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REVIEW ARTICLE

Sarcopenia in gastric cancer: when the loss costs too much

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Abstract Sarcopenia is a complex syndrome characterized by progressive and generalized loss of skeletal muscle mass and strength. Malignancy is a major determinant of sarcopenia, and gastric cancer (GC) is among the most common causes of this phenomenon. As sarcopenia is a well-recognized poor prognostic feature in GC and has been associated with worse tolerance of surgical and medical treatments, members of the multidisciplinary team should be aware of the clinical relevance, pathogenic mechanisms, and potential treatments for this syndrome. The importance of sarcopenia is often underestimated in everyday practice and clinical trials, particularly among elderly or fragile patients. As treatment options are improving in all disease stages, deeper knowledge and greater attention to the metabolic balance in GC patients could further increase the benefit of novel therapeutic strategies and dramatically impact on quality of life. In this review, we describe the role of sarcopenia in different phases of GC progression. Our aim is to provide oncologists and surgeons dealing with GC patients with a useful tool for comprehensive assessment and timely management of this potentially life-threatening condition.

Introduction

Gastric cancer (GC) is the fifth most common cancer and the third leading cause of cancer death worldwide [1]. Despite some improvements, GC prognosis is still poor, with surgical resection remaining the most effective therapy for potentially curable GC. However, as the population ages and an increasing number of older patients requires complex gastrointestinal surgical procedures, gastrectomy is associated with higher complication and postoperative mortality rates [2], while the underpinning cancer may promote muscle atrophy, particularly in the elderly.

The definition of sarcopenia encompasses decreased muscle strength, fatigue and metabolic disorders initiated by a reduction in skeletal muscle mass, which is characterized by atrophy and reduction of muscle tissue quality. In the sarcopenic processes, muscle fibers are replaced by fibrotic tissue, resulting in increased frailty and function deterioration, with neuromuscular junction degeneration and alterations in oxidative stress and muscle metabolism [3].

The pathogenesis of sarcopenia is complex and multi-factorial. It may include disuse, altered endocrine function, chronic diseases, inflammation, insulin resistance, and nutritional deficiencies [4]. In conditions such as malignancy, rheumatoid arthritis, and aging, the loss of muscle mass may be associated with preserved or even increased

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body fat content. Consequently, there could be marked weakness despite normal weight; this condition is called "sarcopenic obesity" [5] (Fig. 1).

Obesity and sarcopenia may potentiate each other and act synergistically causing physical impairment and metabolic disorders, and worsening prognosis. Moreover, increasing visceral fat content may promote the secretion of proinflammatory cytokines, leading to a catabolic effect on muscles, as well as insulin resistance [6]. Several studies have recently reported that inflammation may be directly associated with sarcopenia [7].

Although sarcopenia may be a component of cachexia, the two conditions differ. "Cachexia" is a term originating from the Greek *kakos* and *hexis,* meaning "bad condition" and defining those patients who lose more than 5% of body weight within 12 months or less [8]. Among GC patients, about 85% develop cachexia [9]. The cachectic state is a life-threatening syndrome observed in many pathological conditions other than cancer, such as chronic obstructive pulmonary disease, sepsis, and chronic heart failure [10, 11]. It encompasses skeletal muscle and adipose tissue loss, and it is frequently associated with muscle atrophy and a deregulated metabolic state with increased basal energy expenditure and resistance to conventional nutritional support [12]. In contrast, the nonmuscle protein compartment is relatively preserved, thus distinguishing cachexia from starvation [13]. Additionally, cachexia–associated cytokines are able to cross the blood–brain barrier and modify the activity of hunger regulatory systems. As a result, cancer patients with cachexia often develop anorexia, the incidence rate of which ranges from 15% to 40% [14].

Cachexia contributes substantially to morbidity and mortality in cancer patients, accounting for more than 20% of cancer deaths [12, 15] [15]. Chronic inflammation with elevated levels of circulating inflammatory cytokines is consistently observed in cachectic cancer patients. Tumor cells produce both proinflammatory and procachectic factors, which stimulate a host inflammatory response. Procachectic factors include proteolysis-inducing and lipid-mobilizing factors [12, 16]. Inflammatory cytokines may trigger muscle wasting by increasing the level of nuclear factor κB or by causing the release of other cytokines. Tumor necrosis factor α and proteolysis-inducing factor cause skeletal muscle atrophy in cachectic patients as they both increase protein degradation through the ubiquitin–proteasome pathway and reduce protein synthesis through phosphorylation of eukaryotic initiation factor 2α [17]. Other factors overexpressed in cancer cachexia include angiotensin II, myostatin, and activin A, whose upregulation inhibits muscle growth [9].
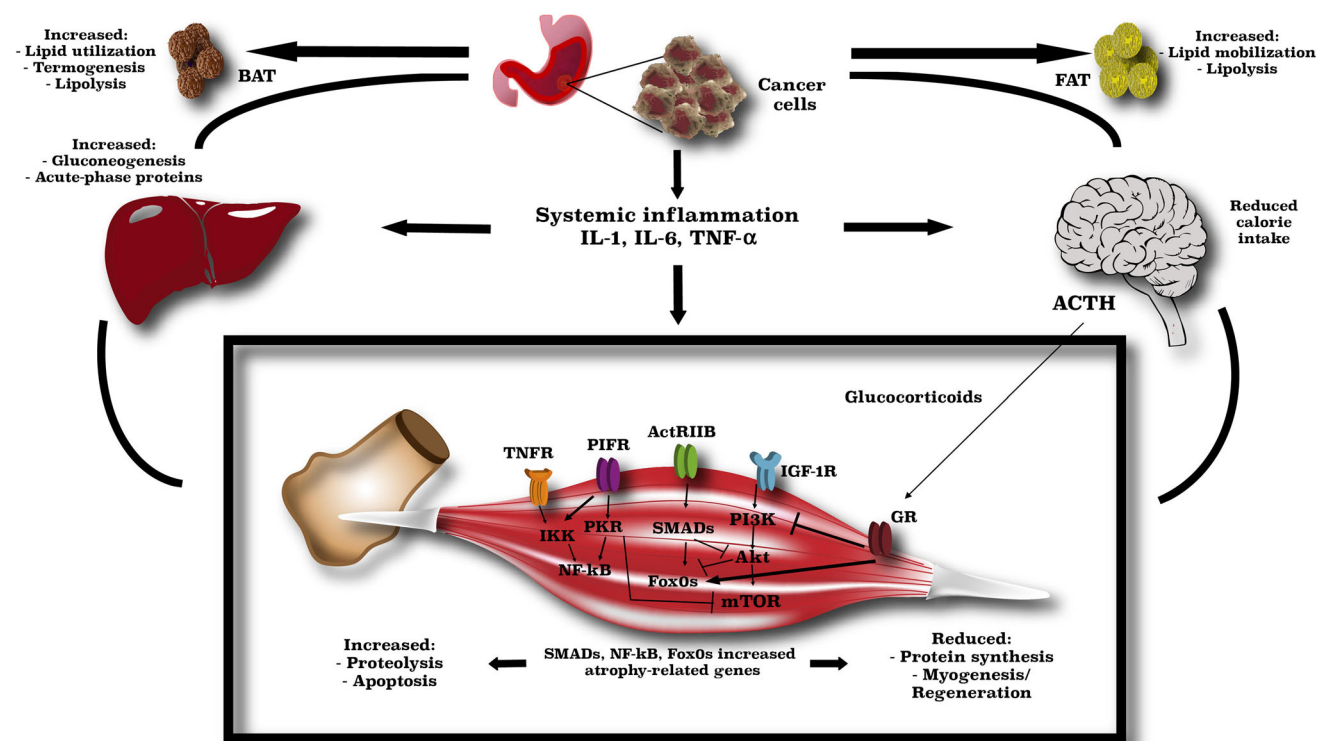

Fig. 1 Principal molecular pathways underpinning sarcopenia development. *ACTH* adrenocorticotropic hormone, *ActRIIB*, *BAT* brown adipose tissue, *GR* glucocorticoid receptor, *IGF-1R* insulin-like growth factor 1 receptor, *IL* interleukin, *IKK* IκB kinase, *mTOR* mammalian target of rapamycin, *NF-κB* nuclear factor κB, *PI3K* phosphatidylinositol 3-kinase, *PIFR*, *PKR*, *TNF* tumor necrosis factor, *TNFR* tumor necrosis factor receptor

Additionally, a number of neuroendocrine factors may also be deregulated, leading to insulin resistance, reduced anabolic activity, and elevated cortisol levels, and are potential targets for therapeutic interventions [16].

Here we review the role of sarcopenia onset in the management of GC to better understand its prognostic impact and potential improvements in all the settings of GC treatment.

Impact of sarcopenia on the surgical management of GC

Despite the development of new therapeutic options, gastric surgery with adequate lymph node dissection remains the mainstay of treatment for patients with resectable GC [18, 19]. However, gastrectomy is associated with significant risks of postoperative complications, morbidity, and death [20]. Moreover, GC mainly affects elderly people, and the association between advanced age and less favorable postoperative outcomes has been widely demonstrated [21, 22]. In addition, since the incidence of malnutrition in GC patients ranges from 60% to 85% [23, 24] and represents a well-known prognostic factor and an important determinant of frailty, a preoperative nutritional assessment is a key step to overcome possible complications.

Sarcopenia is an independent predictor of postsurgical outcomes in many types of gastrointestinal cancers [25–27], including GC [19]. The American College of Surgeons highlighted the importance of incorporating both sarcopenia and frailty in the preoperative risk assessment of older GC patients [28]. Tegels et al. [29] described a strong correlation between these two factors and postoperative mortality after gastric surgery. Additionally, preoperative hypolbuminemia and poor nutritional status, low hemoglobin levels, and the presence of comorbidities such as diabetes were associated with sarcopenia, frailty, and consequently poor short-term and long-term outcomes [22, 30, 31]. The reasons why sarcopenia independently predicts major complications in GC patients undergoing gastrectomy has been hypothesized [2]. Firstly, the association between sarcopenia and indexes of poor nutritional status (low BMI, low albumin levels) could increase the postsurgical complication rate [32]. Secondly, the loss of muscle mass and function would decrease physical ability and autonomy in daily activities, hindering the normal postoperative recovery [33]. Thirdly, sarcopenia correlates with a higher postsurgical infection rate, longer hospitalization, more frequent need for mechanical ventilation, and a greater number of hospital readmissions and rehabilitation programs [34], with increased health care costs [35].

With respect to long-term postsurgical outcome, sarcopenia was independently associated with overall survival and disease-free survival. Compared with indolent tumors, cancers with more aggressive behavior tended to have higher metabolic activity, leading to systemic inflammation and sarcopenia [36]. Some authors have also suggested the potential role of myokines, reporting an increased rate of GC relapse due to the depletion of muscle mass and the consequent reduction of myokine secretion; these molecules seem to inhibit the growth of cancer cells [37]. Moreover, sarcopenia was associated with toxicity in GC patients undergoing neoadjuvant [38] or adjuvant [2] treatment, leading to early discontinuation of chemotherapy, reduced efficacy of anticancer drugs, and poor prognosis. Finally, the previously mentioned high postoperative complication rate contributes to worse long-term prognosis [19, 39].

The effect on overall survival and disease-free survival seems to be more evident in stage II and stage III GC patients; Zhuang et al. [2] found that sarcopenic patients had a significantly shorter overall survival (hazard ratio 1.653, $p < 0.001$) and a significantly lower disease-free survival rate (hazard ratio 1.620, $p < 0.001$) than nonsarcopenic patients when adjustment was made for disease stage. This is probably due to the most likely development of sarcopenia in patients with more aggressive tumors.

Notably, different stages of sarcopenia as defined by the European Working Group on Sarcopenia [5] seem to impact differently on postoperative outcome. Huang et al. [40] highlighted the importance of sarcopenia classification in stratifying the risk of postoperative complications. They reported worse postgastrectomy outcomes with advancing sarcopenia stages; furthermore, the three-grade classification (presarcopenia, sarcopenia, and severe sarcopenia) seemed to independently predict postoperative complications. To distinguish the different grades of sarcopenia, it is crucial to evaluate not only skeletal muscle mass but also muscle function and physical ability.

Sarcopenic obesity is another emerging point to consider in the preoperative evaluation of GC patients. A sixfold increased risk of postoperative complications in obese sarcopenic patients undergoing gastrectomy has been reported [41, 42], as well as a higher risk of infection after laparoscopic gastrectomy.

Finally, the early integration of nutritional screening [23] and prehabilitation programs such as preoperative exercises to increase muscle mass combined with personalized nutritional support [40] was demonstrated to be crucial in reversing sarcopenia and improving short-term and long-term gastrectomy-related outcomes.

Nutrition in GC patients: risk assessments and nutritional treatment

Historically, malnutrition has been recognized as an important prognostic factor in cancer patients, with a shorter survival reported in patients who experienced

weight loss before chemotherapy [43]. In GC patients, malnutrition may arise from the obstructive effect of the tumor [12] and may be increased by treatment-related side effects.

Beyond anthropometric measures, biochemical and functional indicators such as C-reactive protein and albumin blood concentration are helpful to identify malnutrition through grading scales for a risk assessment score [44]. In recent years, several tools for the evaluation of nutritional status have been developed, such as the Mini Nutritional Assessment (MNA) [45] and the Subjective Global Assessment (SGA) [46]. The first one was developed to provide a quick nutritional assessment of elderly patients through the evaluation of their height, weight, weight loss, lifestyle, dietary intake, mobility, and comorbidities. After its validation in clinical practice, it became a useful tool also in oncology. The SGA was compared with six other objective techniques (serum albumin level, transferrin level, anthropometry, ideal weight, body fat percentage, total lymphocyte count, and creatinine–height index) in surgical patients, and was found to be the most sensitive and specific tool to predict nutrition-related complications.

Later, Bauer et al. [47] investigated the potential role of the Patient-Generated SGA (PG-SGA), showing higher accuracy in identifying malnourished cancer patients than the SGA, with a sensitivity of 98% and a specificity of 82%. The PG-SGA provides an overall global rating divided into three categories: well nourished, moderately malnourished or suspected of being malnourished, and severely malnourished. Notably, the Oncology Nutrition Dietetic Practice Group of the American Dietetic Association adopted this scale as the standard tool for nutrition assessment for cancer patients.

The nutritional risk index (NRI) is another useful tool to stratify nutritional risk [48] in GC patients undergoing surgery. The NRI is a simple equation that uses serum albumin concentration and recent weight loss to identify malnourished patients. A low NRI was associated with a higher risk of surgical wound complications. Similarly, the prognostic nutritional index is calculated with the serum albumin concentration and lymphocytes count in peripheral blood [49]. Another nutritional screening tool widely used also in GC surgical patients is the Nutritional Risk Screening 2002 [50, 51], which is endorsed by the European Society for Clinical Nutrition and Metabolism and evaluates nutritional risk, taking into account both the nutritional status and the severity of the disease.

Considering the limitations in the accurate measurement of nutritional status and different available tools, a combination of objective variables (anthropometric and laboratory measurements) and a subjective scoring system is necessary to optimally treat potentially resectable GC patients.

As the preoperative nutritional condition of patients undergoing surgery can directly influence postoperative prognosis, overall survival, and disease-free survival, a timely and appropriate preoperative nutritional support may improve postsurgical outcomes of GC patients [52].

Even though parenteral nutrition or preoperative enteral nutrition was associated with a better prognosis and fewer postoperative complications [53], the addition of immune-stimulating nutrients did not correlate with lower mortality rates in surgically resected GC patients (risk ratio 1.1, 95% confidence interval 0.93–1.31) according to a systematic review of 2419 patients from 22 randomized clinical trials [54].

Similarly, postoperative nutritional support plays a crucial role in the management of the catabolic effect of gastrointestinal surgery. Early enteral feeding soon followed by solid soft food on the third postoperative day is feasible, safe, and associated with shorter hospitalization [55–57].

Moreover, since up to 50% of resected GC patients develop anemia [58–60], because of multifactorial iron, folate, or vitamin B_{12} deficiency, evaluation of hemoglobin level should be planned, and appropriate replacement should be evaluated [61].

Consequences of loss of skeletal muscle mass on chemotherapy tolerance

Loss of muscle mass is a key factor in determining tolerance of chemotherapy, as sarcopenia is associated with increased adverse events [4]. Unfortunately, muscle mass loss due to treatment-related adverse events or cancer itself may easily overlap and, the mechanisms by which this occurs are still unclear.

A first hypothesis to explain the decreased treatment tolerance is linked to pharmacokinetic distribution of chemotherapy drugs [4]. Notably, drug doses are usually administered by calculated body surface area (BSA). However, patients with similar BSA and BMI may have a significantly different body composition. Indeed, this calculation method may be potentially misleading because it does not consider adipose tissue compartment and lean body mass, mainly represented by skeletal muscle mass and tissues. Furthermore, many anticancer agents undergo hepatic and renal metabolism, and BSA is an imperfect indicator of changes concerning the function of the organs involved [62].

Since cytotoxic compounds have a narrow therapeutic index, understanding drug distribution is crucial. Patients with metabolic disorders usually experience variations in the distribution, metabolism, and clearance of chemotherapy agents.

Obesity may mask a loss of muscle mass, with later elimination of highly lipophilic drugs in patients with increased adipose tissue [63]. In these patients, the administration of chemotherapy doses calculated according to the BSA can lead to overdosing of antineoplastic drugs per unit of body weight and to potentially serious side effects [64]. In addition, not only obese cancer patients with low muscle mass were reported to have shorter overall survival compared with patients with healthy muscle mass but also treatment-induced adverse events were increased [64].

Many antineoplastic agents are involved in the development of adverse events in sarcopenic patients [65–68]. Particularly, it has been demonstrated that 5-fluorouracil increases the risk of loss of skeletal muscle mass and that patients treated with 5-fluorouracil who experienced significant adverse events had received higher doses of the drug when the number of kilograms of lean body mass was considered [65], suggesting the need for a dose adjustment according to weight and the lean body mass [69].

Similarly, in the evaluation of the potential role of S-1 in the adjuvant setting in GC, it has been demonstrated that patients with significant loss of muscle had poorer prognosis [70, 71]. Moreover, administration of S-1 for more than 6 months was identified as an independent risk factor for reduced muscle mass. Further, drugs that inhibit the phosphatidylinositol 3-kinase, AKT, and mammalian target of rapamycin pathway might lead to blockade of cellular hypertrophy and subsequently loss of muscle mass [68].

Likewise, esophagogastric cancer patients undergoing neoadjuvant chemotherapy had a shorter overall survival than patients with healthy muscle mass (569 days vs 1013 days respectively; $p = 0.04$) [38]. Furthermore, patients with sarcopenia and chemotherapy-associated adverse events more often experienced dose reductions of 5-fluorouracil than patients without muscle mass loss.

In a trial evaluating malnutrition in gastrointestinal cancer, patients were classified according the SGA scale as well-nourished patients (SGA-A) and malnourished patients (SGA-B and SGA-C), and it was demonstrated that the latter had more dose reductions compared with well-nourished patients. In particular, the proportion of patients who received chemotherapy in the first 8 weeks of treatment was $(88 \pm 17)\%$ among well-nourished upper gastrointestinal tract cancer patients and $(74 \pm 25)\%$ among moderately and severely malnourished upper gastrointestinal tract cancer patients ($p = 0.01$). Furthermore, a greater proportion of moderately and severely malnourished patients than well-nourished patients discontinued treatment because of adverse events (18% vs 9%, $p = 0.08$), demonstrating a potential impact of sarcopenia on drug dose density [72].

As pharmacokinetics variability alone does not fully explain the possible relationship between sarcopenia and increased frequency of chemotherapy-related adverse events, other reasons for this association can be comorbidities and reduced functional status, which often characterize sarcopenic patients [4]. In addition, the link between sarcopenia and systemic inflammation may increase chemotherapy toxicity [44]. Inflammation reduces cytochrome activities, and impacts on drug metabolism and elimination, prolonging the exposure to cytotoxic treatments.

To date, the evidence is insufficient to change clinical practice, and it is still uncertain how to appropriate modify drug doses to prevent chemotherapy-related adverse events in sarcopenic patients.

Hence, further clinical trials should be conducted to evaluate dose reduction according to the calculation of muscle mass and muscle density, in order to prevent adverse events and to ensure greater treatment compliance.

Nutritional support in patients with advanced GC

Even when one is facing patients with inoperable or metastatic diseases, the early evaluation of their nutritional status and nutritional support is key to avoid sarcopenia onset and prevent or delay complications. Malnutrition occurs in up to 80% of advanced GC patients [44], insufficient nutrient absorption may cause severe weight loss [73], and the poor absorption of essential nutrients may further increase the risk of complications.

Similarly to early stages, in advanced GC patients the goal of nutritional therapy is to improve the nutritional status, to increase patients' adherence to systemic therapies, and to improve their quality of life. Nutritional support can be provided by oral, enteral, and/or parenteral nutrition [52]. Intuitively, enteral nutrition is more physiological than parenteral nutrition, preserving the structural and functional integrity of the gastrointestinal tract, is safer, is less expensive, and is a valid option for patients without dysphagia or obstruction [74].

Whenever a mechanical obstruction occurs, the placement of a stent may allow oral physiological nutrition and improve patients' quality of life. However, parenteral nutrition is mandatory in patients with impaired gastrointestinal function when inadequate food intake (less than 60% of the estimated energy intake) for more than 10 days can be expected, as also recommended by the European Society for Clinical Nutrition and Metabolism guidelines [75].

Whereas nourishment by central and peripheral veins ensures optimal nutrition, it increases the risk of infections when compared with enteral nutrition [76]; catheter-related

bloodstream infections are the commonest and most serious complications in adult patients receiving parenteral nutrition [77], although strict adherence to meticulous insertion and management policies may effectively reduce catheter-related complications [78]. In terminal-stage disease the benefit of nutritional support is limited, and may be associated with an increased risk of complications; in these cases, nutritional support is recommended only when benefits prevail over any possible risk [75].

Moreover, home parenteral nutrition is recommended for weight stabilization and therapy continuation for patients experiencing chemotherapy-related gastrointestinal adverse events [75, 79]. In addition, home parenteral nutrition is associated with an improvement in quality of life, performance status, and nutritional status in advanced cancer patients with compromised enteral intake and malnutrition, regardless of their tumor type [80]. Thus, total home parenteral nutrition is mandatory for malnourished patients with peritoneal carcinomatosis and severe impairment of gastrointestinal function [81], as well as in the case of short bowel syndrome due to extensive surgery [82].

Studies show that the main factors influencing the success of parenteral nutrition are patient adherence, adequate support by a professional and committed nutritionist, and effective cooperation between the patient, nutritionist, treating physicians, and home care provider [83].

Target therapies and future perspectives

As sarcopenia and cachexia have an important impact on GC cancer patients' prognosis, many novel molecules, including anabolic agents and anti-inflammatory drugs, have been developed [84]. An extensive amount of data support the administration of megestrol acetate and medroxyprogesterone acetate, with various indications in cancer patients, including appetite stimulation, weight gain, and downregulation of proinflammatory cytokines [85, 86].

To confirm the role in preventing and treating anorexia/cachexia syndrome, the addition of thalidomide to megestrol acetate therapy was investigated. A significant increase in body weight ($p < 0.01$), quality of life ($p = 0.02$), appetite ($p = 0.01$), and grip strength ($p = 0.01$) and a significant decrease in fatigue and Eastern Cooperative Oncology Group performance status ($p = 0.03$) were found in the experimental arm, showing a higher effectiveness for combination treatment [87]. Further combinations of megestrol acetate and other compounds, such as formeterol acetate or mirtazapine, are being evaluated [88, 89]. Similarly, corticosteroids could improve appetite, energy, and well-being.

As melatonin was found to be involved in appetite and nutrient absorption [90], its potential role for appetite improvement in cachectic cancer patients was investigated in a double-blind randomized trial. Patients received 20 mg melatonin per night or matching placebo for 28 days. The trial was closed early because of futility as no differences in appetite were reported between the treatment arms in an interim analysis [91].

After initial enthusiasm [92, 93], enobosarm—a muscular and bone testosterone receptor agonist—failed to result in an improvement in physical function in advanced non-small-cell lung cancer patients despite an increase in lean body mass [94–98].

In addition, anamorelin hydrochloride, an orally active ghrelin receptor agonist, was tested in two parallel phase III trials. In both studies, ROMANA 1 [99] and ROMANA 2 [100], 100 mg anamorelin hydrochloride or matching placebo was given daily at least 1 h before a meal in addition to platinum and taxanes or platinum and non-taxane-based chemotherapy for non-small-cell lung cancer patients. In both trials, patients exposed to anamorelin hydrochloride had a significantly increased lean body mass ($p < 0.0001$) when compared to those treated with placebo; moreover, anamorelin hydrochloride was associated with increased body weight ($p < 0.0001$), and improved patient symptoms ($p = 0.0004$ and $p = 0.0016$).

However, both trials failed to show an increase in handgrip strength, the secondary end point of the two studies. Thus, considering the so far unmet need of active drugs for the treatment of cancer-related anorexia/cachexia syndrome, anamorelin hydrochloride could be considered as an available option [101]. Complete results of further trials investigating the effect of this compound on primary clinical outcomes (e.g., overall survival, disease-free survival, treatment tolerance) are still awaited [102] (Table 1).

Thus, considering the complex pathogenesis of sarcopenia, cachexia, and cancer development, clinical treatment of GC patients should include a multimodal approach. Despite various efforts so far, this multifactorial syndrome still impacts on patient outcome. Hence, extended results of ongoing trials, the development of new drugs, and increased awareness of nutritional support issues among oncologists are eagerly awaited to better tailor GC patients treatments [103].

Conclusions

Sarcopenia is a multifactorial clinical condition that leads to prolonged hospitalization, a higher degree of treatment-related toxicity and postsurgical complications, reduced response to cancer treatment, impaired quality of life, and a worse prognosis in GC patients.

Table 1 Principal compounds tested

Trial	Phase	Population	Treatment	n	Primary end point	Results
Del Fabbro et al. [91]	III	Advanced GC or NSCLC patients	Melatonin vs placebo	73 (R 1:1)	Appetite	$p = 0.78$, NS
López et al. [86]	Cochrane meta-analysis	Unselected patients	MA vs placebo	3368	Appetite	RR 2.31 (95% CI 1.52–3.59)
					Weight gain	RR 1.88 (95% CI 1.43–2.47)
					HRQoL	RR 1.52 (95% CI 1.00–2.30)
Wen et al. [87]	II	Advanced cancer patients	MA plus thalidomide vs MA	102 (R 1:1)	Body weight	$p = 0.05$
					Fatigue	$p < 0.01$
					QoL	$p < 0.01$
Greig et al. [88]	I/II	Advanced cancer patients	MA plus formoterol fumarate	14	Mean quadriceps volume,	$p = 0.012$
					Hand-grip strength	$p > 0.05$
POWER trials [94, 97, 98]	II	Advanced NSCLC patients	Enobosarm vs placebo	600 (R 1:1)	Lean body mass	Ongoing
ROMANA I [99]	III	Advanced NSCLC patients	Anamorelin vs placebo	484 (R 2:1)	Lean body mass	$p < 0.0001$
ROMANA II [100]	III	Advanced NSCLC patients	Anamorelin vs placebo	495 (R 2:1)	Lean body mass	$p < 0.0001$

CI confidence interval, *GC* gastric cancer, *HRQoL* health-related quality of life, *MA* megestrol acetate, *NS* not significant, *NSCLC* non-small-cell lung cancer, *QoL* quality of life *R* randomization, *RR* risk ratio

Early evaluations of nutritional status, including body composition assessment, and timely nutritional support are key aspects in the treatment of GC patients with both operable and advanced disease. A multimodal approach is necessary to improve clinical outcomes and guarantee an appropriate support therapy for cancer patients. It should involve the structured collaboration between oncologists, surgeons, physiatrists, and clinical nutritionists.

New drugs to counteract lean body mass loss and enhance the efficacy of nutritional support in cancer patients are urgently needed. At the same time, clinical trials should be conducted to calculate the appropriate chemotherapy dosage according to muscle mass so as to prevent toxicity and adverse events and to ensure greater treatment adherence and efficacy.

Compliance with ethical standards

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

Ethical standards All the trials reported were conducted in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and later versions. According to the original publications, informed consent or substitute for it was obtained from all patients for their being included in each reported trial.

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