Review Article

Assessment of body composition and impact of sarcopenia and sarcopenic obesity in patients with gastric cancer

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Contributions: (I) Conception and design: All authors; (II) Administrative support: K Obama; (III) provision of study materials or patients: T Nishigori; (IV) Collection and assembly of data: T Nishigori; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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Abstract: Malnutrition is a critical problem in patients with gastric cancer (GC); however, no universally accepted marker that is convenient for clinical use has been defined. Recently, body composition has attracted considerable attention as a means to assess nutrition status in patients with cancer. The clinical role of skeletal muscle mass has also been increasingly recognized. In patients with GC, sarcopenia, which is the loss of skeletal muscle mass, was found to be significantly associated with increased post-surgical complications including hospital stay, healthcare costs, and poor survival. In addition, sarcopenic obesity, which combines the health risks of obesity and sarcopenia, is recognized as a strong risk factor for poor short- and long-term outcomes following gastrectomy. The mechanism linking sarcopenia to worse postoperative outcomes remains unclear; however, skeletal muscle has been found to act as an endocrine organ that produces substances affecting the immune system. In addition, sarcopenia was reported to be associated with toxicity and termination of chemotherapy. Patients with sarcopenia may be unable to react appropriately to the stress of gastrectomy and perioperative chemotherapy. To improve the short- and long-term outcomes of patients with GC and sarcopenia, adequate energy and protein intake are necessary during resistance training. In the present study, we performed a literature review and presented a method to evaluate body composition, the relationship between skeletal muscle mass and GC, and perioperative nutrition and exercise therapy for patients with sarcopenia.

Keywords: Body composition; sarcopenia; obesity; gastric cancer (GC); gastrectomy

Received: 11 September 2019; Accepted: 21 October 2019; Published: 05 April 2020.
doi: 10.21037/tgh.2019.10.13
View this article at: http://dx.doi.org/10.21037/tgh.2019.10.13

Introduction

Gastrectomy is the most effective treatment for gastric cancer (GC) without distant metastasis (1). However, it is associated with the occurrence of postoperative complications, cancer recurrence, and death from other diseases. In addition, the post-surgical incidence of complications and survival rate among patients with similar cancer stage and demographics is heterogeneous. Identifying prognostic factors that allow a more accurate stratification of the preoperative risk remains an interest of GC experts.

To date, various factors such as advanced age, comorbidities, and molecular features have been reported to be associated with unfavorable outcomes following gastrectomy in patients with GC (2,3). However, most of those factors are difficult to manipulate preoperatively. Identifying modifiable factors is therefore necessary to overcome morbidity and cancer death in patients with GC.

Malnutrition is a critical problem, not only in patients with advanced GC, who can suffer from gastric outlet obstruction and bleeding, but also in patients with early GC, as their stomach presents reduced digestive capacity, causing food intake to decrease after gastrectomy (4,5). In addition, neoadjuvant chemotherapy and chemoradiation therapy, which often worsen a patient's nutritional status, have become a standard in Western countries. Preoperative malnutrition therefore has significant room for improvement and several studies have investigated parameters to identify patients at nutritional risk. However, no universally accepted marker that is convenient for clinical use in patients with GC has been defined.

In patients with cancer, body mass composition and associated metabolic dysfunction have become an important preoperative consideration to predict postoperative outcomes. Since patients with GC often have unique metabolic problems, GC experts should understand body composition analysis. In this study, we conducted a literature review and introduce a method to evaluate body composition and the relationship between skeletal muscle mass and GC.

Challenges in defining body mass composition

The body mass index (BMI) has been used for a long time to diagnose malnutrition. Low BMI has been commonly recognized as a marker for poor nutrition status, whereas high BMI is associated with cardiovascular and kidney diseases and diabetes, which is also an important risk factor. However, previous studies investigating the relationship between BMI and clinical outcomes in patients with GC have provided inconsistent results (5-10).

Weight gain and loss are not reliable indicators of body composition changes, due to fluid collection such as ascites or body edema. Males are likely to store body fat in the visceral area while females store it mainly subcutaneously. In addition, people tend to lose muscle mass and gain fat as they get older. Therefore, patients with similar BMIs can have different nutritional status.

Body composition, which is estimated through various simple techniques and precisely reflects a patient's metabolic profile, has recently attracted considerable attention. The clinical role of skeletal muscle mass is being increasingly recognized in patients with various cancers, and the amount of skeletal muscle mass is significantly associated with the post-surgical risk of complications, hospital stay, healthcare costs, and survival (11-18). Understanding the body composition analysis of a patient with GC and the relationship between GC and skeletal muscle mass can help address the potential metabolic problems encountered during the perioperative period.

Sarcopenia

Life expectancy has increased worldwide and aging is known to be associated with progressive loss of muscle mass (19,20). Muscle loss starts at 50 years of age and approximately 50% of the fibers is lost by 80 years of age (21). The term 'sarcopenia' (Greek 'sarx' or flesh + 'penia' or loss) was first proposed by Rosenberg in 1989, to designate the loss of skeletal muscle mass with aging (22). Sarcopenia can be classified into primary, which is caused by aging, and secondary, which is caused by immobility or diseases such as cancer (23). Moreover, sarcopenia can be also caused by both malnutrition, low levels of physical activity, and various diseases (24,25). Since sarcopenia may be caused by insufficient energy and protein intake, its prevalence in patients with GC with decreased food intake can be higher than in other cancer patients (26,27).

Muscle mass in patients with GC can be measured using two common approaches: bioelectrical impedance analysis (BIA) and computed tomography (CT). Dual-energy X-ray absorptiometry, another common method to measure muscle mass, is rarely used in the surgical field. Although BIA avoids exposing the patient to high radiation doses, it is influenced by the patient's fluid status. Although CT exposes the patient to a high radiation dose and requires expensive equipment and image analysis software, it is readily applicable to patients with GC during CT scan for staging and follow-up. Therefore, its clinical use is very convenient for clinical use for surgical candidates, as it requires no extra cost. Additionally, CT scans constitute a precise and gold standard tool to detect sarcopenia (28).

The authors have often adopted CT to identify sarcopenia (29-31). Skeletal muscle, visceral fat, and other tissues can be distinguished using Hounsfield units (HUs), with skeletal muscle's cross-sectional area falling within the range from −29 to 150 HU. Representative images are shown in *Figure 1*, which includes the psoas, erector spinae, quadratus, lumborum, transversus abdominis, external and internal obliques, and rectus abdominis muscles. This landmark is known to correlate with whole-body muscle mass (32).

To calculate the skeletal muscle mass index (SMI), skeletal muscle mass assessed by BIA or CT scan is divided by the square of the patient's height. Sex-specific SMI cut-offs are used to diagnose sarcopenia. Some researchers have used other methods and criteria, such as muscle quality, to report significant clinical impact of skeletal muscle in patients with GC (33-35).

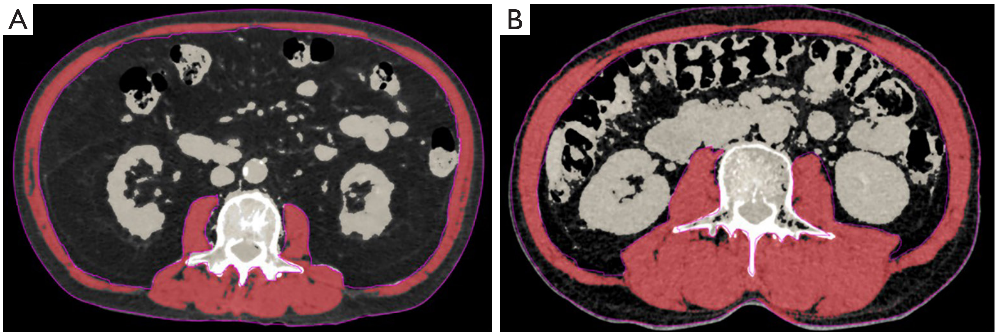

Figure 1 Computed tomography images of the third lumbar vertebra level, used to assess skeletal muscle mass. Subpanels (A) and (B) illustrate the findings of two male patients with gastric cancer who had identical body mass index (22 kg/m^2). Red indicates skeletal muscle mass areas. Patient (A) of age 62 years had sarcopenia with skeletal muscle index (SMI) of 36.0 cm^2/m^2, whereas 72-year-old patient (B) had SMI of 53.3 cm^2/m^2.

Table 1 Previous studies investigating the impact of preoperative SMI-defined sarcopenia on the postoperative outcomes in patients with gastric cancer

Authors	Country	No. of patients, sarcopenia/total	Muscle mass measurement method	SMI cut-offs to define sarcopenia		Significant impact of sarcopenia	
				Male	Female	Postoperative complications	Survival
Fukuda *et al.* (37)	Japan	21/99 (21%)	BIA	8.87	6.42	Yes	N/A
Wang *et al.* (16)	China	32/255 (13%)	CT	36.0	29.0	Yes	N/A
Huang *et al.* (38)	China	176/470 (37%)	CT	40.8	34.9	Yes (only severe sarcopenia)	N/A
Zhang *et al.* (39)	China	24/156 (15%)	CT	40.8	34.9	Yes	N/A
Zhuang *et al.* (44)	China	389/937 (42%)	CT	40.8	34.9	Yes	Yes
Nishigori *et al.* (30)	Japan	76/177 (43%)	CT	53.0 for BMI ≥25.0; 43.0 for BMI <25.0	41.0	N/A	Yes
Kudou *et al.* (40)	Japan	42/148 (28%)	CT	53.0 for BMI ≥25.0; 43.0 for BMI <25.0	41.0	No	Yes
Tegels *et al.* (41)	Netherlands	86/152 (57%)	CT	53.0 for BMI ≥25.0; 43.0 for BMI <25.0	41.0	No	No
Sakurai *et al.* (42)	Japan	142/569 (25%)	CT	43.2	34.6	No	Yes
Tamandl *et al.* (43)	Austria	130/200 (65%)	CT	55.0	39.0	N/A	Yes

Severe sarcopenia was defined as both low muscle strength and low physical performance in addition to low muscle mass. BIA, bioelectrical impedance analysis; CT, computed tomography; SMI, skeletal muscle index (CT: cm^2/m^2, BIA: kg/ m^2); BMI, body mass index (kg/m^2); N/A, not applicable.

Previous studies (16,30,36-44) examining the relationship between SMI and clinical outcomes in patients with GC undergoing surgery are summarized in *Table 1*. Many studies from East Asia have reported an association between preoperative sarcopenia and a higher rate of postoperative complications and a poorer prognosis (16,30,36-44). In those studies, the prevalence of sarcopenia ranged from 13% to 65%, which reflects different countries and ethnicities as well as the unavailability of universally accepted cut-off values to define sarcopenia.

As shown in *Table 1*, the cut-off values reported by Zhuang *et al.* were commonly used in Chinese populations (44). The authors performed a study to determine the optimal sarcopenia cut-off values and to predict the long-term survival of Japanese patients with GC (30). Five definitions of CT-based SMI, previously reported to be associated with prognosis in cancer patients were used to define sarcopenia (16,40,42,44,45). The BMI-incorporated cut-off values reported by Martin *et al.* were associated with survival rate, both in univariate and multivariate analyses (40,46). Although Tegels *et al.* reported sarcopenia based on Martin *et al.*'s definition, which was not associated with postoperative outcomes (41), the prognostic significance of sarcopenia based on the cut-offs reported by Martin *et al.* has been validated in a number of malignancies (40,46-51). The authors believe that this BMI-incorporated definition can be used to determine sarcopenia in various countries and ethnicities.

According to a previous systematic review, preoperative sarcopenia diagnosed according to various definitions has significant impact on the short- and long-term postoperative outcome of GC patients (52). However, the best sarcopenia cut-offs should be determined to realize preoperative risk stratification and counter-measures, as well as to promote shared decision-making.

Several previous studies have identified sarcopenia based on muscle mass alone. However, the European Working Group on Sarcopenia in Older People (EWGSOP) and the Asian Working Group for Sarcopenia (AWGS), recommend the simultaneous evaluation of muscle strength or physical function, to diagnose sarcopenia (28,53). Muscle strength and physical function are commonly measured by grip strength and walking speed, respectively. In the previous studies shown in *Table 1*, Fukuda *et al.*, Wang *et al.*, and Huang *et al.* defined preoperative sarcopenia based on the EWGSOP or AWGS algorithms and demonstrated that it is a risk factor for postoperative outcomes (16,37,38). Future prospective studies investigating the impact of sarcopenia on clinical outcomes of patients with GC should evaluate those parameters simultaneously with skeletal muscle mass.

Although the mechanism linking preoperative sarcopenia to worse postoperative outcomes remains unclear, skeletal muscle has been reported to play a role as an endocrine organ, producing cytokines and peptides that affect the immune system (54,55). Sarcopenic populations have been shown to have impaired cellular immune function and increased inflammatory activity (56). Moreover, in patients with GC, higher neutrophil/lymphocyte and platelet/lymphocyte ratios have been shown to be associated with preoperative sarcopenia (57). An association between sarcopenia and chemotherapy toxicity and termination has also been reported (58-61). In patients with GC receiving chemotherapy for metastatic diseases, low SMI was an independent predictor of poor outcome (36,62). In addition, skeletal muscle is known to constitute a source of amino acids in times of stress (63). Taken together, these findings suggest that sarcopenic patients with GC who are unable to react appropriately to the stress of gastrectomy and chemotherapy have unfavorable postoperative outcomes.

Sarcopenic obesity

The worldwide population is aging and the incidence of obesity rises rapidly (64). The association between visceral fat and metabolic syndrome and other serious diseases is well known (65-68). Moreover, visceral obesity has been reported as associated with high complication rates in patients with GC undergoing surgery (31,69,70).

Sarcopenic obesity combines the health risks of obesity and sarcopenia, and is considered a worst-case scenario (71,72). Although the definition of obesity remains unclear, BMI and visceral fat mass are commonly used to define overweight and obesity (30,31,73,74). In Asian populations, BMI ≥25 or 30 kg/cm^2 and visceral fat area ≥100 cm^2 have been used as a threshold (30,31,75-79). Visceral fat mass can be measured by assessing the cross-sectional area at the level of the umbilicus on CT scan (32,80,81), where fat falls within the range of −190 to −30 HU (32). *Figure 2* shows a representative CT image at the level of the umbilicus. In previous studies, sarcopenic obesity in patients with GC undergoing surgery was strongly associated with poor short- and long-term outcomes (30,31,73,74).

The mechanism linking sarcopenic obesity and poor outcomes also remains unclear. The inflammatory cytokines produced by adipose tissue, especially visceral fat, accelerate muscle catabolism, thereby contributing for the vicious cycle that initiates and sustains sarcopenic obesity (82). This, in turn, is linked with insulin resistance and dysmetabolism (83,84). In sarcopenic obesity patients, the response to the stress of surgery and chemotherapy may be further impaired, resulting in increased complications and poor prognosis.

As shown *Figure 1*, patients with obesity and muscle loss could not be distinguished by appearance, unlike cachexic or underweight ones. Moreover, assessing skeletal muscle mass in patients with GC who are not thin, is very important to

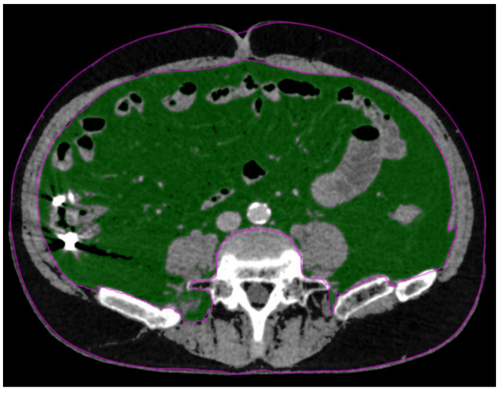

Figure 2 Computed tomography images of the umbilicus level, used to assess visceral fat (green field).

stratify morbidity and mortality outcomes.

Interventions for sarcopenia

In sarcopenic patients with GC, preoperative interventions to improve body composition may lead to favorable outcomes. Fukuda *et al.* reported that sarcopenic patients with GC consumed less energy and protein preoperatively (37). In addition to resistance training, adequate intake of energy and protein is crucial to manage sarcopenia (85,86). Protein supplementation during resistance training, in particular the intake of essential amino acids such as leucine, was reported to increase protein synthesis and skeletal muscle mass (87-90). Although time to surgery is limited in preoperative patients with GC, exercise training was found to improve exercise capacity even during short preoperative periods (91-93). Yamamoto *et al.* reported that 3 weeks of preoperative exercise and nutritional therapy reduced sarcopenia and improved the postoperative outcomes of patients with GC and sarcopenia (94). They used HMB supplementation during resistance training, which was reported to effectively increase the lean body mass and to decrease muscle damage (95,96). Regarding interventions for sarcopenic obesity, energy intake restriction on fat-mass loss alone should not be performed, as it was reported to further decrease skeletal muscle mass (97,98). Cho *et al.* reported that preoperative exercise without diet control reduced visceral fat mass and postoperative complications following gastrectomy, in patients with GC and metabolic syndrome (99). Since few reports have looked into the effects of perioperative nutrition therapy during resistance training, in patients with GC and sarcopenia or sarcopenic obesity, further studies are necessary.

Conclusions

Identifying sarcopenic patients has several potential benefits in terms of GC treatment management. Currently, body composition can be easily evaluated using CT or BIA. A previous study reported that over half of patients with GC undergoing gastrectomy lost 5% or more of lean body mass one month after surgery (100). Loss of skeletal muscle mass is known to be associated with functional limitations, physical disability and decreased quality of life (101). In addition, loss of skeletal muscle mass after gastrectomy has been shown to impair compliance with adjuvant chemotherapy, resulting in poor prognosis (102-104). Medical workers involved in GC treatment should understand the significant role of skeletal muscle mass and perform constant body composition assessment before and after surgery and chemotherapy. In addition, patients with GC and sarcopenia should be provided appropriate energy and protein intake during resistance training, to improve short- and long-term outcomes.

Acknowledgments

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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doi: 10.21037/tgh.2019.10.13
Cite this article as: Nishigori T, Obama K, Sakai Y. Assessment of body composition and impact of sarcopenia and sarcopenic obesity in patients with gastric cancer. Transl Gastroenterol Hepatol 2020;5:22.