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Case report

Imaging biomarkers of adiposity and sarcopenia as potential predictors for overall survival among patients with endometrial cancer treated with bevacizumab

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ABSTRACT

Objective: To examine associations of body mass index (BMI), subcutaneous fat area (SFA) and density (SFD), visceral fat area (VFA) and density (VFD) and total psoas area (TPA) to outcomes among patients receiving chemotherapy with or without bevacizumab for advanced or recurrent endometrial cancer (EC).

Methods: This was a multi-institutional, retrospective study of patients with EC treated with and without bevacizumab as part of front-line, platinum based chemotherapy. Demographics and clinical characteristics were collected. SFA, VFA, SFD, VFD, and TPA were determined from pre-treatment CT scans using a deep learning algorithm. Data was compared with overall survival (OS) and progression free survival (PFS).

Results: Seventy-eight patients were analyzed. The majority were Caucasian (87.2%) with a mean BMI of 34.7 kg/m^2. PFS and OS did not differ between patients with BMI, SFA, VFA, SFD, VFD, or TPA ≥ the 50th percentile compared to < 50th percentile (p = 0.91, 0.45, 0.71, 0.74, 0.60, and 0.74 respectively) and (p = 0.99, 0.59, 0.14, 0.77, and 0.85 respectively). When adjusting for prognostic factors, elevated VFA trended towards shorter OS (25.1 vs 59.5 months, HR = 1.68 [0.92–3.05]).

Patients receiving bevacizumab had similar OS compared to those who did not (37.6 vs 44.5 months, p = 0.409). When stratified by adiposity markers, no subset demonstrated benefit from bevacizumab.

Conclusion: Obesity has been associated with increased levels of vascular endothelial growth factor (VEGF), the main target for bevacizumab therapy. Imaging measurements of VFA may provide prognostic information for patients with EC but no adiposity marker was predictive of improved response to bevacizumab.

1. Background

Obesity is a growing public health crisis, both nationally and internationally. The CDC estimates that approximately 39.8% percent of US adults are obese (BMI > 30) and when considering women only, this number approaches 45 percent (Ogden, 2017). Additionally, it is estimated that 280,000 deaths were attributable to obesity and related sequelae in 2015, making obesity the second most common cause of preventable death in the United States (Ogden, 2017). Many of these deaths are related to the subsequent development of malignancies, including endometrial cancer. Arnold et al showed that endometrial cancer was the second most common cancer among overweight and obese women, accounting for approximately 107,000 cases worldwide (Arnold et al., 2015). Aune et al also demonstrated that the relationship between increasing BMI and endometrial cancer incidence is non-linear, with a summary relative risk for a 5 unit increment in BMI of 1.54. A similar relationship exists between increasing BMI and mortality (Aune et al., 2015).

There are three proposed mechanisms through which increased adiposity is thought to contribute to the development of endometrial cancer. The first is through aromatization of androgens in peripheral fat leading to increased levels of bioavailable estrogen, promoting proliferation and inhibiting apoptosis of endometrial cells. Secondly, obese patients live in a state of chronic hyperinsulinemia which may actually

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promote tumor growth through multiple pathways. Elevated levels of insulin decrease sex-hormone binding globulin (thus increasing bioavailable estrogen) and lead to increases in bioavailable IGF1, which functions at the cellular level as an anti-apoptotic and pro-angiogenic factor. Insulin also acts directly on target cells as a growth factor "primer" and anti-apoptotic agent. Thirdly, obesity promotes an inflammatory state, leading to increased levels of tumor necrosis factor and interleukin-6, promoting tumor development (Renehan et al., 2015). This obese and inflammatory state also contributes to tumor growth through elevated circulating level of vascular endothelial growth factor (VEGF) and angiopoietin-2 (ANGPT2) (Mick et al., 2002; Silha et al., 2005). Additionally, this pro-inflammatory state may lead to a catabolic effect on muscles which promotes decreased muscle mass or sarcopenia (Stenholm et al., 2008).

Guiu et al demonstrated that, in patients with colorectal cancer, those who were obese and treated with bevacizumab had poorer response rates (RR), shorter PFS, and shorter OS (Guiu et al., 2010). Treatment with antiangiogenic therapy has also been associated with more dose limiting toxicities in patients with renal cell carcinoma (Huillard et al., 2013). While anti-angiogenic therapies are not considered first line treatment in patients with endometrial cancer, there is some data to support their use in advanced and recurrent disease (Aghajanian et al., 2011, 2015; Lorusso et al., 2015).

While BMI is a useful population-level measure of obesity, data have demonstrated that it is not the most precise marker of adiposity. Body fat composition, as measured on dual-energy x-ray absorptiometry (DXA) scanner, has been shown to have a complex relationship with BMI that varies based on race, age, and gender (Mills et al., 2007). In trying to identify more precise markers of adiposity and body fat composition, additional data have supported the use of CT scan evaluation of subcutaneous and visceral fat areas as reproducible measures of adiposity. These measures have been correlated with metabolic syndrome and associated medical comorbidities (Fox et al., 2007; Koster et al., 2010). To this end, we examined the association between body mass index (BMI), subcutaneous fat area (SFA), visceral fat area (VFA), subcutaneous fat density (SFD), visceral fat density (SFD), and total psoas area (TPA) to outcomes in patients treated with and without first-line bevacizumab-based chemotherapy for advanced and recurrent endometrial cancer.

2. Methods

This is a multi-institutional, IRB approved, retrospective cohort study of patients with advanced (stage III-IV) and recurrent endometrial cancer. Any woman diagnosed between 2006 and 2012 was evaluated. Patients were dichotomized based on whether treatment incorporated frontline bevacizumab. Demographics, physical exam parameters, surgical data, and tumor characteristics were collected.

To assess a patient's adiposity, SFA, VFA, SFD, and VFD were calculated from pre-treatment CT scans at L3 using a computer-aided detection scheme. The scheme first applies a convolution neural network based deep learning algorithm to automatically detect abdominal region of interest depicting on all CT image slices scanned from one patient and then segment human body depicting on each CT image into three categories of SFA, VFA and other non-fat related human organs or tissues. The fat density threshold is within −140 HU to −40 HU of CT values and total psoas area is within −30–110 HU of CT values (Peng et al., 2012). After segmentation, the scheme computed the cross-sectional size of SFA and VFA, as well as two average density values of two fat areas (SFD and VFD), in each CT slide. By combining the computation results of all involved CT slides in the abdominal region, the volume of SFA and VFA, and overall density of SFD and VFD of each patient are computed and recorded. The details of this computer-assisted image process and feature computation method have been previously reported (Wang et al., 2017). As no "normal" value has been established for any of these markers of adiposity or sarcopenia, patients were dichotomized based on the median. These computed features (SFA, VFA, SFD, VFD, and TPA) were compared with survival data, including overall survival (OS) and progression free survival (PFS). Specifically, each biomarker was dichotomized at the median into "upper 50%" and "lower 50%" strata, then OS and PFS were depicted within strata using the Kaplan-Meier product-limit method, and compared using the log-rank test (for unadjusted results) and Cox proportional-hazards models adjusted for age, stage, and residual disease. SAS 9.3 and R 3.5.1 were used for statistical analyses.

Table 1
Patient demographics.

Variable	Count (%) or Mean ± SD
Total number of patients	**78**
Age at start of chemo	61.5 ± 9.5
Race	
Caucasian	68 (87.2%)
Black	8 (10.3%)
Other	2 (2.5%)
Weight (kg)	92.0 ± 26.4
Height (cm)	162.1 ± 6.1
BMI (kg/m^2)	34.7 ± 9.4
Stage	
III	34 (43.6%)
IV	31 (39.7%)
Recurrent	13 (16.7%)
Residual disease	
No	45 (57.7%)
Yes	33 (42.3%)
Histology	
Serous	17 (21.8%)
Endometrioid	54 (69.2%)
Clear cell	3 (3.9%)
Other	4 (5.1%)
Regimen	
Paclitaxel/Carboplatin	26 (33.3%)
Paclitaxel/Carboplatin/Bevacizumab	33 (42.3%)
Ixabepilone/Carboplatin/Bevacizumab	15 (19.2%)
Other	4 (5.2%)
Best response	
Partial remission	14 (18.0%)
Complete remission	38 (48.7%)
Stable disease	9 (11.5%)
Progressive disease	7 (9.0%)
Not measurable	10 (12.8%)
Computed SFA	326.1 ± 163.8
Computed VFA	174.8 ± 88.6
Computed SFD	−95.1 ± 9.3
Computed VFD	−79.4 ± 27.9
Computed TPA	15.0 ± 7.0
Follow-up time (mo)	45.1 ± 31.5

3. Results

A total of 78 patients were analyzed in this study. The majority were Caucasian with a mean BMI of 34.7 kg/m^2. Stage III disease accounted for 43.6% of cases while 39.7% had stage IV disease and 16.7% had recurrent disease. The median SFA was 326.1 cm^2 and median VFA was 174.8 cm^2. Median SFD and VFD in this population was −95.1 HU and −79.4 HU, respectively. Median TPA was 15 cm^2 (Table 1). There was no significant difference in patient demographics or adiposity markers when patients were dichotomized by treatment with or without bevacizumab. Additionally, those who received platinum/taxane based chemotherapy with bevacizumab vs. platinum/taxane based chemotherapy alone had similar OS (37.6 vs 44.5 months, $p = 0.41$).

When patients were dichotomized by BMI (≥50th percentile vs <

Table 2
Unadjusted and adjusted progression free survival.

Variable	Lower 50% Median PFS (mo.)	Upper 50% Median PFS (mo.)	p-value[a]	Hazard ratio	p-value[b]
BMI (kg/m^2)	25.6 [11.7, 46.7]	42.3 [10.6, –]	0.91	1.36 [0.79, 2.35]	0.26
SFA (cm^2)	24.1 [12.3, –]	42.3 [14.6, –]	0.45	0.88 [0.46, 1.69]	0.70
VFA (cm^2)	25.6 [15.2, –]	21.8 [12.7, –]	0.71	0.97 [0.51, 1.87]	0.93
SFD (HU)	24.1 [17.2, –]	25.3 [11.7, –]	0.74	1.20 [0.65, 2.20]	0.56
VFD (HU)	42.3 [11.6, –]	24.1 [14.6, 51.3]	0.60	1.24 [0.65, 2.38]	0.52
Psoas (cm^2)	25.3 [15.2, 50.4]	21.8 [11.6, –]	0.74	1.09 [0.53, 2.27]	0.81

Numbers within brackets represent 95% confidence limits (with "–" indicating no estimable upper limit).
[a] Log-rank test (unadjusted).
[b] Cox proportional-hazards model (adjusted for age, stage, and residual disease).

50th percentile), there was no significant difference in PFS (21.8 vs 25.3 months, $p = 0.91$). The same was true for both SFA and VFA (42.3 vs 24.1 months, $p = 0.45$ and 21.8 vs 25.6 months, $p = 0.71$). Additionally, when comparing SFD and VFD dichotomized by the median, no significant difference was noted in PFS (25.3 vs 24.1 months, $p = 0.74$ and 24.1 vs 42.3 months, $p = 0.60$). When similarly dichotomized by TPA, there was no difference in PFS either (21.8 vs 25.3 months, $p = 0.74$). When controlling for prognostic factors such as age, stage, and residual disease, no statistically significant difference was noted among adiposity or sarcopenia markers and oncologic outcome (Table 2).

No difference in OS was noted when patients were dichotomized by BMI ($\geq 50^{th}$ percentile vs $<$ 50th percentile (41.8 vs 38.4 months, $p = 0.99$). SFA and VFA were also not associated with a significant difference in OS (26.2 vs 53.8 months, $p = 0.59$ and 25.1 vs 59.5 months, $p = 0.14$). Neither SFD, VFD, nor TPA demonstrated a difference (31.5 vs 38.4 months, $p = 0.77$; 34.1 vs 43.2 months, $p = 0.85$; 33.3 vs 43.2 months, $p = 0.87$) either. However, when adjusting for prognostic factors, increased VFA was associated with a trend toward shorter OS (HR 1.68, [0.92–3.05], $p = 0.09$) (Fig. 1). The remaining markers of adiposity continued to demonstrate no significant difference. After adjustment for prognostic factors and stratification by treatment regimen (treated with or without bevacizumab), no markers of adiposity or sarcopenia were associated with differences in outcomes (Table 3).

4. Discussion

The prevalence of obesity continues to rise, and the Center for Disease Control projects that 50% of American adults will be obese by 2030 (CDC Overweight and Obesity, 2019). Increasing weight and obesity is associated with the development of endometrial cancer through increased aromatization of androgens in peripheral fat cells, chronic hyperinsulinemia and subsequent reduction in circulating sex hormone binding globulin, and promotion of a pro-inflammatory state (Renehan et al., 2015). While obesity has certainly been linked to the development of endometrial cancer, there is conflicting data about its relationship, as measured by BMI, to patient outcomes (Greenlee et al., 2017). Growing data suggest that not just obesity, but body composition and fat distribution, may be an important determinant in outcomes in cancer patients (Strulov Shachar and Williams, 2017).

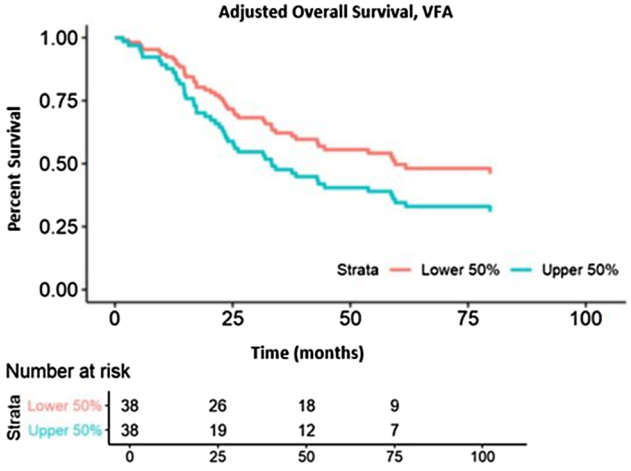

Fig. 1. Adjusted overall survival based on visceral fat area.

Obesity has also been associated with increased circulating levels of vascular endothelial growth factor (VEGF) (Silha et al., 2005). This might imply that treatment in obese patients with bevacizumab, a monoclonal antibody that inhibits angiogenesis through blockade of VEGF-A, would provide improvement in outcomes among obese individuals. In the colorectal literature, however, worse outcomes have been demonstrated with the use of bevacizumab in patients with an elevated BMI, SFA, and/or VFA (Guiu et al., 2010). Antiangiogenic therapy in patients with renal cell carcinoma has also been associated with adverse outcomes, in particular an increase in dose limiting toxicities (Huillard et al., 2013).

Data from Gynecologic Oncology Group (GOG) protocol 86P has demonstrated that, in advanced or recurrent endometrial cancer, the addition of bevacizumab did not improve PFS, at least in comparison to the selected historical control, but did appear to influence OS. This was not, however, a pre-specified endpoint and is hypothesis generating only (Aghajanian et al., 2015.). MITO End-2, which was a randomized, phase 2 trial that evaluated the addition of bevacizumab to carboplatin/paclitaxel in advanced and recurrent endometrial cancer, noted a significant improvement in PFS (13 vs 8.7 months) with the addition of bevacizumab (Lorusso et al., 2015).

Our study evaluated patients with advanced and recurrent endometrial cancer who underwent therapy with platinum/taxane chemotherapy with or without bevacizumab and found that no marker of adiposity (BMI, SFA, VFA, SFD, VFD) or sarcopenia was significantly associated with survival outcomes. Increased visceral fat area, however, did suggest a trend toward shorter OS, though this was independent of treatment with bevacizumab. This may indicate that elevated VFA is a negative prognostic biomarker for this population, the knowledge of which may, in the future, identify patients at high risk for treatment failure for whom novel treatment strategies may be indicated. This would require validation in a larger study. The limitations of this study include the retrospective nature of the data collection, small patient numbers, and potential bias in terms of patient selection in that bevacizumab is not currently indicated as a part of front line therapy so those patients included here may have received bevacizumab as part of clinical trials or off label and may not be representative of the population as a whole.

Patients with advanced and recurrent endometrial cancer traditionally have poor outcomes, with an average OS of approximately 12 months. Novel therapeutic regimens are necessary to improve survival in these women. Imaging biomarkers may provide a modality to

Table 3
Unadjusted and adjusted overall survival.

Variable	Lower 50% Median OS (mo.)	Upper 50% Median OS (mo.)	p-value[a]	Hazard ratio	p-value[b]
BMI (kg/m^2)	38.4 [25.4, 79.7]	41.8 [23.9, 88.8]	0.99	1.48 [0.88, 2.48]	0.13
SFA (cm^2)	53.8 [31.9, –]	26.2 [19.2, –]	0.59	1.68 [0.91, 3.11]	0.10
VFA (cm^2)	59.5 [33.2, –]	25.1 [21.3, 58.7]	0.14	1.68 [0.92, 3.05]	0.09
SFD (HU)	38.4 [31.9, 75.2]	31.5 [22.2, –]	0.77	0.88 [0.49, 1.60]	0.68
VFD (HU)	43.2 [25.1, –]	34.1 [23.2, 79.7]	0.85	1.05 [0.56, 1.98]	0.89
Psoas (cm^2)	43.2 [26.2, –]	33.3 [21.3, –]	0.87	1.83 [0.34, 1.72]	0.09

Numbers within brackets represent 95% confidence limits (with "–" indicating no estimable upper limit).
[a] Log-rank test (unadjusted).
[b] Cox proportional-hazards model (adjusted for age, stage, and residual disease).

improve tailored therapies and further investigation in this field is warranted.

Author contribution section

All authors made substantial contributions to this project.

Declaration of Competing Interest

None of the authors has a conflict to disclose regarding this work.

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