%)	
ECOG performance score [n (%)]			0.3[2]
0	8 (28%)	71 (44%)	
1	19 (65%)	84 (51%)	
2	2 (7%)	8 (5%)	
BMI (Kg/m^2; mean (SD)]	25.0 ± 5.0	28.0 ± 5.3	0.005[3]
PG-SGA [n (%)]			<0.001[2]
PG-SGA A	10 (36%)	121 (73%)	
PG-SGA B	16 (57%)	41 (25%)	
PG-SGA C	2 (7%)	4 (2%)	
PG-SGA score [median (IQR)]	5 (3–11)	3 (1–5)	<0.001[4]
Blood analysis			;
Albumin [g/dl; mean (SD)]	4.1 ± 0.3	4.4 ± 0.4	0.007[3]
CRP [mg/dl; median (IQR)]	0.5 (0.3–1.3)	0.4 (0.2–0.9)	0.2[4]
Lumbar skeletal muscle index [cm^2/m^2; mean (SD)]	39.2 ± 6.1	48.6 ± 8.8	<0.001[3]
Muscle attenuation [HU; mean (SD)]	29.0 ± 8.0	35.0 ± 8.0	<0.001[3]
Intramuscular adipose tissue [cm^2; median (IQR)]	7.6 (3.6–15.6)	7.1 (4.4–12.6)	0.7[4]
Phase Angle (°; mean (SD)]	4.7 ± 0.6	5.7 ± 0.9	<0.001[3]
Handgrip strength [Kg; mean (SD)]	23.1 ± 5.0	31.5 ± 9.0	<0.001[3]
Gait speed [m/s; mean (SD)]	0.99 (0.87–1.11)	1.07 (0.92–1.24)	0.04[4]

ECOG: Eastern Cooperative Oncology Group; BMI: body mass index; PG-SGA: patient-generated subjective global assessment; CRP: high-sensitivity C-reactive protein; SD: standard deviation; IQR: interquartile range;
[3]t-test; [2]Chi-square test; [4]Non-parametric Mann–Whitney test.

(21,53). Recently, some studies have shown that MA is more associated with muscle function than just muscle mass (54).

The prevalence of presarcopenia was found in 29% of the subjects. In fact, presarcopenia assessed by CT is high and is present in between 20 and 70% depending on the tumor type, tumor stage and cut-off points for low of skeletal muscle mass that were used (50,55,56). In addition, presarcopenia was associated with adverse postoperative outcomes, longer length of hospital stay, poorer rehabilitation outcome, higher chemotherapy toxicity, and lower survival (18,44,56–58). However, including a functional aspect to the definition of sarcopenia may result in better prediction of poor outcomes. In recent years, sarcopenia was demonstrated to be a poor prognostic factor for various types of cancer, and impacted clinical outcomes following certain operative procedures (22,23,55,59). A recent study have shown that sarcopenia itself is an independent risk factor for complications after surgery for CRC and had a better predictive power than did presarcopenia (22). Huang et al. (55) found that 30% of elderly patients who underwent surgery for gastric cancer were sarcopenic. Sarcopenia, but not presarcopenia, was an independent risk factor for mortality (55). Furthermore, sarcopenia was also associated with higher hospital costs and longer postoperative length of hospital stay (23). In the present study, the prevalence of sarcopenia (15%) was similar to previous studies (12–30%) (22,23,55,59).

Recently, several studies have also reported that sarcopenic cancer patients had a worse nutritional status and muscle function, and worse clinical condition than those with no sarcopenia (22,23,59,60). Significant clinical implications of sarcopenia suggest that patients should receive early detection and treatment of sarcopenia using different strategies to maintain muscle mass and improve muscle function in order to detect sarcopenia earlier than by changes in clinical parameters (e.g., weight or BMI), which occur at a later and potentially irreversible stage (58). Information gained from the analysis of imaging and physical exam data could be used to adapt patients' nutrition and physical exercise plans (61).

Physical activity in cancer patients is associated with maintenance or significant improvements in aerobic capacity, muscle strength, and with reduction in fatigue (62–64). There is some indication that resistance exercise perhaps is more effective for improving muscle strength than aerobic exercise (62–64). Further evidence suggests that resistance training induced increase in muscle mass and strength can be enhanced by high protein diet and certain nutrients (65,66).

Despite loss of skeletal muscle mass can occur independently of adiposity (18,67), BMI was associated inversely with sarcopenia in the present study. BMI classifications ignore the composition of a unit of weight which has been shown to be clinically important in patients with cancer (18). Of interest is sarcopenic obesity, in which severe obesity and low skeletal muscle mass occur simultaneously (18). This condition represents a worst-case scenario because it combines the health risks of obesity and depleted skeletal muscle mass (21).

PA is the most specified impedance parameter for clinical prognosis (68–70) and it is connected with changes in cellular membrane integrity as well as alterations in fluid balance (71). It reflects changes in the amount and the quality of soft tissue mass (71) and, which is, in turn, related to sarcopenia. Low PA indicates cell death or decreased cell integrity and has been observed in patients with age-related and disease-related muscle loss and those with low muscle function (69,70,72,73).

It has been proposed that SAlb could be a marker of muscle mass and muscle function. Lower SAlb was associated with future loss of muscle mass in older persons and it may be a risk factor for sarcopenia (74). However, SAlb demonstrated modest and inconsistent trends with loss of muscle mass and function in community-dwelling men (75).

The scored PG-SGA is a nutrition assessment tool that identifies malnutrition in patients with cancer (35). It is suitable for use as an outcome measure in clinical nutrition practice and is associated with quality of life (76). Some studies have also shown that cancer patients with sarcopenia had a higher nutritional risk screening (NRS) 2002 score (22,23).

In our study, tumor stage was not associated with sarcopenia. Most of the patients had advanced disease which may affect statistical power. However, some recent studies which investigated the association of sarcopenia with short-term postoperative outcomes in patients with cancer have also found no associations between sarcopenia and tumor stage (22,23).

The strengths of the current study are its sample size and it is the first study in Brazil assessing the prevalence and factors associated with sarcopenia in patients with CRC. However, the study has some limitations as its heterogeneity and long-term follow-up has not been assessed.

In conclusion, CRC patients with sarcopenia had worse nutritional status and muscle function and poor clinical condition than non-sarcopenic patients. BMI, MA, PA, albumin, PG-SGA score were independent predictors of sarcopenia. These results show the importance of investigatong the prevalence of sarcopenia and factors associated with it in order to perform an early individualized intervention to prevent negative clinical outcomes. Long-term follow-ups are needed in future studies to confirm our results and to investigate the relationship between sarcopenia and morbidity.

Acknowledgment

This study was supported by Brazilian National Cancer Institute José Alencar Gomes da Silva (INCA).

References

1. Fitzmaurice C, Dicker D, Pain A, Hamavid H, Moradi-Lakeh M, et al.: The Global Burden of Cancer. *JAMA Oncol* **1**(4), 505–527, 2015.
2. Instituto Nacional de Câncer José Alencar Gomes da Silva. Coordenação de Prevenção e Vigilância *Estimativa 2016: incidência de câncer no Brasil*. Instituto Nacional de Câncer José Alencar Gomes da Silva – Rio de Janeiro: INCA, p. 122.
3. Doat S, Thiebaut A, Samson S, Ricordeau P, Guillemot D, et al.: Elderly patients with colorectal cancer: treatment modalities and survival in France. National data from the ThInDiT cohort study. *Eur J Cancer* **50**(7), 1276–1283, 2014.
4. Lee JY, Lee HS, Lee DC, Chu SH, Jeon JY, et al.: Visceral fat accumulation is associated with colorectal cancer in postmenopausal women. *PLoS One* **9**(11), e110587, 2014.
5. Hu WH, Cajas-Monson LC, Eisenstein S, Parry L, Cosman B, et al.: Preoperative malnutrition assessments as predictors of postoperative mortality and morbidity in colorectal cancer: an analysis of ACS-NSQIP. *Nutr J* **14**, 91, 2015.
6. Pressoir M, Desne S, Berchery D, Rossignol G, Poiree B, et al.: Prevalence, risk factors and clinical implications of malnutrition in French Comprehensive Cancer Centres. *Br J Cancer* **102**(6), 966–971, 2010.
7. Yamano T, Yoshimura M, Kobayashi M, Beppu N, Hamanaka M, et al.: Malnutrition in rectal cancer patients receiving preoperative chemoradiotherapy is common and associated with treatment tolerability and anastomotic leakage. *Int J Colorectal Dis* **31**(4), 877–884, 2016.
8. Ryan AM, Power DG, Daly L, Cushen SJ, Ni Bhuachalla E, et al.: Cancer-associated malnutrition, cachexia and sarcopenia: the skeleton in the hospital closet 40 years later. *Proc Nutr Soc* **75**(2), 199–211, 2016.
9. Liesenfeld DB, Grapov D, Fahrmann JF, Salou M, Scherer D, et al.: Metabolomics and transcriptomics identify pathway differences between visceral and subcutaneous adipose tissue in colorectal cancer patients: the ColoCare study. *Am J Clin Nutr* **102**(2), 433–443, 2015.
10. Tisdale MJ.: Cancer cachexia. *Curr Opin Gastroenterol* **26**(2), 146–151, 2010.
11. Fearon K, Strasser F, Anker SD, Bosaeus I, Bruera E, et al.: Definition and classification of cancer cachexia: an international consensus. *Lancet Oncol* **12**(5), 489–495, 2011.
12. Muscaritoli M, Anker SD, Argiles J, Aversa Z, Bauer JM, et al.: Consensus definition of sarcopenia, cachexia and pre-cachexia: joint document elaborated by Special Interest Groups (SIG) "cachexia-anorexia in chronic wasting diseases" and "nutrition in geriatrics". *Clin Nutr* **29**(2), 154–159, 2010.

13. von Haehling S, and Anker SD. Cachexia as a major underestimated and unmet medical need: facts and numbers. *J Cachexia Sarcopenia Muscle* **1**(1), 1–5, 2010.
14. Evans WJ, Morley JE, Argilés J, Bales C, Baracos V, et al.: Cachexia: a new definition. *Clin Nutr* **27**(6), 793–799, 2008.
15. Fox KM, Brooks JM, Gandra SR, Markus R, and Chiou CF: Estimation of cachexia among cancer patients based on four definitions. *J Oncol* **2009**, 1–7, 2009.
16. Rosenberg IH: Epidemiologic and methodologic problems in determining nutritional status of older persons. Proceedings of a conference. Albuquerque, New Mexico, October 19–21, 1988. *Am J Clin Nutr* **50**(5 Suppl), 1121–1235, 1989.
17. Cruz-Jentoft AJ, Baeyens JP, Bauer JM, Boirie Y, Cederholm T, et al.: Sarcopenia: European consensus on definition and diagnosis: Report of the European Working Group on Sarcopenia in Older People. *Age Ageing* **39**(4), 412–423, 2010.
18. Prado CM, Lieffers JR, McCargar LJ, Reiman T, Sawyer MB, et al.: Prevalence and clinical implications of sarcopenic obesity in patients with solid tumours of the respiratory and gastrointestinal tracts: a population-based study. *Lancet Oncol* **9**(7), 629–635, 2008.
19. Tan BH, Birdsell LA, Martin L, Baracos VE, and Fearon KC: Sarcopenia in an overweight or obese patient is an adverse prognostic factor in pancreatic cancer. *Clin Cancer Res* **15**(22), 6973–6979, 2009.
20. Baracos VE, Reiman T, Mourtzakis M, Gioulbasanis I, and Antoun S: Body composition in patients with non-small cell lung cancer: a contemporary view of cancer cachexia with the use of computed tomography image analysis. *Am J Clin Nutr* **91**(4), 1133S–1137S, 2010.
21. Martin L, Birdsell L, Macdonald N, Reiman T, Clandinin MT, et al.: Cancer cachexia in the age of obesity: skeletal muscle depletion is a powerful prognostic factor, independent of body mass index. *J Clin Oncol* **31**(12), 1539–1547, 2013.
22. Huang DD, Wang SL, Zhuang CL, Zheng BS, Lu JX, et al.: Sarcopenia, as defined by low muscle mass, strength and physical performance, predicts complications after surgery for colorectal cancer. *Colorectal Dis* **17**(11), O256–O264, 2015.
23. Wang SL, Zhuang CL, Huang DD, Pang WY, Lou N, et al.: Sarcopenia adversely impacts postoperative clinical outcomes following gastrectomy in patients with gastric cancer: a prospective study. *Ann Surg Oncol* **23**(2), 556–564, 2016.
24. Heymsfield SB, Wang Z, Baumgartner RN, and Ross R: Human body composition: advances in models and methods. *Annu Rev Nutr* **17**, 527–558, 1997.
25. Mitsiopoulos N, Baumgartner RN, Heymsfield SB, Lyons W, Gallagher D, et al.: Cadaver validation of skeletal muscle measurement by magnetic resonance imaging and computerized tomography. *J Appl Physiol (1985)* **85**(1), 115–122, 1998.
26. Prado CM, and Heymsfield SB: Lean tissue imaging: a new era for nutritional assessment and intervention. *JPEN J Parenter Enteral Nutr* **38**(8), 940–953, 2014.
27. Shen W, Punyanitya M, Wang Z, Gallagher D, St-Onge MP, Albu J, et al.: Total body skeletal muscle and adipose tissue volumes: estimation from a single abdominal cross-sectional image. *J Appl Physiol (1985)* **97**(6), 2333–2338, 2004.
28. Mourtzakis M, Prado CM, Lieffers JR, Reiman T, McCargar LJ, and Baracos VE: A practical and precise approach to quantification of body composition in cancer patients using computed tomography images acquired during routine care. *Appl Physiol Nutr Metab* **33**(5), 997–1006, 2008.
29. Lohman TG, and Roche AF. *Anthropometric Standardization Reference Manual*. Human Kinetics, Champaign, IL, 1988.
30. Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, et al.: Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol* **5**(6), 649–655, 1982.
31. Union for International Cancer Control (UICC). eds. *TNM Classification of Malignant Tumours*. 8th Ed. Wiley Blackwell, Oxford, 2017.
32. Edge SB, Byrd DR, Compton CC, Fritz AG, Greene FL, et al: *AJCC Cancer Staging Manual*. 7th Ed. Springer, New York, NY, 2009.
33. WHO. Physical status: the use and interpretation of anthropometry. Report of a WHO Expert Committee. *World Health Organ Tech Rep Ser* **854**, 1–452, 1995.
34. Gonzalez MC, Borges LR, Silveira DH, Assunção MCF, and Orlandi SP: Validação da versão em português da avaliação subjetiva global produzida pelo paciente. *Rev Bras Nutr Clin* **25**(2), 102–108, 2010.
35. Ottery FD: Definition of standardized nutritional assessment and interventional pathways in oncology. *Nutrition* **12**(1 Suppl), S15–S19, 1996.
36. Hounsfield GN: Computerized transverse axial scanning (tomography). 1. Description of system. *Br J Radiol* **46** (552), 1016–1022, 1973.
37. Kyle UG, Bosaeus I, De Lorenzo AD, Deurenberg P, Elia M, et al.: Bioelectrical impedance analysis–part I: review of principles and methods. *Clin Nutr* **23**(5), 1226–1243, 2004.
38. Barbosa-Silva MC, and Barros AJ: Bioelectrical impedance analysis in clinical practice: a new perspective on its use beyond body composition equations. *Curr Opin Clin Nutr Metab Care* **8**(3), 311–317, 2005.
39. Norman K, Pirlich M, Sorensen J, Christensen P, Kemps M, et al.: Bioimpedance vector analysis as a measure of muscle function. *Clin Nutr* **28**(1), 78–82. 2009.
40. Toso S, Piccoli A, Gusella M, Menon D, Crepaldi G, et al.: Bioimpedance vector pattern in cancer patients without disease versus locally advanced or disseminated disease. *Nutrition* **19**(6), 510–514, 2003.
41. Roberts HC, Denison HJ, Martin HJ, Patel HP, Syddall H, et al.: A review of the measurement of grip strength in clinical and epidemiological studies: towards a standardised approach. *Age Ageing* **40**(4), 423–429, 2011.
42. Guralnik JM, Simonsick EM, Ferrucci L, Glynn RJ, Berkman LF, et al.: A short physical performance battery assessing lower extremity function: association with self-reported disability and prediction of mortality and nursing home admission. *J Gerontol* **49**(2), M85–M94, 1994.
43. Song N, Shin A, Park JW, Kim J, and Oh JH: Common risk variants for colorectal cancer: an evaluation of associations with age at cancer onset. *Sci Rep* **13**(7), 40644, 2017.
44. Thoresen L, Frykholm G, Lydersen S, Ulveland H, Baracos V, et al.: Nutritional status, cachexia and survival in patients with advanced colorectal carcinoma. Different assessment criteria for nutritional status provide unequal

46. Guerra RS, Fonseca I, Sousa AS, Jesus A, Pichel F, et al.: ESPEN diagnostic criteria for malnutrition - A validation study in hospitalized patients. *Clinical Nutrition* **36**(5), 1326–1332, 2017.
47. Kwang AY: Objective and subjective nutritional assessment of patients with cancer in palliative care. *American Journal of Hospice & Palliative Medicine®* **27**(2), 117–126, 2010.
48. Nazha B, Moussaly E, Zaarour M, Weerasinghe C, and Azab B: Hypoalbuminemia in colorectal cancer prognosis: nutritional marker or inflammatory surrogate? *World J Gastrointest Surg* **7**(12), 370–377, 2015.
49. Davies M: Nutritional screening and assessment in cancer-associated malnutrition. *Eur J Oncol Nurs* **9**, Suppl 2, S64–S73, 2005.
50. Barret M, Antoun S, Dalban C, Malka D, Mansourbakht T, et al.: Sarcopenia is linked to treatment toxicity in patients with metastatic colorectal cancer. *Nutr Cancer* **66**(4), 583–589, 2014.
51. Siddiqui NI, Khan SA, Shoeb M, and Bose S: Anthropometric predictors of bio-impedance analysis (BIA) phase angle in healthy adults. *J Clin Diagn Res* **10**(6), CC01–CC04, 2016.
52. Friedman J, Lussiez A, Sullivan J, Wang S, and Englesbe M: Implications of sarcopenia in major surgery. *Nutr Clin Pract* **30**(2), 175–179, 2015.
53. Rier HN, Jager A, Sleijfer S, van Rosmalen J, Kock MC, et al.: Low muscle attenuation is a prognostic factor for survival in metastatic breast cancer patients treated with first line palliative chemotherapy. *Breast* **31**, 9–15, 2017.
54. Williams GR, Deal AM, Muss HB, Weinberg MS, Sanoff HK, et al.: Skeletal muscle measures and physical function in older adults with cancer: sarcopenia or myopenia? *Oncotarget* **8**(20), 33658–33665, 2017.
55. Huang DD, Chen XX, Chen XY, Wang SL, Shen X, et al.: Sarcopenia predicts 1-year mortality in elderly patients undergoing curative gastrectomy for gastric cancer: a prospective study. *J Cancer Res Clin Oncol* **142**(11), 2347–2356, 2016.
56. Lieffers JR, Bathe OF, Fassbender K, Winget M, and Baracos VE: Sarcopenia is associated with postoperative infection and delayed recovery from colorectal cancer resection surgery. *Br J Cancer* **107**(6), 931–936, 2012.
57. van Vledder MG, Levolger S, Ayez N, Verhoef C, Tran TCK, et al.: Body composition and outcome in patients undergoing resection of colorectal liver metastases. *British Journal of Surgery* **99**, 550–557, 2012.
58. Nattenmüller J, Wochner R, Muley T, Steins M, Hummler S, et al.: Prognostic impact of CT-quantified muscle and fat distribution before and after first-line chemotherapy in lung cancer patients. *PLoS One* **12**(1), e0169136, 2017.
59. Fukuda Y, Yamamoto K, Hirao M, Nishikawa K, Nagatsuma Y, et al.: Sarcopenia is associated with severe postoperative complications in elderly gastric cancer patients undergoing gastrectomy. *Gastric Cancer* **19**(3), 986–993, 2016.
60. Makiura D, Ono R, Inoue J, Kashiwa M, Oshikiri T, et al.: Preoperative sarcopenia is a predictor of postoperative pulmonary complications in esophageal cancer following esophagectomy: a retrospective cohort study. *J Geriatr Oncol* **7**(6), 430–436, 2016.
61. Phillips SM: Nutritional supplements in support of resistance exercise to counter age-related sarcopenia. *Adv Nutr* **6**(4), 452–460, 2015.
62. Stene GB, Helbostad JL, Balstad TR, Riphagen II, Kaasa S, et al.: Effect of physical exercise on muscle mass and strength in cancer patients during treatment a systematic review. *Crit Rev Oncol/Hematol* **88**(3), 573–593, 2013.
63. Keilani M, Hasenoehrl T, Baumann L, Ristl R, Schwarz M, et al.: Effects of resistance exercise in prostate cancer patients: a meta-analysis. *Support Care Cancer* **25**(9), 2953–2968, 2017.
64. Strasser B, Steindorf K, Wiskemann J, and Ulrich CM: Impact of resistance training in cancer survivors: a meta-analysis. *Med Sci Sports Exerc* **45**(11), 2080–2090, 2013.
65. Baracos VE: Skeletal muscle anabolism in patients with advanced cancer. *Lancet Oncol* **16**(1), 13–14, 2015.
66. Murphy RA, Mourtzakis M, Chu QS, Baracos VE, Reiman, et al.: Nutritional intervention with fish oil provides a benefit over standard of care for weight and skeletal muscle mass in patients with nonsmall cell lung cancer receiving chemotherapy. *Cancer* **117**(8), 1775–1182, 2011.
67. Prado CM, Cushen SJ, Orsso CE, and Ryan AM: Sarcopenia and cachexia in the era of obesity: clinical and nutritional impact. *Proc Nutr Soc* **75**(2), 188–198, 2016.
68. Selberg O, and Selberg D: Norms and correlates of bioimpedance phase angle in healthy human subjects, hospitalized patients, and patients with liver cirrhosis. *Eur J Appl Physiol* **86**(6), 509–516, 2002.
69. Norman K, Stobaus N, Zocher D, Bosy-Westphal A, Szramek A, et al.: Cutoff percentiles of bioelectrical phase angle predict functionality, quality of life, and mortality in patients with cancer. *Am J Clin Nutr* **92**(3), 612–619, 2010.
70. Norman K, Wirth R, Neubauer M, Eckardt R, and Stobaus N: The bioimpedance phase angle predicts low muscle strength, impaired quality of life, and increased mortality in old patients with cancer. *J Am Med Dir Assoc* **16**(2), 173.e17–e22, 2015.
71. Barbosa-Silva MCG, Barros AJD, Wang J, Heymsfield SB, and Pierson RNJ: Bioelectrical impedance analysis: population reference values for phase angle by age and sex. *Am J Clin Nutr* **82**(1), 49–52, 2005.
72. Marini E, Buffa R, Saragat B, Coin A, Toffanello ED, et al.: The potential of classic and specific bioelectrical impedance vector analysis for the assessment of sarcopenia and sarcopenic obesity. *Clin Interv Aging* **7**, 585–591, 2012.
73. Norman K, Pirlich M, Sorensen J, Christensen P, Kemps M, et al.: Bioimpedance vector analysis as a measure of muscle function. *Clin Nutr* **28**(1), 78–82. 2009.
74. Visser M, Kritchevsky SB, Newman AB, Goodpaster BH, Tylavsky FA, et al.: Lower serum albumin concentration and change in muscle mass: the health, aging and body composition study. *Am J Clin Nutr* **82**(3), 531–537, 2005.
75. Snyder CK, Lapidus JA, Cawthon PM, Dam TT, Sakai LY, et al.: Serum albumin in relation to change in muscle mass, muscle strength, and muscle power in older men. *J Am Geriatr Soc* **60**(9), 1663–1672, 2012.
76. Isenring E, Bauer J, and Capra S: The scored patient-generated subjective global assessment (PG-SGA) and its association with quality of life in ambulatory patients receiving radiotherapy. *Eur J Clin Nutr* **57**(2), 305–309, 2003.

ANEXO F – Artigo publicado em periódico como coautora

European Journal of Clinical Nutrition
https://doi.org/10.1038/s41430-018-0130-1

ARTICLE

Body composition, energy expenditure and physical activity

Muscle mass assessment by computed tomography in chronic kidney disease patients: agreement with surrogate methods

Juliana Giglio[1] · Maria Ayako Kamimura[2] · Nilian Carla Souza[1,3] · Andre Valente Bichels[2] · Antonio Carlos Cordeiro[4] · Nivaldo Pinho[3] · Carla Maria Avesani[1,5]

Received: 14 June 2017 / Revised: 18 December 2017 / Accepted: 10 February 2018

Abstract

Background/objectives Patients with chronic kidney disease (CKD) are subjected to muscle wasting. Therefore, it is important to investigate surrogate methods that enable the assessment of muscle mass loss in the clinical setting. We aimed to analyze the agreement between computed tomography (CT) and surrogate methods for the assessment of muscle mass in non-dialysis CKD patients.

Subjects/methods Cross-sectional study including 233 non-dialysis patients on CKD stages 3 to 5 (61 ± 11 years; 64% men; glomerular filtration rate 22 (14–33) mL/min/1.73 m^2). The muscle mass was evaluated by CT and bioelectrical impedance, skinfold thicknesses, midarm muscle circumference (MAMC), the predictive equations of Janssen and Baumgartner and the physical examination of muscle atrophy from the subjective global assessment.

Results In males, the MAMC showed the best agreement with CT as indicated by the kappa test ($k = 0.57$, $P < 0.01$), sensitivity ($S = 68\%$), specificity ($S = 89\%$) and accuracy (area under the curve—AUC = 0.78), followed by the Baumgartner equation (kappa = 0.46, $P < 0.01$; sensitivity = 60%; specificity = 87% and AUC = 0.73). In female, the Baumgartner equation showed the best agreement with CT (kappa = 0.43, $P < 0.01$; sensitivity = 57%; specificity = 86% and AUC = 0.71).

Conclusions The MAMC and Baumgartner equation showed the best agreement with CT for the assessment of muscle mass in non-dialysis CKD patients.

Introduction

The skeletal muscle mass is a dynamic organ that provides a rich source of amino acids and carbon chains that can be mobilized during stress or chronic pathologic conditions, such as chronic kidney disease (CKD) [1]. Muscle wasting in CKD is progressive and is often observed [2, 3], due to an imbalance characterized by a low protein synthesis and increased protein degradation. The factors inherent to the disease that induce to protein catabolism include hormonal disturbances, metabolic acidosis, physical inactivity, immunologic and myocellular changes, inflammatory condition, reduced protein intake, myostatin expression and reduction in satellite cells function [4–6]. The concern of developing muscle wasting lies on its association with the occurrence of frailty [7] and functional disability [8], which, in turn, leads to worsening quality of life [9]. Moreover, loss of muscle mass itself has been shown to increase mortality risk in CKD patients [10–13].

For diagnostic purposes, skeletal muscle mass is the ideal compartment to target in the search for muscle abnormalities in CKD. However, in non-dialyzed CKD patients, one should be aware for clinical signs of edema, as it might impair a proper assessment of muscle mass [14]. In CKD, muscle mass is often assessed by dual-energy X-ray absorptiometry (DXA) and anthropometry. An important limitation related these methods are that

✉ Carla Maria Avesani
carla.avesani@gmail.com

[1] Nutrition Graduate Program in Food, Nutrition and Health, Nutrition Institute, Rio de Janeiro State University, Rio de Janeiro, Brazil

[2] Nutrition Graduate Program, Federal University of São Paulo, Rio de Janeiro, Brazil

[3] National Institute of Cancer, Rio de Janeiro, Brazil

[4] Department of Hypertension and Nephrology, Dante Pazzanese Institute of Cardiology, Rio de Janeiro, Brazil

[5] Nutrition Institute, Rio de Janeiro State University, Rio de Janeiro, Brazil

Published online: 20 March 2018

measurements are subjected to errors when hydration status is not constant. DXA, for instance, assumes a uniform hydration of 73% of the lean body mass [15] and, fluctuations in the hydration status because of the illness such as CKD, results in over or underestimation of the lean body mass quantification [16]. Similarly, the anthropometric measurements (midarm circumference, midarm muscle circumference, calf circumference and adductor pollicis muscle thickness), although validated for screening for low muscle mass, can show reduced accuracy when clinical edema is present, a condition that can occur in the stages 4 and 5 of CKD [14]. Therefore, methods able to assess the skeletal muscle mass that does not suffer influence from the hydration status can offer better precision than the former ones.

The European Consensus Statement has, to its high precision, accuracy, and reliability [17], identified the computed tomography (CT) as the gold-standard method for the detection of muscle wasting in clinical trials. In addition, CT is not influenced by the hydration status, making this a method of preference to be applied in patients with CKD [14]. However, the radiation exposure and its high cost restrict the use of CT to the research setting. There are few studies applying CT for the assessment of skeletal muscle mass in dialyzed patients [18, 19] and none of them explored the use of this technique to validate surrogate methods for the assessment of muscle mass. Therefore, it is necessary to investigate the single cross-sectional image area that shows the highest accuracy to estimate or represent the total body skeletal muscle. Shen et al. [20] showed in healthy adult (123 men and 205 women) that among the abdominal skeletal muscle slice areas, the one located 5 cm above L4–L5, which corresponds to the third lumbar vertebra, had the highest correlation with total body skeletal muscle volume, assessed by magnetic resonance imaging (MRI). In addition, the authors showed that this single slice area accurately predicted total body skeletal muscle volume in a model validation including healthy subjects [20]. Subsequently, a study performed in oncologic patients showed that the skeletal muscle volume from the slice area located in the third lumbar vertebra was highly correlated with fat-free mass and with appendicular skeletal muscle mass as assessed by DXA [21]. Although the site at the third lumbar vertebra to assess muscle mass has not yet been tested in CKD individuals, the results obtained in the previous studies suggests this as an accurate slice area to assess whole-body skeletal mass. Moreover, CT images offer the assessment of muscle quality by the infiltration of fat in the muscle, an attribute not available through DXA. Therefore, considering the accuracy of CT and the importance of assessing muscle mass in CKD patients to screen for muscle wasting, we aimed to identify the surrogate method with higher agreement, sensitivity, specificity and accuracy as compared with CT in CKD patients on stages 3–5 (non-dialysis dependent).

Materials and methods

Subjects and study design

This study is included in the project entitled Malnutrition, Inflammation and Vascular Calcification (MIVC) cohort (Dante Pazzanese Institute of Cardiology in Sao Paulo, Brazil), which aimed to assess the association between traditional, novel and uremic risk factors with cardiovascular and general morbimortality [22, 23]. The patients were enrolled from March 2010 until March 2013. CKD was defined as glomerular filtration rate (GFR) below 60 mL/min/1.73 m^2. The exclusion criteria included clinical signs of acute infection in the month before enrollment, active cancer or liver disease, diagnosis of immunological diseases and denial to participate in the study. The patients were submitted to thoracoabdominal CT analysis without contrast for the evaluation of the coronary arteries calcium score and abdominal visceral fat. For the present study, patients were included if measurements of CT from the thoracic and abdominal scan imaging were available. Out of 300 patients, 67 were excluded due to lack of CT scans or due to the CT scan without images from the third lumbar vertebra. Therefore, 233 patients were included as depicted in Fig. 1. No difference regarding age, gender and presence of diabetes was observed between the excluded patients ($n = 67$) and included sample, except for GFR (18.0 (9.8; 27.6) vs 22.3 (13.8; 32.9) mL/min/1.73 m^2, $P < 0.01$, respectively). The Research Ethical Committee from Dante Pazzanese Institute of Cardiology approved the study and informed consent was obtained from each subject before inclusion in the study.

Subjective global assessment (SGA)

The 7-point subjective global assessment (SGA) was employed to evaluate the nutritional status. A score of 1–2

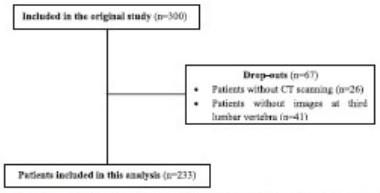


Fig. 1 Flow chart of study inclusion and exclusion. CT computed tomography

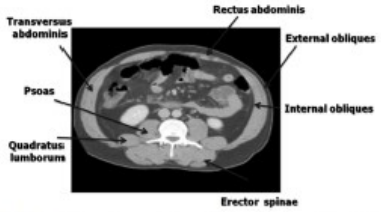


Fig. 2 Description of cross-section evaluation of the muscles located at the third lumbar vertebra by computed tomography

Laboratorial parameters

Blood samples were acquired after an overnight fast. Plasma and serum were stored at −70 °C, if not immediately analyzed. Serum dosages of urea (kinetic method), creatinine (colorimetric method—Jaffe) and albumin (green bromocresol) were evaluated, in addition to the creatinine in the 24 h urine sample (colorimetric method—Jaffe). The laboratorial analysis was performed at the Dante Pazzanese Institute of Cardiology laboratory.

Statistical analyses

Continuous variables will be presented as mean ± SD or median and interquartile range, depending on its normality distribution (assessed by Kolmogorov–Smirnov test). Categorical variables will be shown as the absolute value and its correspondent percentage. The univariate association between muscle mass evaluated by the CT and the surrogate methods will be assessed by Pearson or Spearman test, depending on the variable distribution. The agreement between CT and the surrogate methods for the assessment of low muscle mass will be evaluated by kappa test. The kappa value of agreement can be interpreted as follows: 0.20 poor, 0.21 to 0.60 moderate, 0.61 to 0.80 good and 0.81 to 1.00 very good [31]. The sensitivity and specificity of the surrogate methods were assessed through a cross-reference table and the area under the curve (AUC) by the receiver operator curve (ROC) analysis, using CT as the reference method. Diagnostic accuracy was deemed excellent for AUC values in the range of 0.90–1.00, good or discrete for 0.80–0.70; poor for 0.60–0.70, and absent for values between 0.50 and 0.60 [32]. A post hoc analysis calculated a power of 90% to assess the agreement between CT with the surrogate methods. Statistical significance was defined as *P*-values below 0.05. The statistical package for the social sciences (SPSS) version 18.0 (SPSS, Inc., Chicago, IL, USA) was used for the statistical analyses.

Table 1 Main demographic and clinical characteristics of non-dialyzed patients on CKD stages 3 to 5 under conservative treatment ($n = 233$)

Variables	All patients ($n = 233$)
Gender (male) [*n* (%)]	149 (63.9)
Age (years)	60.5 ± 10.6
BMI (kg/m^2)	29.2 ± 5.5
SGA [*n* (%)]	
6,7 (well nourished)	176 (75.5)
3,4,5 (moderately to mildly malnourished)	55 (23.6)
1,2 (severely malnourished)	2 (0.9)
Albumin (g/dL)	3.9 (3.6, 4.2)*
us-CRP (mg/dL)	0.37 (0.13; 0.8)*
Creatinine (mg/dL)	3.0 (2.3, 4.3)*
GFR (mL/min)	22.3 (13.8, 32.9)*
CKD stages	
3a	20 (8.6)
3b	53 (22.7)
4	89 (38.2)
5	71 (30.5)
Urea (mg/dL)	100.0 (77.0, 128.5)*
DM [*n* (%)]	117 (50.2)
Hypertension [*n* (%)]	227 (97.4)

Data are expressed as means±SD except for those with * which are expressed as median and interquartile range

BMI body mass index, *SGA* subjective global assessment, *GFR* glomerular filtration rate, *CKD* chronic kidney disease, *us-CRP* ultrasensitive C-reactive protein, *DM* diabetes mellitus

Results

The demographic and clinical characteristics of the sample are described in Table 1. Regarding the nutritional status, the mean BMI was indicative of overweight [33], the majority of the patients had a SGA score indicative of adequate nutritional status and serum albumin was within the appropriate value (>3.8 g/dL) [27]. Moreover, majority of the patients were on CKD stages 4 and 5. The prevalence of low muscle mass assessed by the cutoffs established for the general elderly or CKD individuals were investigated. For SMM-Baumgartner (cutoffs of appendicular skeletal mass index <7.26 kg/m^2 for men and <5.5 kg/m^2 for women [17]) the prevalence observed was 7.4% for men and 3.6% for women, for SMM-Janssen (cutoff skeletal muscle index <10.76 kg/m^2 for men and <6.76 kg/m^2 for women [17]) was 23.5% for men and 6% for women, for MAMC adequacy <90% [27] was 26.8% for men and 11.9% for women and for SGA-muscle mass physical exam with a score <5[24] the prevalence was 18.8% for men and 17.9% for women.

The agreement between CT and the surrogate methods for the assessment of low muscle mass (applying the

cutoffs described in Table 2) is shown in Table 3. In males, the kappa coefficients were indicative of moderate agreement and the specificity (true negative values) was higher than the sensitivity (true positive values). In addition, the AUC was indicative of a good accuracy, except for MM-SGA. In female, a moderate kappa agreement was observed for FFM-BIA, SMM-Baumgartner, SMM-Jansen and MAMC. The specificity, similar to that observed in male, was higher than the sensitivity and the AUC indicated a good accuracy for SMM–Baumgartner and FFM-BIA. Among the methods tested, the MAMC and the Baumgartner predictive equation and FFM-BIA were the methods with higher agreement and accuracy in males and females, respectively, when compared with CT. A significant and positive association between the CT and the surrogate methods were observed for all methods in both genders.

Table 2 Cutoffs to define low muscle mass (lowest 25th percentile) according to gender of non-dialyzed patients on CKD stages 3 to 5 ($n = 233$)

	Men ($n = 149$)	Women ($n = 84$)
SMM-CT (cm^2)	139.1	97.5
FFM-ANT (kg)	52.4	39.1
FFM-BIA (kg)	56.8	41.4
SMM-Baumgartner (kg)	21.4	14.8
SMM-Janssen (kg)	29.3	18.2
MAMC (cm)	24.4	22.9

SMM skeletal muscle mass, *CT* computed tomography, *FFT* fat-free mass, *ANT* anthropometry, *BIA* bioelectrical impedance analysis, *MAMC* midarm muscle circumference

Discussion

This study aimed to evaluate the agreement between CT and surrogate methods highly applied in the clinical setting for the assessment of muscle mass. To the best of our knowledge, this is the first study evaluating muscle mass by CT at the third lumbar vertebra in CKD patients before renal replacement therapy.

The use of CT image analysis is considered a gold-standard imaging method at the tissue-organ level for the assessment of body composition, especially muscle mass, since it gathers characteristics such as high accuracy, precision and reliability [34, 35]. The site located at the third lumbar vertebra has been validated in healthy individuals for the assessment of whole-body skeletal muscle mass [20] and in oncologic patients the CT scans at this site showed to be highly associated with fat-free mass and with appendicular skeletal mass assessed by DXA [21]. Considering that the site located at the third lumbar vertebra is representative of whole-body skeletal muscle mass in healthy individuals [20], the assessment of muscle mass by CT in CKD patients is likely to be superior to other reference methods such as DXA, since the assessment of muscle mass by CT is not subjected to errors coming from fluctuations in hydration status [14]. However, the high cost and possible limited access to the equipment, the requirement of appropriate

Table 3 Agreement and univariate association between muscle mass evaluated by computed tomography and methods applied in clinical practice in non-dialyzed patients on CKD stages 3 to 5, according to gender ($n = 233$)

	Kappa test (r;p)	Sensibility (%)	Specificity (%)	AUC (95% CI)	Univariate association (r;p)
Male ($n = 149$)					
CT vs FFM-ANT	0.50 (<0.01)	62.2	87.4	0.75 (0.65, 0.85)	0.57 (<0.01)[a]
CT vs FFM-BIA	0.43 (<0.01)	57.1	85.7	0.71 (0.61, 0.82)	0.55 (<0.01)[a]
CT vs SMM-Baumgartner	0.46 (<0.01)	59.5	86.6	0.73 (0.63, 0.83)	0.55 (<0.01)[a]
CT vs SMM-Janssen	0.41 (<0.01)	57.1	85.1	0.70 (0.60, 0.81)	0.51 (<0.01)[b]
CT vs MAMC	0.57 (<0.01)	67.6	89.3	0.78 (0.69, 0.88)	0.62 (<0.01)[a]
CT vs MM-SGA	0.32 (<0.01)	40.5	88.4	0.64 (0.53, 0.76)	–
Female ($n = 84$)					
CT vs FFM-ANT	0.11 (0.309)	33.3	77.8	0.56 (0.41, 0.70)	0.52 (<0.01)[a]
CT vs FFM-BIA	0.45 (<0.01)	57.9	86.9	0.72 (0.58, 0.87)	0.61 (<0.01)[a]
CT vs SMM-Baumgartner	0.43 (<0.01)	57.1	85.7	0.71 (0.58, 0.85)	0.58 (<0.01)[a]
CT vs SMM-Janssen	0.39 (<0.01)	55.0	84.4	0.69 (0.55, 0.83)	0.62 (<0.01)[b]
CT vs MAMC	0.24 (0.03)	42.9	81.0	0.62 (0.47, 0.77)	0.50 (<0.01)[a]
CT vs MM-SGA	−0.12 (0.25)	9.5	79.4	0.44 (0.34, 0.58)	—

AUC area under the curve, *CI* confidence interval, *CT* computed tomography, *FFM* fat-free mass, *ANT* anthropometry, *BIA* bioelectrical impedance analysis, *SMM* skeletal muscle mass, *MAMC* midarm muscle circumference, *MM* muscle mass, *SGA* subject global assessment

[a] Pearson correlation test

[b] Spearman correlation test

software to analyze body composition and trained personnel with knowledge on anatomy, restrict the use of CT to research purposes [34, 35], which emphasize the importance of testing surrogate methods in relation to CT. Moreover, the exposition to radiation dose generated by CT limits its use in repeated measurements solely for the purpose of conducting body composition research [34–36]. Regardless of these limitations, CT images can be applied when obtained from screening of the medical diagnosis and were digitally stored in the patient's medical record, as the case of the current study. By using the medical records with CT images available, we were able to analyze muscle mass with no harm for the patient and show that the MAMC, the Baumgartner predictive equation and FFM-BIA were the methods with higher agreement and accuracy in males and females, respectively, when compared with CT. In addition, these methods showed the highest sensitivity and specificity to detect low muscle mass, a characteristic of high importance when testing diagnostic methods. However, it should be noticed that the sensitivity (that is, the true positive cases) for both methods showed a misclassification of low muscle mass as compared to CT.

Our results toward the good agreement of MAMC in males is in accordance with that proposed by the International Society in Renal Nutrition and Metabolism to screen for muscle wasting [27]. Supporting this statement, studies that investigated the use of the MAMC found a good correlation with gold-standard methods, such as DXA and CT [37, 38]. In a previous study in hemodialysis patients, which examined whether several anthropometric and biochemical measurements were correlated with the lean body mass assessed by DXA, it was shown that MAMC was strongly associated with the reference method ($r = 0.72$, $P < 0.001$) [37]. In addition, MAMC has being pointed as a predictor of mortality in incident dialysis patients [13]. In another study including adults patients with liver cirrhosis, Giusto et al. reported that the MAMC showed good agreement with muscle mass assessed by CT at the third lumbar vertebra in males ($r = 0.48$; $P < 0.001$), but not in females ($r = 0.18$; $P = 0.435$) [38]. The finding of a more reliable result of MAMC in male than in females observed in our study and by Giusto et al. [38] can be explained by the fact that loss of muscle mass is not uniform in the body and can affect distinct sites according to gender. For example, the proportion of the upper limbs muscles is usually higher in males than in females [39], which can lead to distinct muscle loss depending on the gender. Nevertheless, one should be aware of the misclassification error coming for low muscle mass assessed by MAMC given a sensitivity lower than the specificity.

For females, on the other hand, among the methods tested, the FFM-BIA and Baumgartner equation showed the highest agreement, accuracy, sensitivity and specificity to detect low muscle mass. Of note, the Baumgartner equation showed a good performance also in males, making this equation an option for the assessment of muscle mass in both genders. The Baumgartner equation was developed in a study aiming to estimate the prevalence of sarcopenia in elderly participants of The New Mexico Elder Health Survey by using a random subsample of participants, which was then extended to the total sample [26]. This predictive equation, which uses easy-to-measure variables (weight, height, hip circumference and grip strength) was validated against DXA for the assessment of appendicular skeletal muscle mass [26]. In a previous study from our group [40], we showed that this predictive equation showed good agreement with appendicular muscle mass assessed by DXA in a sample comprised by elderly hemodialysis patients. Some studies, in non-CKD individuals, applied the Baumgartner equation to assess the appendicular skeletal muscle mass and found that low muscle mass was associated with mobility and basic activities of daily living [41, 42]. These findings show that this equation was able to predict clinical morbidity due to low muscle mass.

The limitations and strengths from the current investigation should be discussed. As a limitation, we applied the cutoff point below the 25th percentile for gender, in each method, to define low muscle mass. This threshold was arbitrary, since there is no established value for the diagnosis of low muscle mass in non-dialyzed CKD and dialyzed patients. It would be desirable to apply a cutoff able to predict a worse clinical outcome, such as low quality of life and/or higher hospitalization rate and mortality. On the other hand, when we assessed the prevalence of low muscle mass according to the cutoffs established for the elderly population or CKD individuals for each method by gender, the values observed were similar or lower than the lowest quartile of our sample. In addition, although validated in healthy individuals and in oncologic patients, the site located at the third lumbar vertebra has not yet been tested in CKD individuals for the assessment of muscle mass. It should also be mentioned that there was a lower proportion of females and of patients in CKD stage 3a (GFR between 45 to 59 ml/min/1.73 m^2), which might limit the representativeness of the studied sample. The strengths worth highlighting include the use of CT as the reference method, which is a well known for its high precision, accuracy and reliability [34, 35]. Also, the fact that the same observer read all the images from CT minimizes errors coming from interobserver readings. Finally, the surrogates tested had high clinical applicability, characterized by low cost and portable equipment requiring minimum training, which allows an affordable assessment of muscle mass.

In conclusion, in both genders, the Baumgartner equation showed to be a good surrogate method to assess the muscle mass in CKD patients under conservative treatment. The

MAMC showed higher agreement and accuracy in males, but not in females. Finally, clinicians should be aware of the lack of threshold values for muscle depletion, which consist a limitation of the use of CT scan in the evaluation of muscle mass. Upcoming works should focus on the identification of normal threshold values to offer a better evaluation of low muscle mass in CKD patients under conservative treatment.

Acknowledgements This manuscript was supported by Fundação de Amparo à Pesquisa do Estado de São Paulo [FAPESP] (Process number: 2010/16593-2), and Adib Jatene's Foundation.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Price SR, Gooch JL, Donaldson SK, Roberts-Wilson TK. Muscle atrophy in chronic kidney disease results from abnormalities in insulin signaling. J Ren Nutr. 2010;20(5 Suppl):S24–8.
2. Workeneh BT, Mitch WE. Review of muscle wasting associated with chronic kidney disease. Am J Clin Nutr. 2010;91:1128S–32S.
3. Qureshi AR, Alvestrand A, Danielsson A, Divino-Filho JC, Gutierrez A, Lindholm B, et al. Factors predicting malnutrition in hemodialysis patients: a cross-sectional study. Kidney Int. 1998;53:773–82.
4. Stenvinkel P, Carrero JJ, von Walden F, Ikizler TA, Nader GA. Muscle wasting in end-stage renal disease promulgates premature death: established, emerging and potential novel treatment strategies. Nephrol Dial Transplant. 2016;31:1070–7.
5. Carrero JJ, Stenvinkel P, Cuppari L, Ikizler TA, Kalantar-Zadeh K, Kaysen G, et al. Etiology of the protein-energy wasting syndrome in chronic kidney disease: a consensus statement from the International Society of Renal Nutrition and Metabolism (ISRNM). J Ren Nutr. 2013;23:77–90.
6. Wang XH, Mitch WE. Mechanisms of muscle wasting in chronic kidney disease. Nat Rev Nephrol. 2014;10:504–16.
7. Johansen KL, Dalrymple LS, Delgado C, Kaysen GA, Kornak J, Grimes B, et al. Association between body composition and frailty among prevalent hemodialysis patients: a US Renal Data System special study. J Am Soc Nephrol. 2014;25:381–9.
8. Johansen KL, Shubert T, Doyle J, Soher B, Sakkas GK, Kent-Braun JA. Muscle atrophy in patients receiving hemodialysis: effects on muscle strength, muscle quality, and physical function. Kidney Int. 2003;63:291–7.
9. Alston H, Burns A, Davenport A. Loss of appendicular muscle mass in haemodialysis patients is associated with increased self-reported depression, anxiety and lower general health scores. Nephrology (Carlton). 2017, http://onlinelibrary.wiley.com/doi/10.1111/nep.13075/abstract.
10. Huang CX, Tighiouart H, Beddhu S, Cheung AK, Dwyer JT, Eknoyan G, et al. Both low muscle mass and low fat are associated with higher all-cause mortality in hemodialysis patients. Kidney Int. 2010;77:624–9.
11. Wang J, Streja E, Rhee CM, Soohoo M, Feng M, Brunelli SM, et al. Lean body mass and survival in hemodialysis patients and the roles of race and ethnicity. J Ren Nutr. 2016;26:26–37.
12. Wilson FP, Xie D, Anderson AH, Leonard MB, Reese PP, Delafontaine P, et al. Urinary creatinine excretion, bioelectrical impedance analysis, and clinical outcomes in patients with CKD: the CRIC study. Clin J Am Soc Nephrol. 2014;9:2095–103.
13. Araújo IC, Kamimura MA, Draibe SA, Canziani ME, Manfredi SR, Avesani CM, et al. Nutritional parameters and mortality in incident hemodialysis patients. J Ren Nutr. 2006;16:27–35.
14. Carrero JJ, Johansen KL, Lindholm B, Stenvinkel P, Cuppari L, Avesani CM. Screening for muscle wasting and dysfunction in patients with chronic kidney disease. Kidney Int. 2016;90:53–66.
15. Roubenoff R, Kehayias JJ, Dawson-Hughes B, Heymsfield SB. Use of dual-energy x-ray absorptiometry in body-composition studies: not yet a "gold-standard". Am J Clin Nutr. 1993;58:589–91.
16. Abrahamsen B, Hansen TB, Høgsberg IM, Pedersen FB, Beck-Nielsen H. Impact of hemodialysis on dual X-ray absorptiometry, bioelectrical impedance measurements, and anthropometry. Am J Clin Nutr. 1996;63:80–6.
17. Cruz-Jentoft AJ, Baeyens JP, Bauer JM, Boirie Y, Cederholm T, Landi F, et al. Sarcopenia: European consensus on definition and diagnosis: Report of the European Working Group on Sarcopenia in Older People. Age Ageing. 2010;39:412–23.
18. Fukasawa H, Kaneko M, Niwa H, Matsuyama T, Yasuda H, Kumagai H, et al. Lower thigh muscle mass is associated with all-cause and cardiovascular mortality in elderly hemodialysis patients. Eur J Clin Nutr. 2016;71:64–69.
19. Ohkawa S, Odamaki M, Yoneyama T, Hibi I, Miyaji K, Kumagai H. Standardized thigh muscle area measured by computed axial tomography as an alternate muscle mass index for nutritional assessment of hemodialysis patients. Am J Clin Nutr. 2000;71:485–90.
20. Shen W, Punyanitya M, Wang Z, Gallagher D, St-Onge MP, Albu J, et al. Total body skeletal muscle and adipose tissue volumes: estimation from a single abdominal cross-sectional image. J Appl Physiol (1985). 2004;97:2333–8.
21. Mourtzakis M, Prado CM, Lieffers JR, Reiman T, McCargar LJ, Baracos VE. A practical and precise approach to quantification of body composition in cancer patients using computed tomography images acquired during routine care. Appl Physiol Nutr Metab. 2008;33:997–1006.
22. Cordeiro AC, Qureshi AR, Lindholm B, Amparo FC, Tito-Paladino-Filho A, Perini M, et al. Visceral fat and coronary artery calcification in patients with chronic kidney disease. Nephrol Dial Transplant. 2013;28(Suppl 4):iv152–9.
23. Cordeiro AC, Moraes AA, Cerutti V, França F, Quiroga B, Amodeo C, et al. Clinical determinants and prognostic significance of the electrocardiographic strain pattern in chronic kidney disease patients. J Am Soc Hypertens. 2014;8:312–20.
24. Steiber A, Leon JB, Secker D, McCarthy M, McCann L, Serra M, et al. Multicenter study of the validity and reliability of subjective global assessment in the hemodialysis population. J Ren Nutr. 2007;17:336–42.
25. Frisancho AR. New norms of upper limb fat and muscle areas for assessment of nutritional status. Am J Clin Nutr. 1981;34:2540–5.
26. Baumgartner RN, Koehler KM, Gallagher D, Romero L, Heymsfield SB, Ross RR, et al. Epidemiology of sarcopenia among the elderly in New Mexico. Am J Epidemiol. 1998;147:755–63.
27. Fouque D, Kalantar-Zadeh K, Kopple J, Cano N, Chauveau P, Cuppari L, et al. A proposed nomenclature and diagnostic criteria for protein-energy wasting in acute and chronic kidney disease. Kidney Int. 2008;73:391–8.
28. Durnin JV, Womersley J. Body fat assessed from total body density and its estimation from skinfold thickness: measurements

on 481 men and women aged from 16 to 72 years. Br J Nutr. 1974;32:77–97.
29. Siri WE. Body composition from fluid spaces and density: analysis of methods. 1961. Nutrition. 1993;9:480–91. discussion, 92
30. Janssen I, Heymsfield SB, Baumgartner RN, Ross R. Estimation of skeletal muscle mass by bioelectrical impedance analysis. J Appl Physiol (1985). 2000;89:465–71.
31. Fleiss J. The design and analysis of clinical experiments. New York, USA, 1986, pp 1-33.
32. Harrell Frank E. Regression modeling strategies: With applications to linear models, logistic regression and survival analysis.. New York, USA: Springer; 2001.
33. Physical status: the use and interpretation of anthropometry. Report of a WHO Expert Committee. World Health Organ Tech Rep Ser. 1995;854:1–452.
34. Heymsfield SB, Wang Z, Baumgartner RN, Ross R. Human body composition: advances in models and methods. Annu Rev Nutr. 1997;17:527–58.
35. Ross R, Janssen I. Computed tomography and magnetic resonance imaging. In: Heymsfield SB, Lohman T, Wang Z, Going S, eds. Human Body Composition. 2nd ed. Champaign, IL: Human Kinetics; 2005. p. 89–108.
36. Prado CM, Heymsfield SB. Lean tissue imaging: a new era for nutritional assessment and intervention. JPEN J Parenter Enter Nutr. 2014;38:940–53.
37. Noori N, Kopple JD, Kovesdy CP, Feroze U, Sim JJ, Murali SB, et al. Mid-arm muscle circumference and quality of life and survival in maintenance hemodialysis patients. Clin J Am Soc Nephrol. 2010;5:2258–68.
38. Giusto M, Lattanzi B, Albanese C, Galtieri A, Farcomeni A, Giannelli V, et al. Sarcopenia in liver cirrhosis: the role of computed tomography scan for the assessment of muscle mass compared with dual-energy X-ray absorptiometry and anthropometry. Eur J Gastroenterol Hepatol. 2015;27:328–34.
39. Janssen I, Heymsfield SB, Wang ZM, Ross R. Skeletal muscle mass and distribution in 468 men and women aged 18-88 yr. J Appl Physiol (1985). 2000;89:81–8.
40. Giglio J, Kamimura MA, Lamarca F, Rodrigues J, Santin F, Avesani CM. Association of sarcopenia with nutritional parameters, quality of life, hospitalization and mortality rates of elderly patients on hemodialysis. J Ren Nutr (in press), https://doi.org/10.1053/j.jrn.2017.12.003.
41. Velázquez Alva Me C, Irigoyen Camacho ME, Delgadillo Velázquez J, Lazarevich I. The relationship between sarcopenia, undernutrition, physical mobility and basic activities of daily living in a group of elderly women of Mexico City. Nutr Hosp. 2013;28:514–21.
42. Chávez-Moreno DV, Infante-Sierra H, Serralde-Zúñiga AE. Sarcopenia and functionality in elderly inpatient. Nutr Hosp. 2015;31:1660–6.