Neuro-Oncology Advances

7(1), vdae209, 2025 | https://doi.org/10.1093/noajnl/vdae209 | Advance Access date 28 November 2024

Abdominal myosteatosis measured with computed tomography predicts poor outcomes in patients with glioblastoma

Farzaneh Rahmani, Garrett Camps, Olesya Mironchuk, Norman Atagu, David H. Ballard, Tammie L.S. Benzinger, Vincent Tze Yang Chow, Sonika Dahiya, John Evans, Shama Jaswal, Sara Hosseinzadeh Kassani, Da Ma, Muhammad Naeem, Karteek Popuri, Cyrus A. Raji, Marilyn J. Siegel, Yifei Xu, Jingxia Liu, Mirza Faisal Beg, Michael R. Chicoine, and Joseph E. Ippolito

All author affiliations are listed at the end of the article

Corresponding Author: Joseph E. Ippolito, MD, PhD, Mallinckrodt Institute of Radiology, Washington University School of Medicine, 660 South Euclid Avenue, Campus Box 8131, St. Louis, MO 63110, USA (ippolitoj@wustl.edu).

Abstract

Background. Alterations in cellular metabolism affect cancer survival and can manifest in metrics of body composition. We investigated the effects of various body composition metrics on survival in patients with glioblastoma (GBM).

Methods. We retrospectively analyzed patients who had an abdominal and pelvic computed tomography (CT) scan performed within 1 month of diagnosis of GBM (178 participants, 102 males, 76 females, median age: 62.1 years). Volumetric body composition metrics were derived using automated CT segmentation of adipose tissue, skeletal muscle, and aortic calcification from L1 to L5. Univariable and multivariable Cox proportional hazards models were performed separately in males and females using known predictors of GBM overall survival (OS) as covariates. A sex-specific composite score of predisposing and protective factors was constructed using the relative importance of each metric in GBM OS.

Results. Higher skeletal muscle volume and lower skeletal muscle fat fraction were associated with better OS in the entire dataset. A robust and independent effect on GBM OS was seen specifically for fraction of inter/intramuscular adipose tissue to total adipose tissue after correction for known survival predictors and comorbidities. Worse OS was observed with increased abdominal aortic calcification volume in both sexes. There was a significant difference in GBM OS among participants stratified into quartiles based on sex-specific composite predisposing and protective scores.

Conclusion. The relationship between body composition and GBM OS provides an actionable advancement toward precision medicine in GBM management, as lifestyle and dietary regimens can alter body composition and metabolism and from there GBM survival.

Key Points

- Higher myosteatosis, measured by inter/intramuscular fat volume, independently predicts worse glioblastoma (GBM) survival.
- A sex-specific computed tomography composite score of favorable and adverse metrics can stratify patients based on GBM survival.

Importance of the Study

Obesity, traditionally measured with body mass index is related to poor outcomes in several cancers, including glioblastoma (GBM). However, there are a lack of data on how quantitative volumetric abdominal body composition measurements could be used to leverage outcomes assessments in such patients. We propose a novel proof of concept approach to predict GBM outcomes using body composition metrics obtained through computed tomography imaging of the abdomen and pelvis. We report for the first time, an independent relationship between worse overall survival and a higher fraction of inter/intramuscular fat. We also report a survival benefit for individuals with higher muscle mass and lower burden of abdominal aortic atherosclerosis and a sexually dimorphic response on GBM outcomes in some metrics. Our road map to construct sex-specific composite scores of favorable and adverse metrics is a step toward precision medicine, allowing for the incorporation of sex differences in body composition to improve patient outcomes.

Glioblastoma (GBM) is the most common malignant central nervous system (CNS) pathology in adults with an incidence of 3.5 per 100 000 people.[1] Despite advances in surgical techniques and chemoradiation, the prognosis of GBM is extremely poor with a median survival of 8–9 months and 5-year survival of 6.9%.[1–3] One avenue that could provide new insights into improving outcomes in these patients is by understanding how systems physiology can both influence and be influenced by tumorigenesis within the CNS.

Obesity as measured with body mass index (BMI) or visceral adiposity is associated with mortality in several cancer types including GBM.[4] Higher BMI, particularly in the context of overweight and obesity, has been linked to conflicting findings: some studies report lower progression-free survival in GBM patients,[5,6] while others suggest higher overall survival (OS) in newly diagnosed GBM patients[7,8] with higher BMI. Higher abdominal adiposity measured as waist circumference is also related to worse OS in GBM.[4,7] Sarcopenia, characterized by reduced muscle volume and elevated intramuscular fat, has synergistic effects with visceral adiposity in predicting increased cancer mortality,[9,10] including GBM mortality when measured in the head.[11] Given these observations, it is possible that quantification of abdominal body composition could be a more robust source of metabolism estimation in GBM patients compared to BMI alone, as it allows for simultaneous estimation of visceral, subcutaneous, and intramuscular adipose tissue contents as well as various muscle groups. Furthermore, biomarkers derived from abdominal and pelvic organs could provide insights into alternative mechanisms by which cellular metabolism can affect cancer survival.

Interestingly, sex differences in body composition exist, where males have higher amounts of visceral fat and muscle mass and females have higher amounts of subcutaneous fat.[12] This has implications in cancer outcomes, as sex differences in phenotype and cellular metabolism affect cancer survival,[13–15] and those males with GBM typically have worse survival than females.[13,16,17] Furthermore, our group has used abdominal computed tomography (CT) to demonstrate an interaction between visceral fat and sex predicting survival in renal cell carcinoma, pancreatic cancer, and lymphoma.[14,18,19] This raises the question whether abdominal body composition metrics could be used to predict survival differently in males and females with GBM.[20,21]

To our knowledge, the association between abdominal body composition measures and GBM outcomes has not been evaluated. In this study, we examined the association between abdominal body composition metrics, including sex differences, in predicting OS in patients diagnosed with GBM.

Materials and Methods

Participants

Through a retrospective cohort design, we used participants who were recruited from the Multi-Center Intraoperative MRI (iMRI) Neurosurgery Database (I-MiND). I-MiND is a prospective multisite Research Electronic Data Capture (REDCap) registry, supported by an educational grant from the IMRIS intraoperative MRI system, with ongoing recruitment of patients receiving preoperative MRI for resection of brain tumors.[22] For this study, we first identified all I-MiND participants who were recruited from referrals to the Barnes-Jewish Hospital System—affiliated with Washington University School of Medicine—between January 2006 and January 2017 and had at least one abdominal and pelvic CT scan at any time in their medical record. The date of brain MRI at the time of recruitment in the study was considered as diagnosis or baseline date. The following additional inclusion criteria were then applied to select participants for the current study: (1) having a postoperative tissue diagnosis of GBM, (2) GBM being the only malignancy on record for that patient, and (3) CT performed with ±1 month of diagnosis or baseline date. This led to the inclusion of 178 participants (102 males, 76 females, median age [Q1–Q3]: 62.1 [56.3–73.1] years). If multiple CT scans were available for 1 participant, the scan closest to the baseline date was selected for analyses. All CT scans were contrast-enhanced. The most common indication for CT scans was postoperative abdominal pain (34.6%), suspected bowel obstruction (23.1%), epigastric pain (8%), and suspected abdominal infection (5.9%).

Abdominal and Pelvic CT Scan Body Composition Analysis

Body composition analysis was performed using the Data Analysis Facilitation Suite (DAFS, version 3)

platform provided by Voronoi Health Analytics (https://www.voronoihealthanalytics.com). This software has been validated in the assessment of body composition for outcomes assessment using CT datasets and optimized to work effectively for both contrast and non-contrast images.[9,23–25] In brief, individual axial CT images are fed into a nonlinear image processing algorithm that provides a multi-slice, multi-tissue segmentation of the entire field of view and labeling of each axial slice by the vertebral body present on each slice. For this study, body composition metrics were all measured as a volume (cm^3) encompassing the entire L1–L5 vertebral segments. The segmentations and slice labels generated by DAFS were reviewed and manually corrected, if necessary, by a subspecialized radiologist with 15 years of experience in abdominal imaging.

Supplementary Table 1 provides a description of body composition variables included from the DAFS segmentation output. A total of 11 variables in the volumes (cm^3) and ratios of body composition metrics were extracted or synthesized from the DAFS output that included the inter/intramuscular adipose tissue (IMAT), visceral adipose tissue (VAT), subcutaneous adipose tissue (SAT), total adipose tissue (TAT), iliopsoas muscles, total skeletal muscle, and abdominal aortic calcifications (AAC). Supplementary Figure 1 demonstrates examples of axial CT images and corresponding DAFS outputs for 2 representative participants with similar demographics and tumor size and location.

Demographic and Clinical Parameters

The total OS was recorded as the time difference, in months, between the date of surgery and the last date the participant was recorded alive. The following demographic and clinical variables were obtained from the electronic medical record: (1) age at diagnosis, (2) sex, (3) race, (4) height, (5) weight, (6) BMI at the time of surgery, (7) history of diabetes mellitus (DM), (8) hypertension (HTN), (9) chronic kidney disease (CKD), (10) current or past history smoking, (11) methylation status of O^6-methylguanine-DNA methyltransferase (MGMT) gene promoter—which, if methylated, confers favorable response to treatment,[26] (12) isocitrate dehydrogenase (IDH) mutation status, (13) extent of tumor resection including gross total resection, subtotal resection, or biopsy only, (14) adjuvant chemotherapy, (15) adjuvant radiation therapy, (16) last follow-up date, and (17) last recorded alive date.

As a standard tool for preoperative assessment of physical status, the American Society of Anesthesiologists (ASA) score measured according to the latest available update was also extracted from the I-MiND database, with ASA scores 1–2 representing a healthy to mildly limited individual and scores 3–4 representing severe systemic illness with or without threat to life.[27] Presence or absence of comorbidities like diabetes (DM), hypertension (HTN), and CKD was determined either based on the explicit mention of the condition or the use of related medications, such as glycemic control agents or antihypertensives upon the extensive review of electronic medical records.

Statistical Analysis

Statistical analyses were performed using the R software version 4.3.2 (https://www.r-project.org/). Between group comparisons, univariable, and multivariable Cox proportional hazards models were performed using the R packages *dplyr*, *survival*, and *survminer*. All continuous variables including demographic, clinical, and body composition metrics were tested for the assumption of normality of residuals using the Shapiro–Wilks test and described using median and interquartile range if the normality assumption was not met or mean ± standard deviation if the assumption was met. Between groups, comparisons of males and females were conducted using the Mann–Whitney *U* test or *t*-test for continuous variables and the Chi-square or Fisher's exact for categorical variables.

The R package *survival* was used to perform Cox proportional hazards univariable regression models to identify variables that significantly predicted OS separately in the entire dataset, males, and females. Analyses were conducted using both continuous form of body composition variables and dichotomized variables based on population median values (50th percentile). A hazard ratio (HR) below 1 indicates a protective effect and better OS. Multivariable analysis through stepwise selection was performed using the *step* function from package *StepReg* to select variables for multivariable models by iteratively adding and removing variables based on statistical criteria. A *P*-value threshold of 0.25 was set for a variable to enter the model and *P*-value of 0.2 was used to keep a variable in the model. A final multivariable regression model was then fit using variables with *P*-value of <.1 with the addition of demographic and clinical covariates irrespective of their *P*-values. These covariates included: age at diagnosis, ASA score, MGMT promoter methylation status, receipt of adjuvant chemotherapy, receipt of adjuvant radiation therapy, extent of resection, history of HTN, DM, or CKD, and history of past or current smoking. Importantly, since the majority of I-MiND participants were recruited before IDH mutation status became standard for glial tumor classification, only 54.5% of our participants had this information available, among which only 1 participant had IDH mutation. Therefore, IDH mutation status was not used in any of the univariable or multivariable survival analyses.

All *P*-values were corrected for multiple comparisons using the Benjamini–Hochberg method.[28] A *P*-value of <.05 was considered statistically significant.

Composite Score Calculation for Outcomes

Functions *xgb.train* and *xgb.importance* from the R package *xgboost* were used to evaluate the relative importance of significant univariable body composition metrics in predicting GBM OS. Variables that were significant in the univariable analyses were used to craft separate predisposing and protective CT composite scores in males and females. We first used a tree-learning algorithm with 100 boosting rounds to partition the data into training (80%) and test (20%) datasets based on the OS status to generate feature importance matrices for these predisposing and protective variables separately for males and females.[29] Next, to construct this composite score, we normalized the selected body composition metrics and multiplied them by their respective normalized gains (ie, weights) from the feature importance matrices and

subsequently summed them for each participant. Finally, we used Cox proportional hazards and pairwise log-rank test models to evaluate survival distribution between participants in different quartiles of the composite scores and the utility of 25th and 75th percentile as arbitrary cutoffs.

Results

Patient Demographic and Clinical Characteristics

Table 1 demonstrates the demographic and clinical characteristics of participants stratified by sex showing no difference in age, race, MGMT status, IDH mutation status, follow-up time, or treatment between males and females. Table 2 demonstrates differences in body composition metrics between sexes where males had larger absolute and fractional visceral adipose tissue (VAT and VAT/TAT) and larger skeletal muscle volume including iliopsoas muscle volume. Females, on the other hand, had a larger fractional SAT and skeletal muscle fat fraction (SAT/TAT and SKM fat fraction).

Before investigating body composition metrics, we used univariable Cox proportional hazard models to investigate GBM OS in relation to known predictors of GBM survival. As seen in Table 2 younger age, lower ASA scores (1 and 2), gross total resection of the tumor, receipt of adjuvant chemotherapy, and receipt of adjuvant radiation therapy were associated with improved OS in both males and females. Comorbidities such as DM, CKD, smoking, and overweight (BMI $\geq$ 25 kg/m^2) or obesity (BMI $\geq$ 30 kg/m^2) were not associated with significant differences in OS in our population, while there was a 2 times increased risk of death among females with hypertension (Table 2). Among participants with available IDH mutation status, all but one male participant had wild-type IDH. As a result, survival analyses based on IDH status were not performed.

Higher Fractional IMAT is an Independent Predictor of OS in GBM

Univariable analyses using body composition metrics as continuous variables revealed that the most consistent adipose tissue metric that was associated with significantly poorer GBM OS when all patients (ie, males and females) were considered as a higher absolute and fractional inter/intramuscular adipose tissue (IMAT and IMAT/TAT) (Figure 1 and Table 2 middle panel). Interestingly, when males and females were analyzed independently, this significant finding held in males, but not females. This pattern was also observed for IMAT/TAT when it was considered as a dichotomous variable with the median as a threshold. For example, fractional IMAT (IMAT/TAT) above the median was associated with an increased risk of death in both males (HR [95% CI]: 1.8 [1.2–2.8]; $P = .004$) and the entire dataset (HR [95% CI]: 1.5 [1.1–2.1]; $P = .01$) (Figure 1 and Table 2 bottom panel). Additionally, in males only, a higher fraction of subcutaneous adipose tissue (SAT/TAT) above population median, was predictive of better outcome (HR [95% CI]: 0.6 [0.4–0.9]; $P = .04$) (Table 2 bottom panel).

When considered in a multivariable model, higher fractional IMAT emerged as independently associated with poorer outcomes in the entire dataset and males ($P = .007$ and $P = .001$, respectively) (Table 3 and Figure 2). Expectedly, IMAT was not selected during the stepwise regression model in females and therefore not evaluated in the multivariable analyses. SAT/TAT was selected for multivariable analyses in the entire cohort and men but did not retain significance in either group (Table 3). Together, these findings indicate a robust biological effect of IMAT that is associated with worse OS in GBM, especially in males.

Skeletal Muscle Mass and Skeletal Muscle Fat Faction Predict Worse OS in GBM

Because of the significant results with IMAT, muscles were then evaluated using 3 different approaches: the volume of the iliopsoas muscles, the total volume of all abdominal muscles (including the iliopsoas), referred to as total SKM volume, and the SKM fat fraction. In univariable analyses using continuous variables, the most robust marker of survival was the SKM fat fraction which was predictive of worse OS in all patients, as well as in males and females separately (Table 2 middle panel) (HR [95% CI]: 2.8 [1.4–5.5]; $P = .03$). Previous studies have demonstrated a beneficial effect of muscle mass on brain tumor patients based upon masseter muscle measurements.[11] In our cohort, total skeletal muscle volume as well as iliopsoas volume were both associated with better OS in all patients, but not in males or females separately (Figure 1 and Table 2 middle panel).

The iliopsoas muscle volume was the only muscular health marker that survived in the stepwise regression model for the entire cohort and males and was therefore included in the multivariable regression model. However, it did not demonstrate independent significance when adjusted for clinical markers or survival-related comorbidities in either group (Table 3).

Abdominal Aortic Atherosclerosis is Associated With Worse Outcomes in Females With GBM

In addition to fat and muscle, we measured abdominal aortic calcification volume from L1 to L5, which is a marker of cardiovascular health. Using the group medians as cutoff, participants with higher volume of AAC had worse outcomes, both in the entire dataset (HR [95% CI]: 2 [1.04–2.7]; $P < .001$) and across sex groups (HR [95% CI]: 1.8 [1.2–2.7]; $P = .009$ in males and HR [95% CI]: 2.2 [1.3–3.8]; $P = .002$ in females) (Figure 1 and Table 2 bottom panel). AAC were selected for multivariable analyses in females but did not retain significance as an independent predictor of OS (Table 3).

A CT-Assigned Composite Predisposing Score Predicts GBM Survival

We used a tree-learning model to evaluate the relative importance of significant body composition metrics and to craft weighted sums of these metrics as composite

Table 1. Summary of Patients Demographic and Clinical Information

	Total (*N* = 178)	Male (*N* = 102)	Female (*N* = 76)	*P*-value[b]
Demographic and clinical[a]				
Age at diagnosis, y	62.1 (55.1–72.3)	62.3 (54.9–71.8)	62.1 (56.3–73.1)	.3
Race, *n* (%)				
Asian	2 (1.1)	1 (1)	1 (1.3)	.7
African American	12 (6.7)	8 (7.8)	4 (5.3)	
Caucasian	164 (92.1)	93 (91.2)	71 (93.4)	
Follow-up time, months	37.7 (21.5–59.1)	33.2 (20.7–56.7)	42.7 (24.2–62)	.1
ASA score, *n* (%)				
1	2 (1.1)	1 (1)	1 (1.3)	.8
2	33 (18.5)	22 (21.6)	11 (14.5)	
3	113 (63.5)	62 (60.8)	51 (67.1)	
4	9 (5.1)	5 (4.9)	4 (5.3)	
Unknown	21 (11.8)	12 (11.8)	9 (11.8)	
Medical comorbidities, *n* (%)				
HTN	90 (50.5)	52 (50.9)	38 (50)	.9
DM	24 (13.4)	14 (13.7)	10 (13.1)	.9
CKD	21 (11.8)	13 (12.7)	8 (10.5)	.6
Smoking	24 (13.4)	13 (12.7)	11 (14.4)	.9
BMI, kg/m^2	28 (24–31)	28.2 (24.7–31.3)	27.3 (23.6–31.3)	.7
MGMT status, *n* (%)				
Methylated	37 (20.8)	24 (23.5)	13 (17.1)	.3
Non-methylated	80 (44.9)	41 (40.2)	39 (51.3)	
Unknown	61 (34.4)	37 (36.3)	24 (31.6)	
IDH status, *n* (%)				
Wild-type	96 (54)	63 (61.8)	33 (43.4)	
Mutated	1 (0.5)	1 (1)	0 (0)	.3
Unknown	81 (45.5)	38 (37.2)	43 (56.6)	
Extent of resection, *n* (%)				
Gross total resection	54 (30.3)	26 (25.5)	28 (36.8)	.1
Subtotal resection	79 (44.4)	52 (51)	27 (35.5)	
Biopsy only	45 (25.3)	24 (23.5)	21 (27.6)	
Adjuvant chemotherapy, *n* (%)				
Yes	133 (74.7)	77 (75.5)	56 (73.7)	.9
No	26 (14.6)	15 (14.7)	11 (14.5)	
Unknown	19 (10.7)	10 (9.8)	9 (11.8)	
Adjuvant radiation therapy, *n* (%)				
Yes	135 (75.8)	79 (77.5)	56 (73.7)	.8
No	23 (12.9)	12 (11.8)	11 (14.5)	
Unknown	20 (11.2)	11 (10.8)	9 (11.8)	
Adipose tissue[a]				
IMAT, cm^3	276 (197–359)	270 (197–359)	280 (202–355)	.8
VAT, cm^3	2339 (1462–3448)	3045 (1850–4155)	1636 (1119–2500)	***<.001***
SAT, cm^3	3344 (2216–4539)	3065 (2057–4226)	3713 (2456–4903)	.07
TAT, cm^3	6191 (4452–8413)	6588 (4603–8859)	5589 (3845–7554)	.1
IMAT/TAT	0.04 (0.03–0.06)	0.04 (0.03–0.05)	0.04 (0.03–0.06)	.3
VAT/TAT	0.4 (0.3–0.5)	0.5 (0.3–0.5)	0.3 (0.2–0.3)	***<.001***
SAT/TAT	0.6 (0.5–0.7)	0.5 (0.4–0.6)	0.7 (0.6–0.7)	***<.001***

Table 1. Continued

	Total (*N* = 178)	Male (*N* = 102)	Female (*N* = 76)	*P*-value[b]
Skeletal muscle[a]				
Total SKM volume, cm^3	1512 (1869– 2473)	2038 (2410– 2763)	1259 (1442– 1610)	***<.001***
Iliopsoas muscle volume, cm^3	271.7 (195.7–372.6)	355.7 (299.7–433.4)	190.3 (161.2–217.1)	***<.001***
SKM fat fraction	0.09 (0.14–0.21)	0.07 (0.11–0.16)	0.13 (0.19–0.25)	***.01***
Vascular[a]				
Aortic calcification volume, cm^3	0.1 (0–1.1)	0.1 (0–1.1)	0.1 (0–0.9)	.2

Abbreviations: ASA score = American Society of Anesthesiologists physical status classification; BMI = body mass index [weight (kg) / height $(m)^2$]; CKD = chronic kidney disease; DM = diabetes mellitus; HTN = hypertension; IMAT = inter/intramuscular adipose tissue; MGMT = O^6-methylguanine-DNA methyltransferase gene promoter methylation; SAT = subcutaneous adipose tissue; SKM fat fraction = ratio of intramuscular adipose tissue over the total skeletal muscle volume, IMAT/(SKM + IMAT); smoking = current or former smoker; TAT = total adipose tissue; total SKM volume = total skeletal muscle; VAT = visceral adipose tissue.
[a]All *continuous* variables are described as median (first quartile to third quartile) as none of the variables met the normality assumption. *Categorical* variables are described as frequency (percentage).
[b]*P*-values of Mann–Whitney *U* test comparing the demographic and clinical variables between males and females. All *P*-values are corrected for multiple comparison using the Benjamini–Hochberg method. Significant *P*-values are bolded and italicized.

predisposing and protective scores separately in the entire cohort, male and female. Variables that were significant in the univariable analyses were used in the composite predisposing and protective factor analyses. For the entire dataset, the composite predisposing score included the following variables: IMAT, IMAT/TAT, SKM fat fraction, and AAC (Table 2). The composite protective score incorporated iliopsoas and total skeletal muscle volumes, with SAT/TAT added specifically for males (Table 2).

In the entire dataset having a composite predisposing score above 75th percentile was associated with 1.9 times higher risk of death (HR [95% CI]: 1.9 [1.3–2.7], $P < .001$), while scoring below 25th percentile in composite protecting score—lower cumulative protective metrics—was associated with significantly improved OS (HR [95% CI]: 0.6 [0.4–0.9], $P = .02$). Those with lowest burden of the adverse factors (composite predisposing within first quartile) had 50% higher chance of survival compared to those in fourth quartile (HR [95% CI]: 0.5 [0.2–0.8], $P < .001$) (Figure 3A). Similarly, a cumulatively higher burden of protective factors—fourth quartile in composite protecting score—conferred 60% higher OS rates compared to those in the first quartile (HR [95% CI]: 0.4 [0.3–0.6], $P < .001$) (Figure 3B).

In males, having a cumulatively higher burden of predisposing factors—aka. composite predisposing score above 25th percentile—was associated with 90% lower OS in GBM (HR [95% CI]: 1.9 [1.3–2.7], $P < .001$). Additionally, scoring above the 75th percentile in the composite predisposing score in males was associated with significantly worse OS when compared to those with a composite predisposing score below the 25th percentile (Figure 3C). When the composite protective score was used, there was a statistically significant difference in OS of males, scoring above 25th percentile compared to those below this cutoff (HR [95% CI]: 0.5 [0.3–0.9], $P < .03$) (Figure 3D).

In females, OS was significantly worse in those with the higher composite predisposing score in the third and fourth quartiles who had a higher burden of predisposing scores—compared to those within the first quartile—lower burden of predisposing scores (Figure 3E). Similarly having a higher composite protective score in quartile 4 was associated with higher chances of survival compared with composite protective score in the first and second quartile (Figure 3F). On the other hand, scoring below 25th percentile in the composite protecting score conferred a 50% increased risk of death when compared to scores below 25th percentile (HR [95% CI]: 0.5 [0.3–0.8], $P = .007$) (Figure 3F).

Discussion

Genetic and acquired variations in cellular biology and metabolism dynamically shape individual differences in body composition throughout the lifetime. The idea behind using body composition metrics to predict cancer survival is based on the premise that the cellular mechanisms that govern differences in body composition could alter susceptibility to different cancer types, thus affecting cancer cell biology and survival outcomes. Of these, visceral adiposity and sarcopenia are associated with increased overall and cause-specific mortality across several cancer types.[10,30] While studies have linked obesity (measured by BMI and waist circumference) and temporalis muscle sarcopenia to worse OS in GBM,[4,7,11] there are a lack of data on how the distribution and composition of adipose tissue, skeletal muscle, and vascular biomarkers might relate to survival in these patients.

Quantitative imaging of the abdomen and pelvis enables simultaneous measurement of a variety of body composition metrics that cannot be achieved through brain imaging alone. Using participants with newly diagnosed GBM we demonstrate proof of concept for a novel paradigm to predict GBM outcomes using abdominal and pelvic body composition metrics obtained through CT imaging. We report for the first time, a relationship between worse OS in GBM and higher IMAT, lower skeletal muscle mass, and higher volume of AAC in the abdomen and pelvis. Notably,

Table 2. Univariable Models to Predict Overall Survival in GBM using Demographic, Clinical, and Continuous Versions of Body Composition Metrics

Variable	HR [95% CI] Total[a]	*P*-value Total[b]	HR [95% CI] Male[a]	*P*-value Male[b]	HR [95% CI] Female[a]	*P*-value Female[b]
Demographic and clinical variables						
Age at diagnosis	1.03 [1.01–1.04]	***.0001***	1.02 [1.004–1.04]	***.01***	1.04 [1.01–1.06]	***.002***
Race[a]						
African American	1.1 [0.5–2.2]	.6	1.2 [0.5–2.8]	.6	1 [0.3–3.5]	.8
Asian	1 [0.2–4.1]	.8	3.5 [0.4–26]	.2	0.6 [0.5–4.6]	.6
High ASA score[a]	1.6 [1.06–2.4]	***.02***	1.8 [1.06–3.1]	***.03***	1.3 [0.7–2.5]	.4
Comorbidities, n (%)						
HTN	1.3 [0.9–1.8]	.06	1.05 [0.9–1.6]	.8	2 [1.2–3.2]	***.01***
DM	1.4 [0.8–2.3]	.1	1.1 [0.6–2.2]	.6	2 [0.9–4.3]	.07
CKD	0.7 [0.4–1.3]	.3	0.8 [0.4–1.8]	.2	0.5 [0.2–1.6]	.7
Smoking	1.1 [0.8–1.6]	.5	1.3 [0.8–2]	.4	1 [0.6–1.7]	.7
Overweight[a]	0.9 [0.6–1.3]	.8	0.7 [0.5–1.2]	.2	1.2 [0.7–2.1]	.3
Obese[a]	1.07 [0.7–1.5]	.6	1.07 [0.7–1.7]	.7	1.1 [0.8–1.9]	.6
MGMT promoter[a]						
Methylated	0.7 [0.5–1.1]	.1	0.7 [0.4–1.3]	.2	0.7 [0.3–1.4]	.3
Adjuvant chemotherapy[a]						
Yes	0.3 [0.2–0.5]	***<.001***	0.3 [0.2–0.5]	***<.001***	0.3 [0.1–0.5]	***<.001***
Unknown	0.6 [0.3–1.2]	.1	0.5 [0.2–1.2]	.1	0.8 [0.3–2]	.6
Adjuvant radiation[a]						
Yes	0.3 [0.2–0.5]	***<.001***	0.3 [0.2–0.7]	***.005***	0.3 [0.2–0.6]	***<.001***
Unknown	0.7 [0.4–1.4]	.3	0.7 [0.3–1.7]	.4	0.8 [0.3–2]	.6
Extent of resection[a]						
GTR	0.2 [0.1–0.4]	***<.001***	0.2 [0.1–0.4]	***<.001***	0.3 [0.2–0.6]	***<.001***
Subtotal	0.3 [0.2–0.5]	***<.001***	0.1 [0.07–0.3]	***<.001***	0.5 [0.2–0.8]	***.01***
Body composition metrics as continuous variables[c]						
IMAT volume	1.001 [1.002–1.003]	***.02***	1.002 [1–1.003]	***.03***	1.001 [0.9–1.003]	.2
SAT volume	1 [0.99–1.001]	.5	0.99 [0.98–1.001]	.2	1 [0.9–1.0001]	.8
VAT volume	1 [0.99–1.001]	.7	1 [0.9–1.0002]	.6	1.001 [0.9–1.003]	.3
TAT volume	1 [0.99–1.001]	.8	1 [0.9–1.0001]	.6	1 [0.9–1.001]	.6
IMAT/TAT	5.5 [2–14]	***<.001***	9.7 [2.7–34.6]	***<.001***	2.3 [0.4–12]	.3
SAT/TAT	0.4 [0.1–1.5]	.1	0.2 [0.03–1.2]	.08	0.08 [0.004–1.7]	.1
VAT/TAT	1.5 [0.5–4.2]	.4	2.3 [0.4-12]	.3	4.3 [0.5-37]	.1
Total SKM volume	0.96 [0.93–1]	***.02***	0.99 [0.98–1.001]	.1	0.98 [0.97–1]	.053
Iliopsoas volume	0.98 [0.96–0.99]	***.02***	0.97 [0.99–1.001]	.06	0.96 [0.91–1.01]	.1
SKM Fat fraction	2.8 [1.4–5.5]	***.002***	3 [1.1–8.2]	***.02***	3.4 [1.1–12]	***.049***
AAC volume	1.2 [1.04–1.4]	***.01***	1.1 [0.9–1.3]	.2	1.6 [1.2–2.3]	***.001***
Body composition metrics as dichotomous variables[c]						
IMAT volume	1.3 [0.9–1.7]	.1	1.1 [0.7–1.7]	.5	1.2 [0.7–1.9]	.5
SAT volume	0.9 [0.7–1.3]	.6	0.7 [0.4–1]	.053	1 [0.6–1.7]	.9
VAT volume	0.9 [0.7–1.3]	.7	1 [0.7–1.5]	.9	1.4 [0.8–2.3]	.2
TAT volume	1.1 [0.8–1.5]	.7	1.1 [0.7–1.6]	.7	1 [0.6–1.7]	.9
IMAT/TAT	1.5 [1.1–2.1]	***.01***	1.8 [1.2–2.8]	***.004***	1.3 [0.8–2.2]	.2
SAT/TAT	1.04 [0.8–1.4]	.8	0.6 [0.4–0.9]	***.04***	0.6 [0.4–1.04]	.07
VAT/TAT	0.9 [0.7–1.3]	.6	1.4 [0.9–2.2]	.1	1.5 [0.9–2.5]	.1
Total SKM volume	0.8 [0.6–1.1]	.1	0.7 [0.5–1.1]	.1	0.6 [0.4–1.02]	.1
Iliopsoas volume	0.9 [0.7–1.3]	.6	0.8 [0.5–1.2]	.2	0.7 [0.4–1.2]	.2

Table 2. Continued

Variable	HR [95% CI] Total[a]	*P*-value Total[b]	HR [95% CI] Male[a]	*P*-value Male[b]	HR [95% CI] Female[a]	*P*-value Female[b]
SKM Fat fraction	1.5 [1.1–2]	.01	1.6 [1–2.4]	***.03***	1.4 [0.8–2.3]	.2
AAC volume	2 [1.4–2.7]	***<.001***	1.8 [1.2–2.7]	***.009***	2.2 [1.3–3.8]	***.002***

Abbreviations: AAC = abdominal aortic calcification; ASA score = American Society of Anesthesiologists physical status classification; BMI = body mass index; CKD = chronic kidney disease; DM = diabetes mellitus; GBM = glioblastoma; HR [95% CI] = hazard ratio with 95% confidence interval; HTN = hypertension; IMAT = intramuscular adipose tissue; MGMT = O^6-methylguanine-DNA methyltransferase gene promoter methylation; SAT = subcutaneous adipose tissue; SKM = total skeletal muscle; SKM fat fraction = ratio of IMAT over the SKM volume; smoking = current or former smoker; TAT = total adipose tissue; VAT = visceral adipose tissue.
[a]Reference levels: race: *Caucasian*; ASA score: *low ASA scores (1–2)*; *overweight*: BMI ≥ 25 kg/m^2; *obese*: BMI ≥ 30 kg/m^2; MGMT and IDF: *un-methylated promoter;* resection: *biopsied only (no resection)*; adjuvant chemotherapy or radiation therapy: *no treatment*; HTN, DM, and CKD: *absence of these comorbidities*. Smoker: current or former smoker to *never smoker*. Hazard ratio above 1 indicates increased odds of death from GBM.
[b]All *P*-values were corrected for multiple comparisons using Benjamini–Hochberg method. Significant *P*-values are bolded and italicized.
[c]*Middle panel*: hazard ratios are reported for body composition metrics as *continuous variables* [per each unit increase of the variable, 1 cm^3 for volumes and 1 for ratios. *Bottom Panel*: hazard ratios are reported for body composition metrics as *dichotomous* variables using 50th percentile as cut off (values above median vs. values below median).

sex differences in the effects of these biomarkers on GBM patient survival may also be present. Using a tree-learning algorithm, we curated composite scores based on the relative importance of predisposing and protective body composition metrics that were able to predict OS in GBM. The utility of our proposed method is further supported by the ubiquitous use of CT imaging in clinical cancer care.

Obesity is not only a risk for all-cause mortality but is also related to higher cancer-related deaths, a relationship that is heavily modified by sex and distribution of adiposity.[31–33] Specifically, higher VAT associated with worse outcomes in cancers.[34] Conversely, increased SAT predicts better OS in gastrointestinal, lung, and renal cancers.[35] While we observed favorable outcomes in males with SAT/TAT above the 50th percentile, no significant difference in OS was found related to VAT or VAT/TAT. This could be due to the generally lower survival rates in GBM patients leaving little variability that diminishes the impact of these body composition metrics as a result (aka. survival bias).[36] Another possible explanation for lack of significant effect with dichotomized values involves the optimization of the cutoff point in our specific population as we used the 50th percentile as an arbitrary cutoff. Future studies can focus on optimizing age and sex-specific cutoffs for our population. Improved OS in males with higher relative SAT is in keeping with the male-dominant all-cause mortality risk related to higher VAT and low SAT reported in the literature.[30,34]

We report an effect of total skeletal muscle volume and iliopsoas muscle volume as significant predictors of OS in GBM patients across the entire dataset. Both IMAT/TAT and SKM fat fraction are markers of fatty infiltration in skeletal muscle, normalized to total adipose tissue and skeletal muscle volume, respectively. This finding is consistent with reports linking sarcopenia—especially when combined with obesity, known as sarcopenic obesity—to worse disease-specific survival across various malignancies.[37,38] In GBM specifically, temporalis muscle thickness, a surrogate marker of sarcopenia, is independently related to improved OS.[11,39–41] Our findings, add on to the existing literature by demonstrating skeletal muscle fat fraction can be used as a novel biomarker of skeletal muscle health, outperforming skeletal muscle volume in GBM OS prediction. On the other hand, fatty infiltration of skeletal muscle is shown to predict worse survival in critically ill patients,[42,43] and is associated with comorbidities such as CKD and diabetes.[44,45] The finding that IMAT/TAT is an independent predictor of OS in GBM, even after adjusting for clinical predictors and comorbidities like CKD and DM, suggests a robust and independent influence on GBM survival.

An important finding in our study is the effect of AAC in predicting OS in all patients, and specifically in females with GBM as a continuous variable. AAC are nearly as strong as coronary artery calcifications in predicting cardiovascular events.[46] Our findings are supported by evidence from the literature that AAC is a robust predictor of mortality from cardiovascular disease, especially in females.[46–48] To the extent that cardiovascular events affect OS in GBM, the relationship between AAC and OS in GBM in our cohort is likely reflective of how much aortic calcifications are representative of the overall atherosclerotic disease burden within the body. In keeping with this theory, internal carotid artery calcium scores are shown to be related to OS in GBM.[49] The relationship between AAC and OS in our cohort could also to some extent, be indicative of the inflammatory underpinnings of atherosclerosis. Atherosclerosis itself is a chronic inflammatory disease and its progression is worsened by other chronic inflammatory conditions.[50] Inflammation is also associated with GBM tumorigenesis and progression, as demonstrated by the correlation between traumatic brain injury and GBM, along with the inflammatory characteristics of the tumor microenvironment.[51,52] Consequently, the observed correlation between AAC and GBM OS may stem from shared inflammatory underpinnings.

Finally, we propose a road map to build composite scores based on the relative importance of these metrics that provide a significant predictive value for GBM survival. This is a proof of concept that quantitative assessment of

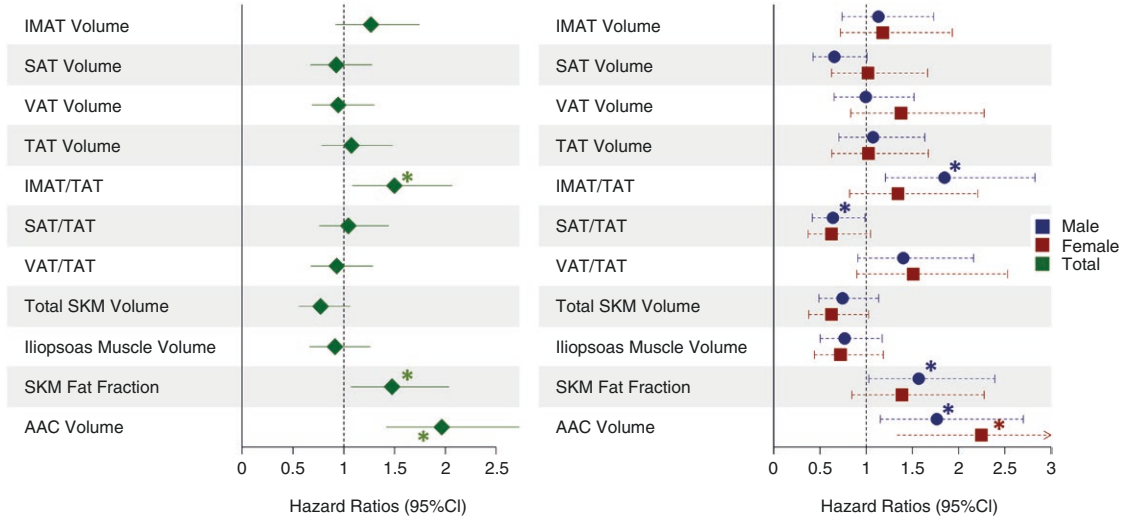

Figure 1. Univariable glioblastoma overall survival models using adipose tissue and skeletal muscle metrics.

*Asterisks denote significant univariable Cox-regression models using the group median value (50th) percentile as cutoff (Table 2, lower panel). All variables represent volumes of the respective metrics measured from the level of L1 through the L5 vertebrae. Abbreviations: AAC = abdominal aortic calcification; IMAT = intramuscular adipose tissue volume; SAT = subcutaneous adipose tissue volume; SKM fat fraction = ratio of IMAT over the SKM volume; SKM = total skeletal muscle (iliopsoas + abdominal wall muscles); TAT = total adipose tissue volume; VAT = visceral adipose tissue volume.

Table 3. Multivariable Models to Predict Overall Survival in GBM Using Body Composition Metrics as Continuous Variables

	HR [95% CI][a]	*P*-value[b]
Total		
SAT/TAT	0.9 [0.2–3.9]	.9
SAT	0.99 [0.98–1.02]	.1
Iliopsoas volume	0.98 [0.97–1.04]	.2
IMAT/TAT	4.4 [1.5–13]	***.007***
Female		
AAC volume	1.001 [0.64–1.56]	.9
Male		
IMAT/TAT	9.6 [2.4–19]	***.001***
SAT/TAT	0.2 [0.02–1.9]	.1
Iliopsoas volume	0.98 [0.95–1.08]	.2

Abbreviations: AAC = abdominal aortic calcifications; GBM = glioblastoma; HR [95% CI] = hazard ratio with 95% confidence interval; IMAT = intramuscular adipose tissue; SAT = subcutaneous adipose tissue; TAT = total adipose tissue; VAT = visceral adipose tissue.

[a]Body composition variables selected for the multivariable comparison in each group, as described in the methods section, were imputed in a multivariable Cox proportional hazards model with the following covariates: (1) age at diagnosis, (2) American Society of Anesthesiologists (ASA) physical status classification, (3) MGMT promoter methylation status, (4) receipt of adjuvant chemotherapy, (5) receipt of adjuvant radiation therapy, (6) extent of resection, (7) history of hypertension, (8) history of diabetes, (9) history of chronic kidney disease, and (10) history of past or current smoking. Hazard ratios above 1 indicate increased risk of death from GBM.

[b]All *P*-values are corrected for multiple comparisons using Benjamini–Hochberg method. Significant *P*-values are bolded and italicized.

abdominal imaging biomarkers could provide insights into the overall health of the cancer patient and from there, predict outcomes. Given the life-long effects of diet, exercise, and metabolism on body composition, our findings have implications for lifestyle and dietary interventions in conjunction with conventional therapy to improve GBM outcomes.

Limitations

Our study is limited by its retrospective nature. Since the majority of I-MiND participants were recruited before IDH mutation status became standard for glial tumor classification, only 54.5% of our participants had this information available and we could not perform survival analyses

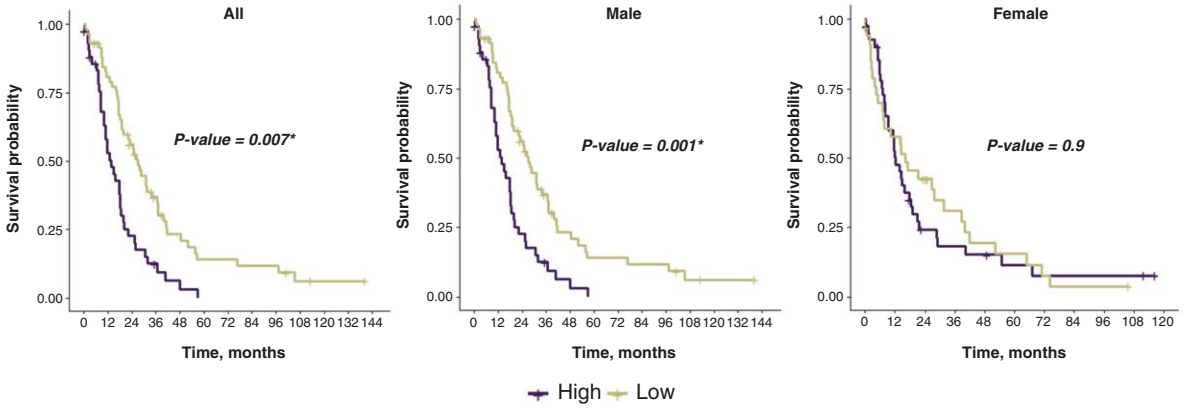

Figure 2. Kaplan–Meier survival curves in individuals with high vs. low relative intramuscular adipose tissue.

**P*-values from adjusted pairwise log-rank test denoting significant comparisons between high (above median [50th percentile]) vs. low (below median [50th percentile)] IMAT/TAT in a multivariable Cox proportional hazards model. Covariates included (1) age at diagnosis, (2) American Society of Anesthesiologists (ASA) physical status classification, (3) MGMT promoter methylation status, (4) receipt of adjuvant chemotherapy, (5) receipt of adjuvant radiation therapy, (6) extent of resection, (7) history of hypertension, (8) history of diabetes, (9) history of chronic kidney disease, and (10) history of past or current smoking. Hazard ratios can be found in Table 3.

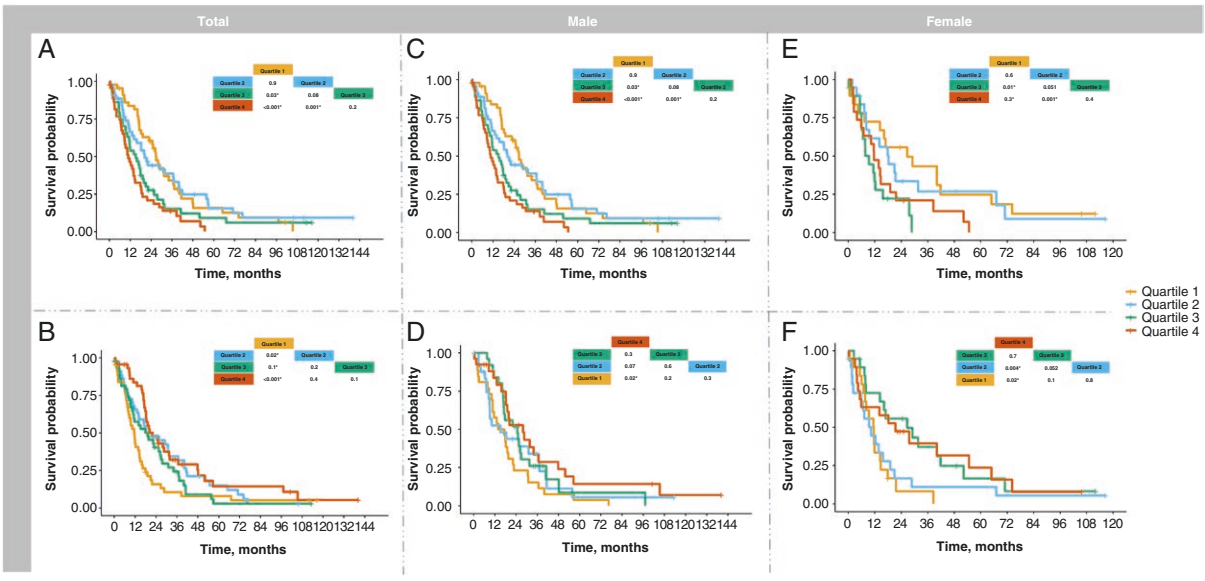

Figure 3. Difference in glioblastoma overall survival using CT composite score quartiles.

**P*-values from pairwise log-rank test denoting significant comparisons between quartiles. Quartiles 1 through 4 indicate the lowest through highest. Plots demonstrate unadjusted Kaplan–Meier survival curves separately for composite predisposing and protecting score in the total cohort (A–B), males (C–D) and females (E–F). Variables that survived the multivariable analyses were all measured and included in the composite scores included: for the *Composite Predisposing score*: IMAT volume, IMAT/TAT, SKM fat fraction and abdominal aortic calcification volume, and for the *Composite Protecting score*: Iliopsoas volume, total skeletal muscle volume, with SAT/TAT added specifically for males. All variables were measured from L1 through L5.

based on this important genetic factor, nor we could use it in our multivariable analyses. Moreover, only the overall, and not cancer-specific, survival rate were available limiting any evaluation of the relationship between the body composition metrics and cancer-specific causes of death. A prospective, validation study considering cancer-specific causes of death and/or progression-free survival might help confirm these results.

Supplementary material

Supplementary material is available online at *Neuro-Oncology Advances* (https://academic.oup.com/noa).

Keywords

atherosclerosis | body composition | computed tomography | GBM | myosteatosis | skeletal muscle

Funding

This work was supported by National Institutes of Health [R21CA242221, R00CA218869, and UL1TR002345 to J.E.I.]; American Cancer Society [RSG-231156822-01-TBE to J.E.I.]; and Barnes-Jewish Hospital Foundation and Siteman Cancer Center (J.E.I.).

Conflict of interest statement

V.T.Y.C., D.M., K.P., and M.F.B. developed the software through Voronoi Health Analytics, Inc. that was used for this study. This had no influence on the data analysis, data interpretation, or manuscript preparation and submission at any point.

Authorship statement

Conceptualization (J.E.I.), Supervision (J.E.I.), Funding (M.R.C. and J.E.I.), Methodology (F.R., J.E., C.A.R., M.R.C., S.H.K., and J.E.I.), Software (V.T.Y.C., D.M., K.P., S.H.K., and M.F.B.), Formal Analysis (F.R., G.C., O.M., and J.E.I.), Investigation (F.R. and J.E.I.), Data curation (F.R., N.A., D.H.B., S.D., J.E., S.J., M.N., and S.H.K), Writing—draft (F.R. and J.E.I.), Writing—revision (F.R., G.C., O.M., N.A., D.H.B., V.T.Y.C., S.D., J.E., S.J., D.M., M.N., K.P., C.A.R., M.F.B., M.R.C., and J.E.I.).

Ethics approval

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Institutional Review Board of Washington University School of Medicine in Saint Louis under IRB number 201706171.

Consent to participate

This was a retrospective study that was performed under a waiver of consent.

Consent to publish

Not applicable.

Data availability

The data supporting these findings are available on request to and review by the corresponding author and coauthors. The data are not publicly available due to privacy and ethical restrictions.

Affiliations

Mallinckrodt Institute of Radiology, Washington University School of Medicine in Saint Louis, St. Louis, Missouri, USA (F.R., D.H.B., T.L.S.B., S.H.K., C.A.R., M.J.S., J.E.I.); Graduate Medical Education, St. Joseph's Medical Center, Stockton, California, USA (G.C.); University of Washington School of Medicine, Seattle, Washington, USA (O.M.); Russell H. Morgan Department of Radiology and Radiological Science, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA (N.A.); School of Engineering Science, Simon Fraser University, Burnaby, British Columbia, Canada (V.T.Y.C.); Department of Pathology, Washington University School of Medicine, Saint Louis, Missouri, USA (S.D.); Department of Neurosurgery, Washington University School of Medicine, Saint Louis, Missouri, USA (J.E.); Department of Radiology, Weill Cornell Medical Center/New York Presbyterian Hospital, New York City, New York, USA (S.J.); Department of Internal Medicine, Section of Gerontology and Geriatric Medicine, Wake Forest University School of Medicine, Winston-Salem, North Carolina, USA (D.M.); Department of Radiology and Imaging Sciences, Emory University School of Medicine, Atlanta, Georgia, USA (M.N.); Department of Computer Science, Memorial University of Newfoundland, St. John's, Newfoundland and Labrador, Canada (K.P.); Department of Surgery, Washington University School of Medicine, Saint Louis, Missouri, USA (Y.X., J.L.); School of Engineering Science, Simon Fraser University, Burnaby, British Columbia, Canada (M.F.B.); Department of Neurosurgery, University of Missouri, Columbia, Missouri, USA (M.R.C.); Department of Biochemistry and Molecular Biophysics, Washington University School of Medicine, Saint Louis, Missouri, USA (J.E.I.)

References

1. Ostrom QT, Price M, Neff C, et al. CBTRUS statistical report: primary brain and other central nervous system tumors diagnosed in the United States in 2016—2020. *Neuro-Oncol*. 2023;25(Supplement_4):iv1–iv99.
2. Perry JR, Laperriere N, O'Callaghan CJ, et al.; Trial Investigators. Short-course radiation plus temozolomide in elderly patients with glioblastoma. *N Engl J Med*. 2017;376(11):1027–1037.

3. Baumgarten P, Prange G, Kamp MA, et al. Treatment of very elderly glioblastoma patients ≥ 75 years of age: whom to treat. *J Neurooncol.* 2023;165(3):509–515.
4. Ahn S, Han K, Lee JE, et al. Associations of general and abdominal obesity with the risk of glioma development. *Cancers.* 2021;13(12):2859.
5. Weller J, Schäfer N, Schaub C, et al. Prognostic impact of obesity in newly-diagnosed glioblastoma: a secondary analysis of CeTeG/NOA-09 and GLARIUS. *J Neurooncol.* 2022;159(1):95–101.
6. Petrelli F, Cortellini A, Indini A, et al. Association of obesity with survival outcomes in patients with cancer: a systematic review and meta-analysis. *JAMA Network Open.* 2021;4(3):e213520.
7. Cha JY, Park JS, Hong YK, Jeun SS, Ahn S. Impact of body mass index on survival outcome in patients with newly diagnosed glioblastoma: a retrospective single-center study. *Integr Cancer Ther.* 2021;20:1534735421991233.
8. Potharaju M, Mangaleswaran B, Mathavan A, et al. Body mass index as a prognostic marker in glioblastoma multiforme: a clinical outcome. *Int J Radiat Oncol Biol Phys.* 2018;102(1):204–209.
9. Cespedes Feliciano EM, Popuri K, Cobzas D, et al. Evaluation of automated computed tomography segmentation to assess body composition and mortality associations in cancer patients. *J Cachexia Sarcopenia Muscle.* 2020;11(5):1258–1269.
10. Au PC, Li HL, Lee GK, et al. Sarcopenia and mortality in cancer: a meta-analysis. *Osteoporos Sarcopenia.* 2021;7(Suppl 1):S28–S33.
11. Morshed RA, Young JS, Casey M, et al. Sarcopenia diagnosed using masseter muscle diameter as a survival correlate in elderly patients with glioblastoma. *World Neurosurg.* 2022;161:e448–e463.
12. Mauvais-Jarvis F. Sex differences in metabolic homeostasis, diabetes, and obesity. *Biol Sex Differences.* 2015;6(1):14.
13. Tavelin B, Malmström A. Sex differences in glioblastoma—findings from the Swedish National Quality Registry for primary brain tumors between 1999-2018. *J Clin Med.* 2022;11(3):486.
14. Nguyen GK, Mellnick VM, Yim AK, Salter A, Ippolito JE. Synergy of sex differences in visceral fat measured with CT and tumor metabolism helps predict overall survival in patients with renal cell carcinoma. *Radiology.* 2018;287(3):884–892.
15. Ippolito JE, Yim AK, Luo J, Chinnaiyan P, Rubin JB. Sexual dimorphism in glioma glycolysis underlies sex differences in survival. *JCI Insight.* 2017;2(15):e92142.
16. Siegel RL, Miller KD, Wagle NS, Jemal A. Cancer statistics, 2023. *CA Cancer J Clin.* 2023;73(1):17–48.
17. Dong M, Cioffi G, Wang J, et al. Sex differences in cancer incidence and survival: a pan-cancer analysis. *Cancer Epidemiol Biomarkers Prev.* 2020;29(7):1389–1397.
18. Jaswal S, Sanders V, Pullarkat P, et al. Metabolic biomarkers assessed with PET/CT predict sex-specific longitudinal outcomes in patients with diffuse large B-cell lymphoma. *Cancers.* 2022;14(12):2932.
19. Ballard DH, Nguyen GK, Atagu N, et al. Female-specific pancreatic cancer survival from CT imaging of visceral fat implicates glutathione metabolism in solid tumors. *Acad Radiol.* 2024;31(6):2312–2323.
20. Karastergiou K, Smith SR, Greenberg AS, Fried SK. Sex differences in human adipose tissues—the biology of pear shape. *Biol Sex Differences.* 2012;3(1):13.
21. Gavin KM, Bessesen DH. Sex differences in adipose tissue function. *Endocrinol Metab Clin North Am.* 2020;49(2):215–228.
22. Chicoine MR, Lim CC, Evans JA, et al. Implementation and preliminary clinical experience with the use of ceiling-mounted mobile high-field intraoperative magnetic resonance imaging between two operating rooms. *Acta Neurochir Suppl.* 2011;109:97–102.
23. Anyene I, Caan B, Williams GR, et al. Body composition from single versus multi-slice abdominal computed tomography: concordance and associations with colorectal cancer survival. *J Cachexia Sarcopenia Muscle.* 2022;13(6):2974–2984.
24. Mai DVC, Drami I, Pring ET, et al.; BiCyCLE Research Group. A systematic review of automated segmentation of 3D computed-tomography scans for volumetric body composition analysis. *J Cachexia Sarcopenia Muscle.* 2023;14(5):1973–1986.
25. Ma D, Beg MF, Popuri K, Chow V. Comprehensive validation of automated whole body skeletal muscle, adipose tissue, and bone segmentation from 3D CT images for body composition analysis: towards extended body composition.2021. https://arxiv.org/abs/2106.00652
26. Hegi Monika E, Diserens A-C, Gorlia T, et al. MGMT gene silencing and benefit from temozolomide in glioblastoma. *N Engl J Med.* 2005;352(10):997–1003.
27. Doyle. *American Society of Anesthesiologists Classification.* Treasure Island, FL: StatPearls Publishing; 2023.
28. Benjamini Y, Hochberg Y. Controlling the false discovery rate: a practical and powerful approach to multiple testing. *J R Stat Soc Series B.* 1995;57(1):289–300.
29. Yadav S, Zhou S, He B, Du Y, Garmire LX. Deep learning and transfer learning identify breast cancer survival subtypes from single-cell imaging data. *Commun Med.* 2023;3(1):187.
30. Xiao J, Mazurak VC, Olobatuyi TA, Caan BJ, Prado CM. Visceral adiposity and cancer survival: a review of imaging studies. *Eur J Cancer Care (Engl).* 2018;27(2):e12611.
31. Recalde M, Pistillo A, Davila-Batista V, et al. Longitudinal body mass index and cancer risk: a cohort study of 2.6 million Catalan adults. *Nat Commun.* 2023;14(1):3816.
32. Bhaskaran K, Douglas I, Forbes H, et al. Body-mass index and risk of 22 specific cancers: a population-based cohort study of 5·24 million UK adults. *Lancet (London, England).* 2014;384(9945):755–765.
33. Koster A, Murphy RA, Eiriksdottir G, et al. Fat distribution and mortality: the AGES-Reykjavik study. *Obesity (Silver Spring, Md.).* 2015;23(4):893–897.
34. Bradshaw PT. Body composition and cancer survival: a narrative review. *Br J Cancer.* 2024;130(2):176–183.
35. Ebadi M, Martin L, Ghosh S, et al. Subcutaneous adiposity is an independent predictor of mortality in cancer patients. *Br J Cancer.* 2017;117(1):148–155.
36. Pasqualetti F, Barberis A, Zanotti S, et al. The impact of survivorship bias in glioblastoma research. *Crit Rev Oncol Hematol.* 2023;188:104065.
37. Au PCM, Li HL, Lee GKY, et al. Sarcopenia and mortality in cancer: a meta-analysis. *Osteoporosis Sarcopenia.* 2021;7(Supplement_1):S28–S33.
38. Liu C, Liu T, Deng L, et al. Sarcopenic obesity and outcomes for patients with cancer. *JAMA Network Open.* 2024;7(6):e2417115–e2417115.
39. Mi E, Mauricaite R, Pakzad-Shahabi L, et al. Deep learning-based quantification of temporalis muscle has prognostic value in patients with glioblastoma. *Br J Cancer.* 2022;126(2):196–203.
40. An G, Ahn S, Park JS, Jeun SS, Hong YK. Association between temporal muscle thickness and clinical outcomes in patients with newly diagnosed glioblastoma. *J Cancer Res Clin Oncol.* 2021;147(3):901–909.
41. Furtner J, Weller M, Weber M, et al.; EORTC Brain Tumor Group. Temporal muscle thickness as a prognostic marker in patients with newly diagnosed glioblastoma: translational imaging analysis of the CENTRIC EORTC 26071–22072 and CORE Trials. *Clin Cancer Res.* 2022;28(1):129–136.
42. Faron A, Kreyer S, Sprinkart AM, et al. CT fatty muscle fraction as a new parameter for muscle quality assessment predicts outcome in venovenous extracorporeal membrane oxygenation. *Sci Rep.* 2020;10(1):22391.
43. Erley J, Roedl K, Ozga AK, et al. Dual-Energy CT muscle fat fraction as a new imaging biomarker of body composition and survival predictor in critically ill patients. *Eur Radiol.* 2024;34:7408–7418.

44. Lu X, Yue J, Liu Q, et al. Thigh muscle fat fraction is independently associated with impaired glucose metabolism in individuals with obesity. *Endocrine Connections*. 2023;12(11):e230248.
45. Avesani CM, de Abreu AM, Ribeiro HS, et al. Muscle fat infiltration in chronic kidney disease: a marker related to muscle quality, muscle strength and sarcopenia. *J Nephrol*. 2023;36(3):895–910.
46. Jurgens PT, Carr JJ, Terry JG, et al. Association of abdominal aorta calcium and coronary artery calcium with incident cardiovascular and coronary heart disease events in black and white middle-aged people: the coronary artery risk development in young adults study. *J Am Heart Assoc*. 2021;10(24):e023037.
47. Forbang NI, Michos ED, McClelland RL, et al. Greater volume but not higher density of abdominal aortic calcium is associated with increased cardiovascular disease risk. *Circulation*. 2016;9(11):e005138.
48. Wilson PWF, Kauppila LI, O'Donnell CJ, et al. Abdominal aortic calcific deposits are an important predictor of vascular morbidity and mortality. *Circulation*. 2001;103(11):1529–1534.
49. Pasqualetti F, Gabelloni M, Faggioni L, et al. Glioblastoma and internal carotid artery calcium score: a possible novel prognostic partnership? *J Clin Med*. 2024;13(5):1512.
50. Kobiyama K, Ley K. Atherosclerosis. *Circ Res*. 2018;123(10):1118–1120.
51. Chen N, Peng C, Li D. Epigenetic underpinnings of inflammation: a key to unlock the tumor microenvironment in glioblastoma. *Front Immunol*. 2022;13:869307. https://www.frontiersin.org/journals/immunology/articles/10.3389/fimmu.2022.869307
52. An J, Freeman E, Stewart IJ, Dore M. Association of traumatic brain injury and glioblastoma multiforme: a case series. *Mil Med*. 2024;189(1-2):e391–e395.