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Contents

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REVIEW

- 1188 Sarcopenia in patients with colorectal cancer: A comprehensive review
Vergara-Fernandez O, Trejo-Avila M, Salgado-Nesme N

MINIREVIEWS

- 1203 Thoracic hydatid disease: A radiologic review of unusual cases
Saeedan MB, Aljohani IM, Alghofaily KA, Loufi S, Ghosh S

ORIGINAL ARTICLE**Case Control Study**

- 1213 Clinical significance and prognostic value of tumor necrosis factor- α and dickkopf related protein-1 in ankylosing spondylitis
Xiong JH, Liu J, Chen J

Retrospective Study

- 1223 Reconstruction of Paprosky type IIIB acetabular bone defects using a cup-on-cup technique: A surgical technique and case series
Du YQ, Liu YP, Sun JY, Ni M, Zhou YG

Prospective Study

- 1232 Depression and myocardial injury in ST-segment elevation myocardial infarction: A cardiac magnetic resonance imaging study
Sun ZQ, Yu TT, Ma Y, Ma QM, Jiao YD, He DX, Jia-KeWu, Wen ZY, Wang XN, Hou Y, Sun ZJ

CASE REPORT

- 1241 Long-term survival of two patients with recurrent pancreatic acinar cell carcinoma treated with radiofrequency ablation: A case report
Di Marco M, Carloni R, De Lorenzo S, Grassi E, Palloni A, Formica F, Brocchi S, Filippini DM, Golfieri R, Brandi G
- 1251 Acute myeloid leukemia with t(11;19)(q23;p13.1) in a patient with a gastrointestinal stromal tumor undergoing imatinib therapy: A case report
Kim HJ, Baek SK, Maeng CH, Kim SY, Park TS, Han JJ
- 1257 CD56+ lymphoepithelioma-like carcinoma of the lung: A case report and literature review
Yang L, Liang H, Liu L, Guo L, Ying JM, Shi SS, Hu XS
- 1265 Atypical presentation of SARS-CoV-2 infection: A case report
Li RL, Chu SG, Luo Y, Huang ZH, Hao Y, Fan CH

- 1271** Spinal intraosseous schwannoma without spinal canal and neuroforamina involvement: A case report
Xu ZQ, Zhang P, Zhong ZH, Zhou W, Yu HT
- 1278** Chidamide based combination regimen for treatment of monomorphic epitheliotropic intestinal T cell lymphoma following radical operation: Two case reports
Liu TZ, Zheng YJ, Zhang ZW, Li SS, Chen JT, Peng AH, Huang RW
- 1287** Scaphoid metastasis as the first sign of occult gastroesophageal junction cancer: A case report
Zhang YJ, Wang YY, Yang Q, Li JB
- 1295** Pleural effusion in an immunocompetent host with cryptococcal pneumonia: A case report
Wu HH, Chen YX, Fang SY
- 1301** Rigid ureteroscopy in prone split-leg position for fragmentation of female ureteral stones: A case report
Huang K
- 1306** Multiple neurofibromas plus fibrosarcoma with familial NF1 pathogenicity: A case report
Wang Y, Lu XF, Chen LL, Zhang YW, Zhang B
- 1311** Severe venous thromboembolism in the puerperal period caused by thrombosis: A case report
Zhang J, Sun JL
- 1319** Disseminated histoplasmosis in primary Sjögren syndrome: A case report
Li JA, Cheng YY, Cui ZT, Jiang W, Zhang WQ, Du ZH, Gao B, Xie YY, Meng HM
- 1326** Clinical effects of apatinib mesylate for treatment of multiple brain micrometastases: Two case reports
Guo JH, Wang YY, Zhang JW, Liu PM, Hao YJ, Duan HR
- 1337** Systemic treatment for severe concentrated sulfuric acid burns in an adult male at high altitude: A case report
Zhao RM, Li Y, Chao SW, Wang HJ

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Sarcopenia in patients with colorectal cancer: A comprehensive review

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Abstract

Colorectal cancer (CRC) is the third most commonly diagnosed cancer globally and the second cancer in terms of mortality. The prevalence of sarcopenia in patients with CRC ranges between 12%-60%. Sarcopenia comes from the Greek “sarx” for flesh, and “penia” for loss. Sarcopenia is considered a phenomenon of the aging process and precedes the onset of frailty (primary sarcopenia), but sarcopenia may also result from pathogenic mechanisms and that disorder is termed secondary sarcopenia. Sarcopenia diagnosis is confirmed by the presence of low muscle quantity or quality. Three parameters need to be measured: muscle strength, muscle quantity and physical performance. The standard method to evaluate muscle mass is by analyzing the tomographic total cross-sectional area of all muscle groups at the level of lumbar 3rd vertebra. Sarcopenia may negatively impact on the postoperative outcomes of patients with colorectal cancer undergoing surgical resection. It has been described an association between sarcopenia and numerous poor short-term CRC outcomes like increased perioperative mortality, postoperative sepsis, prolonged length of stay, increased cost of care and physical disability. Sarcopenia may also negatively impact on overall survival, disease-free survival, recurrence-free survival, and cancer-specific survival in patients with non-metastatic and metastatic colorectal cancer. Furthermore, patients with sarcopenia seem prone to toxic effects during chemotherapy, requiring dose deescalations or treatment delays, which seems to reduce treatment efficacy. A multimodal approach including nutritional support (dietary intake, high energy, high protein, and omega-3 fatty acids), exercise programs and anabolic-orexigenic agents (ghrelin, anamorelin), could contribute to muscle mass preservation. Addition of sarcopenia screening to the established clinical-pathological scores for patients undergoing oncological treatment (chemotherapy, radiotherapy or surgery) seems to be the next step for the best of care of CRC patients.

Key words: Colorectal cancer; Sarcopenia; Nutrition; Muscle mass loss; Oncologic outcomes; Survival

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Core tip: The prevalence of sarcopenia in patients with colorectal cancer ranges between 12%-60%. The diagnosis of sarcopenia is established by the presence of low muscle quantity or quality (muscle strength, muscle quantity and physical performance). Sarcopenia may negatively impact on the postoperative outcomes of patients with colorectal cancer undergoing surgery. Sarcopenia may also negatively impact on overall survival, disease-free survival, recurrence-free survival, and cancer-specific survival in patients with colorectal cancer. Furthermore, patients with sarcopenia seem prone to toxic effects during chemotherapy. A multimodal approach including nutritional support, exercise programs and anabolic-orexigenic agents, could contribute to muscle mass preservation.

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INTRODUCTION

The incidence and mortality of cancer are rapidly increasing worldwide^[1]. Noncommunicable diseases (like cancer), are now accountable for the majority of worldwide deaths^[1]. Colorectal cancer (CRC) is the third most commonly diagnosed cancer globally and has the second highest mortality^[1,2]. Prognostic stratification in CRC patients is usually determined by tumor stage (clinical and pathological) and potentially curative surgery; however, long-term survival can also be negatively influenced by surgical complications and patient-related factors^[3]. Body composition and functional status are important patient-related factors, and changes or alterations may influence the oncological outcomes.

Acute and chronic diseases in most organ systems have pronounced effects on metabolism, mainly increasing the catabolism, which lead to nutritional-related poor conditions that are associated with increased morbidity and potentially mortality^[4]. Cancer is often associated with weight loss and muscle mass deterioration^[5]. Among patients with cancer, muscle loss may be attributed to sarcopenia, and in the clinical setting, this condition should be differentiated with malnutrition^[6]. Low skeletal muscle mass is common among cancer patients and predicts postoperative complications, treatment toxicity (chemotherapy), poor quality of life, and decreased survival^[7-10].

Sarcopenia comes from the Greek “sarx” for flesh and “penia” for loss, and was first defined by Rosenberg^[11] in 1988. It is considered a more robust measure of frailty and might give a more objective assessment of patients functional reserve^[12]. The prevalence of sarcopenia in healthy individuals increases with advanced age, ranging from 9% at 45 years and up to 64% in individuals aged over 85 years^[13]. The frequency seems to be higher in patients with CRC, ranging between 12%-60%^[14-16].

Previous studies have shown that sarcopenia is a predictor of overall mortality among geriatric patients^[17], and currently special attention is focused on the association between sarcopenia and cancer. Sarcopenia, identified by computed tomography (CT), is associated with impaired overall survival in several gastrointestinal malignancies, and with increased postoperative morbidity in patients with CRC with or without hepatic metastases^[8]. This condition impacts on oncological outcomes by decreasing overall survival (OS), disease-free survival (DFS), progression-free survival (PFS), and cancer-specific survival (CSS), additionally it seems to predispose to toxic effects during chemotherapy^[3].

This review aims to present the current definition of sarcopenia, an assessment of patients with CRC and sarcopenia, the effects of sarcopenia on the oncological outcomes of patients with non-metastatic and metastatic CRC, and the emerging trends in therapeutics.

DEFINITION OF SARCOPENIA

Sarcopenia is an evolving concept, and currently a universal definition for sarcopenia does not exist^[5]. Several groups, like the International Working Group on Sarcopenia^[18], the Society of Sarcopenia, Cachexia, and Wasting Disorders^[19], the European Society of Parenteral and Enteral Nutrition^[20], Asian Working Group for Sarcopenia^[21], and the European Working Group on Sarcopenia in Older People^[9], have addressed this problem and proposed diagnostic criteria.

Sarcopenia is a disorder (muscle failure) characterized by progressive loss of skeletal muscle mass, strength and function (performance), with an increased odds of adverse outcomes^[4,9]. Sarcopenia is considered a phenomenon of the aging process and precedes the onset of frailty (primary sarcopenia), but sarcopenia may also result from pathogenic mechanisms (inflammatory and neoplastic process) and that disorder is termed secondary sarcopenia^[4].

According to the European Working Group on Sarcopenia in Older People, the 2018 operational definition says that sarcopenia is probable when low muscle strength is detected (Criterion 1); that the diagnosis is confirmed when there is documentation of low muscle quantity or quality (Criterion 2); and that when patients with low muscle strength, low muscle quantity/quality and low physical performance are all detected, the sarcopenia is considered severe (Criteria 1, 2 and 3)^[9]. Sarcopenia that has lasted less than 6 mo is considered an acute condition, and if it lasts ≥ 6 mo, it is considered a chronic condition^[9].

Another important concept is sarcopenic obesity. This is a condition of reduced lean body mass in patients with excess of adiposity^[22,23]. It has been noted that obesity exacerbates sarcopenia, specially in older people, by increasing the infiltration of fat into muscle, and lowering physical function.

Although the sarcopenic phenotype is associated with malnutrition, the last is considered a separated condition. Malnutrition (synonym to undernutrition) is defined as the state resulting from lack of intake or uptake of calories that leads to altered body composition and body cell mass, leading to diminished function and impaired clinical outcome from illness^[4]. Concerning patients with cancer, a sub-classification englobes the chronic disease-related malnutrition with inflammation (synonym of cachexia), and is termed cancer cachexia^[4].

Cancer cachexia is defined as a multifactorial and complex metabolic syndrome with progressing loss of skeletal muscle mass (with or without loss of fat mass) that cannot be fully reversed by conventional nutritional support and leads to progressive functional impairment^[24]. It is defined by a $> 5\%$ involuntary loss of edema-free body weight over 1 year, or with loss $> 2\%$ if body mass index is reduced ($< 20 \text{ kg/m}^2$) or fat free mass is reduced^[4,24].

PHYSIOLOGIC DERANGEMENTS IN SARCOPENIA

Muscle mass and strength vary across a lifetime^[9]. Normal aging is associated with a 1%-2% muscle loss after the age of 50 years^[25]. Aging is characterized by an accelerated muscle loss and higher adipose tissue accumulation within skeletal muscle (myosteatosis)^[26]. The skeletal muscle consists of the largest pool of proteins in the entire organism. As previously defined sarcopenia is characterized by progressive and generalized loss of skeletal muscle mass (myopenia), strength and function^[9].

This condition represents a muscle wasting disease involving inflammation and oxidative stress, where regulating molecules associated with wasting are activated (myostatin and ubiquitin-proteasome system) or repressed (insulin-like growth factor 1 [IGF-1] and peroxisome proliferator-activated receptor-gamma co-activator [PGC-1alpha])^[27]. Another major contributor to muscle wasting is a lack of physical activity, which is often exacerbated by chronic disease and age^[27]. Evidence have suggested that alteration of muscle homeostasis via deterioration and decreased synthesis of proteins can promote muscle mass loss in patients with cancer^[28]. Several molecular mechanisms of sarcopenia have been described. These mechanisms participate in muscle growth and muscle wasting, and alterations in these mechanisms induce sarcopenia. These mechanisms are: Protein synthesis, protein degradation, mitochondrial abnormalities, inflammation, oxidative stress and regeneration of muscle tissue by satellite cells^[27]. Skeletal muscle mass depends on fibre protein content which is determined by a balance between protein breakdown and synthesis (protein turnover). Some factors like cellular energy status, alterations in the endocrine system (IGF-1), cytokines induced by inflammation, alterations or changes of molecular muscle growth-degradation systems, myostatin, availability of metabolic substrates, and physical exercise influence together in the rates of protein turnover

and in the regulation of muscle mass. Adequate dietary protein ingestion and anabolic hormones are important determinants of protein synthesis^[27]. One of the most important anabolic hormone is IGF-1^[29]. Other molecular regulators, like PGC-1 α , participates in cellular energy metabolism and mitochondrial biogenesis in skeletal muscle^[27]. Alterations in anabolic signaling seems to facilitate sarcopenia. Also, the activation of skeletal muscle proteolytic pathways (*via* ubiquitin-proteasome system, calpain, caspase and autophagy-lysosomal pathways) facilitates protein degradation^[27,30,31]. Mitochondrial abnormalities or dysfunction, which is believed to be induced by aging, participates in sarcopenia by increasing reactive oxygen species and by inducing apoptosis^[6]. Inflammation predisposes to sarcopenia by reducing muscle mass and strength, mostly mediated by inflammatory cytokines (*e.g.*, TNF- α , IL-4, IL-6)^[32]. Satellite cells, which are stem cells, contribute to muscle regeneration. Reductions in satellite cells, a phenomenon described in elderly humans and correlated with sarcopenia, are influenced by specific genes and growth factors (*e.g.*, Pax7, myostatin)^[27,33]. Finally, alterations in the homeostasis of the oxidative system (occurring with aging), promotes oxidative damage of mitochondrial DNA^[34].

Although several factors, such as the listed in previous lines, in addition to anorexia due to organ dysfunction by distant metastases, adverse effects of chemotherapy, and decreased physical activity can induce sarcopenia in CRC patients, emerging evidence suggest that skeletal muscle loss might be induced in metastatic CRC patients by circulating over-expressed and pro-apoptotic microRNA released from metastatic tissues^[28].

ASSESSMENT OF SARCOPENIA IN COLORECTAL CANCER PATIENTS

Sarcopenia diagnosis is corroborated by the presence of diminished muscle quantity or quality^[27,35]. Three parameters need to be measured: muscle strength, muscle quantity and physical performance. Muscle strength can be measured by grip strength (with a Jamar dynamometer, which is a validated tool) and by the chair stand test (chair rise test)^[9]. Muscle quantity or mass can be measured by several techniques, and can be reported as total body Skeletal Muscle Mass (SMM), as Appendicular Skeletal Muscle Mass (ASM), or as CT muscle cross-sectional area of specific muscle groups. The gold standards for non-invasive evaluation of muscle mass are CT and magnetic resonance imaging (MRI)^[9,35,36]. Dual-energy X-ray absorptiometry (DXA), which is more available instrument in contrast to MRI and CT, can determine total body lean tissue mass or appendicular skeletal muscle mass^[9]. An alternative to DXA is the bioelectrical impedance analysis. Muscle mass is correlated with body size and SMM and ASM should be adjusted to height squared, weight, or body mass index. When no other muscle mass diagnostic methods are available, calf circumference measures can predict performance and survival in order people^[9,35,37].

Physical performance is a multidimensional concept that includes body function related to locomotion^[9]. This parameter can be assessed by gait speed^[9], the Timed-Up and Go test^[38], the Short Physical Performance Battery, and the 400-m walk test^[39].

Newer tests and tools are being used for sarcopenia. Some of these alternative methods are: The lumbar 3rd vertebra imaging by CT^[40], mid-thigh muscle measurement (by MRI or CT), psoas muscle determination with CT^[41], muscle quality measurement (by MRI or CT), and the ultrasound assessment of muscle^[42].

CT scans have emerged as a common reference method, due to the fact that this imaging modality are a routine part of diagnosis, staging and surveillance in the majority of cancers^[7]. The third lumbar vertebra (L3) is now considered the standard marker for body composition analyses^[43]. At L3 the skeletal muscle and adipose tissue correlate with the whole-body tissue quantities^[43]. CT analysis at L3 can distinguish adipose tissue from skeletal tissue (psoas, paraspinal muscles, transversus abdominus, external and internal obliques, and rectus abdominus)^[43]. The standard method for evaluating muscle mass is a manual analysis of the total cross-sectional area of all muscle groups at L3^[7,35]. Specific tissues are identified based on their anatomical features and then demarcated and quantified based on reestablished thresholds of Hounsfield units (HU) (-29-150 for skeletal muscle) with commercially available software^[43]. Cross sectional muscle areas can be measured rapidly by analysis of abdominal CT scan analysis, and this measure is highly correlated with whole muscle volumes, and has a low level of interobserver variability^[9]. The majority of studies employed the cutoff points according to Prado *et al.*^[44] by calculating the skeletal muscle index (SMI, cm²/m²) (38.5 cm²/m² for females and 52.4 cm²/m² for males).

Measurements of psoas muscle included total psoas area, total psoas volume, and

SMI or psoas index (PI) (psoas area/height squared)^[45-47]. Another way to determine the muscle mass is by calculating the skeletal muscle radio density (SMD)^[48]. We present in **Table 1** some of the recent publications concerning CRC patients and the methods of measuring sarcopenia in each study.

A clinic-friendly approach to assess linear area from CT scans has been recently described, which consisted in assessing the area of the psoas and paraspinous muscles and computing their combined linear area in centimeters squared. These measures were highly correlated with total cross-sectional area and subsequently were associated with mortality after CRC^[7].

Imaging techniques are the most accurate methods for assessing body composition and sarcopenia, as mentioned in previous paragraphs. These techniques require equipment and well-trained personnel^[35]. Several biochemical markers for muscle mass estimation have been developed and validated. Some of these biomarkers are: The creatine dilution test^[49], total body potassium, and the deuterated creatine (D3-creatine) dilution method. This research area is under development and currently under investigation.

EFFECTS OF SARCOPENIA ON NON-METASTATIC DISEASE

The prevalence of sarcopenia in patients undergoing surgery for CRC has been reported in several studies (see **Table 1**). Lieffers *et al.*^[15] found an overall 38.9% prevalence of sarcopenia in a cohort of 234 patients with stage II-IV CRC. Miyamoto *et al.*^[50] reported a 25% of sarcopenia in 220 patients with stage I-III CRC. Vashi *et al.*^[47] described a 41.1% of sarcopenia in a series of 112 CRC patients with stage I to IV. Nakanishi *et al.*^[51] found in a study of 494 patients a 60% prevalence of sarcopenia, and an association with males ($P < 0.0001$) and low body mass index ($P < 0.0001$). Jochum *et al.*^[52] reported a cohort of 47 patients with locally advanced rectal cancer with a prevalence of 51.1%. More prevalence rates as well as characteristics of recent studies are shown in **Table 1**.

In a cohort study that included 3262 patients with stage I-III CRC, with 49.9% females and a mean age of 62.6 years, sarcopenia was highly prevalent (42.4%). They found a higher odds of sarcopenia (OR = 6.19) in older patients (70-80 years) in comparison with patients aged less than 50 years. They also examined the relation of race/ethnicity with sarcopenia and found that African Americans had 47% lower odds of sarcopenia, as well as Latin-Americans had 33% lower odds to have sarcopenia, in comparison with Caucasians^[53].

In patients with stage III colon cancer, a multivariate analysis ($n = 229$) showed that a 1 standard deviation diminution in the PI increased the hazard of mortality by 85% (HR: 1.85)^[46]. Miyamoto *et al.*^[50] in a retrospective analysis of 220 stage I-III CRC patients that underwent curative resection, found that sarcopenic patients experienced significantly shorter recurrence free survival (RFS) (5-year RFS of 56% *vs* 79%; $P = 0.006$), overall survival (OS) (5-year OS, 68 *vs* 85%; $P = 0.015$), and cancer specific survival (5-year OS, 82% *vs* 91%; $P = 0.026$) than those patients without sarcopenia. However in a Japanese study of 494 stage I-III CRC patients^[51], sarcopenia did not significantly correlated with the OS ($P = 0.31$) or RFS ($P = 0.09$). In a recent population-based cohort study (total of 1924 patients), the authors found that muscle wasting was associated with overall and cancer-specific mortality in patients with non-metastatic CRC (stages I-III)^[54].

A meta-analysis of 12 studies that included 5337 patients with non-metastatic CRC, the authors concluded that sarcopenia could be a negative predictor of postoperative and survival outcomes^[3]. Sarcopenia predicted reduced overall survival (HR: 1.63, 95%CI: 1.24-2.14, $P < 0.01$), disease-free survival (HR: 1.70, 95%CI: 1.24-2.31, $P < 0.01$), and cancer-specific survival (HR: 1.62, 95%CI: 1.16-2.27, $P < 0.01$) for non-metastatic CRC patients. Furthermore, progressive sarcopenia after CRC diagnosis (changes in CT within the 6 to 18 month interval after CRC diagnosis) has a significant negative prognostic association with OS and PFS^[55].

There is growing evidence that body composition parameters, specifically reduced skeletal muscle mass (sarcopenia), reduced skeletal muscle radio-density (myosteotosis) and visceral adipose tissue (visceral obesity), provide prognostic implications for patients with CRC, resulting in worse OS and RFS^[56]. The joint effects of these parameters may produce the poorest survival risk in patients with stage I to III CRC being treated with curative intent^[56,57]. Hopkins *et al.*^[56] described a model that considered joint effects of sarcopenia and myosteotosis, and the presence of both predicted the poorest OS (HR: 2.23), RFS (HR: 1.53) and CSS (HR: 2.40). Another interesting association was described between sarcopenia and inflammation (neutrophil to lymphocyte ratio)^[7]. Sarcopenia combined with inflammation nearly

Table 1 Current studies of the effects of sarcopenia in patients with colorectal cancer

Ref.	Population (n)/ Age (yr)/Study type	CRC stage (%) /Surgery/ chemo (%) /radio (%)	Evaluation of sarcopenia/ Sarcopenia prevalence (%)	Morbidity/ Complications	DFS/RFS/CSS	OS/Mortality
Hopkins <i>et al</i> ^[56]	n = 968/mean 65.8 yr/RS	CC (60.6) RC (39.4)/ Stage I (10.3), II (38.6), III (51)/ Surgery	CT cross sectional muscle analysis, skeletal muscle area/27.5% prevalence		Sarcopenia worse RFS (HR: 1.32) and CSS (HR: 1.46)	Sarcopenia worse OS (HR: 1.45)
Dolan <i>et al</i> ^[60]	n = 163/median 70 yr/PS	CC (44.2), RC (55.8)/ Stage 0 (4.9), I (20.9), II (35), III (32.5), IV (6.7)/ Surgery	CT cross sectional TPA at L3 and PI/19.6% prevalence	Sarcopenia associated with 30-d mortality (P = 0.042)		Sarcopenia associated with 1-year mortality (P = 0.046)
Da Cunha <i>et al</i> ^[74]	n = 72/mean 59.4/RS	CC (58.3) RC (41.7)/all stage IV/ Surgery (29.2) Chemo (76.4)	CT cross sectional SMI at L3 (cutoffs SMI < 41 cm ² /m ² women, < 43 cm ² /m ² men)/ 44.4% prevalence		Sarcopenia reduced PFS (P < 0.001), HR: 1.78	Sarcopenic reduced OS (HR: 1.86, P = 0.043)
Jochum <i>et al</i> ^[52]	n = 47/mean 59.3 yr/RS	All RC/ stage II (40), III (60)/Neo-A and surgery	CT Cross sectional skeletal muscle mass index at L3, SMI/ 51.1% prevalence	Sarcopenia associated with blood transfusion (P = 0.001). Higher postoperative complications in sarcopenic (OR= 3.81)		
Herrod <i>et al</i> ^[62]	n = 169/mean 72 yr/RS	CRC/stage not reported/all had CRC resection	CT Cross sectional mean psoas density at L3/30% prevalence	Sarcopenia associated with: High grade complications (OR: 6.33, P = 0.007), increased anastomotic risk (OR: 14.37, P = 0.026)		Sarcopenia not associated with 1-year mortality (OR: 2.08, P = 0.23)
Vashi <i>et al</i> ^[47]	n = 112/median 53.3 yr/RS	CC (75.9), RC (24.1)/ Stage I (1.8), II (6.3), III (33), IV (58.9)/ A-Chemo.	CT cross-sectional PM area at L3. Skeletal muscle index cm ² /m ² (< 38.5 women and < 52.4 men)/ 41.1% prevalence			Median survival in sarcopenia 17.8 vs 38.6 mo in non-sarcopenia (P = 0.001). Less survival in stage IV + sarcopenia (mortality HR: 4.0, P = 0.001)
Park <i>et al</i> ^[58]	n = 65/median 71 yr/RS	RC stage I (12.3), II (36.9), III (41.5)/ LAR (86.2), APR (13.8)/ Neo-A or A-Chemo	CT Cross sectional muscle mass (cm ²) at L3, SMI or PI. (49 cm ² /m ² men, 31 cm ² /m ² women)/ 38.5% prevalence		5-year DFS: Lower in sarcopenic (37.4% vs 81.6%, HR: 3.52, P = 0.001)	5-year OS: Lower in sarcopenia (38.0% vs 92.5%, P < 0.001). HR: 6.08; P = 0.001
Kroenke <i>et al</i> ^[48]	n = 3262/ >70 yr (n = 1083)/ RS	CRC/ stages I-III/ all surgery	CT cross sectional muscle area at L3. Skeletal muscle radio density and muscle mass			Low SMD had higher overall mortality (HR: 1.61). Patients with low SMD and sarcopenia: Highest mortality (HR: 2.02)
Nakanishi <i>et al</i> ^[51]	n = 494/mean 66.1 yr/RS	CC (58), RC (42)/stage I (22), II (25), III (36), IV (17)/ A-Chemo	CT Cross sectional muscle mass (cm ²) at L3, SMI. (52.4 cm ² /m ² men, 38.5 cm ² /m ² women)/ 60% prevalence	Sarcopenia associated with higher overall complications (OR: 1.82, P = 0.01), longer hospital stay (P = 0.02).	Worse RFS of sarcopenic patients, but not significant (P = 0.09)	Sarcopenia did not correlate with OS (P = 0.31)
Womer <i>et al</i> ^[45]	n = 180/mean 62.7 yr/RS	RC Stage I (8.4), II (25.7), III (39.7), IV (13.4)/LAR (73.9), APR (26.1)/ Neo-A (86.1%)	CT cross-sectional PM at L3. Total psoas area, total psoas volume	Major 90-d morbidity with smaller TPA (6.7 vs 10.5 cm ² /m ² , P = 0.04) and TPV (26.7 vs 42.2 cm ² /m ² , P = 0.04)		

Choi <i>et al</i> ^[59]	n = 188/mean 61.3/RS	All RC/stage II (18.1), III (81.9)/ Neo-A and surgery	CT Cross sectional skeletal muscle mass index at L3, SMI (52.4 cm ² /m ² men, 38.5 cm ² /m ² women)/ 39.4% prevalence		Sarcopenia did not shorten DFS (P = 0.900)	Sarcopenic had shorter OS (P = 0.004)
Miyamoto <i>et al</i> ^[50]	n = 220/mean 70 yr/RS	CC Stage I (35%), II (38), III (27)/ A-Chemo (25%)	CT Cross sectional muscle mass (cm2) at L3, with a three dimensional system. Normalized by height (m ²)/25% prevalence		5-y RFS: 56 (sarcopenia) vs 79%, log-rank P = 0.006/ Shorter RFS HR: 2.1 (P = 0.010)	5-y OS: 68 (sarcopenia) vs 85%, log-rank P = 0.015/ Shorter OS HR 2.2 (P = 0.019)
Reisinger <i>et al</i> ^[61]	n = 310/ > 70 yr (51.3%)/PS	CC (66.1), RC (33.9)/ Stage I (5.5), II (70.6), III (20), IV (3.9)/ surgery	CT cross-sectional muscle area surface at L3, muscle index (52.4 cm ² /m ² men, 38.5 cm ² /m ² women)/47.7% prevalence	30-d and in-hospital mortality: 8.8% sarcopenia vs 0.7% non-sarcopenia (OR: 15.5, P = 0.001) Sarcopenia was not predictive for anastomotic leaks or sepsis		
Huang <i>et al</i> ^[14]	n = 142/mean 62.03 yr/PS	CC (54.2) RC (45.3)/ Stage I (26), II (44.4), III (29.6)/ Surgery, Neo-A	CT Cross sectional muscle index at L, handgrip strength, gait speed/ 11.9% prevalence	Patients with sarcopenia had a higher incidence of postoperative complications (OR: 4.524, P = 0.007) and higher infectious complications (OR: 3.2, P = 0.052)		
Jung <i>et al</i> ^[46]	n = 229/ Median 61 yr/RS	All stage III CC/ Curative surgery/ A-Chemo (FOLFOX4)	CT Cross sectional PM at L4, psoas index (psoas area(cm ²)/height (m ²)/ 25.3% prevalence	Increase in grade 3-4 chemotherapy toxicities (OR: 1.67), grade 3-4 neutropenia (OR: 1.56)		HR for mortality: 1.85 (P = 0.022)
Van Vledder <i>et al</i> ^[12]	n = 196/median 64.5 yr/RS	CC (59.2), RC (40.8)/ all stage IV (liver)/ surgery for metastases	CT cross-sectional muscle areas at L3. (< 41.1 cm ² /m ² women and < 43.75 men)/19.4% prevalence		Sarcopenia: Shorter median DFS (8.7 vs 15.1 mo; P = 0.002)	Sarcopenia: Worse median overall survival (23.8 vs 59.8 mo; P = 0.001)
Peng <i>et al</i> ^[16]	n = 259/ median 58 yr/RS	CC (74), RC (27)/all stage IV (liver)/surgery for metastases	CT Cross sectional muscle mass at L3. TPA at L3 (mm ² /m ²)/ 16% prevalence	Sarcopenia associated with overall morbidity risk (OR: 2.2; P = 0.02).; Sarcopenia associated with major complications (OR: 3.33; P = 0.008) and Longer stays (> 2 d; P = 0.004)	5-year RFS: 23% in sarcopenia vs 27% in non-sarcopenia (P = 0.78)	Sarcopenia was not associated with long-term OS.

CRC: Colorectal cancer; DFS: Disease free survival; RFS: Recurrence free survival; CSS: Cancer Specific Survival; OS: Overall survival; RS: retrospective study; PS: Prospective study; CC: Colon Cancer; RC: Rectal Cancer; LAR: Low anterior resection; APR: Abdominoperineal resection; A-Chemo: Adjuvant Chemotherapy; Neo-A: Neoadjuvant therapy; CT: Computed tomography; PM: Psoas muscle; OR: Odds ratio; HR: Hazard ratio.

doubled the risk of mortality, overall (HR: 2.12) and CRC related (HR: 2.43), providing a potential powerful prognostic indicator in patients with non-metastatic CRC^[7].

Previous studies have reported overall outcomes mixing patients with colon and rectal cancers. But, it is important to differentiate between both malignancies because the treatment strategies are different. Actual treatment strategies for rectal cancer included chemo and radiotherapy (either pre- or post-operatively), and then the surgical procedure (low anterior resection, abdominoperineal resection). Analyzing sarcopenic patients with rectal cancer, with neoadjuvant or adjuvant chemoradiotherapy, needs separation from colon cancers. Park *et al*^[58] analyzed 65 rectal cancer patients, with 38.5% prevalence of sarcopenia. They found that sarcopenia is a poor prognostic factor in older patients with locally advanced rectal cancer who received neoadjuvant or adjuvant therapy. Sarcopenia was the only independent prognostic factor for OS (HR: 6.087; 95%CI: 2.078-17.828, P = 0.001). Choi *et al*^[59] analyzed 188 patients with locally advanced rectal cancer and found in a multivariate analysis that

sarcopenia (HR: 3.55; 95%CI: 1.31-9.65; $P = 0.013$) and initial carcinoembryonic antigen (HR: 1.13; 95%CI: 1.025-1.246; $P = 0.014$) were independent predictors for poorer OS. Despite all the information presented in previous lines, the exact mechanisms by which sarcopenia affect OS and RFS in patients with colorectal cancer have yet to be determined.

EFFECTS OF SARCOPIENIA ON SHORT-TERM AND POSTOPERATIVE OUTCOMES

Associations between sarcopenia and numerous poor outcomes, such as reduced survival, elevated postoperative mortality, higher infection rates, postoperative sepsis, increased length of stay, increased cost of care, and physical disability have been described^[15,60,61]. Currently, the risk factors commonly employed to predict outcomes after oncological surgery may not totally reflect the patients' general status, functionality and physiological reserves^[8]. Including sarcopenia as a risk prediction of peri-operative morbidity can provide prognostic information to the surgeons and to the patients^[16].

Sarcopenic patients undergoing surgery for CRC and hepatic CRC metastases had prolonged length of stay and elevated postoperative complication rates compared to those without sarcopenia^[8]. In the field of rectal cancer surgery, some studies have corroborated the propensity towards smaller psoas area and psoas volume among patients who experience complications after surgery^[45].

It seems that sarcopenia predispose to septic complications after CRC elective surgery. In a prospective study by Huang *et al*^[14] 142 patients were included after surgery and the authors found that sarcopenic had a higher incidence of postoperative complications (OR: 4.524, $P = 0.007$) and a propensity to a higher incidence of septic complications (OR: 3.277, $P = 0.052$). Reisinger *et al*^[61] found that combining sarcopenia with a high score in a nutritional questionnaire (Short Nutritional Assessment Questionnaire) and a high score in a frailty questionnaire (Groningen Frailty Indicator) predicted postoperative sepsis (OR: 25.1; 95%CI: 5.11-123; $P = 0.001$) with 46% sensitivity and 97% specificity.

In a multivariate model of stage II-IV CRC patients, older than 65 years, sarcopenia was a predictor of postoperative infection (OR: 4.6, 95%CI: 1.5-13.9; $P < 0.01$) and inpatient rehabilitation care with longer length of stay (OR: 3.1, 95%CI: 1.04-9.4, $P < 0.04$)^[15]. A Japanese study also found a longer hospital stays in sarcopenic patients (16.3 *vs* 19.4 d, $P < 0.01$)^[51]. In a meta-analysis published in 2018^[3], patients with sarcopenia displayed a significant longer length of hospital stay when compared to patients without sarcopenia after CRC surgery (weighted mean difference [WMD] = 1.29, 95%CI: 0.50-2.08, $P < 0.01$).

Nakanishi *et al*^[51] retrospectively analyzed 494 patients with CRC. They found that sarcopenia was not significantly correlated with operative time ($P = 0.93$), intraoperative bleeding ($P = 0.98$), or blood transfusion ($P = 0.19$), but was related with all postoperative morbidities ($P = 0.02$), especially those of major grade ($P = 0.0007$). In their multivariate models adjusted for some factors (sex, diabetes, tumor site, open or laparoscopic surgery), sarcopenia was independently associated with postoperative complications (OR: 1.82; $P = 0.001$). A recently reported retrospective cohort of 47 patients with locally advanced rectal cancer, showed that blood transfusions ($P = 0.001$) and overall postoperative complications ($P = 0.03$) were higher in sarcopenic patients, with almost four-fold higher odds of having complications as compared with non-sarcopenic (OR: 3.81)^[52]. However in that study, sarcopenia in rectal cancer was not associated with increased readmissions or length of stay.

Regarding the studies reporting on anastomotic leakage following surgical resection of CRC, mixed results have been reported^[51,61]. In a recent meta-analysis^[3], postoperative sepsis, anastomosis leakage and intestinal obstruction were the most common complications after CRC surgery. Patients with sarcopenia were found to have a significantly higher rate of postoperative infection than non-sarcopenic patients (OR: 2.21, $P < 0.01$), but the incidence of anastomosis leakage (OR: 0.73, 95%CI: 0.51-1.05, $P = 0.09$) and obstruction (OR: 1.13, $P = 0.73$) were similar^[3]. However, in a recent study by Herrod *et al*^[62], the authors reported that sarcopenia was associated with an increased risk of anastomotic leak (adjusted OR: 14.37; 95%CI: 1.37-150.04; $P = 0.026$). They also reported an increased risk of high grade complications, defined as Clavien-Dindo grade 3-4 (OR: 6.33; 95%CI: 1.6-24.24; $P = 0.007$). Chen *et al*^[63] described that patients with sarcopenia and visceral obesity had the highest incidence of complications, had longer hospital length of stays and higher hospitalization costs. Surgical complications included wound infection, anastomotic

leakage, intestinal obstruction and bleeding. In the same study, they found that laparoscopic surgery was a protective factor for total (OR: 0.431; 95%CI: 0.255-0.730; $P = 0.002$) and medical complications (OR: 0.187; 95%CI: 0.070-0.496; $P = 0.001$).

Pędziwiatr *et al*^[64] proposed that operating patients with laparoscopic surgery and within an Enhanced Recovery After Surgery protocol does not affect negatively the surgical results in patients with sarcopenia. They included 124 patients, 58.5% males, with 69.4% colon and 30.6% rectal cancers, and with a 27.4% prevalence of sarcopenia. The overall complication rate was similar between patients with and without sarcopenia (27.8% *vs* 29.4%, $P = 0.855$), and sarcopenia was not associated with delayed recovery.

EFFECTS OF SARCOPENIA ON CHEMOTHERAPY

Patients with sarcopenia seem susceptible to toxic effects during chemotherapy, requiring dose deescalations or treatment delays, which seems to decrease treatment efficacy^[24,65]. Oxaliplatin side effects include reduced nutritional intake and reduced physical activity^[66]. There is evidence from pre-clinical and animal studies that oxaliplatin may produce skeletal muscle damage by targeting mitochondria^[66,67]. Furthermore, muscle area of patients with metastatic CRC decreases significantly during three months of chemotherapy by 6.1% ($P < 0.001$)^[68].

Prado *et al*^[65] showed that lean body mass was a significant independent risk factor of 5-FU (fluorouracile) toxicity, specially in female patients with colon cancer (OR: 16.73; $P = 0.021$). The most common toxicity found was neutropenia. They determined that a cut point of 20 mg 5-FU/kg of lean body mass seemed to be the threshold for developing toxicities. The authors proposed that 5-FU dose should be normalized to lean body mass, instead of using the body surface area.

In a study of patients with stage III colon cancer ($n = 229$) who received adjuvant FOLFOX4 chemotherapy, a decrease of one standard deviation in the PI was associated with an increase in all grade 3-4 toxicities in univariate (OR: 1.69, 95%CI: 1.18-2.27) and multivariate (OR: 1.56, 95%CI: 1.05-2.38) analyses. This study also associated a decrement in the PI with the development of grade 3-4 neutropenia (OR: 1.56, 95%CI: 1.18-2.06)^[46].

The effect of sarcopenia on chemotherapy toxicity among metastatic CRC patients has been evaluated by Barret *et al*^[69]. Sarcopenia was observed in 71% of patients, and in multivariate analysis sarcopenia was the only factor associated with Grade 3-4 toxicities (OR: 13.55; 95%CI: 1.08-169.31; $P = 0.043$). Toxicities included severe nausea or vomiting, neutropenia and anemia, and peripheral neuropathy. Chemotherapy protocols included 5-FU alone or with oxaliplatin or irinotecan, and irinotecan alone. Sasaki *et al*^[70] described the skeletal muscle loss at 3 mo (but not at baseline) after systemic chemotherapy for metastatic CRC was associated with poor treatment response. Skeletal muscle loss was associated with an incidence of adverse events ($P = 0.01$), poor objective response rate ($P < 0.001$), and poor PFS ($P = 0.03$). Developing sarcopenia at the early phase of chemotherapy may have an effect on the time to treatment failure and to the chemotherapy response.

In the context of palliative systemic treatment regimens, SMM loss seems to be reversible and to be influenced by the intensity of systemic treatment^[66]. Kurk *et al*^[66] found that SMM loss during initial treatment with 6 cycles CAPOX-B (capecitabine + oxaliplatin + bevacizumab) was reversible during subsequent maintenance therapy with CAP-B (capecitabine + bevacizumab) or during observation, furthermore after reintroduction of intensive treatment (CAPOX-B) SMM decreased again. Although the precise mechanism of sarcopenia on chemotherapy had not been found, the muscle syndrome could influence on pharmacokinetic parameters, as well as sarcopenic patients could be more prone to complications and toxicities associated with chemotherapeutics^[71].

EFFECTS OF SARCOPENIA ON METASTATIC DISEASE

Increasing evidence demonstrates that loss of muscle mass is associated with worse outcomes in metastatic CRC^[72]. It seems that SMM loss is more frequent during periods of progressive disease and at the end of life^[72]. In a study that included 1270 individuals with first-time colonoscopy, Park *et al*^[73] found an association with sarcopenia and an increased risk of advanced colorectal neoplasia (Multivariate analysis OR: 2.347; 95%CI: 1.311-4.202; $P = 0.004$). The authors hypothesized about the relationship between common mechanisms and risk factors shared by sarcopenia and CRC progression pathways. Also, there is emerging evidence that various secretory

products from metastatic tumors (cytokines, microRNAs, exosomes) can influence host organs and promote sarcopenia^[28]. Patients with metachronous metastases lost three percent more muscle mass during initial systemic therapy in comparison with patients with synchronous metastases^[72].

In a recent study, Vashi *et al*^[47] described that among stage IV CRC patients ($n = 66$), those with sarcopenia had higher risk of mortality than those without it (HR: 4.0; $P = 0.001$). The results of this study are relevant because they adjusted the prognostic effect of sarcopenia for potential confounding effects such as malnutrition, age and sex. Da Cunha *et al*^[74] demonstrated that sarcopenia is associated with decreased PFS (HR: 1.78; $P = 0.048$) and OS (HR: 1.86; $P = 0.043$) in patients with metastatic CRC.

Approximately 30%-50% of CRC patients develop hepatic metastasis during the evolution of their disease. Among them, 25%-30% of patients with metastatic liver tumors are considered to be resectable. Complete resection or ablation of colorectal liver metastases (CLM) offers the best alternative for cure, with a 5-year survival of 50%-55% when complete resection is achieved^[12,16]. However, high complication rates following CLM resection are expected to be between 20%-50%, with a mortality rate less than 5%^[16]. Identification of high-risk patients and stratification its critical, but current classification tools are not totally successful. Sarcopenia as a predictor of outcome in CLM has been reported in several studies.

The effect of sarcopenia on survival of patients undergoing liver resection for CLM was analyzed in a series of 196 patients^[12]. They found a 19.4% prevalence of sarcopenia, and sarcopenia resulted to be an independent risk factor of worse recurrence-free (HR: 1.88; $P = 0.002$) and overall (HR: 2.53; $P < 0.001$) survival on patients undergoing metastases resection. In an other study of 259 patients undergoing liver resection for CLM, 16% of patients had sarcopenia^[16]. The presence of sarcopenia was associated with an increased risk of major postoperative complications (OR: 3.33; $P = 0.008$), longer hospital stays (6.6 *vs* 5.4 d; $P = 0.03$), and extended intensive care unit stay (> 2 d; $P = 0.004$). In this group of patients, sarcopenia was not predictive of RFS or OS. Other studies found similar results (no impact of sarcopenia on prognosis), and added to the findings that sarcopenia is associated with reduced functional liver volume^[75], and higher readmission rates when associated with obesity^[76].

Understanding the determinants of skeletal muscle mass loss during treatment in metastatic CRC may contribute to the development of interventions that could potentially avoid sarcopenia. Derksen *et al*^[72] found that patients with higher initial SMI, active smoking, and metachronous metastases are factors independently associated with SMI loss, while undergoing tumor resection before initial therapy was associated with a gain in SMI.

THERAPEUTIC STRATEGIES

Sarcopenia is a human condition that requires both prevention and treatment^[77]. Understanding the interactions between age and lifestyle factors with body composition is fundamental for preventive and therapeutic strategies^[26]. Therapeutic approaches are being tested on key molecules in signaling muscle catabolism and reversion of muscle wasting^[15]. Although anthropometric factors (age, race and ethnicity) and clinical factors (CRC stage, tumor biology) cannot be changed, some lifestyle risk factors are modi-fiable (comorbidities, exercise, diet, smoking)^[26]. Exercise and diet are common ways for prevention and treatment of sarcopenia for cancer patients. It has been described that physical activity interventions have the potential to reverse sarcopenia in cancer patients^[72].

A multimodal approach including nutritional support (dietary intake, high energy, high protein, and omega-3 fatty acids), exercise programs and orexigenic agents (ghrelin, anamorelin), could contribute to muscle mass preservation^[72]. Nutritional support with oral solutions supplemented with glutamine, leucine, the metabolic derivative of leucine (hydroxy methylbutyrate), and omega-3 fatty acids (eicosapentaenoic acid), are considered to improve muscle mass loss in cancer patients^[77,78].

Consulting with a nutritionist to assess the dietary patterns, the adequacy of calorie and protein intake, and the quality of calories ingested is recommended. A recent meta-analysis concluded that nutritional interventions may be effective in improving muscle strength after 3 mo of intervention, although this is based on very low-quality evidence^[79]. The international clinical practice guidelines for sarcopenia recommends protein supplementation and a protein rich diet for adults (specially older adults) with sarcopenia^[80].

According with the international clinical practice guidelines for sarcopenia, the pre-

scription of resistance based training could increase muscle strength, muscle mass and function^[80]. Examples of resistance training are free weights, elastic therapy bands, and dumbbells^[79,80]. Physical therapies and training programs are better tailored by physiotherapists^[80]. Increasing physical activity with exercise programs improves physical fitness, muscle strength and muscle function. These programs reduce cancer and treatment symptoms like fatigue and anxiety/depression^[77-79]. In patients with sarcopenia that are severely deconditioned, passive physical therapy like neuromuscular stimulation could be employed^[78]. Yoshimura *et al*^[79] reported that comprehensive training was effective in improving ASM ($P = 0.04$), usual walking speed ($P = 0.004$), maximum walking speed ($P < 0.001$), and knee extension strength ($P < 0.001$) after 3 mo of intervention.

Drug therapies for inducing muscle mass and strength included hormones and orexigenics. Some of the employed hormones are testosterone and selective androgen receptor modulators^[77,78]. Low testosterone levels has been associated with higher prevalence of sarcopenia, however supplementation has not been demonstrated to be effective in older patients with sarcopenia^[80]. Ghrelin and ghrelin analogues (anamorelin) stimulate appetite and muscle anabolism. Vitamin D supplementation improves muscle strength, but not muscle mass, although there is insufficient evidence to support the supplementation regime^[80,81]. Other possible candidate drugs for sarcopenia treatment include angiotensin-converting enzyme inhibitors, insulin-growth factor 1, and myostatin inhibitor^[77,79]. All these alternatives are under evaluation and the actual evidence to support or implement their use is very poor.

Even with all of the multimodal treatment strategies to decrease muscle loss, strength and function as described above, it is unknown if treatment for sarcopenia may improve CRC oncological outcomes. Furthermore, the current evidence and recommendations are based on very low quality studies, as found by current practice guidelines, systematic reviews and meta-analyses^[79-82].

CONCLUSION

Sarcopenia diagnosed by measuring muscle strength, muscle quantity (CT cross sectional L3 psoas mass area) and physical performance may negatively impact on the postoperative outcomes of patients with colorectal cancer undergoing surgical resection. Sarcopenia may also negatively impact on overall survival, disease-free survival, recurrence-free survival, and cancer-specific survival in patients with non-metastatic and metastatic colorectal cancer. CRC patients should ideally be screened for sarcopenia during their first visit, either by medical oncologists or surgeons, to inform the patients of the potential negative effects of sarcopenia. Prevention and treatment strategies for sarcopenia should be offered to patients. Addition of sarcopenia screening to the established clinical-pathological scores for patients undergoing oncological treatment (chemotherapy, radiotherapy or surgery) seems to be the next step for the best of care of CRC patients.

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