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RESEARCH

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The role of radiotherapy planning images in monitoring malnutrition and predicting prognosis in head and neck cancer patients: a pilot study

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Abstract

Background Adaptive treatment planning can be made in radiotherapy of head and neck cancer patients for reasons such as changes in tumor volume or weight loss. This study aims to find the role of treatment planning images in monitoring radiotherapy-induced malnutrition and predicting the malnutrition-induced prognosis in head and neck cancer patients.

Methods For this study, we analyzed 30 patients who received radiotherapy in our clinic between September 2018 and September 2021. Those patients, both regular and completed weekly dietitian counseling notes during radiotherapy and available adaptive radiotherapy planning images, were included in the analysis. All patients had weekly nutritional interventions, including nutritional and anthropometric changes in weight, height, body mass index (BMI), and lean body mass (LBM). Skeletal muscle volume, called cervical muscle gauge (CMG), was measured from the simulation images of beginning and adaptive radiotherapy. Inflammatory parameters, including the neutrophil-lymphocyte ratio (NLR), the platelet-lymphocyte ratio (PLR), and the systemic inflammatory index (SII), were also calculated from weekly total blood counts. For the analysis, anthropometric measurements were compared at the beginning and adaptive treatment time. Progression-free (PFS) and overall (OS) survival were calculated according to weight and CMG changes.

Results The median weight loss percentage was 4.8% (0 to 24%). The mean percentage of weight changes, LBM, and CMG were 6.33%, 3.47%, and 9.28%, respectively. Results indicated that BMI ($p = 006$), weight ($p < 0.001$), LBM ($p < 0.001$), and CMG ($p = 0.057$) decreased during radiotherapy. Hemoglobin levels decreased ($p = 0.005$), and inflammatory markers increased. There were significant correlations between weight and LBM ($p < 0.0001$) and CMG ($p = 0.005$) loss. The median follow-up was 26 months. Loss of weight (PFS; 65.5% vs. 35.7%, $p = 0.09$, OS; 73.7% vs. 32.1%, $p = 0.09$), LBM (PFS; 75% vs. 41.1%, $p = 0.118$, OS; 65.6% vs. 52%, $p = 0.221$) and CMG (PFS; 56.3% vs. 47.1%, $p = 0.516$, OS;76.9% vs. 32.4%, $p = 0.059$) negatively affected three-year survival.

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Conclusions Cervical muscle volume measurement may help predict malnutrition in patients receiving radiotherapy for head and neck cancer. Our study shows adaptive planning images may be used for this approach. In addition, this method may help to predict prognosis due to malnutrition in patients undergoing radiotherapy.

Keywords Adaptive radiotherapy images, Cervical muscle gauge, Head and neck cancer, Malnutrition, Radiotherapy

Introduction

Radiotherapy is one of the primary treatment modalities for head and neck cancer patients [1]. Despite technological advances, early and late side effects may negatively affect functional outcomes and quality of life [2–5]. Malnutrition is among one of the most challenging obstacles during the treatment of head and neck cancer patients [6–8]. Patients who suffer from malnutrition have a worse prognosis, and radiotherapy itself is a significant risk for malnutrition in these patients [9–11]. Therefore, early detection of malnutrition, nutritional intervention, and support are crucial during and after radiotherapy [11–13].

As mentioned in the guidelines, head and neck cancer patients are at high risk for malnutrition [14]. Anthropometric measurements like weight, height, body mass index (BMI), fat mass, and lean body mass (LBM) are important in evaluating the nutritional status of patients diagnosed with head and neck cancer, as in all cancer patients [14, 15]. Reduced skeletal muscle is also essential to measure, as it predicts the prognosis of patients, especially those with sarcopenia [16–18]. Skeletal muscles can be measured by computerized tomography images [19, 20]. Muscularity is expressed as skeletal muscle index (SMI) (cm^2/m^2), and it is calculated as total cross-sectional skeletal muscle area (cm^2) from computed tomography (CT) images at the third lumbar (L3), normalized for height (m^2) [21, 22]. SMI depletion may increase the mortality risk in a cancer patient [23]. However, taking L3 measurements for head and neck cancer patients is not always possible [24]. So, the third cervical (C3) usage may be recommended for these cases [25, 26]. However, a correlation is required between C3 and L3 skeletal muscle mass to detect sarcopenia, and several studies suggest a positive correlation for C3 level skeletal muscle, which some others do not [27–29]. According to a recent meta-analysis, SMI measured at C3 may represent a precise marker for the detection of sarcopenia [30]. Moreover, studies evaluating the head and neck region muscles for malnutrition and sarcopenia suggest also considering the masticatory muscles [31].

Although regular and intense nutritional support, weight changes can occur during radiotherapy, affecting the accuracy of treatment planning by volumetric and dosimetric changes in the patient's head and neck regions [32, 33]. This is the radiotherapy approach, where the treatment plan is adjusted or modified during radiotherapy based on changes observed in the patient's anatomy. Therefore, the treatment plan may need to be anatomically adapted to account for weight and tumor volume changes during treatment. The main goal of this process is to improve the treatment outcomes and reduce side effects while maintaining a precise and accurate treatment.

This study aims to detect and measure the dynamic changes of all nutritional parameters to predict patients' prognoses before radiotherapy completeness. We asked about the role of adaptive images in following and detecting the skeletal muscle volume changes in patients who received regular nutritional interventions. We measured and compared the fundamental nutritional parameters at the beginning of radiotherapy and the time of adaptive planning. We also calculated the cervical skeletal muscle mass from images and made a correlation analysis, including all changes to patients' prognoses.

Materials and methods

This study, with reference number 09.2021.647, was approved by Marmara University School of Medicine Noninterventional Ethics Committee on 7 May 2021.

Study

This retrospective study included patients who received radiotherapy in our clinic between September 2018 and September 2021. Of the 74 head and neck patients who underwent adaptive radiotherapy, 30 patients who had regular weekly dietitian follow-up and measurements were included in the analyses. Patients who did not receive at least one weekly dietitian visit were excluded from the study. Weekly dietitian assessments included anthropometric measurements, food consumption records, and nutritional changes resulting from radiotherapy. The dietitian adjusted the patients' energy and protein needs according to changing weekly conditions and side effects that altered nutritional intake. Patients' computed tomography (CT) images performed for initial simulation and adaptive planning were retrieved. The median time between the first and adaptive CT was 42 days (18 to 57 days). Study population characteristics are summarized in Table 1.

Study measures

Our clinic's calibrated electronic scale (Densi GL-150 Automatic Height Weight BMI Measurer, Bursa, Türkiye) was used for patients' weight and height. Body Mass Index (BMI) is calculated using the patient's weight in

Table 1 Characteristics of the study population

Demographic variable	
Age (year)	
Median (min-max)	62 (22–88)
	***n* (%)**
Gender	
Male	23 (76.7)
Female	7 (23.3)
Disease characteristics	
Stage	
Early (I-II)	7 (23.3)
Local advanced (III-IV)	23 (76.7)
Tumor Site	
Oral Cavity	11 (36.7)
Larynx	7 (23.3)
Nasopharynx	6 (20)
Paranasal sinuses	2 (6.7)
Hypopharynx	2 (6.7)
Oropharynx	1 (3.3)
Thyroid	1 (3.3)
Treatment charcteristics	
Previous Surgery	
Yes	16 (53.3)
No	14 (46.7)
Concurrent chemotherapy	
Yes	22 (73.3)
No	8 (26.7)
Anthropometric measurements	**Mean ± SD**
Height (m)	1.7 ± 0.1
Weight (kg)	72.11 ± 12.65
BMI (kg/m2)	25.68 ± 4.54
LBM (kg)	52.81 ± 8.07
CMG	1219.35 ± 559.94
Biochemical measurements	
SII	1218.99 ± 1289.32
NLR	4.03 ± 2.97
PLR	206.13 ± 126.60
Hb (g/dL)	12.67 ± 2.08

BMI: body mass index, LBM: lean body mass; CMG: cervical muscle gauge; LBM: lean body mass, Hb: Hemoglobin; SII: systemic inflammatory index; NLR: neutrophil lymphocyte ratio, PLR: platelet lymphocyte ratio

kilograms divided by their height in square meters. Lean body mass (LBM) is calculated using the formula for male 0.407Weight + 0.267Height − 19.2 and for female 0.252Weight + 0.473Height − 48. 3 [34].

Physicians contoured the sternocleidomastoid and paracervical muscles on axial images at the C3 level in Eclipse radiotherapy planning software (v11.0 Varian, USA) to calculate skeletal muscle volume on retrieved images. The muscle contouring process was double-checked using ProKnow Contouring Software (Elekta) on transferred data of images. Figure 1 shows an example of muscle contouring at the C3 level.

Three skeletal muscle measures were used to obtain muscle mass: skeletal muscle index (SMI), skeletal muscle density (SMD), and cervical muscle gauge (CMG). The axial cross-sectional area of sternocleidomastoid and paravertebral muscles at the third cervical vertebra was chosen for skeletal muscle gauge (CMG) calculations as recommended in previous studies [35]. Based on the skeletal muscle area at the C3 level, the skeletal muscle area at the L3 level was predicted using a previously published formula [25]:

$$\begin{gathered} CSA\,at\,L3\;(cm2) = 27.304 + 1.363 \times CSA\,at\,C3\;(cm2) \\ -0.671 \times age\,(years) + 0.640 \times weight\,(kg) + 26.442 \times \\ gender\,(1\,for\,female,\;2\,for\,male) \\ (CSA : cross - \sec tional\,area)\,. \end{gathered}$$

The skeletal muscle area at the L3 level was then normalized for height to calculate the lumbar skeletal muscle index (SMI), as shown in formula [22]:

$$Lumbar\;SMI\left(cm^2/m^2\right) = CSA\,at\,L3/length\left(m^2\right)$$

The malnutrition assessment was done using the SMI formula (lumbar SMI (cm^2)/height (m^2)) [25]. The SMI area was defined as the pixel area within a radiodensity between − 29 and + 150 Hounsfield units, specifically for smooth muscle tissue [36].

CMG was calculated as the product of SMI and SMD (SMI× SMD) [37].

In addition, the weekly hemoglobin derived from an electronic database were used to obtain the inflammatory parameters at the beginning and the time of adaptive treatment. Therefore, hemoglobin (g/dL), neutrophil-lymphocyte ratio (NLR = the ratio of neutrophil count to lymphocyte count (103/L)) (cut off 4.350), the platelet-lymphocyte ratio (PLR = the ratio of platelet count (103/L) to lymphocyte count (103/L)) (cut off 235.86), and the systemic inflammatory index (SII = platelet count (103/L) to NLR) (cut off 573.84), were noted [38, 39].

Progression-free survival (PFS) was defined as the time between the date of histologic diagnosis and the date of clinical or radiological recurrence (pathologic confirmed or not) or the date of last follow-up, whichever occurred first. Overall survival (OS) was defined as the time between the date of histologic diagnosis and death or the date of the last follow-up.

Statistical analysis

Descriptive statistics were employed to characterize continuous variables, including mean, standard deviation, minimum, median, and maximum values. The average distribution suitability of continuous variables was examined using the Shapiro-Wilk test. According to the Shapiro-Wilk test, skewness and kurtosis values between − 1.5 and + 1.5 were considered to determine whether the study measurements were normally distributed. If the

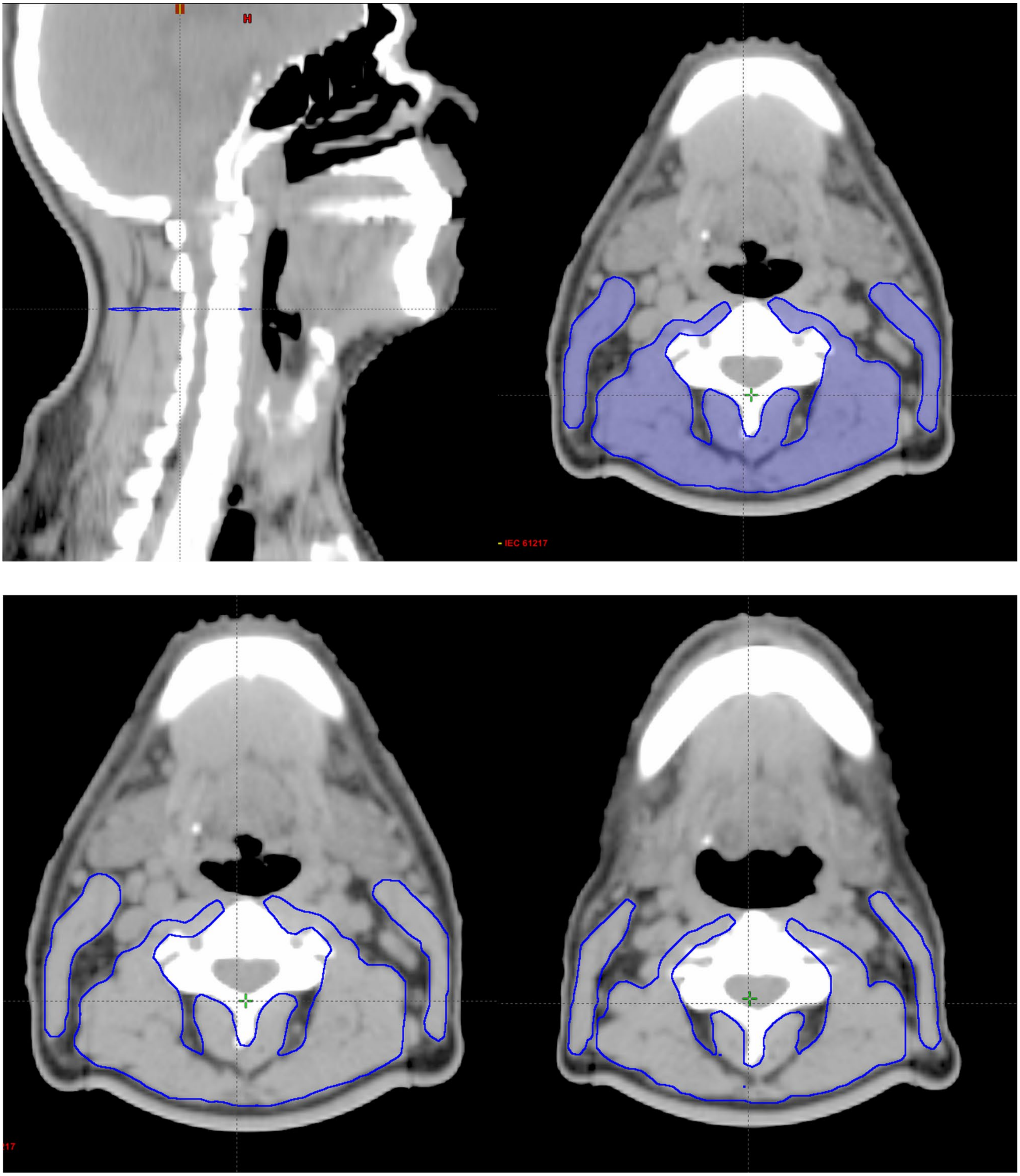

Fig. 1 (Upper) Contouring of skeletal muscle tissue (both sternocleidomastoid and paravertebral muscles) at the level of the third cervical vertebra (C3) (blue). (Lower) Two identical axial computed tomography (CT) slides at the C3 level. In blue, the skeletal muscles are radiotherapy's initial (left) and the adaptive period (right)

Table 2 Comparison of study measurements between the beginning and the adaptive time of radiotherapy

	All patients (n = 30)		p
	Beginning of RT	Adaptive RT	
	Mean ± SD		
BMI (kg/m^2)	25.68 ± 4.54	24.52 ± 4.06	**0.006**
Weight (kg)	72.11 ± 12.65	67.65 ± 11.12	**< 0.001**
LBM (kg)	52.81 ± 8.07	51.20 ± 7.20	**< 0.001**
CMG	1219.35 ± 559.94	1071.92 ± 492.18	0.057
Hb (g/dL)	12.88 ± 1.90	11.96 ± 1.99	**0.005**
SII	1038.70 ± 756.60	1195.11 ± 906.77	**0.400**
NLR	4.00 ± 2.98	4.85 ± 2.68	**0.153**
PLR	198.52 ± 112.137	346.86 ± 236.30	**0.002**

BMI: body mass index, LBM: lean body mass; CMG: cervical muscle gauge; LBM: lean body mass, Hb: Hemoglobin; SII: systemic inflammatory index; NLR: neutrophil lymphocyte ratio, PLR: platelet lymphocyte ratio

p: Paired sample t-test (< 0.05 significant)

distribution was not normally distributed Wilcoxon test was used for analysis. The two independent groups were compared using the paired sample t-test. The correlation between continuous variables was assessed using the Pearson correlation coefficient. The strength of the positive correlation increases for results close to 1.OS and PFS were analyzed by generating Kaplan–Meier survival curves and compared using the log-rank test. In comparison, weight loss ≥ 5%, LBM Analyses were performed using MedCalc® Statistical Software version 19.7.2 (MedCalc Software Ltd, Ostend, Belgium; https://www.medcalc.org; 2021). All statistical tests were two-sided, and a p-value of < 0.05 was considered significant.

Results

None of the patients had tumor or disease progression or any infection at the time of adaptive images obtained. Seven patients gained weight, whereas nine patients lost less than 5%. The rest of the patients (n = 14) lost weight a median of 9% (5.1–25%). The median weight loss percentage in the whole group was 4.8% (0 to 24%). The mean percentage of weight changes, LBM, and CMG were 6.33% (p < 0.0001), 3.47% (p < 0.0001), and 9.28% (p = 0.057), respectively. The results indicated that BMI (p = 006), weight (p < 0.001), LBM (p < 0.001), and CMG (p = 0.057) decreased during radiotherapy. Hemoglobin levels decreased (p = 0.005), and inflammatory markers increased, especially the PLR ratio (p = 0.004) (Table 2). BMI (p = 0.006), CMG (p = 0.039) and LBM (< 0.001) values were significantly lower in patients with weight loss over 5% (Table 3). According to CMG loss, BMI (p = 0.018), weight (< 0.001) and LBM (< 0.001) values were significantly lower in patients (Table 4).

The correlation analysis based on a percentage of changes in parameters is shown in Table 5. There were significant correlations between CMG and weight loss (p = 0.005). Figure 2 represents the three-year survival results according to weight status and CMG. Median follow-up was 26 months (range, 3 to 46 months). Weight

Table 3 Comparison of study measures according to weight loss status

	No weight loss (< 5%) n = 14			Weight loss (≥ 5%) n = 16		
	Mean ± SD	95% CI (lower-upper)	p	Mean ± SD	95% CI (lower-upper)	p
Nutritional parameters						
BMI(kg/m^2)						
	25.02 ± 5.07	(-0.29) -(0.65)	0.433	26.52 ± 4.08	(0.905) -(4.29)	**0.006**
	24.84 ± 4.77			23.92 ± 3.27		
CMG						
	1031.90 ± 459.66	(-105.12) -(110.66)	0.957	1498.54 ± 611.73	(21.85) -(715.69)	**0.039**
	1029.13 ± 438.71			1130.27 ± 574.15		
LBM (kg)						
	49.17 ± 7.91	(-0.510) -(1.58)	0.295	57.40 ± 5.74	(2.31) -(4.59)	**< 0.001**
	48.64 ± 7.74			53.94 ± 5.60		
Inflammatory parameters						
SII						
	909.66 ± 585.04	(-335.08) -(529.46)	0.635	11177.67 ± 910.58	(-1177.18)-(318.14)	0.235
	812.46 ± 504.36			1607.18 ± 1072.91		
NLR						
	3.78 ± 3.04	(-1.82) -(1.82)	1	4.23 ± 3.03	(-4.49) -(0.95)	0.183
	3.78 ± 1.80			6.00 ± 3.05		
PLR						
	210.90 ± 122.96	(-197.08) -(10.82)	0.075	185.20 ± 102.43	(-388.13-(-27.45)	**0.027**
	304.03 ± 157.15			392.99 ± 299.63		

CMG: Cervical muscle gauge, BMI: body mass index, LBM: lean body mass, SII: systemic inflammatory index, NLR: neutrophil lymphocyte ratio, PLR: platelet lymphocyte ratio

Table 4 Comparison of study measures according to cervical muscle gauge (CMG) status

	No CMG loss *n* = 14			CMG loss *n* = 16		
	Mean ± SD	**95% CI (lower-upper)**	***p***	**Mean ± SD**	**95% CI (lower-upper)**	***p***
BMI(kg/m^2)						
	24.68 ± 4.34	(-0.35) -(1.64)	0.186	26.61 ± 4.81	(0.378) -(3.36)	**0.018**
	24.04 ± 3.75			24.74 ± 4.48		
Weight (kg)						
	68.28 ± 14.15	(-0.89) -(4.47)	0.172	75.78 ± 10.79	(4.05) -(10.32)	**< 0.001**
	66.49 ± 12.59			68.60 ± 10.10		
LBM (kg)						
	51.29 ± 9.30	(-0.281) -(2.46)	0.109	54.65 ± 6.71	(1.37) -(43.89)	**< 0.001**
	50.20 ± 8.80			52.01 ± 5.76		
SII						
	1029.56 ± 698.54	(-508.88) -(471.53)	0.935	1046.01 ± 824.36	(-937.83) -(404.64)	0.409
	1048.23 ± 777.80			1312.61 ± 1009.14		
NLR						
	3.83 ± 3.12	(-3.61) -(1.45)	0.367	4.13 ± 2.97	(-2.85) -(1.52)	0.525
	4.91 ± 2.42			4.80 ± 2.95		
PLR						
	299.91 ± 126.54	(-157.57) -(41.49)	0.226	173.41 ± 96.18	(-378.09) -(-63.05)	**0.009**
	287.96 ± 137.49			393.99 ± 288.95		

CMG: Cervical muscle gauge, BMI: body mass index, LBM: lean body mass, SII: systemic inflammatory index, NLR: neutrophil lymphocyte ratio, PLR: platelet lymphocyte ratio

Table 5 The correlation analysis based on a percentage of changes

	Pearson correlation coefficient	*p*
Weight and LBM	0.746**	**< 0.0001**
Weight and CMG	0.574**	**0.005**
Weight and Hb	0.232	0.299
Weight and SII	-0.426*	**0.048**
Weight and NLR	-0.299	0.177
Weight and PLR	-0.460*	**0.031**
LBM and CMG	0.389	0.074
LBM and Hb	-0.620	0.785
LBM and SII	0.060	0.790
LBM and NLR	0.006	0.978
LBM and PLR	0.49	0.828
CMG and Hb	0.377	0.083
CMG and SII	-0.95	0.675
CMG and NLR	0.202	0.368
CMG and PLR	-0.254	0.253
Hb and SII	-0.290	0.191
Hb and NLR	0.011	0.960
Hb and PLR	-0.527*	**0.012**
SII and NLR	0.800**	**< 0.0001**
SII and PLR	0.919**	**< 0.0001**
NLR and PLR	0.660**	**0.001**

**. Correlation is significant at the 0.01 level (2-tailed)

*. Correlation is significant at the 0.05 level (2-tailed)

The strength of the positive correlation increases for results close to 1

LBM: lean body mass; CMG: Cervical muscle gauge; Hb: Hemoglobin; SII: systemic inflammatory index; NLR: neutrophil lymphocyte ratio, PLR: platelet lymphocyte ratio

loss (PFS; 65.5% vs. 35.7%, $p = 0.09$, and OS; 73.7% vs. 32.1%, $p = 0.09$), LBM (PFS; 75% vs. 41.1%, $p = 0.118$ and OS; 65.6% vs. 52%, $p = 0.221$) and CMG loss (PFS; 56.3% vs. 47.1%, $p = 0.516$, and OS;76.9% vs. 32.4%, $p = 0.059$) negatively affected patients' survival.

Discussion

Our findings revealed a significant correlation between decreased cervical skeletal muscle volume from C3 and malnutrition indicators of weight loss, BMI, and LBM. Additionally, we found that, patients who was detected their muscle loss in adaptive images of radiotherapy had worse survival outcomes than those without (Fig. 2). Elevated inflammatory markers in cancer patients are associated with poor prognosis in the literature [38, 39]. Although radiotherapy has its effect via reactive oxygen species (indirect effect), inflammation is still a worse indicator for prognosis in cancer patients who receive radiotherapy [40]. The relationship between malnutrition and inflammatory indexes is a new context in cancer. More information should be available to interpret the exact role of these parameters. Meanwhile, we would like to add this information to our study since deterioration in nutritional parameters, including CMG, was accompanied by increasing inflammatory parameters.

Although technological advances, normal tissues of the mucosa, oral cavity, pharynx, and salivary glands in the head and neck treatment area inevitably lead to weight loss as a side effect [10]. For those reasons, guidelines and several studies recommend thorough nutrition

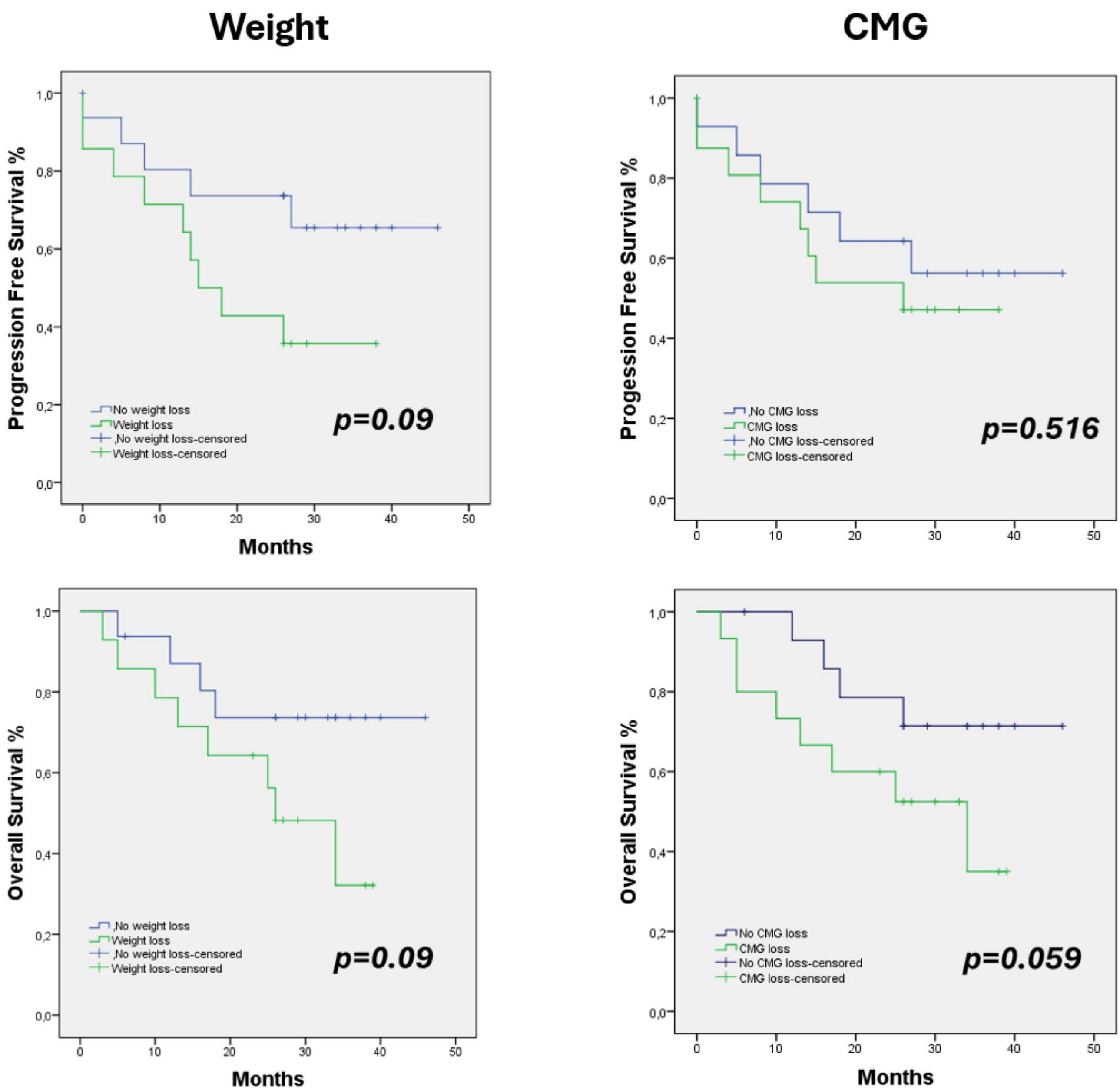

Fig. 2 Kaplan-Meier curves for progression-free survival (PFS) and overall survival (OS) due to weight status and cervical muscle gauge (CMG) status

assessment, adequate nutritional counseling, and, if necessary, nutritional support according to symptoms and nutritional status for head and neck cancer patients [6, 41]. Despite regular weekly dietitian assessments and personalized dietary counseling, patients may lose weight during radiotherapy [42, 43].

There has been a growing body of research examining the impact of cervical muscle volume on malnutrition, toxicity, and survival outcomes in head and neck cancer patients. Becker et al. [44] reported that patients with low cervical muscle volume experienced more significant chemoradiotherapy toxicity. Similarly, Brill et al. [45] emphasized a significant association between decreased muscle volume measured before treatment and chemotherapy-related toxicity in their study. Sealy et al. [46] reported an association between lower muscle mass and a higher risk of early termination of main treatment in head and neck cancer patients. Ganju et al. [47] showed that patients who lost muscle volume are more face to undesired treatment breaks and toxicity during concurrent chemoradiation. Weight loss may be a restriction factor for the completeness of standard therapies [48]. There are some patient related risk factors defined for treatment interruptions i.e. older age, low initial performance score and patient compliance [42]. Our study did not observe any treatment interruption or early termination. Despite the fact that we observed weight loss in study patients, we think that regular weekly registered dietitian visits and assessments may have an positive effect on this issue. The patients were also enthusiastic about these visits and fully complied with the recommendations.

However, the prognosis declined in patients who lost cervical muscle volume during radiotherapy, as the fundamental nutritional parameter of weight loss shows. Moreover, the literature has also demonstrated the utility of cone-beam CT scans taken at any time during radiotherapy in assessing malnutrition and CMG loss [49].

To our knowledge, this is the first study showing that neck cervical muscle values obtained from adaptive radiotherapy images can be evaluated regarding malnutrition and prognosis. In addition to its retrospective nature, our study's limitation is the small number of patients. Future studies with larger patient cohorts could further investigate the impact of muscle loss during radiotherapy on prognosis and the effect of the rate or percentage of loss on survival outcomes.

Conclusions

Cervical muscle volume measurement may have a role in predicting malnutrition in patients with head and neck cancer. Our study shows that adaptive planning images may be used to predict prognosis due to malnutrition in patients undergoing radiotherapy. Volume calculation may easily be done in the auto-contouring implemented planning systems.

Abbreviations

BMI	Body mass index
CMG	Cervical muscle gauge
CSA	Cross-sectional area
CT	Computerized tomography
LBM	Lean body mass
NLR	Neutrophil-lymphocyte ratio
PFS	Progression-free survival
PLR	Platelet-lymphocyte ratio
OS	Overall survival
SII	Systemic inflammatory index
SMD	Skeletal muscle density
SMI	Skeletal muscle index

Supplementary Information

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Supplementary Material 1

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Author contributions

BMA was involved in the conception and design of the work, data analysis, and interpretation, manuscript drafting, modification of the last version before submission, and approval of the manuscript as the corresponding author. FEÖ, BD ZNK, and DG were involved in the design of the work, the acquisition, analysis, and interpretation of data, the modification of the last version, and the approval of the manuscript before submission. All authors agreed to be personally accountable for their contributions and to ensure that questions related to the accuracy or integrity of any part of the work, even ones in which the author was not personally involved, are appropriately investigated, resolved, and the resolution documented in the literature.

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Data availability

The data was attached as a supplemental file.

Declarations

Ethics approval and consent to participate

This study was approved by Marmara University School of Medicine Noninterventional Ethics Committee on 7 May 2021 (reference number: 09.2021.647).

Competing interests

The authors declare no competing interests.

Clinical trial number

Not applicable.

Consent for publication

This is a retrospective study that has no need to receive patient informed consent.

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