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REVIEW ARTICLE

Current status of perioperative nutritional intervention and exercise in gastric cancer surgery: A review

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Abstract

Patients with gastric cancer are often malnourished or sarcopenic during tumor progression. Perioperative malnutrition, including sarcopenia, is strongly related to postoperative complications and long-term outcomes. To improve outcomes, nutritional intervention is common for patients with gastric cancer, especially for those undergoing elective surgery. Several clinical trials evaluating perioperative nutritional intervention have set postoperative loss of body weight and lean body mass as endpoints; however, the results were inconsistent. Therefore, recently, perioperative multimodal interventions that are expected to have a synergistic effect between nutritional intervention and exercise have gained attention. Furthermore, supplementing with leucine, a branched-chain amino acid, in addition to exercise, may be promising for preventing perioperative sarcopenia. However, whether perioperative nutritional intervention and exercise has clinical benefits in gastric surgery is unclear. With the aging of gastric cancer patients, measures to address sarcopenia will become more important in the future. Understanding the significance of nutritional intervention and exercise in patients undergoing gastric cancer surgery will help achieve good outcomes.

KEYWORDS

exercise, gastric cancer, nutrition therapy, sarcopenia, surgery

1 | INTRODUCTION

Although it is steadily declining in incidence, gastric cancer remains one of the most common and deadly neoplasms worldwide.[1] Gastrectomy with sufficient lymph node dissection is recommended for patients with gastric cancer in whom endoscopic resection is not indicated.[2] However, gastric cancer surgery may be associated with several complications. Recent studies have reported that postoperative surgical complications affect the long-term oncological outcomes of gastric cancer.[3-5] Therefore, it is necessary to take measures to prevent postoperative complications.

Various patient-related factors, such as age, sex, and performance status, influence the development of postoperative complications after gastrectomy for gastric cancer.[6,7] Among these factors, perioperative malnutrition and sarcopenia are strongly related to developing postoperative complications and poor survival outcomes.[8-10] Impaired nutritional status is common in cancers of the gastrointestinal tract, where the prevalence of malnutrition ranges from 20% to 70%.[11] In gastric cancer patients, insufficient oral intake related to disease-specific symptoms can induce more severe nutritional depletion than in other cancer patients, and this may result in an increased prevalence of sarcopenia.

Nutritional intervention is common in patients with gastric cancer, especially for those undergoing elective surgery. Various clinical trials evaluating nutritional intervention have been conducted; however, the results were inconsistent.[12-15] Furthermore, clinical trials evaluating preoperative nutritional intervention with exercise in gastric cancer have been performed[16]; however, how patients undergoing gastrectomy may benefit from this intervention is unclear. The purpose of this review was to summarize the current evidence supporting perioperative nutritional intervention and exercise for gastrectomy. The particular focus is on measures of preventing sarcopenia perioperatively.

2 | CLINICAL IMPACT OF PERIOPERATIVE SARCOPENIA ON GASTRIC CANCER REGARDING GASTRECTOMY

Sarcopenia was initially proposed to represent loss of skeletal muscle mass with aging.[17] However, recently, in addition to loss of skeletal muscle mass, functional decline with advancing age has become important. Sarcopenia is defined as loss of muscle mass plus low muscle strength and/or low physical performance, according to the European Working Group on Sarcopenia in Older People (EWGSOP)[18] and the Asian Working Group for Sarcopenia (AWGS) criteria.[19] Although the cut-off values are not contained in this review, these criteria recommend measuring bioimpedance analysis (BIA) and dual energy X-ray absorptiometry (DXA) to evaluate skeletal muscle mass, handgrip strength for muscle strength, and walking speed for physical function, clinically.

Many studies have suggested that sarcopenia is associated with postoperative complications and poor prognosis in various gastrointestinal cancer patients,[10,20-25] although several studies have shown the opposite outcomes.[26-28] In a study of 491 gastric cancer patients who underwent gastrectomy, Kuwada et al[27] reported that although sarcopenia was not associated with postoperative complications, it was an independent prognostic factor for overall survival. In addition, Tegels et al[28] reported a high prevalence of sarcopenia in their study (57.7%); however, sarcopenia was not a prognostic factor for severe postoperative complications and 6-month survival in patients with gastric cancer. Although the reasons for the difference between these studies, which showed opposite outcomes, are unclear, the differences might be affected by differing methods of evaluating and determining cut-off values for sarcopenia. In many studies, skeletal muscle mass index (SMI), which is skeletal muscle mass normalized by height, was used as a sarcopenia index.[20,22,24-26] However, to reduce the effect of obesity, Kuwada et al[27] used a different index, SMI divided by body surface area, and Tegels et al[28] used different cutoff values for SMI in males with a BMI of ≥25 vs <25.

As shown above, many studies evaluated only one item, such as loss of skeletal muscle mass or muscle strength, and few reports evaluated sarcopenia according to the diagnostic criteria. In gastric cancer, two retrospective studies evaluated sarcopenia according to the diagnostic criteria in the EWGSOP algorithm. Huang et al[22] described the results of 470 patients aged ≥18 years who underwent gastrectomy. Among them, 47 patients (10%) and 32 patients (6.8%) were diagnosed as having sarcopenia and severe sarcopenia, respectively. The overall complication rate increased with advancing sarcopenia stages in normal (non-sarcopenic) vs sarcopenia vs severe sarcopenia patients as 18.7% vs 27.7% vs 68.8%, respectively. In addition, Fukuda et al[23] reported that 21 of 99 patients (21.2%) with gastric cancer older than 65 years were diagnosed with sarcopenia preoperatively. The rate of severe postoperative complications (Clavien-Dindo grade ≥ IIIa) was significantly higher in the sarcopenic group than in the non-sarcopenic group (28.6% vs 9.0%, respectively). With the aging of the cancer population, perioperative assessment and intervention for sarcopenia is becoming increasingly important.

3 | SIGNIFICANCE OF NUTRITIONAL INTERVENTION

3.1 | Preoperative immunonutritional intervention

Recently, enteral immunonutrition with omega-3 fatty acids, glutamine, arginine, and nucleotides has received increasing attention. A meta-analysis reported that preoperative immunonutritional intervention should be encouraged in routine practice in patients undergoing surgery for gastrointestinal cancer because preoperative immunonutritional intervention for a minimum of 5 days before surgery reduced postoperative complications and shortened the hospital stay.[29] However, the results of published meta-analyses are difficult to interpret owing to the heterogeneity of the available studies, which include different types of cancers, surgical procedures, and nutritional status. Therefore, the recommendation to implement preoperative immunonutrition in major nutritional guidelines varies. The American Society for Parenteral and Enteral Nutrition (ASPEN) guidelines recommend that individuals undergoing gastrointestinal surgery in whom there is preexisting malnutrition would benefit from 5 to 7 days of preoperative supplementation.[30] In contrast, the European Society for Clinical Nutrition and Metabolism (ESPEN) Clinical Guideline states that immune-modulating oral nutritional supplements, including arginine, omega-3 fatty acids, and nucleotides, can be preferred preoperatively as there is no clear evidence for the preoperative use of immunonutrients compared with standard oral nutritional supplements exclusively.[31]

Fujitani et al[12] reported that preoperative immunonutrition (Impact®; Nestle Japan Health Science, Tokyo, Japan) for 5 consecutive days before gastrectomy in well-nourished patients did not reduce the incidence of postoperative complications. In the study, more than 95% of the enrolled patients were well-nourished, and the authors stated that this might have influenced the results. In addition, there was a possibility that recent procedural standardizations and sophisticated perioperative management might have contributed to the study results; therefore, it might be difficult to evaluate

the effect of immunonutrition alone. Currently, there is no evidence to support preoperative immunonutrition alone for gastric cancer.

3.2 | Postoperative intervention

The effectiveness of postoperative enteral nutrition in gastric cancer has not been fully demonstrated. Ida et al[14] and Aoyama et al[15] reported that perioperative immunonutrition (with ProSure®; Abbott Japan, Tokyo Japan, an eicosapentaenoic acid-enriched enteral formula) for 7 days before and 21 days after total gastrectomy did not prevent loss of body weight and lean body mass. In contrast, Imamura et al[13] reported positive results in an RCT evaluating 300 kcal/day of an elemental diet (Elental®; EA Pharma, Tokyo, Japan, an amino-acid-rich enteral formula) for 6-8 weeks after gastrectomy. The authors reported that elemental diet intervention suppressed body weight loss significantly, especially in patients who underwent total gastrectomy (controls: 9.13% ± 5.43%, intervention group: 5.03% ± 3.65%; $P = .012$). In addition, it is interesting that suppressing body weight loss was seen both 6-8 weeks postoperatively and 1 year postoperatively in patients who underwent total gastrectomy.[32] The reason for the discrepancy between these two RCTs (Ida et al's study[14]: negative results; Imamura et al's study[13]: positive results) is unclear, however, there are possible explanations. The first explanation is the difference in the content of the nutritional supplement. Amino acids may have affected the results, such as by suppressing lean body mass loss. Second, differences in the compliance rate and duration of nutritional intervention may also have affected the results. Imamura et al's study had a higher postoperative compliance rate (median: 81.2%) and a longer administration period (42-56 days) compared with Ida et al's study (median: 54% and 21 days after surgery, respectively). In addition, the possible effects of dose and duration can be inferred from the results of another prospective interventional study. Kobayashi et al conducted a prospective study of 400 kcal/day of Racol® NF (Otsuka Pharmaceutical Factory, Tokushima, Japan) for 3 months after gastrectomy.[33] The authors reported a significant reduction in body weight loss for patients who tolerated ≥200 mL/day compared with those who could not tolerate this amount.[33] A summary of these three studies is shown in Table 1. These studies indicate that postoperative nutritional intervention for gastric cancer may be significant; however, there is no evidence supporting perioperative nutritional intervention. There are still issues to consider, such as selecting the appropriate risk groups, content of the supplements, and the administration period.

4 | PERIOPERATIVE MULTIMODAL INTERVENTION FOR SARCOPENIA

4.1 | Exercise

Resistance exercise is an important factor that directly stimulates protein synthesis in skeletal muscle, and at low to moderate intensity, the rate of protein synthesis increases, depending on the intensity.[34] Aerobic exercise training improves maximal oxygen uptake, mitochondrial oxidative enzyme activity, and insulin sensitivity.[35] In addition, aerobic exercise also improved protein synthesis when

TABLE 1 Significance of perioperative nutritional intervention for gastrectomy

References	Imamura et al[13]	Ida et al[14]	Kobayashi et al[33]
Date	2016	2017	2017
Design	RCT	RCT	Prospective, single arm
Sample size	106	123	82
Type of gastrectomy	TG and DG	TG	TG and DG
Formula	Elental®	ProSure®	Racol®NF
Calorie (kcal/day)	300	600	400
Periods (days)			
Pre-	0	7	0
Post-	42-56	21	90
Compliance rate: mean (%)			
Pre-	N/A	92	N/A
Post-	68.7	61	52.7
Primary outcome: BW loss rate (%)	Control: 6-8W (mean ± SD) 6.60 ± 4.90	Control: 1 M:3 M (median) 8.9:13.0	<200 mL: 1 M:3 M (mean ± SD) 7.7 ± 2.6:10.4 ± 5.2
	Intervention: 6-8 W 4.86 ± 3.72*	Intervention: 1 M:3 M 8.8:12.9	≧200 mL: 1 M:3 M 6.3 ± 2.7*: 6.1 ± 4.3*

Abbreviations: BW, body weight; DG, distal gastrectomy; M, months; N/A, not applicable; RCT, randomized control trial; SD, standard deviation; TG, total gastrectomy; W, weeks.

*Statistical significance: $P < .05$.

combined with resistance exercise.[36] Furthermore, improving flexibility, i.e. stretching, can enhance the overall physical performance of other types of exercise. Furthermore, it is interesting to note that regular physical exercise induces anti-inflammatory cytokines and may suppress skeletal muscle wasting associated with cancer-induced inflammation.[37]

The Borg scale is used as an indicator of exercise intensity, and the scale is a self-monitoring visual scale on which patients are asked to rate the intensity of their effort, from 6 (no perceived effort) to 20 (maximal exertion).[38] Patients should be instructed to rehabilitate with a goal of moderate intensity as "somewhat hard," which is quantified as 12-14 on the Borg scale.

In real world daily practice, we may face several questions regarding exercise intervention for high-risk cancer patients, such as whether older adult patients or those with severe comorbidities are suitable candidates for this intervention, i.e. can it be done, and if so, how? Karlsson et al[39] conducted a randomized feasibility study of preoperative exercise in older adults scheduled to undergo colorectal cancer surgery. The median age of the intervention group was 83.5 years. The exercises (respiratory, strength, and aerobic) comprised two to three supervised sessions each week in the participants' homes, for at least 2-3 weeks or until surgery, and a self-administered exercise program between visits. The resistance level started at 50% of maximal capacity and was gradually adjusted with reference to the Borg scale. The self-administered exercise was performed 2-3 times/week and comprised 150 min/week of moderate physical activity, functional strength exercises (chair stands and step-up) 2-3 times/week, and inspiratory muscle training for 30 breaths twice a day. The compliance rate was 97%, and no severe adverse events occurred during training. In addition, a statistically significant between-group difference was found only for inspiratory muscle strength ($P < .01$). Chia et al[40] also conducted a perioperative exercise study involving frail elderly patients with colorectal cancer. The study included education and ensuring compliance, cardiovascular strengthening, mobilizing, muscle strengthening, and attention to nutrition. The authors reported that even in the high-risk group of patients, with a median age of 79 years and an American Society of Anesthesiologists (ASA) class ≥3 in 26% of the patients, an 80% adherence rate was achieved. Although selection bias in these studies must be considered, home-based exercise with attention to its intensity may be safe and feasible even for high-risk patients.

Perioperative exercise intervention is a possible means to enhance physical fitness and quality of life; however, the effect of perioperative exercise intervention alone is currently unclear regarding clinical outcomes (e.g. reduced postoperative complications).

4.2 | Amino acid supplements with exercise

After a single bout of resistance exercise, muscle protein synthesis and muscle protein breakdown are simultaneously stimulated in healthy individuals.[41] Indeed, exercise alone, in the absence of adequate nutrition, such as occurs perioperatively, does not lead to muscle protein accretion or maximal improvements in functional capacity.

Leucine, a branched-chain amino acid (BCAA), is a key nutrient in multimodal intervention. Oral administration of leucine stimulates muscle protein synthesis by activating the mammalian target of rapamycin (mTOR).[42] In addition, muscle protein synthesis is efficiently induced by a single intake of leucine-enriched essential amino acids (3 g of 40% leucine).[43] Furthermore, administration of 3 g of essential amino acids containing 40% leucine for 3 months combined with exercise for elderly Japanese people improved both muscle mass and muscle strength, and walking speed.[44,45]

Based on these findings, 3 g of essential amino acids containing 40% leucine was set as the optimum amount for muscle protein synthesis. However, leucine supplementation may not further enhance muscle protein synthesis in patients already consuming a protein/leucine-sufficient diet (i.e. >1.0 g/kg/d).[46]

4.3 | Clinical impact of preoperative nutritional intervention with exercise for gastrectomy

There is a preoperative interventional strategy called prehabilitation, which capitalizes on the waiting period before surgery, to optimize the patient's physical condition and promote earlier postoperative recovery.[37] Prehabilitation includes exercise as well as several preoperative management measures, such as nutritional intervention or psychological intervention, but involves mainly preoperative nutritional intervention and exercise.[47]

Yamamoto et al[16] evaluated the effects of preoperative nutritional intervention with exercise in 22 sarcopenic gastric cancer patients who were ≥65 years old. Although the study was a single-arm pilot study, it is the only interventional study of gastric cancer patients diagnosed with sarcopenia preoperatively. Table 2 shows the summary of this study. The nutritional intervention constituted adding 2.4 g of daily oral supplementation with the leucine metabolite, β-hydroxy-β-methylbutyrate (HMB). In addition, the preoperative exercise program constituted handgrip training, walking, and resistance training at home every day until admission for surgery. The mean age of the 22 enrolled patients was 75 years, and the median period of intervention was 16 days. During the program, no adverse events were observed. The results showed that handgrip strength improved significantly after exercise (20.0 ± 5.3 kg vs 21.2 ± 5.2 kg, before exercise vs after exercise, respectively; $P = .022$). In addition, four patients (18.8%) became non-sarcopenic after the exercise program. They concluded that preoperative nutritional intervention with exercise might reduce sarcopenia in older adult sarcopenic gastric cancer patients.

There is no consensus on the optimal duration of nutritional intervention and exercise; however, Yamamoto et al[16] reported that patients who underwent ≥3 weeks of intervention showed significant increases in lean body mass compared with those who participated for less than 3 weeks before gastrectomy. In addition, previous studies have identified 4 weeks as sufficient time

TABLE 2 Summary of preoperative multimodal intervention for gastrectomy

Reference	Yamamoto et al[16]
Date	2017
Design	Pilot study
Sample size	22
Age (mean)	75
Nutritional intervention	Daily oral supplementation with 2.4 g HMB
Exercise intervention	HGS training: 10 kg*20 times/d Walking: ≥7500 steps/day (for 1 h/d) Resistance training: three sets of 10 repetitions with 40%-60% maximum intensity
Timing	From diagnosis until operation
Duration	Median: 16 days (depends on the surgery date)
Outcomes	GS, HGS, body composition

Abbreviations: GS, gait speed; HMB, β-hydroxy-β-methylbutyrate; HGS, hand grip strength.

to modify behavior to improve physical function before colorectal surgery.[48] That is, the effect of nutritional intervention and exercise takes time. Therefore, it is necessary to develop a program that starts as soon as the diagnosis is made and that can be performed at home before admission.

4.4 | Clinical impact of exercise after gastrectomy

Cho et al[49] evaluated the safety and feasibility of a postoperative recovery exercise program (without nutritional intervention) in gastric cancer patients undergoing laparoscopic or robot-assisted gastrectomy. The exercise program comprised three phases: in-hospital exercise (1 week), home exercise (1 week), and fitness improvement exercise (8 weeks). In-hospital exercise was selected to increase the range of motion after gastrectomy and was performed under the supervision of an exercise specialist. Walking was encouraged as much as possible, without supervision. The home exercise was designed to improve the range of motion after hospital discharge. Patients were encouraged to complete the home exercise regimen in addition to the previous in-hospital exercise regimen more than once per day. The fitness improvement exercise program focused mainly on resistance exercises to improve postoperative function and reduction in muscle volume. Patients exercised three times a week. Among 24 patients enrolled in this study, 20 completed the study without adverse events related to exercise. The adherence and compliance rates for the fitness improvement exercises were 79.4% and 99.4%, respectively. Upon completing this program, patients showed significant improvement in cardiopulmonary function and muscular strength. Additionally, muscle volume was preserved between the preoperative period and after completing the program.

This study has some limitation, namely, the population was younger (mean age: 45.9 years) and the patients underwent minimally invasive surgery only. However, a systemic exercise intervention program might have some benefit for postoperative sarcopenia after gastrectomy.

5 | FUTURE PERSPECTIVE

Two clinical trials evaluating preoperative or postoperative multimodal intervention for gastric cancer patients are ongoing. One is an RCT being conducted in Lithuania (ClinicalTrials.gov identifier: NCT04223401) that is investigating the efficacy of preoperative intervention (nutritional intervention, psychological intervention, and exercise) for 128 patients undergoing gastrectomy for gastric cancer. The primary endpoint is the postoperative morbidity rate, and the secondary endpoints are physical function and quality of life up to 1 year after gastrectomy. Another RCT involving 242 Japanese patients aims to verify the effect of leucine administration and exercise on lean body mass loss 3 months after gastrectomy (UMIN000042307). Changes in physical function and activity up to 1 year after surgery are included as secondary endpoints. The results of these RCTs may contribute to developing an optimal program and may provide evidence supporting beneficial clinical outcomes in patients with gastric cancer.

6 | CONCLUSION

Perioperative nutritional intervention and exercise might have clinical benefit in gastric cancer patients. However, each intervention alone might be insufficient to improve the short- and long-term outcomes; therefore, it is necessary to establish a novel multimodal intervention program (nutritional intervention with exercise) and clarify its benefit in short- and long-term outcomes. With aging of the cancer population, understanding the importance of nutritional intervention and exercise will help achieve good outcomes in patients undergoing gastric cancer surgery.

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