Low Subcutaneous Adiposity and Mortality in Esophageal Cancer

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ABSTRACT

Background: Recent data suggest that subcutaneous adiposity represents an independent prognostic marker in cancer. We aimed to determine whether subcutaneous adiposity estimated by the subcutaneous adiposity tissue index (SATI) was associated with mortality in esophageal cancer.

Methods: We conducted a retrospective analysis of a prospectively enrolled cohort from 2009 to 2015 with esophageal cancer at two major cancer centers. CT scans for initial staging were used to quantify adiposity and skeletal muscle areas. Subjects were categorized as above or below median SATI using sex-specific values. Sarcopenia was defined using previously established skeletal muscle area cutoffs. Cox proportional hazards modeling was performed to determine associations between SATI and all-cause mortality.

Results: Of the original 167 patients, 78 met inclusion criteria and had CT images available. Mean age was 67 years, 81.8% had adenocarcinoma, and 58.9% had stage 3 or 4 disease. Median follow-up time was 29.5 months. Overall 5-year survival was 38.9% [95% confidence interval (CI), 26.8–50.7]. Lower body mass index, higher Charlson comorbidity score, and more advanced stage were independently associated with low SATI. Patients with low SATI had increased mortality (unadjusted HR 2.23; 95% CI, 1.20–4.12), even when adjusted for sarcopenia or for percent weight loss. In a multivariable model including age, histology, stage, and receipt of curative surgery, the association between low SATI and mortality was attenuated (adjusted HR 1.64; 95% CI, 0.81–3.34).

Conclusions: Low subcutaneous adiposity as estimated by SATI may be associated with increased mortality in esophageal cancer.

Impact: Interventions to reduce loss of subcutaneous fat may improve survival in esophageal cancer.

Introduction

Outcomes for esophageal cancer remain dismal despite advances in treatment, with 5-year survival still less than 20% (1). The incidence of weight loss in patients with esophageal cancer is one of the highest among cancer types, likely due to a combination of cancer cachexia and decreased calorie intake as a result of mechanical tumor obstruction (2). In the past decade, the effects of weight loss have been studied in various cancers in an effort to better understand cancer cachexia, which has been previously defined in a consensus guideline as significant weight loss or the loss of skeletal muscle mass, with or without the loss of fat mass (3). Overall weight loss has been found to be associated with poor prognosis in patients with cancer (4, 5), and previous studies have demonstrated that obese patients with cancer may have better outcomes than their nonobese counterparts (4, 6, 7). However, many of these studies have relied on body mass index (BMI) to estimate body composition. Recent studies have utilized CT imaging to quantify muscle and fat, with presumably more accurate estimates of body composition in patients with cancer and understanding of their associations with clinical outcomes (8, 9).

Sarcopenia, the depletion of skeletal muscle mass, has been studied as a marker of cachexia and has been found to be an independent predictor of increased mortality in several types of cancer (4, 9), including esophageal cancer (5, 10, 11). The role of adiposity in cancer outcomes, however, is less well understood. Few studies have investigated the role of adiposity in esophageal cancer, and results have been mixed (5, 12, 13). Recent findings have suggested that increased visceral adiposity, measured as either visceral fat area (VFA) or as a ratio in comparison with subcutaneous fat area (SFA), may be associated with increased mortality in patients with either esophageal squamous cell carcinoma or adenocarcinoma (12, 13). In contrast, a large study published in 2017 of patients with various cancer types, including cancers of the gastrointestinal (GI) tract, respiratory tract, and kidney, did not find visceral adiposity to be significantly associated with increased mortality, and in fact demonstrated that patients with low subcutaneous adiposity were at highest risk of mortality (8). This study characterized subcutaneous adiposity using the subcutaneous adiposity tissue index (SATI)—defined as the SFA normalized by height squared, with cutoffs set by sex—and was the first study to investigate the impact of the specific marker SATI on survival in cancer.

Since then, few studies have examined the impact of subcutaneous adiposity on mortality in specific cancer populations, and no study to date has investigated the impact of SATI on mortality in patients specifically with esophageal cancer. We sought to assess whether the SATI, either alone or in conjunction with sarcopenia, was associated with mortality in a dedicated cohort of patients with esophageal cancer.

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As a secondary aim, we also sought to investigate the impact of other previously studied body composition variables [including skeletal muscle index (SMI), visceral adiposity tissue index (VATI), and total adiposity tissue index (TATI)] on mortality in our patient cohort.

Materials and Methods

Population

This was a retrospective analysis of a prospectively enrolled cohort of patients with newly diagnosed esophageal cancer at two major cancer centers in New York, NY, from 2009 to 2015. Full details of the cohort have been reported previously (14, 15). Subjects were excluded if they were enrolled >180 days following diagnosis, had high-grade dysplasia as their highest degree of neoplasia, or had a coexisting malignancy (besides nonmelanoma skin cancers) within 3 years before diagnosis. For the current analyses, patients were also excluded if they did not report current weight or weight 1 year prior to diagnosis in the administered questionnaire or did not have baseline pretreatment CT images available for review. The Institutional Review Boards at Columbia University Irving Medical Center and Weill Cornell Medical Center approved the study.

Patient characteristics

Upon enrollment, a questionnaire assessing baseline characteristics, including demographics, medical history, medication use, family history of cancer, tobacco use history, and alcohol use history, was administered to subjects. Self-reported height and weight values were used to calculate BMI 1 year prior to diagnosis, percent weight change in the year prior to diagnosis, and BMI at the time of diagnosis. Both patient self-report and medical records were used to document medical comorbidities, and the Charlson comorbidity index was used to assess disease burden, excluding esophageal cancer (16).

Tumor characteristics

Variables including diagnosis date, tumor histology, tumor differentiation, and, if applicable, HER2 status were extracted from pathology and surgery reports. If tumor differentiation included two grades, the worse of the two grades was assigned. Tumor stage was classified based on the American Joint Committee on Cancer, 7th edition (17), using a combination of pathologic and clinical staging information as published previously from this cohort (14, 15). Pathologic T stage was obtained from operative reports in those who underwent curative resection (esophagectomy or endoscopic mucosal resection) and clinical T stage from endoscopic ultrasound reports. Clinical T stage was used in the analyses unless the patient underwent surgery or endoscopic resection without neoadjuvant therapy, in which case we used pathologic T stage from the resection specimen. Lymph node status was classified as positive if there was any clinical or pathologic evidence of lymph node involvement prior to neoadjuvant therapy. Celiac, paraesophageal, and cervical lymph node involvement were defined as positive lymph nodes rather than distant metastases. Presence of distant metastases was recorded based on imaging and pathology reports (18).

Definition of body composition variables and use of CT

CT scans utilized for initial cancer staging were used to quantify SFA, VFA, paraspinal skeletal muscle area, whole skeletal muscle area, and muscle attenuation. Adipose and muscle areas were measured at the third lumbar vertebral level (L3), which has been shown to correlate with whole body fat and muscle mass, respectively (19). A muscle segmentation software developed by a member of the research team (X. Guo) was used to quantify muscle area and muscle attenuation (20). Using this software, paraspinal and abdominal musculature for three adjacent axial images at L3 were manually contoured (**Fig. 1A**). The software then performed basic image preprocessing and muscle segmentation, retaining only those pixels within the designated range $[T_{low}\ T_{high}]$. Muscle tissue was designated using a threshold of 0–100 Hounsfield units (HU) based on recent descriptions of CT numbers for muscle tissue and to minimize possible overlap with adipose tissue (21). A similar software developed by X. Guo was also adopted for fat segmentation based on prior software used for automated quantification of fat distribution on CT. Similarly, subcutaneous and visceral adipose tissues for three adjacent axial images at L3 were contoured manually (**Fig. 1A**), and the software then performed image preprocessing and fat segmentation, retaining only pixels within the range of -190 to -30 HU previously established for adipose tissue (22). This software for both muscle and fat segmentation was implemented in the MATLAB programming language. The software provides an interface allowing a user to draw free contours on the image and also enables editing, such as removing or adding parts of the contoured area, after image processing for muscle (or fat) segmentation. The muscle (or fat) segmentation is thus supervised by the user, which provides a quality control mechanism via manual review of the automated segmentation to correct any significant errors.

Measurements across the three axial images were averaged to yield mean values for subcutaneous and VFA as well as paraspinal and whole muscle cross-sectional area in cm^2. Muscle attenuation was defined as mean HU of the contoured muscle area. SFA was defined as the cross-sectional area of the adipose tissue superficial to the abdominal wall musculature, whereas VFA was defined as the cross-sectional area of the adipose tissue deep to the abdominal wall musculature. Total fat area (TFA) was calculated as the sum of the SFA and VFA. SATI was calculated as the SFA normalized by the patient's height and was reported as cm^2/m^2. VATI was similarly calculated using the VFA, and TATI was calculated using the TFA. Paraspinal muscle area included the cross-sectional area of the paraspinal musculature, whereas whole muscle area included the cross-sectional area of both the paraspinal and abdominal wall musculature. SMI was computed as the muscle cross-sectional area normalized by the patient's height and was reported as cm^2/m^2.

Sarcopenia was defined using whole muscle SMI cutoff values from Martin and colleagues that were previously shown to be associated with differences in survival for GI and respiratory cancers (4). Men with a BMI < 25 and SMI < 43 cm^2/m^2 or with a BMI ≥ 25 and SMI < 53 cm^2/m^2, and women of any BMI with SMI < 41 cm^2/m^2 were considered sarcopenic in this study. Because SATI cutoff values have not been extensively studied, we used sex-specific median values of SATI from the current study as the thresholds for low and high SATI. Thus, women with SATI < 87.6 cm^2/m^2 and men with SATI < 58.1 cm^2/m^2 were considered to have low SATI in this study. CT image examples of patients with variations in SATI and SMI are shown in **Fig. 1B**.

Follow-up

Data regarding death and date of death were obtained through chart review, the Social Security Death Index, and contacting next of kin (23). Follow-up data were collected through June 30, 2018.

Outcomes

The primary outcome of this study was all-cause mortality, defined as the time from diagnosis to death due to any cause. Postoperative complications were analyzed as a secondary outcome and were

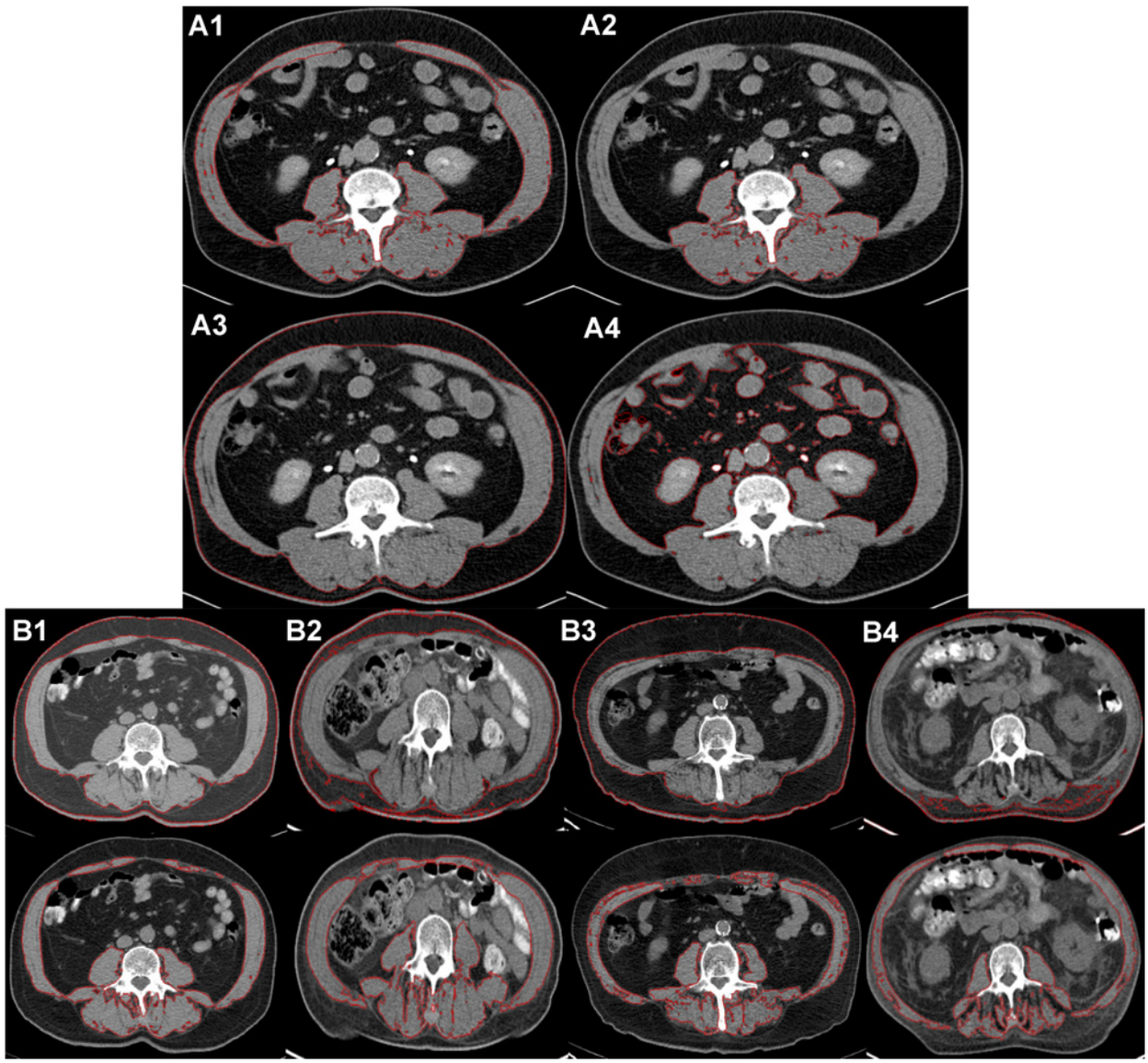

Figure 1.

Axial CT images of the third lumbar vertebral level (L3). **A,** Highlighted regions of whole skeletal muscle area (A1), paraspinal skeletal muscle area (A2), SFA (A3), and VFA (A4). **B,** Comparisons of images from male patients with variable SATI (top row) and SMI (bottom row): high SATI/nonsarcopenic (B1), low SATI/nonsarcopenic (B2), high SATI/sarcopenic (B3), and low SATI/sarcopenic (B4).

obtained from manual review of the electronic medical record. Complications were defined based on guidelines from the Esophagectomy Complications Consensus Group and included pulmonary, cardiac, GI, urologic, thromboembolic, neurologic, and infectious complications associated with esophagectomy (24). Any complication outlined in this consensus document that occurred within 30 days of esophagectomy was included as a postoperative complication.

Statistical approach

We used Student *t* tests and Wilcoxon rank-sum tests to analyze continuous variables, and Fisher exact and Kruskal–Wallis tests for categorical variables. To assess factors associated with low SATI, univariate and multivariable logistic regressions were performed. To build the final multivariable model, all variables that changed the beta coefficient for SATI by ≥10% were included; variables with the highest *P* value that was >0.15 were then removed one at a time. For time-to-event analyses, the date of diagnosis was used as time zero. Time to death was calculated for individuals who died, and all other individuals were censored at the last time point at which they were known to be alive. The log-rank test was used to compare survival curves between patient groups. Univariate Cox modeling was performed to determine the unadjusted associations between demographic, clinical, and tumor variables and mortality. Cox proportional hazards modeling was used to calculate HRs and 95% confidence intervals (CI). The association between SATI and all-cause mortality was analyzed using a series of models: model 1—unadjusted; model 2—adjusted for sarcopenia;

Table 1. Baseline patient characteristics of an esophageal cancer cohort ($n = 78$) at Columbia University Irving and Weill Cornell Medical Centers (2009–2015).

	All patients	Low SATI	High SATI	*P* value
Age at diagnosis, mean (SD)	66.8 (11.3)	68.5 (10.5)	65.2 (11.9)	0.20
Sex, male (%)	64 (82.1)	31 (81.6)	33 (82.5)	0.92
Race, white (%)	68 (87.2)	29 (76.3)	39 (97.5)	0.01
Tobacco exposure (%)				0.36
Never	20 (25.6)	7 (18.4)	13 (32.5)	
Former	49 (62.8)	26 (68.4)	23 (57.5)	
Current	9 (11.5)	5 (13.2)	4 (10.0)	
Charlson comorbidity index, median (IQR)	0 (1–2)	1 (0–2)	0 (0–1.5)	0.05
Charlson comorbidity index[a] (%)				0.11
0	34 (43.6)	12 (31.6)	22 (55.0)	
1	19 (24.4)	11 (29.0)	8 (20.0)	
>1	25 (32.1)	15 (39.4)	10 (25.0)	
BMI at diagnosis, median (IQR)	26.5 (23.3–29.2)	24.1 (21.4–26.5)	28.1 (26.4–32.3)	<0.001
BMI category				0.001
≤20	5 (6.4)	5 (13.5)	0	
>20–25	18 (23.1)	13 (35.1)	5 (12.5)	
>25–30	28 (35.9)	13 (35.1)	15 (37.5)	
>30 (Obese)	26 (33.3)	6 (16.2)	20 (50.0)	
Weight loss (%),[b] median (IQR)	4.6 (0–10.2)	5.6 (0–10.6)	4.2 (0–10)	0.60
Weight loss category				0.48
No weight loss	25 (32.1)	12 (31.6)	13 (32.5)	
>0%–<5%	17 (21.8)	11 (29.0)	6 (15.0)	
≥5%–<10%	15 (19.2)	6 (15.8)	9 (22.5)	
≥10%	21 (26.9)	9 (23.7)	12 (30.0)	
Received surgery (%)	51 (65.4)	26 (68.4)	25 (64.1)	0.69
Received any chemotherapy or radiotherapy (%)	61 (78.2)	33 (86.8)	28 (70)	0.07
Neoadjuvant (%)	39 (50.0)	21 (55.3)	18 (45.0)	
Adjuvant (%)	6 (7.7)	2 (5.3)	4 (10.0)	
Received endoscopic therapy (%)	5 (6.5%)	0	5 (12.8)	0.02

Abbreviation: IQR, interquartile range.
[a]Excluding cancer.
[b]Percent weight loss over 1 year prior to diagnosis of esophageal cancer.

model 3—adjusted for percent change in weight in the year prior to diagnosis; and model 4—the final multivariable model. The final multivariable model was built using the same methods as described above for the logistic regression model. The associations between SMI, VATI, and TATI with all-cause mortality were also assessed to determine the associations between these other body composition variables and mortality. In all models, complete subject analyses were used. All statistical analyses were performed using Stata 15.0 for Mac (StataCorp), and statistical significance was defined as $P < 0.05$.

Results

Study population

The original study cohort enrolled 167 patients with esophageal cancer over 6 years, consisting of 100 patients from Columbia University Irving Medical Center and 67 patients from Weill Cornell Medical Center. Of this group, 33 patients were excluded due to enrollment >180 days after diagnosis ($n = 16$), coexisting malignancy within 3 years before diagnosis ($n = 6$), high-grade dysplasia as the highest degree of neoplasia ($n = 5$), reclassification as gastric cancer ($n = 1$), withdrawal of consent ($n = 1$), or failure to report weight on the baseline questionnaire ($n = 4$; ref. 14). An additional 56 patients were excluded from this current analysis due to lack of baseline pretreatment CT images available for review (Supplementary Fig. S1). Characteristics of the 78 included subjects are summarized in **Table 1**. Of this cohort, 54 patients were from Columbia University Irving Medical Center and 24 patients from Weill Cornell Medical Center. Mean age at time of diagnosis was 67 years. The majority of patients were men (82.1%), of white race (87.2%), and had stage 3 or 4 disease (59.0%). Most tumors were adenocarcinomas (81.8%) and located at the gastroesophageal junction or lower third of the esophagus (79.2%; **Table 2**). Median time from diagnosis to baseline pretreatment CT imaging was 15.5 days [interquartile range (IQR), 7–30 days]. Fifty-one patients (65.4%) underwent surgery with curative intent, and 61 (78.2%) received any chemotherapy or radiotherapy (**Table 1**). Median follow-up time was 29.5 months (IQR, 10–55) for all patients and 54.5 months (IQR, 43–71) among patients who were still alive at the time of analysis. Among the 78 patients in this study, 44 patients (56.4%) died by the end of the study follow-up period.

Median BMI at the time of diagnosis was 26.5 (IQR, 23.3–29.2). Fifty-three patients (70.0%) were sarcopenic. Median SATI was 59.3 cm^2/m^2 (IQR, 35.9–79.0) among all patients and was significantly lower in men compared with women, with median SATI of 58.1 cm^2/m^2 (IQR, 35.1–76.2) for male patients and 87.6 cm^2/m^2 (IQR, 53.7–103.4) for female patients ($P = 0.04$).

In unadjusted analyses, patients with low SATI were significantly more likely to be non-white, have a Charlson comorbidity index >1, have lower BMI at the time of diagnosis, have squamous cell histology, and have received chemotherapy or radiotherapy (**Table 3**). Patients with low and high SATI were similarly likely to have received surgery.

Table 2. Tumor characteristics of an esophageal cancer cohort ($n = 78$) at Columbia University Irving and Weill Cornell Medical Centers (2009–2015).

	All patients	Low SATI	High SATI	*P* value
Histology[a] (%)				0.002
Adenocarcinoma	63 (81.8)	25 (67.6)	38 (95.0)	
HER2 positive	11 (22.5)	5 (13.5)	6 (15.0)	
Squamous cell carcinoma	14 (18.2)	12 (32.4)	2 (5.0)	
Grade[a] (%)				0.81
Well or moderately differentiated	28 (36.4)	14 (37.8)	14 (35.0)	
Poorly differentiated	32 (41.6)	16 (43.2)	16 (40.0)	
Unknown	17 (22.1)	7 (18.9)	10 (25.0)	
Location[a] (%)				0.19
GE junction or lower esophagus	61 (79.2)	27 (73.0)	34 (85.0)	
Mid- or upper esophagus	16 (20.8)	10 (27.0)	6 (15.0)	
Tumor–node–metastasis stage (%)				0.19
1	13 (16.7)	3 (7.9)	10 (25.0)	
2	19 (24.4)	9 (23.7)	10 (25.0)	
3	33 (42.3)	18 (47.4)	15 (37.5)	
4	13 (16.7)	8 (21.1)	5 (12.5)	

Abbreviation: GE, gastroesophageal.
[a]Tumor histology, grade, and location missing for one subject.

In multivariable logistic regression analyses, lower BMI, higher Charlson comorbidity index, and more advanced tumor stage were independently associated with low SATI.

Survival

In the study cohort, 3-year overall survival was 52.0% (95% CI, 40.0–62.7), and 5-year survival was 38.9% (95% CI, 26.8–50.7). There was no significant difference in overall survival between the included 78 patients versus the 56 patients excluded due to unavailable imaging (log-rank $P = 0.81$). On univariate analyses, patients with low SATI had increased all-cause mortality compared with high SATI (log-rank $P = 0.008$; **Fig. 2**). Low SATI remained significantly associated with increased all-cause mortality when adjusted for sarcopenia (adjusted HR 2.09; 95% CI, 1.12–3.88) and for weight loss (adjusted HR 3.00; 95% CI, 1.54–5.82; **Table 4**). In the final multivariable model, which included SATI, age, histology, stage, and receipt of curative surgery, the association between low SATI and mortality was somewhat attenuated and no longer significant (adjusted HR 1.64; 95% CI, 0.81–3.34).

Several sensitivity analyses were performed. The association between low SATI and mortality was not qualitatively altered with addition of receipt of neoadjuvant therapy (low SATI aHR 1.67; 95% CI, 0.81–3.45) or adjuvant therapy (low SATI aHR 1.60; 95% CI, 0.78–3.27) to the final model (model 4). In a sensitivity analysis excluding the 13 patients with stage 4 disease, overall results in the four models were again similar (low SATI: model 1, unadjusted HR 2.25, 95% CI, 1.08–4.69; model 2, aHR 2.14, 95% CI, 1.03–4.46; model 3, aHR 3.52, 95% CI, 1.56–7.94; and model 4, aHR 1.64, 95% CI, 0.75–3.66).

Because sarcopenia has previously been established as a predictor of increased mortality in esophageal cancer, a composite variable for SATI and sarcopenia was created, dividing patients into four groups based on SATI and sarcopenia (high SATI/nonsarcopenic, high SATI/sarcopenic, low SATI/nonsarcopenic, and low SATI/sarcopenic). There was a significant trend toward increased mortality across groups; high SATI/nonsarcopenic patients had the lowest mortality, and low SATI/sarcopenic patients had the highest mortality (log-rank $P = 0.02$; **Fig. 3**).

On univariate analysis, VATI, TATI, and muscle attenuation were not associated with all-cause mortality.

Complications

Among the 51 patients who underwent curative surgery in our cohort, 23 (45.1%) had a postoperative complication. This included 3 patients with chyle leaks, 5 patients with anastomotic leaks, and 5 patients who developed postoperative pneumonia. On univariate analysis, there were no significant predictors of complications, including low SATI or presence of sarcopenia.

Discussion

The results of the current study suggest that low subcutaneous adiposity as estimated by the SATI may be associated with increased mortality in patients with esophageal cancer. Low SATI was associated with increased mortality even after adjusting for sarcopenia, which suggests that low SATI and sarcopenia may be important yet distinct predictors of poor outcomes in esophageal cancer. Although SATI did not remain independently associated with mortality in the final multivariable model, the study may have been underpowered to detect small yet clinically meaningful associations. To our knowledge, this is the first study investigating the effect of SATI in a dedicated cohort of patients with esophageal cancer.

Prior studies investigating the effects of body composition on cancer survival have generally focused on sarcopenia, with fewer studies focused on adiposity. Investigation of subcutaneous fat have inconsistently used distinct cutoffs by sex, despite the significant sex differences in subcutaneous adiposity (25). Determining the optimal index and cutoffs for capturing adiposity will be an important step in utilizing this variable as a prognostic factor. Previous studies have demonstrated that relative body fat is best predicted by adjusting for height, similar to the determination of BMI (26, 27). These studies further support the use of SATI as opposed to absolute subcutaneous adiposity as a better measure of relative adiposity. Two studies that have evaluated height-adjusted subcutaneous adiposity index and cancer outcomes did find an independent association between low SATI and increased mortality, whereas several studies that have investigated the impact of absolute SFA have not demonstrated an association with mortality (8, 12, 13, 28). Most notably, the study by Ebadi and colleagues of over 1,700 patients with GI, respiratory, and

Table 3. Factors associated with low SATI in an esophageal cancer cohort ($n = 78$) at Columbia University Irving and Weill Cornell Medical Centers (2009–2015).

	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Age at diagnosis		
<65	(Ref.)	
≥65	1.82 (0.73–4.51)	
Sex		
Female	(Ref.)	
Male	0.94 (0.30–2.99)	
Race		
White	(Ref.)	
Non-white	12.1 (1.45–101)	
Tobacco exposure		
Never	(Ref.)	
Former	2.10 (0.72–6.16)	
Current	2.32 (0.47–11.5)	
Charlson comorbidity index		
0	(Ref.)	(Ref.)
1	2.52 (0.80–7.97)	2.45 (0.49–12.2)
>1	2.75 (0.95–7.98)	**15.7 (2.11–117)**
BMI at diagnosis	0.72 (0.61–0.85)	**0.62 (0.49–0.79)**
Weight loss (%)		
No weight loss	(Ref.)	(Ref.)
>0%–<5%	1.99 (0.56–7.05)	1.69 (0.23–12.2)
≥5%–<10%	0.72 (0.20–2.64)	0.77 (0.09–7.02)
≥10%	0.81 (0.25–2.61)	**0.11 (0.01–0.90)**
Received surgery		
No	(Ref.)	(Ref.)
Yes	1.21 (0.47–3.13)	4.16 (0.69–24.9)
Received chemotherapy or radiotherapy		
No	(Ref.)	
Yes	3.54 (1.02–12.2)	
Histology		
Adenocarcinoma	(Ref.)	
Squamous cell	9.12 (1.88–44.3)	
Grade		
Well or moderately differentiated	(Ref.)	
Poorly differentiated	1.00 (0.36–2.76)	
Unknown	0.70 (0.21–2.36)	
Location		
GE junction/lower third	(Ref.)	
Middle/upper third	2.10 (0.48–1.32)	
Tumor–node–metastasis stage		
1	(Ref.)	(Ref.)
2	3.00 (0.62–14.5)	6.55 (0.56–76.3)
3	4.00 (0.93–17.2)	**14.4 (1.25–94.6)**
4	5.33 (0.97–29.4)	**42.4 (1.66–105)**

Note: Numbers in bold in adjusted analyses are statistically significant.
Abbreviation: GE, gastroesophageal.

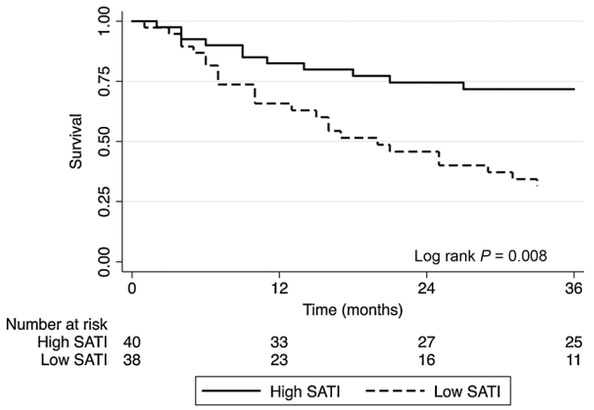

Figure 2.
Kaplan–Meier survival curves in a cohort of patients with esophageal cancer comparing high versus low SATI.

renal cell carcinoma found that SATI, regardless of visceral adiposity or presence of sarcopenia, was an independent prognostic factor for increased mortality (8). Their group used cutoffs of SATI <50.0 cm^2/m^2 in males and <42.0 cm^2/m^2 in females, which were defined as the SATI values associated with the highest mortality in their study. Only 23 patients in their cohort had esophageal cancer, and furthermore their study did not report median SATI values by cancer type, so it is difficult to compare our study results.

In the current study, we found that more comorbidities and more advanced stage of disease were independently associated with low SATI on multivariable analysis. These predictors of low SATI may contribute to the trend toward worse outcomes among low-SATI patients. Interestingly, although low BMI was an independent predictor of low SATI, we found that greater percent weight loss was associated with high SATI in multivariable analyses. Reasons for this finding are unclear, although a possible explanation may relate to differential loss of adipose and muscle mass in various compartments in the setting of cancer cachexia. In addition, it is possible that patients with a higher starting weight are more likely to lose a greater percentage of their body weight compared with patients with a lower starting weight, and those with a higher starting weight may be more likely to have high SATI at diagnosis.

In contrast to prior studies investigating the impact of obesity in esophageal cancer (12, 13), we did not find visceral adiposity to be a significant predictor of mortality. Saeed and colleagues demonstrated that among patients with esophageal adenocarcinoma, increased VFA, but not total or SFA, was significantly associated with increased mortality (13). Similarly, Okamura and colleagues demonstrated that among patients with esophageal squamous cell carcinoma, a high ratio of VFA to SFA was associated with increased mortality (12). These studies included only patients who underwent curative surgical resection (esophagectomy), in which case medical comorbidities associated with higher visceral adiposity—such as pre-existing cardiovascular disease or diabetes—may have confounded the association between visceral adiposity and survival (29). The authors hypothesized that the association between visceral adiposity and increased mortality could be attributed to poorer surgical outcomes and response to preoperative treatment (12, 13). Our current study, however, did not find a significant association between VATI or VFA and survival or surgical complications, although the small sample size may have limited our ability to detect such a difference.

The mechanism behind a potential protective effect of subcutaneous adiposity in patients with esophageal cancer is unclear. Subcutaneous adipose tissue is the primary producer of leptin, which plays an important role in insulin sensitivity and leads to more favorable glucose and lipid metabolism (30–32). Loss of subcutaneous adipose tissue has been shown to be a risk factor for higher glucose and lipid levels and thus increased risk of insulin resistance, diabetes, and dyslipidemia (33, 34). In contrast, visceral adipose tissue is more metabolically active than subcutaneous fat and predominantly produces adipokines and cytokines associated with increased systemic inflammation and increased insulin resistance (35). Hyperinsulinemia

Table 4. Cox proportional hazards models for the associations between SATI and all-cause mortality.

	HR (95% CI)
Model 1 (unadjusted)	
SATI	
High	(Ref.)
Low	2.23 (1.20–4.12)
Model 2	
SATI	
High	(Ref.)
Low	2.09 (1.12–3.88)
SMI	
Nonsarcopenic	(Ref.)
Sarcopenic	1.84 (0.90–3.76)
Model 3	
SATI	
High	(Ref.)
Low	3.00 (1.54–5.82)
Weight loss (%)	
No weight loss	(Ref.)
>0%–<5%	0.90 (0.37–2.21)
≥5%–<10%	2.66 (1.12–6.35)
≥10%	2.18 (0.97–4.93)
Model 4	
SATI	
High	(Ref.)
Low	1.64 (0.81–3.34)
Age	
<65	(Ref.)
≥65	1.80 (0.91–3.56)
Histology	
Adenocarcinoma	(Ref.)
Squamous cell carcinoma	1.85 (0.82–4.17)
Tumor–node–metastasis stage	
1	(Ref.)
2	3.85 (0.79–18.8)
3	8.15 (1.76–37.6)
4	5.89 (1.20–29.0)
Received surgery	
No	(Ref.)
Yes	0.22 (0.09–0.52)

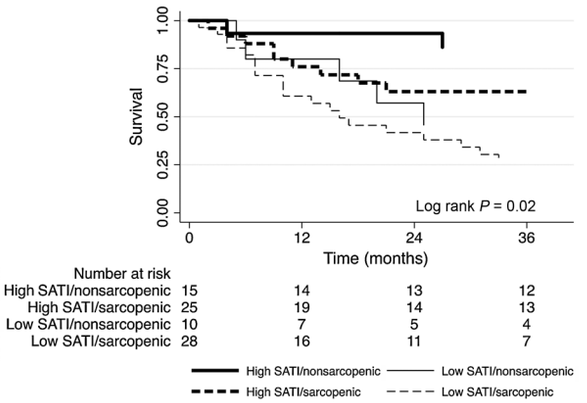

Figure 3.
Kaplan–Meier survival curves in a cohort of patients with esophageal cancer comparing outcomes based on a combination of SATI and sarcopenia.

and elevated C-peptide, markers of increased insulin resistance, have been associated with increased mortality in breast and prostate cancer (36, 37), possibly due to tumor progression associated with hyperinsulinemia via upregulation of insulin receptors or insulin-like growth factor I (38). Thus, loss of potentially protective effects of subcutaneous fat may lead to increased insulin resistance and systemic inflammation promoted by visceral adipose tissue.

The current study has several strengths. The association between low SATI and increased mortality was consistent and persisted after adjustment both for sarcopenia and for weight loss. Our cohort consisted of newly diagnosed patients with esophageal cancer, and data were prospectively collected. We took a thorough approach to evaluating various body composition variables, and our use of SATI may be a more optimal measurement of subcutaneous adiposity than has been used in prior studies. We were also able to follow patients for a significant amount of time, with median follow-up time for survivors of almost 5 years. Finally, the associations between low SATI and all-cause mortality remained qualitatively unaltered in various sensitivity analyses.

There are, however, certain limitations of this study. The sample size precluded comparisons of potentially important subgroups, such as histologic subtype, and the effect estimates may be imprecise in light of the wide confidence intervals. In addition, the study may have been underpowered to detect a smaller yet clinically meaningful association between low SATI and mortality in the final multivariable model. In addition, due to variation in disease stage, not all patients underwent surgery for curative intent. Baseline CT images were not available for a proportion of the original cohort of patients with esophageal cancer, which limited our study size. Comparing characteristics of the included patients who had imaging available versus those who did not, there were no significant differences. Thus, it is unlikely that our results were markedly biased by excluding patients without available imaging. There also may have been subtle differences in imaging quality and protocols between CT images, and thus there may be some limitations in terms of comparability and reproducibility. We used a marginally narrower HU range for muscle segmentation compared with some other studies, which may limit generalizability. However, this was done to increase specificity of our software and to prevent potential overlap with adiposity detection. Lastly, it is not possible to determine whether decreased subcutaneous adiposity contributes to worse survival, or whether patients with more aggressive disease lose more subcutaneous adipose tissue.

In summary, in this prospective cohort of patients with esophageal cancer, low SATI was a predictor of increased mortality, independent of sarcopenia and of prediagnosis weight loss. Larger studies are warranted to determine the potential clinical utility of SATI as a prognostic marker in esophageal cancer. The difference in impact on mortality between subcutaneous and visceral adiposity, as well as the difference in metabolic properties associated with these tissue subtypes, suggests that further study of their effects in cancer is needed. Interventions that may help prevent loss of adiposity, in particular subcutaneous fat, may be beneficial in improving survival in patients with esophageal cancer.

Authors' Disclosures

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Authors' Contributions

M.J. Zhou: Conceptualization, data curation, formal analysis, validation, investigation, visualization, methodology, writing–original draft, project administration, writing–review and editing. **L. Tseng:** Data curation, investigation, writing–review and editing. **X. Guo:** Data curation, software, writing–original draft, writing–review and editing. **Z. Jin:** Formal analysis, validation. **S. Bentley-Hibbert:** Resources. **S. Shen:** Data curation, writing–review and editing. **J.L. Araujo:** Resources. **C.F. Spinelli:** Resources. **N.K. Altorki:** Resources. **J.R. Sonett:** Resources. **A.I. Neugut:** Resources. **J.A. Abrams:** Conceptualization, resources, data curation, formal analysis, supervision, validation, investigation, visualization, methodology, writing–original draft, writing–review and editing.

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