Short- and long-term outcomes of sarcopenia in gastric cancer patients

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BACKGROUND: *Sarcopenia, defined as loss of skeletal muscle mass and associated with lower outcomes in gastrointestinal tumors. This study aimed to show the effects of sarcopenia on prognosis, morbidity, and mortality in patients diagnosed with gastric cancer in light of these data.*
METHODS: *This single-center retrospective cohort study evaluated patients aged 18 to 80 years who were diagnosed with gastric cancer between 2010 and 2015. Preoperative CT images of the patients were examined. The muscle area was calculated at the L3 vertebra level on CT images the values of <43 cm^2/m^2 for men and <41 cm^2/m^2 for women, which were determined and shown to be associated with reduced survival, on the tomography scans obtained from all oncological patients for screening purposes*
RESULTS: *The SMI ranged from 26.2 to 73.8 (cm^2/m^2) in men and 24.8 to 55.07 (cm^2/m^2) in women. The mean SMI was 48.97 (cm^2/m^2) in men and 39.07 (cm^2/m^2) in women. Among study patients, 43 men and 33 women were sarcopenic. Sarcopenia was statistically significantly more common in men than in women. Comorbidities were more common in the Sarcopenic group. However, there was no statistically significant difference (p = 0.49). In the Sarcopenic group, forty-nine patients were referred to neoadjuvant therapy, while fifty-three patients were referred to neoadjuvant therapy in non-sarcopenic group.*
CONCLUSION: *The present study shows the effects of CT-based measured sarcopenia on short- and long-term outcomes in gastric cancer patients. It is believed that the detection and correction of sarcopenia in these patients would positively affect the early and late outcomes.*

KEY WORDS: Cancer Cachexia, Gastric Cancer, Sarcopenia

Introduction

Gastric cancer is the fifth most common cancer and the third leading cause of cancer deaths worldwide [1].

Despite the advanced surgical techniques and medical treatments today, the rate of gastric cancer mortality remains high [2]. In addition, the operative mortality and morbidity rates are still high despite the advanced surgical techniques [3]. However, despite the high morbidity rates, R0 surgical resection remains the most effective treatment method [4,5].

In the early stages, gastric cancer causes symptoms such as loss of appetite and dyspepsia. Therefore, patients with reduced oral intake often present with malnutrition at the time of diagnosis [6]. Sarcopenia is a very common

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condition in these patients, resulting in progressive and generalized loss of muscle and function [7]. In sarcopenia, muscle quality decreases and muscle fibers turn into fibrotic tissue, resulting in increased fractures and loss of function [8]. However, there are many definitions of sarcopenia in the literature. One of the initial definitions for sarcopenia was a skeletal muscle mass two standard deviations below that of the reference group [9].

Studies have showed that sarcopenia causes increased mortality and infection rates in patients [10]. Moreover, the quality of life of patients decrease due to loss of function caused by sarcopenia [11]. Many factors are involved in the pathogenesis of sarcopenia. Especially factors such as chronic diseases, insulin resistance, inflammation, and increased immune response play a role in the pathogenesis of sarcopenia [12]. Today, many different methods are used to demonstrate the presence of sarcopenia in a patient.

These methods vary by patients, resources of healthcare centers, and clinics. The European Working Group on Sarcopenia in Older People (EWGSOP) and the Asian Working Group for Sarcopenia recommend the use of low muscle mass and/or poor physical performance in the diagnosis of sarcopenia [7]. While muscle mass can be measured by many different methods, computed tomography (CT) imaging is generally considered the gold standard [7,14]. Multiplying the muscle area at the L3 vertebra level by the density gives the total muscle mass [15]. In conclusion, muscle imaging at the L3 vertebra level helps in both calculating muscle mass and determining the prognosis. This retrospective study aimed to show the effects of sarcopenia on prognosis, morbidity, and mortality in patients diagnosed with gastric cancer in light of these data.

Materials and Methods

Patients

This single-center retrospective cohort study evaluated patients aged 18 to 80 years who were diagnosed with gastric cancer between 2010 and 2015. Patients who had preoperative CT images, who had surgery in our clinic, and who had been postoperatively followed up in our clinic were included in the study. Patients whose images could not be assessed since the imaging was performed at an external center, who did not have sufficient file information, and who had surgery in other centers were excluded from the study. The study was approved by the hospital ethics committee (Date: 22/02/2022, No: 343).

Information collection

All information was extracted retrospectively from the hospital registry system. The laboratory and pathology results of the patients were examined. The postoperative ward follow-up charts were examined. Preoperative and postoperative staging of the patients was performed.

CT Examinations

Preoperative CT images of the patients were examined. The muscle area was calculated at the L3 vertebra level on CT images. All calculations were made by the same radiologist (BAU), avoiding calculation differences. The surface areas were normalized to cm2/m2 by dividing by the mean surface areas for the genders to minimize any confusion in data comparisons.

Sarcopenia definition

The most commonly used definition for sarcopenia is an appendicular SMI two standard deviations below that of a healthy individual (7.26 kg/m^2 for men; 5.45 kg/m^2 for women). We do not use X-ray absorptiometry, so we did not use the abovementioned values as measurement values. We used the values of <43 cm^2/m^2 for men and <41 cm^2/m^2 for women, which were determined by Martin et al [16] and shown to be associated with reduced survival, on the tomography scans obtained from all oncological patients for screening purposes.

Statistics

The SPSS 23.0 program was used for the statistical analysis of the data. Categorical data were expressed as counts and percentages, while continuous data were expressed as mean, deviation, and minimum-maximum values. The normality of the variables was tested using visual (histograms and probability graphics) and analytic methods (Kolmogorov-Smirnov/Shapiro-Wilk tests). The Chi-square test and Fisher's exact test were used to compare categorical variables. The Independent Student's t-test was used for normally distributed parameters and Mann-Whitney U test for non-normally distributed groups. The level of statistical significance was set to 0.05 for all analyses. The Kaplan-Meier analysis and Log-Rank test were used to examine survival. The level of statistical significance was set to 0.05 for all analyses.

Results

Distribution Of Skeletal Muscle Index (Smi)

The SMI ranged from 26.2 to 73.8 (cm^2/m^2) in men and 24.8 to 55.07 (cm^2/m^2) in women. The mean SMI was 48.97 (cm^2/m^2) in men and 39.07 (cm^2/m^2) in women.

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Characteristics

The characteristics of the study groups are presented in (Table I).

The mean age of the study patients was 63.04 ± 12.5 (years) and the median age was 65. The mean number of lymph nodes removed after surgery was 27.13 ± 13.9 (n), and the mean number of positive lymph nodes was 6.77 ± 9.55 (n). The mean survival of the patients was 23.24 ± 16.99 (months). The mean preoperative albumin value of the patients was 3.67 ± 0.58 g/dl.

Among study patients, 43 men and 33 women were sarcopenic. Sarcopenia was statistically significantly more common in men than in women. Comorbidities were more common in the Sarcopenic group. However, there was no statistically significant difference (p = 0.49). In the Sarcopenic group, forty-nine patients were referred to neoadjuvant therapy, while fifty-three patients were referred to neoadjuvant therapy in non-sarcopenic group. Despite the higher rate of indication for neoadjuvant therapy in Sarcopenic group, the difference was not statistically significant.

Total gastrectomy was the more frequently performed surgery in both groups. Although total gastrectomy percentage was higher in the Non-Sarcopenic group, no statistically significant difference was found. Concerning tumor localization, distal tumors were more common in the Sarcopenic group. However, no statistically significant difference was found between the two groups. Additional organ resection was required in a total of forty patients in the two groups. Twenty-one of these patients were in the Sarcopenic group.

Table I - *The characteristics of the study.*

	Mean±SD	Med (Min-Max)
Age (years)	63.040 ± 12.564	65 (27-91)
Number of Lymph nodes (n)	27.13 ± 13.92	24 (1-93)
Positive lymph nodes (n)	6.77 ± 9.55	3 (0-43)
Survival (months)	23.24 ± 16.99	24 (0-72)
Preoperative albumin (g/dl)	3.67 ± 0.58	3.7 (2.3-4.9)
Preoperative HGB (g/dl)	11.44 ± 1.85	11.4 (7-16.1)
CEA (ng/ml)	14.54 ± 61.58	2.4 (0.35 - 571.4)

Table II - *Association of pathologic results, operational outcomes, gender.*

		Sarcopenia (n: 76) n (%)	Non-Sarcopenia (n: 117) n (%)	p
Gender, n (%)	Male	43(56)	97 (83)	<0.001
	Female	33 (44)	20 (17)	
T, n (%)	T1	6 (7.8)	19 (16.2)	0.063
	T2	4 (5.2)	14 (11.9)	
	T3	39 (51.3)	42 (35.8)	
	T4	27 (35.5)	42 (35.8)	
N, n (%)	N0	20 (26.3)	46 (39.3)	0.004
	N1	18 (23.6)	27 (23.0)	
	N2	10 (13.1)	26 (22.2)	
	N3	28 (36.8)	18 (15.3)	
Stage, n (%)	1	9 (11.8)	29 (25.4)	0.111
	2	22 (29.3)	25 (21.1)	
	3	41 (53.9)	60 (50.8)	
	4	4 (5.3)	3 (2.5)	
Neoadjuvant, n (%)	No	27 (35.5)	64 (54.7)	0.009
	Yes	49 (64.4)	53 (45.2)	
Comorbidity (n, %)	No	34 (44.7)	67 (57.2)	0.088
	Yes	42 (55.2)	50 (42.8)	
Type of operation, n (%)	Total gastrectomy	54 (71.0)	74 (63.2)	0.262
	Distal subtotal gastrectomy	22 (28.9)	43 (36.7)	
Tumor location, n (%)	Upper	21 (27.6)	20 (17.0)	0.173
	Middle	38 (50.0)	72 (61.5)	
	Lower	17 (22.3)	25 (21.3)	
Additional organ resection, n (%)	No	51 (72.4)	98 (83.7)	0.564
	Yes	21(27.6)	19 (16.3)	
Anastomotic leak, n (%)	No	68 (89.4)	109 (93.1)	0.363
	Yes	8 (10.6)	8 (6.9)	

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Table III - *Association between study groups.*

	Sarcopenia(n: 76) Med (Min-Max)	Non-Sarcopenia(n: 117) Med (Min-Max)	p
Age (years)	67 (31-91)	61.5 (27-91)	0.054
Number of Llymph nodes (n)	24 (1-73)	25.5 (4-93)	0.103
Positive lymph nodes (n)	4 (0-39)	1.5 (0-43)	0.659
Survival (months)	18 (0-60)	24 (1-72)	0.071
Preoperative albumin (g/dl)	3.6 (2.3-4.8)	3.9 (2.3-4.9)	<0.001
Preoperative HGB (g/dl)	11.1 (7.6-15.8)	11.45 (7-16.1)	0.001
CEA (ng/ml)	3.1 (0.35-571.4)	2.07 (0.52-18.8)	0.936
Ca19*9	12.8 (0.6-1025)	10.5 (0.6-7835.0)	0.597

Table IV - *Survival rates according to groups.*

	Mean		95% Confidence Interval					
	Estimated Mean	Std.	Lower Bound	Upper Bound	1-year Survival %	3-year Survival %	5-year Survival %	
Sarcopenia	29.60	1.79	26.08	33.13	85.4	37.9	0.06	0.018
Non-Sarcopenia	36.72	2.36	32.08	41.35	91.3	53.2	19.5	

Additional organ resection was required in approximately 27.6% of patients in this group, and there was no statistically significant difference in this rate between the two groups. Anastomotic leaks were detected in sixteen patients in the two groups. Eight of these patients were in the low SMI group. However, there was no significant difference between the two groups (Table II).

When we evaluated the patients clinically and pathologically, sarcopenic patients were found to be older. The median value was 67 in this group of patients ($p<0.05$). No significant difference was found in the number of positive lymph nodes, the total number of lymph nodes, and the depth of invasion (T) between the groups. Preoperative hemoglobin, albumin, and CEA levels were also examined in all patients.

Hemoglobin levels were lower in the Sarcopenic group; however, there was no significant difference (HGB: 11.1 vs. 11.4 g/dl; $p=0.33$). The CEA value was 3.1 (ng/ml) in the sarcopenic group and 2.07 (ng/ml) in non sarcopenic group (Table III).

Long-term survival was also evaluated by comparing the groups. The groups were evaluated for 1-year, 3-year, and 5-year survival. The median survival was 24 months (2-72 months). Survival was statistically significantly lower in Sarcopenic group. The 1-year, 3-year, and 5-year survival were (85.4 vs. 91.3%) (37.9% vs. 53.2%), and (0.06% vs. 19.5%) in the Sarcopenic and Non-sarcopenic groups, respectively ($p=0.018$) (Table IV).

Discussion

Sarcopenia is a condition characterized by progressive and generalized muscle loss and decreased muscle strength [7]. Many tests are used to assess sarcopenia.

CT measurement of muscle mass is one of the gold standard methods used to diagnose sarcopenia [17].

Preoperative CT imaging in gastric cancer patients is also used for clinical and radiological staging [18].

Studies on the coexistence of sarcopenia and gastric cancer report a sarcopenia incidence of up to 57.7% in gastric cancer cases [19]. Our study found this rate to be 53.8%.

Sarcopenia occurs due to a combination of several mechanisms. Sarcopenia is considered a predisposing factor for osteopenia, weakness, and loss of function. Sarcopenia is also associated with insulin resistance, type 2DM, metabolic syndrome, and cardiovascular diseases.

Sarcopenia adversely affects surgical treatment in patients with gastric cancer.

The literature includes studies showing sarcopenia and poor nutritional status as an independent risk factor for early postoperative complications [20,21], as well as studies reporting it to be negative predictive factors for long-term survival [22]. When we evaluated the early postoperative period in our study, we found additional organ resections to be more common in sarcopenic patients (27.6% vs. 16.3%). Anastomotic leaks, which we also evaluated in the early postoperative period, were detected in 10.6 % of sarcopenic patients, compared with only 6.9 % in non-sarcopenic patients.

Several studies have observed that sarcopenia is more commonly accompanied by preoperative low hemoglobin, hypoalbuminemia. In our study, the hemoglobin levels in preoperative tests were lower in sarcopenic patients than in those without sarcopenia. As well, the albumin value was 3.6 in sarcopenic patients, compared with 3.9 in non sarcopenic patients. It is believed that

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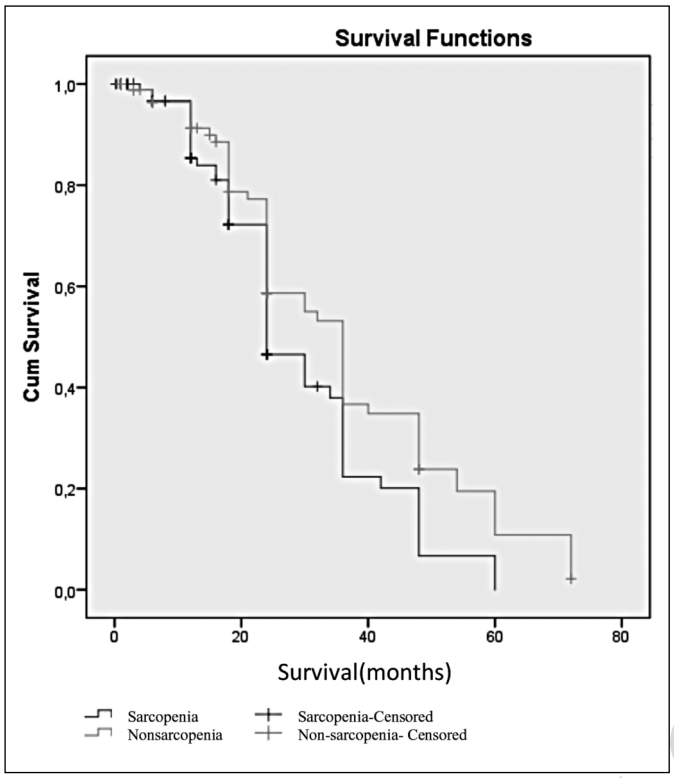

Fig. 1: Overall survival in terms of Sarcopenia.

this causes more early and late postoperative complications in sarcopenic patients.

Concerning long-term survival in our study, the 1-year, 3-year, and 5-year survival rates were 91.3%, 53.2%, and 19.5%, respectively in non-sarcopenic patients, compared with 85.4%, 37.9%, and 0.06%, respectively in non-sarcopenic patients. The mean overall survival was 18 months in sarcopenic patients and 24 months in non-sarcopenic patients. Sarcopenia was shown to be a negative predictor of long-term survival (Fig. 1).

Our study found that sarcopenia was much more common in men than in women. Of the patients with sarcopenia, 56% were male and 44% were female.

According to the European Working Group on Sarcopenia in Older People (EWGSOP), sarcopenia is categorized into primary and secondary sarcopenia. Primary sarcopenia is considered age-dependent sarcopenia, while secondary sarcopenia is defined as sarcopenia that develops due to such reasons as malignancy and inflammatory disorders [7]. One of the problems in sarcopenia studies is calculating the cut-off values due to body composition differences depending on ethnicity. The optimal SMI may vary by cut-off points, diseases, patient-related factors, and countries. Prospective randomized studies involving the whole population will be needed to determine the exact cut-off point.

There are many advantages of using computed tomography in skeletal muscle measurement. Among these is the availability of tomography in many healthcare institutions. Also, tomography is considered very useful because it is fast, images can be stored and compared, and it is absolutely requested for preoperative screening of almost all cancer patients. Serum markers that indicate the nutritional status of the body may vary according to several conditions such as infections and inflammation, and thus they are unfortunately not always determinative. For these reasons, the skeletal muscle mass measured on the sections at the L3 vertebra level seems to be very useful in calculating body muscle mass [23]. In the present study, we used the CT images acquired during preoperative screening of patients diagnosed with gastric cancer.

Sarcopenia should not be confused with cachexia. Sarcopenic patients may have normal weight as well as a normal or high BMI [15,24]. One of the reasons for this type of sarcopenia in patients with malignancies is increased metabolic activity due to aggressive tumor biology [25].

The effects of sarcopenia on long-term survival cannot be considered only based on the operative morbidity and mortality. Studies show that sarcopenia causes toxicity, reduced efficacy of anticancer agents, and treatment non-response during neoadjuvant and adjuvant chemotherapy [2,26]. The study by Hayashi et al [27] with metastatic gastric cancer patients reported low SMI to be an independent risk factor. Today, neoadjuvant therapy is performed as a standard approach to locally advanced gastric cancer.

Meta-analysis showed, neoadjuvant chemotherapy is associated with significant improvement in disease free and long term survivals [28,29]. However, on the contrary, the incidence of sarcopenia was shown to increase after neoadjuvant chemotherapy [30,10].

This study has some limitations. The negative aspects of this study include its retrospective design, the relatively low number of patients, and the lack of muscle weakness calculation. For more reliable results, prospective randomized studies with a large number of patient groups are required.

Conclusion

The present study shows the effects of CT-based measured sarcopenia on short- and long-term outcomes in gastric cancer patients. It is believed that the detection and correction of sarcopenia in these patients would positively affect the early and late outcomes.

Riassunto

Per sarcopenia si intende una perdita di massa muscolare scheletrica, che si associa con esiti meno positivi nei tumori dell'apparato digerente. Con questo studio ci si propone di valutare gli effetti della sarcopenia sulla prognosi, morbilità e mortalità nei pazienti con diagnosi di

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cancro dello stomaco alla luce di questa condizione.
METODI: Lo studio monocentrico e retrospettivo ha valutato pazienti di età compresa tra 18 e 80 anni a cui era stato diagnosticato un cancro gastrico nel periodo compreso tra il 2010 e il 2015.
Sono state esaminate le immagini TC preoperatorie dei pazienti, e la superficie muscolare è stata calcolata sulle immagini TC a livello della vertebra L3, e i valori di <43 cm^2/m^2 per gli uomini e <41 cm^2/m^2 per le donne, sulle scansioni tomografiche ottenute da tutti i pazienti oncologici a fini di screening sono stati associati a ridotta sopravvivenza,
RISULTATI: L'SMI (Skeletal Muscle Index) variava da 26,2 a 73,8 (cm2/m2) negli uomini e da 24,8 a 55,07 (cm^2/m^2) nelle donne.
L'SMI medio era 48,97 (cm^2/m^2) negli uomini e 39,07 (cm^2/m^2) nelle donne. Tra i pazienti dello studio, 43 uomini e 33 donne erano sarcopenici. La sarcopenia era statisticamente significativamente più comune negli uomini rispetto alle donne. Le comorbidità erano più comuni nel gruppo Sarcopenico. Tuttavia, non vi era alcuna differenza statisticamente significativa (p=0,49). Nel gruppo sarcopenico, quarantanove pazienti sono stati indirizzati a terapia neoadiuvante, mentre cinquantatré pazienti nel gruppo non sarcopenico sono stati indirizzati a terapia neoadiuvante .
CONCLUSIONE: Questo studio ha dimostrato gli effetti della sarcopenia misurata mediante TC sugli esiti a breve e lungo termine nei pazienti con cancro gastrico. Si ritiene che il rilevamento e la correzione della sarcopenia in questi pazienti influenzerebbe positivamente gli esiti precoci e tardivi.

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