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Measurements of adiposity as prognostic biomarkers for survival with anti-angiogenic treatment in epithelial ovarian cancer: An NRG Oncology/Gynecologic Oncology Group ancillary data analysis of GOG 218

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CONFLICT OF INTEREST

The authors wish to report that there are no conflict of interest to disclose with the exception of Dr. Krishnansu Tewari who reports that he has participated on two Advisory Boards for Genentech and that his institution, UC Irvine Medical Center, participated in the GOG-0218 study. Additionally, Dr. Robert Burger reports having received personal fees from each of the following: Amgen, Astra Zeneca, Tesaro, Genentech, Clovis Oncology, Roche, Gradalis, Invitae, Janssen, Merck, Morphotek and VBL Therapeutics, outside of the submitted work. Finally, Dr. Kathleen Moore reports other from Clovis, other from Astra Zeneca, other from Tesaro, other from Immunogen, other from Genentech/Roche, other from VBL Therapeutics, other from Merck, outside of the submitted work.

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Abstract

Objective: Adiposity has been hypothesized to interfere with the activity of bevacizumab (BEV), an anti-angiogenic agent. Measurements of adiposity, BMI, surface fat area (SFA), and visceral fat area (VFA) were investigated as prognostic of oncologic outcomes among patients treated with chemotherapy, with or without BEV, on GOG 218, a prospective phase III trial.

Method: Pretreatment computed tomography (CT) for 1538 GOG 218 participants were analyzed. Proportional hazards models assessed association between adiposity and overall survival (OS) adjusted for other prognostic factors. The predictive value of adiposity as a function of BEV treatment was assessed in 1019 patients randomized to either chemotherapy (CT) + placebo (P) →P or CT + BEV→BEV.

Results: After adjusting for prognostic factors, SFA was not associated with the overall hazard of death (p=0.981). There was a non-significant 0.1% (p=0.062) increase in hazard of death associated with a unit increase in VFA. When comparing the treatment HRs for patients who did and did not receive BEV, there was no association with SFA (p=0.890) or VFA (p=0.106). A non-significant 0.8% increase in the hazard of death with unit increase in BMI (p=0.086) was observed. BMI values were not predictive of a longer survival for patients with BEV vs placebo (p=0.606).

Conclusion: Measures of adiposity strongly correlated to one another but were not predictive of efficacy for BEV. VFA is a weak prognostic factor.

INTRODUCTION

Epithelial ovarian cancer (EOC) is diagnosed in more than 22,000 women in the United States each year and results in approximately 14,000 deaths annually [1]. There is a need to identify predictive biomarkers of therapeutic agents used to treat this deadly disease. Advances in the understanding of the molecular pathogenesis of EOC have highlighted the importance of the expression of growth factors, such as vascular endothelial growth factor (VEGF), in the promotion of tumor growth, ascites and metastases. Consequently, VEGF inhibition has become an attractive therapeutic target in patients with metastatic EOC, and pharmacologic agents targeting VEGF, such as BEV, have been evaluated in the treatment of EOC in several randomized phase III trials. The Gynecologic Oncology Group (GOG) 218 was a 3 arm study that compared paclitaxel/carboplatin/placebo and placebo maintenance (maximum 22 treatment cycles) versus paclitaxel/carboplatin/BEV and placebo maintenance vs. carboplatin/paclitaxel/BEV and BEV maintenance in the first-line setting [2]. Progression-free survival (PFS) benefit was seen only in women who received concurrent and maintenance BEV compared with chemotherapy alone and there was no difference in overall survival (OS) [2]. ICON7 also evaluated incorporation of BEV into first-line therapy with a 2 arm trial of carboplatin/paclitaxel/BEV and BEV maintenance vs. carboplatin/paclitaxel/placebo and placebo maintenance [3]. Similar to GOG 218, PFS was enhanced in the BEV arm versus chemotherapy alone and showed only a trend toward improved OS [3].

Subgroup analysis of high risk patients in ICON7 did suggest an OS advantage leading to approval of incorporation of BEV into front line therapy by the European Medicines Agency (EMA) in this sub-population [4]. Incorporation of BEV into front line therapy based on GOG 218 data was approved by US Food and Drug Administration (FDA) in June 2018. The results of GOG 218 and ICON7 raise questions regarding patient selection, optimal dose and schedule for anti-angiogenic therapy. There is a lack of reliable indicators to predict which patients will benefit most from BEV-based therapy.

Obesity is a known risk factor for the development of many different types of cancer [5]. The mechanistic association of obesity with malignancy is incompletely understood, but may involve the production of factors that may promote tumor growth such as VEGF and angiopoeitin-2 by adipose tissue [6, 7] and increased levels of insulin and insulin-like growth factor 1 (IGF-1). Obesity can be measured by body mass index (BMI) and defined into 3 classes: class I obesity BMI 30–34, class II BMI 35–40, and class III BMI > 40. Obesity can also be defined by computed tomography (CT) by measuring visceral fat area (VFA) and subcutaneous fat area (SFA) on the same section [8, 9]. Additionally, an increasing body of evidence indicates that cytokine production profiles differ between subcutaneous and visceral fat and these differential levels may play a role in the cytokine milieu that impacts cancer behavior [7, 10, 11]. In particular, ovarian cancer has the propensity to metastasize to the omentum, which may be related to fat-driven signaling.

Recognizing that obesity is associated with increased circulating levels of VEGF, a key regulator of tumor angiogenesis and the main target of BEV, Guiu et al. tested the hypothesis that excess body fat adversely impacts outcomes in patients with metastatic colorectal cancer undergoing primary treatment with BEV-based chemotherapy [12]. Compared to patients treated with conventional chemotherapy, obese patients treated with BEV had poorer response rates, shorter PFS and OS, specifically those obese patients with high visceral fat area (VFA).

In a pilot study we found that among patients with EOC treated with front-line BEV-based chemotherapy those with high BMI had a significantly shorter PFS compared to those with low BMI (10.0 vs 20.9 months). On univariate and multivariate Cox regression neither BMI, SFA nor VFA were predictive of PFS or OS in the chemotherapy group. However, in the BEV group BMI was significantly associated with PFS (p=0.02). After accounting for age, stage, and residual disease the adjusted HR was 5.16 (95% CI 1.31–20.24) for high vs. low BMI. Additionally in the BEV group SFA was significantly associated with OS (p=0.03). After accounting for age, stage, and residual disease the adjusted HR was 3.58 (95% CI 1.12–11.43) for high vs. low SFA [17]. These results suggest advanced EOC patients with high levels of adiposity may not derive benefit from BEV and that measurements of adiposity before starting first-line BEV-based treatment may be a useful prognostic biomarker. We sought to validate and extend these findings among patients prospectively enrolled and treated on GOG 218 in an ancillary data analysis. To evaluate the predictive relationship of adiposity with BEV treatment patients randomized to chemotherapy (CT) + placebo (P) + maintenance P and CT + BEV (B) + maintenance B were analyzed.

METHODS

This was an analysis of patients who were enrolled in GOG 218. The details of inclusion and exclusion criteria were reported in the original manuscript [2]. All patients gave written informed consent prior to study entry in compliance with local institutional review board and federal guidelines. Institutional Review Board and Institutional Biosafety Committee approvals were obtained at each institution, and all eligible patients signed an informed consent before study entry in compliance with institutional, state, and federal regulations. Permission to perform this retrospective analysis was obtained from the GOG.

Pre-treatment computed tomography (CT) scans for 1538/1873 (82%) of participants of GOG 218 met radiologic inclusion criteria and were used in this analysis. VFA and SFA were measured using a validated protocol on CT scans performed after primary cytoreductive surgery but before chemotherapy initiation as described by Yoshizumi et al. [9]. Briefly, at the level of the umbilicus, we measured cross-sectional area in cm^2 of the subcutaneous and visceral compartments with pixel attenuation restricted to −140 to −40 Hounsfield unit range (CT equivalent of fat density). The measurements were performed by a radiologist blinded to patient outcome information.

Proportional hazards models were used to assess the association between adiposity and OS. These multivariate models for OS were specified with main effects for the continuous adiposity measures. All estimates were adjusted for the possible confounding effects of assigned study regimen, performance status, stage (FIGO stage III vs IV) and residual disease status (< 1cm vs >1 cm). Patients' adiposity values were categorized by deciles or quartiles in order to graphically display the relationships between adiposity values and OS. When the prognostic association between adiposity score and OS was assessed all 1538 patient were used in the analysis. When the predictive relationship with BEV treatment is assessed, only the 1019 patients who were randomized to chemotherapy (CT) + placebo (P) + maintenance P and CT + BEV (B) + maintenance B were included in the analysis. The predictive relationship of each adiposity score was assessed with a proportional hazards model which included an interaction term between the continuous adiposity score and the dichotomous bevacizumab treatment indicator.

RESULTS

Demographic and tumor characteristic distributions for patients included in this analysis as shown in Table 1 did not differ from the entire cohort as published in the primary manuscript. The median BMI was 26 (range 15 – 61). Mean SFA was 276.9 cm^2 (± 124.9) and VFA was 107.7 cm^2 (± 66.7). Not surprisingly, there was a strong correlation among the various measures of adiposity as demonstrated in Figure 1a and Figure 1b between BMI and SFA (Pearson correlation coefficient, r = 0.800) and VFA (r = 0.681), respectively. (Figure 1).

There was a non-significant 0.8% increase in the hazard of death associated with an increase BMI (p=0.086) by 1 unit, after adjusting for treatment, size of residual disease, stage of

disease and performance status. In addition, a test of BEV treatment and BMI (measured value) interaction was not statistically significant (p=0.606).

There was no significant association between the hazard of death (HR) and SFA after adjusting for stage, treatment, and performance status (p=0.981). There was similarly no association between the BEV vs no BEV treatment HR and SFA (p=0.890).

There was an estimated 0.1% increase in the hazard of death associated with a 1 unit increase in VFA after adjusting for treatment, residual disease, stage of disease and performance status, but this was not statistically significant (p=0.062). Note the inconsistency in the order of survival between the 2nd and 3rd quartiles in the Kaplan-Meier plot. (Figure 2) If patients are grouped by the quartiles of VFA, then a logrank test indicated that there was a statistically significant difference in OS among groups (p=0.031), but it appeared that the differences in survival times were primarily at the extreme values of the VFA.

There appears to be a slight increase in the relative hazard of death associated with increasing deciles of VFA. (Figure 3). Once again, however, we observed the inconsistency in the order of log relative hazards in the middle ranges of deciles, and the slight differences in hazards were primarily seen among those with the highest and lowest VFA values.

When evaluating VFA as a predictive biomarker for use of BEV, there was weak evidence that patients with lower VFA values (1st and 2nd deciles) tended to have longer survival when treated with BEV compared to placebo. However, a test of BEV treatment and VFA value interaction was not statistically significant (p=0.106). (Figure 4)

DISCUSSION

In this study of patients prospectively enrolled on a phase III trial, measures of adiposity were strongly correlated to one another but weakly prognostic of ovarian cancer outcomes or predictive of response to BEV. The trend towards better survival with BEV among lower levels of VFA and BMI of patients treated on GOG 218 are consistent with our pilot data [17]. There is an established link between obesity and cancer; the definition of obesity is controversial and it is unclear whether BMI is the most appropriate measure of obesity. It has been suggested that BMI provides and incomplete measure of body fat distribution, failing to distinguish between visceral and subcutaneous fat [18]. Abdominal fat can be measured on CT and additional measurements of adiposity, VFA and SFA, can be accurately quantified [9]. Of note, it has been proposed that chemotherapy doses may be better calculated based on visceral adiposity than BMI is patients with rectal cancer [19, 20]. In patients with colorectal cancer treated with BEV, increased VFA was associated with worse prognosis and OS, and this study suggested the utility of VFA as a biomarker for antiangiogenic therapy [12]. Higher levels of obesity are seen in the colorectal population, perhaps contributing to the differences seen with ovarian cancer patients.

In an ancillary analysis of two large phase III studies (CAIRO and CAIRO2) of patients with advanced colorectal cancer, Simkens et al. showed body mass index (BMI) was an independent prognostic factor for longer survival in patients receiving chemotherapy, but not

in patients receiving chemotherapy plus BEV, postulating a decreased efficacy of BEV in obese patients [13]. Additionally, high VFA has been shown to be independently associated with shorter time-to-progression and OS in patients given first-line anti-angiogenic agents for metastatic renal cell carcinoma [14]. Conversely, a study by Choueiri et al. evaluated the effect of BMI and body surface area (BSA) on the prognosis of metastatic renal cell carcinoma patients treated with VEGF-targeted therapy (sunitinib, sorafenib, and BEV) [15]. They found that obesity (measured by high BMI and BSA) was independently associated with better clinical outcomes. Also evaluating patients with metastatic renal cell carcinoma, Steffens et al. found that high VFA was a significant predictor of longer PFS and OS [16]. One theory for the preferential decrease in efficacy for patients with high VFA treated with BEV is that peripheral VEGF is adipose tissues bind and neutralize the therapeutic antibody and thus exerts less effect on local tumor VEGF.

Adipose tissue contains specific adipocytokines including adiponectin, leptin, resistin, and visfatin [21]. The anti-inflammatory adipocytokine adiponectin is decreased in persons with large amounts of visceral fat. Additionally, adiponectin has been shown to be antiangiogenic and have anti-tumor effects [22]. In order to vascularize large amounts of adipose tissue, obesity is associated with increased levels of pro-angiogenic cytokines, including VEGF, angiopoietin-2 and angiogenin [6]. This pre-existence of up-regulated pro-angiogenic cytokines may confer resistance to BEV. Additional theories for mechanisms of resistance include the upregulation of inflammatory cytokines in obese patients which can offer vascular protection [23]. Further, inflammatory cytokines can inhibit the induction of vasohibin-1 (VASH1), which normally serves to inhibit angiogenesis; and thus angiogenesis may continue in an unchecked fashion in obese patients [24].

This study is the first to investigate the role of BMI, SFA, and VFA and its association with VEGF-targeted chemotherapy outcomes in EOC from a large prospective randomized phase III trial. Although the findings did not confirm the hypothesis there are encouraging trends towards better survival with BEV among patients with lower VFA and BMI. The results provide some support for the theory of “adiposity” as a possible prognostic biomarker for treatment with anti-angiogenic therapy. Further refinements in measuring adiposity may provide more definitive evidence for the use of adiposity as a predictive or prognostic biomarker. Limitations of our study include the relatively small number of patients at the extremes of VFA and BMI. In our pilot data the median BMI was higher than the current study, providing a possible explanation for why this data was not confirmatory of the original research. Additionally, a single radiologist performed the measurements of SFA and VFA. Ideally multiple radiologic reviews would have been completed to limit the bias of intra-observer variability.

In conclusion, our results provide potential evidence that measurements of adiposity before starting first-line BEV-based chemotherapy may be a simple prognostic biomarker in patients with EOC. If further studies expand upon these results it may influence stratification schema for future clinical trials, BEV dosing strategies, and the evaluation of new antiangiogenic agents in obese patients.

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Research Highlights:

- Surface and visceral fat area as validated measurements of adiposity beyond BMI and have been shown to correlate.
- Markers of adiposity are a potential clinical biomarker for efficacy of bevacizumab
- Optimizing oncologic outcomes for patients with epithelial ovarian cancer using personalized clinical biomarkers

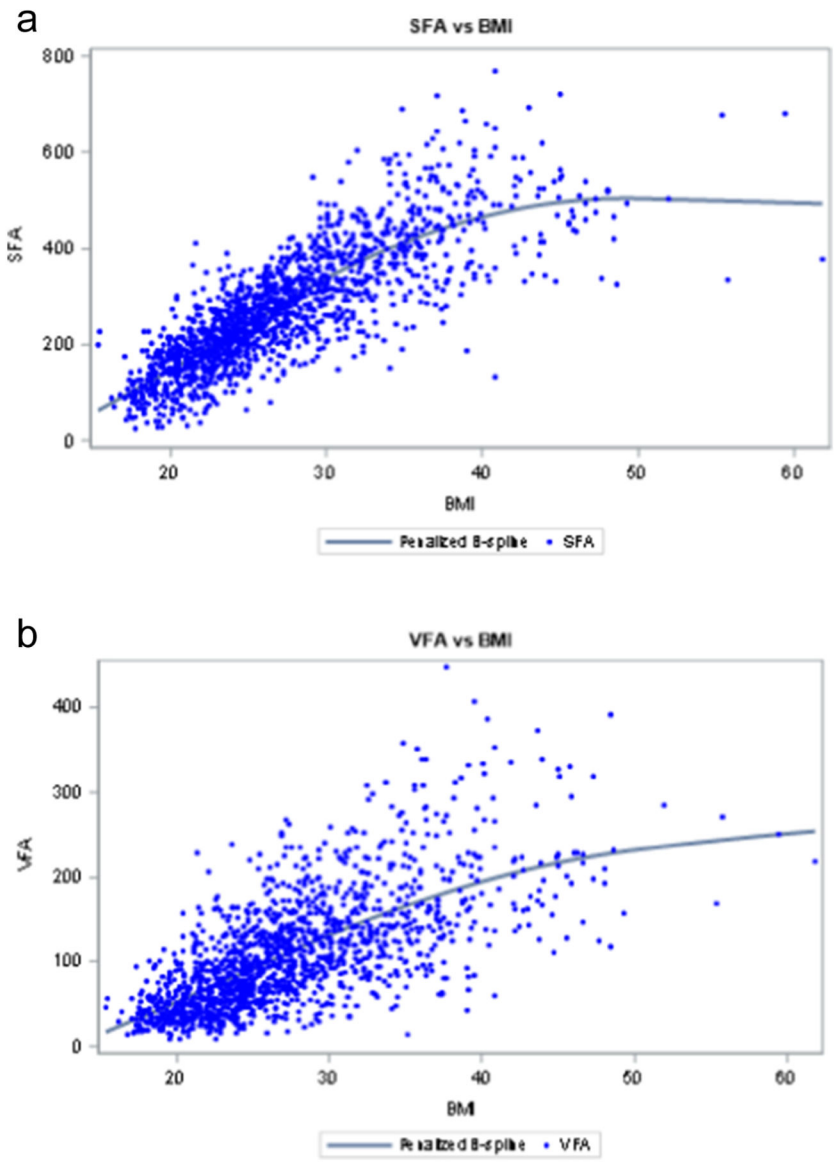

Figure 1:
Scattergram of BMI, SFA (a) and BMI, VFA (b) with penalized B spline

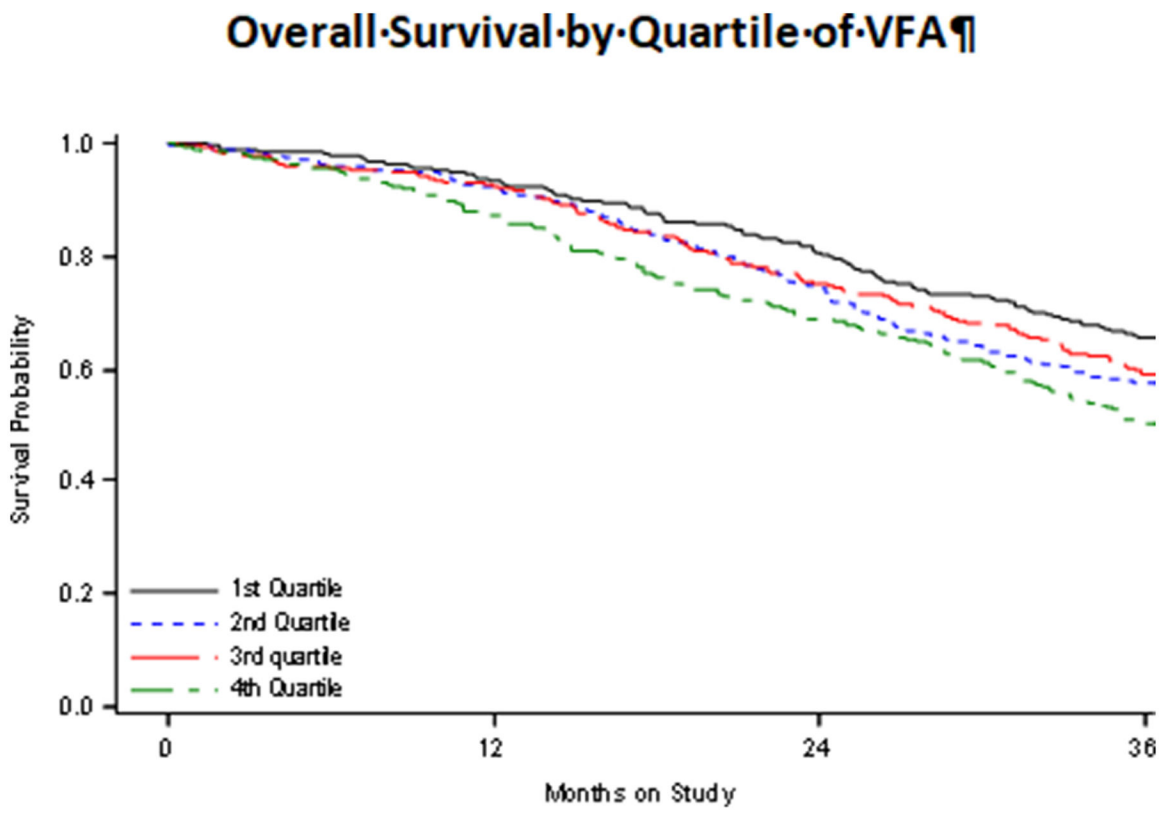

Figure 2:
Overall Survival by Quartile of visceral fat area (VFA).

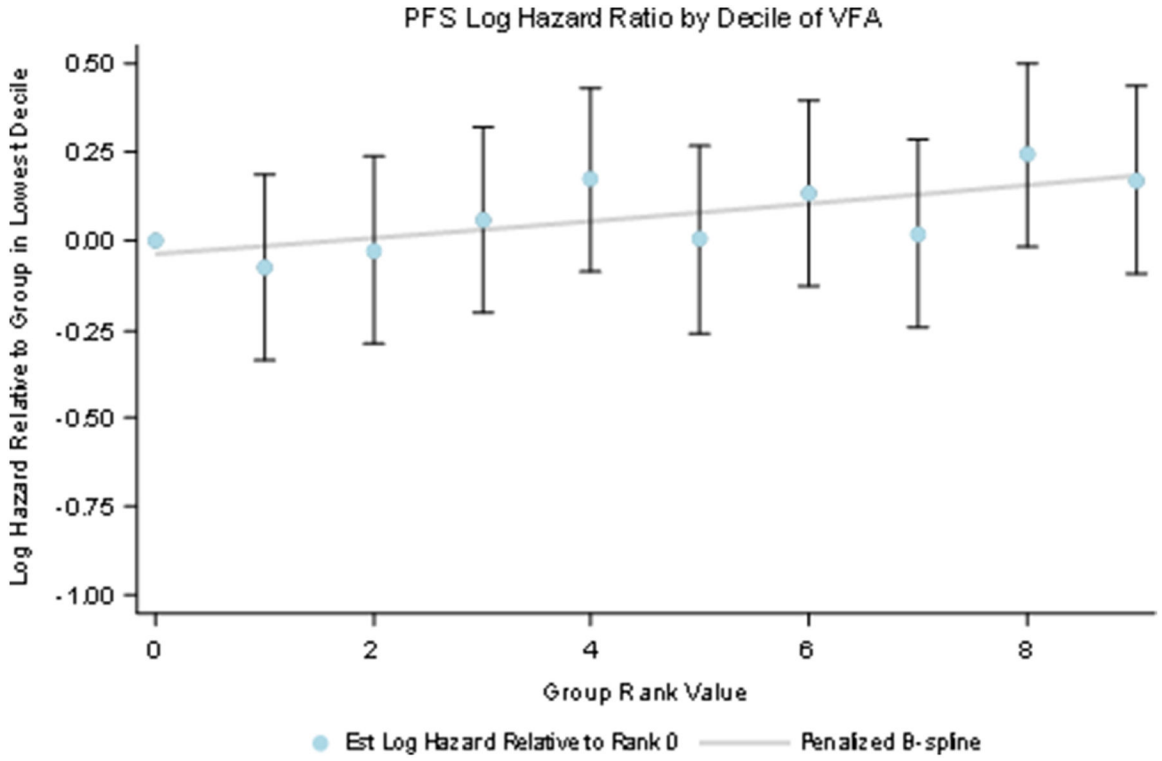

Figure 3:
Progression free survival (PFS) log hazard ratio by decile of visceral fat area (VFA)

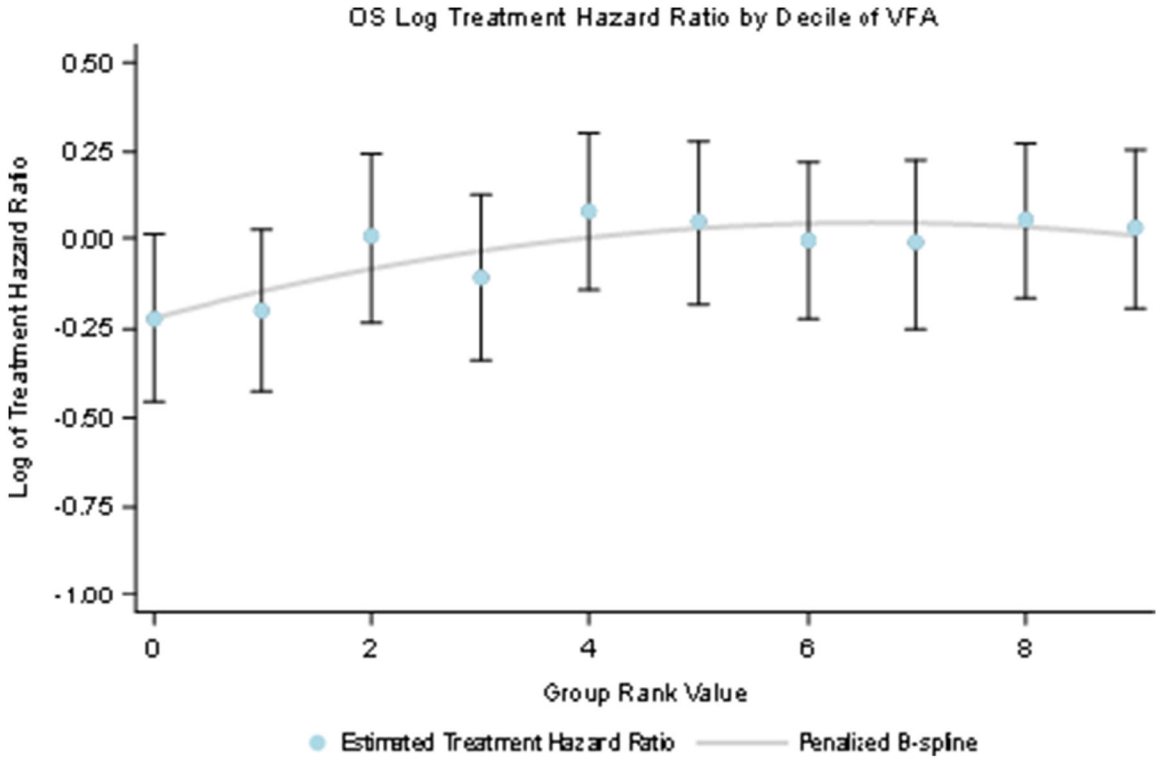

Figure 4:
Overall survival treatment log hazard ratios (CT+Bev→Bev: CT + P→P) within deciles of VFA

Table 1

Demographics.

Characteristic	Treatment Regimen						Total	
	CT+P−>P		CT+B−>P		CT+B−>B			
	N	%	N	%	N	%	N	%
Age Group								
<40	26	5.2	13	2.5	14	2.7	53	3.4
40–49	66	13.1	71	13.7	87	16.8	224	14.6
50–59	157	31.3	172	33.1	168	32.5	497	32.3
60–69	170	33.9	170	32.8	156	30.2	496	32.2
70–79	78	15.5	79	15.2	83	16.1	240	15.6
>=80	5	1.0	14	2.7	9	1.7	28	1.8
Race/ethnicity								
Non Hispanic Black	22	4.4	23	4.4	23	4.4	68	4.4
Non Hispanic White	421	83.9	431	83.0	438	84.7	1290	83.9
Hispanic	19	3.8	22	4.2	18	3.5	59	3.8
Asian	29	5.8	32	6.2	29	5.6	90	5.9
Pacific Islander	5	1.0	2	0.4	1	0.2	8	0.5
A.Indian/Alaska N.	2	0.4	2	0.4	2	0.4	6	0.4
Other	1	0.2	0	0	0	0	1	0.1
Not specified	3	0.6	7	1.3	6	1.2	16	1.0
Performance Status								
0	253	50.4	259	49.9	254	49.1	766	49.8
1	216	43.0	228	43.9	225	43.5	669	43.5
2	33	6.6	32	6.2	38	7.4	103	6.7
Primary Site								
Ovary	406	80.9	422	81.3	434	83.9	1262	82.1
Fallopian Tube	8	1.6	14	2.7	10	1.9	32	2.1
Primary Peritoneum	88	17.5	83	16.0	73	14.1	244	15.9
Histology and grade								
Papillary Serous	431	85.9	433	83.4	440	85.1	1304	84.8
Endometrioid	17	3.4	12	2.3	19	3.7	48	3.1
Clear Cell Carcinoma	10	2.0	19	3.7	16	3.1	45	2.9
Mucinous Adenocarcinoma	5	1.0	5	1.0	3	0.6	13	0.8
Adenocarcinoma, NS	4	0.8	7	1.3	7	1.4	18	1.2
Transitional Cell Carcinoma	3	0.6	9	1.7	3	0.6	15	1.0
Mixed Adenocarcinoma	23	4.6	27	5.2	20	3.9	70	4.6
Undiff. Carcinoma	5	1.0	4	0.8	7	1.4	16	1.0
Other/Not specified	4	0.8	3	0.6	2	0.4	9	0.6
Stage/Residual size								

Characteristic	Treatment Regimen						Total	
	CT+P−>P		CT+B−>P		CT+B−>B			
	N	%	N	%	N	%	N	%
III-optimal	178	35.5	180	34.7	180	34.8	538	35.0
III-suboptimal	202	40.2	208	40.1	204	39.5	614	39.9
IV	122	24.3	131	25.2	133	25.7	386	25.1
Total	502	32.6	519	33.7	517	33.6	1538	100.0