# The Association between Sarcopenia and Overall Survival among Patients with Non-

Small Cell Lung Cancer

Thesis

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#### Abstract

#### Introduction

Lung cancer is prevalent and deadly and contributes to approximately 25% of all cancer-related mortalities. With incidence rates rising globally, new treatment options have increased patient overall survival. Lung cancer is unique from other cancer types in that there is a correlation between a patient's body mass index (BMI) and overall survival. Sarcopenia is a skeletomuscular system disorder characterized by a loss of skeletal muscle mass, size, and function. It is identified to be correlated with worse treatment outcomes and survival in several cancer types. Thus, this study explored the relationship between anatomically measured sarcopenia and survival. We hypothesized that sarcopenia would be correlated with a worse overall survival among patients with non-small cell lung cancer. Additionally, we tested two anatomically different measurement methods.

#### Methods

We abstracted data from both chest and abdominal CT scans from 22 patients consented and enrolled in the FITNESS Study: Longitudinal Geriatric Assessment, Treatment Toxicity, and Biospecimen Collection to Assess Functional Disability Among Older Adults with Lung Cancer at the Ohio State Wexner Medical Center's James Cancer Hospital and Solove Research Institute. Using the NilRead software, the skeletal muscle index (SMI) was analyzed by finding the paravertebral muscles at the T12 level, and the psoas major muscle at the L3 level, and manually tracing it to calculate the SMI. Additionally, the patient's weight, in kg, and height, in meters, were used to calculate their BMI as the same date of their baseline CT scans. The patient's body mass index (BMI) and SMI values for both methods were analyzed and further assessed by patient sex. From there, previously established equations were utilized to calculate the sarcopenic and normal range SMI values for both methods. Next, univariate and multivariate Hazard Cox Ratio tests were run to analyze the impact on survival. A paired samples T-Test was utilized to assess the significance between the two methods in diagnosing sarcopenia.

#### Results

The SMI cutoff for sarcopenia was determined by calculating the mean and standard deviation (SD) of SMI values for both the male and female patient populations. Previous research established that subtracting two times the SD from the mean SMI value is the sarcopenic cutoff. None of the patient's SMI values were equal to or below the sarcopenia cutoff. Neither SMI value, sex, or age were associated with patients' overall survival. The T12 and L3 methods were significantly correlated but significantly different.

#### Conclusion

Overall, our study results did not align with our hypothesis. We had no patients who met the definition of sarcopenia and found no significant association between SMI, age, or sex and overall survival. Additionally, we found that our two methods were significantly different and thus did not measure sarcopenia in a similar manner. The study was limited by a small sample size and a lack of automated data abstraction software. We encourage future projects to expand their scope into the longitudinal changes in patient SMI and its relationship to patient outcomes. Additionally, we suggest expanding research into testing the novel T12 method for diagnosing sarcopenia.

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# List of Abbreviations

ATP	Adenosine Triphosphate
BMI	Body Mass Index
CI	Confidence Interval
HR	Hazards Ratio
NSCLC	Non-Small Cell Lung Cancer
OS	Overall Survival
SCLC	Small Cell Lung Cancer
SD	Standard Deviation
SMA	Skeletal Mass Area
SMI	Skeletal Mass Index

#### **Chapter 1. Introduction**

#### Lung Cancer As a Global Health Issue

Lung cancer is a common disease that has the highest mortality rate of all cancers worldwide, as it accounts for 1 in 5 of all cancer deaths. Its incidence rates are increasing globally, as there are an estimated two million new cases per year [1]. There are several factors that can explain such a high mortality rate. When patients begin to experience symptoms and receive screening, the cancer has already progressed to an advanced stage (III or IV). Traditionally, the therapeutic approach for lung cancer has been through the use of surgical excision, chemotherapy, immunotherapy, radiotherapy, or targeted therapies. With expanding treatment options, the latest 5-year survival rate (from 2013 to 2018) in the United States is 28% for patients with non-small cell lung cancer (NSCLC) and 7% for small cell lung cancer (SCLC) [2].

#### Association Between Patient's Weight and Lung Cancer Outcomes

Previous literature has well established the association between patients' weight and cancer treatment outcomes, particularly survival rates. Obesity has been associated with worse cancer outcomes [3]. However, lung cancer does not behave as other solid tumors, and an association has been identified that obese and overweight patients with body mass indexes (BMIs) between 25 and 40 kg/m<sup>2</sup> have better outcomes and improved overall survival rates [4].

A study by Shepshelovich, et al., in 2019 demonstrated a U-shaped association, where the lowest mortality rates were among patients with lung cancer patients whose BMIs were in the middle range (18.5 kg/m<sup>2</sup> – 24.5 kg/m<sup>2</sup>) and the peaks at the lowest and highest BMI ranges [4]. Those who were underweight (BMI < 18.5 kg/m<sup>2</sup>) and morbidly obese (BMI > 40 kg/m<sup>2</sup>) had the highest mortality rates, where the best outcomes were in overweight and obese patients (BMI 25 kg/m<sup>2</sup> – 40 kg/m<sup>2</sup>). These findings were consistent in both NSCLC and SCLC [4]. Patients who are in an underweight BMI category are at higher risk for having cancer-related cachexia and sarcopenia, which in turn plays a role in the patient's overall survival (OS). To further understand how sarcopenia impacts the musculoskeletal system, it is necessary to have a foundational understanding of skeletal muscle.

#### **Overview of the Anatomy and Physiology of Skeletal Muscle**

The musculoskeletal system is a large organ system spanning the entire body. Within this system are three different types of muscle, each serving its own function: skeletal, cardiac, and smooth muscle. While all three are important, for the scope of this research, we focused on skeletal muscle. Skeletal muscle provides humans the ability to move by attaching to bones through tendons, as well as serves as structural support and a heat source for the body. Each muscle is comprised of thousands of muscle fibers surrounded by three sheaths of connective tissue with each bundle being referred to as a fascicle, as seen in Figure 1 below [5]. The outermost layer of connective tissue that surrounds the entire muscle is the epimysium. The perimysium refers to the connective tissue that surrounds each muscle fascicle. Lastly, the endomysium makes up the connective tissue that surrounds each individual muscle fiber, which is composed of a multitude of myofibrils. It is the striped, banded appearance of these myofibrils through forming sarcomeres in the muscle fibers that characterize skeletal muscle as striated, as seen in Figure 2 [6].



### Figure 1: Organization of Skeletal Muscle

The figure demonstrates the organization of muscle and highlights the different layers of connective tissue encasing different structures within the muscle. Dalley, A. F., Agur, A. M. R., & Moore, K. L. (2023). Muscle Tissue and Muscular System. In *Moore's Clinically Oriented Anatomy* (9th ed., pp. 28–35). essay, Wolters Kluwer.



Figure 2: Histological H&E Slide of Skeletal Muscle

The figure displays a traditional H&E stain of skeletal muscle at a 50-micrometer view. The striations from the sarcomeres can be seen alongside the dark purple nuclei scattered about. Paxton, S., Peckham, M., & Knibbs, A. (2004, January 1). The Leeds Histology Guide. Home: The Histology Guide.

 $https://www.histology.leeds.ac.uk/tissue\_types/muscle/Three\_muscle\_types.php$ 

The sarcomeres, as demonstrated in Figure 3, are the functional unit of the muscle cells and are what gives skeletal muscle the ability to contract. Each sarcomere is

composed of thick and thin filaments laying in a parallel structure, with some areas of

overlap. The thick filament is mainly composed of myosin. Myosin is a six-polypeptide

molecule containing two heavy chains and four light chains, that bind to the neck and give it its rigidity to leverage force. Myosin has binding sites for both adenosine triphosphate (ATP) and actin. The thin filament is composed primarily of actin but also contains tropomyosin and the troponin complex. It is the binding of actin to myosin that causes the muscle to contract as myosin slides actin and shortens the sarcomere by pulling the Z-lines together and reducing the width of the I-bands [7].

The sarcomere is broken down into different zones that can be seen histologically. Figure 3 below outlines these zones [7]. The center of the sarcomere contains a line called the M-line. Surrounding the M-line is the H-zone, which is composed only of the thick myosin filaments. Both of these structures are located within the A-band, which is the full length of the thick filament and contains some area of overlap between the thick and thin filaments. Between the A-bands is the I-band, which is composed of only thin filaments and is the area of the sarcomere that changes shape during contraction. Within the center of the I-band is the Z-line, which represents the termination point of one sarcomere [7].



#### **Figure 3: Sarcomere Structure**

The figure above displays the different areas within the sarcomere. The M-line in the center represents the center line of the sarcomere. The M-line is located within the H-zone, an area only made up of thick filaments (displayed as a thick navy line). Both of those structures lie within the A-band, which accounts for the entire length of the thick filaments, as well as the area of thick and thin filament overlap. The I-band represents the area of thin filaments (represented as a thin red line). Within the I-band is the Z-line, which demonstrates the end point of one sarcomere unit. Davis, J. (2023, October). *Skeletal Muscle Structure: From Fiber to Molecules. Muscle Physiology.* Columbus, OH; Davis Heart and Lung Research Institute 170.

In resting skeletal muscles, tropomyosin blocks actin's binding sites to prevent the binding of myosin. The troponin complex then rests on top of the tropomyosin, with each of its proteins fulfilling a different function. Within the troponin complex are troponin C, I, and T. Troponin C works to bind calcium, which acts to allow movement and is relevant to the actin sites when contraction is needed. Troponin I works to inhibit

contraction by stopping cross-bridge binding. Lastly, the troponin T works to bind and anchor the complex to the tropomyosin [7]. It is these building blocks of muscle fibers that physiologically differ depending on the muscle fiber type it is and thus impact its precise function.

#### Classification of Skeletal Muscle Fiber Types

Muscle fibers are further physiologically classified into three groups: I, IIa, and IIb types. The smallest type of skeletal muscle fibers are Type 1 muscle fibers, also known as slow oxidative fibers. These fibers are slow-twitching and are characterized by their low level of fatigue which makes them useful for endurance muscles, such as those that contribute to posture. Their slow contraction speed can be separated into low glycogen content and low myosin ATPase activity [8].

Type IIa muscle fibers, also known as fast oxidative fibers, are fast-twitching fibers due to their high myosin ATPase activity. They are characterized by their intermediate level of fatigue, which makes them the ideal muscle fiber type for moderateduration activities such as walking or biking [8]. Both Type I and IIa muscle fibers share the title of red fibers due to a high concentration of myoglobin, mitochondria, and capillaries [8]. An important distinction for these red fiber types is that they receive ATP mainly from oxidative phosphorylation [8].

The final, and largest, muscle fiber type is Type IIb fibers. These are also referred to as fast glycolytic fibers due to their ATP source primarily being anaerobic glycolysis. These fibers are larger in size due to an increased density of the actin and myosin proteins in each myofibril. These muscles have a fast rate of fatigue which makes them best suited for short-duration and intense movements like sprinting or heavy weightlifting. Like Type IIa, they have a high myosin ATPase activity contributing to its fast twitch. However, it stands alone in its white fiber distinction, which is due to its low concentration of mitochondria and myoglobin [8]. Research has worked to determine exactly which muscle fiber type is impacted in muscle wasting disorders like sarcopenia.

#### Sarcopenia as a Component of the Normal Ageing Process

As human beings age, it is normal for them to have a decrease in their skeletal muscle mass and strength as time goes on. One study by Mitchell and colleagues in 2012 found that after 70 years of age, people lose between 0.5% to 1.0% of their skeletal muscle mass each year [9]. Additionally, muscle strength is also seen to decline 10% to 15% per decade until the age of 70 which increases to a loss of 25% to 40% per decade [9]. Research has devoted lots of time to understanding exactly what processes are happening within the body over time to result in primary sarcopenia being a natural part of aging.

A large part of aging that results in sarcopenia can be seen within the muscle cells themselves. Numerous studies have identified a decrease in skeletal muscle cell numbers over time, thus decreasing muscle cells' sarcoplasmic reticulum volume and calcium pumping abilities [10]. This decrease is impactful as the sarcoplasmic reticulum and calcium are physiologically essential for facilitating actin and myosin interactions that result in muscle contractions, as well as play a role in transmitting nerve impulses to the muscles from the nerves. Thus, there is a decrease in the nerve firing rate to the muscles and the number of active motor neurons, alongside decreased muscle contractions. Other changes at the cellular level include disorganized spacing of the sarcomere, increased motor unit sizes, and an increased concentration of fat accumulating inside and surrounding the muscle cells [10].

Beyond changes in the actual muscle cells themselves, other systemic processes are impacted as individuals age that contribute to the formation of primary sarcopenia. Muscle is a very vascular and metabolically active tissue. Thus, the efficiency of transporting oxygen throughout the body is vital to its proper functioning. As individuals age, their muscle endurance capacity is found to decline by 10% per decade when measured by maximal oxygen consumption [11]. Thus, the muscle becomes less efficient at utilizing the oxygen it is provided to function which decreases its aerobic energy consumption. This is further demonstrated by other studies that have documented the enzymatic changes over time with anaerobic enzymes staying constant while aerobic enzymes decrease with age [11].

In addition to the decrease in muscle's energy consumption, the hormonal fluctuations as humans age have been found to impact skeletal muscle mass, function, and strength. Hormones, such as human growth hormone (HGH), testosterone, estrogen, thyroid hormone, and insulin-like growth factors, all play a role in muscle mass and strength. As humans age, these hormones (among many others) change in their secretion rates and concentration. These hormonal changes contribute to the breakdown in muscle mass and strength over time [12].

Lastly, there are many lifestyle changes that occur with age that contribute to the development of sarcopenia. As individuals age, they tend to decrease their level of physical activity. It is well documented throughout all ages that decreased muscle use through lack of exercise and everyday movement results in a loss of muscle mass and strength. In conjunction with decreased physical activity, as people age, their diet can be inadequate nutritionally, specifically due to reduced protein intake and low vitamin D levels [12]. Together, all these factors collaborate to induce sarcopenic development.

# Sarcopenia and Its Association with Overall Survival Among Patients with Lung Cancer

Cachexia is a metabolic condition characterized by a loss of overall body mass due to an increase in muscle protein synthesis and degradation, energy consumption, inflammation, and insulin resistance [11]. Cachexia is typically related to an underlying illness, such as cancer. Sarcopenia is a disorder defined by loss of skeletal muscle mass, strength, and muscle function. While both conditions share a decrease in a patient's body mass, sarcopenia is specifically the loss of skeletal muscle which is linked to decreased bone density, increased joint stiffness, and a small reduction in overall stature [1, 10]. Due to this loss of function and strength, sarcopenia increases patients' likelihood of falling, bone fractures, functional impairment, and hospitalizations [13]. Histological findings show that the size of type II (fast twitch) muscle fibers is reduced by up to 50% in sarcopenia, as well as loss of anterior horn cells and ventral root fibers, thus indicating not only the reduction of muscle size but also reduction in number of fibers and loss of motor neurons [14]. While it is a condition that occurs during the normal human aging process, it is not exclusive to older adults and often accompanies many other diseases, such as cancer [1].

Sarcopenia is a disorder that can be further broken down into two categories: primary and secondary sarcopenia. Primary sarcopenia is associated with the normal aging process, whereas secondary sarcopenia is concomitant to diseases, such as lung cancer, and thus has been a topic of research interest in its impact on patients' treatment and survival outcomes [15]. One study found that sarcopenia's prevalence in lung cancer is higher than in any other cancer type. The overall prevalence of severe muscle depletion (sarcopenia) was 46.8% and was present in patients in all BMI categories. A much higher proportion of men (61%) than women (31%) met the criteria for sarcopenia. [16]. A meta-analysis from 2019 illustrated that patients with sarcopenia had a significantly worse overall survival rate regardless of tumor type or cancer staging [17]. Another study demonstrated sarcopenia's impact on lung cancer patients' treatment outcomes and found it to be an independent risk factor for higher mortality rates regardless of treatment type (surgery, targeted therapy, chemotherapy, radiotherapy, or a combination) [18]. Thus, previous research has identified the importance of clinicians screening for sarcopenia among patients with lung cancer as a preemptive measure to help tailor patients' treatment plans to include exercise and lifestyle changes patients can make to reverse and reduce sarcopenic symptoms. In order to screen for sarcopenia, physicians need to be aware of the scientifically proven methods they can use to diagnose it as early as possible.

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#### Methods for Screening Sarcopenia Among Patients with Lung Cancer

Multiple methods have been utilized in research to help clinicians diagnose sarcopenia with the most prevalent method using the psoas major muscle index. This method refers to analyzing cross-sectional CT scans and measuring the skeletal mass area (SMA) of the psoas major muscle at the L3 vertebral level. The psoas major muscle is a paraspinal muscle located deep in the body that originates from the transverse processes and vertebral bodies of T12 to L5. Given its location deep in the abdomen, it is considered an abdominal muscle and thus is an appropriate measure of skeletal muscle mass as, unlike appendicular skeletal muscle, it is independent of activity level [17]. This method has been shown to be an effective marker of sarcopenia and had been able to predict outcomes in a wide range of surgical procedures [19-21].

In addition to the popularized L3 psoas major muscle index method, researchers are exploring a new method to diagnose sarcopenia among patients with lung cancer. Given that most patients frequently have chest CT scans rather than abdominal, a new study from Takamori's team in 2020 looked at taking the framework of the previous L3 method and applying it to the paravertebral muscles at the T12 vertebral level, as these muscle size also remains independent of patient activity level [22]. At the T12 level, the paravertebral muscle group was defined as the erector spinae muscle group, rotatores, and multifidus.

The erector spinae muscle group is composed of three muscles: iliocostalis, longissimus, and spinalis. Each of these muscles can continue to be divided into sections; capitis, cervicis, thoracis, and lumborum dependent on which part of the vertebral column they are located. Using the T12 method we documented the distal end of the thoracis segment of longissimus and iliocostalis. The spinalis muscle is excluded from being measured in the T12 method due to its lowest insertion point being the spinous process of the T8 vertebrae. Together all the erector spinae muscles work together to bilaterally extend the vertebral column. Unilaterally, they work to lateral flex the vertebral column to the ipsilateral side.

Beyond just the erector spinae muscles, the T12 method also accounts for the rotatores and multifidus muscles in the skeletal muscle surface area calculation. The rotatores muscles are the deepest muscles of the intrinsic back muscles in the transversopinales muscle group. They span the entirety of the vertebral column but are most prominent in the thoracic region. Similarly to the erector spinae, they are further subdivided into the cervicis, thoracis, and lumborum regions. Utilizing the T12 method, it is the rotatores thoracis that is of special interest. They function to rotate the vertebral column, as well as contribute to stabilizing and extending the spine.

The multifidus is the final muscle incorporated in the T12 method. It is located in the deep muscles of the back in the transversospinales muscles group alongside the rotatores and semispinalis. In the thoracis region of interest, multifidus originates on the transverse processes of the thoracis vertebrae and inserts onto the spinous processes of all vertebrae from T8 to L5. Bilaterally it functions to extend the vertebral column and unilaterally it contralaterally contracts to rotate the vertebral column. It is also said to contribute to the stabilization of the spine, specifically in upright postures. The logic of

why these muscles are good markers to assess skeletal muscle mass is the same as the psoas major muscle in that they are deep muscles of the back that, unlike appendicular skeletal muscles, do not depend on activity levels. As new research publications have been exploring using the T12 paravertebral muscle index for sarcopenia, we were inspired to continue contributing to this research and study this method in a cohort of older adults with lung cancer. Once healthcare providers are able to identify sarcopenia in their patients, they then have the ability to employ a variety of treatment options to minimize sarcopenia's impact on their patient's quality of life and overall survival.

#### Treatment Options for Sarcopenia

Given the clinical implications sarcopenia has on patients' overall survival during cancer treatment, it is important for healthcare providers to be aware of the various sarcopenia treatment options available. When employed properly, these options can work to reduce, or even reverse, the impacts of sarcopenia. Through lifestyle changes and medicine options, there are many ways patients can work to combat the effects of sarcopenia both on their everyday quality of life and their cancer treatment.

One of the most straightforward, and well-researched, treatment options to help alleviate sarcopenia is by increasing physical activity through exercise. Patients can perform either anaerobic or aerobic exercise as a way to remedy sarcopenia. Anaerobic exercise refers to short bursts of high-intensity movement that are fueled by the energy stored within the muscle cells. Alternatively, aerobic exercise involves continuous movement that is fueled by oxygen via respiration. The most popular anaerobic method of exercise researched was resistance training. Resistance training refers to programs in which participants exercise against an increasing load, typically using weights or resistance bands. Resistance training programs are effective in improving and maintaining muscle strength and function, body composition, and overall physical function. It is also known to reduce the length of hospital stays and increase both grip strength and muscle cross-sectional area in older adults [12,15]. Another physical treatment option is aerobic exercise.

Aerobic exercise, such as cycling and swimming, is an excellent option for combating sarcopenia's impact as it induces ATP production in the mitochondria of the muscle cells. This enhances the body's metabolic control and increases cardiovascular function, thus improving the circulation of oxygen throughout the body, including skeletal muscle. Stimulating ATP formation also works to restore lost mitochondrial metabolism and can help increase muscle protein synthesis [12]. A study from Bori and collogues from 2012 demonstrated that older adults who completed a 12-week aerobic exercise training program using a treadmill had improved mitochondrial biogenesis and fission protein [23]. While both anaerobic and aerobic exercise have demonstrated promising results in managing or improving sarcopenic symptoms, there are other nonexercise-based options available for patients who have other physical limiting comorbidities.

Beyond exercising, one lifestyle change that can be offered to patients is nutrition therapy. Our diets change often throughout our lifetime and continue to alter with age. A decrease in protein, vitamin D, and long-chained polyunsaturated fatty acid consumption is seen in older adults and is thought to contribute to decreased muscle functioning. One dietary change that older adults could consider is an increase in fish consumption. A diet supplemented with fish protein consumption was found to help in delaying the onset of sarcopenia due to its high protein, vitamin D and E, magnesium, and omega-3 contents [12]. Another option is for older adults to add vitamin D supplements into their daily routine. Beaudet et al demonstrated that women with post-stroke hemiplegia who consumed vitamin D supplements over a two-year time period had an increase in type II muscle fibers, which are precisely the muscle fiber type reduced in sarcopenia. The women also displayed increased muscle strength and a reduction in falls and hip fractures when compared to the control group [24]. These vitamin D supplements are just one medicine option that can produce beneficial results in treating sarcopenia.

One additional therapy option for those struggling with sarcopenia is through the use of androgen therapy. Hormonal changes, such as a drop in androgen levels, occur over time as humans age in both females and males. Males begin to decrease testosterone levels by 1% to 3% per year starting at the age of 35, while females start to have a large hormone level drop at the onset of menopause [11]. These androgens work to increase muscle mass and strength among other vital bodily functions [25]. When these hormones start to decrease in concentration with age, it results in decreased muscle mass, and strength, and increases bone's fragility. Hormone supplementation research as a treatment to slow down, or possibly reverse, sarcopenias is ongoing [11]. However, hormone therapies can have dangerous impacts such as increasing the risk of prostate cancer and

cardiovascular events in men and increased ovarian cancer rates and venous thromboembolism in women [11].

These adverse effects have led researchers to look into using selective androgen receptor modulators (SARMs). One study from 2008 looked into a SARM called ostarine [26]. After 86 days of use, the study found both elderly men and women increased their lean body mass and demonstrated an improved ability to climb up the stairs. However, the most important discovery of the study was that the male participants did not have any increased risk of prostate-specific antigen levels and the women had no increase of hair growth. These two markers suggested that the risk of SARM side effects was lower than traditional hormonal therapies[26]. It is through all these therapy options that healthcare providers can help manage and alleviate sarcopenia's impact on their patients and improve their patient's prognosis.

#### The Clinical Impact of Treating Sarcopenia among Patients with Cancer

Sarcopenia has been established to have an adverse effect on patients with cancer treatment and overall survival. Low muscle mass and strength have been proven to negatively impact cancer-related symptoms and increase infection rates, length of hospitalization, and mortality rates. However, when actions are taken to preserve muscle mass and strength studies have shown that it is significantly related to lower cancer treatment toxicities and complications during chemotherapy [15].

A systemic review from Jang and colleagues in 2023 found resistance training exercises to be the most promising strategy for improving patients' muscle strength, function, and quality of life. They found that when utilizing a resistance training regime, skeletal muscle mass and lead body mass did not significantly change. This was very important when compared to another meta-analysis of 2,662 patients with cancer treated with chemotherapy who had a significant decrease in SMI during treatment. Thus, the review indicated resistance exercise's ability to reduce SMI loss in patients receiving chemotherapy [15]. These findings aligned with a student from Adams and team in 2016 where they implemented a three-arm randomized controlled study that included resistance exercise, aerobic exercise, vs. usual care. They found that resistance exercise demonstrated a significant effect in reversing sarcopenia when compared to the other two treatment options [27].

The implications of prior studies demonstrate that the treatment of sarcopenia can have clinically meaningful improvements in the quality of life for patients with cancer. This is especially relevant to our study as research has demonstrated that patients with NSCLC often have the highest prevalence of sarcopenia prior to cancer treatment [15]. Thus, these patients are more susceptible to sarcopenia decrease in functional status, and decreased survival rates and could benefit greatly from sarcopenic intervention.

#### Research Questions, Study Aims, and Significance of Study

This study was designed to address two specific aims. Our first research aim was to analyze data from patients with lung cancer to identify if there was any correlation between skeletal muscle area (SMA) and overall survival. We hypothesized that patients who had a low SMA level in the sarcopenic range would experience worse overall survival outcomes than patients who had a normal to high SMA level.

Our second research aim was to compare and contrast the effectiveness of the new T12 paravertebral SMA method for sarcopenia to the well-established L3 psoas major muscle method. The significance of our study is not only to continue to contribute to research looking into the relationship of sarcopenia on patient outcomes and emphasize its clinical implications but to also identify if the new T12 method is effective as a sarcopenic screening method, particularly among older adults.

#### **Chapter 2. Methods**

#### **Patients**

The patient population used in our study were lung cancer patients who enrolled and consented to participate in a related study called the FITNESS Study: Longitudinal Geriatric Assessment, Treatment Toxicity, and Biospecimen Collection to Assess Functional Disability Among Older Adults with Lung Cancer (IRB #2018C0069) at the James Cancer and Solove Research Institute at the Ohio State University Wexner Medical Center in Columbus, Ohio. The inclusion criteria for the FITNESS study were patients aged  $\geq 60$  years who were diagnosed with NSCLC of any stage within the past year (starting in 2018). Additionally, the patients must have met our studies' inclusion criteria, which was that the patients must have had both chest and abdominal CT scans available on the date of their baseline and BMI information available at the time of imaging. For this study, we evaluated at patient's baseline CT scans, which were the first CT scans available after the patients consented to the FITNESS study. Most baseline scans were conducted within 30 days of the consent date, while the remainder were conducted between 30-90 days after consent. The exclusion criteria for our study within the FITNESS cohort was any patient who was younger than 60 years of age or who did not have available baseline chest and abdominal CT scans.

#### Imaging and Assessment of Skeletal Muscle Area (SMA)

This study evaluated two different methods: the L3 psoas major muscle index method and the T12 paravertebral muscle index method. Thus, we had two similar modes of data abstracted that differed based on the anatomical location of the skeletal muscle analyzed.

For the L3 psoas major muscle abstraction, we had found the abdominal CT scan taken on our target date, which was a scan within 30 days of the patient enrolling in our study, which we referred to as the patient's baseline scan. Once the CT scan had been located, we opened the file using 2022 NilRead software version 5 by Hyland. To anatomically locate the L3 vertebrae, we identified the top of the iliac crest on the axial view to locate the L4 vertebral body. From there, we then moved up through the axial slices one full vertebral level and found the L3 vertebral body. This was cross-checked by identification of the L3 vertebrae in the sagittal view (when available). Next, the free roam annotation tool on NilRead was used to manually trace the psoas major muscle on the left side, as seen in Figure 4. The same steps were then used to manually trace the right side. Finally, the SMA of the psoas major muscle was calculated by adding the left and right sides together and dividing it by the patient's height in meters squared (cm^2/m^2).



# Figure 4: Axial Cross-Section of an Abdominal CT scan at the L3 Vertebral Level

The figure displayed an axial cross-section image of a patient's L3 vertebrae. The yellow encircled area represents the psoas major muscle laying along each side of the vertebral body. (NilRead version 5)



Figure 5: Axial Cross Section of an Abdominal CT scan at the L3 Vertebral Level with Segmented Muscles

The figure displayed an axial cross-section image of a patient's superior L3 vertebrae with "R" standing for the right side and "L" for the left side. The muscles are color coordinated as follows: rectus abdominis m. with linea alba (pink), external and internal oblique with transversus abdominis mm. (green), quadratus lumborum m. (orange), erector spinae mm. (purple), multifidus and rotatores mm. (light blue), and psoas major m. (yellow). The main viscera within the CT scan slice had been labeled accordingly on the image with blue arrows pointing to the small intestine, inferior pole of the right kidney, inferior vena cava, descending colon, and aorta. (Nilread version 5).

For the T12 paravertebral muscle data abstraction, we used a very similar methodology. We begun by finding a chest CT taken on our target date, which was a scan within 30 days of the patient enrolling in our study, which we refer to as the patient's

baseline scan. Once the CT scan file was located in EPIC, it was opened using NilRead

software. To find T12, we started at the bottom of the CT scan's axial slices and worked

our way up. The chest CTs ended on the L1/L2 vertebral level, so to find T12 we looked

through each CT image until we noticed the shape of the vertebra changing from the wide-bodied and transverse processes of the lumbar vertebra to the smaller vertebral bodied and costal facets of the thoracic vertebra. The presence of the celiac trunk branching off the top of the abdominal aorta was an additional marker utilized. This was cross-checked by identifying the T12 vertebrae in the sagittal view (when available). Once we found T12, we used the free roam annotation tool on NilRead to manually trace the paravertebral muscles on the left and then on the right side as seen in Figure 6. For the basis of this study, we defined the paravertebral muscles as the erector spinae group (composed of iliocostalis, longissimus, and spinalis), rotatores, and multifidus. Similarly to the L3 method, we then calculated the SMA of the paravertebral muscles by adding together the left and right muscle areas and dividing it by the patient's height squared (cm^2/m^2).



Figure 6: Axial Cross-Section of Chest CT Scan at the T12 Vertebral Level

The figure displayed an axial cross-section image of a patient's superior T12 vertebrae. The yellow highlight is the free roam annotation tool that encircled the paravertebral muscles: erector spinae, multifidus, and rotatores muscles (NilRead version 5).



Figure 7: Axial Cross-Section of Chest CT Scan at the T12 Vertebral Level with Segmented Muscles

The figure displayed an axial cross-section image of a patient's superior T12 vertebrae. The muscles are color coordinated as follows: rectus abdominis m. with linea alba (dark pink), diaphragm m. (light pink), external and internal oblique with transversus abdominis mm. (green), intercostal mm. (yellow), erector spinae mm. (purple), multifidus and rotatores mm. (light blue), and latissimus dorsi m. (orange). IVC stands for inferior vena cava. Additionally, the liver, portal vein, stomach, duodenum, pancreas, celiac trunk, aorta, and spleen are labeled alongside the orange arrows. (Nilread version 5).

### Statistical Analysis

We had two outcomes examined in this study. For our first study aim we evaluated any correlation between sarcopenia and overall survival. For this aim, the outcomes we were interested in were BMI, SMA, and overall survival (OS). We defined OS as the number of months between patient study enrollment and either their date of death or date of last contact depending on the patient's current life status. Both a univariate and multivariate Cox proportional hazard ratio were used to analyze overall survival via SPSS version 28.0 software. A Cox Hazard Ratio test was selected as it uniquely allowed the inclusion of covariates known to be associated with overall survival (age and sex), whereas Kaplan Meier is used to predict a binary response. Given that we analyzed multiple values, SMI, BMI, and sex, on patient overall survival we needed a test that was able to analyze not only at each independently but in conjunction with selected covariates. The p-value set to determine statically significance was less than or equal to 0.05.

For our second aim, the effectiveness of the newer T12 method in being able to diagnose sarcopenia was placed in comparison to the previously established L3 method. Here the outcome we were interested in were the SMA and BMI of the patients for both methods. To assess this a paired T-Test was run using the SPSS version 28.0 software.

#### **Chapter 3. Results**

#### **Patient Demographics**

A total of 22 patients met the inclusion criteria out of the 50 patients enrolled in the original FITNESS study. The inclusion criteria were patients who were  $\geq 60$  years old, diagnosed with NSCLC within the past year of enrollment in the FITNESS study, and had baseline chest and abdominal CT scans. The remaining 28 patients were excluded due to a lack of abdominal CT scans at the time of baseline.

Patient characteristics of the pooled population are displayed in Table 1. The mean age of the cohort was 71 years, with patients ranging from 61 to 88 years old. The majority of the study population were male (55%), white (95.5%), of a non-Hispanic background (86%), and with previous smoking history (73% former smokers and 9% current smokers). All patients had a diagnosis of NSCLC. The majority had an adenocarcinoma histologic subtype diagnosis (62.8%) and a late-stage diagnosis of stage III (22.8%) or IV (72.7%).

Characteristics	n (%)
Mean Age (SD, min-max), years	71 (61-88)
Sex	
Female	10 (45)
Male	12 (55)
Ancestry	
White	21 (95.5)
Black	0 (0)
Asian	1 (4.5)
Ethnicity	
NOT Hispanic	19 (86)
Hispanic	0 (0)
Unknown / not reported	3 (14)
Smoking Status	
Never Smoker	4 (18)
Current Smoker	2 (9)
Former Smoker	16 (73)
Histology	
Adenocarcinoma	15 (68.2)
Nonsquamous	6 (27.3)
Squamous	1 (4.5)
Lung Cancer Stage at Diagnosis	
I	1 (4.5)
Π	0 (0)
III	5 (22.8)
IV	16 (72.7)

Table 1: Patient Characteristics, N = 22

 Table 1 displays the demographic information on the study population (n=22).

#### Average Skeletal Muscle Index (SMI) and BMI in Patient Populations

After the patient population demographics were analyzed, the average baseline BMI and SMI were calculated for use in the further statistical analysis items below. BMI was calculated by dividing the patient's weight in kilograms by their height in meters squared (kg/m<sup>2</sup>). Patient SMI was calculated by adding the right and left muscle area and dividing it by the patient's height squared (cm<sup>2</sup>/m<sup>2</sup>). These results were demonstrated in Table 2. Of the 22 patients in the study population, only 17 (77%) of the patients had their weight assessed at the time of their first available CT scans. Of those 17 patients, 5 (23%) had a normal BMI, 7(31%) had an overweight BMI, and 5(23%) had an obese BMI.

Additionally, both SMI methods data were averaged for further calculations. Using the L3 SMI method the overall mean standardized psoas area for the population was  $5.526 \text{ cm}^2/\text{m}^2$  with a standard deviation of  $1.494 \text{ cm}^2/\text{m}^2$ . The mean standardized psoas area for male participants was  $5.827 \text{ cm}^2/\text{m}^2$  with a standard deviation of  $1.609 \text{ cm}^2/\text{m}^2$  as demonstrated in Figure 8. The mean standardized psoas area among female participants was lower at  $5.164 \text{ cm}^2/\text{m}^2$  with a standard deviation of  $1.333 \text{ cm}^2/\text{m}^2$  as depicted in Figure 9.

Utilizing the T12 SMI method the overall mean standardized paravertebral area was  $11.758 \text{ cm}^2/\text{m}^2$  with a standard deviation of  $3.532 \text{ cm}^2/\text{m}^2$ . Again, having stratified the data by sex there were slight differences in the mean SMI. For the male participants, the mean standardized paravertebral area was  $11.916 \text{ cm}^2/\text{m}^2$  with a standard deviation of

 $4.510 \text{ cm}^2/\text{m}^2$  as visualized in Figure 10. The mean standardized paravertebral area for female participants was slightly lower at  $11.570 \text{ cm}^2/\text{m}^2$  with a standard deviation of  $2.042 \text{ cm}^2/\text{m}^2$  as depicted in Figure 11.

Previous literature had established sarcopenic cutoff value as the mean SMI minus the standard deviation multiplied by two (Mean – 2SD) [18,19,30]. This methodology was utilized and defined the sarcopenic cutoff when using the L3 SMI method was less than or equal to  $2.609 \text{ cm}^2/\text{m}^2$  for males and for females was 2.498 cm<sup>2</sup>/m<sup>2</sup>. At the T12 SMI method, the sarcopenic cutoff value was established as less than or equal to  $2.896 \text{ cm}^2/\text{m}^2$  for males and 7.486 cm<sup>2</sup>/m<sup>2</sup> for females (Table 2). Given these established values, none of the patients were defined as sarcopenic for either method.

Prior literature has stated that the value of a normal SMI is equal to or greater than the average SMI minus one SD [30]. Utilizing this formula, the normal SMI cutoff value when the L3 SMI abstraction method was used was 4.218 cm<sup>2</sup>/m<sup>2</sup> for males and 3.831 cm<sup>2</sup>/m<sup>2</sup> for females. When the T12 SMI method was examined, the normal SMI cutoff value was determined to be 7.406 cm<sup>2</sup>/m<sup>2</sup> for males and 9.528 cm<sup>2</sup>/m<sup>2</sup> for females (Table 2). Given these established values, using L3 methods values, only one female fell in the low SMI category. When utilizing the T12 methods values, one male and one female fell into the low SMI category. However, it is worth noting that the female classified as having low SMI values in both categories was not the same individual, but two different female participants.

Variable	N (%)	
BMI, kg/m <sup>2</sup>		
BMI < 18.5 (underweight)	0 (0)	
BMI 18.5 – 24.9 (normal weight)	5 (23)	
BMI 25 – 29.9 (overweight)	7 (31)	
BMI > 30 (obese)	5 (23)	
Unknown BMI	5 (23)	
L3 Psoas Major M. Method		
Overall Mean Standardized Psoas Area (SD), cm <sup>2</sup> /m <sup>2</sup>	5.526 (1.494)	
Male		
Mean Standardized Psoas Major Area (SD), cm <sup>2</sup> /m <sup>2</sup>	5.827 (1.609)	
Sarcopenic Cutoff Value (Mean $- 2SD$ ), cm <sup>2</sup> /m <sup>2</sup>	2.609	
Normal SMI Cutoff Value (Average SMI – SD), $cm^2/m^2$	4.218	
Female		
Mean Standardized Psoas Major Area (SD), cm <sup>2</sup> /m <sup>2</sup>	5.164 (1.333)	
Sarcopenic Cutoff Value (Mean $- 2SD$ ), $cm^2/m^2$	2.498	
Normal SMI Cutoff Value (Average SMI – SD), $cm^2/m^2$	3.831	
T12 Paravertebral Mm. Method		
Overall Mean Standardized Paravertebral Area (SD), cm <sup>2</sup> /m <sup>2</sup>	11.758 (3.532)	
Male		
Mean Standardized Paravertebral Area (SD), cm <sup>2</sup> /m <sup>2</sup>	11.916 (4.510)	
Sarcopenic Cutoff Value (Mean $- 2SD$ ), $cm^2/m^2$	2.896	
Normal SMI Cutoff Value (Average SMI – SD), cm <sup>2</sup> /m <sup>2</sup>	7.406	
Female		
Mean Standardized Paravertebral Area (SD), cm <sup>2</sup> /m <sup>2</sup>	11.570 (2.042)	
Sarcopenic Cutoff Value (Mean $- 2$ SD), cm <sup>2</sup> /m <sup>2</sup>	7.486	

Table 2: Patient Body Mass Index and Skeletal Muscle Index Data, N = 22

Normal SMI Cutoff Value (Average SMI – SD), $cm^2/m^2$	9.528

**Table 2** displays the mean BMI and SMI results for the overall population (N=22) as well as broken down by each SMI method and sex.





Figure 8 displayed a histogram demonstrating the SMI values of our male patient cohort using the SMI values abstracted from the L3 psoas major muscle. The x-axis represents the SMI values in  $cm^2/m^2$ . The y-axis represents the number of male patients for each SMI value. The blue bars indicate the number of patients within the SMI range spanning  $1 cm^2/m^2$ . In the top right corner, the mean of  $5.83 cm^2/m^2$ , the standard deviation of  $1.609 cm^2/m^2$ , and the size of our cohort is N=12.



### Figure 9: Female Patient SMI Values Utilizing the L3 Psoas Major M. Method

Figure 9 displayed a histogram demonstrating the SMI values of our female patient cohort using the SMI values abstracted from the L3 psoas major muscle. The x-axis represents the SMI values in  $cm^2/m^2$ . The y-axis represents the number of female patients for each SMI value. The blue bars indicate the number of patients within the SMI range spanning 1  $cm^2/m^2$ . In the top right corner, the mean of 5.16  $cm^2/m^2$ , the standard deviation of 1.333  $cm^2/m^2$ , and the size of our cohort in N=10.



## Figure 10: Male Patient SMI Values Utilizing the T12 Paravertebral Method

Figure 10 displays a histogram demonstrating the SMI values of our male patient cohort using the SMI values abstracted from the T12 paravertebral muscles. The x-axis represents the SMI values in  $\text{cm}^2/\text{m}^2$ . The y-axis represents the number of male patients for each SMI value. The blue bars indicate the number of patients within the SMI range spanning 1  $\text{cm}^2/\text{m}^2$ . In the top right corner, the mean of 11.92  $\text{cm}^2/\text{m}^2$ , standard deviation of 4.510  $\text{cm}^2/\text{m}^2$ , and the size of our cohort is N=12.



Figure 11: Female Patient SMI Values Utilizing the T12 Paravertebral Method

Figure 11 displays a histogram demonstrating the SMI values of our female patient cohort using the SMI values abstracted from the T12 paravertebral muscles. The x-axis represents the SMI values in  $\text{cm}^2/\text{m}^2$ . The y-axis represents the number of female patients for each SMI value. The blue bars indicate the number of patients within the SMI range spanning 1 cm<sup>2</sup>/m<sup>2</sup>. In the top right corner, the mean of 11.57 cm<sup>2</sup>/m<sup>2</sup>, the standard deviation of 2.042 cm<sup>2</sup>/m<sup>2</sup>, and the size of our cohort is N=10.

#### Cox Hazard Ratio Analysis of SMI, Covariates, and Overall Survival

To investigate the impact of a patient's SMI (independent variable) on their overall survival (dependent variable) the Cox Hazards Ratio was performed using both a univariate and multivariate approach. The first hazards ratio (HR) test conducted, as displayed in Table 3, was a univariate test between the independent variable, SMI, and the dependent variable, overall survival. This test was performed three times, using three independent variables: 1) L3 SMI, 2) T12 SMI, and 3) BMI. All HR values were close to 1, with results of 1.021 for L3 SMI, 1.011 for T12 SMI, and 1.054 for BMI. The 95% confidence interval (CI) was calculated for each test run and were recorded in Table 3. Additionally, all three univariate tests came back with p-values of insignificance as they were greater than a 0.05 p-value. P-values equal 0.890 for L3 SMI, 0.852 for T12 SMI, and 0.369 for BMI.

Variable	Hazard Ratio (HR)	95% Cl for HR	p-value
		Lower   Upper	Significant < 0.05
L3 SMI	1.021	0.758   1.376	0.890
T12 SMI	1.011	0.898   1.139	0.852
BMI	1.054	0.939   1.183	0.369

Table 3: Univariate Cox Hazards Ration on Overall Survival

**Table 3** displays the results of the univariate Cox Hazards Ratio tests for three

 independent variables.

Alongside the univariate Cox Hazards Ratio, two multivariate Cox Hazards Ratio were performed to further analyze their impact on patient's OS. These two test results are demonstrated in Table 4. The first multivariate evaluated the association between the L3 SMI method, female sex, and age on OS. All HR results were close to 1 with HR values of 1.001, 0.769, and 0.998 respectively. The 95% confidence interval (CI) was calculated for each test run and were displayed in Table 4. Additionally, all three p-values came back insignificant, with values of 0.993, 0.637, and 0.963 respectively. The second multivariate HR looked at the impact of the T12 SMI method, female sex, and age on patient OS. These results are displayed in Table 4 as well. The HR for all the variables was close to 1, with results of 1.007, 0.771, and 0.999 respectively. The p-values for this analysis were also insignificant as the results were 0.908 for T12 SMI, 0.630 for female sex, and 0.992 for age. The CI was listed in Table 4 for each variable.

Variable	Hazards Ratio (HR)	95% Cl for HR	p-value
		Lower   Upper	Significant < 0.05
L3 SMI	1.001	0.736   1.362	0.993
Female	0.769	0.258   2.291	0.637
Age	0.998	0.912   1.092	0.963
T12 SMI	1.007	0.892   1.137	0.908
Female	0.771	0.267   2.222	0.630
Age	0.999	0.910   1.098	0.992

Table 4: Multivariate Cox Hazards Ratio on Overall Survival

**Table 4** displays the results of both multivariate Cox Hazard Ratio tests.

#### Statistical Analysis of Both Methods Using a Paired T-Test

A paired sample t-test was used to analyze the relationship between the L3 and T12 SMI methods. The mean was found to be 6.23318 with a standard deviation of 3.11623. The CI was calculated and listed in Table 5. With both the one-sided and two-sided p-values of <0.001, the results indicated that the two methods were significantly different.

Pair 1	Mean	SD	95% Cl	Significance
			Lower   Upper	One-Sided p   Two-Sides p
SMI T12 –	6.23318	3.11623	4.85152   7.61484	< 0.001   < 0.001
SMI L3				

Table 5: Paired Samples T-Test of T12 and L3 SMI Methods

Table 5 displays the results of a paired t-test looking at two SMI methods run on the

same population.

#### **Chapter 4. Discussion**

#### Interpretation and Implications of Study Results

Our study was designed with two main objectives, the first of which was to examine the relationship between patients with a new diagnosis of NSCLC with sarcopenia and their overall survival rates. Previous literature had demonstrated that patients with sarcopenia had clinically significant shorter median survival rates in both extended and limited staged lung cancer [28,29]. Other studies had stated that sarcopenia also had an impact on both short-term and long-term survival rates, as well as increased the risk of postoperative complications, of those with NSCLC who underwent a lobectomy [30,31]. Two ways that these studies looked into diagnosing sarcopenia was through examining CT scans at the L3 and T12 vertebral levels, with the L3 method being by far the most commonly used [32-36]. Prior research demonstrated that the presence of sarcopenia based on the psoas major muscle L3 method had a negative impact on both in-patient and long-term survival [36] and increased postoperative complications [33, 34].

All of these studies had important implications, as approximately one in two patients with lung cancer were sarcopenic, and thus based on previous findings would adversely impact their survival [37]. Given the high prevalence of sarcopenia among patients with lung cancer, it was interesting to find that no one in our patient cohort had met the criteria of a sarcopenia diagnosis.

In order to analyze sarcopenia in our patient population outcomes, we first needed to determine the sarcopenic cutoff. Following in the footsteps of previously established research, the cutoff was determined by subtracting two times the standard deviation from the population's mean SMI (Mean SMI - 2SD) [20,21, 38]. Through calculating and defining our sarcopenic cutoff in both the L3 and T12 methods, we determined that none met the criteria for sarcopenia. This was due to no patient's baseline SMI being less or equal to the calculated cutoff values. This was not too surprising as the patients' scans were all assessed at baseline, which does not give the cancer enough time to progress to induce secondary sarcopenia. We would expect more patients to be sarcopenic as their diseases progressed over time and they were receiving cancer treatment.

When analyzing the data utilizing the L3 method, we found that the mean SMI, sarcopenic cutoff and normal SMI cutoff value were less in the female population than in the male population. This was anticipated, as females typically have smaller skeletal muscle mass than males do. Both our male and female cohorts had one outlier who had a much higher SMI value than the rest. While we should have initially excluded these patients, it was not as entirely detrimental to the overall relationship as each having a proportionate outlier somewhat equalized the data set.

However, this differed when looking at the T12 paravertebral method where our female population, while still having a decreased mean SMI value, had a higher sarcopenic cutoff value and normal SMI cutoff value than our male population. While

this was initially surprising, we realized this was due to the male cohort having one large outlier while the female cohort did not have any outliers. Due to the inclusion of this outlier with a significantly higher SMI rate than the other males, the standard deviation was much larger in the male cohort, as the male's SD was  $4.510 \text{ cm}^2/\text{m}^2$  and the female's SD was only  $2.042 \text{ cm}^2/\text{m}^2$ . This highly skewed the sarcopenic and normal SMI cutoff values since both equations relied on the SD to be subtracted in some manner from the cohort mean.

The values for sarcopenia that we obtained were different than previously established literature values. For example, one study from 2017 defined the sarcopenic cutoff SMI values utilizing both the psoas major m. at L4 and the paravertebral muscles at T12 in healthy kidney donors that were aged 18-40. They found the sarcopenic cutoffs to be  $10.9 \text{ cm}^2/\text{m}^2$  in males and  $7.8 \text{ cm}^2/\text{m}^2$  in females when the T12 method was used, while the values were  $7.5 \text{ cm}^2/\text{m}^2$  in males and  $5.2 \text{ cm}^2/\text{m}^2$  in females when looking at the psoas major muscle at L4 [42]. Given that this analyzed a younger and healthier patient population, we anticipated that our patient cohorts' cutoff values would be sustainably lower due to age-related, and possibly disease-related at this stage, impact on the patient's skeletal muscle mass.

Initially, we wanted to explore the longitudinal impact of cancer progression and treatment with sarcopenia diagnoses. However, given that our sample size was already small at 22 patients with baseline scans, we found that our patient cohort dwindled even smaller if we were to include scans at either 3 months, 6 months, or even 12 months CT scans. Thus, in order to maximize our study sample size, we assessed baseline scans only.

However, this had unwanted and unpredicted implications for our study, as we could no longer assess sarcopenia's impact on the patient's overall survival. Instead, we pivoted our original hypothesis to look at patients' SMI's impact on their overall survival, regardless of whether they met the clinical criteria for sarcopenia.

To identify if patients had a normal or low SMI, we used a previous publication's standard for normal SMI of it being higher than one SD below the average SMI value [38]. After the normal SMI value was calculated for males and females on both methods, we determined that using the L3 data one male and one female had a low SMI. When using the T12 method, only one female was determined to have a low SMI, although this was not the same female as classified as low in the L3 method.

There appeared to be a research gap in the field, as only a limited number of studies focused on the relationship between non-sarcopenic patients SMI's and its association with overall survival. However, one study evaluated patients with a lobectomy's SMI outcomes and found that patients with a higher-than-average SMI had fewer postoperative complications and survival than those who fell at a less-than-average SMI category [39]. While only three patients had a low SMI category within a least one abstraction method, we did not find any significant relationship between patient SMI and overall survival, even after patient sex was accounted for.

The second aim of our study was to determine if the new T12 method was as effective in diagnosing sarcopenia as the previously proven L3 method. In order to test this, we ran a paired T-Test on SPSS since the same population was analyzed. The test came back as showing the two methods were significantly different and did not test the same things. This implied that T12 may not be as effective in the diagnosing sarcopenia as we had hypothesized.

This result was also expected as previously established publications had evaluated both methods as a way to diagnose sarcopenia and found significant differences. One study from 2020 found that the prevalence of patients with sarcopenia was 15% using the L3 method while only 10% were when using the T12 method [39]. Another study looked into not only abstracting data at T12 and L3 but also at the L4 level. Interestingly, while they found significant differences in SMI distributions when comparing the L3 and T12 methods, they found that the L4 method was similar to the L3 method and had higher test reliability [40]. Other published literature found that the different methods each had different associations. Adults with sarcopenia using the T12 method were found to have increased length of stays in the hospital but not any association with mortality [41], while the same study found no L3 associations.

#### Future Study Recommendations

Given the vast previous research that had exhibited the impact of sarcopenia on cancer patients' outcomes and overall survival, we believe this is an important topic of research that needs to be further explored. For future studies, we have a few recommendations that we believe will further enrich the data available. First, we suggest adding a longitudinal component. Initially, our study aimed to analyze the SMI changes in patients throughout their cancer treatment. Due to starting off with a small sample size, as we continued to look into our included patients scans, we saw our sample size diminish as few patients had a baseline scan along with either a 3-, 6-, or 12-month scan. Thus, this component was cut out from our study so we would highly encourage future research to devolve into the impact on changes in patients' body composition as they progress through treatment. Many patients experience weight loss and lifestyle changes as a side effect of their treatment and/or cancer symptoms, which could result in a decrease in skeletal muscle mass. We believe it would be beneficial to see if the rate of patients who are sarcopenic increases over time of their treatment and/or cancer progression, and if this impacts survival.

Additionally, we recommend that future studies evaluate the T12 paravertebral SMI method. Compared to other established screening methods the T12 method had less research conducted utilizing it. Thus, upcoming research should continue to test this method's validity to assess sarcopenia. This would be a very beneficial method due to most lung cancer patients regularly receive chest CT scans rather than abdominal CT scans, which makes the T12 paravertebral method a more accessible way to screen for sarcopenia.

Lastly, in order to get an accurate representation of sarcopenias prevalence, we suggest having a larger patient cohort with a control group. It is vital to have a control group of healthy individuals within the age range to determine if the rates of primary and secondary sarcopenia differ.

#### Study Limitations

The largest limitation of our study was the small sample size used. Given the criteria we had for selecting participants, we had to exclude over half of the available participants from the original FITNESS study. The vast majority of participants only had chest CT scans to track their cancer progression, not any abdominal scans. Thus, we had no way to measure their psoas major muscle at the L3 level. We recommend having a larger sample size, as this would increase the number of patients available that would meet the criteria for sarcopenia.

Another limitation our study has is the lack of advanced software to calculate the SMI. Most of the previous literature publicized had automated software systems that analyzed the CT scans and calculated the patients' SMI. Our study did not have the financial support to afford such expensive programs and thus had to rely on manual abstraction and calculation. This opens up the door to natural human error when it comes to tracing the muscle. Thus, we recommend future replications utilize automated systems, such as Slice-O-Matic, to abstract all data.

Lastly, our greatest error was not excluding our outliers when computing our statistics. While this would have decreased our patient cohort to an even smaller number, it would have displayed a more accurate average SMI, sarcopenic cutoffs, and normal SMI cutoff values in our patient population.

#### **Chapter 5. Conclusion**

In conclusion, our study did not find any significant relationship between SMI and overall survival among patients with NSCLC. The major study limitation was the small sample size of which none were sarcopenic. The second aim of our study was to analyze the effectiveness of a novel T12 paravertebral muscles abstraction method in the diagnosis of sarcopenia in comparison to the previously researched and proven L3 psoas major muscle method. Through a paired T-test, it was found that the two methods were significantly different. This is an important step in understanding alternate techniques to diagnose sarcopenia in patients with lung cancer and requires further research.

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