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Increased Visceral to Subcutaneous Fat Ratio is Associated with Decreased Overall Survival in Patients with Metastatic Melanoma Receiving Anti-Angiogenic Therapy

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Abstract

Background: Body fat distribution is an emerging prognostic indicator in patients treated with anti-angiogenic (AA) therapy. We sought to evaluate the association of visceral and subcutaneous fat with progression free survival (PFS) and overall survival (OS) in patients with metastatic melanoma treated with AA therapy.

Methods: Stage IV melanoma patients received bevacizumab $\pm$ interferon-alpha. Total abdominal fat, visceral fat area (VFA) and subcutaneous fat area (SFA) were measured at L3-L4 on CT images (cm²). PFS and OS were estimated by the Kaplan-Meier method. Cox proportional hazards model was used to assess the association of fat and clinical variables with PFS and OS. Prediction accuracy was evaluated using receiver operating characteristic curve with area under the curve (AUC).

Results: Forty-two patients were evaluated. Median VFA/SFA and body mass index (BMI) were used to group patients into high and low cohorts. PFS and OS were significantly decreased in patients with high VFA/SFA versus low (PFS, $p=0.009$; OS, $p=0.007$), but not for BMI (PFS, $p=0.774$; OS, $p=0.881$). VFA/SFA, LDH and liver metastasis (LM) were predictors of PFS and OS on multivariate analysis. A prognostic score combining VFA/SFA, LDH, and presence or absence of LM had a higher accuracy for predicting PFS at 3 months (AUC 0.759) and OS at 24 months (AUC 0.846) than LDH and LM alone (PFS, AUC 0.705; OS, AUC 0.786).

Conclusion: Increased VFA/SFA is associated with decreased PFS and OS in patients with metastatic melanoma treated with AA therapy, indicating body fat distribution is an important prognostic factor.

Keywords

melanoma; visceral fat; anti-angiogenic therapy; abdominal fat

INTRODUCTION

Obesity has been identified as a risk factor for the development of many cancers including melanoma¹⁻³. Several cytokines and hormones associated with adipose tissue have been implicated in the obesity-cancer connection. One hypothesis for the contribution of obesity to tumor growth is that adipocytes produce high levels of vascular endothelial growth factor (VEGF)⁴. VEGF is a well-known factor in tumor growth and angiogenesis, and its production is strongly associated with visceral fat versus subcutaneous fat⁵.

The use of targeted anti-angiogenic therapy has shown favorable results in multiple tumor types. However the identification of a biomarker to select patients for these treatments is still being investigated. Computed tomography (CT) can be used to measure abdominal fat distribution using measurements of subcutaneous fat and visceral fat⁶. Studies in colorectal and renal cell carcinoma have shown a strong association between increased visceral fat and decreased progression free survival (PFS) and overall survival (OS) in patients receiving anti-angiogenic therapy⁷⁻⁸.

Melanoma metastases are highly vascular tumors. Recent studies have shown response to anti-angiogenic therapy as well as an improvement in PFS and OS in patients with metastatic melanoma⁹⁻¹⁴. However, predicting response to therapy with these new agents remains a challenge. We hypothesized that patients with increased visceral fat treated with bevacizumab and interferon-alpha (IFN- α) would have decreased survival. Therefore, our objective was to evaluate the association of visceral and subcutaneous fat measurements with PFS and OS in patients with metastatic melanoma treated with bevacizumab $\pm$ IFN- α .

METHODS

IRB approval was obtained and informed consent was waived for this retrospective analysis of a randomized phase II clinical trial. In that trial patients with metastatic melanoma were treated with bevacizumab with or without IFN- α . The trial was conducted between December 2001 and April 2012. In the first two treatment arms patients were randomized to receive bevacizumab with or without low dose IFN- α (1 MU/m²). A third arm was added in which patients received bevacizumab with high dose IFN- α (10 MU/m²). Eligible patients (N = 62) had histologically confirmed malignant melanoma, evidence of metastatic disease and met the following criteria: age $\geq$ 18 years, life expectancy $\geq$ 6 months, ECOG status $\leq$ 1, normal organ function and ability to provide informed consent. The aim of the trial was to access objective response rate to the combination of bevacizumab $\pm$ IFN- α , as well as PFS and OS. Patients were staged every 3 months by CT scan and patients with progressive disease were removed from the trial. For inclusion in this retrospective analysis, patients had to have pre-therapy CT imaging of the abdomen that included at least the junction of the third and fourth lumbar regions (L3-L4). Patients with unavailable CT imaging (N=13), insufficient clinical and laboratory data (N=3), and CT imaging that did not include the L3-L4 area (N=4) were excluded from our secondary analysis. A total of 42 patients were included in this post-hoc secondary analysis study.

Clinical and Imaging Data Transfer

Baseline clinical data and CT images were de-identified and coded for analysis. Clinical data evaluated included the following patient characteristics: age, gender, body mass index (BMI), ECOG performance status, time from diagnosis to start of therapy, type of melanoma, specific therapeutic regimen, duration of PFS and OS, reason for termination of therapy, and baseline laboratory measures including serum lactate dehydrogenase (LDH), hemoglobin, platelets, corrected calcium, absolute neutrophils, and serum alkaline phosphatase levels. All patients were followed for a period of two years after completion of treatment in this study. Progression free survival was defined as the time from start of therapy until progressive disease (PD) by RECIST or death. Patients who did not progress or expire (N = 2) were censored at the last available assessment. Overall survival was defined as the time from start of therapy until death from any cause or censored at the date the patient was last known to be alive.

CT Imaging

CT imaging of the chest, abdomen, and pelvis was conducted at baseline with multi-detector row helical acquisitions. The slice thickness for the CT examinations ranged from 3.0 to 7.5 mm; with 88% (37/42) having 5 mm slice thickness. Only one patient had non-contrast CT imaging, while the remaining 41 patients had CT imaging with intravenous contrast. The digital imaging and communication of medicine (DICOM) format CT images were uploaded to Tera Recon iNtuition Cloud for measurement of abdominal fat.

Fat and abdominal circumference measurements utilizing CT images were performed by an imaging research fellow with final review of all images and measurements by a fellowship-trained abdominal radiologist with 7 years of experience in advanced image processing and volumetric analysis. A single slice at the L3-L4 level was used to make all measurements. The software automatically measures the abdominal circumference in centimeters (cm) at the chosen level. Standard attenuation threshold technique with manual image segmentation of anatomic regions was used to quantify fat area, with fat defined by attenuation thresholds between -30 and -190 Hounsfield Units (HU). Total abdominal fat (TAF) included all fat measured in the slice. Subcutaneous abdominal fat (SAF) segmentation included fat external to the abdominal wall and paravertebral muscles. Visceral abdominal fat (VAF) segmentation included fat deep to the abdominal wall and paravertebral muscles.

Statistical Analysis

The PFS and OS were estimated by the Kaplan-Meier method. Comparison of PFS and OS between subgroups was evaluated by the log-rank test. Univariate Cox proportional hazards models of PFS and OS were repeatedly constructed by including only one demographic, laboratory, clinical or fat variable in each model. The most significant fat variable in the univariate analysis was included in the final multivariate Cox models on PFS and OS. The demographic, laboratory and clinical variables were selected using the backward selection method. The time-dependent variables were created and temporarily included in the Cox models to test the proportional hazards assumption. To assess the prediction accuracy attributable to the fat variable, the reduced models were obtained by removing the fat variable from the final models on PFS and OS. The prediction accuracy of two multivariate

Cox models was evaluated by computing the area under the receiver operating characteristic curve (AUC) based on the PFS status at 3 months and OS status at 24 months after initiation of therapy. The difference in AUC was calculated between the final model on PFS or OS and the corresponding reduced model. The bootstrap method was used to find the p value associated with AUC comparison. The Spearman correlation coefficient was used to determine association between VEGF and VFA, SFA and VFA/SFA. All p values were two-sided and p values less than 0.05 being considered significant.

RESULTS

Forty-two patients had adequate imaging for evaluation of visceral and subcutaneous fat area. Patient demographics and characteristics are presented in Table 1. The average body mass index was 27 (range 17–39). The majority of patients had two sites of metastatic disease (40%). The most common sites of disease were lymph node and subcutaneous metastasis (64%) followed by lung (52%). LDH levels ranged from 71–608 U/L (mean = 215 ± 134 U/L). Most patients (30/42) received the combination of bevacizumab and high dose IFN- α (5–10MU/m²), as this arm of the trial had an overall response rate of 44% (24% PR, 20% SD) and met the full accrual.

A single slice at L3–4 was used to make measurements of abdominal fat (Figure 1). Mean total abdominal fat area was 400 cm² (± 170 cm²), subcutaneous fat area (SFA) was 205.6 cm² (± 103.7) and visceral fat area (VFA) was 187.6 cm² (± 104.5 cm²). The ratio of VFA/SFA was 1.01 (± 0.54). Using the median VFA/SFA (0.91) and BMI (27) patients were grouped into high and low VFA/SFA or BMI cohorts. A significant decrease in PFS was observed for patients with high VFA/SFA versus low (p=0.009) but not in patients with high BMI versus low (p=0.881; Figure 2 a,b). Similarly OS was significantly decreased in patients with high VFA/SFA vs low (p=0.007) and no difference was observed for BMI (p=0.774; Figure 2 c,d). Median PFS was 3.25 months and OS was 14.5 months. Cox models were used to evaluate the effects of patient demographics, LDH, site of metastasis, treatment type, VFA, SFA, and the ratio of VFA/SFA on PFS and OS. In the univariate analysis LDH (HR 1.38, 95% CI 1.08–1.76, p=0.009) and liver metastasis (HR 2.82, 95% CI 1.35–5.92, p=0.006), were significant predictors of PFS (Table 2A). When overall survival was analyzed VFA/SFA (HR 1.38, 95% CI 1.04–1.82, p=0.023) was a significant predictor of OS in addition to LDH (HR 1.36, 95% CI 1.07–1.74, p=0.014) and liver metastasis (HR 3.58, 95% CI 1.66–7.72, p=0.001; Table 2B). BMI and treatment type (bevacizumab alone vs combination with low or high dose IFN- α) were not predictive of either PFS or OS. Due to the significance of VFA/SFA on survival in the Kaplan-Meier estimates this factor was included in the multivariate analysis for PFS in addition to the other significant variables. Interestingly, VFA/SFA approached significance (HR 1.32, 95% CI 0.99–1.74, p=0.056) in the multivariate analysis for PFS. LDH and liver metastasis remained significant (HR 1.38, 95% CI 1.05–1.81, p=0.019 and HR 2.41, 95% CI 1.12–5.18, p=0.025) in the multivariate analysis for PFS. The multivariate analysis confirmed that VFA/SFA (HR 1.60, 95% CI 1.18–2.19, p=0.003), LDH (HR 1.4, 95% CI 1.05–1.86, p=0.021), and liver metastasis (HR 3.52, 95% CI 1.58–7.83, p=0.002) were predictors of OS.

To determine the accuracy of the Cox models for predicting PFS at 3 months and OS at 24 months (Table 3), AUC estimates were calculated using LDH and liver metastasis with or without VFA/SFA. For predicting PFS at 3 months the AUC for LDH and liver metastasis was moderate (AUC = 0.705), this was improved by adding VFA/SFA to the model (AUC = 0.759, AUC 0.054, $p=0.373$; Figure 2a). AUC for LDH and liver metastasis was also moderate (AUC = 0.786) for predicting OS at 24 months. An improved accuracy was seen with the addition of VFA/SFA to the model for predicting OS at 24 months (AUC = 0.859), however the difference in AUC was not significant (AUC 0.073, $p=0.326$) (Figure 2b).

In a subset ($n=17$) of the study population, baseline VEGF was measured as previously described (9). The mean baseline VEGF was 95.9 (0–139). On univariate analysis, VEGF levels were not significantly associated with overall survival (HR 1.0, 95% CI 0.99–1.0, $p=0.598$). Baseline VEGF levels were compared to VFA, as visceral fat is known to produce high levels of VEGF. There was a weak correlation between baseline VEGF and VFA ($r=0.33$). SFA and VFA/SFA were also compared to VEGF, and no correlation was identified ($r=0.048$ and $r=0.011$, respectively).

DISCUSSION

In this study we found VFA/SFA to be a significant predictor of OS, in addition to LDH and liver metastasis. LDH has been established as a predictive biomarker in metastatic melanoma. Specifically, we have shown it to be predictor of PFS and OS in this study population¹⁷. Melanoma metastasis to visceral organs other than lung has the worst prognosis with a 1 year overall survival of 33% as compared to subcutaneous or lung metastasis (62% and 53% respectively)¹⁸. The addition of VFA/SFA improved the accuracy of predicting PFS at 3 months and OS at 24 months over LDH and liver metastasis alone in this group of patients treated with bevacizumab $\pm$ IFN- α .

There has long been a link between obesity and cancer; however, BMI has not been able to be specifically linked to outcomes. Abdominal fat can be measured on CT and accurately discerns the contribution of visceral fat and subcutaneous fat⁶. In colorectal cancer patients increased VFA/SFA is associated with decreased disease-free survival and a trend towards decreased OS. In rectal cancer, it has been postulated that chemotherapy doses may be better calculated based on visceral adiposity than BMI^{19,20}. In patients with colorectal cancer treated with bevacizumab, increased VFA was associated with worse response, time to progression (TTP) and OS. There was no association between VFA and response, TTP or OS in the chemotherapy group. This suggests that VFA may be a specific biomarker for patients treated with antiangiogenic therapy⁷. Similarly in a study of renal cell carcinoma patients that were treated with anti-angiogenic versus cytokine therapy, VFA was associated with shorter TTP and OS.

Visceral fat appears to be the major contributor to the cytokine derangements that are associated with obesity and cancer. The cytokine profile of adipose tissue includes specific adipocytokines; adiponectin, leptin, resistin and visfatin. It also produces cytokines that can be generated at multiple sites in the body such as TNF, IL-6, IL-1 and CCL2²¹. Adiponectin is anti-inflammatory and levels of this cytokine are decreased in persons with a large visceral

fat component. Notably, adiponectin has been shown to be anti-angiogenic and have anti-tumor effects²². Conversely, leptin exerts pro-inflammatory and pro-angiogenic effects and has been shown to promote tumor growth in melanoma and upregulate the secretion of VEGF^{21,23}. Visceral fat has been shown to be a greater source of VEGF as compared to subcutaneous fat²⁴. We found a weak association between serum VEGF levels and VFA, though our samples size was small (N = 17), making it difficult to draw conclusions regarding this data.

Survival in metastatic melanoma is improving with the use of new targeted agents. In metastatic melanoma, anti-angiogenic therapy has provided stability of disease but has not had a large treatment effect. As the use of target therapies such as anti-angiogenic therapies increases, the need for biomarkers to predict response and aid in choosing therapies is needed. In this study, VFA/SFA was a predictor of OS in addition to other well-known factors in melanoma. Taken together with other studies of body fat distribution, it appears that measurements of abdominal fat compartments are emerging as a potential biomarker for predicting response to anti-angiogenic therapy.

Abbreviations:

VFA	Visceral fat area
SFA	Subcutaneous fat area

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Figure 1.

CT imaging of patient with SFA 208 cm² and VFA 199 cm² (VFA/SFA = 1.0). a) A single slice at the L3-L4 level was used to make all measurements. b) Total abdominal fat (TAF) included all fat measured in the slice. c) Subcutaneous abdominal fat (SAF) segmentation included fat external to the abdominal wall and paravertebral muscles. d) Visceral abdominal fat (VAF) segmentation included fat deep to the abdominal wall and paravertebral muscles.

Figure 2.

Kaplan-Meier estimated PFS and OS in patients with (a,c) high VFA/SFA versus low and (b,d) high BMI vs low. Significantly worse PFS and OS were observed for those with VFA/SFA above the median. No difference was seen for BMI.

Figure 3. Receiver operating characteristics analysis shows accuracy (AUC) of various models for predicting (a) PFS at 3 months and (b) OS at 24 months.

Table 1.**Patient Characteristics**

Sex		
	Male	27 (64%)
	Female	15 (36%)
Age (y) [Mean, range]		
		59 (31–80)
BMI [Mean, range]		
		27 (17–39)
ECOG		
	0	33 (79%)
	1	9 (21%)
Number of metastatic sites		
	1	13 (31%)
	2	17 (40%)
	3	6 (14%)
	4	6 (14%)
Sites of metastasis		
	Lung	22 (52%)
	Liver	14 (33%)
	Lymph node/Subcutaneous	27 (64%)
	Visceral	13 (36%)
Treatment		
	Bevacizumab	6 (14%)
	Bevacizumab + Low Dose IFN- α	6 (14%)
	Bevacizumab + High Dose IFN- α	30 (71%)
LDH (U/L) [Mean, range]		
		215 (71–608)
Visceral Fat Area cm ² (L3–4) [Mean, St Dev]		
		187.6 ($\pm$ 104.5)
Subcutaneous Fat Area cm ² (L3–4) [Mean, St Dev]		
		205.6 ($\pm$ 103.7)
Visceral Fat/Subcutaneous Fat (L3–4) [Mean, St Dev]		
		1.01 ($\pm$ 0.54)

Note-Data are number for clinical characteristics and treatment.

Table 2.

Univariate Analysis of Clinical Characteristics and Fat Variables Associated with Progression Free and Overall Survival

A. Progression Free Survival			
	HR	95% CI	p
BMI (each increment of 5)	1.04	(0.76, 1.41)	0.822
Age (each increment of 10 years)	1.27	(0.97, 1.67)	0.087
LDH (each increment of 100 IU/L)	1.38	(1.08, 1.76)	0.009
Gender	1.33	(0.70, 2.53)	0.389
ECOG	0.72	(0.34, 1.52)	0.385
Treatment			
Bevacizumab vs Low Dose IFN + Bevacizumab	2.35	(0.72, 7.67)	0.155
Bevacizumab vs High Dose IFN + Bevacizumab	1.51	(0.61, 3.76)	0.375
Lung Metastasis	1.13	(0.60, 2.11)	0.709
Liver Metastasis	2.82	(1.35, 5.92)	0.006
Lymph node metastasis	0.75	(0.39, 1.46)	0.398
Visceral Fat Area (each increment of 100)	1.13	(0.85, 1.49)	0.397
Subcutaneous Fat Area (each increment of 100)	0.89	(0.68, 1.18)	0.421
Ratio Visceral Fat Area/Subcutaneous Fat Area (each increment of 0.5)	1.19	(0.91, 1.54)	0.200
B. Overall Survival			
	HR	95% CI	p
BMI (each increment of 5)	1.15	(0.81, 1.63)	0.442
Age (each increment of 10 years)	1.24	(0.95, 1.61)	0.114
LDH (each increment of 100 IU/L)	1.36	(1.07, 1.74)	0.014
Gender	1.65	(0.86, 3.20)	0.134
ECOG	0.93	(0.44, 1.98)	0.852
Treatment			
Bevacizumab vs Low Dose IFN + Bevacizumab	2.04	(0.63, 6.61)	0.233
Bevacizumab vs High Dose IFN + Bevacizumab	1.09	(0.44, 2.72)	0.854
Lung Metastasis	1.05	(0.56, 1.97)	0.879
Liver Metastasis	3.58	(1.66, 7.72)	0.001
Lymph node metastasis	0.52	(0.27, 1.01)	0.055
Visceral Fat Area (each increment of 100)	1.24	(0.94, 1.64)	0.133
Subcutaneous Fat Area (each increment of 100)	0.92	(0.70, 1.20)	0.523
Ratio Visceral Fat Area/Subcutaneous Fat Area (each increment of 0.5)	1.38	(1.04, 1.82)	0.023

HR; Hazard Ratio, CI; Confidence Interval

Table 3.

Multivariate Analysis of Clinical Characteristics and Fat Variables Associated with Progression Free Survival and Overall Survival

A. Progression Free Survival			
Model 1			
	HR	95% CI	p
LDH (each increment of 100 IU/L)	1.30	(1.00, 1.70)	0.053
Liver Metastasis	2.35	(1.09, 5.05)	0.029
Model 2			
	HR	95% CI	p
LDH (each increment of 100 IU/L)	1.38	(1.05, 1.81)	0.019
Liver Metastasis	2.41	(1.12, 5.18)	0.025
Visceral Fat/Subcutaneous Fat Ratio (each increment of 0.5)	1.32	(0.99, 1.74)	0.056
B. Overall Survival			
Model 1			
	HR	95% CI	p
LDH (each increment of 100 IU/L)	1.30	(0.98, 1.71)	0.070
Liver Metastasis	3.10	(1.42, 6.76)	0.005
Model 2			
	HR	95% CI	p
LDH (each increment of 100 IU/L)	1.40	(1.05, 1.86)	0.021
Liver Metastasis	3.52	(1.58, 7.83)	0.002
Visceral Fat/Subcutaneous Fat Ratio (each increment of 0.5)	1.60	(1.18, 2.19)	0.003

HR; Hazard Ratio, CI; Confidence Interval