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Psoas Muscle Loss During Treatment is a Negative Predictive Factor in Gastric Cancer Patients

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ABSTRACT

Objective: Our aim in this study is to examine the changes in the psoas muscle during the gastric cancer treatment process and to evaluate the effects on prognosis.

Methods: Twenty-eight gastric cancer patients underwent curative surgery, and chemoradiotherapy were analyzed. Changes were noted by calculating the psoas muscle areas before and after the cancer treatment. Patients were classified as high delta and low delta according to median change. The effect of muscle loss on progression-free and overall survival was examined using the logistic regression model.

Results: Psoas muscle loss was observed in all patients during the treatment. While the median psoas muscle area before treatment was 14.5 cm^2, it was calculated to be 11.8 cm^2 after treatment ($P=.0$).

In the high-delta group with excessive muscle loss, 3-year progression-free survival was 38%, compared with 80% in the low delta group ($P=.07$). The 3-year overall survival was found to be 42% in the high-delta group, while it was 84% in the group with less muscle loss ($P=.05$).

Conclusion: Muscle loss is a negative predictive factor in gastric cancer patients undergoing surgery and chemoradiotherapy. Dynamic psoas muscle area changes during treatment may play a role in survival.

Keywords: Adjuvant radiochemotherapy, concurrent radiochemotherapy, gastric cancer, nutrition therapy, sarcopenia

INTRODUCTION

Gastric cancer is the sixth most common cancer and the second cause of cancer death in 2018 Worldwide.[1] In Western reports, 5-year overall survival has been found 10%-30% in regional disease.[2,3] While sole locoregional failure is observed in 16% patients, this rate can increase to 36% in metastatic condition.[4] Surgery is the mainstay of gastric cancer treatment and adjuvant therapies are needed due to the local and distant recurrences. Today, total/subtotal gastrectomy and lymph node dissection with neoadjuvant and/or adjuvant chemotherapy or adjuvant chemoradiotherapy (CRT) is the standard care of therapy in locally advanced gastric cancer patients. While all these treatments like surgery, chemotherapy, and radiotherapy are improving oncological outcomes, they may also cause gastrointestinal toxicities and complications, resulting in loss of weight, lean body mass loss, and malnutrition.

Altered body composition in malnutrition usually manifests with a decrease in muscle mass, and this may lead to sarcopenia, a syndrome defined as progressive and generalized skeletal muscle loss, related to increased adverse outcomes.[5-7] Dual-energy x-ray absorptiometry, computed tomography scanning (CT), magnetic resonance imaging (MRI), and bioelectrical impedance (BIE) are validated methods used to measure skeletal muscle loss.[8] Several studies have shown that the psoas muscle area (PMA) in a single abdominal section can estimate the overall muscle mass in the whole body.[9,10] In studies with surgical or chronic patients, the sum of the right and left PMA has been shown to be an independent risk factor for adverse outcomes.[11-14]

The purpose of this study is to calculate the PMA loss during gastric cancer treatment as an indicator of sarcopenia and to examine the effect of this change on progression-free and overall survival.

This study was presented as an oral presentation at 11th International Gastrointestinal Cancers Conference in December 2011.

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METHODS

Patients and Data Collection

Patients who received adjuvant chemo radiotherapy (CRT) after surgery for local gastric cancer were reviewed in a single institution, and a total of 28 patients, whose computerized tomography (CT) images could be obtained and allowed evaluation just before surgery and after the end of CRT, were recruited into this study. Clinically or pathologically proven stage 4 patients were excluded from the study. Age, sex, pathological staging, and survival data were collected for the entire cohort. Data on the chemotherapy regimens, treatment breaks, histopathological features, and type of surgery were also documented. The American Joint Cancer Committee on Cancer (AJCC) criteria (8th edition) was used for staging. The patients were followed up every 3 months for 2 years and every 6 months thereafter. This study was approved by the local ethics committee of Yıldırım Beyazıt University Medical School (Date: December 24, 2020, No: 26379996/136). Locoregional recurrence was defined as recurrence at the anastomosis and regional lymph nodes. Any radiological or pathologic verified metastases outside of the radiation portal or solid organs like liver, lung, brain, or malign ascites were defined as distant recurrences. Intergroup 0116 study CRT protocol was used for the majority of the patients.[15] Patient demographics, pathological reviews, radiotherapy and chemotherapy data, surgical information, and CT images and reports were collected from the hospital registry and patient files, retrospectively. Overall survival was calculated from the date of surgery to death, and progression-free survival was determined from the date of surgery to local or distant progression.

Assessment of Psoas Muscle Area

Psoas muscles were delineated at the third lumbar vertebrae level where both pedicles of this vertebrae are completely visible in 2 different CT sets as before and after on axial images for each patient (Figure 1). These CT images were obtained from the local hospital registry database. ExtremePacs Teleradiology (ExtremePacs, Ankara, 2017) software program was used for measurements with the region of interest (ROI) tool in square centimeter.

Main Points

- Psoas muscle changes during gastric cancer treatment may play a role in treatment success.
- Dynamic measurement of psoas muscle mass over the course of treatment may better predict nutritional status than cross-sectional measurement.
- Psoas muscle loss during gastric cancer treatment adversely affects progression-free and overall survival.

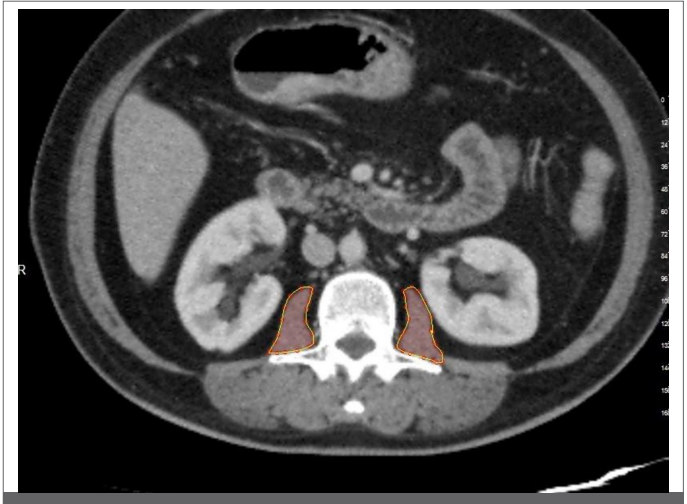

Figure 1. Delineation and measurement of psoas muscle area (PMA).

Predetermined Hounsfield units −30 and +400 were used to separate the psoas muscle from other abdominal structures.[16] Total PMA was defined with a sum of the area of the right and left psoas muscles as an indicator of muscle loss in both preoperative and post-adjuvant therapy CT scans. The changes were recorded as delta PMA (Δ PMA), using [(PMA (cm^2) after CRT-PMA (cm^2) before CRT)/PMA (cm^2) after CRT] × 100 formula. Median proportional PMA changes were calculated. These data were dichotomized due to this median change as high- or low-Δ PMA groups.

Statistical Analysis

Categorical data are presented in count and proportion. The median and minimum-maximum values were used for non-normally distributed continuous variables and mean and SD for normally distributed continuous variables. The variables were compared with the Student's *t*-test, Fisher's exact test, and Wilcoxon rank-sum test between groups. Kaplan–Meier test for survival estimation and log-rank test for survival comparisons were performed. The proportional PMA changes were dichotomized as ≥20% or <20% according to the median proportional change 20%. Statistical significance was considered at a P value ≤ .05.

RESULTS

Patient Characteristics

Gastric cancer patients treated in a single institution radiation oncology department were reviewed. Metastatic patients at the time of diagnosis and the patients whose images were not found in the hospital's local image database were excluded. Patient characteristics and demographics are listed in Table 1. Patient characteristics were quite well balanced. Totally, 28 patient data and 56 CT images were analyzed. The median age was found as 58 (range: 30, 78). The majority of patients were male (21,

Table 1. Patient Demographics and Clinical Data				
	Overall	**High-Δ PMA Group**	**Low-Δ PMA group**	***P***
Sex, n (%)				
Female	7 (25)	3 (23.1)	4 (26.7)	1
Male	21 (75)	10 (76.9)	11 (73.3)	
Age, median (minimum–maximum)	58 (30-78)	56 (45-74)	66 (30-78)	.78
≥65 (n)	13	5 (38.5)	8 (53.3)	.54
<65 (n)	15	8 (61.5)	7 (46.7)	
Stage				
I and II	10	3 (23.1)	7 (46.7)	.25
III	18	10 (76.9)	8 (53.3)	
Tumor location, n (%)				
Cardia	7 (25)	5 (38.5)	2 (13.3)	.13
Fundus	2 (7.1)	1 (7.7)	1 (6.7)	
Corpus	6 (21.4)	4 (30.8)	2 (13.3)	
Antrum and pylorus	13 (46.4)	3 (23.1)	10 (66.7)	
Surgery, n (%)				
Total gastrectomy	13 (46.4)	9 (69.2)	4 (26.7)	.024*
Subtotal gastrectomy	15 (53.6)	4 (30.8)	11 (73.3)	
Dissected LN (median)	27 (4-68)	36 (17-68)	21 (4-51)	.14
RT technic, n (%)				
Conformal	24	11 (84.6)	13 (86.7)	1
IMRT	4	2 (15.4)	2 (13.3)	
RT dose (median)	45 Gy	45 Gy (41.4-50.4)	45 Gy (36-45)	
Concomitant CT, n (%)				
Yes	25 (89.3)	11 (84.6)	14 (93.3)	.58
No	3 (10.7)	2 (15.4)	1 (6.7)	
CT protocol, n (%)				
FUFA	18 (64.3)	7 (53.8)	11 (73.3)	.65
Xelox	7 (25)	4 (30.8)	3 (93.3)	
Unknown	3 (10.7)	2 (15.4)	1 (6.7)	

CT, chemotherapy; FUFA, 5-FU and folinic acid; IMRT, intensity-modulated radiotherapy; LN, lymph nodes; PMA, psoas muscle area: high-delta PMA ≥20, low-delta PMA group <20; RT, radiotherapy; Xelox, capecitabine and oxaliplatin; *, statistically significant.

75%) and total/subtotal gastrectomy was performed without any surgical positivity except for 2 patients. No patient received neoadjuvant chemotherapy. One patient was staged as 1, and 9 and 18 patients were staged 2 and 3, respectively. Three patients were not able to complete adjuvant CRT because of gastrointestinal toxicity. These 3 patients received 3600 cGy, 3780 cGy, and 4140 cGy. One patient received 5040 cGy because of the margin positivity. For all remaining patients, 4500 cGy RT concurrent with chemotherapy were administered.

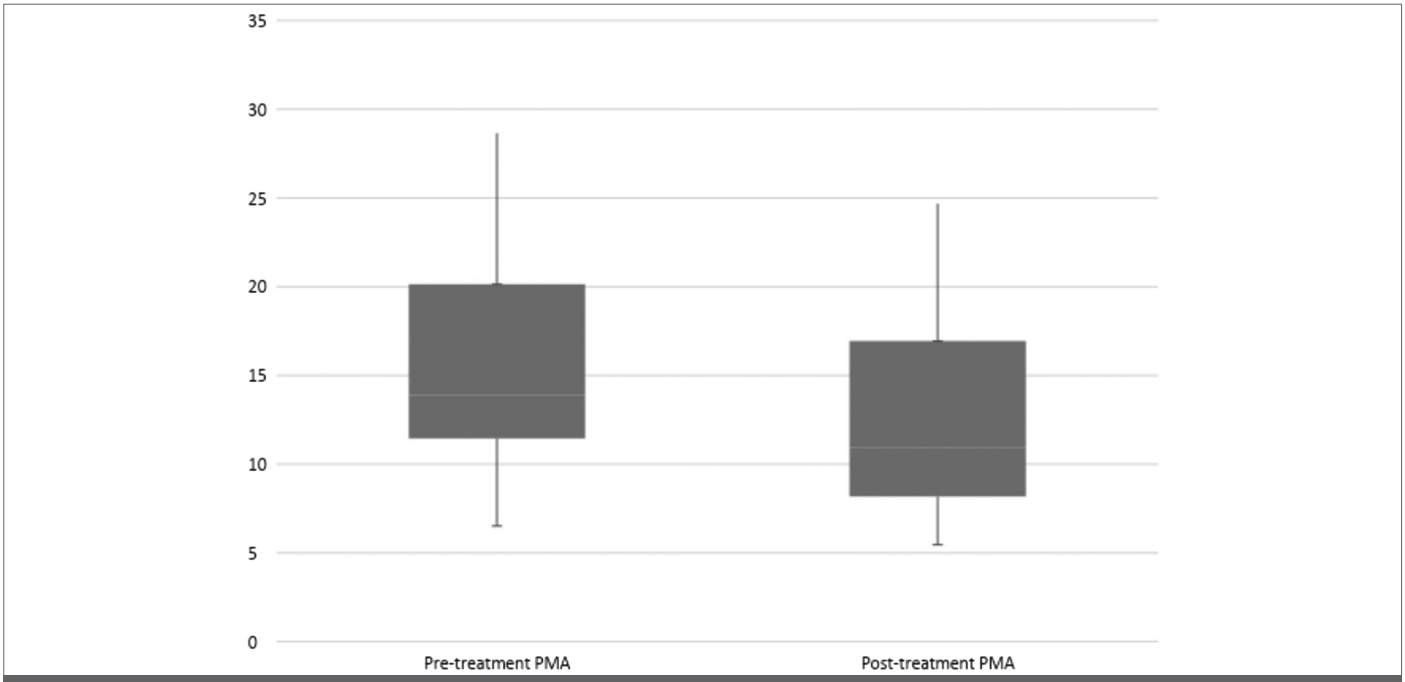

Figure 2. Pre-treatment and post-treatment psoas muscle area changes (cm^2, $P < .001$).

Psoas Muscle Changes and Survival

Median preoperative PMA was calculated as 14.5 cm^2 and was found as 11.8 cm^2 after completion of surgery and adjuvant CRT. This change in PMA was statistically significant ($P = .0$) (Figure 2). All the patients showed a psoas muscle decrease, and the median proportional change

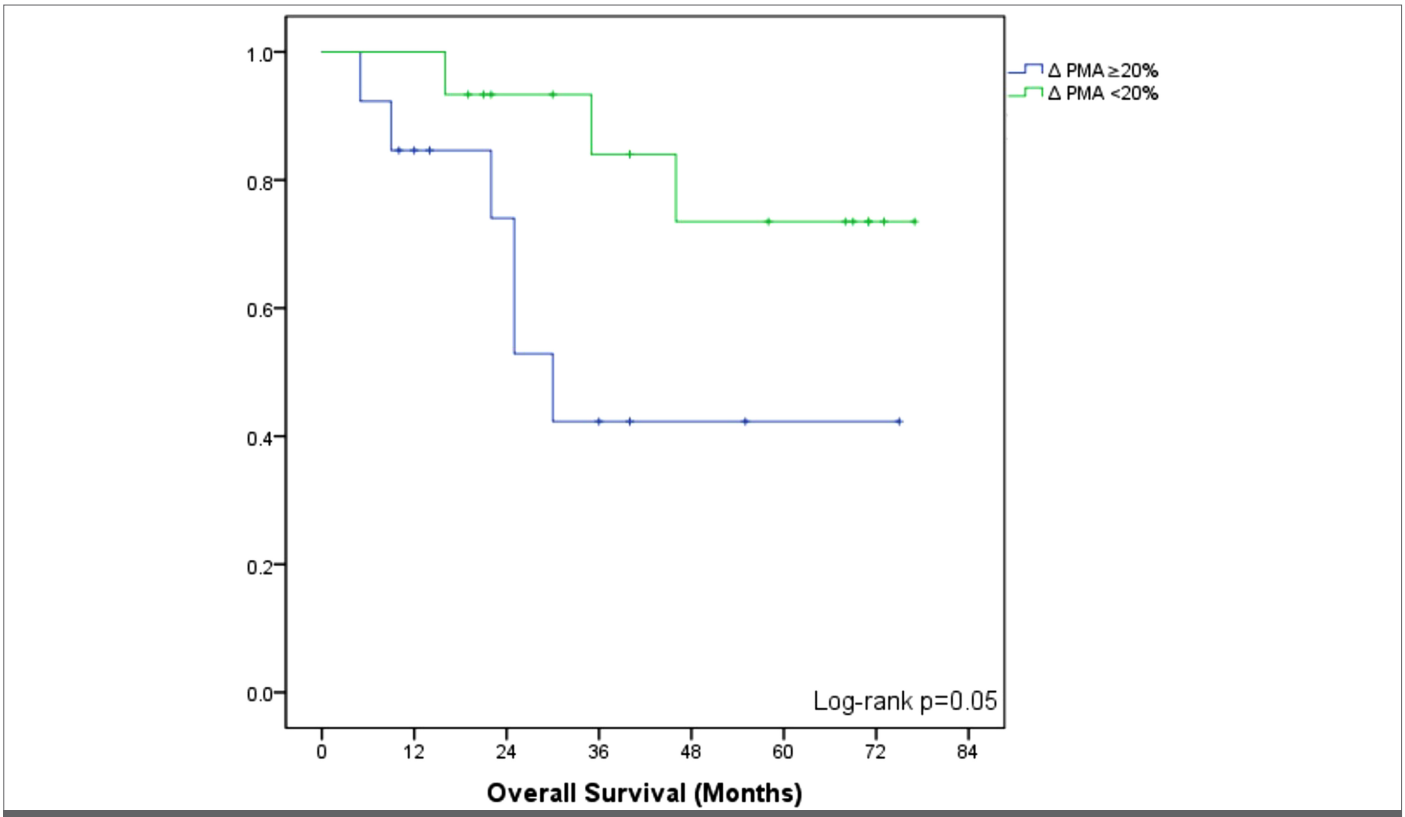

Figure 3. Kaplan–Meier survival curves for overall survival for high- and low-Δ psoas muscle area (PMA) groups. The 3-year overall survival rates were 42% and 84% in the high- and low-Δ group, respectively ($P = .05$).

was found as 20%. In 13 patients, this change was equal to or higher than the median change. After dichotomization regarding the median proportional change of 20%, the patients were classified into 2 groups as low- and high-Δ PMA.

Three-year overall survival was found to be 65%, and the median survival has not been reached at the time of analysis. Three-year progression-free survival was calculated as 62% for the entire cohort. Univariate analysis revealed that high-Δ groups are related to worse survival. Three-year overall survival rates were found to be 42% and 84% in the low- and high-Δ group, respectively ($P=.05$) (Figure 3). Three-year progression-free survival rates were also found lower in the high-Δ PMA group as 80% vs. 38% ($P=.07$) (Figure 4)

In our cohort, 10 patients were at stages 1 and 2, 18 patients were at stage 3. Three-year overall survival rates were found to be 90% and 50% between early- and late-stage groups, respectively ($P=.06$). We also examined the effect of age on survival, and no difference was found in survival between the patients older than 65 and the others ($P=.74$).

DISCUSSION

This current study showed that psoas muscle loss during treatment affects survival negatively in non-metastatic gastric cancer patients.

Despite the emerging new strategies, historically locally advanced gastric cancer treatment includes surgery +/− CRT or perioperative chemotherapy plus surgery. During all these treatments, oral intake can be deteriorated due to the disease itself, surgical morbidity, and toxicities. In the cornerstone, Intergroup 0116 trial, 33% grade 3 gastrointestinal toxicity was observed during adjuvant CRT,[15] which brings a malnutrition risk and weight loss, especially in this patient group.

Malnutrition is one of the most important prognostic factors in cancer patients. Some studies showed an adverse relationship between malnutrition and survival.[17,18] This syndrome is not only related to poor oncological outcomes but also associated with deterioration of the immune system, delayed wound healing, higher infection rate, and longer hospital stay.[19-22] All these negative factors may also diminish the patient's compliance with the

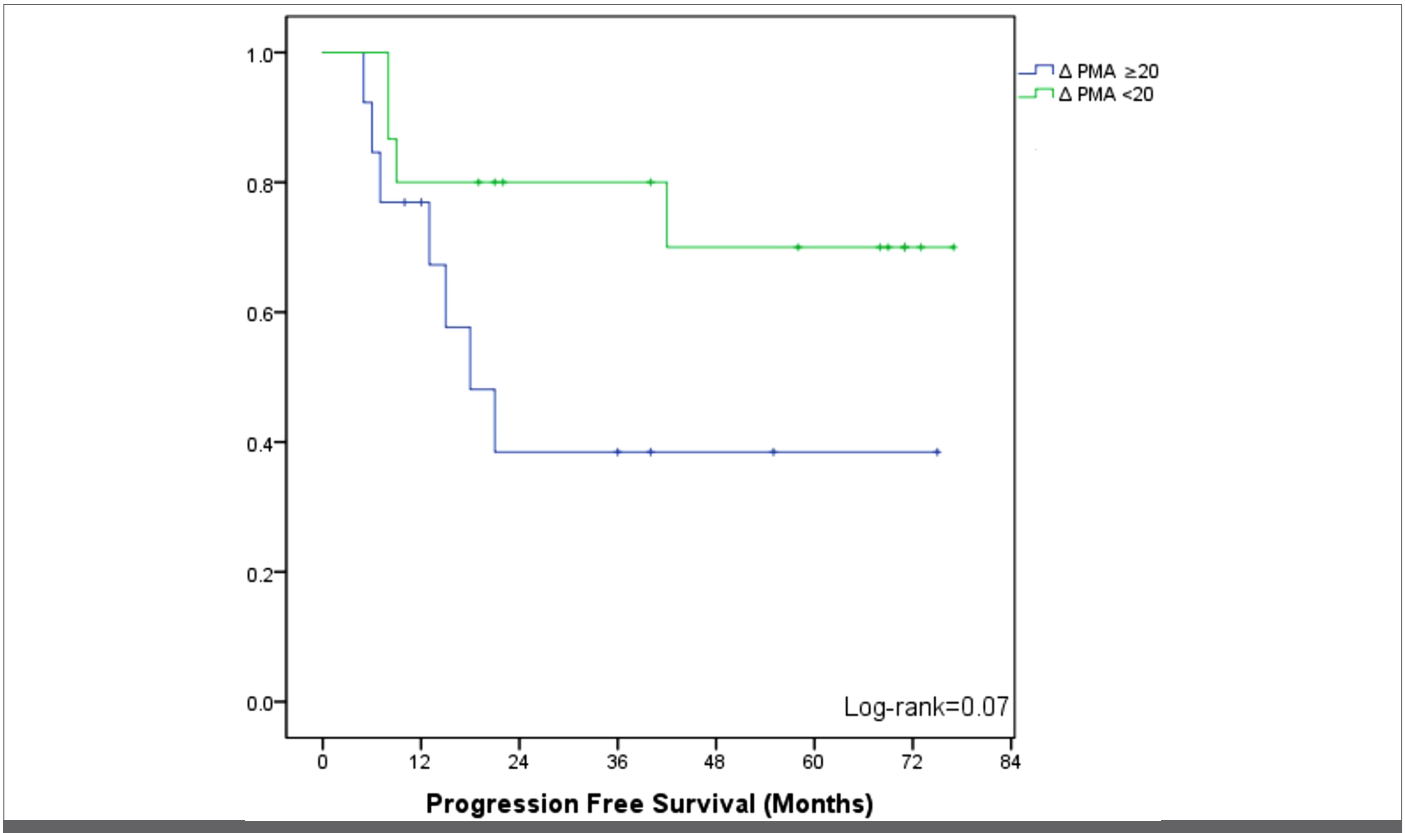

Figure 4. Kaplan–Meier survival curves for progression-free survival for high- and low-Δ psoas muscle area (PMA) groups. The 3-year progression-free survival rates were 38% and 80% in the high- and low-Δ PMA group, respectively ($P=.07$).

treatment. In the recent GLIM consensus, reduced muscle loss was accepted as one of the strongest phenotypic criteria of malnutrition. Chronic inflammation and reduced food intake lead cancer patients to altered metabolism and body composition that manifests with a decrease in any marker of muscle mass like fat-free mass, muscle mass index, or body cell mass.[23]

There are several techniques to measure lean body mass and detect muscle loss. Magnetic resonance imaging (MRI) and CT are the best methods to quantify the skeletal muscle mass (SMM) highly correlated with cadaveric measurements.[24,25] Despite the high accuracy and reproducibility, these techniques are not easy to perform for each patient and have a high cost of instrumentation. Bioelectric impedance is also used for this purpose. This noninvasive technique measures the body composition indirectly using electric signals.[26] This method is faster and easier than whole-body MRI and CT, but this also needs extra effort and cost. The psoas muscle is one of the most important muscle groups for the perpendicular system. This muscle group can be evaluated on CT images for staging and follow-up periods, without an extra process and that can bring an easier evaluation of muscle mass status instead of the whole-body muscle mass evaluation. So, calculating the PMA for detecting reduced muscle mass on CT images in cancer patients seems to be reasonable. In recent trials, measuring PMA on CT images was found as a non-invasive tool to predict SMM.[16,28]

In the cross-sectional analysis of healthy donors with a mean age of 32.5 before liver transplantation, the cutoff values for PMA in the Turkish patient population were found to be 16 cm^2 for the male patient group and 9 cm^2 for the female population.[28]

Some studies showed that perioperative nutritional support for gastrointestinal malignancies reduces the number and severity of postoperative complications even if they do not have any sign of malnutrition.[29,30] In a study of 100 patients undergoing surgery for colorectal cancer, the number of patients with grade 3 or higher perioperative complications was found to be significantly higher in the sarcopenic group with 8to5 patients compared to the non-sarcopenic group.[11] In a recently published meta-analysis of 81 studies, mostly consisting of gastrointestinal system (GIS) cancers and investigating the relationship between muscle mass loss and mortality, hazard ratio (HR) for mortality was 1.41 (95% CI, 1.24-1.59) in all cancer patients, while this rate was found to be 1.56 (1.36 to 1.78) in patients with GIS cancer.[31] These studies also underlie the important role of nutritional support on morbidity and mortality, especially in gastrointestinal cancers. In this study, we hypothesized that psoas muscle loss as a sign of SMM loss, sarcopenia, and malnutrition during the treatment is a negative prognostic factor on survival.

Cheng-Le Zhuang et al[32] retrospectively reviewed the gastric cancer patients who had undergone curative surgery, and they found that low skeletal muscle index, calculated with PMA and patient height, was related to postoperative severe complications as an independent risk factor. They also found sarcopenia as an independent risk for overall and disease-free survival especially in stage 2 and 3 patients, as well. They found the 3-year overall survival to be 53.8% vs. 73.6% ($P < .001$) and 3-year disease-free survival to be 54.7% vs. 73.5% ($P < .001$) in favor of patients without sarcopenia. A similar study was held in bladder cancer patients and sarcopenia was also found as related to a longer hospital stay, higher rate of perioperative complications, and worse overall survival.[33] Park et al[16] also found preoperative low PMA as a negative risk factor for overall survival in surgically treated esophageal cancer patients. They found 3-year overall survival 64.9% in the high-PMA group vs. 37.1% in the low-PMA group ($P=.002$). The results were similar in patients with upper urinary tract urothelial carcinoma among preoperative cases[34] and rectal cancer patients before neoadjuvant CRT.[35] A systematic review of 13 studies and meta-analysis also denote that sarcopenia is significantly related to all-cause mortality in hepatocellular cancer patients.[36]

These trials in different types of cancer patients showed that muscle loss is related to poorer outcomes, but all these trials were based on only a single measurement of the PMA before surgery or CRT. In this trial, we aimed to assess the change in the PMA before and after the whole cancer treatment modalities, including surgery, chemotherapy, and radiation therapy, and to investigate the effects of the change on survival as well. All these treatments have serious surgical complications and gastrointestinal side effects like nausea, vomiting, and diarrhea, and these treatment-related factors may let the patients get deteriorated; so, we tried to evaluate the impact of all treatment procedures on SMM and we found a 2.7 cm^2 PMA decrease during gastric cancer treatment and an inverse relationship between PMA loss and overall survival was found (42% vs. 84%, $P=.05$).

Two studies from the United States and South Korea examined the change of psoas muscle volume (PMV) and area and its effects on patients treated with chemotherapy and radical cystectomy for muscle-invasive bladder cancer and surgically treated esophageal cancer patients, respectively. Zargar et al[37] from the United States measured all psoas volumes and calculated the change during

the neoadjuvant chemotherapy undergoing radical cystectomy in bladder cancer. In this study, median 5% PMV and higher loss are associated with decreased but not statistically significant complete and partial pathological complete response rates and overall survival. Park et al[16] also focused on the prognostic effect of the PMA change in esophageal cancer patients after 1 year who underwent surgery, and they found that psoas muscle loss of more than 10% was a significant risk factor for overall survival. In the low-Δ PMA group, they found a 3-year overall survival rate of 58.2% and 18.9% in the high-Δ PMA group (P=.049). Three-year disease-free survival rates were 47.3% and 18.8% in favor of low-Δ PMA group. We have found 3-year overall and progression-free survival rates as 84% vs. 42% (P=.05) and 80% vs. 38% (P=.07) in favor of low-Δ PMA group. In our small cohort, we also examined the effects of age and stage on overall and disease-free survival. There was a trend for early-stage and younger ages, but we could not find a statistical difference. The small number of cohorts should be the possible explanation, and studies with a larger number of age groups may help to clarify the relationship between age and psoas muscle loss on survival.

The limitations of our study are primarily its retrospective design and possible selection bias. Although patients who were treated in a single center and whose full data could be accessed were included in this study, our findings should be confirmed by prospective studies. Second, although our study includes a homogeneous patient group, the relatively small number of patients is another weakness of our study. The strength of our study is that it evaluates muscle loss over a treatment period rather than a cross-sectional evaluation at a single moment and reveals the effect of this change on treatment more clearly. Lastly, sarcopenia is an age-related syndrome characterized by a loss of muscle mass and strength, and the onset of sarcopenia often begins in middle age due to an unbalanced diet in association with a lack of physical activity. Therefore, age-related muscle wasting may co-exist with treatment-related muscle wasting. In order to make this distinction, in studies with a larger number of young patients, the amount of muscle loss due to treatment and its effect on treatment can be shown more clearly.

Despite the uncertainties in measuring methods, accessibility, and cutoff values of reduced muscle mass, there is strong evidence to use it as a single phenotypic criterion in the diagnosis of malnutrition.[6] In the current study, we have tried to evaluate the dynamic changes, not a sectional evaluation because our patient population is different from the other chronic diseases and older adults. These gastric cancer patients generally have more acute/subacute reversible changes due to the treatments and treatment-related toxicities, and so dynamic measurements should be better than sectional measurement to estimate survival or morbidity.

This study examines dynamic PMA changes and their impact on survival in gastric cancer patients. These outcomes highlight the importance of muscle loss changes on survival and nutritional assessment and support in locally advanced gastric cancer patients during all treatment steps. On behalf of emerging data, muscle loss cutoff values and methods should be validated in a prospective randomized trial as a predictive factor, and this may lead us to give further attention to nutritional status as a cause and/or effect in cancer patients. Further prospective trials are needed to prove these retrospective small cohort data.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Yıldırım Beyazıt University (Date: December 24, 2020, Number: 26379996/136).

Informed Consent: Due to the retrospective design of the study, informed consent was not taken.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – H.F.Ö.; Design – H.F.Ö.; Supervision – S.A.A., Y.T.; Resources – i.P.A., G.A.İ.; Materials – H.F.Ö.; Data Collection and Processing – H.F.Ö., G.A.İ., İ.P.A.; Analysis and Interpretation – H.F.Ö., İ.P.A.; Literature Search – H.F.Ö., G.A.İ.; Writing Manuscript – H.F.Ö.; Critical Review – S.A.A.

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