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DISEASES OF THE ESOPHAGUS

**Original article**

# Decreased core muscle size is associated with worse patient survival following esophagectomy for cancer

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*SUMMARY.* **Preoperative risk assessment, particularly for patient frailty, remains largely subjective. This study evaluated the relationship between core muscle size and patient outcomes following esophagectomy for malignancy. Using preoperative computed tomography scans in 230 subjects who had undergone transhiatal esophagectomy for cancer between 2001 and 2010, lean psoas area (LPA), measured at the fourth lumbar vertebra, was determined. Cox proportional hazards regression was employed to analyze overall survival (OS) and disease-free survival (DFS) adjusted for age, gender, and stage, and the Akaike information criterion was used to determine each covariate contribution to OS and DFS. Univariate analysis demonstrated that increasing LPA correlated with both OS ($P = 0.017$) and DFS ($P = 0.038$). In multivariate analysis controlling for patient and tumor characteristics, LPA correlated with OS and DFS in patients who had not received neoadjuvant treatment ($n = 64$), with higher LPA associated with improved OS and DFS. Moreover, LPA was of equivalent, or slightly higher importance than pathologic stage. These measures were not predictive among patients ($n = 166$) receiving neoadjuvant chemoradiation. Core muscle size appears to be an independent predictor of both OS and DFS, as significant as tumor stage, in patients following transhiatal esophagectomy. Changes in muscle mass related to preoperative treatment may confound this effect. Assessment of core muscle size may provide an additional objective measure for risk stratification prior to undergoing esophagectomy.**

*KEY WORDS*: **esophageal cancer, esophageal surgery, risk stratification.**

## INTRODUCTION

Identifying novel measures of preoperative risk is important for improving the care of surgical patients. Understanding these measures may be particularly germane in evaluating patients with advanced age and comorbid disease burden, as this population has a propensity for poor outcomes.[1–5] As surgeons currently assimilate relevant clinical data and case complexity to assess a patient's overall suitability for major surgery, the introduction of novel, objectively measured domains of preoperative risk has the potential to improve overall risk stratification and patient selection.

Over the past 30 years, the incidence of esophageal adenocarcinoma has increased substantially, greater than that of any other malignancy in the United States. Concomitantly, disease-specific mortality from esophageal malignancy has increased from 2 to 15 deaths per million over the same period.[6] Regardless of surgical approach, transthoracic or transhiatal, esophageal resection is accepted as standard of care for patients with resectable esophageal malignancy, but also carries considerable associated morbidity and mortality.[7–9]

Morphometric measures, such as core muscle size, obtained from cross-sectional imaging may offer unique insight regarding both specific and global measures of patient health. Previous work by our group has demonstrated the relationship between core muscle size and postoperative morbidity and mortality following major operations.[10,11] The use of core muscle size as a predictor of outcomes has not yet been applied to patients undergoing major

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operations for cancer. We hypothesize that core muscle size assessment provides an objective marker of physiologic fitness which can be used for prospective risk stratification in patients undergoing esophageal resection for cancer.

## METHODS

### Study population

Permission for this retrospective cohort study was provided by the Institutional Review Boards of the University of Michigan Medical School. Between 2001 and 2010, patients undergoing transhiatal esophagectomy for malignancy were identified utilizing both medical records and the Section of Thoracic Surgery prospective esophagectomy database. Patients undergoing esophagectomy and found to have premalignant lesions such as Barrett's esophagus were included in the study. Case totals were evenly dispersed throughout the study period. Patient demographics, cancer stage, and tumor pathology were identified. As patients had undergone operation prior to the implementation of the most recent iteration for staging of esophageal carcinoma, cancer stage was determined using the criteria established in the 6th edition of the *American Joint Committee on Cancer Staging Manual*.[12] Patient follow-up was obtained by review of medical records and query of the Social Security Death Index.

### Measurement of psoas muscle area

Lean core muscle area using the psoas muscle was determined from preoperative chest and abdominal computed tomography (CT).[13,14] The cross-sectional area and density of the left and right psoas muscles were measured at the fourth lumbar (L4) vertebral level (Fig. 1). This was accomplished by first identifying individual vertebral levels on the patient's CT scan in sagittal section. The individual transverse imaging slice at the inferior border of L4 was then used to outline the region of each muscle using an edge-detecting algorithm. The areas of the enclosed muscle regions were then computed and summed to generate the total cross-sectional area of the psoas muscle. In order to account for fatty infiltration, the average density in Hounsfield units of the outlined muscle region was also measured. A correction factor was then computed and multiplied by the total psoas area. This was used to exclude fatty infiltration and to generate the lean psoas area (LPA). These steps were carried out in a semi-automated fashion using algorithms programmed in MATLAB v13.0 (MathWorks, Natick, MA, USA).

### Statistical analyses

LPA served as the primary exposure variable for statistical analyses. Two-sample *t*-test was employed to compare the mean LPA between patients with and

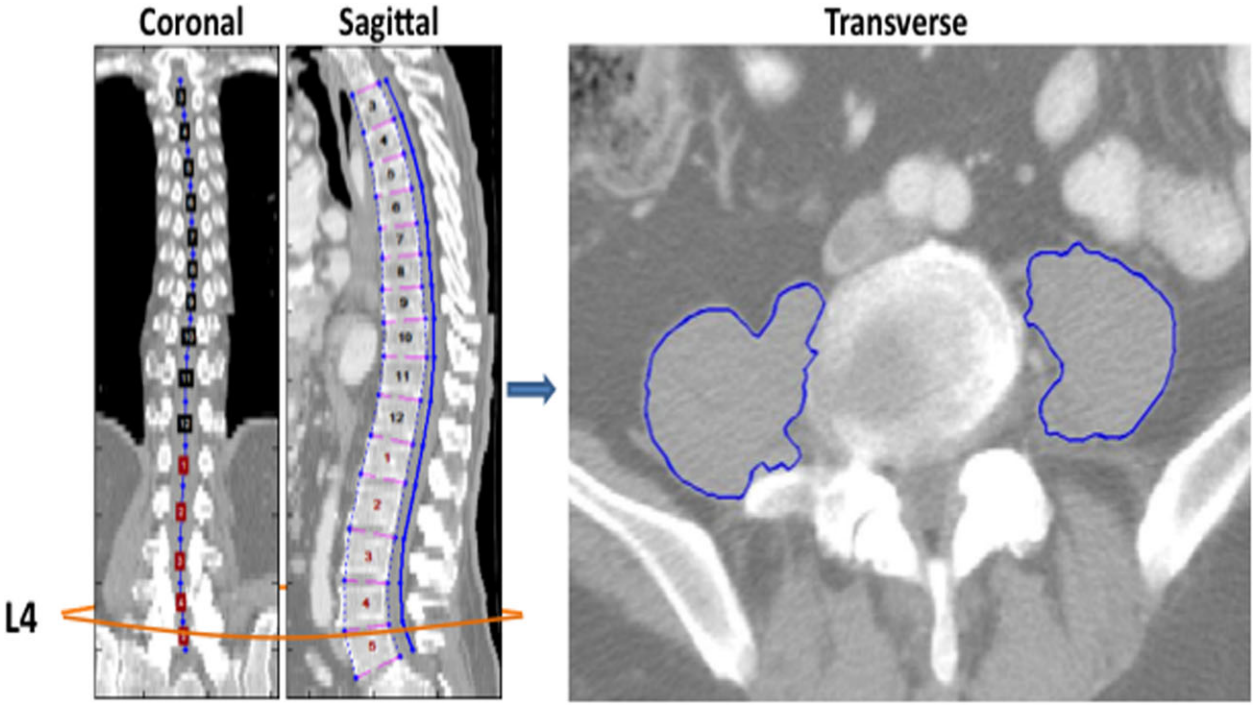


**Fig. 1** Sagittal and coronal computed tomography (CT) images are used to identify the fourth lumbar (L4) vertebra and adjacent paraspinous muscles.

without postoperative complication. Monitored complications included myocardial infarction, cardiac arrest, atrial fibrillation, pneumonia, reintubation, pneumothorax, respiratory distress not requiring intubation, gastrointestinal, renal insufficiency, deep venous thrombosis or pulmonary embolus, surgical site infection, urinary tract infection, need for splenectomy, noninfectious wound dehiscence, and any intraoperative occurrences (including both major and minor complications). The Spearman's correlation coefficient was calculated to evaluate associations between LPA and the total number of complications per subject. Cox proportional hazards model[15] was used to assess the effect of LPA on overall survival (OS) and disease-free survival (DFS). Covariates in the multivariate analysis are patient age, gender, and cancer stage. Cancer stage was stratified by nodal status, i.e. stage I and IIA (N0), IIB and III (N1). The Akaike information criterion (AIC) was used to determine each covariate contribution to OS and DFS. AIC is a measure of the relative goodness of fit of a statistical model. The AIC can be viewed as the amount of information lost when a model is used to describe the data, which is defined as $AIC = -2\log L + 2K$, where $\log L$ is the log likelihood of the proposed model, and k is the number of model parameters. The reported AIC values (AIC – factor) reflect the contribution of the removed factor to OS or DFS.

The reporting of this study conforms to the 'Strengthening the Reporting of Observational Studies in Epidemiology' statement.[16]

## RESULTS

Over the study period, 867 patients underwent transhiatal esophagectomy for cancer at a single institution. Of these patients, 230 (26.5%) had preoperative CT scans available in our institutional archives for processing, and these subjects comprised the study cohort (Table 1). The mean age for the study cohort was 62.3 ± 9.4 years. In addition, 166 subjects (72.2%) had received concurrent neoadjuvant chemoradiation. Median OS was similar between the study cohort (27.1 months; 95% confidence interval [CI]: 19.5, 34.9 months) and the entire population of 867 patients undergoing esophagectomy (29.7 months; 95% CI: 26.1, 34.6 months). Overall distribution of comorbid conditions was not significantly different between patients with and without neoadjuvant chemoradiation (Table 1). Median follow-up time was 12.8 (0.23–108.5) months.

Men were found to have a significantly greater LPA as compared with women (Fig. 2). The mean LPA for men was 2020.07 ± 513.4 $mm^2$ while that for women was 1248.27 ± 434.8 $mm^2$ ($P < 0.0001$).

**Table 1** Subject demographics, stratified by the use of neoadjuvant chemotherapy and radiation prior to esophagectomy

| | Total | No neoadjuvant Rx ($n = 64$) | Neoadjuvant Rx ($n = 166$) | Comparison |
|---|---|---|---|---|
| Characteristic | | Mean ± SD | | *P*-value (No Rx-Rx) |
| Age, years | 62.25 ± 9.48 | 65.71 ± 11.5 | 60.92 ± 8.20 | 0.0031 |
| Height, m | 1.75 ± 0.08 | 1.74 ± 0.09 | 1.77 ± 0.08 | 0.048 |
| Weight, Kg | 194.95 ± 44.76 | 188.5 ± 39.7 | 197.5 ± 46.4 | 0.17 |
| BMI, $Kg/m^2$ | 28.63 ± 5.75 | 28.17 ± 5.61 | 28.81 ± 5.81 | 0.439 |
| Gender | *n* (%) | | | |
| Male | 202 (87.8) | 54 (84.3) | 148 (89.1) | 0.32 |
| Female | 28 (12.2) | 10 (15.7) | 18 (10.8) | |
| Stage (p or yp) | *n* | | | |
| 0 | 22 | 2 (3.1) | 20 (12.1) | 0.19 |
| I | 56 | 32 (50.0) | 24 (14.5) | |
| IIA | 45 | 5 (7.8) | 40 (24.1) | |
| IIB | 32 | 8 (12.5) | 24 (14.5) | |
| III | 63 | 16 (25.0) | 47 (28.3) | |
| IV | 12 | 1 (1.6) | 11 (6.6) | |
| Pathology | *n* (%) | | | |
| SCC | 18 (7.8) | 8 (12.5) | 10 (6.0) | 0.102 |
| Adenocarcinoma | 205 (89.1) | 55 (85.9) | 150 (90.3) | 0.336 |
| Barrett's HGD | 18 (7.8) | 22 (34.4) | 44 (26.5) | 0.230 |
| Other | 10 (4.3) | 1 (1.6) | 9 (5.4) | 0.200 |
| Comorbidity | *n* (%) | | | |
| Cardiac | 48 (20.8) | 19 (29.7) | 29 (17.5) | 0.061 |
| Diabetes mellitus | 33 (14.3) | 11 (17.2) | 22 (13.3) | 0.525 |
| Hypertension | 100 (43.5) | 29 (45.3) | 71 (42.8) | 0.929 |
| Renal | 2 (0.8) | 1 (1.6) | 1 (0.6) | 0.504 |
| Vascular | 13 (5.7) | 3 (4.7) | 10 (6.0) | 0.645 |

For TNM stage groups, pathologic (pTNM) or posttreatment pathologic (ypTNM) stage criteria are used for the untreated and neoadjuvant-treated groups. *P*-values were calculated from two-sample *t*-tests for age, height, weight, and BMI, and from chi-square tests for gender, pathology, and stage grouped as low (0, I, IIA) and high (IIB, III, IV). Multiple pathologic diagnoses for an individual patient may be recorded. HGD, high-grade dysplasia; Rx, therapy; SCC, squamous cell carcinoma; SD, standard deviation.

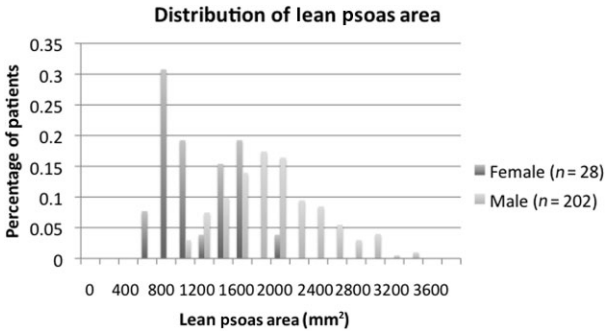


**Fig. 2** Histogram of the distribution of measured lean psoas cross-sectional area in men and women.

LPA decreased with increasing age in both men (r = –0.295, $P < 0.0001$) and women (r = –0.565, $P < 0.0017$) consistent with trends described in similar studies showing that LPA decreases with age.[10,11] We observed moderate positive correlation between body mass index and LPA (r = 0.236, $P = 0.0003$). There was no statistically significant difference between pathologic stage (0–IIA and IIB–IV) and LPA ($P = 0.19$). Additionally, there was no significant relationship between LPA and the number of comorbid conditions in a patient (r = 0.11; $P = 0.10$) (Fig. 3).

In our study cohort, there were four (1.8%) in-hospital deaths. At least one complication occurred in 133 (57.8%) subjects, but LPA was not a significant factor ($P = 0.12$) for developing complications, including anastomotic leak, pulmonary complications, or other major morbidity, following esophagectomy in this study population (Table 2). We observed no association between LPA and the number of complications following esophagectomy (r = –0.11; $P = 0.09$ with the null hypothesis that r is zero) (Fig. 4).

In univariate analysis, increasing LPA was correlated with both OS (hazard ratio [HR] = 0.660; 95% CI: 0.469, 0.928; $P = 0.017$) and DFS (HR = 0.719; 95% CI: 0.527, 0.981; $P = 0.038$) (Table 3). As expected, stage also correlated with OS and DFS in univariate analysis. In multivariate analysis adjusted for patient age, gender, and tumor stage, LPA was not a significant predictor of OS ($P = 0.311$) or DFS ($P = 0.433$) among patients receiving neoadjuvant chemoradiation. However, in those patients not receiving neoadjuvant chemoradiation, higher LPA correlated significantly with improved OS (HR = 0.308; 95% CI: 0.116, 0.820; $P = 0.018$) and DFS (HR = 0.334; 95% CI: 0.139, 0.802; $P = 0.014$) (Table 4). While pathologic stage remained a significant predictor in multivariate analysis of long-term OS, when adjusting for LPA as well as patient age and sex, pathologic stage is marginally significant in predicting DFS among patients who had not received neoadjuvant therapy (HR = 0.456; 95% CI: 0.197, 1.054; $P = 0.067$).

AIC scores were calculated in order to determine the relative contribution of each covariate to model strength. AIC scores in Table 4 reflect model

**Table 2** Univariate analysis of relationship between lean psoas area (LPA) and postoperative complications

| Category | *n* (%) | LPA, mm² (±SD) | *P* |
|---|---|---|---|
| Any complication | | | |
| No | 97 (42.2) | 1993 ± 578 | |
| Yes | 133 (57.8) | 1877 ± 550 | 0.12 |
| Anastomotic leak | | | |
| No | 203 (88.3) | 1922 ± 573 | |
| Yes | 27 (11.7) | 1953 ± 524 | 0.40 |
| Vocal cord paresis | | | |
| No | 212 (92.2) | 1943 ± 564 | |
| Yes | 18 (7.8) | 1727 ± 534 | 0.12 |
| Chylothorax | | | |
| No | 222 (96.5) | 1940 ± 561 | |
| Yes | 8 (3.5) | 1555 ± 545 | 0.06 |
| Other complication | | | |
| No | 119 (51.7) | 1978 ± 551 | |
| Yes | 111 (48.3) | 1870 ± 574 | 0.15 |
| Atrial fibrillation | 48 (20.9) | | |
| Pulmonary | 33 (14.3) | | |
| Gastrointestinal | 24 (10.4) | | |
| Other infection | 23 (10.0) | | |
| Technical | 14 (6.1) | | |
| Thrombotic | 9 (3.9) | | |
| Renal | 5 (2.2) | | |
| Cardiac | 4 (1.7) | | |

*P*-values were calculated from two-sample *t*-tests. SD, standard deviation.

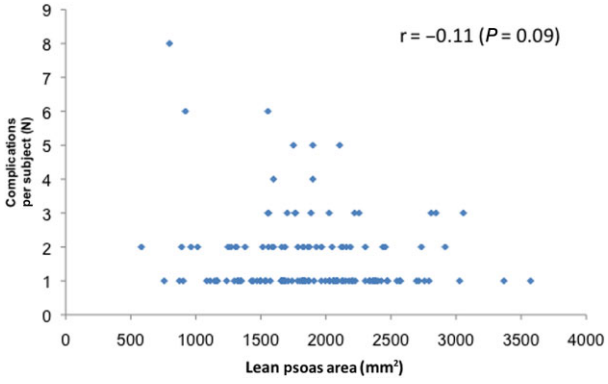


**Fig. 3** Scatter plot of the relationship between lean psoas area and total number of comorbid conditions per subject.

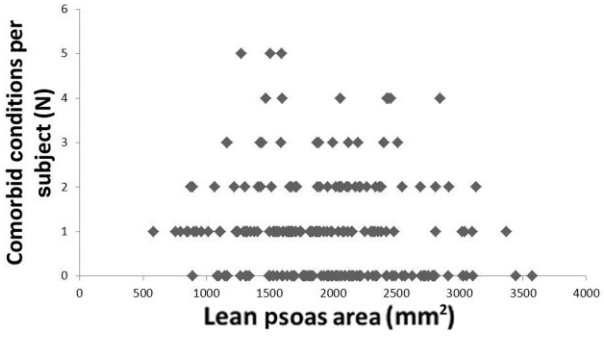


**Fig. 4** Scatter plot of the relationship between lean psoas area and total number of complications per subject.

**Table 3** Univariate analysis of relationship between risk factors, including higher lean psoas area (LPA), age, pathologic stage and patient sex, and (A) overall survival and (B) disease-free survival

| Measure | *n* | *P*-value | HR (95% CI) |
|---|---|---|---|
| A. Overall survival | | | |
| Lean psoas area | 230 | 0.017 | 0.660 (0.469–0.928) |
| Age | 230 | 0.447 | 1.009 (0.987–1.031) |
| Stage | 230 | 0.028 | 0.634 (0.423–0.951) |
| Gender | 230 | 0.942 | 1.021 (0.579–1.800) |
| B. Disease-free survival | | | |
| Lean psoas area | 230 | 0.038 | 0.719 (0.527–0.981) |
| Age | 230 | 0.651 | 0.624 (0.428–0.908) |
| Stage | 230 | 0.014 | 0.644 (0.450–0.920) |
| Gender | 230 | 0.721 | 1.101 (0.648–1.871) |

*P*-values and hazard ratio (HR) were calculated from Cox proportional hazards regression models; pathologic stage (high stage as the reference) and patient sex (male as the reference). CI, confidence interval.

strength when the given covariate is removed from the model, and higher AIC indicates greater importance of the removed covariate. Factors with *P*-values less than 0.05 in the multivariate model are significant predictors for survival. To provide information regarding the relative contribution of a factor, the AIC was calculated by the removal of that factor from the final model. Higher values of AIC indicate greater importance of the omitted factor.[17] LPA is a strong predictor ($P = 0.018$ in OS and $P = 0.014$ in DFS), slightly more contributory than pathologic stage, of OS (AIC-LPA = 145.64; AIC-stage = 144.21) and DFS (AIC-LPA = 170.34; AIC-stage = 167.60) in patients not receiving neoadjuvant chemoradiation.

## DISCUSSION

Risk assessment models including the Physiological and Operative Severity Score for the enUmeration of Mortality and Morbidity, modified for Oesophagogastric surgery, or other simpler models typically identify surrogates for patient fitness using a variety of parameters such as age, physiologic measures, presence of comorbid diseases, and/or the use of preoperative chemo- or radiation therapy.[18–20] Although investigators have developed predictive models for risk stratification,[20,21] such predictors have tended to overestimate the risk for morbidity and mortality, particularly in older patients.[22,23] Additional objective measures, including morphologic parameters such as lean psoas muscle cross-sectional area, may augment clinicians' ability to assess pretreatment or preoperative fitness, with the intention of optimizing both postoperative and long-term outcomes in oncologic patients.

Frailty is independently associated with an increased risk of postoperative complication, longer hospital length of stay and discharge to skilled nursing, or assisted-living facility following elective operation.[24] The frailty phenotype can be defined by the presence of several components,[25] including unintentional weight loss, weakness, poor endurance, slowness, and low physical activity, of which sarcopenia is a major factor.[26] Loss of core muscle area, as a surrogate for central sarcopenia, has been shown to be associated significantly with worse 1- and 3-year survival following liver transplantation[10] and open abdominal aortic aneurysm repair,[11] respectively. The psoas muscle was specifically targeted in our study based on three qualitative factors; (i) It is a core muscle and therefore relatively uninfluenced by deliberate weight training/exercises. (ii) It is not surrounded by other muscles or bony anatomy that would obscure isolation of the muscle from structures of similar radiodensity. (iii) The L4 vertebral level is included in nearly all abdomen and pelvis protocol CT scans.

In addition to assessing clinical risk factors for major surgery, the acquisition of morphometric measures from cross-sectional imaging provides

**Table 4** Multivariate analysis of the risk factors associated with overall and disease-free survival in subjects treated with and without neoadjuvant chemoradiation

| | | Overall survival | | | Disease-free survival | | |
|---|---|---|---|---|---|---|---|
| Neoadjuvant treatment | Factor | Hazard ratio (95% CI) | *P* | AIC (-factor) | Hazard ratio (95% CI) | *P* | AIC (-factor) |
| No ($n = 64$) | pStage | 0.373 (0.144, 0.963) | 0.042 | 144.21 | 0.456 (0.197–1.054) | 0.067 | 167.60 |
| | Lean psoas area | 0.308 (0.116, 0.820) | 0.018 | 145.64 | 0.334 (0.139–0.802) | 0.014 | 170.34 |
| | Age | 1.001 (0.962–1.042) | 0.961 | 139.80 | 0.986 (0.945–1.030) | 0.535 | 164.51 |
| | Sex | 0.455 (0.113–1.825) | 0.267 | 141.10 | 0.419 (0.116–1.514) | 0.184 | 166.03 |
| Yes ($n = 166$) | ypStage | 0.803 (0.500–1.291) | 0.365 | | 0.745 (0.480–1.156) | 0.189 | |
| | Lean psoas area | 0.767 (0.459–1.281) | 0.311 | | 0.829 (0.518–1.326) | 0.433 | |
| | Age | 1.009 (0.978–1.041) | 0.572 | | 0.992 (0.964–1.021) | 0.584 | |
| | Sex | 0.810 (0.357–1.838) | 0.614 | | 1.093 (0.507–2.358) | 0.820 | |

*P*-values and hazard ratio (HR) were calculated from Cox proportional hazards regression models with covariates LPA, stage, age, and patient sex. Akaike information criteria (AIC) was calculated by the removal of each variable from the final model, indicating the contribution of that variable to overall or disease-free survival. Higher values of resultant AIC indicate greater importance of the omitted variable. CI, confidence interval.

objective, granular data that may aid in both preoperative decision making as well as preparation prior to esophagectomy. As a potential measure of overall physiologic status in the surgical patient, assessment of core muscle size may also allow clinicians to monitor patient fitness leading up to esophagectomy. Results of exercise training have been shown to be quantifiable by CT scan to determine skeletal muscle cross-sectional area.[27] Future studies will focus on whether quantitative physiologic and morphometric re-assessment following targeted intervention aimed to improve patient fitness (e.g. strength and aerobic capacity) can identify patients more likely to have adverse outcomes following major abdominal and thoracic operations for cancer.

In the cohort of patients that did not receive neoadjuvant therapy, LPA served as an independent predictor of OS and DFS, even when adjusting for risk factors such as age and cancer stage. These data suggest that preoperative cross-sectional lean psoas muscle area appeared to have as significant impact on long-term survival as posttreatment cancer stage, suggesting that patient fitness or frailty contributes to long-term survival as much as tumor stage. While this initially might seem counterintuitive, these findings can be interpreted such that within any given cancer stage, patient frailty is a significant and important contributor to long-term survival. The AIC and other means of model testing provide a more robust assessment of the significance of otherwise statistically significant covariates identified in multivariate analyses.[17]

In patients with more advanced cancer, combined modality therapy including preoperative chemotherapy and radiation followed by esophageal resection is our preferred approach. Patients are likely to receive neoadjuvant chemoradiation at our center if they are found to have locoregionally advanced disease – including significant primary tumor burden and/or evidence of lymph node involvement on radiographic and pathologic investigation. We found that the predictive ability of lean psoas cross-sectional area was attenuated among patients who had received preoperative chemotherapy and radiation. It is possible that changes in core muscle mass directly attributable to chemotherapy and/or radiation therapy may confound the use of this measurement in direct determination of preoperative risk. It also is possible that the use of such preoperative treatment regimens may have selected for those patients sufficiently fit to undergo the rigors of such multimodality therapy. Low body mass has been associated with increased chemotherapy-related toxicity[28,29] and more rapidly progressing disease[29] in small cohorts of patients with colorectal or breast carcinoma. It is also plausible that changes in nutritional status during neoadjuvant chemoradiation exert variable effects on patients' core musculature. Moreover, there is inevitable variability in the chronology of diagnosis, initial neoadjuvant treatment, and referral to the operative institution prior to resection. As such, it is technically difficult to account for these variables objectively in the current analysis.

Despite these significant findings, this study has several limitations. In this study, we describe an association between survival following esophagectomy and core muscle cross-sectional area which, as a marker for sarcopenia, is but one contributor to patient frailty. In a prospective study of patients, 65 years or older undergoing elective operation, the presence of frailty, as determined by a validated scoring system, was associated with greater risk of surgical complication.[24] The scoring system in this study included the following criteria: weight loss, muscle weakness, exhaustion, low physical activity, and decreased walking speed. Further exploration of frailty assessment is an ongoing area of interest particularly for patients being evaluated for surgical treatment of thoracic malignancies.

For this retrospective study, we found that only a relatively small cohort of patients had preoperative CT scans archived at our institution and available for data acquisition. Additional variability introduced by the temporality between imaging studies and preoperative chemoradiation was addressed by dividing the primary study cohort based on neoadjuvant treatment status. While our findings might be related to confounding effects related to analyzing only a subset of the population undergoing operation at our institution, this does not seem likely as there was no systematic selection of the preoperative CT scans utilized for this study. As advances in data storage allow for more consistent archiving of digital imaging studies, more comprehensive studies using such data should become increasingly feasible.

Lastly, our analysis cohort represents a group of patients already selected by their surgeon(s) as being candidates 'suitable' for esophagectomy. At the initial surgical consultation for treatment planning, esophageal cancer patients at our institution are counseled to abstain from cigarette smoking, to begin a regimen of regular, twice-daily ambulation and are instructed in the use of an incentive spirometer.[9] Patients who are estimated to be unfit for operation, particularly upon completion of neoadjuvant chemotherapy and radiation therapy, are advised to delay esophageal resection in order to recover further from their preoperative treatment. As described in our results, we did not observe that lower lean psoas cross-sectional area was associated with increased perioperative complications. Depending on patient compliance, preoperative education and training potentially could have attenuated the predictive accuracy of prior core muscle assessment. Furthermore, preselection bias would exclude patients felt by the attending/consultant surgeon to

be too frail or otherwise unfit for operation, thereby attenuating the potential predictive strength of LPA for predicting perioperative surgical outcomes in our study cohort. In other reports where an association was identified between core muscle mass and perioperative complications and mortality, the urgency of the underlying disease, e.g. open abdominal aortic aneurysm and hepatic transplantation, and dearth of alternative therapies precluded such patient selection. Despite these potential confounders, we were able to observe that lower core muscle cross-sectional area was associated with worse long-term survival.

This study demonstrates that core muscle size appears to be an independent predictor of OS and DFS in a subset of patients undergoing esophagectomy without prior chemoradiation, and that core muscle size may be a novel measure for risk assessment in patients undergoing esophagectomy for cancer. Further investigation is required regarding the relationships between morphometric measures, the frailty phenotype, and long-term patient outcomes following major operations such as esophagectomy, particularly for those patients who require multimodality therapy for locoregionally advanced esophageal cancer.

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