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**Sarcopenia in patients with colorectal cancer: A comprehensive review**

Vergara-Fernandez O *et al*. Sarcopenia in patients with colorectal cancer

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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.

**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 kg/m2) 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-1alpha, 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-alpha, 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[8]. 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 paraspinal 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 rent 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 (myosteatosis) 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 myosteatosis, 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 doubled the risk of morality, 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 SARCOPENIA 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 modifiable (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 prescription 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 phyisiotherapists[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.

**REFERENCES**

1 **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**: 394-424 [PMID: 30207593 DOI: 10.3322/caac.21492]

2 **Siegel RL**, Miller KD, Fedewa SA, Ahnen DJ, Meester RGS, Barzi A, Jemal A. Colorectal cancer statistics, 2017. *CA Cancer J Clin* 2017; **67**: 177-193 [PMID: 28248415 DOI: 10.3322/caac.21395]

3 **Sun G**, Li Y, Peng Y, Lu D, Zhang F, Cui X, Zhang Q, Li Z. Can sarcopenia be a predictor of prognosis for patients with non-metastatic colorectal cancer? A systematic review and meta-analysis. *Int J Colorectal Dis* 2018; **33**: 1419-1427 [PMID: 29987364 DOI: 10.1007/s00384-018-3128-1]

4 **Cederholm T**, Barazzoni R, Austin P, Ballmer P, Biolo G, Bischoff SC, Compher C, Correia I, Higashiguchi T, Holst M, Jensen GL, Malone A, Muscaritoli M, Nyulasi I, Pirlich M, Rothenberg E, Schindler K, Schneider SM, de van der Schueren MA, Sieber C, Valentini L, Yu JC, Van Gossum A, Singer P. ESPEN guidelines on definitions and terminology of clinical nutrition. *Clin Nutr* 2017; **36**: 49-64 [PMID: 27642056 DOI: 10.1016/j.clnu.2016.09.004]

5 **Peterson SJ**, Mozer M. Differentiating Sarcopenia and Cachexia Among Patients With Cancer. *Nutr Clin Pract* 2017; **32**: 30-39 [PMID: 28124947 DOI: 10.1177/0884533616680354]

6 **Petersen KF**, Befroy D, Dufour S, Dziura J, Ariyan C, Rothman DL, DiPietro L, Cline GW, Shulman GI. Mitochondrial dysfunction in the elderly: possible role in insulin resistance. *Science* 2003; **300**: 1140-1142 [PMID: 12750520 DOI: 10.1126/science.1082889]

7 **Cespedes Feliciano EM**, Avrutin E, Caan BJ, Boroian A, Mourtzakis M. Screening for low muscularity in colorectal cancer patients: a valid, clinic-friendly approach that predicts mortality. *J Cachexia Sarcopenia Muscle* 2018; **9**: 898-908 [PMID: 30066490 DOI: 10.1002/jcsm.12317]

8 **Levolger S**, van Vugt JL, de Bruin RW, IJzermans JN. Systematic review of sarcopenia in patients operated on for gastrointestinal and hepatopancreatobiliary malignancies. *Br J Surg* 2015; **102**: 1448-1458 [PMID: 26375617 DOI: 10.1002/bjs.9893]

9 **Cruz-Jentoft AJ**, Bahat G, Bauer J, Boirie Y, Bruyère O, Cederholm T, Cooper C, Landi F, Rolland Y, Sayer AA, Schneider SM, Sieber CC, Topinkova E, Vandewoude M, Visser M, Zamboni M; Writing Group for the European Working Group on Sarcopenia in Older People 2 (EWGSOP2), and the Extended Group for EWGSOP2. Sarcopenia: revised European consensus on definition and diagnosis. *Age Ageing* 2019; **48**: 16-31 [PMID: 30312372 DOI: 10.1093/ageing/afy169]

10 **Evans WJ**, Campbell WW. Sarcopenia and age-related changes in body composition and functional capacity. *J Nutr* 1993; **123**: 465-468 [PMID: 8429405 DOI: 10.1093/jn/123.suppl\_2.465]

11 **Rosenberg IH**. Sarcopenia: origins and clinical relevance. *J Nutr* 1997; **127**: 990S-991S [PMID: 9164280 DOI: 10.1093/jn/127.5.990S]

12 **van Vledder MG**, Levolger S, Ayez N, Verhoef C, Tran TC, Ijzermans JN. Body composition and outcome in patients undergoing resection of colorectal liver metastases. *Br J Surg* 2012; **99**: 550-557 [PMID: 22246799 DOI: 10.1002/bjs.7823]

13 **Cherin P**, Voronska E, Fraoucene N, de Jaeger C. Prevalence of sarcopenia among healthy ambulatory subjects: the sarcopenia begins from 45 years. *Aging Clin Exp Res* 2014; **26**: 137-146 [PMID: 24129803 DOI: 10.1007/s40520-013-0132-8]

14 **Huang DD**, Wang SL, Zhuang CL, Zheng BS, Lu JX, Chen FF, Zhou CJ, Shen X, Yu Z. Sarcopenia, as defined by low muscle mass, strength and physical performance, predicts complications after surgery for colorectal cancer. *Colorectal Dis* 2015; **17**: O256-O264 [PMID: 26194849 DOI: 10.1111/codi.13067]

15 **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**: 931-936 [PMID: 22871883 DOI: 10.1038/bjc.2012.350]

16 **Peng PD**, van Vledder MG, Tsai S, de Jong MC, Makary M, Ng J, Edil BH, Wolfgang CL, Schulick RD, Choti MA, Kamel I, Pawlik TM. Sarcopenia negatively impacts short-term outcomes in patients undergoing hepatic resection for colorectal liver metastasis. *HPB (Oxford)* 2011; **13**: 439-446 [PMID: 21689226 DOI: 10.1111/j.1477-2574.2011.00301.x]

17 **Liu P**, Hao Q, Hai S, Wang H, Cao L, Dong B. Sarcopenia as a predictor of all-cause mortality among community-dwelling older people: A systematic review and meta-analysis. *Maturitas* 2017; **103**: 16-22 [PMID: 28778327 DOI: 10.1016/j.maturitas.2017.04.007]

18 **Fielding RA**, Vellas B, Evans WJ, Bhasin S, Morley JE, Newman AB, Abellan van Kan G, Andrieu S, Bauer J, Breuille D, Cederholm T, Chandler J, De Meynard C, Donini L, Harris T, Kannt A, Keime Guibert F, Onder G, Papanicolaou D, Rolland Y, Rooks D, Sieber C, Souhami E, Verlaan S, Zamboni M. 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**: 249-256 [PMID: 21527165 DOI: 10.1016/j.jamda.2011.01.003]

19 **Morley JE**, Abbatecola AM, Argiles JM, Baracos V, Bauer J, Bhasin S, Cederholm T, Coats AJ, Cummings SR, Evans WJ, Fearon K, Ferrucci L, Fielding RA, Guralnik JM, Harris TB, Inui A, Kalantar-Zadeh K, Kirwan BA, Mantovani G, Muscaritoli M, Newman AB, Rossi-Fanelli F, Rosano GM, Roubenoff R, Schambelan M, Sokol GH, Storer TW, Vellas B, von Haehling S, Yeh SS, Anker SD; Society on Sarcopenia, Cachexia and Wasting Disorders Trialist Workshop. Sarcopenia with limited mobility: an international consensus. *J Am Med Dir Assoc* 2011; **12**: 403-409 [PMID: 21640657 DOI: 10.1016/j.jamda.2011.04.014]

20 **Muscaritoli M**, Anker SD, Argilés J, Aversa Z, Bauer JM, Biolo G, Boirie Y, Bosaeus I, Cederholm T, Costelli P, Fearon KC, Laviano A, Maggio M, Rossi Fanelli F, Schneider SM, Schols A, Sieber CC. 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**: 154-159 [PMID: 20060626 DOI: 10.1016/j.clnu.2009.12.004]

21 **Chen LK**, Lee WJ, Peng LN, Liu LK, Arai H, Akishita M; Asian Working Group for Sarcopenia. Recent Advances in Sarcopenia Research in Asia: 2016 Update From the Asian Working Group for Sarcopenia. *J Am Med Dir Assoc* 2016; **17**: 767.e1-767.e7 [PMID: 27372539 DOI: 10.1016/j.jamda.2016.05.016]

22 **Prado CM**, Wells JC, Smith SR, Stephan BC, Siervo M. Sarcopenic obesity: A Critical appraisal of the current evidence. *Clin Nutr* 2012; **31**: 583-601 [PMID: 22809635 DOI: 10.1016/j.clnu.2012.06.010]

23 **Prado CM**, Cushen SJ, Orsso CE, Ryan AM. Sarcopenia and cachexia in the era of obesity: clinical and nutritional impact. *Proc Nutr Soc* 2016; **75**: 188-198 [PMID: 26743210 DOI: 10.1017/S0029665115004279]

24 **Fearon K**, Strasser F, Anker SD, Bosaeus I, Bruera E, Fainsinger RL, Jatoi A, Loprinzi C, MacDonald N, Mantovani G, Davis M, Muscaritoli M, Ottery F, Radbruch L, Ravasco P, Walsh D, Wilcock A, Kaasa S, Baracos VE. Definition and classification of cancer cachexia: an international consensus. *Lancet Oncol* 2011; **12**: 489-495 [PMID: 21296615 DOI: 10.1016/S1470-2045(10)70218-7]

25 **Kim TN**, Choi KM. Sarcopenia: definition, epidemiology, and pathophysiology. *J Bone Metab* 2013; **20**: 1-10 [PMID: 24524049 DOI: 10.11005/jbm.2013.20.1.1]

26 **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; **9**: 654-663 [PMID: 29675984 DOI: 10.1002/jcsm.12301]

27 **Bowen TS**, Schuler G, Adams V. Skeletal muscle wasting in cachexia and sarcopenia: molecular pathophysiology and impact of exercise training. *J Cachexia Sarcopenia Muscle* 2015; **6**: 197-207 [PMID: 26401465 DOI: 10.1002/jcsm.12043]

28 **Okugawa Y**, Toiyama Y, Hur K, Yamamoto A, Yin C, Ide S, Kitajima T, Fujikawa H, Yasuda H, Koike Y, Okita Y, Hiro J, Yoshiyama S, Araki T, Miki C, McMillan DC, Goel A, Kusunoki M. Circulating miR-203 derived from metastatic tissues promotes myopenia in colorectal cancer patients. *J Cachexia Sarcopenia Muscle* 2019; **10**: 536-548 [PMID: 31091026 DOI: 10.1002/jcsm.12403]

29 **Rasmussen BB**, Fujita S, Wolfe RR, Mittendorfer B, Roy M, Rowe VL, Volpi E. Insulin resistance of muscle protein metabolism in aging. *FASEB J* 2006; **20**: 768-769 [PMID: 16464955 DOI: 10.1096/fj.05-4607fje]

30 **Altun M**, Besche HC, Overkleeft HS, Piccirillo R, Edelmann MJ, Kessler BM, Goldberg AL, Ulfhake B. Muscle wasting in aged, sarcopenic rats is associated with enhanced activity of the ubiquitin proteasome pathway. *J Biol Chem* 2010; **285**: 39597-39608 [PMID: 20940294 DOI: 10.1074/jbc.M110.129718]

31 **Sandri M**. Protein breakdown in muscle wasting: role of autophagy-lysosome and ubiquitin-proteasome. *Int J Biochem Cell Biol* 2013; **45**: 2121-2129 [PMID: 23665154 DOI: 10.1016/j.biocel.2013.04.023]

32 **Visser M**, Pahor M, Taaffe DR, Goodpaster BH, Simonsick EM, Newman AB, Nevitt M, Harris TB. Relationship of interleukin-6 and tumor necrosis factor-alpha with muscle mass and muscle strength in elderly men and women: the Health ABC Study. *J Gerontol A Biol Sci Med Sci* 2002; **57**: M326-M332 [PMID: 11983728 DOI: 10.1093/gerona/57.5.m326]

33 **Tedesco FS**, Dellavalle A, Diaz-Manera J, Messina G, Cossu G. Repairing skeletal muscle: regenerative potential of skeletal muscle stem cells. *J Clin Invest* 2010; **120**: 11-19 [PMID: 20051632 DOI: 10.1172/JCI40373]

34 **Bua E**, Johnson J, Herbst A, Delong B, McKenzie D, Salamat S, Aiken JM. Mitochondrial DNA-deletion mutations accumulate intracellularly to detrimental levels in aged human skeletal muscle fibers. *Am J Hum Genet* 2006; **79**: 469-480 [PMID: 16909385 DOI: 10.1086/507132]

35 **Tosato M**, Marzetti E, Cesari M, Savera G, Miller RR, Bernabei R, Landi F, Calvani R. Measurement of muscle mass in sarcopenia: from imaging to biochemical markers. *Aging Clin Exp Res* 2017; **29**: 19-27 [PMID: 28176249 DOI: 10.1007/s40520-016-0717-0]

36 **Jones DJ**, Lal S, Strauss BJ, Todd C, Pilling M, Burden ST. Measurement of Muscle Mass and Sarcopenia Using Anthropometry, Bioelectrical Impedance, and Computed Tomography in Surgical Patients with Colorectal Malignancy: Comparison of Agreement Between Methods. *Nutr Cancer* 2019; 1-10 [PMID: 31482717 DOI: 10.1080/01635581.2019.1659381]

37 **Landi F**, Onder G, Russo A, Liperoti R, Tosato M, Martone AM, Capoluongo E, Bernabei R. Calf circumference, frailty and physical performance among older adults living in the community. *Clin Nutr* 2014; **33**: 539-544 [PMID: 23948128 DOI: 10.1016/j.clnu.2013.07.013]

38 **Podsiadlo D**, Richardson S. The timed "Up & Go": a test of basic functional mobility for frail elderly persons. *J Am Geriatr Soc* 1991; **39**: 142-148 [PMID: 1991946 DOI: 10.1111/j.1532-5415.1991.tb01616.x]

39 **Pavasini R**, Guralnik J, Brown JC, di Bari M, Cesari M, Landi F, Vaes B, Legrand D, Verghese J, Wang C, Stenholm S, Ferrucci L, Lai JC, Bartes AA, Espaulella J, Ferrer M, Lim JY, Ensrud KE, Cawthon P, Turusheva A, Frolova E, Rolland Y, Lauwers V, Corsonello A, Kirk GD, Ferrari R, Volpato S, Campo G. Short Physical Performance Battery and all-cause mortality: systematic review and meta-analysis. *BMC Med* 2016; **14**: 215 [PMID: 28003033 DOI: 10.1186/s12916-016-0763-7]

40 **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 [PMID: 18923576 DOI: 10.1139/H08-075]

41 **Baracos VE**. Psoas as a sentinel muscle for sarcopenia: a flawed premise. *J Cachexia Sarcopenia Muscle* 2017; **8**: 527-528 [PMID: 28675689 DOI: 10.1002/jcsm.12221]

42 **Perkisas S,** Baudry S, Jürgen BauerDavid BeckwéeAnne-Marie De Cock, Hans Hobbelen, Harriët Jager-Wittenaar, Agnieszka Kasiukiewicz, Francesco Landi, Ester Marco, Ana Merello, Karolina Piotrowicz, Elisabet Sanchez, Dolores Sanchez-Rodriguez, Aldo Scafoglieri, Alfonso Cruz-Jentoft, Maurits Vandewoude. SARCUS working group on behalf of the Sarcopenia Special Interest Group of the European Geriatric Medicine Society. Application of ultrasound for muscle assessment in sarcopenia: towards standardized measurements. Eur J Med 2018; 9: 739-757 [DOI: 10.1007/s41999-018-0104-9]

43 **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**: 199-211 [PMID: 26786393 DOI: 10.1017/S002966511500419X]

44 **Prado CM**, Lieffers JR, McCargar LJ, Reiman T, Sawyer MB, Martin L, Baracos VE. 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**: 629-635 [PMID: 18539529 DOI: 10.1016/S1470-2045(08)70153-0]

45 **Womer AL**, Brady JT, Kalisz K, Patel ND, Paspulati RM, Reynolds HL, Pawlik TM, Steele SR. Do psoas muscle area and volume correlate with postoperative complications in patients undergoing rectal cancer resection? *Am J Surg* 2018; **215**: 503-506 [PMID: 29277239 DOI: 10.1016/j.amjsurg.2017.10.052]

46 **Jung HW**, Kim JW, Kim JY, Kim SW, Yang HK, Lee JW, Lee KW, Kim DW, Kang SB, Kim KI, Kim CH, Kim JH. Effect of muscle mass on toxicity and survival in patients with colon cancer undergoing adjuvant chemotherapy. *Support Care Cancer* 2015; **23**: 687-694 [PMID: 25163434 DOI: 10.1007/s00520-014-2418-6]

47 **Vashi PG**, Gorsuch K, Wan L, Hill D, Block C, Gupta D. Sarcopenia supersedes subjective global assessment as a predictor of survival in colorectal cancer. *PLoS One* 2019; **14**: e0218761 [PMID: 31220163 DOI: 10.1371/journal.pone.0218761]

48 **Kroenke CH**, Prado CM, Meyerhardt JA, Weltzien EK, Xiao J, Cespedes Feliciano EM, Caan BJ. Muscle radiodensity and mortality in patients with colorectal cancer. *Cancer* 2018; **124**: 3008-3015 [PMID: 29797673 DOI: 10.1002/cncr.31405]

49 **Clark RV**, Walker AC, Miller RR, O'Connor-Semmes RL, Ravussin E, Cefalu WT. Creatine ( methyl-d3) dilution in urine for estimation of total body skeletal muscle mass: accuracy and variability vs. MRI and DXA. *J Appl Physiol (1985)* 2018; **124**: 1-9 [PMID: 28860169 DOI: 10.1152/japplphysiol.00455.2016]

50 **Miyamoto Y**, Baba Y, Sakamoto Y, Ohuchi M, Tokunaga R, Kurashige J, Hiyoshi Y, Iwagami S, Yoshida N, Yoshida M, Watanabe M, Baba H. Sarcopenia is a Negative Prognostic Factor After Curative Resection of Colorectal Cancer. *Ann Surg Oncol* 2015; **22**: 2663-2668 [PMID: 25564158 DOI: 10.1245/s10434-014-4281-6]

51 **Nakanishi R**, Oki E, Sasaki S, Hirose K, Jogo T, Edahiro K, Korehisa S, Taniguchi D, Kudo K, Kurashige J, Sugiyama M, Nakashima Y, Ohgaki K, Saeki H, Maehara Y. Sarcopenia is an independent predictor of complications after colorectal cancer surgery. *Surg Today* 2018; **48**: 151-157 [PMID: 28699003 DOI: 10.1007/s00595-017-1564-0]

52 **Jochum SB**, Kistner M, Wood EH, Hoscheit M, Nowak L, Poirier J, Eberhardt JM, Saclarides TJ, Hayden DM. Is sarcopenia a better predictor of complications than body mass index? Sarcopenia and surgical outcomes in patients with rectal cancer. *Colorectal Dis* 2019; **21**: 1372-1378 [PMID: 31276286 DOI: 10.1111/codi.14751]

53 **Xiao J**, Caan BJ, Cespedes Feliciano EM, Meyerhardt JA, Kroenke CH, Baracos VE, Weltzien E, Kwan ML, Alexeeff SE, Castillo AL, Prado CM. The association of medical and demographic characteristics with sarcopenia and low muscle radiodensity in patients with nonmetastatic colorectal cancer. *Am J Clin Nutr* 2019; **109**: 615-625 [PMID: 30850836 DOI: 10.1093/ajcn/nqy328]

54 **Brown JC**, Caan BJ, Meyerhardt JA, Weltzien E, Xiao J, Cespedes Feliciano EM, Kroenke CH, Castillo A, Kwan ML, Prado CM. The deterioration of muscle mass and radiodensity is prognostic of poor survival in stage I-III colorectal cancer: a population-based cohort study (C-SCANS). *J Cachexia Sarcopenia Muscle* 2018; **9**: 664-672 [PMID: 29766660 DOI: 10.1002/jcsm.12305]

55 **Deng CY**, Lin YC, Wu JS, Cheung YC, Fan CW, Yeh KY, McMahon CJ. Progressive Sarcopenia in Patients With Colorectal Cancer Predicts Survival. *AJR Am J Roentgenol* 2018; **210**: 526-532 [PMID: 29364725 DOI: 10.2214/AJR.17.18020]

56 **Hopkins JJ**, Reif RL, Bigam DL, Baracos VE, Eurich DT, Sawyer MB. The Impact of Muscle and Adipose Tissue on Long-term Survival in Patients With Stage I to III Colorectal Cancer. *Dis Colon Rectum* 2019; **62**: 549-560 [PMID: 30789442 DOI: 10.1097/DCR.0000000000001352]

57 **Caan BJ**, Meyerhardt JA, Kroenke CH, Alexeeff S, Xiao J, Weltzien E, Feliciano EC, Castillo AL, Quesenberry CP, Kwan ML, Prado CM. Explaining the Obesity Paradox: The Association between Body Composition and Colorectal Cancer Survival (C-SCANS Study). *Cancer Epidemiol Biomarkers Prev* 2017; **26**: 1008-1015 [PMID: 28506965 DOI: 10.1158/1055-9965.EPI-17-0200]

58 **Park SE**, Hwang IG, Choi CH, Kang H, Kim BG, Park BK, Cha SJ, Jang JS, Choi JH. Sarcopenia is poor prognostic factor in older patients with locally advanced rectal cancer who received preoperative or postoperative chemoradiotherapy. *Medicine (Baltimore)* 2018; **97**: e13363 [PMID: 30508928 DOI: 10.1097/MD.0000000000013363]

59 **Choi MH**, Oh SN, Lee IK, Oh ST, Won DD. Sarcopenia is negatively associated with long-term outcomes in locally advanced rectal cancer. *J Cachexia Sarcopenia Muscle* 2018; **9**: 53-59 [PMID: 28849630 DOI: 10.1002/jcsm.12234]

60 **Dolan DR**, Knight KA, Maguire S, Moug SJ. The relationship between sarcopenia and survival at 1 year in patients having elective colorectal cancer surgery. *Tech Coloproctol* 2019; **23**: 877-885 [PMID: 31486988 DOI: 10.1007/s10151-019-02072-0]

61 **Reisinger KW**, van Vugt JL, Tegels JJ, Snijders C, Hulsewé KW, Hoofwijk AG, Stoot JH, Von Meyenfeldt MF, Beets GL, Derikx JP, Poeze M. Functional compromise reflected by sarcopenia, frailty, and nutritional depletion predicts adverse postoperative outcome after colorectal cancer surgery. *Ann Surg* 2015; **261**: 345-352 [PMID: 24651133 DOI: 10.1097/SLA.0000000000000628]

62 **Herrod PJJ**, Boyd-Carson H, Doleman B, Trotter J, Schlichtemeier S, Sathanapally G, Somerville J, Williams JP, Lund JN. Quick and simple; psoas density measurement is an independent predictor of anastomotic leak and other complications after colorectal resection. *Tech Coloproctol* 2019; **23**: 129-134 [PMID: 30790102 DOI: 10.1007/s10151-019-1928-0]

63 **Chen WZ**, Chen XD, Ma LL, Zhang FM, Lin J, Zhuang CL, Yu Z, Chen XL, Chen XX. Impact of Visceral Obesity and Sarcopenia on Short-Term Outcomes After Colorectal Cancer Surgery. *Dig Dis Sci* 2018; **63**: 1620-1630 [PMID: 29549473 DOI: 10.1007/s10620-018-5019-2]

64 **Pędziwiatr M**, Pisarska M, Major P, Grochowska A, Matłok M, Przęczek K, Stefura T, Budzyński A, Kłęk S. Laparoscopic colorectal cancer surgery combined with enhanced recovery after surgery protocol (ERAS) reduces the negative impact of sarcopenia on short-term outcomes. *Eur J Surg Oncol* 2016; **42**: 779-787 [PMID: 27156809 DOI: 10.1016/j.ejso.2016.03.037]

65 **Prado CM**, Baracos VE, McCargar LJ, Mourtzakis M, Mulder KE, Reiman T, Butts CA, Scarfe AG, Sawyer MB. Body composition as an independent determinant of 5-fluorouracil-based chemotherapy toxicity. *Clin Cancer Res* 2007; **13**: 3264-3268 [PMID: 17545532 DOI: 10.1158/1078-0432.CCR-06-3067]

66 **Kurk SA**, Peeters PHM, Dorresteijn B, de Jong PA, Jourdan M, Kuijf HJ, Punt CJA, Koopman M, May AM. Impact of different palliative systemic treatments on skeletal muscle mass in metastatic colorectal cancer patients. *J Cachexia Sarcopenia Muscle* 2018; **9**: 909-919 [PMID: 30144305 DOI: 10.1002/jcsm.12337]

67 **Sorensen JC**, Cheregi BD, Timpani CA, Nurgali K, Hayes A, Rybalka E. Mitochondria: Inadvertent targets in chemotherapy-induced skeletal muscle toxicity and wasting? *Cancer Chemother Pharmacol* 2016; **78**: 673-683 [PMID: 27167634 DOI: 10.1007/s00280-016-3045-3]

68 **Blauwhoff-Buskermolen S**, Versteeg KS, de van der Schueren MA, den Braver NR, Berkhof J, Langius JA, Verheul HM. Loss of Muscle Mass During Chemotherapy Is Predictive for Poor Survival of Patients With Metastatic Colorectal Cancer. *J Clin Oncol* 2016; **34**: 1339-1344 [PMID: 26903572 DOI: 10.1200/JCO.2015.63.6043]

69 **Barret M**, Antoun S, Dalban C, Malka D, Mansourbakht T, Zaanan A, Latko E, Taieb J. Sarcopenia is linked to treatment toxicity in patients with metastatic colorectal cancer. *Nutr Cancer* 2014; **66**: 583-589 [PMID: 24707897 DOI: 10.1080/01635581.2014.894103]

70 **Sasaki S**, Oki E, Saeki H, Shimose T, Sakamoto S, Hu Q, Kudo K, Tsuda Y, Nakashima Y, Ando K, Akagi Y, Kakeji Y, Baba H, Maehara Y. Skeletal muscle loss during systemic chemotherapy for colorectal cancer indicates treatment response: a pooled analysis of a multicenter clinical trial (KSCC 1605-A). *Int J Clin Oncol* 2019; **24**: 1204-1213 [PMID: 31062115 DOI: 10.1007/s10147-019-01460-8]

71 **Antoun S**, Borget I, Lanoy E. Impact of sarcopenia on the prognosis and treatment toxicities in patients diagnosed with cancer. *Curr Opin Support Palliat Care* 2013; **7**: 383-389 [PMID: 24189893 DOI: 10.1097/SPC.0000000000000011]

72 **Derksen JWG**, Kurk SA, Oskam MJ, Peeters PHM, Punt CJA, Koopman M, May AM. Factors Contributing to Cancer-Related Muscle Wasting During First-Line Systemic Treatment for Metastatic Colorectal Cancer. *JNCI Cancer Spectr* 2019; **3**: pkz014 [PMID: 31360897 DOI: 10.1093/jncics/pkz016]

73 **Park YS**, Kim JW, Kim BG, Lee KL, Lee JK, Kim JS, Koh SJ. Sarcopenia is associated with an increased risk of advanced colorectal neoplasia. *Int J Colorectal Dis* 2017; **32**: 557-565 [PMID: 28013337 DOI: 10.1007/s00384-016-2738-8]

74 **da Cunha LP**, Silveira MN, Mendes MCS, Costa FO, Macedo LT, de Siqueira NS, Carvalheira JBC. Sarcopenia as an independent prognostic factor in patients with metastatic colorectal cancer: A retrospective evaluation. *Clin Nutr ESPEN* 2019; **32**: 107-112 [PMID: 31221274 DOI: 10.1016/j.clnesp.2019.04.004]

75 **Dello SA**, Lodewick TM, van Dam RM, Reisinger KW, van den Broek MA, von Meyenfeldt MF, Bemelmans MH, Olde Damink SW, Dejong CH. Sarcopenia negatively affects preoperative total functional liver volume in patients undergoing liver resection. *HPB (Oxford)* 2013; **15**: 165-169 [PMID: 23020663 DOI: 10.1111/j.1477-2574.2012.00517.x]

76 **Lodewick TM**, van Nijnatten TJ, van Dam RM, van Mierlo K, Dello SA, Neumann UP, Olde Damink SW, Dejong CH. Are sarcopenia, obesity and sarcopenic obesity predictive of outcome in patients with colorectal liver metastases? *HPB (Oxford)* 2015; **17**: 438-446 [PMID: 25512239 DOI: 10.1111/hpb.12373]

77 **Brotto M**, Abreu EL. Sarcopenia: pharmacology of today and tomorrow. *J Pharmacol Exp Ther* 2012; **343**: 540-546 [PMID: 22929991 DOI: 10.1124/jpet.112.191759]

78 **Hilmi M**, Jouinot A, Burns R, Pigneur F, Mounier R, Gondin J, Neuzillet C, Goldwasser F. Body composition and sarcopenia: The next-generation of personalized oncology and pharmacology? *Pharmacol Ther* 2019; **196**: 135-159 [PMID: 30521882 DOI: 10.1016/j.pharmthera.2018.12.003]

79 **Yoshimura Y**, Wakabayashi H, Yamada M, Kim H, Harada A, Arai H. Interventions for Treating Sarcopenia: A Systematic Review and Meta-Analysis of Randomized Controlled Studies. *J Am Med Dir Assoc* 2017; **18**: 553.e1-553.e16 [PMID: 28549707 DOI: 10.1016/j.jamda.2017.03.019]

80 **Dent E**, Morley JE, Cruz-Jentoft AJ, Arai H, Kritchevsky SB, Guralnik J, Bauer JM, Pahor M, Clark BC, Cesari M, Ruiz J, Sieber CC, Aubertin-Leheudre M, Waters DL, Visvanathan R, Landi F, Villareal DT, Fielding R, Won CW, Theou O, Martin FC, Dong B, Woo J, Flicker L, Ferrucci L, Merchant RA, Cao L, Cederholm T, Ribeiro SML, Rodríguez-Mañas L, Anker SD, Lundy J, Gutiérrez Robledo LM, Bautmans I, Aprahamian I, Schols JMGA, Izquierdo M, Vellas B. International Clinical Practice Guidelines for Sarcopenia (ICFSR): Screening, Diagnosis and Management. *J Nutr Health Aging* 2018; **22**: 1148-1161 [PMID: 30498820 DOI: 10.1007/s12603-018-1139-9]

81 **Beaudart C**, Buckinx F, Rabenda V, Gillain S, Cavalier E, Slomian J, Petermans J, Reginster JY, Bruyère O. The effects of vitamin D on skeletal muscle strength, muscle mass, and muscle power: a systematic review and meta-analysis of randomized controlled trials. *J Clin Endocrinol Metab* 2014; **99**: 4336-4345 [PMID: 25033068 DOI: 10.1210/jc.2014-1742]

82 **Cruz-Jentoft AJ**, Landi F, Schneider SM, Zúñiga C, Arai H, Boirie Y, Chen LK, Fielding RA, Martin FC, Michel JP, Sieber C, Stout JR, Studenski SA, Vellas B, Woo J, Zamboni M, Cederholm T. Prevalence of and interventions for sarcopenia in ageing adults: a systematic review. Report of the International Sarcopenia Initiative (EWGSOP and IWGS). *Age Ageing* 2014; **43**: 748-759 [PMID: 25241753 DOI: 10.1093/ageing/afu115]

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**Figure Legends**

**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 *et al*[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 *et al*[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 *et al*[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 cm2/m2 women, < 43 cm2/m2 men)/ 44.4% prevalence |  | Sarcopenia reduced PFS (*P* < 0.001), HR: 1.78. | Sarcopenic reduced OS (HR: 1.86, *P* = 0.043) |
| Jochum *et al*[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 *et al*[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 *et al*[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 cm2/m2 (< 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 *et al*[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 (cm2) at L3, SMI or PI. (49 cm2/m2 men, 31 cm2/m2 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 *et al*[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 *et al*[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 (cm2) at L3, SMI. (52.4 cm2/m2 men, 38.5 cm2/m2 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 *et al*[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 cm2/m2, *P* = 0.04) and TPV  (26.7 *vs* 42.2 cm2/m2, *P* = 0.04) |  |  |
| Choi *et al*[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 cm2/m2 men, 38.5 cm2/m2 women)/ 39.4% prevalence |  | Sarcopenia did not shorten DFS (*P* = 0.900) | Sarcopenic had shorter OS (*P* = 0.004) |
| Miyamoto *et al*[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 (m2)/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 *et al*[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 cm2/m2 men, 38.5 cm2/m2 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 *et al*[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 *et al*[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(cm2)/height (m2)/ 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 *et al*[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 cm2/m2 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 *et al*[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/m2)/ 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.