



Sarcopenia is Associated with Postoperative Complications in Patients Undergoing D2 Gastrectomy for Gastric Cancer

Mide Kanseri Nedeniyle D2 Gastrektomi Uygulanan Hastalarda Sarkopeni Ameliyat Sonrası Komplikasyonlarla İlişkilidir

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ABSTRACT

Objective: This study aimed to investigate the relationship of sarcopenia with early postoperative complications in patients undergoing curative D2 dissection due to gastric cancer.

Methods: Patients with gastrectomy and D2 lymph node dissection for gastric cancer (GC) were retrospectively evaluated. Sarcopenia was diagnosed with computed tomography (CT) scan for pre-operative staging. Post-operative complications were determined according to Clavien-Dindo (CD) classification.

Results: Sarcopenia was seen in 59 (40.7%) of the 145 patients included in the study. The rate of overall postoperative complications in sarcopenic patients was higher than in non-sarcopenic patients. Surgical complications and medical complications were higher in sarcopenic patients. Severe surgical complications (CD Grade III and above) were significantly higher in the sarcopenia group. Sarcopenia (4.63, 95% confidence interval, 1.76-12.18; p=0.002) was a prognostic risk factor for postoperative complications.

Conclusion: Sarcopenia is associated with early postoperative complications in many types of cancer. This study showed that sarcopenia was associated with complications after D2 lymph node dissection in GC surgery. CT use in pre-operative clinical staging of patients and taking the necessary precautions make it easier to address post-operative complications.

Keywords: Sarcopenia, gastric cancer, gastrectomy, D2 lymph node dissection, postoperative complications.

ÖZ

Amaç: Bu çalışma mide kanseri (MK) nedeniyle küratif D2 lenf nodu diseksiyonu yapılan hastalarda sarkopeninin erken postoperatif komplikasyonlarla olan ilişkisini araştırmayı amaçlamaktadır.

Yöntemler: MK nedeniyle gastrektomi ve D2 lenf nodu diseksiyonu yapılan hastalar retrospektif olarak incelendi. Sarkopeni tanısı ameliyat öncesi evrelemede bilgisayarlı tomografi (BT) ile kondu. Ameliyat sonrası komplikasyonlar Clavien-Dindo (CD) sınıflamasına göre belirlendi.

Bulgular: Sarkopeni, çalışmaya katılan 145 hastanın 59'unda (%40,7) görüldü. Sarkopenik hastalarda ameliyat sonrası komplikasyon oranı sarkopenik olmayanlara göre daha yüksekti. Cerrahi ve medikal komplikasyonlar sarkopenik hastalarda daha yüksekti. Ciddi cerrahi komplikasyonlar (CD evre 3 ve üzeri) sarkopeni grubunda anlamlı olarak daha yüksekti. Sarkopeni (4,63, %95 güven aralığı, 1,76-12,18; p=0,002) postoperatif komplikasyonlar için prognostik bir risk faktörüdür.

Sonuç: Sarkopeni birçok kanser türünde erken postoperatif komplikasyonlarla ilişkilidir. Bu çalışma, mide kanseri cerrahisinde sarkopeninin D2 lenf nodu diseksiyonu sonrası komplikasyonlarla ilişkili olduğunu göstermiştir. Hastaların ameliyat öncesi klinik evrelemede BT kullanımı ve gerekli önlemlerin alınması ameliyat sonrası komplikasyonların ele alınmasını kolaylaştırmaktadır.

Anahtar Sözcükler: Sarkopeni, mide kanseri, gastrektomi, D2 lenf nodu diseksiyonu, ameliyat sonrası komplikasyonlar

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Introduction

Gastric cancer (GC) is the fifth most commonly diagnosed malignancy and the third leading cause of cancer-related deaths among all cancers (1). After discussing for a long time, radical gastrectomy and D2 lymph node dissection in locally advanced GC was considered as standard surgical treatment in the western and eastern worlds (2,3). Despite advances in perioperative care and surgical techniques, after gastric resection and D2 dissection, postoperative mortality (5%) and morbidity (62%) rates are still high (4-6). In many studies, advanced age, presence of comorbidity/comorbidities, high body mass index (BMI), and malnutrition have been defined as risk factors for postoperative complications after GC surgery (7-9).

Rosenberg first described sarcopenia as age-related progressive skeletal muscle (SM) loss (10). The current definition by the European Working Group on Sarcopenia in Older People (EWGSOP) and The Asian Working Group for Sarcopenia state that sarcopenia is a syndrome that involves a decrease in a generalized loss of muscle mass, muscle strength, and function (11,12). Although sarcopenia is mainly seen in older ages; it can also be seen at an early age along with malnutrition, inactivity, and cancer. Patients with GC have a high risk of developing sarcopenia due to intestinal obstruction, vomiting, and decreased food intake (11).

Routine computerized tomography (CT) is performed in pre-operative clinical staging in cancer patients. Especially in clinical trials, CT is defined as one of the most recommended methods for diagnosing sarcopenia (11,12). Sarcopenia is diagnosed by calculating the SM index (SMI) from axial sections that pass through the third lumbar vertebrae (L3) (13,14). Sarcopenia is known to adversely affect early post-operative complications and survival in different types of cancer (15,16).

Several studies have reported that sarcopenia causes an increase in early postoperative complication rates in GC (14,17-19). Increased complication rates lead to prolonged hospital stays and increases in costs, mortality, and morbidity. In some studies involving populations of patients who were operated due to GC, the prevalence of sarcopenia was reported as high compared to other abdominal surgical oncology populations, but sarcopenia was not associated with postoperative morbidity or mortality (20).

This study aimed to investigate whether sarcopenia is associated with early postoperative complications in patients who have had gastrectomy and D2 lymph node dissection with the diagnosis of GC in our clinic.

Methods

Ethical committee approval (2018-980) was obtained from Okmeydanı Training and Research Hospital. Patients with locally advanced gastric adenocarcinoma that underwent surgery for consecutive curative purposes between January 2013 and June 2020 were retrospectively evaluated. Patients over 18 years of age, histological type of gastric adenocarcinoma, and an

Eastern Cooperative Oncology Group performance score (0-2) were considered as the inclusion criteria for the study. Metastatic patients and those with second primary cancer were not included in the study. Based on CT findings, patients were divided into two groups consisting of sarcopenic and non-sarcopenic patients. The same surgical team performed curative gastric resection and D2 lymph node dissection. Roux en Y anastomosis was preferred for reconstruction. Complication data were retrieved from the prospectively generated database. Complications that developed within the 30 days of surgery were considered early postoperative complications. Early postoperative complications and duration of hospital stay were evaluated. Post-operative complications were evaluated according to Clavien-Dindo (CD) Classification (21). Grades I and II were identified as mild and Grade III and above as severe complications. Complications were defined as surgical complications that were directly related to the surgical field. Systemic complications that developed outside the surgical area were defined as medical complications. Severe complications were considered based on the CD scans when more than one complication was seen in the same patient. Operative mortality was assessed as death within the first 30 days of the postoperative period or deaths due to post-operative complications. Tumor staging was performed according to the American Joint Committee on Cancer Staging 8th edition (22).

The CT images taken within three weeks of pre-operative staging or re-staging in patients receiving neoadjuvant therapy were evaluated. CT evaluation was performed by radiologists experienced in gastrointestinal tract radiology. The assessment was carried out by transferring images to high-resolution medical monitors with picture archiving communication systems. Three consecutive axial CT images with a thickness of 5 mm were taken, passing through the upper, middle, and lower levels of the lumbar vertebra (L3) corpus. Using advanced image processing methods on these three sections, the muscles were separated from other tissues by selecting Hounsfield Unit (HU) values -29 and $+150$ HU. The muscles on the chosen section (rectus abdominus, transversus abdominus, external oblique, internal oblique, psoas, erector spina, and quadratus lumborum) were manually painted in a different color, and the surface measurement of the muscles was obtained (Figure 1A and B). The surface of the muscles was then expressed as cm^2 by obtaining the average of these three separate sections. INFINITT software (version 3.0.11.3, INFINITT Healthcare Co. Ltd., Seoul, Korea) was used for this measurement. The surface area of these muscles (cm^2) was divided into the square of the patient's height, and the total skeletal musculoskeletal mass index ($\text{SMI} = \text{cm}^2/\text{m}^2$) was obtained. BMI and different cut-off values by gender were used to diagnose sarcopenia. Male patients with a BMI ≥ 25 and an SMI below $53 \text{ cm}^2/\text{m}^2$ or a BMI of < 25 and SMI $< 43 \text{ cm}^2/\text{m}^2$ were accepted as sarcopenic. In women, patients with SMI below $41 \text{ cm}^2/\text{m}^2$ were considered sarcopenic (20,23).

Statistical Analysis

Statistical analysis of data was obtained using the Statistical Package for the Social Sciences (SPSS)22.0 (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk,

NY: IBM Corp.) program. The mean ± standard deviation was used as descriptive statistics when summarizing variables. The Student's t-test or Mann-Whitney test was used for continuous variables when making cross-group comparisons. In evaluating categorical data, the chi-square test was used for binary variables. We assessed the prognostic effects of sarcopenia-related parameters on complications. We analyzed clinical and pathological factors that affected complications. For this, we applied the logistic regression model 24. Post-operative complications and clinicopathological factors affecting these complications were analyzed together with multivariable logistic regression models. Each parameter was analyzed individually. Results were defined as odds ratios and 95% confidence interval (CIs), and a p-value <0.05 was considered statistically significant.

Results

The mean age of the 145 study patients was 60.2±12.2, and 98 were males (67%). Fifty-nine (40.7%) patients were sarcopenic. Thirty-seven out of 80 patients receiving neoadjuvant therapy were sarcopenic. No differences in terms of age, BMI, tumor localization, type of surgery, histological differentiation, and tumor stage between sarcopenic and non-sarcopenic patients were noted.

The mean SMI of the patients was 38 (29-52) in the sarcopenic and 51 (41-66) in the non-sarcopenic groups.

Demographic and clinical patient information are given in Table 1. Of 145 patients, 60 patients had subtotal, and 85 patients had total gastrectomy. All patients underwent curative R0 resection, D2 dissection, and Roux N Y esophagojejunostomy/gastrojejunostomy anastomosis. The mean operative time was 225 minutes, and no difference between sarcopenic and non-sarcopenic patients was found. The mean number of lymph nodes removed was 36 (10-83).

Post-operative complications are shown in Table 2. The total number of patients with at least one post-operative complication was 36 (24.8%). The postoperative complication rate was significantly higher in the sarcopenic group (42.4%) than in the non-sarcopenic group (12.8%; p=0.008). Most of the complications (n=25) were mild (<grade III). The surgical complication rate was 20.7%, and the medical complication rate was 4.1%. The most common mild complication was wound as infection (n=13). Of these 11 patients with severe complications, nine were surgical (≥ CD grade III), and two were medical complications. The most common severe surgical complication was pancreatic fistula (n=4). Eight of the patients who developed severe surgical complications were in the sarcopenic group, and a statistically significant difference between the groups was found (p=0.009). Medical, surgical, and overall complications in sarcopenic and nonsarcopenic patients are shown in Figure 2. The number of patients who underwent repeat surgeries was three. One patient underwent three repeat surgeries for an anastomotic leak and pancreatic fistula. Two patients underwent repeat surgery, one with intra-abdominal bleeding and the other with anastomotic leakage. Two of the three patients who underwent repeat surgeries were in the sarcopenic group. Mortality occurred in three patients (2.1%). On the seventh postoperative day, a patient died due to myocardial infarction, one patient died of pulmonary embolism on the sixth day, and one died on the 39th day due to anastomotic leakage.

The median hospital stay was 8.5 (6-49) days in the non-sarcopenic group and 12.9 (5-155) in the sarcopenic group. A statistically significant difference between the two groups was found in terms of hospital stay (p=0.008).

Univariate and multivariate analysis results associated with complications are shown in Table 3. Multivariate logistic regression analysis was performed according to age, sex, duration

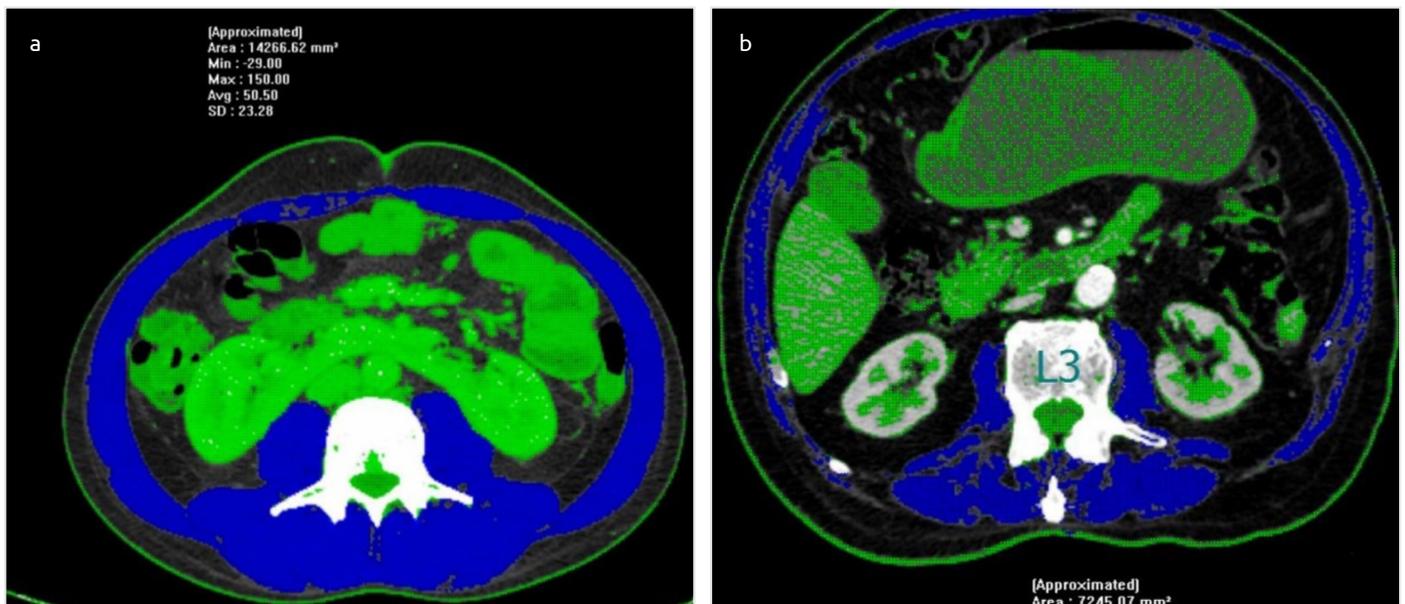


Figure 1. a) Non-sarcopenic patient CT image, b) Sarcopenic patient CT image

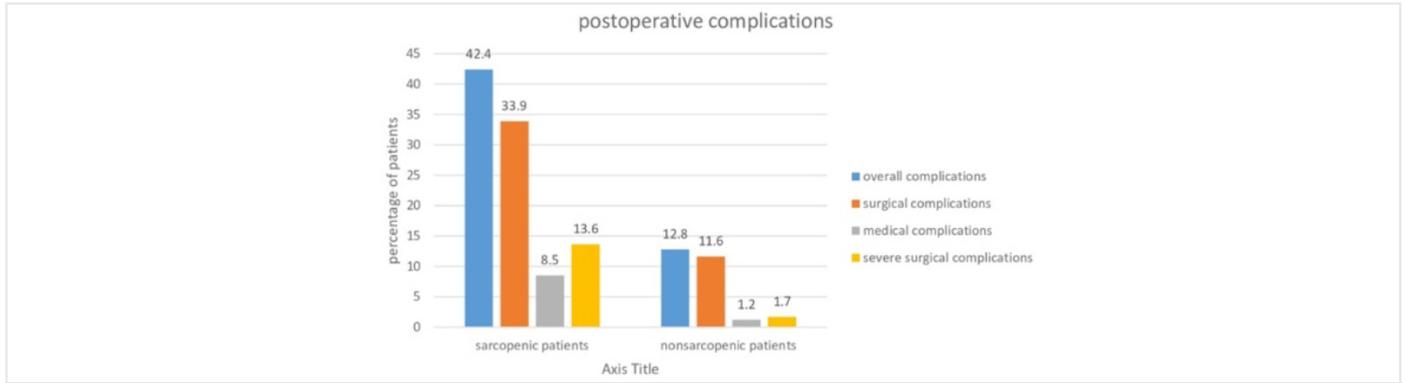


Figure 2. Incidence of overall, surgical, medical and severe surgical complications in sarcopenic and non-sarcopenic patients

Table 1. Patients' demographic and clinicopathological features

| | Sarcopenia (n=59) | Non-sarcopenia (n=86) | All (n=145) | p value |
|--|-------------------|-----------------------|------------------|---------|
| Age (years) | 61.7±12.5 | 59.1±12.0 | 60.2±12.2 | 0.161 |
| Sex | | | | |
| Male | 30 (50.8) | 68 (79.1) | 98 (67.6) | 0.0001 |
| Female | 29 (49.2) | 18 (20.9) | 47 (32.4) | |
| Preoperative chemotherapy | 37 (62.7) | 43 (50.0) | 80 (55.2) | 0.09 |
| Additional organ resection | 7 (11.9) | 12 (14.0) | 19 (13.1) | 0.45 |
| BMI (kg/m ²) | 25.0 (18.0-32.0) | 24.9 (18.6-43.0) | 25.0 (18.0-43.0) | 0.97 |
| SMI (cm ² /m ²) | 38.0 (29.0-52.0) | 51.0 (41.0-66.0) | 46.0 (29.0-66.0) | 0.0001 |
| Histologic type | | | | |
| Well differentiated | 9 (15.3) | 14 (16.3) | 23 (15.7) | 0.88 |
| Moderately differentiated | 18 (30.5) | 29 (33.7) | 47 (32.4) | |
| Undifferentiated | 32 (54.2) | 43 (50.0) | 75 (51.7) | |
| Tumor location | | | | |
| Cardia | 16 (27.1) | 16 (18.6) | 32 (22.1) | 0.11 |
| Corpus | 21 (35.6) | 27 (31.4) | 48 (33.1) | |
| Antrum | 22 (37.3) | 43 (50.0) | 65 (44.8) | |
| TNM stage | | | | |
| Stage I | 14 (23.7) | 23 (26.7) | 37 (25.5) | 0.61 |
| Stage II | 21 (35.6) | 23 (26.7) | 44 (30.3) | |
| Stage III | 21 (35.6) | 37 (43.0) | 58 (40.0) | |
| Stage IV* | 3 (5.1) | 3 (3.4) | 6 (4.1) | |
| Type of gastrectomy | | | | |
| Total gastrectomy | 38 (65.5) | 47 (54.7) | 85 (58.6) | 0.30 |
| Subtotal gastrectomy | 21 (36.2) | 39 (45.3) | 60 (41.4) | |
| Operation duration (minutes) | 225 (180-360) | 225 (150-360) | 225 (150-360) | 0.87 |
| Tumor size (cm) | 4.0 (0.2-13) | 4.0 (0.1-20) | 4.0 (0.1-20) | 0.20 |
| Number of harvested lymph nodes | 33 (10-79) | 37 (13-83) | 36 (10-83) | 0.45 |
| Length of hospital stay (days) | 12.9 (5-155) | 8.5 (6-49) | 10.3 (95-155) | 0.008 |

BMI: Body mass index, SMI: Skeletal muscle index

Data presented as mean ± standard deviation, median (1st-3rd quartiles) or n (%).

*: Malignant cells in peritoneal washings

of surgery, sarcopenia, tumor stage, neoadjuvant chemotherapy, gastrectomy type, additional organ resection, tumor diameter, and total number of removed lymph nodes. Sarcopenia (4.63, 95% CI 1.76-12.18, p=0.002) emerged as an independent prognostic factor for postoperative complications.

Discussion

Studies related to sarcopenia are rapidly increasing. Standardization, cut-off values, and diagnostic criteria should be determined. The EWGSOP and Asian Sarcopenia Study groups have defined new diagnostic criteria for sarcopenia (11,12). CT is one of the diagnostic methods that can be used to diagnose sarcopenia. Since we used CT in the clinical staging of pre-operative tumors in our patients, we diagnosed sarcopenia according to these values. Sarcopenia rates are shown in the literature over a wide range from 12.5% to 72.2%. (14,18,20,25). The different rates in these studies vary depending on the selected cut-off values. In our study, we found that the sarcopenia rate was 40.7%.

Systemic inflammation, hyper-catabolism, and nutritional disorders lead to sarcopenia regardless of age in cancer patients. Sarcopenia causes an increase in postoperative complication rates in studies of different cancer patients (26,27). Although GC surgery is the most effective treatment for the disease, postoperative complication rates are high (4-6). GC is a biologically aggressive tumor. Patients cannot get enough calories due to obstruction or neoadjuvant treatment in the pre-operative period. Due to insufficient caloric intake and the effect of the tumor on the inflammatory system, patients with GC also have a high risk of sarcopenia development (14,18,20). In studies, sarcopenia caused an increase in the rates of early

postoperative complications in patients who underwent surgery for gastric adenocarcinoma (14,17-19,28). In our study, patients in both groups underwent the same surgical approach by the same surgical team. Our total complication rate (p=0.008) and surgical complication rates (CDIII) ≥ were higher in sarcopenic patients (p=0.009).

When postoperative hospital stay is evaluated, the average hospital stay in sarcopenic patients is longer (25). We found that the sarcopenic group had a higher hospital stay (p=0.008).

In a study of 152 patients, Tegels showed that the sarcopenia rate was 57.7%, but it did not increase the risk of post-operative complications (20). In this study by Tegels, the curative resection rate was 69.7%, and the results might be associated with a low curative resection rate. In our study, curative resection and D2 lymph node dissection were performed to all patients.

Advanced age, malnutrition, and decreased physical activity are among the causes of sarcopenia (11). In our study, no difference in terms of age between the sarcopenic and nonsarcopenic groups was found. Considering that the elderly population will increase and patients will have GC in older age, evaluating these patients for sarcopenia and taking necessary precautions will help reduce post-operative complications. Pre-operative calorie and protein intake in sarcopenic patients are significantly lower than in non-sarcopenic patients. Providing adequate pre-operative calorie and protein support to these patients can reduce postoperative complication rates. A decrease in muscle strength in patients with sarcopenia leads to impaired physical performance, decreased cardiopulmonary capacity, impaired endothelial function, and decreased tissue oxygenation (29,30). These issues will negatively affect wound healing. In our study, respiratory physiotherapy

Table 2. Postoperative complications

| | Sarcopenia n=59 (%) | Non-sarcopenia n=86 (%) | All n=145 (%) | p value |
|---|------------------------|----------------------------|------------------|--------------|
| All postoperative complications | 25 (42.4) | 11 (12.8) | 36 (24.8) | 0.008 |
| All surgical complications | 20 (33.9) | 10 (11.6) | 30 (20.7) | |
| Wound complications | 7 (11.9) | 6 (7.0) | 13 (9.0) | |
| Intra-abdominal bleeding | 1 (1.7) | 1 (1.2) | 2 (1.4) | |
| Anastomotic leakage | 1 (1.7) | 1 (1.2) | 2 (1.4) | 0.084 |
| Chylous leakage | 6 (10.2) | 2 (2.3) | 8 (5.5) | |
| Pancreatic fistula | 4 (6.8) | 1 (1.2) | 5 (3.4) | |
| Evisceration | 1 (1.7) | - | 1 (0.7) | |
| All medical complications | 5 (8.5) | 1 (1.2) | 6 (4.1) | |
| Miyocardial infarction | 1 (1.7) | - | 1 (0.7) | |
| Pneumonia | 3 (5.1) | 1 (1.2) | 4 (2.8) | 0.041 |
| Pulmonary embolism | 1 (1.7) | - | 1 (0.7) | |
| Severe surgical complications ≥ grade-III | 8 (13.6) | 1 (1.7) | 9 (6.2) | 0.009 |
| Severe medical complications | 2 (3.4) | 0 | 2 (1.4) | 0.66 |
| Mortality | 2 (3.4) | 1 (1.2) | 3 (2.1) | 0.36 |
| Length of hospital stay (days) | 12.9 (5-155) | 8.5 (6-49) | 10.3 (5-155) | 0.008 |

Data presented as mean ± standard deviation, median (1st-3rd quartiles) or n (%)

and nutritional support were administered to all patients during the pre-operative period depending on their nutritional status. Pre-operative regular repeated physical exercise and nutrition support programs have the potential to reduce sarcopenia and improve the postoperative clinical condition, especially in patients with malnutrition (29,30). Before surgery, the focus should be on improving postoperative clinical outcomes.

Study Limitations

The single-center nature was the main limitation of our study. Multicenter studies with a large number of patients are needed. In addition, the evaluation of sarcopenia diagnosis not only with CT but also with the parameters of muscle strength and physical performance should be supported (11).

In this study, we found that sarcopenia caused an increase in postoperative complications after D2 lymph node dissection

in GC surgery. As a result, it can be said that the diagnosis of preoperative sarcopenia could be effective in terms of the development of postoperative complications. Diagnosing pre-operative sarcopenia with CT, which is used in patients' pre-operative clinical oncologic staging, and taking the necessary precautions can make it easier to deal with postoperative complications.

Conclusion

Sarcopenia, diagnosed by CT findings, is an independent risk factor for postoperative complications after D2 gastrectomy for locally advanced gastric adenocarcinoma. The early postoperative complications were higher in sarcopenic patients. Before surgery, the focus should be on improving sarcopenia to reduce postoperative complications.

Table 3. Univariable and Multivariable analysis of factors associated with complications

| | No complications (n=109) | Complications (n=36) | pvalue | Odds Ratio (95% CI, p value) |
|-------------------------------|-----------------------------|-------------------------|--------|---------------------------------|
| Age (years) | 60.5±12.5 | 59.4±11.6 | 0.65 | 0.99 (0.95-1.04, p=0.818) |
| Sex | | | 0.523 | |
| Male | 74 (75.5) | 24 (24.5) | | 1.13 (0.41-3.18, p=0.811) |
| Female | 35 (74.5) | 12 (25.5) | | |
| Sarkopenia | | | 0.0001 | 4.63 (1.76-12.18, p=0.002) |
| Yes | 34 (57.6) | 25 (42.4) | | |
| No | 75 (87.2) | 11 (12.8) | | - |
| Preoperative chemotherapy | | | 0.001 | 4.64 (1.56-13.80, p=0.006) |
| Yes | 52 (65) | 28 (35) | | |
| No | 57 (87.7) | 8 (12.3) | | - |
| Tumor localisation | | | 0.12 | |
| Cardia | 21 (65.6) | 11 (64.4) | | 0.69 (0.21-2.32, p=0.551) |
| Corpus | 34 (70.8) | 14 (29.2) | | 0.07 (0.01-0.65, p=0.267) |
| Antrum | 54 (83.1) | 11 (16.9) | | |
| Type of gastrectomy | | | 0.092 | 0.10 (0.01-13.7, p=0.356) |
| Total | 60 (70.6) | 25 (29.4) | | |
| Subtotal | 49 (81.7) | 11 (18.3) | | |
| Additional organ resection | | | 0.024 | 0.07 (0.01-0.65, p=0.020) |
| Yes | 18 (94.7) | 1 (5.3) | | |
| No | 91 (72.2) | 35 (27.8) | | |
| Operationduration (minutes) | 219 (150-360) | 240 (180-360) | 0.36 | 1.00 (0.99-1.01, p=0.948) |
| TNM STAGE | | | 0.1 | |
| Stage I | 28 (75.7) | 9 (24.3) | | 1.37 (0.39-4.79, p=0.619) |
| Stage II | 28 (63.6) | 16 (36.4) | | 0.52 (0.12-2.19, p=0.371) |
| Stage III | 47 (81.0) | 11 (19.0) | | - |
| Stage IV | 6 (6) | 0 (0) | | - |
| Tumor size (cm) | 4 (0.1-20) | 3.4 (0.2-12) | 0.21 | 0.94 (0.77-1.14, p=0.514) |
| Number of harvestedlymphnodes | 35 (10-83) | 40.5 (18-78) | 0.18 | 1.02 (0.99-1.06, p=0.203) |

CI: Confidence interval, BMI: Body mass index, SMI: Skeletal muscle index.

Data presented as mean ± standard deviation, median (1st-3rd quartiles) or n (%). Multivariable analysis, Univariable analysis

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