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Review

Increased visceral to subcutaneous fat ratio is associated with decreased overall survival in patients with metastatic melanoma receiving anti-angiogenic therapy

Valerie P. Grignol [a], Andrew D. Smith [b], Darya Shlapak [b], Xu Zhang [c], Sara Martin Del Campo [a], William E. Carson [a, *]

[a] Division of Surgical Oncology, The Ohio State University, Columbus, OH, USA
[b] Department of Radiology, University of Mississippi, Jackson, MS, USA
[c] Center of Biostatistics and Bioinformatics, University of Mississippi, Jackson, MS, USA

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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 ± interferon-alpha. Total abdominal fat, visceral fat area (VFA) and subcutaneous fat area (SFA) were measured at L3-L4 on CT images (cm^2). 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.

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Abbreviations: VFA, Visceral fat area; SFA, Subcutaneous fat area.

* Corresponding author. Division of Surgical Oncology, The Ohio State University, N924 Doan Hall, 410 W. 10th Avenue, Columbus, OH, 43210, USA.
E-mail address: william.carson@osumc.edu (W.E. Carson).

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1. Introduction

Obesity has been identified as a risk factor for the development of many cancers including melanoma [1–3]. 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 fat [5].

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 fat [6]. 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 therapy [7,8].

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 melanoma [9–16]. 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 ± IFN-α.

2. 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/m^2). A third arm was added in which patients received bevacizumab with high dose IFN-α (10 MU/m^2). Eligible patients (N = 62) had histologically confirmed malignant melanoma, evidence of metastatic disease and met the following criteria: age ≥ 18 years, life expectancy ≥ 6 months, ECOG status ≤ 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 ± 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.

2.1. 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.

2.2. 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.

2.3. 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.