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Authors

Zhou, Cathy
Foster, Brent
Hagge, Rosalie
et al.

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Opportunistic Body Composition Evaluation in Patients with Esophageal Adenocarcinoma: Association of Survival with ^{18}F-FDG PET/CT Muscle Metrics

Cathy Zhou[1,*], **Brent Foster**[2,*], **Rosalie Hagge**[1], **Cameron Foster**[1], **Leon Lenchik**[3], **Abhijit J. Chaudhari**[1,#], **Robert D. Boutin**[1,4,#]

[1]Radiology, University of California Davis, Sacramento, CA 95616, USA

[2]Biomedical Engineering, University of California Davis, Sacramento, CA 95616, USA

[3]Radiology, Wake Forest School of Medicine, Winston-Salem, NC 27157, USA

[4]Radiology, Stanford University School of Medicine, Stanford, CA 94305, USA

Abstract

Objective—^{18}F-FDG PET is widely used to accurately stage numerous types of cancers. Although ^{18}F-FDG PET/CT features of tumors aid in predicting patient prognosis, there is increasing interest in mining additional quantitative body composition data that could improve the prognostic power of ^{18}F-FDG PET/CT, without additional examination costs or radiation exposure. The aim of this study was to determine the association between overall survival and body composition metrics derived from routine clinical ^{18}F-FDG PET/CT examinations.

Methods—Patients who received baseline ^{18}F-FDG PET/CT imaging during workup for newly diagnosed esophageal adenocarcinoma (EAC) were included. From these studies, psoas cross-sectional area (CSA), muscle attenuation (MA), SUV_{mean}, and SUV_{max} were obtained. Correlation with overall survival was assessed using a Cox Proportional Hazards model, controlling for age, body mass index, ^{18}F-FDG dose, glucose level, diabetes status, in-hospital status, and tumor stage.

Results—Among the 59 patients studied, psoas MA and SUV_{max} were found to be significant predictors of survival (HR: 0.94, 95% CI: 0.88–0.99, p=0.04, and HR: 0.37, 95% CI: 0.14–0.97,

Corresponding Author: Abhijit J. Chaudhari, Ph.D., Department of Radiology, UC Davis School of Medicine, 4860 Y Street, Suite 3100, Sacramento, CA 95817, Phone: (916) 734-0833, Fax: (916) 734-7965, ajchaudhari@ucdavis.edu.
*,#These authors have contributed equally to this work

Conflict of Interest: The authors declare that they have no conflict of interest.

ETHICAL APPROVAL

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research board and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. For this type of study formal consent is not required.

p=0.04, respectively) and remained independent predictors. Psoas CSA and SUV_{mean} did not significantly influence survival outcomes.

Conclusions—Characterization of psoas muscles as a surrogate marker for sarcopenia on baseline ^{18}F-FDG PET/CT imaging is relatively easily obtained and may offer additional prognostic value in patients with EAC.

Keywords

PET/CT; body composition; esophageal adenocarcinoma; sarcopenia; myosteatosis

INTRODUCTION

Esophageal adenocarcinoma (EAC) is an aggressive cancer with an incidence that has increased rapidly in the last several decades; the current incidence in the United States is over 4 of 100,000 persons.[1] Despite improvements in early detection and treatment, the current overall 5-year survival is 17.9%.[2] Identifying new prognostic factors, including factors that predict response to treatment, are important for improving patient management and quality of life. ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT) is commonly used for tumor staging and predicting response to therapy.[3–10] A value-added paradigm shift would occur if the same ^{18}F-FDG PET/CT studies were used to assess simultaneously for prognostic factors that are independent of the tumor itself, without additional imaging examination costs or radiation exposure.

Sarcopenia is defined generally as decreased muscle mass and function, and is associated with increased morbidity and mortality.[11, 12] Although we use the term *sarcopenia* here, the etiology of muscle wasting can be multifactorial, and include both age-related muscle loss and cancer-related cachexia. Systemic inflammatory processes are especially important contributing factors in cancer patients.[13, 14] On CT, sarcopenia is commonly measured using the skeletal muscle index (SMI), defined as the cross-sectional area (CSA, in cm^2) of muscle normalized for the patient height (in m^2).[15] In patients with EAC, changes in SMI following treatment have been used to predict post-operative outcomes, including disease-free and overall survival.[10, 16–19] However, measurement of SMI in most research studies requires CT image export to a separate workstation for manual segmentation of numerous muscles and analysis with third party software.[15, 19–22] Alternatively, it may be efficacious – and more practical clinically – to simply measure psoas muscle CSA as a proxy for whole body muscle status. [23–28]

While ^{18}F-FDG PET/CT assessment of primary lesions has demonstrable prognostic value in patients with EAC,[3–10, 29] there is a paucity of outcome data on the opportunistic evaluation of body composition using ^{18}F-FDG PET/CT. Given that higher ^{18}F-FDG uptake reflects increased glucose metabolism, as may be seen with malignant or inflammatory processes, we hypothesized that both increased psoas SUV_{mean} and SUV_{max} would correlate with less favorable survival outcomes. Our objectives were to study psoas CSA, muscle attenuation (MA), and standardized uptake values (SUV_{mean} and SUV_{max}) as predictors of mortality in patients with EAC.

MATERIALS AND METHODS

Patient Selection

This study was approved by our university's Institutional Review Board, and the requirement for informed consent was waived because of its retrospective nature. All patients referred to our institution's cancer center between April 2006 to November 2017 for primary staging of biopsy-proven EAC who received pre-treatment ^{18}F-FDG PET/CT scans were entered into our study database. Seventy-six (n=76) potentially eligible patients were identified. Patients with additional prior or current malignancy (n=8), patients with known genetic syndrome predisposing to malignancy (n=1), and patients with EAC lost to follow-up (n=8) were excluded. Of the 8 patients excluded for additional malignancy, 2 had a history of lung cancer, 2 had a history of testicular cancer, and the remainder had head and neck squamous cell carcinoma, thyroid, pancreatic, and prostate carcinoma.

The electronic health records were reviewed for relevant clinical information compromising of age, sex, body mass index (BMI) at diagnosis and last follow-up, co-morbidities (including diabetes), in-hospital status, vertical length of esophageal involvement, TNM staging, and treatment with chemoradiation and/or esophagectomy. Disease status at the patient's last follow-up was divided into the following categories: no evidence of disease, alive with disease, dead of disease, and dead of other causes (including co-morbidities and post-operative complications). Patient mortality outcomes, if not otherwise indicated in their chart, were obtained via publicly available death records. Overall survival was defined as the time from diagnosis to the last follow-up visit or death.

^{18}F-FDG PET/CT Data Acquisition and Analysis

^{18}F-FDG PET/CT scans were performed on a General Electric (GE) Discovery ST scanner (n=27, prior to May 2012) or a GE Discovery 690 scanner (n=32, after May 2012). All patients were asked to fast for at least 6 hours and avoid vigorous activity prior to scanning in accordance with our institutional protocol. A non-contrast CT scan (8 and 64 slice on the Discovery ST and Discovery 690 scanners, respectively) was acquired from the head to proximal thighs, followed by 3D PET emission data collection, which was reconstructed using an ordered-subset expectation maximization algorithm (2/30 and 2/24 subsets and iterations on the Discovery ST and Discovery 690 scanners, respectively).

For each CT exam, the axial slice at the level of the transverse processes of the L4 vertebra was selected for psoas muscle measurements (Figure 1). For each psoas muscle, short and long axis measurements were recorded and an ellipse area was calculated (area= π(short axis/2)(long axis/2)). The left- and right-sided values were then averaged, resulting in an aggregate CSA value. The attenuation of each psoas muscle was obtained manually in each patient by applying a circular region of interest (ROI) to encompass as much of the muscle as possible. CT-measured attenuation in Hounsfield units (HU) from psoas muscles on both sides was averaged, resulting in mean MA. From the ^{18}F-FDG PET/CT images, SUV_{mean} and SUV_{max} values were also obtained from circular ROIs. When applicable, ROIs on ^{18}F-FDG PET/CT images were adjusted to avoid spillover activity from adjacent bowel or ureter.

Two readers independently performed ^{18}F-FDG PET/CT measurements while blinded to clinical outcomes. The primary reader was a combined nuclear medicine-radiology resident-in-training with more than two years of experience with ^{18}F-FDG PET/CT. The second reader was a radiologist, board-certified in both diagnostic radiology and nuclear medicine, with over 20 years of experience in both. Approximately 2 months after the initial read, the first reader repeated SUV_{mean} and SUV_{max} measurements on all scans while blinded to initial measurements. The second reader independently recorded SUV_{max} values for all available scans. Psoas CSA and MA measurements were repeated on a randomly chosen subset of 23 of the 49 scans by the first reader.

Statistical Analysis

Intraclass correlation coefficient (ICC) calculations were used to evaluate the repeatability of the first reader's initial and subsequent measurements of psoas CSA, MA and SUV_{max}, and the reproducibility of the first and second readers' SUV_{max} measurements. Interpretation of the ICC calculation was based on established guidelines (excellent, between 0.75 and 1.0; good, between 0.60 and 0.74; fair, between 0.40 and 0.59; poor, less than 0.40).

Cumulative survival rates were determined using Kaplan Meier analysis. A Cox proportional-hazards model was used to analyze the association of CT and ^{18}F-FDG PET/CT muscle measurements with survival after adjustment for age, BMI, ^{18}F-FDG dose, glucose level, diabetes status, in-hospital status and tumor stage. A p-value of 0.05 or less was considered statistically significant.

RESULTS

Patient Characteristics and Measurement Analysis

The characteristics of the 59 patients are presented in Table 1. Values are presented as (mean ± standard deviation) where relevant. Briefly, there were 51 (86.4%) men, the age at diagnosis was 61.7 ± 9.4 years, and the BMI was 29.7 ± 6.6. The vertical length of esophageal involvement, obtained from endoscopy reports, was 5.2 ± 2.9 cm. Clinical staging was documented by the primary oncologist, with the exception of 3 (5.1%) patients who did not have reported staging. Most patients received chemotherapy and/or radiation (76.3% and 68.4%, respectively); 33.9% underwent esophagectomy.

As noted in Table 1, the psoas CSA was 16.6 ± 4.4 cm^2. The psoas MA was 45.9 ± 6.9 HU. The psoas SUV_{mean} was 0.8 ± 0.3 g/ml, and the SUV_{max} was 1.3 ± 0.5 g/ml.

Intra- and inter-reader agreement is shown in Table 2. The reliability of observer 1 was good (0.69) for MA measurements, excellent (0.90) for CSA, and excellent (0.93) for SUV_{max}. The inter-observer agreement of SUV_{max} between the first reader and the second reader was excellent at 0.91.

Follow-up and Survival Analysis

At last follow-up (2.04 ± 2.08 years), 15 (25.4%) patients were alive with no evidence of disease, 7 (11.9%) were alive with disease, 33 (55.9%) patients were dead of disease, and 4 (6.8%) were dead of other causes. Survival from the time of diagnosis was 23.90 ± 24.96

months. The Kaplan-Meier survival distribution over 2.5 years is shown in Figure 2. The MA cut-off between high and low risk groups was 47.9 HU, with a value of 51.47 ± 3.21 HU for the low risk group, and 40.84 ± 5.31 HU for the high risk group. The SUV_{max} cut-off between high and low risk groups was 1.2 g/ml, with a value of 1.65 ± 0.61 g/ml for the low risk group, and 0.99 ± 0.15 g/ml for the high-risk group.

Table 3 presents hazard ratios (HR) for mortality using CT and ^{18}F-FDG PET/CT prognostic measures. Psoas MA was significantly associated with survival, independent of age, BMI, diabetes, and in-hospital status (HR: 0.94, 95% CI: 0.88–0.99, p=0.04). Psoas SUV_{max} was also a significantly favorable prognostic factor after adjusting for age, BMI (which accounts for height), ^{18}F-FDG dose, blood glucose level, diabetes, and in-hospital status (HR: 0.37, 95% CI: 0.14–0.97, p=0.04). Psoas SUV_{max} remained significant when adjusting for psoas CSA (HR: 0.37, 95% CI: 0.14–0.99, p=0.04). Both psoas MA and SUV_{max} were independently associated with survival (HR: 0.92 and 0.33, 95% CI: 0.87–0.98 and 0.12–0.88, p=0.01 and 0.02, respectively). Additionally, both psoas MA and SUV_{mean} were independently associated with survival (HR: 0.91 and 0.11, 95% CI: 0.85–0.97 and 0.02–0.63, p=0.003 and 0.01, respectively). Tumor stage and mass size were associated with poorer survival (HR: 1.85 and 1.18, 95% CI: 1.20–2.85 and 1.03–1.36). Psoas CSA, SUV_{mean}, diabetes, or in-hospital status independently did not show a significant association with survival.

DISCUSSION

The present study demonstrates that increased baseline psoas MA and SUV_{max} are independently correlated with improved survival in patients diagnosed with EAC.

Core MA as a prognostic factor has been investigated for other malignancies, with increased psoas MA associated with better outcomes in patients with adrenocortical carcinoma,[30] melanoma,[31] and sarcoma.[32] In patients with EAC, Tamandl et al.[19] reported that low MA (≤40 HU) of total skeletal muscle at the L3 level was associated with worse outcomes. This is in concordance with our findings that psoas MA is significantly associated with survival in patients with EAC. Miller et al.[30] further segregated psoas MA by adrenocortical carcinoma staging. With a larger cohort, a similar approach to patients with EAC could help establish specific prognostic expectations associated with quantitative measures of psoas CSA and MA.

The characterization of skeletal muscle on ^{18}F-FDG PET/CT has also shown promise. [33] For example, in a study analyzing psoas SUV_{max}, increased muscle ^{18}F-FDG activity was associated with metabolic syndrome,[34] a process possibly mediated through inflammatory effects on adipocytes.[35] An additional mechanism for mortality may be the increased expression of pro-inflammatory cytokines in muscle with a higher degree of adipose and fibrotic tissue.[36] Previous studies have found significant association of increased skeletal muscle SUV_{mean} and SUV_{max} with severity of polymyositis and dermatomyositis syndromes, via a proposed mechanism of metabolically active inflammation, necrosis, and muscle fiber regeneration. [37, 38]

However, in our cohort, we found that increased psoas muscle SUV_{max} was a significant positive prognostic factor in patients with EAC, which was contrary to our hypothesis. While the proposed inflammatory component likely affects ^{18}F-FDG uptake in patients with concurrent malignancy, it does not appear to play a dominant role. This may instead be explained by myosteatosis. Intramuscular lipid content increases with age and contributes to impaired muscle quality.[39] Such fatty infiltration has been shown to decrease attenuation of skeletal muscle on CT.[40, 41] Increased fatty infiltration of tissue likely indirectly reflects general deconditioning of the muscle. Thus, increased MA and SUV_{max} may reflect more robust muscle tissue in patients with better general conditioning, leading to better outcomes.

Also contrary to our hypothesis, SUV_{mean} showed no association with mortality. These findings are similar to recently published results from Park et al.[17] that indicated there was no association between psoas muscle CSA and SUV_{mean} with post-esophagectomy outcomes in patients with esophageal carcinoma. We note that SUV_{max} is commonly preferable to SUV_{mean}, including when measuring relatively small ROIs (e.g., psoas muscle). We also note that there was a relatively small range of SUV_{mean} values in our study, which could reflect a baseline homeostasis for core muscle that is relatively unaffected by co-morbidities.

Our findings are of clinical significance for patients with EAC because they may lead to changes in patient management and prognosis. Taaffe et al.[42] demonstrated that a resistance exercise regimen increased MA in healthy older adults, likely owing to decreased fat content in muscle. In patients with breast, colorectal, and prostate cancer, diet and exercise has been shown to be associated with improved survival.[43] In patients with EAC, specific nutritional intervention with the goal of immunomodulation has been associated with improved lean body mass and physical function.[44, 45] Thus, a diet and exercise prescription customized for patients with low MA may possibly benefit patients with EAC.

In our study, psoas CSA was not associated with overall survival. We used CSA as a measure of muscle mass, recognizing that the CT measurement of muscle size has been associated with survival in patients with esophageal cancer in some prior studies. Nakashima et al. [46] reported that low SMI on CT was associated with decreased survival, but only in patients age 65 years and older. However, most other studies of patients with esophageal cancer have found no association between CT-derived SMI [21, 22, 47, 48] or total psoas CSA [49] and overall survival, which is consistent with our findings. The combination of multiple CT-derived body composition metrics may improve prognostic power. For example, Tamandl et al.[19] reported that a composite of three CT parameters (i.e., low SMI, low MA, and high total body fat mass index) was associated with worse overall survival in esophageal cancer patients.

This study has several limitations. This was a retrospective single-institution study with a relatively small number of patients. The number of potential participants was further limited by the lack of uniform workup; in the past, patients were sometimes followed by CT only (with no ^{18}F-FDG PET/CT studies available) or only obtained ^{18}F-FDG PET/CTs after treatment. The increasing use of ^{18}F-FDG PET/CT is likely attributed to a combination of

radiopharmaceutical access, reimbursement, and increased evidence substantiating the use of ^{18}F-FDG PET/CT in patient management.[50] Moreover, the small sample size limited subgroup analyses. Information regarding physical performance status of the patients in this study was not available and may differentially affect CT and PET measurements. Both the General Electric (GE) Discovery ST scanner and the GE Discovery 690 scanners used in this study underwent routine quality control procedures based on standards laid out by the American College of Radiology and National Electrical Manufacturers Association (NEMA). Some of the scanner characteristics were different. For example, the GE Discovery ST scanner has a transverse (axial) spatial resolution of 6.28 (4.56) mm and 6.88 (6.11) mm at 1 cm and 10 cm off axis respectively [51] while the GE Discovery 690 has a transverse (axial) spatial resolution of 4.70 (4.74) mm and 5.06 (5.55) mm at 1 cm and 10 cm off axis, respectively.[52] Although it was not possible to compare scanner performance or control for it, future studies in larger cohorts will need to consider if scanner type influences the outcome measures. A limitation of our study may also be related to our simplified ellipse methodology. Our PACS software did not allow for defining a ROI by predetermined thresholds, which would help delineate psoas muscle boundaries from adjacent fat and bone. Although free hand circumference measurements are possible, these were relatively less reliable. Future research would favor improved methods for psoas segmentation.

CONCLUSION

Increased MA and SUV_{max} of psoas muscles on baseline ^{18}F-FDG PET/CT imaging in patients diagnosed with esophageal adenocarcinoma were associated with improved overall survival and may serve as novel biomarkers of mortality in patients with EAC.

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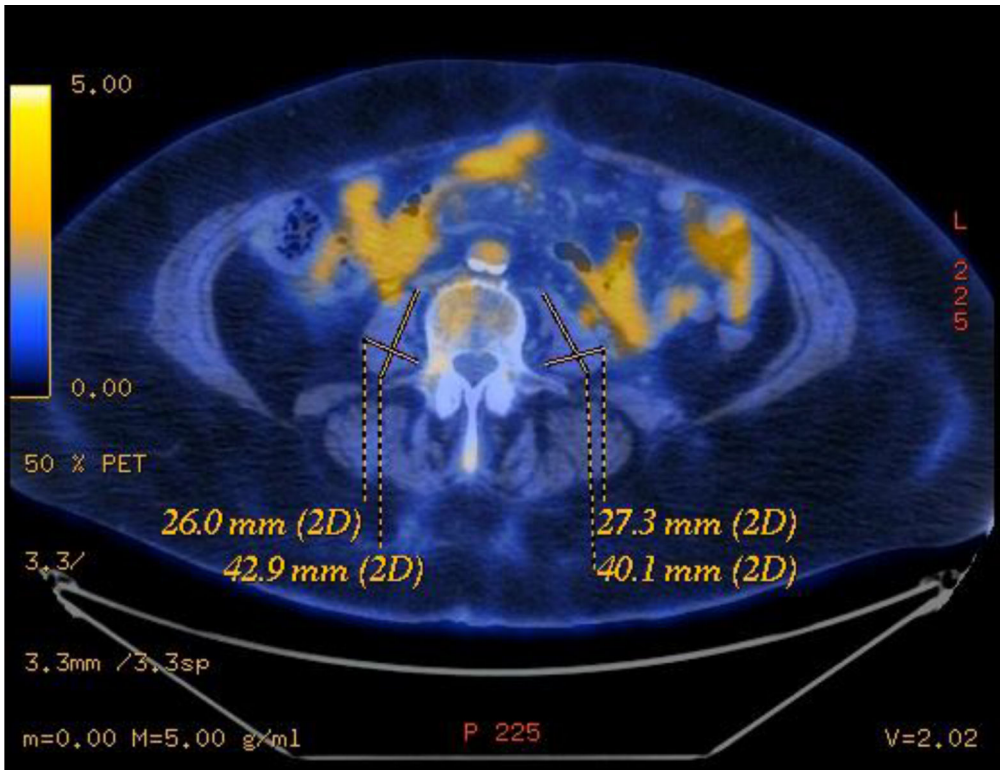

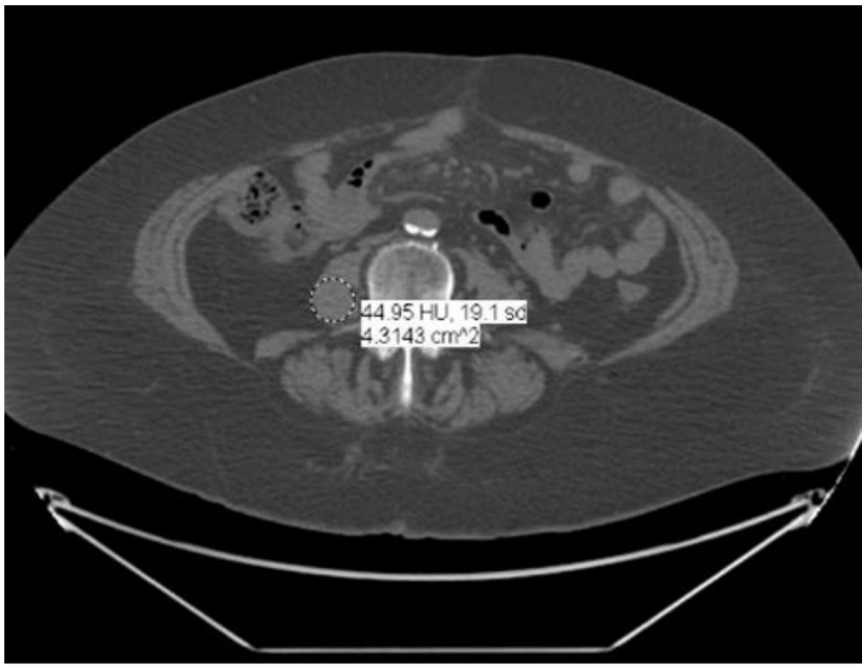

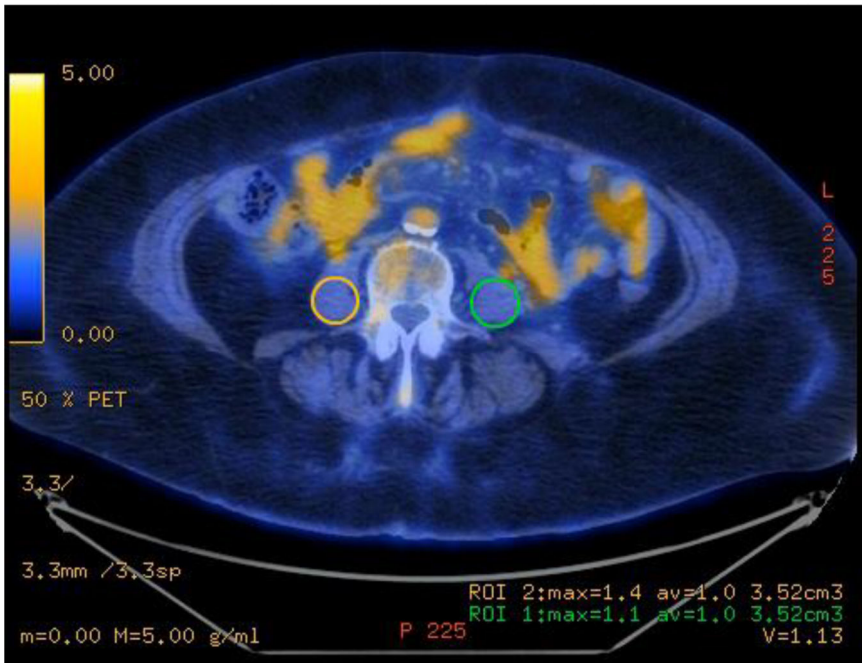

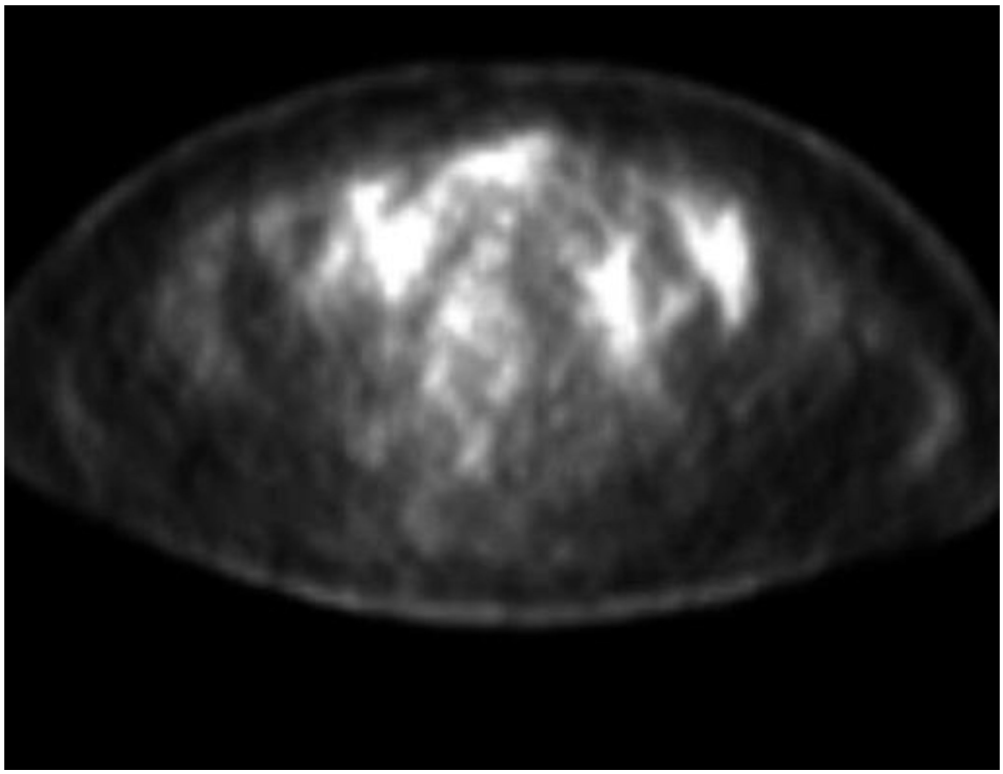

FIGURE 1.
Psoas muscle measurements of (A) cross-sectional area, (B) muscle attenuation, and (C) standardized uptake values (SUV). (D) shows the PET image (same slice) for comparison.

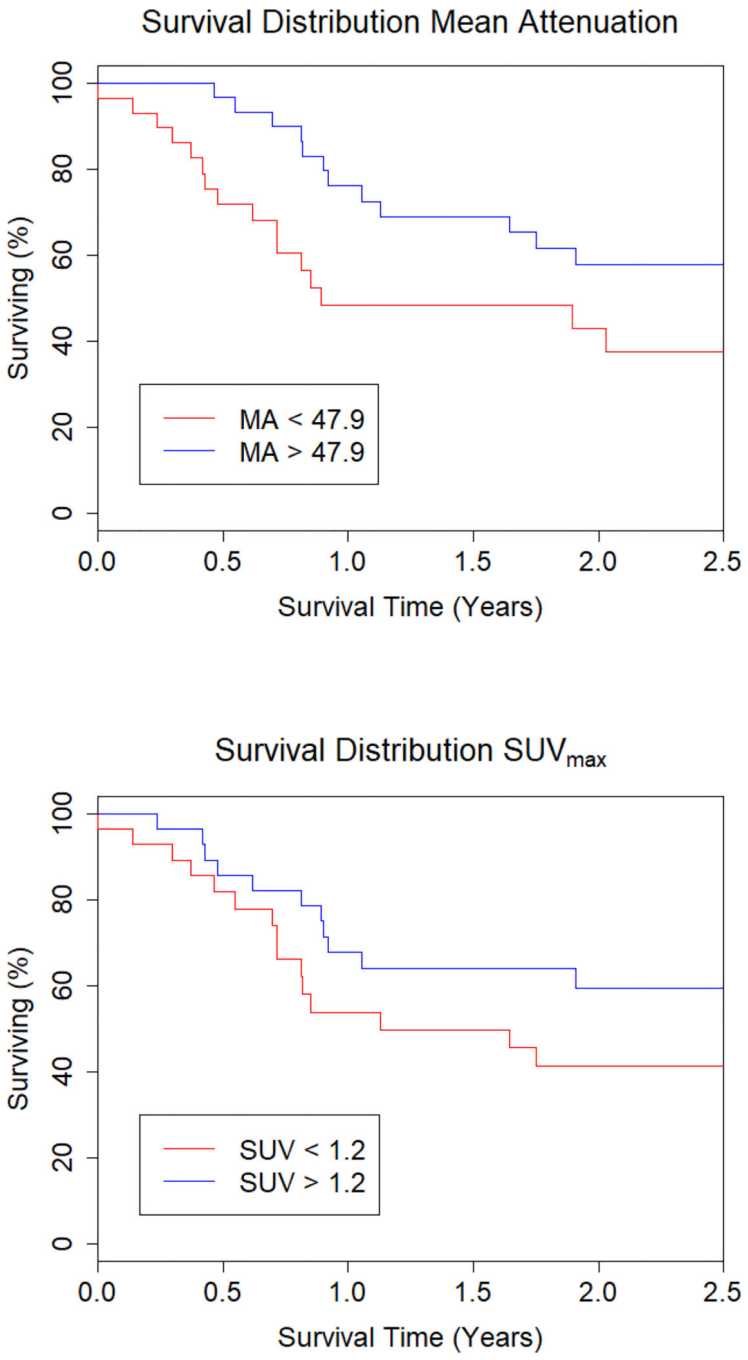

FIGURE 2.

(A) Overall survival comparison between subjects who had a muscle attenuation (MA) value above versus below the median MA (47.9 HU). Patients with a higher MA had better overall survival. (B) Overall survival comparison between subjects who had an SUV_{max} value above versus below the median SUV_{max} (1.2). Patients with a higher SUV_{max} had better overall survival.

Table 1:

Patient characteristics. Data presented as mean ± standard deviation for continuous variables and n (%) for categorical variables.

Number of females	8 (13.6%)
Number of males	51 (86.4%)
Age at time of diagnosis (years)	61.7 ± 9.4
BMI	29.7 ± 6.6
Comorbidities	
Cardiovascular disease	21 (35.6%)
Diabetes mellitus type II	19 (32.2%)
Smoking history	44 (74.6%)
Length of craniocaudal esophageal involvement (cm)	5.2 ± 2.9
Staging at time of diagnosis	
I	11 (18.6%)
II	7 (11.9%)
III	20 (33.9%)
IV	18 (30.5%)
Not available	3 (5.1%)
Treatment	
Chemotherapy	45 (76.3%)
Radiation	39 (66.1%)
Surgery	20 (33.9%)
Patient outcomes	
No evidence of disease (NED)	15 (25.4%)
Alive with disease	7 (11.9%)
Dead of disease	33 (55.9%)
Dead of other causes	4 (6.8%)
Psoas imaging characteristics	
Cross-sectional area (cm^2)	16.6 ± 4.4
Mean attenuation (HU)	45.9 ± 6.9
SUV_{mean} (g/ml)	0.8 ± 0.3
SUV_{max} (g/ml)	1.3 ± 0.5

Table 2:

Intra- and inter-observer agreement. Kappa (95% CI)

Psoas CSA, Observer 1	0.90 (0.83, 0.94)
MA, Observer 1	0.69 (0.50, 0.82)
SUV_{max}, Observer 1	0.93 (0.89, 0.95)
SUV_{max}, Observers 1 and 2	0.91 (0.87, 0.94)

Table 3:

Cox Proportional Hazard ratios. The asterisk indicates $p<0.05$

Predictor	Hazard Ratio	95% CI	p-value
Psoas CSA	0.97	[0.88, 1.05]	0.43
MA	0.94	[0.88, 0.99]	0.04*
SUV_{mean}	0.22	[0.04, 1.01]	0.05
SUV_{max}	0.37	[0.14, 0.97]	0.04*
Tumor Stage	1.85	[1.20, 2.85]	0.005*
Mass Size	1.18	[1.03, 1.36]	0.01*
Diabetes	1.03	[0.51, 2.11]	0.92
In-patient	0.68	[0.34, 1.37]	0.28
CSA, MA	0.99, 0.93	[0.91, 1.07], [0.87, 1.01]	0.76, 0.07
CSA, SUV_{mean}	0.95, 0.19	[0.85, 1.05], [0.03, 1.04]	0.05, 0.06
CSA, SUV_{max}	0.96, 0.37	[0.86, 1.07], [0.14, 0.99]	0.48, 0.04*
MA, SUV_{mean}	0.91, 0.11	[0.85, 0.97], [0.02, 0.63]	0.003*, 0.01*
MA, SUV_{max}	0.92, 0.33	[0.87, 0.98], [0.12, 0.88]	0.01*, 0.02*