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Adipose tissue and muscle attenuation as novel biomarkers predicting mortality in patients with extremity sarcomas

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Abstract

Objectives To assess CT-attenuation of abdominal adipose tissue and psoas muscle as predictors of mortality in patients with sarcomas of the extremities.

Methods Our study was IRB approved and HIPAA compliant. The study group comprised 135 patients with history of extremity sarcoma (mean age: 53 ± 17 years) who underwent whole body PET/CT. Abdominal subcutaneous adipose tissue (SAT), visceral adipose tissue (VAT), and psoas muscle attenuation (HU) was assessed on non-contrast, attenuation-correction CT. Clinical information including survival, tumour stage, sarcoma type, therapy and pre-existing comorbidities were recorded. Cox proportional hazard models were used to determine longitudinal associations between adipose tissue and muscle attenuation and mortality.

Results There were 47 deaths over a mean follow-up period of 20 ± 17 months. Higher SAT and lower psoas attenuation were associated with increased mortality ($p = 0.03$ and $p = 0.005$, respectively), which remained significant after adjustment for age, BMI, sex, tumor stage, therapy, and comorbidities ($p = 0.002$ and $p = 0.02$, respectively). VAT attenuation was not associated with mortality.

Conclusion Attenuation of SAT and psoas muscle, assessed on non-contrast CT, are predictors of mortality in patients with extremity sarcomas, independent of other established prognostic factors, suggesting that adipose tissue and muscle attenuation could serve as novel biomarkers for mortality in patients with sarcomas.

Key Points

- *CT-attenuation of adipose tissue and muscle predict mortality in sarcoma patients*
- *CT-attenuation predicts mortality independent of established prognostic factors*
- *Patients with sarcomas often undergo CT for staging or surveillance*
- *Adipose tissue and muscle attenuation could serve as biomarkers for mortality*

Keywords Computed tomography (CT) · Adipose tissue attenuation · Muscle attenuation · Hounsfield Units · Sarcoma

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Introduction

Sarcomas are a heterogeneous group of malignant neoplasms arising from mesenchymal cells throughout the body. They account for approximately 1 % of all adult malignancies [1]. About 50-60 % of sarcomas occur in the extremities [2, 3]. Established prognostic indicators of survival in patients with extremity sarcomas include histological tumour grade and tumour stage. However, the staging system for sarcomas is controversial. For example, the location of the tumour is not included in the staging system, and extremity, visceral, and retroperitoneal sarcomas are all combined, which precludes association of a particular stage with a uniform surgical approach [2]. Furthermore, biologic subtypes of sarcomas are not included in the staging system and tumour behaviour can vary considerably within a histological subtype [2]. Therefore, identification of additional predictors of survival is of clinical significance.

Recent studies have shown an important link between adipose tissue and tumour growth [4, 5]. Cancer cells can induce dedifferentiation of adipocytes, which secrete their lipids and can elicit systemic metabolic effects [4, 6]. On the other hand, dedifferentiated adipocytes can influence the growth of tumour cells [5, 7]. Furthermore, fatty infiltration of muscle is associated with sarcopenia and poor prognosis in cancer patients [8, 9].

Recent studies have suggested that the attenuation of abdominal adipose tissue, assessed on non-contrast computed tomography (CT), may serve as a biomarker for cardiovascular and cancer mortality [10, 11]. High attenuation of abdominal fat on CT has been found to be correlated with increased extracellular matrix fibrosis and smaller adipocytes on histology [10], findings that are also seen in cancer-associated wasting [12–14]. Furthermore, decreased muscle attenuation by CT has been found to serve as a predictor for all-cause mortality in older men and increased mortality in patients with carcinomas [15–18], and may reflect both quantitative and qualitative alterations of muscle tissue [19–21].

However, no studies have been performed on the use of these measures in patients with sarcomas.

Although MRI is the standard imaging modality for evaluating bone and soft tissue sarcomas, PET/CT is often used for staging and surveillance and adipose tissue and muscle attenuation, assessed on the non-contrast attenuation correction CT, and may serve as novel biomarkers predicting mortality in patients with sarcomas. The purpose of our study was to assess CT attenuation of abdominal adipose tissue and psoas muscle as predictors of mortality in patients with sarcomas of the extremities. We hypothesized that high adipose tissue attenuation and low muscle attenuation would be associated with higher mortality.

Materials and methods

This retrospective study was approved by the Institutional Review Board and complied with the Health Insurance Portability and Accountability Act (HIPAA) with exemption status for individual informed consent.

Subjects

A retrospective search was performed to identify patients with a history of extremity sarcoma who underwent FDG-PET/CT at our institution between April 2004 and December 2014. Inclusion criteria were age ≥18 years, diagnosis of sarcoma of the extremities, and presence of a diagnostic whole body attenuation correction non-contrast 18F-FDG-PET/CT. We selected patients with sarcomas of the extremity to avoid the influence of surgery or radiation therapy on abdominal adipose tissue and muscle attenuation measurements. Exclusion criteria were malignancy other than extremity sarcoma, abdominal surgery, radiation therapy to the abdomen or other pathology which could affect abdominal adipose tissue and muscle attenuation measurements.

Clinical data

The following clinical data were obtained from electronic medical records: age, BMI, smoking status, sarcoma type, sarcoma location, tumour size (cm), tumour grade and stage, type of treatment, presence and types of pre-existing comorbidities, final outcome (alive or deceased) at time of data collection, follow-up time since PET/CT, and date of death.

BMI was calculated as weight (kg) divided by height squared (m^2). Smoking status was recorded according to the following subgroups: 1) never smoked, 2) quit ≥20 years ago, 3) quit <20 years ago, or 4) current smoker defined as having smoked at least one cigarette per day during the past year. Sarcoma type was categorized as bone or soft-tissue sarcoma and sarcoma location was categorized as upper or lower extremity. Sarcoma staging (stage I to IV) was performed using the TNM system of the American Joint Committee on Cancer (https://cancerstaging.org/references-tools/deskreferences/Documents/AJCC6thEdCancerStagingManualPart1.pdf). Type of treatment included surgery, radiation therapy, chemotherapy, or a combination. Pre-existing comorbidities were categorized as cardiovascular disease (coronary artery disease, aortic aneurysm, myocardial infarction, cardiomyopathy, congestive heart failure, cerebrovascular disease, cardiac arrhythmia, pulmonary embolism, hypertension), pulmonary disease (asthma, chronic bronchitis, emphysema), renal disease (nephropathy, chronic renal failure), type II diabetes mellitus (fasting blood sugar level of >126 mg/dL or HbA1c >6.5 %), or a combination of those.

Mortality was determined from medical records and death notes. Follow-up time in months between date of PET/CT and date of death was recorded.

CT attenuation measurements

All patients underwent whole body 18-F-FDG-PET/CT (Siemens Biograph 16 or 64, Siemens, Erlangen, Germany or GE Healthcare discovery, Milwaukee, Wisconsin, USA), per standard clinical protocol as previously described [22]. The CT scanners used in this study were tested on an annual basis according to American Association of Physicists in Medicine (AAPM) and American College of Radiology (ACR) guidelines (AAPM report #74 and #96 and ACR CT QC manual). The non-contrast, attenuation correction CT scans (slice thickness 5 mm; table feed per rotation, 18 mm; time per table rotation, 0.5 s; tube voltage, 120 kVp; tube current, 11 mAs; and field of view, 20 cm) were used for analyses. Standard clinical quality assurance measures were performed to assess for reproducibility of scans over time.

Adipose tissue and muscle measurements were performed in the abdomen, remote from the site of sarcoma, to avoid the influence of the primary tumour and treatment changes (surgery or radiation therapy) on attenuation measurements. Analyses were performed using semiautomated methods at the mid-portion of the fourth lumbar vertebra as this level has been shown to be correlate with whole body adiposity [23]. Analyses were performed using Osirix software version 3.2.1 (www.osirix-viewer.com/index.html). First, automated thresholding methods were applied to identify abdominal adipose tissue, using a threshold set for −50 to −250 Hounsfield units (HU) as described by Borkan et al. [24]. We then manually outlined the subcutaneous and visceral areas and the mean attenuation (HU) was determined for each adipose tissue depot. This has been shown to be a reliable method for adipose tissue attenuation measurements with inter-reader correlation coefficients (r) of 0.99 for VAT and SAT [25]. For muscle attenuation measurements, thresholds were set between -29 to 150 HU [16]. Muscle attenuation was measured within a region of interest of 1 cm^2 in the centre of the right psoas muscle at the same level as the adipose tissue measurements, and mean attenuation (HU) was recorded (Supplemental Figure).

Statistical analysis

Statistical analysis was performed using JMP statistical software version 11.0 (SAS Institute Inc., Cary, NC.). The Shapiro-Wilk test was used to test normality of distribution. In case data were not normally distributed, non-parametric tests were performed. Data in Table 1 are shown as mean ± standard deviation (SD) for normally distributed parameters and median ± interquartile range for not normally distributed

Table 1 Patient characteristics. Data presented as mean ± SD for continuous variables and *n* (%) for categorical variables

	N = 135
Number of females	49
Number of males	86
Age at diagnosis extremity sarcoma (years)	50.8 ± 17.2
Females	50.8 ± 17.8
Males	50.7 ± 17.0
Age at PET/CT (years)	52.5 ± 17.4
Females	52.3 ± 17.9
Males	52.7 ± 17.3
BMI at PET/CT (kg/m^2)[a]	27.7 ± 7.5
Females	25.9 ± 10.2
Males	28.2 ± 6.3
Sarcoma location	
Upper extremity	33 (24.4)
Lower extremity	102 (75.6)
Sarcoma type	
Bone sarcoma	19 (14.1)
Soft tissue sarcoma	116 (85.9)
Sarcoma stage[b]	
1	19 (14.4)
2	63 (47.7)
3	29 (22.0)
4	21 (15.9)
Smoking status	
Never smoked	77 (57.0)
Quit ≥20 years ago	16 (11.9)
Quit <20 years ago	18 (13.3)
Current smoker	24 (17.8)
Number of comorbidities	
0	48 (35.6)
1	53 (39.3)
2	18 (13.3)
≥3	16 (12.9)
Type of comorbidity[c,d]	
Cardiovascular disease	73 (54.1)
Pulmonary disease	22 (16.3)
Diabetes Mellitus type II	14 (10.4)
Renal disease	8 (5.9)
Combination[e]	27 (31.0)
Therapy	
Only surgery	23 (17.0)
Only radiation therapy	8 (5.9)
Only chemotherapy	3 (2.2)
Surgery and radiation therapy	55 (40.7)
Surgery and chemotherapy	11 (8.2)
Radiation therapy and chemotherapy	3 (2.2)
Surgery, radiation therapy and chemotherapy	32 (23.7)

[a] = not normally distributed, data shown as median ± interquartile range

[b] = data of three patients were missing

[c] = diseases shown include those part of a combination

[d] = percentages in relation to total amount of patients (*n* = 135)

[e] = percentage in relation to amount of patients with comorbidities (*n* = 87)

data. The primary outcome of interest was mortality. Cox proportional hazard models were used to explore the longitudinal association between abdominal adipose tissue and muscle attenuation and mortality. Univariate and multivariate analyses of survival were performed using Cox's regression models, and the results are presented as hazard ratios (HR) with 95 % confidence interval (CI). Multivariate analysis was performed by subsequently adding five different covariate models, which included known risk factors for mortality [10, 11, 16]. The first model adjusted for age, sex, and BMI. Model 2 included the first model plus smoking status, whereas model 3 consisted of model 2 plus the patients' number of pre-existing comorbidities. Model 4 included model 3 plus sarcoma stage, whereas the fifth model included model 4 plus therapy type. For all analyses, a two-sided *P*-value of <0.05 was considered statistically significant.

Results

Patient characteristics

Patient characteristics are shown in Table 1. We identified 135 patients who met inclusion criteria (mean age at time of PET/CT: 52.5 ± 17.4 years, range 18 – 101 years). Of the 135 patients, 49 were women (mean age 52.3 ± 17.9 years, range 20 – 101 years) and 86 were men (mean age 52.7 ± 17.3 years, range 18 – 89 years). There were 47 deaths over a mean follow-up period of 20.4 ± 16.6 months (range of follow-up 0.46 and 65.9 months).

Adipose tissue attenuation and mortality

Mean SAT attenuation was -98.7 ± 8.2 HU and mean VAT attenuation was -89.2 ± 9.8 HU. A positive association between SAT attenuation and mortality was found (Table 2). An increase in SAT HU was associated with increased mortality showing an uncorrected HR of 1.05 (95 % CI 1.01-1.10, $p = 0.03$). Correcting for age, sex, and BMI did not alter this relationship (HR 1.07, 95 % CI 1.01-1.12, $p = 0.02$). Adjusting for smoking status enhanced this association (HR 1.09, 95 % CI 1.03-1.15, $p = 0.003$), as did the amount of pre-existing comorbidities (HR 1.10, 95 % CI 1.04-1.16, $p = 0.001$). The relationship remained significant after additional adjustment for sarcoma stage (HR 1.10, 95 % CI 1.04-1.16, $p = 0.002$) and therapy type (HR 1.10, 95 % CI 1.04-1.17, $p = 0.002$).

VAT attenuation was not associated with mortality in any of the models (Table 2).

In patients with soft tissue sarcomas only ($n = 116$) SAT attenuation remained a positive predictor of mortality in the uncorrected and corrected models, while VAT density was not associated with mortality (Table 3).

Muscle attenuation and mortality

Mean psoas attenuation was 44.5 ± 14.7 HU. A positive association between decreased psoas attenuation and mortality was found (Table 2). A decrease in psoas HU was associated with increased mortality showing an uncorrected HR of 0.96 (95 % CI 0.94-0.99, $p = 0.005$). Correcting for age, sex, and BMI enhanced this relationship (HR 0.95, 95 % CI 0.92-0.98, $p = 0.0005$). The relationship remained significant after additional adjustment for smoking status (HR 0.94, 95 % CI 0.91-0.98, $p = 0.0009$), amount of pre-existing comorbidities (HR 0.94, 95 % CI 0.91-0.97, $p = 0.0006$), sarcoma stage (HR 0.93, 95 % CI 0.89-0.97, $p = 0.0005$), and therapy type (HR 0.95, 95 % CI 0.90-0.99, $P = 0.02$).

When psoas and SAT attenuation were entered into the same model, the HR of the model was HR 1.10 , with 95 % CI 1.04 – 1.16.

In patients with soft tissue sarcomas only ($n = 116$), decreased muscle attenuation remained a predictor of mortality in the uncorrected and corrected models (Table 3).

Table 2 Association of fat and muscle attenuation and mortality. Data presented as hazard ratio (95 % CI) per 1 SD increase in HU

	VAT HU	*P*-value	SAT HU	*P*-value	Psoas HU	*P*-value
No covariates	0.99 (0.96-1.02)	0.44	1.05 (1.01-1.10)	0.03	0.96 (0.94-0.99)	0.005
Model 1[a]	0.99 (0.94-1.02)	0.45	1.07 (1.01-1.12)	0.02	0.95 (0.92-0.98)	0.0005
Model 2[b]	1.00 (0.95-1.05)	0.91	1.09 (1.03-1.15)	0.003	0.94 (0.91-0.98)	0.0009
Model 3[c]	0.97 (0.91-1.04)	0.55	1.10 (1.04-1.16)	0.001	0.94 (0.91-0.97)	0.0006
Model 4[d]	0.98 (0.91-1.03)	0.30	1.10 (1.04-1.16)	0.002	0.93 (0.89-0.97)	0.0005
Model 5[e]	0.95 (0.88-1.01)	0.09	1.10 (1.04-1.17)	0.002	0.95 (0.90-0.99)	0.02

[a] = Adjusted for age, sex, and BMI

[b] = Adjusted for Model 1 plus smoking status

[c] = Adjusted for Model 2 plus amount of pre-existing comorbidities

[d] = Adjusted for Model 3 plus sarcoma stage

[e] = Adjusted for Model 4 plus therapy type

VAT = visceral adipose tissue; SAT = subcutaneous adipose tissue; HU = Hounsfield Units

Table 3 Association of fat and muscle attenuation and mortality in patients with soft tissue sarcomas ($n = 116$). Data presented as hazard ratio (95 % CI) per 1 SD increase in HU

	VAT HU	*P*-value	SAT HU	*P*-value	Psoas HU	*P*-value
No covariates	1.01 (0.97-1.05)	0.68	1.06 (1.01-1.10)	0.03	0.96 (0.94-0.99)	0.006
Model 1[a]	1.00 (0.95-1.05)	0.96	1.06 (1.00-1.11)	0.05	0.94 (0.91-0.98)	0.0008
Model 2[b]	1.00 (0.95-1.05)	0.96	1.10 (1.04-1.16)	0.002	0.95 (0.91-0.98)	0.006
Model 3[c]	1.05 (0.97-1.13)	0.19	1.14 (1.10-1.21)	<0.0001	0.93 (0.89-0.98)	0.003
Model 4[d]	1.02 (0.94-1.10)	0.67	1.14 (1.06-1.22)	0.0002	0.94 (0.89-0.99)	0.03
Model 5[e]	1.05 (0.95-1.16)	0.31	1.13 (1.05-1.25)	0.002	0.98 (0.92-1.04)	0.47

[a] = Adjusted for age, sex, and BMI

[b] = Adjusted for Model 1 plus smoking status

[c] = Adjusted for Model 2 plus amount of pre-existing comorbidities

[d] = Adjusted for Model 3 plus sarcoma stage

[e] = Adjusted for Model 4 plus therapy type

VAT = visceral adipose tissue; SAT = subcutaneous adipose tissue; HU = Hounsfield Units

Discussion

Our study shows that higher abdominal SAT attenuation and lower psoas muscle attenuation, assessed on non-contrast CT, are positive predictors of mortality in patients with extremity sarcomas, independent of other established prognostic factors, such as age, BMI, tumour stage, and comorbidities. These data suggest that adipose tissue and muscle attenuation could serve as novel biomarkers for mortality in patients with sarcomas, who often undergo CT as part of staging or surveillance.

Two recent large community-based cohort studies have suggested that increased adipose tissue attenuation on non-contrast CT might serve as a biomarker for all-cause mortality, including cancer mortality [10, 11]. In addition, a large longitudinal community-based cohort study in older men [17] and studies in patients with hepatocellular [16], pancreatic [15], and gastro-oesophageal [18] carcinoma found low muscle attenuation to be predictive of mortality. However, no study has been performed to assess the predictive value of tissue attenuation by CT on mortality in patients with sarcomas.

Sarcomas are relatively rare but challenging neoplasms with an incidence of about 1.5 per 100,000 [1]. They arise from mesenchymal cells, encompass multiple histological subtypes, and can occur at any anatomic site. In a large multicenter European study, analyzing 76 cancer registries, 84 % of sarcomas were soft tissue sarcomas and 14 % were bone sarcomas [1]. In contrast to the biological behaviour of carcinomas, which depends largely on the site and cell type of origin, the management and outcome of sarcomas is based primarily on the anatomic location [2]. However, the biological behaviour and prognosis also depend on the histological tumour grade and tumour stage. Therefore, the complex relationship between anatomic site and histology as well as the overall rarity of sarcomas adds to the challenges in managing patients with these neoplasms [1, 2]. Established prognostic factors of mortality in extremity sarcomas include tumour stage, therapy response, age, and associated comorbidities [2, 26–28]; however, these factors do not always correlate with outcome [29, 30].

In our study, increased SAT attenuation and decreased psoas attenuation were predictors of mortality, independent of prognostic factors such as tumour stage, age, sex, therapy, BMI, and comorbidities. Patients with sarcomas often undergo PET/CT for staging and surveillance [31, 32] and the non-contrast attenuation correction CT can be used to determine tissue attenuation. Adipose tissue and muscle attenuation can be easily measured on any clinical workstation by placing a ROI in the subcutaneous abdominal tissues and the psoas muscle and these measurements could be included on routine scans to provide additional information on prognosis. Furthermore, these biomarkers might help in identifying patients with muscle wasting and impaired nutritional status, who might benefit from intensive nutritional/exercise support.

There is an important link between adipose tissue and tumour growth [5]. Cancer cells can cause dedifferentiation of adipocytes and reprogramming into cancer-associated adipocytes [4]. During this process adipocytes secrete their lipids and these reprogrammed lipid-poor adipocytes secrete adipokines, which stimulate invasion of tumour cells and can cause systemic metabolic effects [4, 6]. In addition, cancer-associated cachexia results in adipose tissue atrophy and increased lipolysis and inability to store triacylglycerol [33]. Conversely, the tissue microenvironment can influence the growth of tumour cells, supporting tumorigenesis and metastases [5, 7]. Biopsy studies in animals have shown that high attenuation adipose tissue by CT corresponds to smaller adipocytes with lower lipid content and increased extracellular matrix fibrosis [10]. Our finding of increased adipose tissue attenuation in patients with increased mortality may reflect reprogrammed adipocytes with decreased lipid content

and inability to store lipids. Alternatively, increased adipose tissue attenuation may reflect an adipocyte microenvironment promoting tumour cell growth. There is a potential systemic effect of chemo- or radiation therapy on adipose tissue. However, we controlled for the type of therapy in and our analyses, and this did not adversely affect our results.

Our findings of an independent association between low psoas muscle attenuation and increased mortality is consistent with a study by Fujiwara et al., which demonstrated an inverse association between muscle attenuation and mortality in patients with hepatocellular carcinoma [16], and a study by Miljkovic et al., which found low muscle attenuation to be a predictor of all-cause and cardiovascular mortality in older men [17]. Low muscle attenuation by CT reflects increased lipid content [34] and is associated with sarcopenia [8] and poor prognosis in cancer patients[9, 35]. In addition, low muscle attenuation has been identified as a risk factor for insulin resistance [36], decreased muscle strength [37], and increased fracture risk [38]. An additional mechanism for increased mortality in sarcoma patients with muscle fatty infiltration may be the secretion of pro-inflammatory cytokines from adipocytes surrounding muscle fibres [19, 20]. Increased secretion of pro-inflammatory cytokines has been found to promote tumorigenesis [21].

Our study had several limitations. First, the retrospective study design limits our ability to infer causality. Second, we did not obtain adipose tissue or muscle biopsies to investigate potential mechanisms linking adipose tissue and muscle attenuation to mortality, and we did not have laboratory data, such as serum albumin available, which has been associated with mortality [39]. Third, we combined sarcoma subtypes in the analyses. The strengths of our study include the large number of patients with extremity sarcomas and detailed measures of tissue attenuation on non-contrast CTs. Moreover, we controlled our analyses for a wide variety of covariates.

In conclusion, our study shows that high adipose tissue attenuation and low muscle attenuation are positive predictors of mortality in patients with extremity sarcomas, independent of established prognostic factors. These results suggest that adipose tissue and muscle attenuation may serve as novel biomarkers of mortality in sarcoma patients.

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Compliance with ethical standards

Conflict of interest The authors have no conflict of interest to declare.

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