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Visceral fat area and subcutaneous fat area as measures of body composition in soft tissue sarcoma

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Abstract

Background and Objectives: Soft tissue sarcomas (STS) are a heterogenous group of malignancies of mesenchymal origin. Given recent data linking obesity as well as site of fat deposition with cancer outcomes, we sought to investigate the association of visceral fat area (VFA) and subcutaneous fat area (SFA) with oncologic outcomes in patients with STS undergoing surgery.

Methods: We analyzed data from 88 patients with STS diagnosed from 2008–2022. Predictor variables included body mass index (BMI), VFA, and SFA. VFA and SFA were obtained from computed tomography of the abdomen and pelvis. Univariable and multivariable Cox regression analysis was used to analyze associations between predictor variables and overall survival and recurrence free survival.

Results: Although BMI was closely correlated with VFA ($r=0.64$, $P<0.0001$) and SFA ($r=0.86$, $P<0.0001$), there was no significant association between high BMI, VFA, or SFA and worse oncologic outcomes.

Conclusions: Although VFA and SFA are strongly correlated with BMI, we did not observe BMI nor imaging metrics of fat composition to be associated with worse oncologic outcomes.

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Further research is needed to elucidate any links between body fat content and metabolic or immune factors governing oncologic outcomes in STS.

Keywords

Soft tissue sarcoma; visceral fat area; subcutaneous fat area; obesity; body mass index

Introduction

Soft tissue sarcomas (STS) are a heterogenous group of malignancies from mesenchymal origin with diverse biological behavior[1]. Overall, STS are rare, accounting for less than 1% of all new cancer cases in the United States with a relative 5-year survival of 65.8%[2]. When localized, the primary treatment for STS is surgical resection in the context of multidisciplinary treatment planning frequently combined with radiotherapy (RT)[3].

Body mass index (BMI) has been widely used in biomedical research to classify patients into categories based on their weight-to-height ratio[4]. A BMI <25 kg/m^2 is accepted as the cutoff for a normal BMI. Obesity (BMI ≥ 30 kg/m^2) has been associated with an increased risk of various cancers, poor overall oncologic mortality, and increased postsurgical complications[5–8]. Specifically in STS, obesity has been linked with higher incidence of postoperative wound complications[9–14], but there is currently a lack of evidence to suggest a link with long-term outcomes like recurrence or survival[9,11–13,15].

Body fat content is composed of visceral fat (VF) and subcutaneous fat (SF). VF is found within the abdominal cavity surrounding organs and the omentum. VF accounts for a larger percentage of total fat in men and is associated with greater mortality from metabolic diseases[16]. VF is associated with insulin resistance, metabolic syndrome (insulin resistance, visceral adiposity, dyslipidemia, and hypertension), and increased risk of cancer mortality[17–21]. SF is deposited within the subcutaneous tissues, immediately deep to the dermis, representing about 80% of body fat, and it is commonly stored in the femoral-gluteal tissues, back, and abdominal wall[16,22]. In comparison to SF, VF poses a higher risk for metabolic syndrome, inflammation, and a cancer promoting inflammation. VF secretes free fatty acids that contribute to insulin resistance and inflammatory cytokines (interleukins and tumor necrosis factor-alpha, among others) stimulating a pro-cancer state[23–26].

Given that BMI may be an imperfect measure, question remains whether there are other potential metrics that may be superior to BMI in assessing body composition and surgical and oncologic risk profiles. Previous studies have analyzed the prognostic factor of a wide array of imaging adipose markers in different types of cancers, and results have shown variable associations with survival outcomes[27–29]. These markers include, but are not limited to, visceral fat area (VFA), subcutaneous fat area (SFA), total body fat, visceral fat volume, subcutaneous fat volume, fat body mass, visceral fat mass, and subcutaneous fat mass[30].

Given increasing obesity epidemic worldwide with implications for cancer initiation and promotion as well as risk of surgical complications, we aimed to analyze if VFA and

SFA were predictors of oncologic outcomes in STS. Given prior studies linking VF with increased inflammation and cardiometabolic disease, we hypothesized high VFA would be associated with poor recurrence and survival outcomes in STS.

Methods

Patient cohort

We identified 88 patients who underwent surgical resection for STS of all anatomic sites at the University of California, Davis, Medical Center between the years 2008 and 2022. Institutional Review Board approval was obtained (IRB #484670-4). Patients ≥ 18 years of age who underwent surgical resection with curative intent for primary STS of all anatomic sites were included.

Clinicopathologic data

Deidentified data were obtained from the electronic medical record and included: age, sex, BMI, tumor size, tumor site, histology, tumor grade, AJCC stage, treatment sequence, recurrence event, most recent vital status, and date of death or last follow up.

Imaging assessment

VFA and SFA were calculated using pre-operative axial computed tomography of the abdomen and pelvis at the lumbar spine third level (Figure 1). Measurements were performed by a board-certified musculoskeletal radiologist with > 10 years of clinical experience using TeraRecon® artificial intelligence software-Durham, North Carolina[31]. Images were deidentified when uploaded to TeraRecon® and reviewed to ensure appropriate segmentation and verification of computations. Fat segmentation was measured with a threshold between −30 and −90 Hounsfield units[32]. Of the 88 patients, 21 (24%) were diagnosed with an extremity tumor and did not undergo CT of the abdomen and pelvis for staging, resulting in absent VFA and SFA data in those patients. We were unable to calculate VFA and SFA measurements for 5 additional patients due to cross-sectional imaging without intravenous contrast or the presence of a retroperitoneal liposarcoma affecting measurements.

Outcome variables

Our primary outcome variables were patient death from the time of diagnosis (overall survival; OS) and STS recurrence (local or distant) from the time of surgery (recurrence free survival; RFS). Both endpoints were calculated in months as described previously[33–35].

Statistical analysis

R version 4.3.1 (R Foundation for Statistical Computing, Vienna, Austria), SAS version 9.4 (SAS Institute, Cary, NC), Prism 10 (GraphPad Software) and Excel (Microsoft) were used for graph generation and statistical analysis. BMI was categorized into <25 (normal), 25≤BMI<30 (overweight), and ≥30 (obese) for statistical analysis. VFA and SFA were categorized into low and high groups by their median values. Baseline demographics and patient characteristics were expressed as mean ± SD where appropriate and summarized

using descriptive statistics. Fisher exact tests were used for categorical variables and Kruskal-Wallis tests for continuous variables. Correlations between BMI, VFA and SFA were estimated using Pearson correlation coefficients. OS and RFS were evaluated using Kaplan-Meier curves using log-rank (Mantel-Cox) tests. In addition, univariate and multivariate survival analyses were performed for OS and RFS using Cox proportional hazards models. Separate models were fitted for each interested variable (BMI, VFA, SFA, either continuous and categorical), and the multivariable analysis model further adjusted for confounders including sex, age, tumor size, STS subtype, and tumor grade. To determine if the proportional hazards assumption holds, we tested this assumption using Schoenfeld residuals. P values were derived from two-tailed tests. Results were considered statistically significant when $P \leq 0.05$.

Results

Demographics and clinicopathologic characteristics

The clinicopathologic characteristics of our cohort are depicted in Table 1. The mean age was 64.6 ± 16.1 years, 55.7% (49/88) of patients were male, and 76.1% (67/88) were Caucasian. 63.6% (56/88) of tumors were located on an extremity, and the mean tumor size overall was 12.3 ± 7.9 cm. There were 49 (55.7%) patients who received neoadjuvant RT, 23 (26.1%) patients who received upfront surgery, 14 (15.9%) who received neoadjuvant chemoradiation, and 2 (2.3%) who received neoadjuvant chemotherapy. The mean BMI for the entire cohort was 28.2 ± 6.0 kg/m^2 with 29.5% (26/88) of patients considered obese (BMI≥30).

Oncologic outcomes

With a median follow up of 35.3 months, there were 41 (36%) recurrence events and 23 (26%) deaths. 87% (20/23) of the deaths were secondary to STS progression with three deaths secondary to other causes. Median OS for the entire cohort was 90.5 (5.8–151.5) months. Median RFS was not reached given the high number of censored events early in the time course preventing RFS to meet this endpoint.

BMI, VFA, and SFA are positively correlated

As shown in Figure 2, we observed a strong linear correlation between BMI and measures of radiographic adiposity, including VFA and SFA, respectively (r=0.64 VFA, r=0.86 SFA, P< 0.001 for both). These trends were consistent even when patients were stratified by sex with males shown in Figure 2B (r=0.71 VFA, r=0.87 SFA, P<0.0001 for both respectively) and females in Figure 2C (r=0.68 VFA, r=0.86 SFA, P<0.0001 for both respectively). Table 2 further supports a positive correlation between BMI, VFA, and SFA when patients were stratified by BMI into lean, overweight, and obese categories (p<0.001for both).

Fat body composition between male and female

We also examined the distribution of VFA and SFA among males and females given data from other studies showing sex-based differences with males have greater VFA and females having greater SFA[16,36,37]. Table 3 shows that 61.3% (19/31) of males belonged to the low SFA group (SFA<215), whereas 58.1% (18/31) of females belonged to the high SFA

group (SFA≥215). Although these proportions were numerically different and potentially clinically significant, they were not statistically different, P=0.204. Similarly, when patients were stratified into high and low VFA levels based on median values, 61.3% (19/31) of males belonged to the high VFA group (VFA≥127), compared to 58.1% (18/31) of females who belonged to the low VFA group (VFA<127) (P=0.204, Table 3).

Primary oncologic outcomes

Although body and imaging metrics of obesity were tightly correlated, we did not observe any association between these variables and oncologic outcomes. For BMI, there was no significant association of the three BMI categories (BMI<25 for lean, 25≤BMI<30 for overweight, and BMI≥30 for obese) with regards to RFS or OS (P=0.36, P=0.89, respectively, Figure 3A and 3B). Similarly, there was no difference between low VFA (VFA<127) and high VFA (VFA≥127) subgroups for RFS and OS (P=0.45, P=0.078, respectively, Figure 3C and 3D) nor between low SFA (SFA<215) and high SFA (SFA≥215) subgroups for RFS and OS (P=0.57, P=0.38, respectively, Figure 3E & 3F). These results were similar on both univariable and multivariable survival analysis (Supplementary Table 1 & 2), although when analyzing SFA as a continuous variable, SFA approached statistical significance for the outcome of OS, indicating a trend for improved survival among patients with increasing SFA (HR = 0.99, 95% CI = (0.98–1.00), P=0.057, Supplementary Table 2).

Discussion

Although obesity has been linked with oncologic outcomes in many tumor types, it has only been linked with postoperative complications in STS without a strong association with long-term oncologic outcomes[9–15]. There is likely a complex explanation for this since obesity has pleotropic effects on multiple metabolic, immunologic, and cancer-related processes which are likely context dependent. However, an important issue relates to potential limitations of using BMI as a readout to categorize patients into lean, overweight, and obese. As has been noted by multiple expert panels, BMI is an indirect and imperfect marker since it does not describe fat content nor the distribution of adipose tissues and only measures excess weight in relation to height[38]. Thus, individuals like athletes with increased muscle mass and low/normal body fat may be categorized incorrectly as obese[39]. Similarly, individuals with low muscle mass and high body fat (frequently the elderly or other frail patients) may be categorized as non-obese by BMI calculation, but are at risk for metabolic disease and functional impairment because of relative increases in body fat content [40]. In fact, patients with sarcopenic obesity have been shown to carry the poorest cancer prognosis in several population-based analyses [41].

The goal of our study was to determine if VFA and SFA were better predictors of obesity related oncologic outcomes in STS, given the limitations with BMI. We hypothesized VFA would be associated with worse oncologic outcomes since VF has been shown to be pro-inflammatory and promote a tumor microenvironment protective to cancer cells and suppressive to the immune system[17–21,23–26,42], and differences between the metabolic and immunologic effects of VFA versus SFA would shed greater light on why the impact of obesity on STS has been equivocal in studies to date.

Our results showed VFA and SFA to be positively correlated with BMI, independent of sex, consistent with prior studies[43–45]. In our data, SFA showed a stronger correlation than VFA, likely because SF represents about 80% of total body fat. Importantly, our results did not show any of the predictor variables (BMI, VFA or SFA) to be associated with recurrence or survival outcomes, although we did observe a near-significant association between higher SFA and improved OS. This may suggest high SFA, or obesity defined by SFA, can be advantageous given the metabolic and inflammatory differences between visceral and subcutaneous fat as noted above. However, it remains unclear if SF is advantageous or compensating for the negative effects of high VF, since SFA and VFA were positively linked in our data. We also acknowledge that this trend for SFA to be associated with OS may be a false positive finding or not specific to STS outcomes since SFA did not associate with RFS in our analysis.

Overall, our findings may contribute to the literature on the “obesity paradox” where obesity (based on BMI) has been linked with favorable oncologic outcomes. For example, obesity has been linked with improved immunotherapy response in melanoma murine models and human patients in the context of obesity-induced defective antitumor T-cell response [46–48]. It is important to underscore the importance of using more sensitive measures of obesity, instead of BMI, since BMI does not account for important confounding factors like sarcopenia, which is known to be associated with poor OS and frailty in retroperitoneal STS in particular as in other cancers[35].

Ultimately, we observed that SFA and VFA do not provide additional stratification for OS and RFS in a heterogeneous cohort of STS patients. The lack of significant results in our data may be related to an underpowered study along with confounding factors from a heterogenous cohort. Our patient group included multiple histologies, retroperitoneal and extremity sarcoma, and variable treatment approaches, all of which can influence prognosis over and above the potential impact of obesity and body fat composition. For example, a large STS database from Memorial Sloan Kettering found extremity/trunk tumors to have superior local disease-free survival and disease specific survival when compared to retroperitoneal/intrabdominal tumors[49]. Our data may also indicate that the metabolic and immunologic implications of VFA and SFA do not exert major impact in STS outcomes. This is challenging to definitively assess at this time since we do not present data on metabolic endpoints or inflammatory markers.

Our results are similar to current published work, showing no strong indication that obesity is associated with long-term outcomes in STS. One study on retroperitoneal and trunk STS with 95 patients found intramuscular adiposity associated with OS and disease specific survival, but no association with VF[50]. A 14 study meta-analysis analyzing body composition on STS found two studies where intramuscular fat and SF attenuation was associated with reduced OS[51]. Research on other cancer types also shows varying results. A study on advanced gastric cancer observed that patients with high SFA had better prognosis than patients with low SFA, similar to our results [28]. However, there was no association between VFA and OS.

There are many reasons for variable results that include, but not limited to, the cancer type, treatment, and method of measuring fat content. There is no current standardized way of measuring fat body composition. VFA alone could be affected by contrast vs non-contrast study, Hounsfield Unit (HU) range, vertebral level analyzed by sex, and lung inflation-particularly in the thoracic region[52]. Moreover, there are ample ways by which VF is measured and reported, like visceral fat mass, visceral fat area, visceral to subcutaneous adipose ratio, etc. This applies to SF as well. The goal for future studies may be to investigate the different measures of body fat content with the same patient cohort and see how they compare.

In summary, we observed that SFA and VFA did not provide superior prognostic information than BMI in assessing oncologic outcomes in STS. We did not observe any association of increased or excess adiposity with worse OS or RFS in STS, suggesting that obesity may not be an adverse predictor of oncologic outcome in STS. However, given the limitations of our retrospective study, additional research is needed to evaluate the metabolic and immunologic implications of obesity in STS.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Abbreviations list:

STS	soft tissue sarcoma
VFA	visceral fat area
SFA	subcutaneous fat area
BMI	body mass index
RT	radiation therapy
VF	visceral fat
SF	subcutaneous fat
AJCC	American joint Committee on Cancer
CT	computed tomography
OS	overall survival
RFS	recurrence free survival
HU	Hounsfield units

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Synopsis for Table of Contents.

We sought to investigate the association of body mass index (BMI), visceral fat area, and subcutaneous fat area with oncologic outcomes in patients with soft tissue sarcoma (STS) to further understand obesity's effect on STS, obesity classification with BMI, and imaging metrics of fat composition in STS.

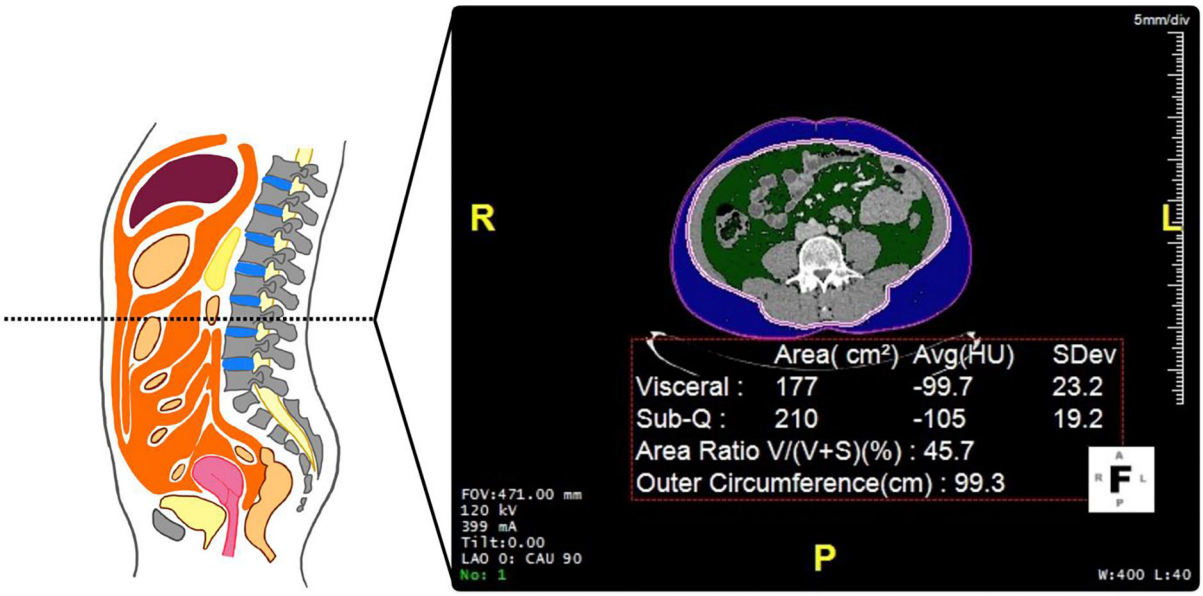

Figure 1.

Measurement of Visceral Fat Area and Subcutaneous Fat Area by Computed Tomography. TeraRecon® artificial intelligence program was used for segmentation analysis of abdominal/pelvic computed tomography images at the lumbar spine third level (left). VFA is depicted in green, while SFA is depicted in blue (right). Fat segmentation was measured with a threshold between −30 and −90 HU. Graphic was created using the application Freeform from Apple ®. CT, computed tomography, VFA, visceral fat area (cm^2), SFA, subcutaneous fat area (cm^2), and HU, Hounsfield units.

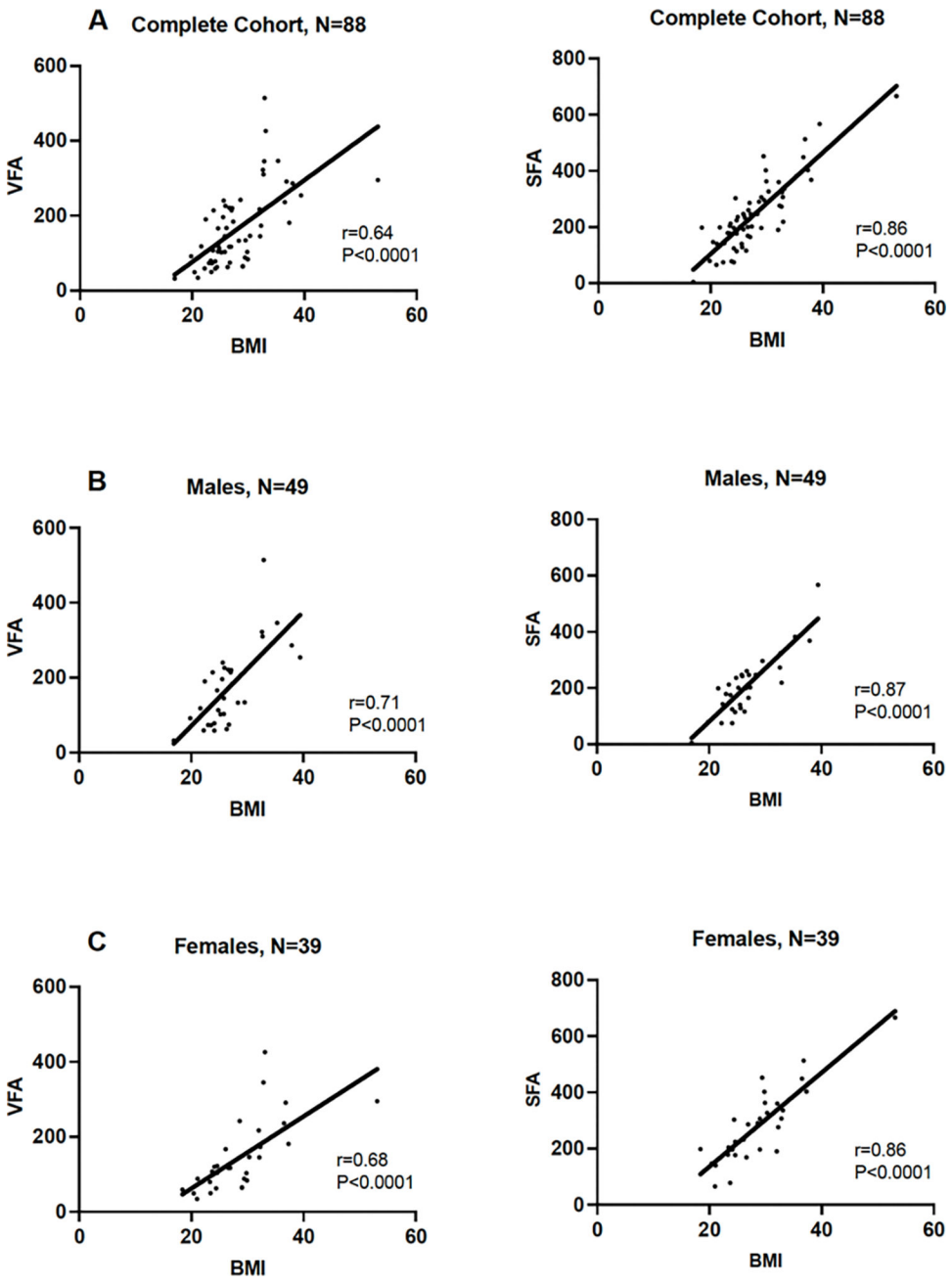

Figure 2.

VFA and SFA Correlations with BMI for All Patients and Stratified by Sex.

BMI correlates with body fat content measured by VFA and SFA. Panel A shows a positive correlation between BMI and VFA/SFA for the complete cohort (r=0.64, P<0.0001, n=62 and r=0.86, P<0.0001, n=62). Panel B shows positive a correlation between BMI and VFA/SFA for males (r=0.71, P<0.0001, n=32 and r=0.87, P<0.0001, n=32). Panel C shows positive a correlation between BMI and VFA/SFA for females (r=0.68, P<0.0001, n=30 and r=0.86, P<0.0001, n=30). Correlations are determined by two-tailed Pearson coefficient (alpha = 0.05). BMI, body mass index (kg/m^2), VFA, visceral fat area (cm^2), SFA, subcutaneous fat area (cm^2).

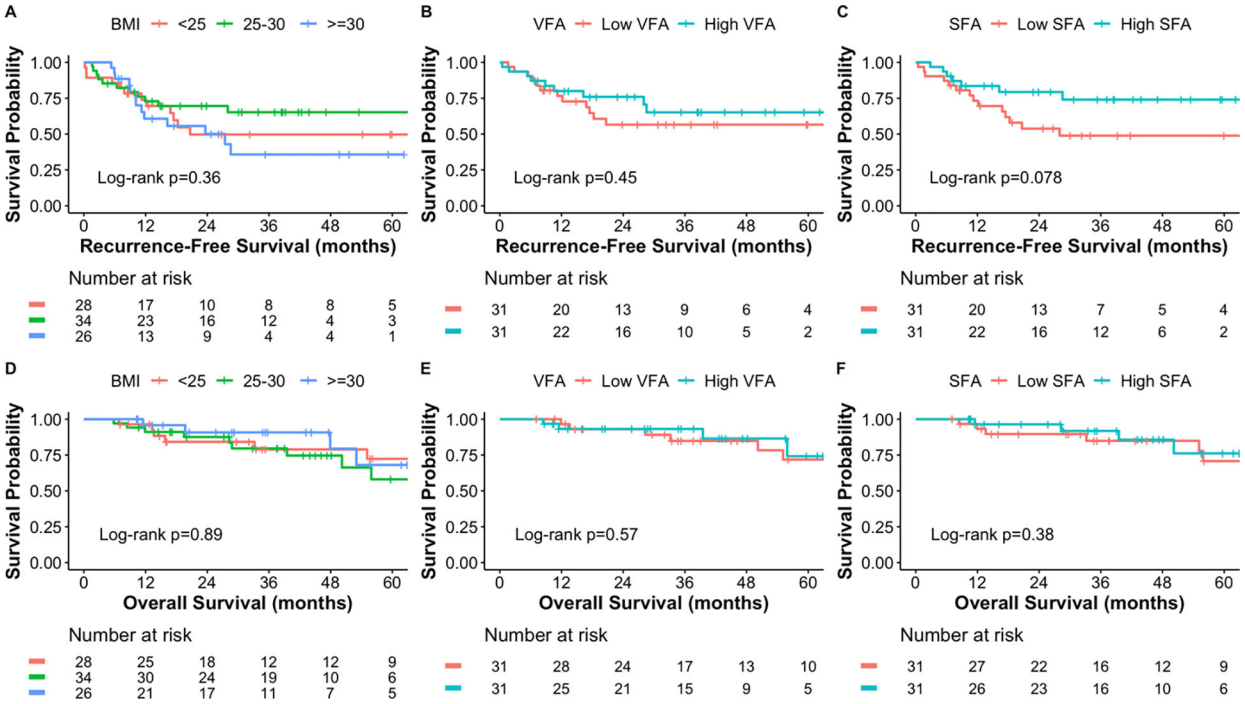

Figure 3.

Recurrence free survival and overall survival.

Panels A, C, and E show no difference in recurrence-free survival across three BMI groups, high and low VFA, and high and low SFA (P=0.36, P=0.45, P=0.078, respectively). Similarly, panels B, D, and F show no difference in overall survival across three BMI groups, high and low VFA, and high and low SFA (P=0.89, P=0.57, P=0.38, respectively). Significance of Kaplan-Meier analysis was determined by log-rank test. High and low groups were determined by median VFA and SFA. BMI groups represented normal (<25), overweight (25≤BMI<30), obese (≥30). BMI, body mass index (kg/m^2), VFA, visceral fat area(cm^2), SFA, subcutaneous fat area (cm^2).

Table 1.

Patient cohort, clinicopathologic characteristics, and outcomes for cohort of 88 patients.

Characteristics		Number	%
Age at diagnosis, mean (SD)		64.6 (±16.1)	
	Age < 65	37	42.1%
	Age ≥ 65	51	57.9%
Sex			
	Male	49	55.7%
	Female	39	44.3%
Ethnicity			
	Caucasian	67	76.1%
	Hispanic	7	8.9%
	Asian	6	6.8%
	Black	4	4.5%
	Other	4	4.5%
Tumor size, cm, mean (SD)		12.3 (±7.9)	
BMI, kg/m^2, mean (SD)		28.2 (±6.0)	
Tumor site			
	Extremity	56	63.6%
	Retroperitoneal	19	21.6%
	Trunk	12	13.6%
	Head and Neck	1	1.1%
Histology			
	Liposarcoma[a]	21	23.9%
	Myxofibrosarcoma	21	23.9%
	Undifferentiated pleomorphic sarcoma	21	23.9%
	Leiomyosarcoma	8	9.1%
	Other[b]	17	19.3%
Tumor grade			
	High	77	87.5%
	Intermediate	4	4.6%
	Low	7	7.9%
AJCC Stage at Presentation			
	Stage 2	11	12.5%
	Stage 3	77	87.5%
Treatment Sequence			
	Radiation	49	55.7%

Characteristics		Number	%
	Upfront surgery	23	26.1%
	Chemoradiation	14	15.9%
	Chemotherapy only	2	2.3%
Recurrence Events (local and distant)		36	40.9%
Vital status			
	Alive without evidence of disease	43	48.9%
	Alive with disease	22	25.0%
	Dead	23	26.1%

[a] Liposarcoma group includes 16 dedifferentiated, 3 myxoid, 1 myxoid pleomorphic and 1 pleomorphic.

[b] Group ‘other’ includes 1 angiosarcoma, 1 Ewing, 1 fibromyxoid, 1 rhabdomyosarcoma, 1 solitary fibrous tumor, 7 synovial, 3 MPNST, 1 PNET, and 1 DSRCT.

BMI, body mass index (kg/m^2), VFA, visceral fat area (cm^2), SFA, subcutaneous fat area (cm^2).

Table 2.

Patient Characteristics stratified by BMI levels.

		BMI<25 (n=28)	25≤BMI<30 (n=34)	BMI≥30 (n=26)	P value[a]
		Mean (SD)	Mean (SD)	Mean (SD)	
Age (year)					
		66.7 (16.6)	64.9 (17.7)	62 (13.5)	0.278
Tumor size (cm)					
		14.4 (7.9)	12.5 (8.8)	9.7 (5.8)	0.087
VFA					
		93.2 (47.1)	143.6 (62)	280.4 (100.6)	<.001
SFA					
		153.4 (68.8)	242.6 (84.3)	372.5 (125.7)	<.001
		N (%)	**N (%)**	**N (%)**	
Age					
	<65	12 (42.9%)	12 (35.3%)	13 (50%)	0.523
	≥65	16 (57.1%)	22 (64.7%)	13 (50%)	
Sex					
	Female	14 (50%)	11 (32.3%)	14 (53.9%)	0.181
	Male	14 (50%)	23 (67.7%)	12 (46.1%)	
Tumor size (cm)					
	<5	3 (10.7%)	6 (17.7%)	7 (26.9%)	0.278
	5–10	7 (25%)	10 (29.4)	10 (38.5%)	
	>10	18 (64.3%)	18 (52.9%)	9 (34.6%)	
Histology					
	Liposarcoma	9 (32.1%)	9 (26.5%)	3 (11.5%)	0.672
	Leiomyosarcoma	3 (10.7%)	2 (5.9%)	3 (11.5%)	
	Myxofibrosarcoma	7 (25%)	8 (23.5%)	6 (23%)	
	UPS[b]	5 (17.9%)	7 (20.6%)	9 (34.6%)	
	Other[c]	4 (14.3%)	8 (23.5%)	5 (19.2%)	
Grade					
	Low	4 (14.3%)	2 (5.9%)	1 (3.9%)	0.592
	Intermediate	2 (7.1%)	1 (2.9%)	1 (3.9%)	
	High	22 (78.6%)	31 (91.2%)	24 (92.3%)	

[a] P-values to compare variables between the three BMI groups from Fisher exact tests for categorical variables, and Kruskal-Wallis tests for continuous variables.

BMI, body mass index (kg/m^2), VFA, visceral fat area(cm^2), SFA, subcutaneous fat area (cm^2).

Table 3.

Fat body composition between males and females

Low vs High Groups	Female	Male	P value[a]
	N (%)	N (%)	
SFA<215 (n=31)	12 (38.7%)	19 (61.3%)	0.204
SFA≥215 (n=31)	18 (58.1%)	13 (41.9%)	
VFA<127 (n=31)	18 (58.1%)	13 (41.9%)	0.204
VFA≥127 (n=31)	12 (38.7%)	19 (61.3%)	

[a]P-values to compare variables between low and high SFA/VFA groups from Fisher exact tests for categorical variables, and Kruskal-Wallis tests for continuous variables.

VFA, visceral fat area(cm^2), SFA, subcutaneous fat area (cm^2).