Title Page

**The Impact of Sarcopenia on Esophageal Cancer Treatment Outcome**

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2019

Abstract

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**Abstract**

**Objective:** Esophageal cancer is of public health significance as the eighth most common cancer worldwide and the 6th leading cause of cancer deaths. The treatment options include medical (chemoradiation) and surgical (esophagectomy) interventions. The favored surgical method, minimally invasive esophagectomy (MIE), is associated with significant morbidity and mortality. Currently research is focused on determining prognostic indicators for outcomes following MIE, one of which is sarcopenia. Sarcopenia has been found to be associated with increased morbidity following chemoradiation, but little is known about its effect on perioperative complications following MIE. We hypothesize that sarcopenia is associated with perioperative complications and worse overall survival for patients receiving MIE as seen in patients receiving chemoradiation.

**Method:** In a retrospective study of 102 patients with esophageal cancer who underwent minimally invasive esophagectomy available CT images of each patient, taken within three months prior to the date of surgery, were analyzed to measure total skeletal muscle cross sectional area. These values were then used to calculate skeletal muscle index (SMI), which is skeletal muscle mass cross sectional area normalized by height (cm2/m2). This value was used to identify patients with sarcopenia, defined as SMI less than 52.4 cm2/m2 for men and SMI less than 35 cm2/m2 for women. We then evaluated the association of sarcopenia with outcomes after MIE.

**Results:** Among the 102 patients who underwent MIE, the prevalence of sarcopenia was 49.0% of which 46 (53.5%) of men and 4 (25%) of women were classified as having sarcopenia. The perioperative 30-day mortality was 0%. Those with sarcopenia were found to have an increase in perioperative morbidity including pneumonia (p = .032) and anastomotic leak (p = .049). Sarcopenia was also found to have a significant effect on overall survival with an over two-time increase from 28 months for patients with sarcopenia to 62 months for patients without (p=0.0065).

**Conclusions:** This analysis demonstrates that sarcopenia, was associated with an increase in the perioperative complications such as pneumonia, and anastomotic leak. Overall survival appeared to be decreased in patients with sarcopenia. This essay demonstrates that regardless of treatment method, sarcopenia leads to more complications for patients with esophageal cancer due to poorer treatment response thus decreasing overall survival and increasing mortality.

Table of Contents

[Preface ix](#_Toc7777357)

[1.0 Introduction 1](#_Toc7777358)

[2.0 Methods 7](#_Toc7777359)

[2.1 Study Population 7](#_Toc7777360)

[2.2 CT analysis of the body composition variables 7](#_Toc7777361)

[2.3 Statistical Analysis 8](#_Toc7777362)

[3.0 Results 9](#_Toc7777363)

[4.0 Discussion 11](#_Toc7777364)

[4.1 Public Health Relevance 12](#_Toc7777365)

[Appendix Tables and Figures 13](#_Toc7777366)

[Bibliography 16](#_Toc7777367)

List of Tables

[Table 1 Patient Characteristics 13](#_Toc7176096)

[Table 2 Perioperative Complications In Patients with Sarcopenia 14](#_Toc7176097)

List of Figures

[Figure 1 Overall Survival by Sarcopenia Status 15](#_Toc7176155)

Preface

I would like to acknowledge my research mentor Dr. Arjun Pennathur for his support throughout the research process. I would also like to thank William Gooding for helping me with the statistics in my study. Lastly, I would like to thank my essay readers Dr. David Finegold,

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# Introduction

Esophageal cancer, which includes squamous cell carcinoma (SCC) and adenocarcinoma (ADC), is currently ranked as the eighth most common cancer worldwide. 1 In 2018, the number of new cases of esophageal cancer worldwide was approximately 500,000, up from 450, 000 new cases in 2012, indicating a rise in the incidence of this cancer.2 Unfortunately, esophageal cancer also has a high fatality rate as the sixth leading cause of death from cancer in the world making it a public health concern across the globe.1 According to the American Cancer Society, in the United States, the incidence of esophageal cancer is expected to be approximately 17,650 people in 2019 with the number of deaths at approximately 16,080 people.3 While the incidence of esophageal cancer has remained steady in the United States it has continued to rise in other parts of world.

Before we discuss why there is a difference in incidence in esophageal cancer between the United States and the rest of world, we must first understand that esophageal cancer has differing histologies. Mainly, squamous cell carcinoma (SCC) of the esophagus, which arises from the stratified epithelial lining of the organ, and adenocarcinoma which develops from the columnar glandular cells that replace the squamous epithelium of the esophagus.4 Other types of cancer histologies such as sarcoma, small cell carcinomas, melanomas, and leiomyosarcomas make up less than 1-2% of the total number of cancers of the esophagus.5 SCC is the predominate type of esophageal cancer worldwide and is usually found in the upper 2/3rd of the esophagus.5 However, over the past decade there has been a shift in the type of esophageal cancer in United States towards a higher prevalence of adenocarcinoma as oppose to squamous cell carcinoma.4 This shift in the type of esophageal cancer is associated with predominance in the specific risk factors associated with the two differing histological types of esophageal cancer.

The risk factors for esophageal SCC include tobacco smoking, low intake of fresh fruits and vegetable, achalasia, alcohol consumption, and low socioeconomic status.6, 1 Other factors believed to be associated with SCC include poor oral hygiene, HPV infection, and intake of hot drinks.6 The link between nutrition and esophagitis (inflammation of the esophagus) suggest a possible method of primary prevention of esophageal cancer worldwide.7 The major risk factors for esophageal adenocarcinoma include gastroesophageal reflux disease (GERD), obesity, Barrett’s esophagus, age, and the male sex.(4,1) Countries that have lower socioeconomic development are more likely to have esophageal cancer, specifically SCC, because of higher rates of malnutrition, poor dentition, and tobacco use.8 The highest number of new diagnoses of esophageal cancer, specifically SCC, is seen among men in Eastern Asia, Southern Africa and Eastern Africa.1 From a public health prospective, in order to address the high incidence of SCC in impoverished nations there needs to be a focus on primary prevention through initiatives that help improve nutrition, oral hygiene, and decrease tobacco use. Nations with higher socioeconomic development such as Northern Europe and North America, have a higher rate of adenocarcinoma do to a decrease in tobacco use and increase in obesity.8 This suggest a need for initiatives focused on addressing obesity and GERD in developed nations.

The 5-year survival rate for patients with esophageal cancer is less than 20% up from 5% in 2006.9 The mortality rate among people with esophageal cancer is higher in countries of lower socioeconomic development with the highest mortality seen in males in Western Africa, Middle Africa, and Eastern Asia.2 Interestingly, esophageal cancer is four times more common and slightly more lethal in men that in women across the world, emphasizing the need for men to be screened for this disease.9 One explanation for the reduction of mortality trends over the last decade may be due to technological advancement of esophageal cancer such as endoscopic detection and therapy for early stage disease.8 Of note, Barrett’s esophagus is the single most important precancerous disease for esophageal cancer. It refers to the progression of squamous cells that normally line the esophagus being replaced by the columnar cells that line the stomach as they migrate up from the stomach to the lower esophagus.10 Patients with Barrett’s esophagus have a 50 to 100-time increase in the risk of developing esophageal cancer when compared to the general population.9 With the current advances in endoscopic surveillance programs after Barrett’s esophagus is diagnosed, physicians could detect more early stage cancer and this could facilitate earlier management.8 The higher mortality rate observed in people of low socioeconomic nations could be explained by the availability and accessibility of healthcare services which are necessary for early diagnosis and management.

Treatment of esophageal cancer is best handled with a multidisciplinary approach using both non-surgical and surgical treatment options. Currently treatment options include medical treatment (chemoradiation) and surgical treatment (esophagectomy). Chemoradiation is the option most useful for patients with metastasis for which local surgical resection is not an option.7 Surgical interventions are used for patients with locally advanced esophageal carcinoma with high resectability. As surgical interventions have improved it has become the treatment of choice for both SCC and adenocarcinoma of the esophagus.11 Minimally invasive esophagectomy (MIE) has mostly replaced open esophagectomy, as it has been shown to decrease overall mortality by an average of two percent.12 In a systematic review of over 1100 patients using MIE and open esophagectomy, MIE was shown to be associated with decreased hospital stay and morbidity when compared to open esophagectomy.11 The so-called Ivor Lewis MIE approach is favored over both the McKeown MIE approach and open esophagectomy because it allows for better access to the distal esophagus and gastroesophageal junction where the vast majority of tumors are encountered.13 Although surgical resection is considered the treatment of choice for esophageal cancer it is also associated with considerable morbidity and mortality. In an attempt to improve postsurgical outcomes in patients receiving MIE new prognostic indicators are currently being studied and evaluated.14 One potential indicator of patient outcomes following esophagectomy is sarcopenia which has been shown to be associated with poor outcomes in patients for a number of different cancer types.15

Sarcopenia is a syndrome characterized by the progressive and generalized loss of skeletal muscle mass and strength with risk of adverse outcome such as physical disability and quality of life. Sarcopenia is specifically defined as muscle mass two standard deviations below the mean muscle mass of healthy younger adults, and has been shown to be prevalent in adults with cancer and other common chronic comorbidities.16 Many studies have shown a high prevalence of sarcopenia in adults with cancer, 57% of patients with gastric cancer, 27.5% of patients with advanced hepatocellular carcinoma, and 29% of patients with metastatic renal cell carcinoma.17 Sarcopenia in adults with cancer has been associated with postoperative complications and poorer overall survival.18 While previous studies have shown that sarcopenia is associated with decreased disease free survival and overall survival for patient that have surgical resection for a number of different cancer types, there is currently little information on sarcopenia and its effects on patient outcomes following minimally invasive esophagectomy.16

Does sarcopenia affect outcomes of patients receiving medical management for esophageal cancer? For 50% of the patients with advanced tumor invading adjacent organs or distant metastasis the use of surgery as a curative measure is not possible.5 The standard treatment for these patients is definitive chemoradiation therapy. Studies have shown that survival rates remain low both because of the stage of the cancer and the likelihood of remission using chemoradiation therapy.7 In a study done by Sho Sato et al., looking at the effect of pretreatment sarcopenia on long-term prognosis of patients with locally advanced esophageal cancer, they found that patients with sarcopenia had poorer overall survival than those without.19 They postulated that the tumor in the sarcopenia group has poorer sensitivity to chemoradiation. The 3-year survival rate in patients without sarcopenia was reported as 64% following chemoradiation for esophageal cancer, while those with sarcopenia had a 3-year survival rate of 37% (p=0.01)19 In addition, recent studies have postulated that in patients with sarcopenia there is a more robust inflammatory response, increasing the skeletal muscle depletion and worsening their outcomes following medical treatment for esophageal cancer.20 Sarcopenia is also associated with cachexia and is believed to be an independent measure of nutritional status that effects long term prognosis of patient with unresectable esophageal cancer. Not only is nutritional status associated with esophageal cancer it is also associated with sarcopenia. From a public health standpoint, optimizing nutritional status has the added benefit of decreasing likelihood of developing esophageal cancer but also addressing sarcopenia by improving overall muscle mass. In conclusion, sarcopenia worsens the long term prognosis of patients with unresectable locally advanced esophageal cancer, however more research needs to be done to fully understand the mechanism driving this outcome.

How does sarcopenia affect outcomes following MIE? While MIE is becoming the most widely utilized option for surgical management of esophageal cancer, little is known about the impact of sarcopenia on the outcome of patients that receive this treatment. We conducted a study at The University for Pittsburgh with N=102, to determine how sarcopenia affects outcome of patients with esophageal cancer treated with MIE. While qualification of skeletal muscle mass is not a standard aspect of patient assessment prior to esophagectomy, CT images are regularly collected prior to surgery and can be used to assess skeletal muscle mass and provide prognostic information on the patient. We hypothesized that sarcopenia as measured by skeletal muscle mass calculated from CT images taken of L3 lumbar spine region prior to surgery, would be indicative of worse perioperative outcomes following MIE. In our study, we aimed to identify an association between sarcopenia and treatment outcomes for patients receiving MIE. We also compared the results of our study to the current data on the impact of sarcopenia on patient outcomes following medical management (chemoradiation treatment) for esophageal cancer.

# Methods

## Study Population

Permission for this retrospective cohort study was acquired from the Institutional Review Board of the University of Pittsburgh. We included all 102 patients who underwent minimally invasive esophagectomy for malignancy between 2008 and 2009 at a UPMC hospital with corresponding CT images for analysis and utilized their medical records for this study. Patient demographics, cancer stage, tumor pathology, and complications were abstracted. From each patient, Computed tomography (CT) images were done within a three-month time prior to their date of surgery.

## CT analysis of the body composition variables

Computed tomography (CT) images that were done within three months of surgery were evaluated for each patient. Skeletal muscle and abdominal adipose tissue areas were measured from the abdominal CT at the third lumbar vertebra (L3). This was done by identifying the L3 vertebra on the patient’s CT scan in the sagittal section. Each L3 image was then analyzed using the Slice-O-Matic software to determine skeletal muscle and abdominal adipose tissue area. The Tissue Hounsfield unit (HU) thresholds were used to identify the skeletal muscle area (-29 to 150 HU).21 The skeletal muscle area includes the psoas, erector spinae, quadratus lumborum, external and internal oblique, transversus abdominus, and rectus abdominus muscles. The body composition variables were normalized by height in meters squared and expressed as cm2/m2. We termed the measurement of skeletal muscle index (SMI). 22 For accuracy two slices were measured at the level of L3 and the SMI were averaged together. Then to account for reproducibility a second person measured the exact same images a month apart to access between observer reproducibility. Sarcopenia was defined by using sex-specific cut-off points for L3 SMI. SMI was calculated as the area of total L3 skeletal muscle (cm2) divided by height square (m2). Cut-off points of SMI for sarcopenia was 52.4 cm2/m2 for men and 38.5 cm2/m2 for women.22

## Statistical Analysis

Quantitative variables are expressed as medians with interquartile ranges, unless otherwise indicated. Numbers and percentages are used to express the qualitative variables. Differences between groups were analyzed using Wilcoxon’s test for continuous variables and Fisher’s exact test for categorical data. Survival time was defined as the interval between the first admission to our department for their esophagectomy and death. Univariate and multivariate analyses of overall survival were performed using Cox’s regression models, and the results are presented as HRs with 95% CIs. p values were derived using the Wald test. Variables exhibiting significant associations after univariate analyses were included in the multivariate analysis.

# Results

 The results in *Table 1* demonstrate that out of atotal of 102 patients (86 men and 16 women), 50 patients (49.0%) had preoperative sarcopenia compared to 52 patients (50.9%) that did not meet the cutoff for sarcopenia as established in the literature.22 The median age for patients with sarcopenia was 70 years old, while the median age for patients without sarcopenia was 64 years old, a statistically significant difference (p< 0.001). Patients with sarcopenia also had a statistically significantly lower median BMI (26.9kg/m2) than patients without sarcopenia (30.7kg/m2). Similar to Sho Sato et al., who did a study on sarcopenia and chemoradiation, we also found that patients with sarcopenia had a lower BMI prior to the operation and this group of patients had worse perioperative complications , likely due to poor nutritional level prior to the operation.19

There were a number of perioperative complications associated with sarcopenia as indicated in *Table 2*. The median length of stay in the hospital was 6 days for patient without sarcopenia and 9.5 days for patients with sarcopenia (p<0.001). It has been well-studied that an increase in hospital stay is associated with worst long term outcomes as it makes patient susceptible to a number of complications, and likely means a more complicated post-operative course. However, sarcopenia had no effect on 30 day in hospital mortality as zero patients died within 30 days following there procedure. One major post-operative complication that was affected by sarcopenia was pneumonia, 10/13 (77% p=0.04), likely due to poor pulmonary function seen with longer hospital stays. The other significant complication was anastomotic leaks (p=0.049) which may be associated with an increased inflammatory response following the procedure inhibiting good wound healing. Of note in *Figure 1*, there was a decline in overall survival observed in the cohort of patients with sarcopenia, with a median survival of 28 months compared to 62 months for patients without sarcopenia (p=0.0065) - thus indicating a survival benefit for patients without sarcopenia.

# Discussion

Sarcopenia has been shown to cause an increase in post-operative complications in patients receiving an esophagectomy for esophageal cancer.14 However there has been limited data on the impact of sarcopenia on patients being treated with MIE. In this study of 102 patient receiving MIE for esophageal cancer, 50 patients were found to have sarcopenia. Previous literature indicates that age is correlated with an increase in sarcopenia and an overall decrease in body muscle mass, and that was also seen in this study as sarcopenia was more prevalent in older patients with the median age of 70 compared to 64 years for patients without sarcopenia.23

Our study indicates that patients with preoperative sarcopenia, as measured by a decrease in skeletal muscle mass, have an increase in postoperative complications, specially pneumonia and anastomotic leaks. There appears to be an association with pneumonia given that 77% of the patients with postoperative pneumonia also had sarcopenia. Those patients with anastomotic leak were corrected with medical intervention, the majority of which were found to have preoperative sarcopenia. In addition, sarcopenia was found to have a significant effect on overall survival with an over two-time increase from 28 months for patients with sarcopenia to 62 months for patients without. Going forward the presence of sarcopenia may serve as a biomarker, for outcomes and length of overall survival after resection for esophageal cancer.

## Public Health Relevance

Sarcopenia can be found in all people, from athletes to the elderly. However, studies have shown that physical inactivity hastens the progression of sarcopenia and contributes to disability, reduced ability to cope with the stress of a major illness, and to mortality in the elderly.23 In this essay we examined whether sarcopenia is related to an increase in perioperative complications in patients receiving treatment for esophageal cancer regardless of the treatment type. Undernutrition has been reported to be as frequent as 79% in patients with advanced esophageal cancer before starting treatment.23 In these patients, anorexia and dysphagia are the main factors involved in the onset of undernutrition.24 Limitation of oral intake can be caused by tumor obstruction. Results from our study and the study by Sho Sato et al. demonstrate that sarcopenia leads to more complications for patients with esophageal cancer due to poorer treatment response thus decreasing overall survival and increasing mortality. Unfortunately, these findings are not exclusive to esophageal cancer, as there is significant evidence demonstrating that sarcopenia is independently associated with poor response to cancer therapy in pancreatic, breast, colorectal, and renal-cell, and hepatic cancer.19 In addition, sarcopenia is a prominent feature of malnutrition causing cancer progression.Undernutrition has been reported as a factor predictive of treatment discontinuation and poor outcomes in patients treated at the palliative stage.23 Currently there is much debate about what can be done to improve outcomes for people with sarcopenia. Studies have shown that by increasing physical activity in the elderly you can slow down the progression of their sarcopenia and increase overall functional status.15 However, as the number of elderly persons increases exponentially, a public health approach to prevention and treatment of sarcopenia, with an emphasis on increasing nutritional status and individual physical activity at all ages will be crucial to avoiding an epidemic of disability in the future.19

Appendix Tables and Figures

Table 1 Patient Characteristics

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | Overall (n=102) | Sarcopenia (n=50) | Non-sarcopenia (n=52) | P value\* |
| Age, Years [median]  | 65.5 |  70 | 64 | .001 |
| Gender (n(%)) Male |  86 (84%) |  46 (92%) | 40 (77%) | .04 |
| Body Mass index, kg/m2 (median) | 28.1 | 26.9 | 30.7 | <.001 |
| SmokerHx (n(%))  | 71 (70%)  | 33 (66%)  | 38 (73%) | .44 |
| Zubrod (n (%)) 0 1 2 | 8 ( 8%)93 (91%)1 (0.98%) | 4 (8%)46(92%)0 (0%) | 4 (8%)47 (90%)1 (2%) | .62 |
| Cancer Type (n(%)) Adenocarcinoma  Squamous CC  |  80 (78%)6 (6%) | 39 (78%)4 (8%) | 41 (78%)2 (4%) | .74 |
| Received induction Tx(%) | 26 (25%)  | 14 (28%) | 12(23%) | .57 |
| Operation Type (n(%)) MIE Ivor Lewi  MIE McKeown  |  97 (95%)5 (5%) | 48 (96%)2 (4%) | 49 (94%)3 (6%) | .62 |
| Age-Adjusted Charlson Comorbidity Index Median IQR | 30 – 4 | 30 – 4.75 | 30-4  | .41 |

\*Wilcoxon’s test for continuous variables and Fisher’s exact test for categorical data

Table 2 Perioperative Complications In Patients with Sarcopenia

|  |  |  |  |
| --- | --- | --- | --- |
|  | Overall | Sarcopenia | P Value (Fisher’s Exact Test) |
|  | **N = 102** | **Yes (N = 50)** | **No (N = 52)** |  |
| In Hospital Mortality | 1 (.98%) | 1 (2%) | 0 | .31 |
| 30 day mortality (%) | 0 | 0 | 0 |  |
| Length of Stay (median) (4-66 days) | 7 | 9.5 | 6 | <.001 |
| Recurrent Nerve Palsy | 0 | 0 | 0 |  |
| Cardiac ComplicationsAtrial arrhythmiaMIDVT | 29 (28%)1 (.98%)5 (5%) | 19 (38%)1 (2%)3 (6%) | 10 (19%)0 (0%)2 (4%) | .04.31.62 |
| Pulmonary ComplicationsPneumoniaARDS | 13 (13%)2 (2%) | 10 (20%)1 (2%) | 3 (6%)1 (2%) | .032.98 |
| Reintubation | 17 (17%) | 10(22%) | 7 (17%) | .16 |
| UrologicAcute Renal failureUrinary tract Infection | 3 (3%)4 (4%) | 2 (4%)3 (6%) | 1 (2%)1 (2%) | .54.29 |
| Wound InfectionSkin DehiscingInfections Requiring Open Drain | 2 (2%)0 (0%)1 (1%) | 0 (0%)0 (0%)1 (2%) | 2 (4%)0 (0%)0 (0%) | .16.31 |
| Anastomotic Leak Medical or Surgical Intervention | 10 (10%) | 8 (16%) | 2 (4%) | .049 |



Figure 1 Overall Survival by Sarcopenia Status

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