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The Predictive and Prognostic Value of Skeletal Muscle Mass in Cancer Patients with Distant Metastases

Uzak Metastazlı Kanser Hastalarında İskelet Kası Kütlesinin Prediktif ve Prognostik Değeri

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ABSTRACT

Aim: Skeletal muscle loss is an indicator of cachexia and a strong prognostic factor for some types of cancer. After strict standardization, we aim to evaluate both the predictive and prognostic value of low muscle mass (LMM) in common cancer types for first-line chemotherapy.

Method: This retrospective single-center study was conducted in a regional hospital between 2015 and 2020. Patients diagnosed with distant metastatic cancer were screened and included in the study if they had abdominal computed tomography 45 days prior to first-line chemotherapy. The relationship between LMM and progression-free survival (PFS), overall survival (OS), and objective response rate (ORR) was evaluated.

Results: Initially, 289 patients with metastatic cancer were included. The median duration of follow-up was 17 months, with a mean age of 61.09±13.03 years (range 25 to 95), and 45.9% of patients were female. In total, 50.5% of patients had LMM, which was adjusted for gender. LMM was associated with worse OS and PFS in univariate analysis (HR:1.598;1.216-2.100; p=0.001 for OS and HR:1.583;1.216-2.059; p=0.001 for PFS), and this positive association was maintained after adjusted for diagnosis and age. Better ORRs were obtained in respiratory and gastrointestinal tract cancers, breast, prostate and gynecological cancer in non-LMM groups.

Conclusions: LMM has not only prognostic value but also predictive value for many types of cancer. Therefore, the assessment of muscle loss should be incorporated as part of the initial routine clinical evaluation.

Key Words: Prediction, Muscle Mass, Prognostic Value, Cancer, Muscle Index

ÖZET

Amaç: İskelet kası kaybı, kaşeksinin bir göstergesi ve bazı kanser türleri için güçlü bir prognostik faktördür. Bu çalışmada sıkı standardizasyon sonrası, birinci basamak kemoterapi için yaygın kanser türlerinde düşük kas kütlesinin (LMM) hem prognostik hem de prediktif değerini değerlendirmeyi amaçlıyoruz.

Yöntem: Bu retrospektif tek merkezli çalışma 2015-2020 yılları arasında bir bölge hastanesinde yapılmıştır. Uzak metastatik kanser tanısı alan hastalar tarandı ve birinci basamak kemoterapiden 45 gün önce abdomen bilgisayarlı tomografisi olan hastalar çalışmaya dahil edildi. LMM ile genel sağkalım (OS), progresyonsuz sağkalım (PFS) ve objektif yanıt oranı (ORR) arasındaki ilişki değerlendirildi.

Bulgular: Çalışmaya metastatik kanserli 289 hasta dahil edildi. Hastaların %45,9'u kadın olup medyan takip süresi 17 ay ve ortalama yaşı 61,09±13,03 yıldır (min-max: 25-95). Cinsiyete göre düzeltme sonrası, toplamda hastaların %50,5'inde LMM vardı. LMM, univariate analizde daha kötü OS ve PFS ile ilişkilendirildi (OS için HR:1,598;1,216-2,100;p=0,001 ve PFS için HR:1,583;1,216-2,059;p=0,001) ve bu pozitif ilişki tanı ve yaşa göre düzeltme yapıldığında da devam etti. LMM olmayan gruplarda solunum sistemi, gastrointestinal sistem, meme, prostat ve jinekolojik kanserlerde daha iyi ORR'ler elde edildi.

Sonuç: LMM sadece prognostik değere sahip değildir, aynı zamanda birçok kanser türü için prediktif değere de sahiptir. Bu nedenle kas kaybının değerlendirilmesi, ilk muayenede rutin klinik değerlendirmede yer almalıdır.

Anahtar Kelimeler: Prediktif Değer, Kas Kütlesi, Prognostik Değer, Kanser, Kas İndeksi

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Introduction

Cachexia has been defined as "a complex metabolic syndrome associated with underlying illness and characterized by the loss of muscle with or without the loss of fat mass"[1]. Cancer cachexia, a multifactorial wasting syndrome, is associated with loss of weight, reduced food intake and elevated inflammatory response along with alterations in metabolism, and is thought to account for 20-30% of cancer related deaths [2, 3]. Recently, calculation of muscle mass mostly determined by computed tomography (CT) scanning, is considered the gold standard way to measure muscle parameters. The strong correlation between the CT-based measurement of cross sectional muscle area and total body muscle mass was previously demonstrated [4]. Skeletal muscle loss is an indicator of cachexia and appears to be a strong negative prognostic factor in aging, various chronic diseases, and also in some malignancies [5]. Most of the studies conducted were designed to assess the relationship between sarcopenia and toxicity, and increased toxicity with chemotherapy is shown in patients with muscle loss for many types of cancer [5]. Therefore, the use of muscle index for chemotherapy dose calculation can provide a more accurate method of toxicity management than body surface area, as well as provide the most appropriate effective dose of chemotherapy for sarcopenic patients.

Moreover, patients with muscle loss are particularly vulnerable to major physiologic stress, therefore, muscle loss is shown to be associated with postoperative outcomes in esophageal carcinoma, colorectal cancer, liver metastasectomy, hepatocellular carcinoma, pancreatic carcinoma, melanoma, bladder cancer and gynecological cancers following malignancy resection [6]. Awareness of the poor prognostic significance of muscle loss for patients undergoing surgical intervention can provide an estimate in terms of weighing clinical benefits versus potential complications. Although inconsistent results have been obtained, the prognostic role of muscle loss has also been investigated for many cancer types in metastatic disease in the last few years [5-14]. To assess only the prognostic and predictive value of muscle loss, it is necessary to study in a standardized patient data set in terms of treatment and clinicopathological prognostic features. We therefore performed a study to evaluate the predictive and prognostic values of skeletal muscle loss (SML) by calculation of muscle area with CT in standardized patients with respiratory tract cancer (RTC), gastrointestinal tract (GIT) cancer, bladder cancer, breast cancer, gynecological cancer, and prostate cancer who were treated with first line chemotherapy.

Materials and methods

Study design

This retrospective single-center study was performed at a regional hospital in Turkey. In this study, all performed procedures involving human participants complied with the ethical standards of the institutional research committee (ethics approval number: 2019/9-13). From June 2015 to December 2020, patients diagnosed with distant metastatic cancer were screened and included if the patients had an abdominal CT 45 days prior to first-line chemotherapy.

The primary study endpoint was to assess the relationship between overall survival (OS) and skeletal muscle index (SMI), and the secondary endpoint was to evaluate in terms of objective response rate (ORR) and progression-free survival (PFS) after first-line chemotherapy.

Treatments

None of the patients were treated with immunotherapy and targeted tyrosine kinase inhibitors or endocrine therapies. In the first line setting platinum doublet therapy was administered to all patients with lung cancer (platinum plus taxanes/pemetrexed/gemcitabine for non-small cell lung cancer [NSCLC] and platinum with etoposide for small-cell lung cancer [SCLC]). Patients with ALK fusion or EGFR mutation were excluded from the NSCLC group. Patients with mesothelioma who were unsuitable for surgical intervention were treated with platinum and pemetrexed with folbiol at the first line setting. Monoclonal antibody was added to backbone chemotherapy with fluoropyrimidine plus oxaliplatin or irinotecan according to K-RAS, BRAF and N-RAS mutation status and tumor sidedness in all patients with colon cancer. Gastric cancer patients were evaluated for her-2 staining and trastuzumab was added to backbone platinum plus fluoropyrimidine-based chemotherapy. Biliary tract cancer patients were treated with platinum plus gemcitabine for the first line. Patients with pancreatic cancer were treated with FOLFIRINOX in the case of better performance status, or otherwise with platinum and gemcitabine. Patients with bladder cancer treated with cisplatin with gemcitabine in the case of suitable performance status, or otherwise with carboplatin plus gemcitabine. Patients with breast cancer were evaluated pathologically in terms of estrogen, progesterone, her-2 stating, and ki-67 proliferation index for the first line optimal treatment option, therefore anthracycline plus cyclophosphamide was initiated in the case of the presence of visceral crisis or symptomatological disease, and trastu-

Acta Medica Alanya 2023;7(2): 117-124
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zumab was added to backbone chemotherapy (platinum with taxanes) in patients with her-2 positive disease. Patients treated with endocrine therapy at the first line were excluded from the study in breast cancer group. Patients with high volume disease treated with docetaxel plus dexamethasone for the first line setting were included in this study. Endometrial and ovarian cancer patients treated with paclitaxel plus carboplatin were evaluated as gynecological cancers. Respiratory tract cancers (RTC) were divided into two groups; NSCLC and SCLC/mesothelioma, and gastrointestinal tract cancers (GIT) were also divided into two groups; colorectal cancer and non-colorectal GIT cancer. Patients who received at least one cycle of chemotherapy were included in the present study.

Assessed Parameters

Medical records were obtained for patient and tumor characteristics, metastatic sites, number of metastatic organs, presence of bone metastasis, body composition parameters (such as height), treatment names and data regarding clinical follow up to assess survival outcomes.

OS was defined as the date of diagnosis to the date of death or the end of follow-up, whichever occurred first. The date of diagnosis was assumed as the date of metastasis. PFS was defined as the date of the first cycle of first line chemotherapy to document disease progression or death, whichever occurred first. Switching to another regimen due to treatment intolerance or patient demand was not considered a progression and these patients were excluded. Response rates were evaluated as partial response, complete response, stable disease and progression according to Recist 1.1 criteria. In the case of complete or partial response, it was assumed that these patients showed an objective response (ORR).

Muscle mass was measured from 2-mm-thick CT images (64-slices, Toshiba Medical System, Otowara, Japan). To calculate muscle mass, the abdominal cross-sectional area of muscle at the level of the L3 vertebra (m.psoas, m.erector spinae, m.transversus abdominis, m.quadratus lumborum, m.rectus abdominis, m.obliquus internus, m.obliquus externus) was calculated by freehand ROI. Muscle mass was measured in cm^2 and corrected for height as m^2, resulting in a lumbar skeletal muscle index (SMI) in cm^2/m^2. Low muscle mass (LMM) was defined as an SMI of 42 cm^2/m^2 for men and 36.8 cm^2/m^2 for women according to the median value of the patients.

Statistical analyses

Quantitative variables were described as median with range and means with standard deviation [SD] while qualitative variables were presented as frequencies with proportions. Chi-square and/or Fischer-exact test for rates were used to detect significant differences between qualitative variables. OS and PFS were estimated by the Kaplan-Meier method and the Log Rank test was used to compare the effect of SMI and other parameters on survival. Then multivariate Cox proportional hazard models were used for PFS and OS. Associations between SMI and ORR were calculated by multivariate logistic regression analysis adjusting for age and diagnosis. The statistical software package SPSS 22.0 (SPSS, Chicago, IL, USA) were carried out for statistical analyses, and $P < .05$ indicated a statistically significant difference.

Results

Patient characteristics and LMM rates

Initially, 341 metastatic cancer patients with available CT scans who received first line chemotherapy were included. Among these, 52 patients who did not have CT imaging up to 45 days before starting chemotherapy were not included in the analysis due to the possible risk of tumor progression during this period. All patients were stage 4 and not amenable to surgery or other curative treatments. All patients' Eastern Cooperative Oncology Group (ECOG) performance scores were 0 or 1. The median duration of follow-up was 17 months (1-60) and 72.1% of patients were lost at follow-up. The mean age was 61.09 ± 13.03 years (range 25 to 95), and 9.7% of patients were over 75 years old. 45.9% of the patients were female, the remaining was male.

In total, 50.5% of the patients had low muscle mass, when the median cutoff value was chosen as SMI of 42 cm2 / m2 for men and 36.8 cm2 /m2 for women, which was adjusted for gender. The rate of LMM was 59.5%, 52.0%, 52.2%, 47.3%, 30.0%, 31.2%, and 41.2%, in patients with RTC, colorectal cancer, non-colorectal GIT cancer, prostate cancer, bladder cancer, breast cancer, gynecological cancer, respectively.

While LMM was more common in patients over 75 years of age, it was less common in patients with bladder and prostate cancer (Table 1).

Progression-free survival and overall survival according to LMM

In total, the median OS was 13 months (95%CI 9.53-16.5) in patients with LMM while it was 21 months (95%CI 17.2-24.8) in patients without LMM (p=0.001). Additionally, median PFS was 5 months (95%CI 3.46-6.53) in patients with LMM whereas it was 9 months (95%CI 6.41-11.58) in patients without LMM (p< 0.001). The median OS and PFS

Table 1. Descriptions and the parameters that can affect low muscle mass

	N (%)	Median SMI cm2 /m2	OR	95%CI	P value
Diagnosis					
RTC*	74 (25.6)	35 (17.6-68)	1 (ref)		
Colorectal cancer	50 (17.3)	37.8 (20.8-67)	0.74	0.36-1.51	0.41
Non-CR GIT	67 (23.2)	38 (20.5-56.7)	0.75	0.38-1.47	0.39
Breast cancer	55 (19.0)	37.5 (27-53.0)	0.61	0.30-1.23	0.17
Bladder cancer	10 (3.5)	44.2 (26.1-60)	0.29	0.07-8.66	0.09; 0.036***
Prostate cancer	16 (5.5)	45.9 (26.2-63)	0.31	0.08-1.02	0.047; 0.036***
Gynecological cancer	17 (5.9)	37.6 (32-53.0)	0.48	0.166-1.14	0.176
Number of metastatic organs					
1 to 4			-	-	0.89
Age					
≤75 vs >75			2.890	1.23-2.94	0.015
Bone metastasis					
Presence vs absence			0.87	0.46-1.67	0.68

*RTC: Respiratory tract cancer, **Non-colorectal gastrointestinal tract cancers, ***adjusted for age. OR: Odds ratio; CI: confidence interval.

were not statistically different according to the number of metastatic sites (p=0.297, p=0.440, respectively) and the presence of bone metastasis (p=0.223, p=0.134, respectively). In general, LMM was associated with worse OS and PFS in univariate analysis (HR: 1.583, 95%CI 1.216-2.059, p=0.001) for PFS and HR: 1.598, 95%CI 1.216-2.100; p=0.001 for OS) and this positive association was maintained after adjusted for diagnosis and age (HR: 1.563, 95%CI 1.191-2.051, p=0.001 for PFS and HR: 1.477, 95%CI 1.110-1966; p=0.008 for OS). The curve of multivariate Cox regression analysis of the effect of LMM on OS and PFS is shown in Figures 1 and 2.

The OS and PFS according to diagnosis and LMM

The median overall survival was 11 (8.4-13.6) months, 10.0 (4.9-15.1) months, 18 (12.0-23.9) months, 8 (4.99-11.0) months, 60 (Non reached [NR]-NR) months, 14 (2.98-19.8) months, 32 (21.2-42.8) months, 25 (19.2-30.8) months in patients with NSCLC, other RTC, colorectal cancer, non-colorectal GIT cancer, bladder cancer, breast cancer, gynecological cancer, and prostate cancer, respectively.

When we evaluated the effect of LMM on survival according to diagnosis; as was shown in Table 2 the negative association of LMM with OS was maintained after adjusting for age in patients with SCLC/mesothelioma and breast cancer on the other hand there was no association between LMM and OS for the other types of cancer.

LMM was associated with worse PFS in patients with SCLC/mesothelioma, breast cancer, and gynecological cancer, whereas the association was not observed for the other cancers (Table 2).

Overall response rates according to diagnosis

In total, higher ORRs were obtained in patients without LMM when compared with the patients with LMM after adjusting for age and diagnosis (HR: 3.410; 95%CI: 1.954-5.951, p<0.001). ORR was assessed for diagnosis, thus better ORRs were achieved in the group of NCSLC, SCLC/mesothelioma, colorectal cancer, non-colorectal GIT cancer, breast cancer, prostate cancer, and gynecological cancer, while statistically significance could not be reached except for NSCLC and gynecological cancer possibly due to the low number of patients (Table 3).

Discussion

In this study, an extremely high rate of 50.5% of the patients had low muscle mass, when the median cutoff value was chosen as SMI of 42 cm2 /m2 for men and 36.8 cm2 / m2 for women after adjusting for gender. In general, LMM was found to be significantly associated with worse OS and PFS in univariate analysis. Additionally, this positive association was maintained after adjusting for diagnosis and age (HR 1.563, 95%CI 1.191-2.051, p=0.001 for PFS and HR 1.477, 1.110-1966; p=0.008 for OS). Unlike other studies, we also studied the effect of LMM on ORR, and we demonstrated that LMM was associated with worse ORR independent of age and diagnosis (HR; 95%CI 3.410; 1.954-5.951, p= <0.001). Therefore, demonstrating the predictive value of muscle loss for treatment response with this patient data set, which we define with sharp lines in the patients' inclusion criteria, can provide guidance for the benefit of additional therapies in addition to conven-

Acta Medica Alanya 2023;7(2): 117-124
Doi: 10.30565/medalanya.1167930

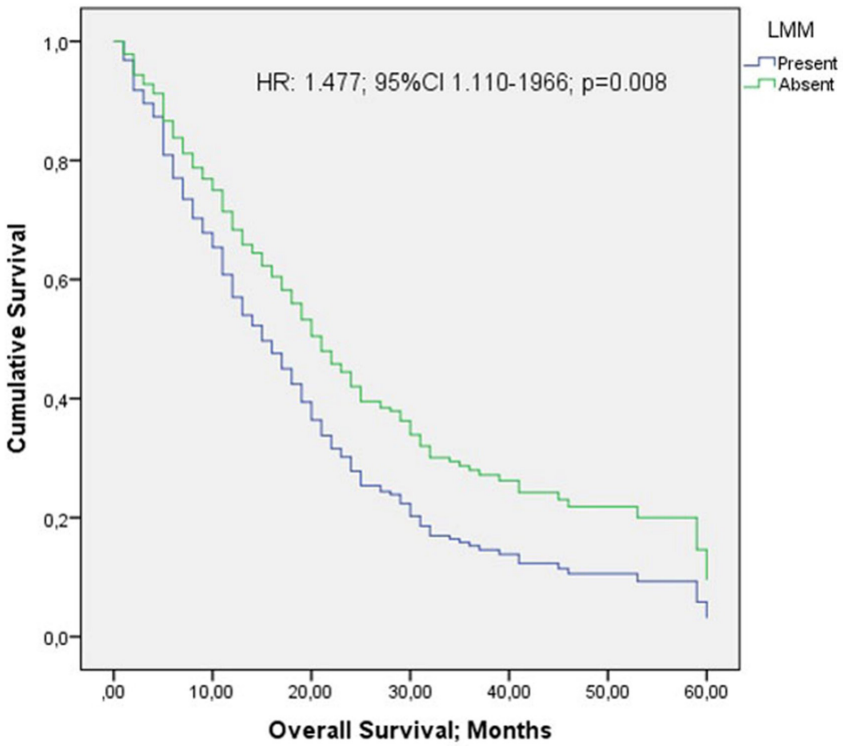

Figure 1. Overall survival curve according to LMM by Cox regression analysis adjusted for age and diagnosis. HR: Hazard ratio; CI: Confidence interval; LMM: Low muscle mass

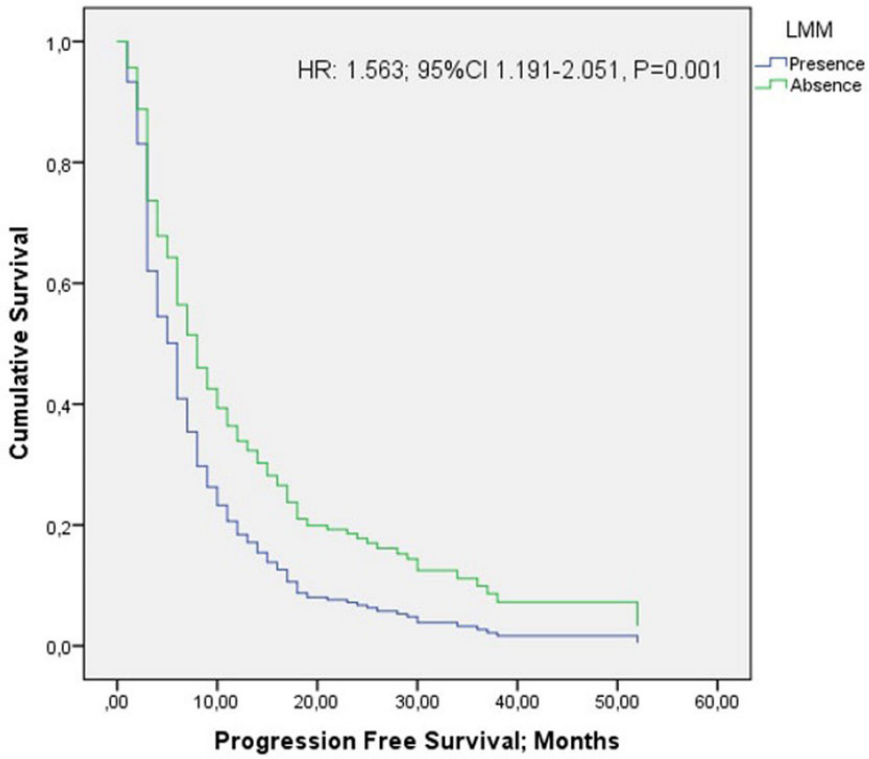

Figure 2. Progression-free survival curve according to LMM by Cox regression analysis adjusted for age and diagnosis. HR: Hazard ratio; CI: Confidence interval; LMM: Low muscle mass

Table 2. Progression-free survival and overall survival according to LMM by Cox proportional hazards models

	median OS, months		PFS		OS	
Diagnosis	**LMM**	**non-LMM**	**HR; 95%CI***	**P valus**	**HR; 95%CI***	**P value**
Respiratory tract						
NSCLC	10	12	1.591 (0.82-3.07)	0.22	1.534 (0.769-3.06)	0.225
SCLC and mesothelioma	5	16	*2.509 (1.00-5.28)*	*0.050*	*2.566 (1.05-6.27)*	*0.039*
GIS						
Colorectal cancer	16	19	0.761 (0.38-1.53)	0.44	0.997 (0.52-1.98)	0.99
Non-CR GIT cancer**	8	12	1.402 (0.83-2.36)	0.20	1.268 (0.75-2.15)	0.38
Breast cancer	32	NR	*3.493 (1.54-7.92)*	*0.003*	*2.647 (1.08-6.49)*	*0.033*
Bladder cancer	5	14	3.155 (0.29-34.84)	0.348	1.295 (0.15-11.2)	0.81
Prostate cancer	30	NR	1.514 (0.32-7.27)	0.611	1.609 (0.34-7.51)	0.54
Gynecological cancer	25	25	*5.480 (1.43-21.01)*	*0.013*	1.646 (0.39-6.98)	0.49

*Adjusted for age, **non-CR GIT: non-colorectal gastrointestinal tract; HR: Hazard ratio; CI: Confidence interval; PSF: Progression-free survival; OS: Overall survival; LMM: Low muscle mass; NSCLC: non-small cell lung cancer; SCLC: small-cell lung cancer, Non reached: NR.

Table 3. Overall response rates according to LMM by multivariate logistic regressions analysis

	N(%)		ORR %		OR; 95%CI	P value
	LMM	non-LMM	LMM	non-LMM		
NSCLC	30 (63.8)	17 (36.2)	18.0%	47.1%	2.120; 1054-4261	*0.043*
SCLC - mesothelioma	14 (51.9)	13 (48.1)	14.3%	46.2%	2.036; 0.999-4.148	0.070
CRC	26 (52.0)	24 (48.0)	57.7%	75.0%	1.545; 0.756-3.159	1.97
Non-CRT GIT cancer	35 (52.2)	32 (47.8)	18.2%	37.5%	1.567; 0.983-2.496	0.082
Breast cancer	26 (47.3)	29 (52.7)	56.5%	78.6 %	1.676; 0.848-3.315	0.091
Bladder cancer	3 (30.0)	7 (70.0)	50.0%	57.1%	1.067; 0.521-2.182	0.858
Prostate cancer	5 (31.2)	11 (68.8)	60.0%	81.8%	1.500; 0.534-4.214	0.35
Gynecological cancer	7 (41.2)	10 (58.8)	42.9%	100%	-	*0.015*

ORR: Overall response rate; CI: Confidence interval; LMM: Low muscle mass; NSCLC: non-small cell lung cancer; SCLC: small-cell lung cancer; CRT: Colorectal cancer; GIT: gastrointestinal tract

tional therapies, especially in patients with muscle loss who need a rapid treatment response.

Among parameters, muscle loss was less common in patients with bladder cancer and prostate cancer, than in other types of cancer in the study, which may be associated with early diagnosis due to the early onset of symptoms. While early diagnosis is generally possible for colon cancer, it can be thought that either a rapid disease course, delayed diagnosis or nutrition intake problems contribute to the achievement of high muscle loss rates in patients with metastatic process. On the other hand, considering the general life span of non-colorectal gastrointestinal system cancers and thoracic cancers with a median of less than 1 year, the high rates of muscle loss observed initially in aggressive cancers seem to be compatible with the natural course. Additionally, the high rates of muscle loss seen in breast cancer at the time of diagnosis were considered as normal, since patients who were not suitable for hormonal intervention and who were indicated for chemotherapy due to high disease burden were included in the study. When we evaluated other parameters, the presence of bone metastasis and metastatic organ involvement did not affect muscle loss levels. Statistically higher LMM was found in patients older than 75 years, so age was included in the multivariate analysis when evaluating the effect of LMM on survival for different types of cancer.

When the type of cancer was evaluated separately; LMM was a significant prognostic factor for OS for SCLC/ mesothelioma and breast cancer, whereas it did not reach a statistically significant level for the NSCLC, colon cancer, non-colorectal GIT cancers, bladder cancer, prostate cancer, and gynecological cancer, although numerical association was obtained (Table 2).

The association of OS and LMM has been studied before for advanced breast cancer patients [7, 8]. There was in-

Acta Medica Alanya 2023;7(2): 117-124
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consistent result about the prognostic significance of muscle loss in patients with metastatic stage breast cancer. According to a meta-analysis of a total of six studies (5497 breast cancer patients), patients with muscle loss were shown to be associated with a significantly higher risk of mortality, compared to breast cancer patients without muscle loss. On the other hand, although the association was valid for the early stage of breast cancer, it was not for metastatic breast cancer [9]. Different from the previous studies, we only included patients who needed chemotherapy at the first line and were not eligible for endocrine treatments. In this regard, muscle loss appears to have prognostic significance for metastatic breast cancer patients with high tumor volume or symptomatic disease with a cut-off value of 36.8 cm^2/m^2. Better PFS and ORR were additionally achieved in patients without LMM in the breast cancer subgroup. Our study showed that screening breast cancer patients with high tumor burden for muscle loss is very important and additional interventions such as physical education, aerobic and resistance exercises, and nutritional supplements may probably prevent loss of muscle mass and reverse this poor prognosis thanks to this awareness [10,11].

Patients with RTC and GTC who are cachexic by the conventional criterion (involuntary weight loss) and by two additional criteria (muscle depletion and low muscle attenuation) presented with a poor prognosis, regardless of overall body weight according to a large scale study [12]. However, the evaluation of RTCs as a single title can produce inaccurate results. Therefore, in this study we divided RTCs into two groups of NSCLC and other respiratory tract cancer, including SCLC and mesothelioma. Additionally, standardization was provided in terms of treatment differences. Thus, worse OS and PFS were observed with LMM in patients with SCLC and mesothelioma, but not in the NSCLC group of RTCs. This can be explained by the fact that if cachexia develops at the beginning in cancers with aggressive prognoses such as SCLC and mesothelioma, although they present early symptoms compared to NSCLC, this may be a biomarker that indicates a more unfavorable prognosis (Table 3).

On the other hand, even though muscle loss had a numerically poor prognostic effect on survival, no statistically significant difference was found for PFS and OS in patients with colorectal and non-colorectal gastrointestinal tract cancer. When we evaluated the effect of muscle loss after adjusting for diagnosis and age, we reached a statistically significant conclusion that LMM is generally an independent prognostic factor for OS and PFS. Therefore, this result can be related to an insufficient number of patients was included in the GIT cancers in the present study. Higher ORR was achieved in patients without LMM, whereas it was more pronounced in patients with non-CR GIT cancers.

In our study, patients with distant metastatic bladder cancer were studied, and OS benefit was demonstrated in patients without LMM, consistent with the literature. Additionally we also showed PFS benefit in patients without LMM, even though it did not reach a statistically significant level, due to the possible low number of patients included in the study. On the other hand, the ORRs were similar between two groups and LMM did not predict the treatment responses with platinum plus gemcitabine.

In this study, we included the castration-sensitive prostate cancer patients with high volume disease who were treated with docetaxel at the first line. Previously it was shown that patients with muscle loss experienced higher toxicity and shorter survival while receiving docetaxel in patients with castration-resistant disease [14]. Additionally, the prognostic significance of muscle loss was shown in patients treated with androgen deprivation therapy at first line [15]. Unlike the previous studies, we demonstrated that LMM did not affect both PFS and OS in castration-sensitive prostate cancer patients treated with docetaxel in the first line. Therefore, predictive/prognostic significance of LMM should be evaluated in different clinical scenarios for prostate cancer.

In this study, we also examined patients with metastatic gynecological cancer for whom cytoreductive surgery is not suitable. Although muscle loss has a prognostic significance in the operable early stages of gynecological cancer, there were discordant results for the advanced stage of gynecological cancers [16, 17]. We found that although the prognostic effect of muscle loss on PFS and predictive value on ORR was observed, it did not translate into an overall survival contribution. Consistent with our study, metastatic gynecological cancers show a lower level of LMM when compared to RTC and GIT, and muscle loss has a lower prognostic significance compared to other cancers. In this regard, thanks to the higher ORR obtained, preoperative chemotherapy can be considered in borderline resectable disease without LMM. However, screening for muscle loss may not be considered a priority in the treatment plan for gynecological cancers for a long time.

This study has a number of limitations. Retrospective data analysis and insufficient number of patients are the main limitations of our study. This situation may have led to statistically negative results, although clinically significant results were obtained. However, we understand that the presence of LMM has not only prognostic value, but also predictive value in general. Our study will shed light on conducting prospective randomized studies comparing the response rate and survival time of patients with and without initial muscle loss by the studies with high statistical power and a number of patients for each type of cancer. When our findings are evaluated together with the results of previous studies, it may be considered that LMM may have a negative prog-

nostic effect, especially for SCLC / mesothelioma and breast cancer. Additionally, although statistically significant results were not obtained for the metastatic stage of non-colorectal GIT cancers and bladder cancers, clinically relevant survival differences were shown. Moreover, lower ORR was obtained in patients with LMM in general except for bladder cancer. Therefore, assessment of muscle loss should be incorporated as part of routine clinical evaluation especially for patients with metastatic SCLC/mesothelioma, breast cancer, non-colorectal GIT cancers, and bladder cancer to guide better additional treatment strategies. Additionally, one of the most important limitations of the study is that only muscle mass was evaluated, and muscle function could not be evaluated due to the retrospective design of our study. Although performing functional evaluation may provide a more optimal evaluation, even muscle mass evaluation alone seems to be a remarkable and predictive and prognostic biomarker that can guide the clinician according to our study.

Conclusions

In conclusion, LMM has not only prognostic value but also predictive value for many types of cancer. Therefore, the assessment of muscle loss should be incorporated as part of the first routine clinical evaluation.

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