Prognostic Significance of Adipose Tissue Distribution and Metabolic Activity in PET / CT in Patients with Metastatic Colorectal Cancer

tuba karaçelik
Necmettin Erbakan Üniversitesi Meram Tıp Fakültesi: Necmettin Erbakan Universitesi Meram Tip Fakultesi

buğra kaya
Necmettin Erbakan Üniversitesi Meram Tıp Fakültesi: Necmettin Erbakan Universitesi Meram Tip Fakultesi

mustafa korkmaz (dr.musstafa@gmail.com)
Necmettin Erbakan University Meram Faculty of Medicine: Necmettin Erbakan Universitesi Meram Tip Fakultesi https://orcid.org/0000-0003-0926-6748

mustafa karaağaç
Necmettin Erbakan Üniversitesi Meram Tıp Fakültesi: Necmettin Erbakan Universitesi Meram Tip Fakultesi

murat araz
Necmettin Erbakan Üniversitesi Meram Tıp Fakültesi: Necmettin Erbakan Universitesi Meram Tip Fakultesi

Melek karakurt eryılmaz
Necmettin Erbakan Üniversitesi Meram Tıp Fakültesi: Necmettin Erbakan Universitesi Meram Tip Fakultesi

hakan şat bozcuk
Medical Park Hospital

mehmet artaç
Necmettin Erbakan Üniversitesi Meram Tıp Fakültesi: Necmettin Erbakan Universitesi Meram Tip Fakultesi

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Abstract

Purpose: In this study, we aimed to evaluate prognostic significance of adipose tissue distribution and metabolic activity in PET/CT to predict survival in patients with metastatic colorectal cancer (mCRC).

Methods: The volume, density (HU) and FDG uptake (standardized uptake value-[SUV]) of visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT) and maximum FDG uptake of the tumor tissue were measured. Subcutaneous adipose tissue of volume-to-density ratio (SAT ratio) was calculated.

Results: The median OS for the patients with SAT ratio value <-1.1 and ≥ -1.1 were 38.5 (95% CI 31.54-45.58) and 24.5 (95% CI 14.13-34.93) months, respectively (p=0.05). During follow up, 69 patients experienced disease progression. The median progression-free survival (PFS) was 11.03 months (95% CI: 9.11-12.95). Median PFS for patients with tumor SUV max value <11.5 and ≥11.5 were 9.2 (95% CI 7.25-11.27) and 12.6 (95% CI 10.02-15.27) months, respectively (p=0.14). 48 patients received bevacizumab therapy. VAT SUV mean (HR: 0.09; 95% CI 0.01-0.52, p=0.008) was significantly associated with PFS in patients receiving bevacizumab. SAT ratio was the significant parameter for the OS (HR: 0.58; 95% CI 0.33-1.01, p=0.05) and PFS (HR: 1.99; 95% CI 1.02-3.91, p=0.043).

Conclusions: SAT ratio was an independent prognostic factor for survival in patients with mCRC. Higher SAT volume is correlated with longer survival in mCRC patients

Introduction

Obesity is an excessive accumulation of fat in adipose tissue. Its prevalence is increasing all over the world [1]. It is one of the important risk factors in terms of increasing the risk of developing various types of cancer including colorectal cancer and affecting the prognosis [2].

Although strong links between obesity and colorectal cancer have been demonstrated in epidemiological studies, the relationship with underlying mechanisms and prognostic factors is not clear [3]. Potential mechanisms that have been shown to be effective in clinical studies are adipose tissue dysfunction, chronic inflammation and insulin resistance [4].

Besides being a lipid and passive energy storage of adipose tissue; it is also known to be a highly active metabolic and endocrine organ. Although the majority of adipose tissue consists of adipocytes, there are also different cell types including fibroblasts, endothelial cells, macrophages, and pluripotent stem cells. Various factors are secreted from adipocytes and other cells. While some of the factors have a pro-inflammatory effect, others have anti-inflammatory, antitumoral, protective effects against diabetes and cardiovascular diseases [5].

Depending on the distribution of adipose tissue, it is classified as visceral or subcutaneous adipose tissue [6]. In addition to anatomical differences in SAT and VAT distribution, there are also differences in

cellular, physiological and clinical aspects. Absorption and accumulation of free fatty acids and triglyceride circulating in the subcutaneous adipose tissue is more [7]. Visceral fat tissue has a higher metabolic activity. Lipolytic activity is increased, free fatty acid production is high. The number of inflammatory cells in visceral adipose tissue is higher than in subcutaneous adipose tissue. Increased production of pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-a), interleukin-6 (IL-6) is associated with the exaggerated inflammatory state [4, 7]. Insulin sensitivity is less in visceral adipose tissue. Insulin resistance, hyperglycemia and formation of hyperinsulinemia are associated with an increased risk of diabetes [6, 7].

Obesity, especially visceral fat, causes adipose tissue dysfunction. The secretion of adipokines becomes erratic. While the secretion of pro-apoptotic, anti-inflammatory adipokine such as adiponectin decreases, the secretion of pro-inflammatory cytokines such as TNF-a and IL-6 increases [8, 9]. Increase of proinflammatory cytokines together with adipose tissue hypoxia caused by obesity trigger chronic inflammation [10]. Obesity itself and adipokines secreted from dysfunctional adipose tissue also cause insulin resistance [11]. All these changes are thought to play a role in the development of carcinogenesis and metastasis due to obesity [12].

BMI is commonly used to define obesity. However, BMI, which fat and muscle mass contribute together, is insufficient to show total body fat and distribution. It does not fully reflect the fat tissue activity [13]. Although FDG uptake in PET / CT was generally used for tumor and metastasis evaluation in previous studies, it has also been used for the evaluation of adipose tissue in various studies recently. FDG uptake, density and volume of adipose tissue were measured in PET / CT in order to evaluate adipose tissue in malignant diseases and determine its relation with tumor development and prognosis [14–16].

Few studies have evaluated the relationship between adipose tissue volume and activity with prognosis in patients with colorectal cancer [15, 17–19]. However, the prognostic value of adipose tissue in colorectal cancer is still uncertain. In this study, it was aimed to determine the distribution and activity of adipose tissue from PET / CT images of patients followed up for metastatic colorectal cancer, and to evaluate the relationship between the obtained data and survival.

Materials And Methods

Patients

Permission for this study was obtained from the Pharmaceuticals and Non-Medical Device Research Ethics Committee of Necmettin Erbakan University.

The medical records of 250 patients, who were followed up at the Medical Oncology Clinic of our university with the diagnosis of metastatic colorectal cancer between January 2010 and December 2018 and who underwent PET / CT were analyzed retrospectively. Eighty three of these patients were included in the study. Patients who did not have PET / CT imaging at the time of the diagnosis of metastasis, had secondary malignancies, had incomplete file and laboratory information were excluded from the study.

^{18} F-FDG PET/CT

All patients fasted for at least 6 hours prior to 18F-FDG (FDG) injection. FDG injection at a dose of 0.140 mCi / kg was administered to patients with blood glucose level < 200 mg / dL. After the injection, the patient was kept in the room inside the PET / CT unit for about 1 hour for the bio-distribution of FDG. Later, imaging was performed with Siemens Biograph 6 TruePoint PET / CT (Siemens, Germany). The body region between the vertex and proximal thigh was taken as the FDG PET / CT imaging area.

First, non-contrast CT imaging (130 kV, 50 mA, 5 mm slice thickness) was performed. Subsequently, PET imaging was performed in 3D mode, with an imaging area of 7–8 beds for each patient and 3 minutes of scanning time for each bed. PET images were reconstructed with the Iterative method.

FDG PET/CT image analysis

PET / CT images were retrospectively evaluated using TrueD software on the Multimodality Workplace (Syngo MMWP, Version VE25A, Siemens, Germany) workstation.

Extraperitoneal adipose tissue between subcutaneous and muscles was defined as subcutaneous adipose tissue (SAT), intraabdominal adipose tissue was defined as visceral adipose tissue (VAT).

The area of interest (ROI) was drawn for SAT and VAT at the level of the L4 vertebra in Computed Tomography (CT) and applied to three consecutive sections. A range of -200 to -50 Hounsfield Units (HU) was chosen for determination of adipose tissue (AT) in areas of interest (ROIs). SAT volume (SAT cm^3), SAT average density (SAT HUavg), VAT volume (VAT cm^3) and VAT average density (VAT HUavg) were calculated for adipose tissue (AT) within SAT and VAT areas of interest (ROIs) (Fig. 1).

Standardized Uptake Value (SUV) for metabolic activity was calculated based on injected FDG dose and body weight. Areas of interest (ROIs) drawn on CT for SAT SUV_{mean} and VAT SUV_{mean} metabolic activity measurements were automatically inserted into PET / CT fusion images. For precise metabolic activity measurement, regions of interest (ROIs) were carefully evaluated and detected ones were manually removed in order to avoid high FDG uptake from adjacent tissues (e.g. intestine, vascular, urinary tract, muscle).

SAT ratio value was obtained by proportion of the calculated volume and density values for subcutaneous adipose tissue. The highest SUV value in the tumor tissue (tumor SUV max) was measured.

Statistical analysis

SPSS 22.0 package program was used in computer environment for data entry and statistical analysis. Ratio and median values were calculated for descriptive data. A p value of < 0.05 was considered statistically significant. Cox regression analysis was used to evaluate the survival effects of clinical and PET / CT data. Kaplan-Meier method was used to determine survival times.

Results

Data of 83 patients were analyzed in the study. Of the patients in the group, 51 (61.5%) were male and 32 (38.5%) were female. The median age of the patients at the time of diagnosis was 61 (21–83), and their body mass index (BMI) was 26.4 (13.8–39.1). The primary tumor site was in the right colon in 13 patients (15.6%) and in the left colon in 70 patients (84.4%). After the diagnosis of metastatic disease, there were 48 (57.83%) patients receiving bevacizumab therapy and 8 (9.63%) patients receiving EGFR-targeted therapy. Chemotherapy regimens without targeted agents were applied to 27 (32.53%) patients. The clinical characteristics of the patients are shown in Table-1.

The median visceral and subcutaneous adipose tissue values of the patients were as follows; VAT volume 77.17 (9.14-239.43), VAT HU -96 (-109 to -78), VAT SUV mean 0.88 (0.41–1.18), SAT volume 112.29 (23.65-379.69), SAT HU -101 (-111 to -75), SAT SUV mean 0.36 (0.19–0.76), tumor SUV max 11.56 (2.47–36.85).

Progression was observed in 69 (83.1%) patients during follow-up. 53 (63.9%) patients died during follow-up. The median PFS and OS were 11.03 months (95% CI: 9.11–12.95) and 33.7 (95% CI: 28.18–39.34) months, respectively.

Disease progression-free survival

In univariate analysis, tumor SUV max (HR: 0.95; 95% CI 0.92–0.99, p = 0.014) and comorbidity (HR: 0.48; 95% CI 0.29–0.78, p = 0.003) were significant factors that affected PFS (Table 2). PFS was worse in patients with at least one of the comorbid diseases. Tumor SUV max was divided into two groups according to the median value of 11.5. Median PFS for patients with tumor SUV max value < 11.5 and ≥ 11.5 were 9.2 (95% CI 7.25–11.27) and 12.6 (95% CI 10.02–15.27) months, respectively (p = 0.14) (Fig. 2). In the multivariate analysis, gender (HR: 1.70; 95% CI 1.00-2.90, p = 0.05) and tumor SUV max (HR: 0.96; 95% CI 0.92–0.99, p = 0.036) were found to be prognostic factor for PFS (Table 3).

Table 1
Characteristics of patients (n = 83)

		No. of patients (%)	Median (range)
Age (years)			61 (21–83)
Gender	Male	51 (61.5)	
	Female	32 (38.5)	
BMI (kg/m^2)			26.4 (13.8–39.1)
Primary tumor location	Right colon	13 (15.6)	
	Left colon	70 (84.4)	
TNM stage	Stage 1–3	31 (37.4)	
	Stage 4	52 (62.6)	
Metastases	Liver	31 (37.3)	
	Peritoneum	10 (12.0)	
	Lung	15 (18.1)	
	Others	9 (10.8)	
	Multiple	18 (21.7)	
Adjuvant treatment	Yes	28 (33.7)	
	No	55 (66.3)	
Comorbidity	Yes	37 (44.5)	
	No	46 (55.5)	
Operation	Yes	73 (87.9)	
	No	10 (12.1)	
Kras	Mutant	42 (50.6)	
	Wild	41 (49.4)	
Treatments	Bevacizumab therapy	48 (57.83)	
	EGFR targeted therapy	8 (9.63)	
	Chemotherapy	27 (32.53)	

BMI, body mass index; NLR, neutrophil-to-lymphocyte ratio; SAT, subcutaneous adipose tissue; VAT, visceral adipose tissue; HU, hounsfield unit; SUV, standardized uptake value; SAT ratio, SAT volume/SAT density.

		No. of patients (%)	Median (range)
Treatment response	Yes	39(46.98)	
	No	44(53.01)	
NLR			2.46 (0.89-10.0)
CRP			6.95 (0.1–228)
Albumin			4.0 (2.8–4.8)
Platelet			291 (95–695)
Progression	Yes	69 (83.1)	
	No	14 (16.9)	
VAT	Volume (cm^3)		77.17 (9.14-239.43)
	Density (HU)		-96.00 (-109 and − 78)
	SUV mean		0.88 (0.41–1.18)
SAT	Volume (cm^3)		112.29 (23.65-379.69)
	Density (HU)		-101 (-111 and − 75)
	SUV mean		0.36 (0.19–0.76)
Tumor SUV max			11.56 (2.47–36.85)
SAT ratio			-1.11 (-3.42 and − 0.32)

BMI, body mass index; NLR, neutrophil-to-lymphocyte ratio; SAT, subcutaneous adipose tissue; VAT, visceral adipose tissue; HU, hounsfield unit; SUV, standardized uptake value; SAT ratio, SAT volume/SAT density.

Table 2
Univariate analysis for PFS and OS

	PFS		OS	
Variables	**Hazard ratio (%95 CI)**	**p value**	**Hazard ratio (%95 CI)**	**p value**
Age	0.99 (0.97–1.01)	0.777	1.012 (0.99–1.03)	0.299
Gender	1.58 (0.95–2.62)	0.073	1.110 (0.63–1.94)	0.717
BMI	0.97 (0.92–1.02)	0.306	0.965 (0.91–1.01)	0.165
Primary tumor location	0.93 (0.48–1.77)	0.825	2.519 (1.27–4.98)	**0.008**
TNM stage	1.29 (0.79–2.11)	0.300	1.041 (0.59–1.82)	0.890
Metastases	0.69 (0.42–1.13)	0.142	0.967 (0.55–1.69)	0.906
Adjuvant treatment	1.37 (0.82–2.28)	0.217	1.223 (0.68–2.18)	0.496
Comorbidity	0.48 (0.29–0.78)	**0.003**	0.789 (0.45–1.35)	0.392
Operation	0.88 (0.43–1.78)	0.730	0.985 (0.42–2.31)	0.972
Kras	1.38 (0.85–2.22)	0.185	1.026 (0.59–1.76)	0.926
Treatment	1.02 (0.63–1.65)	0.928	0.795 (0.45–1.38)	0.416
Treatment response	0.47 (0.29–0.77)	0.003	-	-
VAT volume	1.00 (0.99-1.00)	0.983	0.999 (0.99-1.00)	0.774
VAT density (HU)	0.99 (0.96–1.03)	0.938	0.997 (0.95–1.04)	0.899
VAT SUV mean	0.44 (0.12–1.65)	0.227	1.181 (0.25–5.41)	0.831
SAT volume	0.99 (0.99-1.00)	0.355	0.998 (0.99-1.00)	0.423
SAT density (HU)	1.00 (0.97–1.03)	0.727	0.982 (0.94–1.02)	0.353
SAT SUV mean	0.38 (0.04–3.20)	0.378	0.493 (0.04–5.84)	0.575
SAT ratio	1.2 (0.79–1.94)	0.34	0.586 (0.34-1.00)	**0.053**
Tumor SUV max	0.95 (0.92–0.99)	**0.014**	1.353 (0.45–4.05)	0.589
NLR	1.00 (0.89–1.12)	0.971	1.023 (0.90–1.15)	0.716
CRP	1.00 (0.99-1.00)	0.549	1.00 (0.99-1.00)	0.241
Albumin	0.89 (0.52–1.52)	0.672	0.88 (0.48–1.59)	0.678

PFS, progression-free survival; OS, overall survival; BMI, body mass index; NLR, neutrophil-to-lymphocyte ratio; SAT, subcutaneous adipose tissue; VAT, visceral adipose tissue; HU, hounsfield unit; SUV, standardized uptake value; SAT ratio, SAT volume/SAT density.

	PFS		OS	
Platelet	0.99 (0.99-1.00)	0.214	1.001 (0.99-1.00)	0.686

PFS, progression-free survival; OS, overall survival; BMI, body mass index; NLR, neutrophil-to-lymphocyte ratio; SAT, subcutaneous adipose tissue; VAT, visceral adipose tissue; HU, hounsfield unit; SUV, standardized uptake value; SAT ratio, SAT volume/SAT density.

Table 3
Multivariate analysis for PFS and OS

	PFS		OS	
Variables	**Hazard ratio (%95 CI)**	**p value**	**Hazard ratio (%95 CI)**	**p value**
Gender	1.70 (1.00-2.90)	**0.050**	**-**	**-**
Comorbidity	0.61 (0.36–1.04)	0.073	-	-
Tumor SUV max	0.96 (0.92–0.99)	**0.036**	**-**	**-**
Primary tumor location	-	**-**	0.303 (0.14–0.62)	**0.001**
SAT ratio	-	**-**	0.476 (0.26–0.84)	**0.011**

PFS, progression-free survival; OS, overall survival; SAT, subcutaneous adipose tissue; SAT ratio, SAT volume/SAT density.

Overall survival

In univariate analysis, tumor location (HR: 2.51; 95% CI 1.27–4.98, p = 0.008) and SAT ratio (HR: 0.58; 95% CI 0.34-1.00, p = 0.053) were significant factors that affected OS (Table 2). Overall survival was worse in right colon tumors (Fig. 3a). The patients were divided into 2 groups according to the SAT ratio median value. Median OS for patients with SAT ratio <-1.1 and ≥ -1.1 were 38.5 (95% CI 31.54–45.58) and 24.5 (95% CI 14.13–34.93) months, respectively (p = 0.05) (Fig. 3b). In the multivariate analysis, tumor location (HR: 0.3; 95% CI 0.14–0.62, p = 0.001) and SAT ratio (HR: 0.4; 95% CI 0.26–0.84, p = 0.011) were found to be prognostic factor for OS (Table 3).

Analysis of progression-free survival and overall survival in subgroup of patients who received bevacizumab

Survival analysis of 48 patients in the study who received bevacizumab therapy were also evaluated. On univariate analysis, body mass index (HR: 0.92; 95% CI 0.87–0.99, p = 0.024), VAT SUV mean (HR: 0.09; 95% CI 0.01–0.52, p = 0.008), SAT ratio (HR:1.99; 95% CI 1.02–3.91, p = 0.043), receiving adjuvant chemotherapy (HR:1.9; 95% CI 0.98–3.76, p = 0.05) and tumor SUV max (HR:0.9; 95% CI 0.90–0.99, p = 0.044) were significant parameters for PFS (Table 4). BMI was divided into two groups according to the median value of 26.3. Median PFS for patients with BMI < 26.3 and ≥ 26.3 were 8.9 (95% CI 5.4–12.3) and 14.2 (95% CI 12.5–15.9) months, respectively (p = 0.014) (Fig. 4a). Patients with high VAT SUV mean

and tumor SUV max showed better survival than those with low values. Median PFS for the patients with VAT SUV mean < 0.89 and > 0.89 were 9.7 (95% CI 6.42–13.02) and 14.25 (95% CI 5.52–22.98) months, respectively (p = 0.001) (Fig. 4b). No significant prognostic factor was found for PFS in multivariate analysis (Table 5).

Table 4
Univariate analysis for PFS and OS in patients received bevacizumab therapy

	PFS		OS	
Variables	**Hazard ratio (%95 CI)**	**p value**	**Hazard ratio (%95 CI)**	**p value**
Age	1.000 (0.97–1.09)	0.991	1.018 (0.99–1.04)	0.163
Gender	1.861 (0.94–3.68)	0.075	1.123 (0.63–1.97)	0.688
BMI	0.929 (0.87–0.99)	**0.024**	0.967 (0.92–1.01)	0.185
Tumor location	0.707 (0.29–1.69)	0.438	2.158 (1.26–5.01)	**0.009**
TNM stage	1.679 (0.87–3.21)	0.118	1.041 (0.59–1.82)	0.890
Metastases	0.784 (0.39–1.54)	0.481	0.909 (0.51–1.60)	0.743
Adjuvant treatment	1.928 (0.98–3.76)	**0.054**	1.192 (0.66–2.13)	0.556
Comorbidity	0.526 (0.26–1.03)	0.063	0.714 (0.40–1.25)	0.240
Kras mutation	1.286 (0.67–2.45)	0.446	1.105 (0.62–1.95)	0.732
Treatment response	0.627 (0.33–1.16)	0.140	-	-
VAT volume	0.997 (0.99-1.00)	0.335	1.000 (0.99-1.00)	0.855
VAT density (HU)	1.000 (0.95–1.05)	0.998	0.995 (0.95–1.04)	0.831
VAT SUV mean	0.091 (0.01–0.52)	**0.008**	1.042 (0.21–5.01)	0.959
SAT volume	0.994 (0.98-1.00)	0.065	0.998 (0.99-1.00)	0.462
SAT density (HU)	1.014 (0.96–1.06)	0.598	0.982 (0.94–1.02)	0.365
SAT SUV mean	0.080 (0.004–1.47)	0.089	0.480 (0.04–5.80)	0.564
Tumor SUV max	0.951 (0.90–0.99)	**0.044**	1.361 (0.44–4.18)	0.591
SAT ratio	1.999 (1.02–3.91)	**0.043**	0.581 (0.33–1.01)	**0.055**
NLR	1.026 (0.84–1.23)	0.793	1.026 (0.90–1.16)	0.691
CRP	1.00 (0.99-1.00)	0.718	1.003 (0.99-1.00)	0.316
Albumin	0.92 (0.46–1.84)	0.823	0.852 (0.46–1.54)	0.600
Platelet	0.998 (0.99-1.00)	0.238	1.000 (0.99-1.00)	0.773

PFS, progression-free survival; OS, overall survival; BMI, body mass index; NLR, neutrophil-to-lymphocyte ratio; SAT, subcutaneous adipose tissue; VAT, visceral adipose tissue; HU, hounsfield unit; SUV, standardized uptake value; SAT ratio, SAT volume/SAT density.

Table 5
Multivariate analysis for PFS and OS in patients receiving bevacizumab therapy

	PFS		OS	
Variables	**Hazard ratio (%95 CI)**	**p value**	**Hazard ratio (%95 CI)**	**p value**
Age	-	-	1.025 (1.00-1.05)	**0.045**
BMI	0.956 (0.86–1.05)	0.372	0.989 (0.92–1.06)	0.759
Primary tumor location	-	-	3.501 (1.66–7.38)	**0.001**
Adjuvant treatment	2.075 (0.89–4.83)	0.091	-	-
VAT SUV mean	0.425 (0.05–3.41)	0.421	-	-
Tumor SUV max	0.953 (0.90-1.00)	0.08	-	-
SAT ratio	1.956 (0.70–5.46)	0.200	0.449 (0.21–0.96)	**0.039**

PFS, progression-free survival; OS, overall survival; BMI, body mass index; SAT, subcutaneous adipose tissue; VAT, visceral adipose tissue; SAT ratio, SAT volume/SAT density.

In univariate analysis, tumor location (HR: 2.15; 95% CI 1.26–5.01, p = 0.009), SAT ratio (HR: 0.581; 95% CI 0.33–1.01, p = 0.055) were significant parameters for OS (Table 4). OS was worse in right colon tumors. Median OS for patients with left colon tumors and right colon tumors were 29.9 (95% CI 20.89–38.97) and 21.2 (95% CI 19.06–23.33) months, respectively (p = 0.41). Median OS for patients with SAT ratio <-1.1 and ≥ -1.1 were 43.5 (95% CI 26.4–60.6) and 24.5 (95% CI 15.6–33.4) months, respectively (p = 0.015). In multivariate analysis, the SAT ratio (HR: 0.4; 95% CI 0.21–0.96, p = 0.039) and tumor location (HR: 3.5; 95% CI 1.66–7.38, p = 0.001) showed significant association with OS (Table 5).

Discussion

In this study, the relationship between adipose tissue parameters in PET / CT and survival in mCRC patients was evaluated. A significant relationship was found between SAT ratio and overall survival and progression-free survival. In addition, in the subgroup of patients who received bevacizumab therapy, higher VAT SUV mean value was better in terms of progression-free survival.

Fat tissue is divided into two regions as visceral and subcutaneous fat tissue according to its distribution. Apart from the anatomical location, these two adipose tissues differ in terms of endocrine function, lipolytic activity and molecular aspects. Proinflammatory cytokine production and inflammatory cell number are higher in visceral adipose tissue [6, 7, 20]. We measured the volume and density values in PET / CT to evaluate the prognostic effect of the differences between VAT and SAT in colorectal cancer.

Previous studies on various cancer types have found different results in the effect of VAT and SAT volume on survival. In studies conducted in patients with head and neck cancer and non-small cell lung cancer, those with high BMI have been shown to have better survival [16, 21]. In this condition, which is

called the obesity paradox, VAT and SAT volumes were measured to illuminate the protective effect of obesity. While better survival was observed in patients with high VAT volume in head and neck cancer, better survival was observed in patients with high SAT volume in non-small cell lung cancer. A similar relationship between high SAT volume and better survival has been demonstrated in renal cell carcinoma and prostate cancer studies [22, 23]. In these studies, it was thought that high SAT volume can prevent cancer cachexia against lipolysis and increased energy consumption as the protective mechanism of adipose tissue.

In our study, no relationship was found between VAT and SAT volume and survival. However, the ratio obtained by dividing the volume of SAT by density showed a significant correlation with overall survival in all patients, and progression-free survival and overall survival in patients receiving bevacizumab therapy. At this ratio, higher SAT volume was associated with better survival.

Due to adipose tissue dysfunction, the secretion of proinflammatory cytokines and chemokines increases and macrophage infiltration occurs [24]. As a result of the changes, the adipose tissue microenvironment becomes suitable for cancer development and tumor growth. In this environment, with the effect of cancer cells, adipocytes lose their lipid content and differentiate into fibroblast-like cells [25]. These adipocytes associated with differentiating cancer can increase tumor progression and metastasis. Fat tissue density on CT images was used to evaluate these changes in the adipose tissue environment. In a study conducted on non-human primates, it was found that high adipose tissue density was associated with adipocytes with lower lipid content and fibrotic change [26]. In previous studies conducted with pancreatic cancer, head and neck cancer and stomach cancer, it has been shown that high fat tissue density is worse in terms of prognosis [14, 21, 27]. Unlike the results of these studies conducted on various cancer types, in our study, no significant association was found between SAT and VAT density values and survival. However, it was shown that higher SAT density at SAT ratio may be associated with better survival.

FDG uptake of adipose tissue reflects glucose metabolism and inflammatory status. Conflicting results have been found in previous studies evaluating the relationship between FDG uptake of VAT and SAT with clinical results. In studies conducted with colon cancer, pancreatic and stomach cancer, it has been shown that high FDG uptake in VAT is worse in terms of survival [14, 15, 27]. It has been suggested that high FDG intake in these studies is associated with the inflammatory response that develops due to the increase in the expression of proinflammatory cytokines and macrophage infiltration in visceral adipose tissue. Studies on head and neck cancer and lung cancer did not show a significant relationship between fat tissue FDG uptake and survival [16, 21]. Apart from these, two studies have shown that low FDG uptake in adipose tissue is worse in terms of prognosis. One of the studies was conducted in pancreatic cancer patients, and it was found that SAT FDG uptake is decreased in advanced stage and tumors with high FDG uptake [28]. As an explanation, it has been shown that inhibitors released from tumor cells reduce fatty acid uptake in adipose tissue and inhibit lipoprotein catabolism. The other study is evaluating the relationship between the presence of colorectal adenoma and adipose tissue metabolism [29]. In this study, it was shown that the probability of having a colorectal adenoma was higher in those

with low FDG uptake on VAT, and it was stated that this situation was caused by insulin resistance due to obesity. Decreased glucose metabolism in insulin resistant adipocytes and the increase in this insulin resistant adipocyte mass and low FDG uptake in VAT were explained. In our study, a significant association was found between VAT SUV and progression-free survival in patients receiving bevacizumab therapy. Survival was better in patients with high VAT SUV. In previous studies have been shown that VEGF release is higher in visceral adipose tissue [30, 31]. It has also been found that increased VEGF release is associated with proinflammatory cytokines and inflammation [32, 33]. The high VAT SUV mean may be associated with increased VEGF release. This may affect the response of bevacizumab therapy.

PET / CT is one of the imaging methods used for diagnosis, staging and follow-up of treatment response of colorectal cancer. The standard uptake value (SUV) is the parameter used to evaluate the degree of FDG uptake in PET / CT. Tumor SUV value is thought to be related with tumor aggressiveness and prognosis [34]. Previous studies on colon cancer, non-small cell lung cancer and nasopharyngeal cancer have shown that tumor SUV max value is associated with prognosis and higher SUV max value is associated with poorer survival [34–36]. In our study, PFS was found to be better in patients with high tumor SUV max value in the survival analysis performed in all patients and the group receiving bevacizumab therapy. Perhaps anti-VEGF therapy may be more effective in these patients.

Our study has some limitations. The study was conducted retrospectively in patients who were followed-up in a single center. In addition, there were limitations in the comparisons due to the lack of established method for the evaluation of adipose tissue metabolism and volume measurement.

Conclusıon

SAT ratio obtained by the ratio of SAT volume and SAT density values was found to be an important prognostic factor for PFS and OS in patients with metastatic colorectal cancer. High SAT volume was associated with longer survival in mCRC patients. In patients who received bevacizumab therapy, the VAT SUV mean value was associated with PFS. Progression-free survival was better in those with high VAT SUV mean than those with low. Further studies are needed to confirm the results of the study, as well as to explain the links between colorectal cancer and obesity.

Declarations

Conflicts of interest/Competing interests: None

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Figures

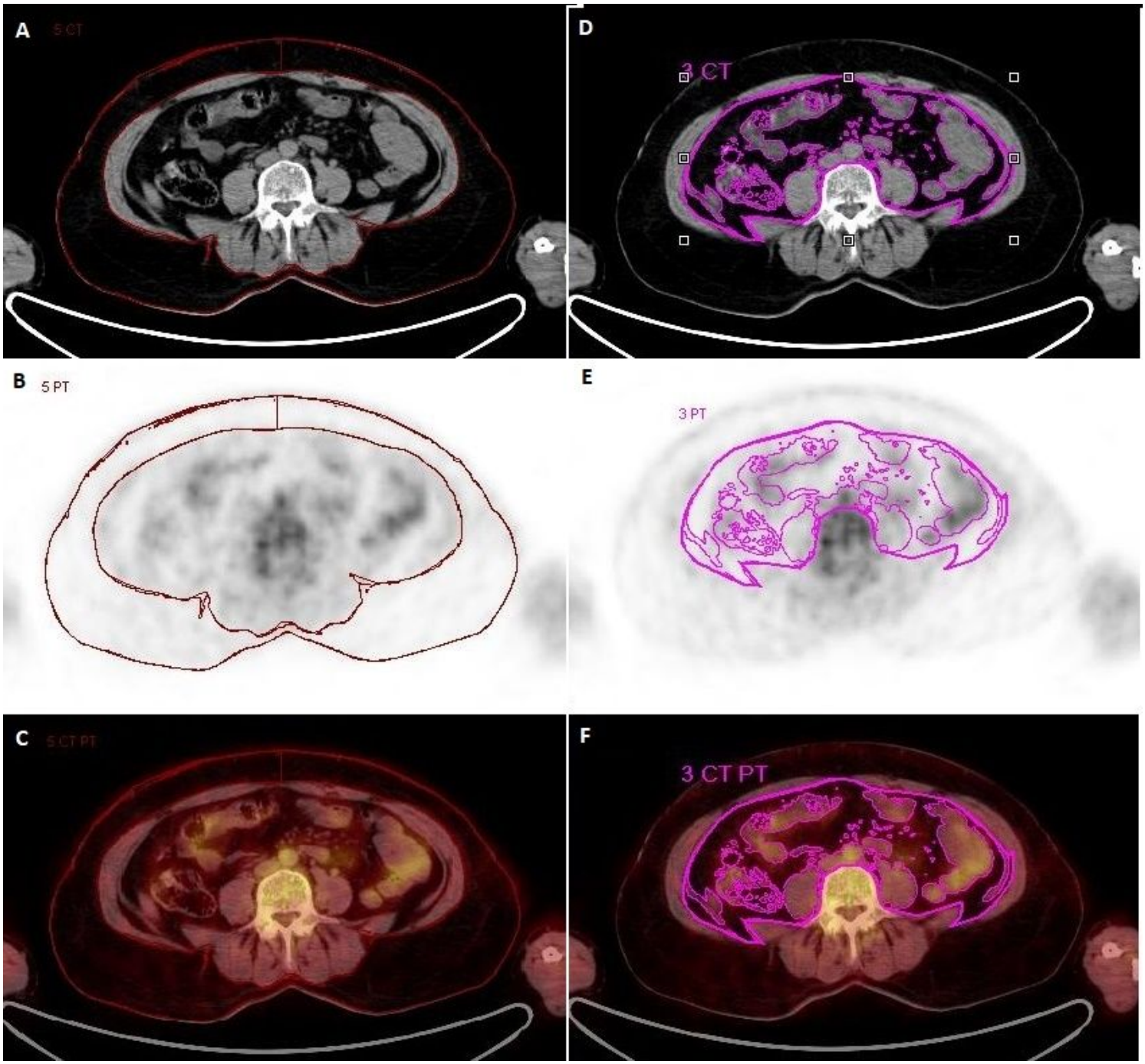

Figure 1

Region of interest (ROI) images; A. SAT (CT), B. SAT (PET), C. SAT (PET/CT), D. VAT (CT), E. VAT (PET), F. VAT (PET/CT).

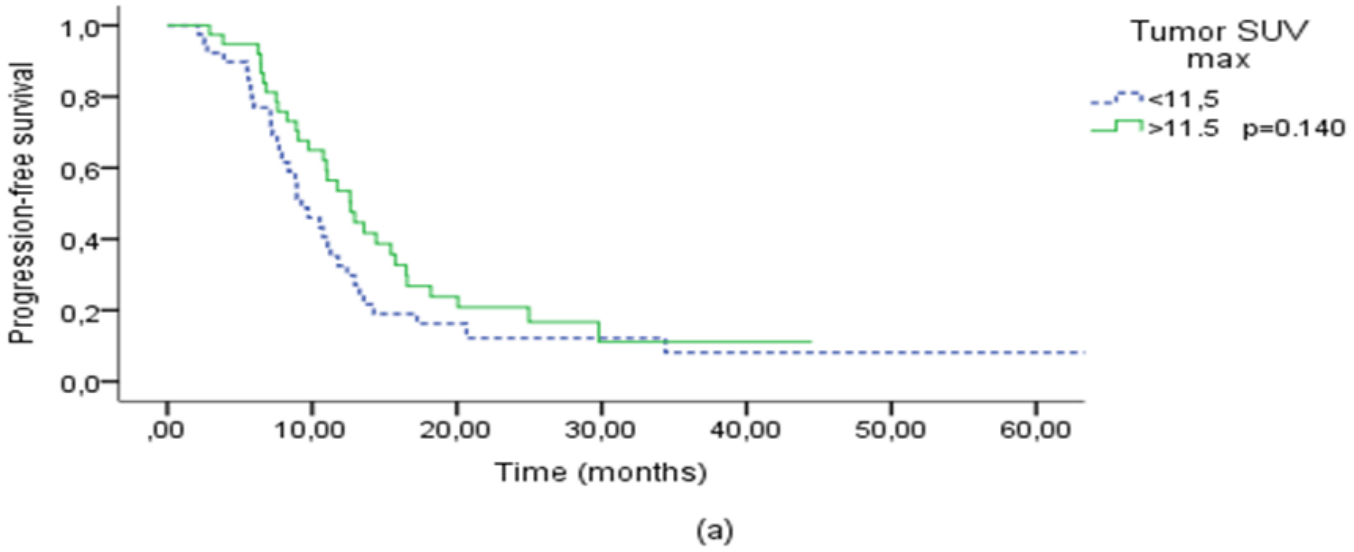

Figure 2

Kaplan-Meier curves for progression-free survival according to Tumor SUVmax (a).

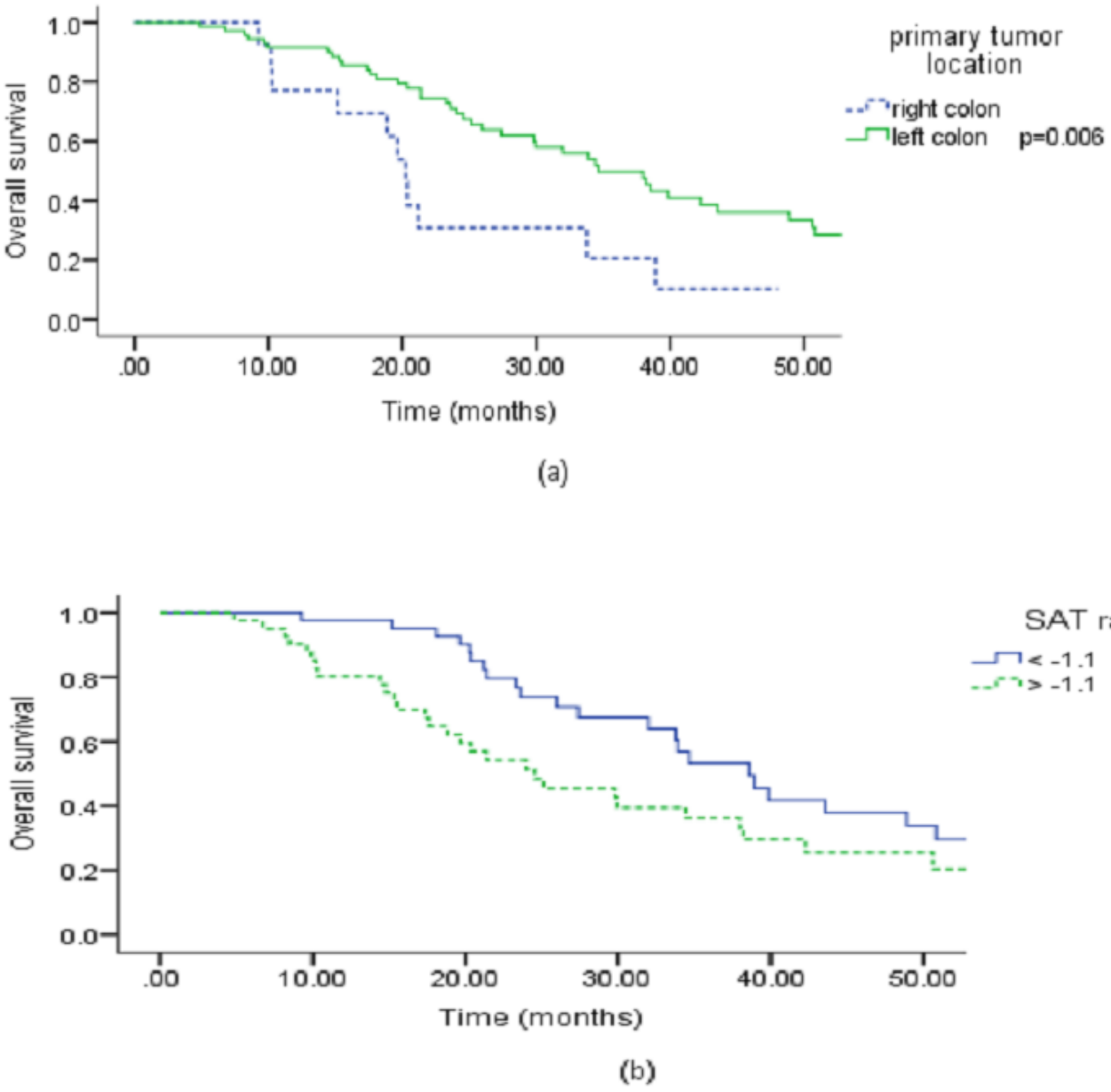

Figure 3

Kaplan-Meier curves for overall survival according to primary tumor location (a) and SAT ratio (b).

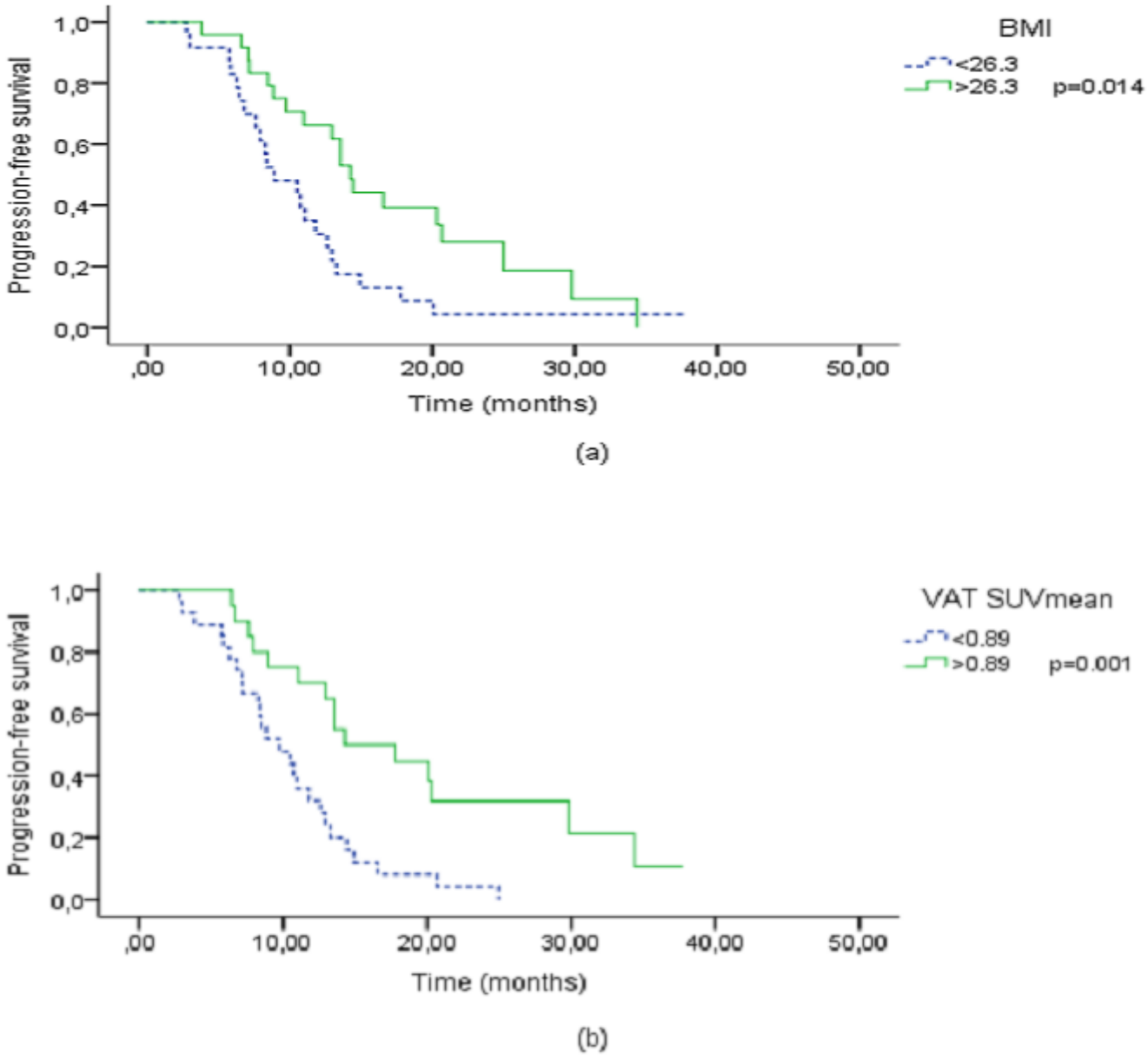

Figure 4

Kaplan-Meier curves for progression-free survival according to BMI (a) and VAT SUVmean (b) in patients receiving bevacizumab therapy