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Kierstin Faw Date

The association between CT scan-based body composition measurements and high grade serous ovarian cancer outcomes

By

Kierstin Faw
Master of Public Health

Epidemiology

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Joellen Schildkraut, PhD, MPH
Committee Chair

# The association between CT scan-based body composition measurements and high grade serous ovarian cancer outcomes

By

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B.S.
Allegheny College
2021

Thesis Committee Chair: Joellen Schildkraut, PhD, MPH

An abstract of
A thesis submitted to the Faculty of the
Rollins School of Public Health of Emory University
in partial fulfillment of the requirements for the degree of Master of Public Health in Epidemiology
2023

# Abstract

The association between CT-based body composition measurements and high grade serous ovarian cancer outcomes
By Kierstin Faw

*Objective*
To evaluate the association between high grade serous ovarian cancer (HGSOC) outcomes (overall survival and disease recurrence) and computed tomography (CT) scan-based body composition measurements (visceral adipose tissue (VAT), subcutaneous adipose tissue (SAT), intermuscular adipose tissue (IMAT), and skeletal muscle index (SMI)).

*Methods*
A retrospective review was conducted using electronic medical records from Emory University Hospital to find pre-treatment CT-scans, vital status, and recurrence status for each participant. The CT-scans were quantified into surface area measurements and multivariate cox proportional hazards models and accelerated time to failure models with a Weibull distribution were utilized to calculate hazard ratios. The association between obesity and HGSOC outcomes were fit stratified by low and high body composition levels. A meta-analysis was conducted with data from the present study in combination with Moffitt Cancer Center and Roswell Park Comprehensive Cancer Institute.

*Results*
In the multivariate survival analysis, VAT was statistically significantly associated with longer time to recurrence (HR = 0.42, 95% CI (0.19, 0.99)). Obesity was significantly associated with overall survival among those with higher SAT area (HR = 0.23, 95% CI (0.07, 0.81)). The results of our meta-analysis revealed evidence of a dose-response for overall survival and VAT area. Medium VAT area suggested greater survival while high VAT area suggested poorer survival (HR = 0.76, 95% CI (0.33, 1.77) and HR = 1.10 (0.87, 1.39), respectively).

*Conclusion*
Future studies need to be conducted to better understand the relationship between CT scan-based body composition measurements and HGSOC outcomes. Missingness of data from electronic medical records needs to be addressed and a larger sample size is necessary to properly understand this relationship.

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*Introduction*

Ovarian cancer and body size

Ovarian cancer remains the deadliest of gynecologic cancers among women in the United States (Siegel et al, 2022). It is estimated that 12,810 women will die from ovarian cancer in 2022 (Siegel et al, 2022). The five-year survival rate for ovarian cancer for all stages is 49% (Siegel et al., 2022). However, there are survival differences among races and ethnic groups. The five-year survival rate for all stages is 48% for White patients and 41% for Black patients. When considering just distant stage disease (cancer that has spread to distant lymph nodes and tissues), the survival rate for white and black patients is 30% versus 23%, respectively (Siegel et al., 2022). The histologic type that is most often diagnosed is epithelial ovarian cancer (EOC), making up roughly 90% of diagnoses (Peres & Schildkraut, 2020). Some of the factors that are suspected to affect a women's risk of EOC include: age at menarche and menopause, nulliparity versus any parity, infertility and fertility drugs, oral contraceptive usage, smoking, and body size (Webb & Jordan, 2017). Most of these factors have been well researched but body size's effect on EOC risk remains inconclusive.

Proposed mechanisms for body size influencing EOC development

There are a few proposed mechanisms for how obesity influences cancer development and survival through excess dysfunctional adipose tissue.

The first is through insulin resistance and the insulin-like growth factor (IGF-1) (van Kruijsdijk et al., 2009). A state of insulin resistance is often seen in obese patients. With high serum levels of insulin in the blood, it upregulates growth hormone (GH) which stimulates production of IGF-1 in the liver. Therefore, it is suspected that IGF-1 levels would be higher in obese individuals. However, IGF-1 levels have been found to be normal or lower in obese

individuals. That is because high insulin levels also lead to inhibiting the secretion of IGF-binding protein-1 and 2, limiting the accessibility of IGF-1 to bind to its necessary sites. Thus, leaving higher free IGF-1 levels in the blood. Both higher levels of insulin and free IGF-1 are problematic because they inhibit apoptosis (the death of cells) and stimulate cell proliferation, making cells more susceptible to forming carcinogenic neoplasms (van Kruijsdijk et al., 2009).

The second potential mechanism is through adipose tissue, which produces hormones and adipokines, a type of cytokine (van Kruijsdijk et al., 2009). Adipose tissue dysfunction can be a direct result from modified serum levels of adipokines. Adiponectin, a type of adipokine, has anti-inflammatory capabilities. Adiponectin has the ability to decrease the production of reactive oxygen species, which may inhibit cell proliferation. Adiponectin concentrations have been found to be lower in obese individuals, potentially increasing inflammation (van Kruijsdijk et al., 2009).

The third mechanism is inflammation. Obesity-induced inflammation is reflected by C-reactive protein (CRP), an inflammatory marker, which is increased in individuals with higher body mass index (BMI) (van Kruijsdijk et al., 2009). Raised levels of CRP have been found to be associated with cancer. Dysfunctional adipose tissue secretes large quantities of proinflammatory cytokines such as tumor necrosis factor (TNF-α). TNF- α has been found to be involved in carcinogenesis because of its role in apoptosis. Tumor cells can also produce TNF-α which has been found in the case of ovarian cancer. It activates transcription networks that advance tumor progression (van Kruijsdijk et al., 2009)

The final potential mechanism is sex steroids. The relationship between sex steroids and breast and endometrial cancer has been well established. It is believed to be rooted in the proliferative effect of estrogen on epithelial tissue. Increased levels of insulin, which as discussed

earlier can be a result of dysfunctional adipose tissue, can cause an increase in ovarian androgen synthesis and reduce hepatic synthesis of sex-hormone binding globulin (SHBG), limiting the transport capabilities for androgens and estrogen within the body. (van Kruijsdijk et al., 2009).

Ovarian cancer risk and body size

The epidemiologic relationship between ovarian cancer risk and body size is not well understood. There is a plethora of studies that have shown that obesity increases the risk for ovarian cancer among women. Researchers in the United Kingdom found an increased incidence among those with increasing BMI, with a relative risk of 1.14 (Reeves et al., 2007). Australian women with a BMI between the 65$^{th}$ and 85$^{th}$ percentile had a 50% increased risk of ovarian cancer and those above the 85$^{th}$ percentile had a 90% increased risk when compared to women whose BMIs were in the normal range (35$^{th}$-65$^{th}$ percentile) (Purdie et al., 2001). A meta-analysis from the United States found a summary relative risk for a five-unit increment increase in BMI to be 1.07, with risk significantly increasing for women with a BMI of 28 kg/m$^2$ or higher (Aune et al., 2015). In a study that looked at the risk of ovarian cancer in African American women, the racial/ethnic group with the highest prevalence of obesity, the odds of ovarian cancer in obese women (BMI of 40 kg/m$^2$ or higher) was 1.72 times that of women who had a BMI less than 25 kg/m$^2$ (Bandera et al., 2016). However, when women were stratified by menopausal status, the association between BMI and EOC risk was limited to women who were postmenopausal. This could be one reason for the inconsistencies in the literature of BMI and EOC risk. Self-reported height and weight which are subject to biases could also be fueling some of the inconsistencies in the literature.

Body size as a predictor of ovarian cancer survival

Similarly, to EOC risk factors, the factors that influence a women's survival of EOC include parity, ovulatory cycles, smoking, and BMI (Kim et al., 2017). A study that examined the effect of obesity on survival (disease free survival, progression free survival, and overall survival), found that women with advanced stage disease who were classified as having BMI over 25 $kg/m^2$, had a decrease in disease-free survival (Pavelka et al., 2006). Progression-free survival (PFS) had been shown to be affected by BMI as well. Patients categorized as "healthy weight" had PFS of 24 months while those who were classified as "obese" had a PFS of 21 months (Pavelka et al., 2006). The hazard ratio (HR) for overall survival (OS) was 1.05 (95% CI 1.01, 1.10) (Pavelka et al., 2006).

Some studies present that there is no association between body composition and survival. A study investigating the association between baseline BMI of advanced staged EOC patients and survival found that OS and PFS had no association with BMI (Hess et al., 2007). Another study looked at BMI 5-years before diagnosis and found that it had a statistically significant HR of 1.11 while adjusting for age at diagnosis, histology, and disease stage. The second model that was run in this study, adjusted for everything in the first model and added recurrence. The HR for BMI in the second model was 1.17 (Kim et al., 2017). BMI was considered a continuous variable in these two models. However, when BMI was analyzed as a categorical variable, there were no statistically significant HRs (Kim et al., 2017). This is one of the reasons that there are inconsistencies within the literature on EOC survival and obesity. Analyzing BMI as a continuous variable gives the study more statistical power (Ragland, 1992). In a meta-analysis of 17 cohort studies, investigators found that evaluating BMI as a continuous variable yielded slightly poorer survival with each incremental increase in BMI, while analysis of BMI as a

categorical variable yielded no effect on cancer survival (Table 1) (Bae et al., 2014). Definitions of what BMI is considered obese in studies is also a potential reason for inconsistencies. Two studies dichotomized BMI (25 $kg/m^2$ or higher was the classification of overweight/obese) (Fotopoulou et al., 2011 & Zhou et al., 2011). One study found an increase in survival for those who were obese and the other found poorer survival for obese patients (Bae et al., 2014). While other studies that classified obese as a BMI of 30 $kg/m^2$ or higher found a hazardous effect of obesity (Bae et al., 2014).

Another potential factor creating inconsistencies is the time of the BMI measurement. Some studies used BMI measurements 5 years prior to EOC diagnosis or 1 year before diagnosis while others measured BMI after treatment (Table 1). The measurement of BMI itself is also a cause of differing results. BMI oversimplifies the distribution of adipose tissue throughout the body (Gibson et al., 2015).

**Table 1**: Studies that have used BMI as a predictor of ovarian cancer survival

| Author | Design | n | Hazard Ratio (95% Confidence intervals) | BMI Modeling |
|---|---|---|---|---|
| Pavelka et al., 2006 | Cohort Study | 216 | 1.05 (1.01-1.10) | BMI as a continuous variable, height and weight measurements were gathered from the first post-cytoreduction surgery visit |
| Kim et al., 2017 | Case-Control Study | 1421 | 1.17 (1.07-1.28) | BMI as a continuous variable, used current patient height and weight from 5-years prior to diagnosis |
| Fotopoulou et al., 2011 | Cohort Study | 306 | 0.73 (0.39-1.37) | Dichotomized BMI (25 or higher), time of measurement not specified |
| Zhou, 2011 | Cohort Study | 388 | 1.30 (0.92-1.83) | Dichotomized BMI (25 or higher), measurements 5-years prior to diagnosis |
| Hess et al., 2007 | Retrospective Review | 792 | 1.00 (0.99-1.01) | BMI as a categorical variable (3 categories: less than 25 $kg/m^2$, 25.0-29.9 $kg/m^2$, and 29.9 or greater), used BMI before starting chemotherapy |

Implications of using body mass index as a survival predictor

BMI assumes that the distribution of adipose and muscle tissue is uniform in everybody, which is problematic because adipose tissue is distributed differently among sexes and age groups (Gibson et al., 2015). Thus, using BMI as a predictor for survival can create misclassification bias. This is especially the case for ovarian cancer patients because approximately 61% of women that are diagnosed with ovarian cancer present advanced staged disease (Purcell et al. 2016 & Torres et al., 2013). Later staged diseases are more likely to have a larger volume of ascites, larger tumor masses, and bowel obstruction which would increase a

women's overall body weight. Increasing body weight will lead to a higher BMI measurement that is not reflective of adipose tissue or muscle mass, but of the volume of ascites, tumor size, and bowel obstruction (Purcell et al., 2016).

There are biological changes in body composition that occur for women after they go through menopause. Visceral fat area tends to be higher in women after they go through menopause and skeletal muscle mass decreases with age (Purcell et al., 2016 & Mittal, 2019). Therefore, using BMI, measured 5 years prior to diagnosis, as a body composition predictor would neglect the weight changes due to aging and disease progression, thus biasing survival outcomes. In order to get more reliable data on how body composition affects survival of EOC, the use of computed tomography (CT) scans can be very beneficial to accurately depict body composition before treatment begins.

Utilization of CT scans

CT scans provide images that can distinguish between muscles, adipose tissue, and organs. They even have the capabilities to further distinguish between skeletal muscle mass (SMM), visceral adipose tissue (VAT), subcutaneous adipose tissue (SAT), and intermuscular adipose tissue areas (IMAT) (Deluche et al., 2018). This is possible by the determination of upper and lower thresholds for adipose tissue and muscle regions in the CT images using Hounsfield units (HU), which is a relative quantitative measurement of radio density (DenOtter, T. D. & Schubert, J., 2019). These thresholds allow for the differentiation between the tissues and quantification of the surface area of each tissue (Del Grande et al., 2021 & DenOtter, T. D. & Schubert, J., 2019).

Distinguishing between different adipose tissues is important because SAT and VAT serve different functional purposes to the body. SAT is beneath the skin and pro-inflammatory gene

expression is much more prominent in SAT than VAT (Mittal, 2019). SAT produces interlukin-6 (IL-6), a pro-inflammatory cytokine like TNF- α (Mittal, 2019). IL-6 levels are elevated in obese individuals and have been correlated with overall cancer mortality (van Kruiksdijk et al., 2009). VAT is mainly found in the abdomen, lining internal organs (Liu & Xiao, 2013). Visceral fat plays a crucial role in insulin resistance and has the ability to produce more free fatty acids than subcutaneous fat (Mittal, 2019, 2013 & Yip et al., 2015). As previously discussed, insulin resistance has the potential to make cells more susceptible to neoplasm formations due to lack of apoptosis and stimulation of cell proliferation (van Kruiksdijk et al., 2009).

CT scans are part of the routine diagnosis procedure for EOC patients (Gibson et al., 2015). CT scans are the gold standard and a non-invasive tool to aid in staging and follow-up by measuring muscle quantity and adipose tissue (Del Grande et al., 2021). One study evaluated the linear relationship between cross-sectional pieces of lumbar vertebra 3 (L3)'s distribution of adipose tissue and skeletal muscle and their distributions throughout the whole body (Mourtzakis et al., 2008). It found that CT images at L3 were strongly associated with full body distribution of fat mass ($r^2$ =0.927) and muscle mass ($r^2$ = 0.855). The L3 cross-sectional CT scans can be extrapolated to represent the muscle and fat distribution of the whole body (Mourtzakis et al., 2008).

Therefore, the ability to distinguish between different adipose tissues is important for understanding potential treatment risks for EOC patients and predicting survival based on the proposed biological mechanisms of how obesity influences cancer progression. The ability to understand treatment risk and outcomes based on body composition will improve treatment efficacy and the cost effectiveness of cancer treatment as well (Prado, 2013).

In this study, we evaluate the association between body composition, survival, and disease recurrence among women diagnosed with high grade serous ovarian cancer (HGSOC), the most common type of EOC. CT scans are utilized to differentiated between SAT, VAT, IMAT, and SMM. This is a pilot study to see the feasibility of utilizing CT scans to create a model that predicts treatment response to better use interventions and treatment strategies for prolonging survival.

*Methods*

Study population

Subjects eligible for the study included women diagnosed with HGSOC who were between the ages of 20 and 85 years old. All cases were diagnosed between January 1st, 2008-December 31st, 2018, and treated within the Emory Healthcare System. The starting date of 2008 was crucial because of the shift to thin slice and higher resolution CT scanners. Participants must have had a routine abdomen and pelvis CT scan before beginning treatment to be included in this study. Those who were diagnosed with non-serous ovarian cancer subtypes and women diagnosed before 2008 were excluded from the study. This study had institutional review board (IRB) approval from Emory University to access electronic medical records and complete a retrospective review.

Medical record abstraction and data

Electronic medical record abstraction was conducted for all patients meeting the eligibility criteria for the study. Information was abstracted from Cerner's Powerchart electronic medical records through the Emory Healthcare network. Variables that were collected included age at diagnosis, race, ethnicity, date of diagnosis, pre-treatment BMI, International Federation of Gynecology and Obstetrics (FIGO) stage, type of first line treatment (neoadjuvant

chemotherapy (a few rounds of chemotherapy before surgery) versus upfront surgical debulking), chemotherapy regimen and doses, recurrence status, CA-125 levels before and after surgery, and CT scans before and after treatment.

All data was collected and stored in REDCap (Version 12.2.0) before being transferred to SAS (Software 9.4) for data cleaning and analysis.

CT scans and adiposity measurements

Participant's CT scans were obtained by requesting pre- and post- treatment scans from the Winship Cancer Institute's radiology department in Atlanta, Georgia. The scans that were obtained were sent to Moffit Cancer Center (MCC) for the quantification of body composition. A data transfer agreement (DTA) was established in order to share CT scans with MCC.

Body composition measurements (BCMs) were observed at the cross-sectional slice of the mid transverse plane of L3. For CT scans that were missing the mid-scan (n = 2), the top scan was used for body composition measurements. Pre-defined Hounsfield units' boundaries were applied as follows: -150 to -50 for VAT, -190 to -30 for SAT, -190 to -30 for IMAT and -29 to 150 for SMM. The surface area of each tissue ($cm^2$) was determined by Data Analysis Facilitation Suite (DAFS) software at MCC by the Qualitative Imaging Core. This software allows for accurate segmentation and identification of tissues. Each tissue is color coded in the output images to differentiate between the tissues' surface areas (shown in Figure 1). Skeletal muscle index (SMI) was calculated by taking SMM and dividing it by the square of the participant's height. Height was obtained through medical record abstraction and was recorded around the time of the participant's pre-treatment CT scan.

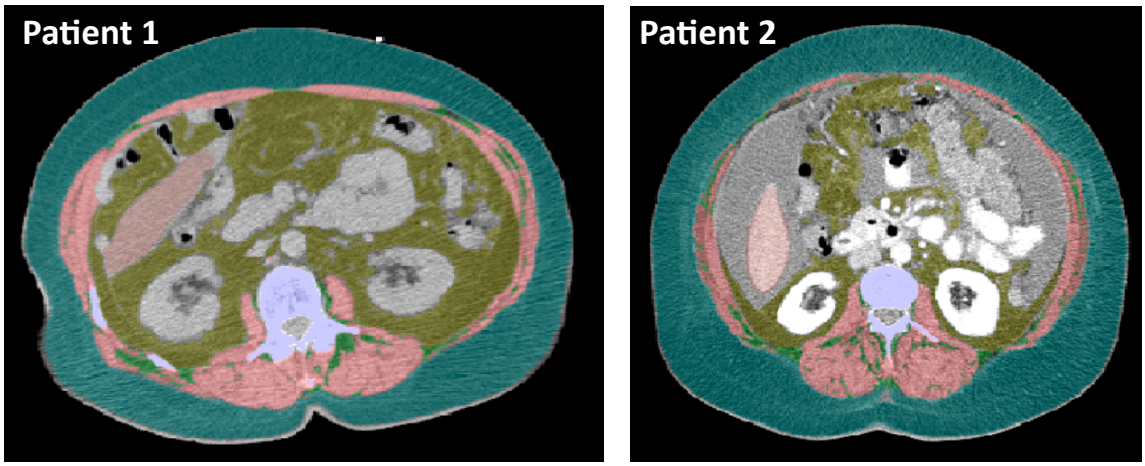



**Figure 1:** Examples of segmentation of two participants that had similar BMI (Patient 1: 32.4 $kg/m^2$ ; Patient 2: 32.5 $kg/m^2$) but different segmentation of body composition measurements: SMM (light red), VAT (yellow), SAT (cyan), and IMAT

Overall survival and recurrence

Overall survival (OS) was measured from the date of diagnosis to date of death (in months). Date of death was determined by using vital status updates in the participant's medical records. For participants whose vital status was not explicitly stated in their medical records, LexisNexis was utilized to confirm vital status and date of death. Those participants that did not die during the study period, were censored at the date that vital status was last determined (i.e., the date that vital status was checked in medical records and/or LexisNexis).

A participant was said to have a recurrence if their medical records explicitly stated that disease recurrence occurred, and the participant's CA-125 levels were steadily increasing after the completion of treatment. Time to recurrence was measured from time of diagnosis to the date the participant's medical record reflected recurrent disease (in months). Patients that did not have a recurrence recorded in their medical record were censored at their last known follow-up at an Emory Healthcare facility.

Statistical Analysis

Statistical analyses were performed using SAS (Software 9.4). The proportional hazard (PH) assumption was tested for each BCMs and covariates by graphing negative log-log curves, goodness-of-fit tests, and testing the interaction of time to evaluate if the variable was time dependent. For the BCMs that met the PH assumption, Cox proportional hazard models were utilized (OS: VAT, SAT, IMAT). Accelerated failure time (AFT) models with a Weibull distribution were performed for BCMs that did not meet the PH assumption (OS: SMI; recurrence: VAT, SAT, IMAT, SMI). The point estimates and Weibull shape parameter were used to convert the parameters to hazard ratios (HR) by using the following formula: $e^{\beta_{\text{body compostion estimate}}*-1(\text{Weibull Shape parameter})}$. All four BCMs were dichotomized using the median as the cutoff point for modeling.

BMI was categorized into non-obese (BMI < 30) and obese (BMI ≥ 30), and PH models for the association between obesity and both OS and recurrence were fit stratified by high or low body composition levels. HRs and 95% confidence intervals were calculated for obesity.

Covariates

Age at diagnosis, stage, race, and first line treatment were considered as potential confounders. Age was modeled as a continuous variable and FIGO stage was categorized into early (I/II) and late-stage disease (III/IV). Race categories available from medical records were Asian, Black, and White. First line treatment was defined as a binary variable based on medical records indicating if patients had neoadjuvant chemotherapy or upfront surgical debulking.

Meta-analysis

A meta-analysis was conducted using the BCM estimates determined from this study (VAT, SAT, IMAT, and SMI) with BCM estimates from subjects at the MCC (n=384) and Roswell Park Comprehensive Cancer Institute (RPCCI) (n= 308). For this meta-analysis, each BCM was categorized into three groups by tertiles: low, medium, and high adipose tissue area. SMI measurements were not available from RPCCI, so the HRs were calculated using Emory University and MCC results only.

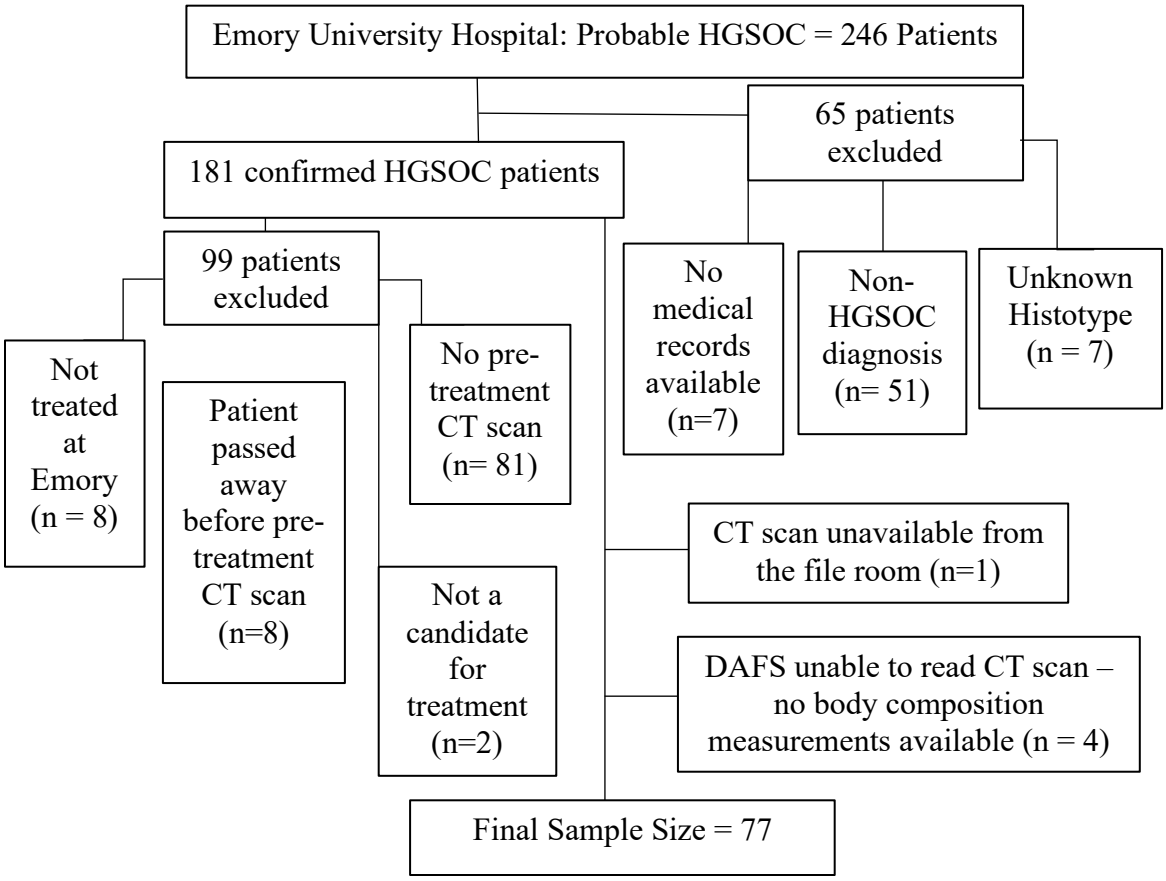
The SAS macro %METAANAL_NOIML (Depuy, 2017), an extended version of the macro %METAANAL (Hertzmark & Spiegelman, 2017), was utilized to calculate the combined HRs and 95% confidence intervals with the DerSimonian-Laird estimators (1986). The macro required the upper and lower bounds of the individual studies' results. The Q statistic and corresponding p-value were generated to test for heterogeneity between the individual studies' results.

*Results*

Figure 2 illustrates the exclusions applied to the women identified at the Emory University Hospital. There were 246 women with a probable diagnosis of HGSOC between 2008-2018. Of those, 181 were confirmed diagnoses by pathology reports in their electronic medical records. Of the confirmed diagnoses, 104 patients were excluded for various reasons: some patients were not treated within the Emory Healthcare System (n=8), some patients passed away before pre-treatment CT scan was obtained (n=8), some patients were not candidates for treatment and were referred to hospice (n=2), some patients did not have a pre-treatment CT scan

in their medical records (n=81), a pre-treatment CT was not available from the file room (n=1) , and some participants' CT scans could not be read by the DAFS software so BCMs could not be obtained (n=4). The final sample size was 77 participants (Figure 2).

**Figure 2:** Flowchart of participants exclusion from the study population.




Sample characteristics

The study population had a mean age at diagnosis of 62.8 years, more than half were White (53.33%) and most of the women were non-Hispanic (96.2%). The average pre-treatment BMI was 29.1 kg/m$^2$. Roughly two-thirds of the women were diagnosed with stage III (A-C) cancer. Approximately three-fourths of participants underwent neoadjuvant chemotherapy as their first-line treatment. The most common co-morbidity was hypertension with 42.9% of

participants being diagnosed with hypertension before or after their cancer treatment. The years that had the most participants diagnosed with HGSOC were 2017 (23.4%) and 2011 (18.2%). The average BCMs were 94.1 $cm^2$ for VAT, 227.4 $cm^2$ for SAT, 12.4 $cm^2$ for IMAT, and 0.00041 for SMI. Roughly 64% of the study population was deceased and 78% of participants experienced a recurrence (Table 2).

**Table 2**: Characteristics of study population

| **Characteristic** | **N (%)** |
|---|---|
| *Vital Status* | |
| Alive | 26 (36.11) |
| Dead | 46 (63.89) |
| Unknown | 5 (-) |
| *Recurrence* | |
| Yes | 45 (77.59) |
| No | 13 (22.41) |
| Unknown | 19 (-) |
| *First line treatment* | |
| Neoadjuvant chemotherapy | 57 (75.00) |
| Upfront debulking surgery | 19 (25.00) |
| Missing | 1 (-) |
| *Race* | |
| Asian | 10 (13.33) |
| Black | 25 (33.33) |
| White | 40 (53.33) |
| Missing | 2 (-) |
| *Ethnicity* | |
| Hispanic | 2 (3.85) |
| Non-Hispanic | 50 (96.15) |
| Missing | 25 (-) |
| *FIGO Stage* | |
| IA-IC | 3 (5.08) |
| IIA-IIC | 6 (10.17) |
| IIIA-IIIC | 40 (67.80) |
| IV | 10 (16.95) |
| Missing | 18 (-) |

| **Characteristic** | N (%) |
|---|---|
| *Co-morbidities* | |
| Diabetes Mellitus | 12 (15.58) |
| Hypertension | 33 (42.86) |
| Cardiac Condition | 11 (14.29) |
| Chronic Kidney Disease | 6 (7.79) |
| Hypercholesterolemia | 4 (5.19) |
| *Year of Diagnosis* | |
| 2008 | 2 (2.60) |
| 2009 | 1 (1.30) |
| 2010 | 5 (6.49) |
| 2011 | 14 (18.18) |
| 2012 | 5 (6.49) |
| 2013 | 3 (3.90) |
| 2014 | 6 (7.79) |
| 2015 | 4 (5.19) |
| 2016 | 7 (9.09) |
| 2017 | 18 (23.38) |
| 2018 | 12 (15.58) |
| **Characteristic** | **Mean (SD)** |
| *Age at diagnosis* | 62.77 (12.11) |
| *Pre-treatment BMI (kg/m$^2$)* | 29.07 (7.36) |
| *VAT (cm$^2$)* | 94.05 (61.31) |
| *SAT (cm$^2$)* | 227.36 (132.55) |
| *IMAT (cm$^2$)* | 12.42 (7.32) |
| *SMI* | 0.00041 (0.00076) |

Body Composition, overall survival, and recurrence

The median OS was 48.9 months. OS did not significantly differ between those with higher and lower VAT, SAT, IMAT, and SMI. Although not significant, higher VAT and SMI were found to be associated with longer OS with HRs less than 1.0 (HR = 0.56, 95% (CI 0.25,

1.23) and HR = 0.61, 95% CI (0.29, 1.27), respectively. While higher SAT and IMAT did appear to poorly influence OS with HRs of 1.17, (95% CI: 0.56, 2.42) and 1.19, (95% CI: 0.52, 2.74), respectively (Table 3).

The median time to recurrence was 18 months. Those with higher VAT area had a statistically significant longer time to recurrence when compared to those with lower VAT area (HR = 0.42, 95% CI (0.18, 0.99)). Although not significant, higher surface area of IMAT and SMI were found to be inversely related to time to recurrence (HR = 0.69, 95 % CI (0.28, 1.69); HR = 0.78, 95% CI (0.35, 1.72), respectively). There appeared to be no association between SAT area and recurrence with a HR of 1.01 (95% CI: 0.44, 2.28) (Table 3).

**Table 3:** CT scan-based body composition measurements, overall survival, and recurrence

| | Overall Survival | | Recurrence | |
|---|---|---|---|---|
| | N (Event N) | HR (95% CI) | N (Event N) | HR (95% CI) |
| VAT | 57 (33) | 0.56 (0.25, 1.23) | 56 (33) | **0.42 (0.18, 0.99)** * |
| SAT | 57 (33) | 1.17 (0.56, 2.42) | 56 (33) | 1.01 (0.44, 2.28) * |
| IMAT | 57 (33) | 1.19 (0.52, 2.74) | 56 (33) | 0.69 (0.28, 1.69) * |
| SMI | 57 (33) | 0.61 (0.29, 1.27) * | 56 (33) | 0.78 (0.35, 1.72) * |

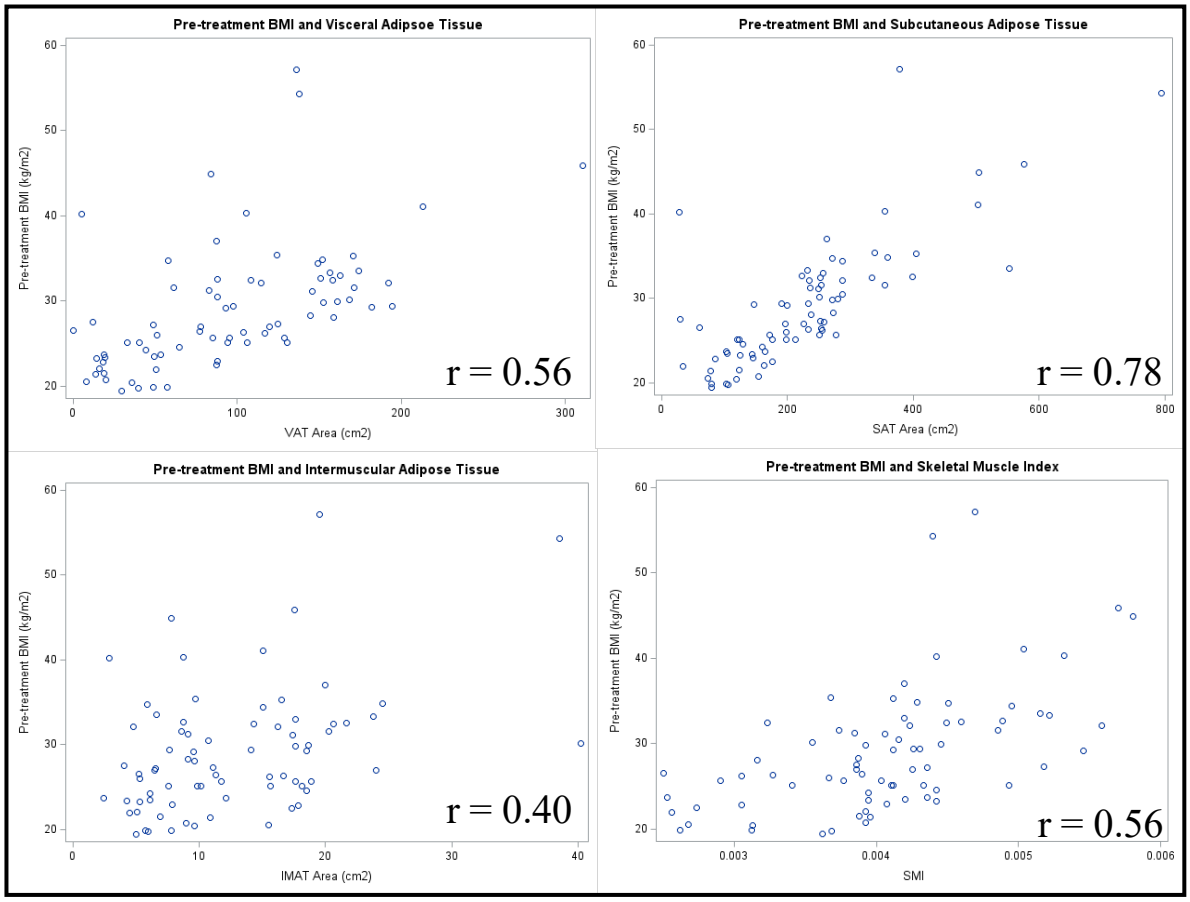
Models were adjusted for stage, age at diagnosis, race, and first line treatment.
*These HRs were transformed from Weibull accelerated failure time models. HRs were calculated as follows: $HR_{Weibull} = e^{(\beta_{body\ composition\ estimate^*} - 1(\text{shape parameter}))}$

BMI Correlation and Stratification

Correlation coefficients were calculated for each of the four CT scan based BCMs and BMI. All were positively correlated with pre-treatment BMI with SAT having the strongest correlation (r = 0.78) followed by VAT, SMI, and IMAT being moderately correlated with pre-

treatment BMI (r = 0.56; r = 0.56; and r = 0.40), respectively. Scatterplots are provided in Figure 3 below.

**Figure 3**: Correlation with CT-Scan based body composition and pre-treatment BMI




Among those have low body composition (BC) area for VAT and IMAT, obesity was not associated with OS (HR= 1.00, 95% CI (0.24, 4.17); HR = 1.06, 95% CI (0.29, 3.93), respectively). For those with low SAT area, obesity was associated with longer survival (HR = 0.63, 95% CI (0.08, 5.08). On the other hand, for those with low SMI, obesity was associated with shorter OS, (HR = 1.18, 95% CI (0.28, 5.44)). However, both confidence intervals are wide and imprecise. Obesity was significantly associated with longer survival among those with high

SAT area (HR = 0.23, 95% CI (0.07, 0.81)). Obesity was associated with longer OS for those with high IMAT and SMI (HR = 0.52, 95% CI (0.18, 1.48) and HR = 0.72, 95% CI (0.22, 2.35), respectively). Among those with high VAT area, obesity was associated with shorter OS with an HR of 1.23 (95% CI 0.32, 4.73) (Table 4).

Among those with low VAT, obesity was observed to lead to shorter time to recurrence, however, the confidence interval is imprecise (HR = 2.90, 95% CI 0.70, 12.00). Obesity led to longer time to recurrence among those with low SAT area and SMI with HRs less than 1.0 (HR = 0.57, 95% CI (0.10, 3.11) and HR = 0.48, 95% CI (0.06, 4.18), respectively). No association was found between obesity and recurrence among those with low IMAT area (HR = 1.11, 95% CI (0.34, 3.60)). Obesity was found to be inversely related to recurrence among those with high BC area for all four BCMs (VAT HR = 0.56, 95% CI (0.17, 1.79); SAT HR = 0.74, 95% CI (0.18, 2.95); IMAT HR = 0.60, 95% CI (0.21, 1.71); and SMI HR = 0.52, 95% CI (0.18, 1.45), respectively) (Table 4).

**Table 4:** The association between obesity, overall survival, and recurrence modified by BCMs.

| | Low BC area | | High BC area | |
|---|---|---|---|---|
| | N (Event N) | HR (95% CI) | N (Event N) | HR (95% CI) |
| *Overall Survival* | | | | |
| Obesity – VAT | 31 (20) | 1.00 (0.24, 4.17) | 26 (13) | 1.23 (0.32, 4.73) |
| Obesity – SAT | 31 (16) | 0.63 (0.08, 5.08) | 26 (17) | **0.23 (0.07, 0.81)** |
| Obesity – IMAT | 26 (15) | 1.06 (0.29, 3.93) | 31 (18) | 0.52 (0.18, 1.48) |
| Obesity - SMI | 25 (16) | 1.18 (0.28, 5.44) | 32 (17) | 0.72 (0.22, 2.35) |
| *Recurrence* | | | | |
| Obesity - VAT | 30 (17) | 2.90 (0.70, 12.00) | 26 (16) | 0.56 (0.17, 1.79) |
| Obesity - SAT | 30 (18) | 0.57 (0.10, 3.11) | 26 (15) | 0.74 (0.18, 2.95) |
| Obesity - IMAT | 25 (16) | 1.11 (0.34, 3.60) | 31 (17) | 0.60 (0.21, 1.71) |
| Obesity - SMI | 25 (14) | 0.48 (0.06, 4.18) | 31 (19) | 0.52 (0.18, 1.45) |

Models were adjusted for stage, age at diagnosis, race, and first line treatment.

Meta-analysis

Table 5 shows the individual study results from this study (Emory University) and the study conducted at MCC/RPCCI. Each BCM was categorized into low, medium, and high BC area using tertiles. Emory University models were adjusted for race, first line treatment, age at diagnosis, and stage for all four BCMs. For VAT, SAT, and IMAT, MCC/RPCCI adjusted for age at diagnosis, stage, first line treatment, and study site. MCC adjusted for age at diagnosis, stage, race/ethnicity, first line treatment, and debulking status for SMI models.

Emory University and MCC/ RPCCI both found no association between medium VAT and medium IMAT area and recurrence (HR VAT Emory = 1.04, 95% CI (0.41, 2.60); HR VAT MCC/RPCCI = 0.97, 95% CI (0.79, 1.20); HR IMAT Emory = 1.07, 95% CI (0.40, 2.86); HR IMAT MCC/RPCCI = 0.98, 95% CI (0.78, 1.21), respectively). Both studies found that medium SAT area was associated with longer time to recurrence (HR Emory = 0.59, 95% CI (0.23, 1.48); HR MCC/RPCCI = 0.87, 95% CI (0.71, 1.08), respectively), however Emory University found no association between medium SAT and OS while MCC/RPCCI found it to lead to slightly longer OS (HR Emory = 0.93, 95% CI (0.38, 2.27) and HR MCC/RPCCI= 0.86, 95% CI (0.67, 1.10), respectively). High SMI was found to be associated with shorter time to recurrence in Emory University and MCC's cohorts (HR Emory = 1.99, 95% CI (0.72, 5.53) and HR MCC = 1.15, 95% CI (0.85, 1.55), respectively) (Table 5).

**Table 5**: Study results from Emory University and Moffitt Cancer Center (MCC) / Roswell Park Comprehensive Cancer Institute (RPCCI) cohorts for CT-based body composition measurements and HGSOC overall survival and recurrence

| | Overall Survival | | Recurrence | |
|---|---|---|---|---|
| | Emory University HR (95% CI) | MCC / RPCCI HR (95% CI) | Emory University HR (95% CI) | MCC / RPCCI HR (95% CI) |
| *VAT* | | | | |
| Low | 1.00 (Referent) | 1.00 (Referent) | 1.00 (Referent) | 1.00 (Referent) |
| Medium | 0.43 (0.16, 1.14) | 1.05 (0.82, 1.34) | 1.04 (0.41, 2.60) * | 0.97 (0.79, 1.20) |
| High | 0.76 (0.33, 1.74) | 1.13 (0.89, 1.45) | 0.48 (0.18, 1.27) * | 0.98 (0.80, 1.21) |
| *SAT* | | | | |
| Low | 1.00 (Referent) | 1.00 (Referent) | 1.00 (Referent) | 1.00 (Referent) |
| Medium | 0.93 (0.38, 2.27) | 0.86 (0.67, 1.10) | 0.59 (0.23, 1.48) * | 0.87 (0.71, 1.08) |
| High | 0.69 (0.29, 1.66) | 1.05 (0.83, 1.34) | 0.60 (0.24, 1.51) * | 1.16 (0.94, 1.43) |
| *IMAT* | | | | |
| Low | 1.00 (Referent) | 1.00 (Referent) | 1.00 (Referent) | 1.00 (Referent) |
| Medium | 0.68 (0.28, 1.69) | 0.90 (0.69, 1.16) | 1.07 (0.40, 2.86) * | 0.98 (0.78, 1.21) |
| High | 0.66 (0.27, 1.65) | 1.44 (1.09, 1.90) | 0.44 (0.16, 1.20) * | 1.15 (0.90, 1.47) |
| *SMI* | | | | |
| Low | 1.00 (Referent) | 1.00 (Referent) | 1.00 (Referent) | 1.00 (Referent) |
| Medium | 0.98 (0.40, 2.40) * | 1.00 (0.72, 1.40) | 0.82 (0.29, 2.33) * | 0.98 (0.74, 1.30) |
| High | 0.79 (0.27, 1.70) * | 1.11 (0.78, 1.60) | 1.99 (0.72, 5.53) * | 1.15 (0.85, 1.55) |

*These HRs were transformed from Weibull accelerated failure time models. HRs were calculated as follows: $HR_{Weibull} = e^{\left(\beta_{body\ composition\ estimate^*} - 1(\text{shape parameter})\right)}$

The results of the meta-analysis conclude that medium VAT area was inversely associated with OS and high VAT area was inversely related to recurrence (HR = 0.76, 95% CI (0.33, 1.77); HR =0.81 (0.43, 1.52), respectively). Medium SAT area was associated with longer OS and longer time to recurrence (HR = 0.86, 95% CI (0.68, 1.10) % and HR = 0.86, 95% CI (0.70, 1.05), respectively). While high SAT area was not associated with survival or recurrence (HR = 1.02, 95% CI (0.81, 1.29); HR= 0.98, 95% CI (0.56, 1.72), respectively).

There was no evidence of an association between OS and IMAT (medium or high) with HRs of 0.88 (95% CI 0.68, 1.13) and 1.11 (95% CI 0.55, 2.26), respectively. Medium IMAT was not associated with recurrence (HR = 0.98, 95% CI (0.79, 1.21)); however, high IMAT area was

associated with longer time to recurrence (HR = 0.81, 95% CI (0.32, 2.01)). Medium and high SMI was not association with OS (HR = 1.00, 95% CI (0.73, 1.37) and HR = 1.05, 95% CI (0.75, 1.46), respectively) and medium SMI was not associated with recurrence (HR = 0.97, 95% CI (0.74, 1.27)). High SMI, however, resulted in shorter time to recurrence (HR = 1.21, 95% CI (0.88, 1.65)) (Table 6).

**Table 6:** Meta-analysis HRs from Moffit Cancer Center, Roswell Park Comprehensive Cancer Institute, and Emory University for CT-based body composition measurements, overall survival, and recurrence.

| | Overall Survival | | Recurrence | |
|---|---|---|---|---|
| | HR (95% CI) | Q-statistic p-value | HR (95% CI) | Q statistic p-value |
| *VAT* | | | | |
| Low | 1.00 (Referent) | | 1.00 (Referent) | |
| Medium | 0.76 (0.33, 1.77) | 0.08 | 0.98 (0.80, 1.20) | 0.90 |
| High | 1.10 (0.87, 1.39) | 0.36 | 0.81 (0.43, 1.52) | 0.15 |
| *SAT* | | | | |
| Low | 1.00 (Referent) | | 1.00 (Referent) | |
| Medium | 0.86 (0.68, 1.10) | 0.87 | 0.86 (0.70, 1.05) | 0.40 |
| High | 1.02 (0.81, 1.29) | 0.36 | 0.98 (0.56, 1.72) | 0.17 |
| *IMAT* | | | | |
| Low | 1.00 (Referent) | | 1.00 (Referent) | |
| Medium | 0.88 (0.68, 1.13) | 0.58 | 0.98 (0.79, 1.21) | 0.85 |
| High | 1.11 (0.55, 2.26) | 0.11 | 0.81 (0.32, 2.01) | 0.07 |
| *SMI* | | | | |
| Low | 1.00 (Referent) | | 1.00 (Referent) | |
| Medium | 1.00 (0.73, 1.37) | 0.96 | 0.97 (0.74, 1.27) | 0.74 |
| High | 1.05 (0.75, 1.46) | 0.30 | 1.21 (0.88, 1.65) | 0.31 |

*Discussion*

In this study's multivariate analysis of the associations between BCMs and HGSOC outcomes, VAT was significantly inversely associated with recurrence and none of the four BCMs were statistically significantly related to OS. However, high SMI was associated with longer OS. This is consistent with other literature because sarcopenia, which is when someone has low SMI, has been found to poorly impact OS among EOC patients (McSharry et al., 2021 & Ubachs et al., 2019). A meta-analysis that evaluated this relationship found a statistically significant association between sarcopenia and poorer OS (HR =1.11, 95% CI 1.03, 1.20). That is reflected in the results that our study found in modeling SMI dichotomously and in tertiles (Table 3 and Table 5). The reason for this could potentially be because, chemotherapy is linked to loss of muscle mass due to increased activity of the ubiquitin-proteasome system (UPS) which leads to an increase in muscle protein degradation (Rier et al., 2016). Therefore, the more SMI a patient has at the start of their treatment, may indicate their likelihood of chemotherapy toxicity and treatment outcomes (Rier et al., 2016).

Obesity was significantly associated with longer OS for those with high SAT area. This finding was consistent with a retrospective cohort study investigating the association between adiposity and several kinds of cancer (gastrointestinal, respiratory, and renal cell carcinoma) (Ebadi et al., 2017). With high adiposity as the reference group, the HR was 1.26 (95% CI: 1.11, 1.43) for the low area SAT group. Although not significant, a similar association was found between VAT and OS (HR = 1.13, 95% CI (0.99, 1.28)), lower VAT area was found to lead to poorer survival (Ebadi et al., 2017).

There is evidence that the relationship between obesity and recurrence could be modified by BCMs, specifically VAT area. Among those with lower VAT area, shorter time to recurrence

was observed while those with higher VAT area exhibited longer time to recurrence. This modification may be an indicator that some VAT is needed to properly respond to chemotherapy and protect vital organs within the abdomen. However, the biological mechanism explaining how high area of VAT and SAT prolong time to HGSOC outcomes is not well understood. Adipose tissue is responsible for storing energy in the form of lipids, so one hypothesis is that obese patients can sustain the decrease in energy intake associated with cancer treatment because of the availability of energy from the stored adipose tissue, increasing the likelihood of better treatment outcomes (Liu & Xiao, 2013 & Hughes, 2013).

Our meta-analysis suggests a dose-response between BCMs and OS. Although the results were mostly null, VAT and IMAT suggest that the higher BCM tertile may be negatively impacting OS. The results suggest that moderate adipose tissue area could potentially not be harmful, but higher area could impact OS. Similar to our results, a retrospective cohort study by Deluche et al., found that higher IMAT was an independent predictor of worse OS for those with breast cancer (HR = 3.60 95% CI (1.20, 10.8)) (Deluche et al, 2016). Similarly, the MCC/RPCCI study found that high IMAT area was significantly associated with shorter HGSOC OS with an HR of 1.44 (95% CI 1.09, 1.90) (Table 5). Deluche et al.'s study had a sample size of 119 patients and the MCC/RPCCI study had a sample size of 656 participants. Perhaps with a larger sample size our current study would have been able to detect a statistically significant trend for IMAT and OS. IMAT is located within muscles. The infiltration of adipose tissue in muscles can cause sensitivity to insulin, lower muscle strength, power, and quality, potentially resulting in sarcopenia (Waters, 2019).

Strengths and limitations

The main strength of this study is the concept of approaching assessment of body composition utilizing CT scans. There are very few studies that use CT scan based BCMs as potential predictors for OS and recurrence for HGSOC. One of the goals of this study was to evaluate the feasibility of obtaining and using CT scan based BCMs for potential future research.

However, this study had several limitations. The first being, the sample size and missingness of data. With only 77 patients getting treated at Emory clinics meeting the full eligibility criteria, the sample size was small to begin with. However, the missingness of information from electronic medical records, limited the number of observations used in the Cox PH and AFT models. Therefore, there is concern of lack of statistical power and external validity of these results. Second is the potential misclassification of the outcomes. The outcomes of OS and recurrence were based on electronic medical records and vital status updates on LexisNexis. Depending on how often LexisNexis is updated, may influence a participant's vital status classification if their medical records were not up to date (Woolpert et al., 2021). Medical records that did not explicitly state recurrence were assumed to not have a recurrence. If patients sought care elsewhere or moved after their first line treatment outside of the Emory Healthcare system, their medical records would not reflect a recurrence and they would be misclassified as not having had a recurrence. Lastly, MCC/RPCCI adjusted for slightly different factors in their models than the present study. Although it is not anticipated to have made a big impact on the results of the meta-analysis, it does have the potential to distort the point estimates and confidence intervals. Possible reasons for the different model adjustments include differences in racial composition among the sites and availability of data from different methods of gathering covariate information. To improve the results of the meta-analysis, the three datasets should be

combined into one and the models should adjust for the same covariates, or a new data analysis could be undertaken to make the adjustments uniform. Either method would improve the validity of the meta-analysis results.

Public health implications and future research

To date, there are limited studies that use CT scan based BCMs to evaluate their effects on OS and recurrence for patients with HGSOC. Although we did not find many significant results with our data, perhaps with a larger and more diverse sample size (i.e., more women that identify as Black/African American, Asian, and Hispanic), the true effect of BCMs on OS and recurrence can be established and generalizable to all women diagnosed with HGSOC. One way to do this is by expanding the study into additional Emory Healthcare clinic sites since this present study only evaluated women at the Emory University Hospital clinic.

Some of the lessons learned from this study include the importance of data sharing. There were a lot of participants excluded because they came to the Emory Hospital system as a second opinion or after they received a CT-scan during diagnosis elsewhere. Some CT-scans were available, but many were not. For future studies, CT-scan requests, and release forms from participants not found in the hospital's medical record system, would be extremely beneficial. Missingness of information in electronic medical records also needs to be addressed. This study found that FIGO stage was missing from 23.4% of participants records, therefore, pathology reports or operation reports should be included in the medical records or obtained from the patient's physician or pathologist to confirm FIGO stage to limit the amount of missing data.

It is important to further investigate the relationships between CT scan based BCMs and HGSOC outcomes because it could potentially provide a patient specific approach to treatment to maximize OS and decrease the likelihood of recurrence.

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