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Review

Clinical Impact of Sarcopenia on Gastric Cancer

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Abstract. *Sarcopenia is a complex syndrome defined by progressive and generalized loss of skeletal muscle mass and strength. Although sarcopenia is mainly associated with aging, cancer is also one of its causes. Sarcopenia is now drawing attention as a poor prognostic factor in cancer. In patients with gastric cancer associated with eating disorders that often leads to loss of weight and muscle, sarcopenia is particularly important. Its definition and method of assessment, however, vary between studies, thus these need to be standardized. Nevertheless, emerging evidence suggests that sarcopenia contributes independently to postoperative complications and overall survival in gastric cancer. Interventions preventing sarcopenia with targeted nutrition and exercise are currently explored. This review aims to provide an understanding of sarcopenia, emphasizing its importance in the management of gastric cancer.*

Aging is associated with progressive loss of muscle mass and physical function that often leads to progressive disability and loss of independence (1). Rosenberg first advocated the coined term "sarcopenia" in 1989, referring to the importance of skeletal muscle mass reduction with aging (2). The amount of muscle begins to decrease after 50 years of age, and approximately 50% of the fibers are lost by 80 years of age (3). Sarcopenia has been defined as the loss of muscle mass and strength that occurs with aging (4). It is, thus, closely related to "flail", so that it can be as a risk factor for fractures and aspiration pneumonia (5, 6). Sarcopenia is divided into primary and secondary, depending on its causes. Primary sarcopenia is caused by aging, while secondary is caused by disuse, malnutrition, organ failure, invasive interventions, malignancy, or other diseases (7). As aging of the population progresses worldwide, cases of primary sarcopenia, as well as secondary sarcopenia due to malignancy, will inevitably increase.

Sarcopenia is gradually being recognized as an important issue even in the field of cancer management. Many reports on the relationship between cancer and sarcopenia have been published in the fields of hepatobiliary (8-14) and gastric cancer (15-17). In advanced gastric cancer, the majority of patients suffer from poor dietary intake, resulting in inadequate nutrition (18). Even in early gastric cancer, surgery reduces the capacity of the stomach to digest, which decreases meal intake and results in prominent weight loss (19). Therefore, we have to keep in mind that patients with gastric cancer have the potential to develop a sarcopenic state, emphasizing the importance of having sufficient knowledge and methodology for the management of gastric cancer.

In this review, we summarize the recent research on the relationship between sarcopenia and gastric cancer and examine the future prospects in the management of gastric cancer.

Evaluation of Sarcopenia

Regarding the evaluation of sarcopenia, diagnostic algorithms were proposed by the European Working Group on Sarcopenia in Older People (EWGSOP) (7) in 2010 and by the Asian Working Group for Sarcopenia (AWGS) (20) in 2014. Sarcopenia in gastric cancer is, thus, currently assessed based mostly on these standards. Essentially, sarcopenia is a disease concept for the elderly, so both the EWGSOP and AWGS classifications target people over 60 or 65 years of age.

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Table I. *Techniques to measure muscle mass, strength, and function.*

Variable	Modalities or Methods	Clinical practice	Research
Muscle mass	Computed tomography (CT)	√	√
	Bioimpedance analysis (BIA)	√	√
	Dual energy X-ray absorptiometry (DEXA)	√	√
	Anthropometry	√	
	Magnetic resonance imaging (MRI)		√
	Total or partial body potassium per fat-free soft tissue		√
Muscle strength	Handgrip strength	√	√
	Knee's flexion strength / extension strength		√
	Peak expiratory flow		√
Physical function	Short physical performance battery	√	√
	Usual gait speed	√	√
	Timed get-up-and-go test	√	√
	Stair climb power test		√

Evaluation of sarcopenia quantifies muscle mass, muscle strength, and physical function. While actual methods of measuring these are proposed for research or clinical practice (Table I), there are multiple methods for the evaluation of each parameter, however, they are not unified.

To measure muscle mass, for example, two approaches, direct and indirect, exist. Direct methods quantify muscle mass of the whole body by analyzing body composition using bioelectrical impedance analysis (BIA) or dual-energy X-ray absorptiometry (DEXA). In turn, indirect methods quantify the area of a sectional plane of the muscle using diagnostic imaging, such as computed tomography (CT), mostly at the third lumbar level as a representative value (21, 22). Yoshida *et al*. have measured the amount of muscle mass using BIA (23, 24), and Kawamura *et al*. have assessed the arm muscle area calculated by the triceps skin fold and arm circumference (25). All other studies have measured muscle mass indirectly using CT (17, 26-28). A recent study has reported good correlation between CT, DXA, and BIA (29). Both direct and indirect measurements provide highly reproducible measured values, but their high cost is a disadvantage. In gastric cancer, since CT is taken for staging or follow-up in almost all cases, the indirect CT method is readily applicable. Muscle strength is mostly evaluated by grip strength, and the usual cutoff value is 26 kg for male and 18 kg for female (30). Concerning physical function evaluation, walking speed is used, and the cutoff value is generally set at 0.8 m/s (23, 31, 32). We, of course, need to consider that deviations in measurement values might occur depending on imaging conditions, and that measuring hardware and methodology need to be uniform in each study.

It is of note that the cutoff value to define sarcopenia differs in each study and has not yet been standardized. There are several reasons why the definitive cutoff value is difficult to set. Fukuda *et al*. have reported that calorie and protein intakes are lower in the sarcopenia group compared to the non-sarcopenia group in patients with gastric cancer (23). Differences in the nutritional status among cancer patients are actually very large, particularly in gastric cancer (33). Another problem in sarcopenia studies is the difficulty of obtaining normal CT values from areas of muscle mass in a healthy cohort due to radiation hazard, which makes it difficult to compare a cancer patient cohort to a healthy cohort.

We have previously evaluated muscle mass in our cohort of those who underwent surgery for gastric cancer using CT within one month before surgery (34). The total cross-sectional skeletal muscle area (SMA) at the third lumbar level was quantified using SYNAPS VINCENT volume analyzer (Fujifilm Medical, Tokyo, Japan) (Figure 1). In our study, the value of SMA was further normalized by body surface area (BSA) to take body weight into account; otherwise the resultant value might underestimate the sarcopenic state in cases of obesity. Notably, most groups used SMA normalized by height as a sarcopenia index (17, 28, 30, 35).

Although optimal cutoff values of muscle mass to define sarcopenia should be elucidated (36), the recent review has highlighted that many studies fail to account for the variation introduced by factors such as sex, race, and tumor stage (37, 38). Therefore, it would be prudent to define sarcopenia by setting the most appropriate cutoff value for each cohort studied.

Sarcopenic Obesity

Sarcopenic obesity is a condition defined as obesity caused by age-induced muscle loss. As the muscle decreases, the body decreases its ability to burn fat, and fat accumulates easily, resulting in progressive obesity (39, 40). The definition of sarcopenic obesity is also not yet clear. Some define the sarcopenia group with a high BMI as sarcopenic

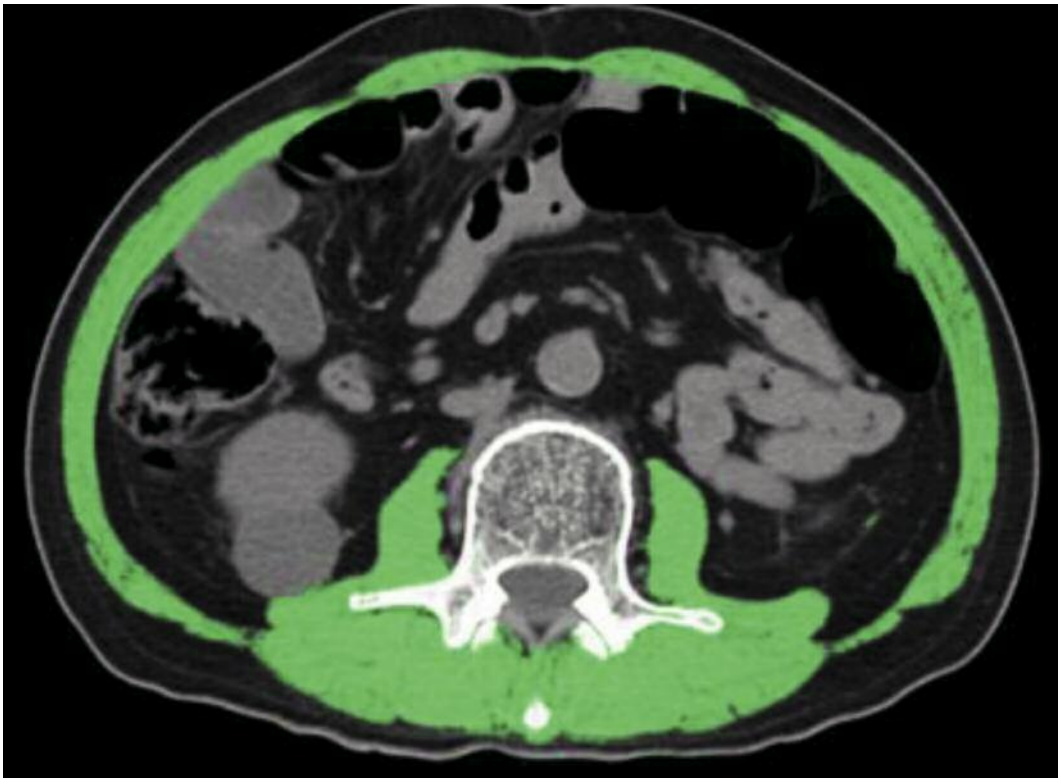

Figure 1. *Evaluation of sarcopenia on CT imaging. The total cross-sectional skeletal muscle area (SMA) (green) at the third lumbar level (white) is evaluated using SYNAPS VINCENT.*

obesity (41), while others measure visceral fat mass by CT to define it (36, 42). Importantly, it has been reported that sarcopenic obesity is associated with higher risks of surgical complications, physical disability, and decreased survival (36, 42, 43). Therefore, we believe that it is important to use a method that can identify patients with sarcopenic obesity and include them in studies as such.

The Influence of Sarcopenia on Postoperative Outcomes of Gastric Cancer Patients

The literature that has demonstrated the relationship between postoperative outcomes of gastric cancer surgery and sarcopenia is summarized in Table II. Tegels *et al*. have reported that sarcopenia is not a prognostic factor for postoperative in-hospital death, severe complications, and 6-month survival (17). In their report, the prevalence of sarcopenia was as high as 57.7%, and the proportion of patients above Stage III was 57.8%. These figures are higher than those of other reports. Because invasive or metastatic gastric cancer frequently causes stenosis of the digestive tract, which leads to emaciation (44, 45), sarcopenia might thus have been confounded with advanced gastric cancer. Tamandl *et al*. have analyzed patients with esophageal or esophagogastric junctional cancer, and they have demonstrated that sarcopenia could be a prognostic factor of overall survival along with the T factor and a positive surgical margin (26). Huang *et al*. have investigated prognostic factors related to the 1-year survival rate in gastric cancer patients (30), and they have also reported that sarcopenia is an independent prognostic factor, in patients aged over 75 years, with NRS 2002 score, degree of differentiation, surgical procedures (total gastrectomy or partial resection), and combined resection of other organs. Furthermore, Fukuda *et al*. have showed that serious postoperative complications of Clavien-Dindo (CD) IIIa or more are significantly more frequent in the sarcopenia group, demonstrating that sarcopenia can be an independent prognostic factor for serious postoperative complications (23). Huang *et al*. have highlighted the importance of sarcopenia stages defined by the European Working Group on Sarcopenia (46). They have reported that patients had worse postoperative outcomes following gastric surgery if in advanced sarcopenia stage. Zhuang *et al*. have similarly reported that sarcopenia is an independent prognostic factor for severe complications following surgery, overall survival

Table II. *Relationship between gastric cancer surgery and postoperative outcomes in sarcopenia.*

Author, Year	Disease	Cases	Modality	Criteria for sarcopenia	Impact on short-term	Impact on long-term
Retrospective studies						
Tegels *et al*. (17), 2015	GC	152	CT	Male: SMI <43 (BMI<25.0) SMI <53 (BMI≥25.0) Female: SMI <41	No	No
Tamandl *et al*. (26), 2015	EC EGC	200	CT	Male: SMI ≤55 Female: SMI ≤39		Yes
Zhuang *et al*. (27), 2016	GC	937	CT	Male: SMI ≤40.8 Female: SMI ≤34.9	Yes	Yes Stage II/III
Prospective studies						
Fukuda *et al*. (23), 2015	GC	99	BIA	Male: SMI ≤8.87, HGS <30, GS ≤0.8 Female: SMI ≤6.42, HGS <20, GS ≤0.8	Yes	
Wang *et al*. (28), 2015	GC	255	CT	Male: SMI ≤36, HGS <26, GS ≤0.8 Female: SMI ≤29, HGS <18, GS ≤0.8	Yes	
Huang *et al*. (30), 2016	GC	173	CT	Male: SMI ≤40.8, HGS <26, GS ≤0.8 Female: SMI ≤34.9, HGS <18, GS ≤0.8		Yes
Kuwada *et al*. (34), 2018	GC	491	CT	Male: SMA/BSA ≤69.7 Female: SMA/BSA ≤54.2	No	Yes

GC: Gastric cancer; EC: esophageal cancer; EGC: esophagogastric cancer; SMI: skeletal muscle index (cm^2/m^2); BMI: body mass index (kg/m^2); BIA: bioelectrical impedance analysis; HGS: Handgrip strength (kg); CT: computed tomography; GS: Gait speed (m/s).

Table III. *Relationship between sarcopenia and chemotherapy in gastric cancer.*

Author, Year	Disease	Type	n	Result
Awad *et al*. (50), 2012	Oesophago-gastric cancer	Neoadjuvant chemotherapy	47	Neoadjuvant chemotherapy increased the proportion of patients with sarcopenia.
Yamaoka *et al*. (60), 2015	Gastric cancer	Neoadjuvant chemotherapy	102	Skeletal muscle loss is exacerbated by extanded adjuvant chemotherapy after TG.
Tan *et al*. (61), 2015	Oesophago-gastric cancer	Neoadjuvant chemotherapy	89	Sarcopenia is significant predictor of DLT.
Hayashi *et al*. (53), 2016	Gastric cancer	Chemotherapy (for metastatic)	53	Low SMD is an independent predictor of poor outcomes.
Mirkin *et al*. (54), 2017	Gastric cancer	Neoadjuvant chemotherapy	36	A significant number of patients with gastric cancer become sarcopenic during NAC.
Palmela *et al*. (56), 2016	Gastric cancer	Neoadjuvant chemotherapy	48	Sarcopenia and sarcopenic obesity are associated with early termination of neoadjuvant chemotherapy.

TG: Total gastrectomy; DLT: dose-limiting toxicity; SMD: skeletal muscle index; NAC: neoadjuvant chemotherapy.

and disease-free survival in stage II/III cases (27). As a result, sarcopenia is more costly due to longer postoperative stay in the hospital (28).

Analysis of the 491 patients who underwent gastrectomy in our study showed that although sarcopenia may not affect short-term postoperative outcomes (postoperative complications), it can be an independent prognostic factor for overall survival (34). Furthermore, we found that patients with sarcopenia and comorbidity had a large increase in eventual death from causes other than gastric cancer (34). Based on these results, both short- and long-term outcomes are certainly worse in gastric cancer patients with preoperative sarcopenia compared to non-sarcopenia patients.

The Effects of Interventions for Sarcopenia in Gastric Cancer Patients

Exercise and nutritional interventions are now recognized to be important for the prevention of postoperative complications. According to the data that resistance exercise promotes muscle protein synthesis (47), Biolo *et al*. have demonstrated that the stimulatory effect of exogenous amino

acids on protein synthesis is enhanced by prior exercise, suggesting the intimate link between nutritional support and exercise for synthesis of muscle proteins (48). Even in the elderly, an increase of protein intake can prevent muscle mass decrease (49). Intake of essential amino acids is necessary for protein synthesis (50), and leucine, one of the branched chain amino acids, is particularly important among the nine essential amino acids (51). Based on these facts, appropriate planning of interventions combining exercise and nutritional support is essential.

Although there are still few reports that have verified the effects of interventions for sarcopenia in gastric cancer, Yamamoto *et al*. have prospectively studied the effects of intervention on sarcopenia in gastric cancer patients (52). Following the identification of lower calorie and protein intake in preoperative sarcopenia group with gastric cancer compared to the non-sarcopenic group (52), they provided with nutritional support aiming for a sufficient daily intake of calories and proteins, as well as with daily oral supplements of 2.4 g b-hydroxy-b-methylbutyrate (HMB), which is reportedly an effective leucine metabolite increasing muscle mass (53). The preoperative exercise intervention consisted of handgrip training, walking, and resistance training. Finally, they conducted these interventions in 22 patients diagnosed with sarcopenia for about 2 weeks and prospectively evaluated the improvement of sarcopenia according to the EWGSOP diagnostic criteria. Almost 20% of patients were converted to be no longer sarcopenic. Comparing before and after the intervention, increases in calorie intake, amount of protein ingested, and grip strength were found to be significant. Interestingly, there were no serious complications greater than CD III in the intervention group. Of note, despite the very short period of intervention, this study showed that preoperative nutritional exercise interventions can be effective. Kobayashi *et al*. have conducted a prospective study to evaluate the efficacy of postoperative oral nutrition supplements in Japan (54). Their results showed that postoperative nutritional supplementation can also lead to a significant reduction of body weight loss for gastrectomized patients. These results suggest that a pre- and postoperative support program has the potential to improve sarcopenia.

Chemotherapy and Sarcopenia in Gastric Cancer

It is well documented that continuation of chemotherapy is difficult in cases with muscle weakness (56, 57). Hayashi *et al*. have reported that low skeletal muscle index is an independent predictor of poor outcome in patients who receive chemotherapy for metastatic gastric cancer (58).

Preoperative chemotherapy has become a standard therapy for advanced gastric cancer in Europe and the United States. Katelin *et al*. have conducted collaborative research in multiple facilities to examine the perioperative outcomes of patients who have undergone gastrectomy following preoperative chemotherapy. They have shown that preoperative chemotherapy increases the prevalence of sarcopenia, and perioperative complications are significantly increased (59). Awad *et al*. have reported similar results showing that the prevalence of sarcopenia increases following neoadjuvant chemotherapy for esophagogastric cancer (60). In addition, Palmela *et al*. have reported that sarcopenia and sarcopenic obesity are associated with early termination of neoadjuvant chemotherapy (61).

Postoperative adjuvant chemotherapy with 1 year of S-1 oral administration is regarded as the standard in Japan, according to the results of the ACTS - GC study, which has shown a significant improvement in the survival of Stage II/III gastric cancer patients (62, 63). However, the S-1 rate for one year was only about 60% of all patients. Aoyama *et al*. have examined the factors that relate to the continuation of S-1 adjuvant chemotherapy following radical gastrectomy, and they have shown that a rate of body weight loss of at least 15% one month following surgery is the only significant independent risk factor (64). They further quantified lean body mass, which is calculated by subtracting body fat weight from total body weight using a body composition meter (impedance method) 1 week before surgery and at 1 month following surgery. Interestingly, the postoperative lean body mass loss is a significant factor for discontinuing S-1 adjuvant chemotherapy (65). Yamaoka *et al*. have studied the clinical factors affecting significant loss of skeletal muscle following total gastrectomy (66). S-1 adjuvant chemotherapy for 6 months has been found to be an independent causal factor for loss of skeletal muscle. They have thus proposed active nutritional intervention in patients undergoing postoperative adjuvant chemotherapy for maintenance of muscle mass. Tan *et al*. have also demonstrated that sarcopenia is associated with dose-limiting toxicity during preoperative chemotherapy, and the overall survival of sarcopenic patients is significantly shorter compared to that of patients who are not sarcopenic (67). Although specific publications on the impact of sarcopenia on chemotherapy outcomes are rather scarce (Table III), these results indicate that prevention of sarcopenia may potentially improve the prognosis of patients with gastric cancer.

Discussion and Future Perspectives

The evaluation of sarcopenia and its impact on prognosis of cancer patients has been attracting attention in clinical oncology. As shown in recent reviews and meta-analyses, compelling evidence has shown that sarcopenia, irrespective of definition, is independently associated with poor prognosis (37, 38, 68-70). Considering the increase of the aged population, the proportion of patients suffering from both sarcopenia and gastric cancer will increase. Since surgery is still the mainstay

of treatment for gastric cancer, we need to be aware of sarcopenia and pay careful attention to it in the perioperative management of patients with gastric cancer (71). Despite the improvements of surgery and anesthesia, the postoperative mortality rate of elderly patients remains significantly higher compared to that of younger patients (72). Of note, elderly colorectal cancer patients who survive the first year have the same cancer-related survival as younger patients (73), which means that perioperative care is essential for the treatment of elderly cancer patients. In view of these facts, sarcopenia must have a critical impact on early postoperative complications and the postoperative prognosis. Although development of perioperative management, such as enhanced recovery after surgery (ERAS) protocols, decreases postoperative weight loss, recent findings suggest that lean body mass, which is a surrogate index of muscle mass, is a risk factor for the postoperative adjuvant chemotherapy continuation rate (65). In other words, focusing on the prophylaxis of muscle mass loss might be more important rather than mere weight control. The disadvantageous aspects of sarcopenia in surgery and chemotherapy have now been proven in gastric cancer, and sarcopenia is a pathological condition that cannot be ignored. Thus, prophylaxis and improvement of sarcopenia will be among the key elements for improving the management of gastric cancer, and it needs to be carefully evaluated as a factor that can help determine treatment options.

As future perspectives in sarcopenia research in gastric cancer, first, standardization of the evaluation methodology will be required; a standardized cutoff value in the CT evaluation would be particularly useful for accurate evaluating sarcopenia in gastric cancer. Second, to examine effective perioperative exercise and nutritional interventions for sarcopenia, a number of prospective clinical studies need to be carried out. Through such studies, the period and intensity of exercise and nutritional intervention could be optimized and introduced into the clinical practice.

Conflicts of Interest

All Authors declare no conflicts of interest for this article.

Authors' Contributions

KK and KS wrote the manuscript and generated the figures; KiS, YR, and NM contributed to the acquisition of clinical data. KaS and FT contributed to editing the manuscript.

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