Sarcopenia in Overweight and Obese Cancer Patients: a predictive value for chemotherapy tolerance, survival and quality of life factors

by

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Background: Alterations to body composition have been shown to be a poor prognostic factor for cancer patients and may lead impaired chemotherapy tolerance and decreased quality of life. Sarcopenia, a type of body composition alteration, is defined as a depletion of muscle mass two or more standard deviations below the mean muscle mass which is measured in young adults. This systematic review set out to analyze the effect of sarcopenia in overweight and obese patients in patients with gastrointestinal cancers with specific focus on chemotherapy tolerance.

Methods: This project used the Academy of Nutrition and Dietetics Evidence Analysis Library methodology to define a question, analyze research and summarize results.

Results: A total of 4 primary research articles were included. Anandavadivelan et al. (2015) identified increased risk for dose-limiting toxicity in patients with sarcopenia and body mass index (BMI) ≥ 25 when compared to those with a BMI ≥ 25 without sarcopenia ($p=0.04$). Prado et al. (2008) conducted a hypothetical 5-FU dosing exercise and compared the results to kilograms fat free mass (FFM). Hypothetical doses ranged from 11.3-31.3 mg 5-FU/kg FFM. A previous study by Prado et al. had identified 20 mg/kg LBM to be the upper limit for dose-limiting toxicity in most individuals, indicating that some of the patients in the 2008 study would be at increased risk for toxicity. Additionally, Prado et al. (2008) found that sarcopenic obese patients reports poor functional status on the Patient Generated- Subjective Global Assessment ($p=0.009$). Tan et al. (2009) and Rollins et al. (2015) found that patients with a sarcopenia and a BMI ≥ 25 had shorter overall survival ($p=0.006$ and $p=0.013$, respectively). Prado et al. (2008) additionally found shorter survival in sarcopenic obese cancer patients ($p<0.0001$).

Conclusion: Sarcopenia and a BMI ≥ 25 in adult patients with gastrointestinal cancers is associated with increased risk of chemotherapy toxicity, poor performance status and shorter overall survival.

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CHAPTER 1: INTRODUCTION

Cancer is a general term for unregulated cell growth. In 2013, it was estimated that 1.6 million new cases of cancer would be diagnosed in addition to the 13 million people in the United States already living with cancer (American Cancer Society, 2013). Cancer is the second leading cause of death in the United States (CDC, 2014). Recent data indicates that 40.8% of men and women will be diagnosed with some form of cancer during their lifetime (National Cancer Institute, 2014).

According to the CDC (2013) and American Cancer Society (2013), being overweight or obese are risk factors for cancer. These factors have been linked to an increased risk of developing breast, colorectal, esophagus, kidney, and uterus cancers (American Cancer Society, 2013). In an analysis of health statistics conducted in 2009-2010, it was found that 69% of adults over the age of 20 in the United States are either overweight or obese (CDC, 2013). Once overweight or obese individuals develop cancer, patients are at an increased risk for other complications; such as body composition changes (Prado et al. 2007, 2008, & 2009). One of the potential body composition changes that this patient population faces is the development of sarcopenia, which is defined as a muscle mass that is two or more standard deviations below the mean muscle mass measured in young adults. This condition is associated with impaired overall health, decreased functional capacities, decreased quality of life, increased chemotherapy toxicity and decreased cancer survival (Thibault & Pichard, 2011).

Aberrations in body composition have implications for cancer treatment. The current standard method for chemotherapy dosing uses body surface area (BSA). However, this method has been questioned, since BSA considers body size and weight, but does not account for body composition. Patients with sarcopenia may have a relatively large body size and weight, but a much smaller lean body mass (LBM). Certain chemotherapies therapies, such 5-fluorouracil (5-FU) which is a common treatment used for gastrointestinal cancers, are thought to be metabolized in LBM but are dosed based on BSA. The existing concern is that the BSA method may lead to overdosing chemotherapy in patients with sarcopenic obesity.

Rationale

While data suggests that the BSA method of chemotherapy dosing has limitations, there are currently no other protocols. As of 2012, the American Society of Clinical Oncology recommends that chemotherapy dosing for overweight and obese patients should be based on actual body weight. The society stated that this method of dosing will not increase risk for toxicity.

The purpose of this evidence analysis project is to examine the current data regarding sarcopenic obesity in patients with gastrointestinal cancer and chemotherapy tolerance. A critical review of existing studies will be conducted and a conclusion statement will be determined based on the findings of the systematic review.

Potential Significance

Many of the patients at Cancer Treatment Centers of America (CTCA) have advanced stage cancer. Often the goal of treatment is to prolong life as opposed to

curing cancer. We want to assure that prolonged time is also quality time by providing adequate chemotherapy while avoiding overdosing, which may lead to better treatment tolerance and thus better quality of life. The results of this evidence analysis project may lead to further discussion at CTCA regarding the use of body composition analysis as part of the chemotherapy dosing protocol.

Research Question

Is lean body mass a better predictor of chemotherapy related toxicity than body surface area for cancer patients with sarcopenic obesity?

Limitations

Due to the nature of an evidence analysis project, a limitation will be the reliance on available research.

Delimitations

The review of literature will only investigate sarcopenia in overweight and obese patients. The evidence analysis will only include chemotherapies that are metabolized in lean body mass.

Assumptions

An assumption of this research is that the information in the studies regarding chemotherapy metabolism are as accurate as possible.

Definition of Terms

Body surface area (BSA) - the area of the external surface of the body, expressed in square meters (Medi Lexicon)

Cytokines- any of a class of immunoregulatory proteins that are secreted by cells, especially of the immune system (Merriam-Webster, 2014)

Karnofsky performance scale- the standard way of measuring the ability of cancer patients to perform ordinary tasks. The scale scores range from 0 to 100. A higher score means the patient is better able to carry out daily activities. (National Cancer Institute)

Pharmacokinetics- the study of bodily absorption, distribution, metabolism, and excretion of drugs (Merriam-Webster, 2014)

CHAPTER 2: LITERATURE REVIEW

Cancer has a significant effect on the United States population. Approximately 13 million Americans have a history of cancer or are currently undergoing treatment for cancer, with an additional 1.6 million new cases estimated to be diagnosed in 2013 (American Cancer Society, 2013). Cancer is currently the second leading cause of death in the United States (American Cancer Society, 2013). Evidence suggests that 1/3 of cancer deaths are related to modifiable risk factors including overweight and obesity, physical inactivity and poor nutrition (American Cancer Society, 2013). The prevalence of overweight and obesity continues to increase in the United States and may be a significant contributing factor to the prevalence of cancer. Approximately 69% of adults are either overweight or obese (CDC, 2013). A study using NCI Surveillance, Epidemeiology and End Results (SEER) data, estimated that in 2007 34,000 new cases of cancer in men and 50,500 new cases of cancer in women were due to obesity (National Cancer Institute, 2012).

The increase in overweight and obese patients being diagnosed with cancer has sparked investigations into body composition amongst these patients. Sarcopenia is a variation in body composition, which is defined as a muscle mass two or more standard deviations below the mean measured in young adults of the same sex and ethnic background (Muscaritoli et al., 2010). Pathophysiological explanations for sarcopenia are the loss of muscle mass as part of aging, decreased physical activity, changes in

metabolic rate, inflammation, and malnutrition (Stenholm et al., 2008). Several of these factors that contribute to the development of sarcopenia are potential complications of cancer treatment, such as malnutrition.

Several studies that will be examined in this literature review and evidence analysis project demonstrate undesirable outcomes for oncology patients with sarcopenia, such as increased risk for chemotherapy related toxicity and decreased cancer survival. The purpose of this literature review is to critically analyze the evidence on the effects of sarcopenia in overweight and obese cancer patients with particular focus on the chemotherapy dosing and chemotherapy related toxicity.

Background

Sarcopenia

Chronic diseases and aging are frequently associated with deterioration of nutrition status, loss of muscle mass and function, impaired quality of life and increased risk for morbidity and mortality (Muscarittoli et al., 2010). Sarcopenia, or reduce lean body mass, is word derived from the Greek words sarx, which means flesh, and penia, which means poverty. This condition may also be accompanied by a change in functional status, such as low gait speed (Muscarittoli et al., 2010). While the definition of the condition is clear, the causes and complications of sarcopenia are more complex.

Causes

Sarcopenia is a condition that may develop as a result of various factors. Some potentially contributing factors include aging, decreased physical activity, inflammation,

and malnutrition. As people age there is a typical decrease in muscle mass that begins around age 30 and becomes accelerated after age 60 (Stenholm et al., 2008). This decline in muscle mass may also be linked to decreased physical activity. Sedentary lifestyle promotes progressive muscle atrophy, or loss of muscle mass (Stenholm et al., 2008). The metabolic functions of fat mass may further contribute to sarcopenia. Adipocytes in adipose tissue secrete pro-inflammatory cytokines that lead to the up-regulation of the inflammatory response in the body, which has been shown to be negatively associated with muscle mass (Stenholm et al., 2008). Malnutrition can also lead to changes in muscle mass. If inadequate protein is consumed, protein muscle turnover may be impaired leading to a decline in muscle mass (Stenholm et al., 2008).

Cancer can also lead to inflammation that may contribute to the development and progression of sarcopenia. A study by Acharyya et al. (2004) discovered several pro-inflammatory cytokines released by the immune system in response to cancer which were linked to increased muscle wasting.

Complications

The loss of muscle mass associated with sarcopenia may lead to physical impairments. In an article by Kilgour et al. (2010), the researchers examined the relationship between cancer related fatigue and sarcopenia and discovered that a decrease in skeletal muscle was linked to a reduction in upper and lower body strength. Both decreased skeletal muscle and decreased strength were significantly associated with increased perceived fatigue and daily limitations. The researchers stated that

increased fatigue may lead to further loss of muscle mass due to decreased physical activity.

Sarcopenia can be further complicated by obesity. Sarcopenic obesity has the same diagnostic criteria as sarcopenia but is specific to individuals classified as obese. Sarcopenic obesity may lead to greater physical impairments due to a greater amount of mass to move in the presence of decreased muscle mass (Stenholm et al., 2008). Sarcopenic obesity is associated with decreased survival, increased therapy toxicity in cancer patients, impaired overall health, and decreased quality of life (Thibault & Pichard, 2012).

Diagnosis/Assesment

While research supports that sarcopenia and sarcopenic obesity may lead to poor outcomes in patients, there is currently no standardized method for evaluating body composition. Weight loss and body mass index (BMI) lack the sensitivity to detect loss of muscle mass (Thibault & Pichard, 2012). Other methods for body composition determination include skinfold calipers, bioelectrical impedance analysis (BIA), dual energy X-ray absorptiometry (DEXA) and computed tomography (CT) scans. Using BIA, DEXA, or CT imaging may provide a more accurate assessment of muscle mass (Thibault & Pichard, 2012). A report examining the current practices for investigating sarcopenic obesity found DEXA to be the most commonly used tool for body composition analysis and the primary reference value to which other methods for analysis are compared to (Prado, Wells, Smith, Stephan & Siervo, 2012). Research

suggests that determining body composition may be an important component in oncology treatment, especially with regards to sarcopenic obesity.

Sarcopenic obesity and chemotherapy

Cancer patients with sarcopenic obesity are at increased risk for chemotherapy related toxicity (Thibault & Pichard, 2012). This is thought to be due to the discrepancy between the assumptions on body composition in the current dosing protocol and actual body composition. The traditional dosing protocol for adult oncology has been the use of BSA (Griggs et al., 2012). BSA method of dosing is thought to be predictive of chemotherapy clearance and helps standardize doses between individuals (Sacco, Botten, Macbeth, Bagust & Clark, 2010). BSA method for chemotherapy dosing was originally studied in animal studies. The results obtained from the animal studies were then used as part of human trials to determine an acceptable method for dosing chemotherapy in order to limit chemotherapy related toxicities over a broad range of adult weights (Lyman & Sparreboom, 2013). Below is a list of standard formulas for determining BSA that American Society for Clinical Oncology (ASCO) approves:

Mosteller- BSA(m²) = $\sqrt{(\frac{[height(cm) \times weight(kg)]}{3600})}$

DuBois and DuBois- BSA(m²) = $0.20247\ x\ height(m)^{0.725}\ \times\ weight(kg)^{0.425}$

Haycock- BSA(m²) = $0.024265\ \times\ height(cm)^{0.3964}\ \times\ weight(kg)^{0.5378}$

Gehan and George- BSA(m²) = $0.235\ \times\ height(cm)^{0.42246}\ \times\ weight(kg)^{0.51456}$

Boyd- BSA(m²) = $0.0003207\ \times\ height(cm)^{0.3}\ \times weight(gm)^{(0.7285-(0.0188\ \times LOG(grams))}$

All of the formulas consider height and weight but have no consideration for body composition. Thibault & Pichard (2012) report that this technique of chemotherapy dosing may lead to increased chemotherapy related toxicity in patients with sarcopenic obesity due to changes in fat free mass throughout cancer treatment (Thibault & Pichard, 2012). However, the most recent guidelines from ASCO support the use of BSA for chemotherapy dosing in obese oncology patients (Griggs et al., 2012). A panel of ASCO experts conducted a systematic review of literature published from 1996 to 2010. The review found that up to 40% of obese patients receive limited chemotherapy doses that were not calculated using actual body weight in a standard BSA formula (Griggs et al., 2012). Many oncologists used some sort of adjustment when calculating doses for obese patients, such as using ideal body weight or adjusted body weight in the BSA formula or restricting BSA doses to no greater than 2 m^2 (Griggs et al., 2012).. Such adjustments translate to patients receiving reduced chemotherapy doses. These types of decisions were contributed to practitioner uncertainty about optimal dosing in this patient population using the BSA method. Research has found that dose reductions, such as the aforementioned adjusted calculation methods, may compromise disease-free survival and overall survival, especially in the curative setting (Griggs et al., 2012). The ASCO report suggests that frequent dose reductions in overweight and obese cancer patients may partially explain the higher rate or mortality in this patient population. The ASCO guidelines state that based on their systematic review, there is no evidence of increased chemotherapy toxicity when full weight was used to calculate doses and note that it is especially important that therapies not be adjusted when the goal of therapy is to cure the patient. However, the panel did acknowledge a few

limitations BSA formulas. The equations were not developed for obese patients, do not account for other comorbid conditions and have no considerations for patient sex (Griggs et al., 2012). The report did state that there are ongoing efforts to improve the BSA dosing method with special consideration for obesity. This is of particular importance considering that approximately 69% of Americans are either overweight or obese. The expert panel stated that a major limitation of this review is the lack of prospective randomized-control trials that directly study the effect of weight-based chemotherapy dosing.

Lyman and Sparreboom (2013) further analyzed chemotherapy dosing in obese oncology patients. Similar to Griggs et al., this article concluded that the existing data supports the ASCO guidelines which state that obese patients should receive full weight based chemotherapy using any BSA formula. This article did identify a potential limitation of the current method of chemotherapy dosing in obese patients. The majority of treatments are primarily metabolized through the liver which may be altered in obese patients secondary to fat in the liver altering hepatic blood flow (Lyman & Sparreboom, 2013). However, there is currently no evidence to show that obese patients would have altered drug clearance due to increased amount of body fat. The article did suggest that lean body mass may be a predictor of drug clearance. An additional limitation of chemotherapy dosing criteria Lyman and Sparreboom (2013) identified is that the clinical trials that are used to determine dosing recommendations frequently exclude obese patients and those with other comorbidities. Therefore, the extrapolated data from these trials may not be completely applicable to underrepresented patients.

Considering the limitations of BSA for chemotherapy dosing identified in the Griggs et al. (2012) article and Lyman & Sparreboom (2013) article, there has been further investigation into alternative dosing methods. One method is flat-fixed dosing, which involves given standard doses to all patients regardless of body size, gender or other pharmacotherapy parameters (Mathijssen, de Jong, Loos, van der Bol, Verweij & Spareboom, 2007). Another method is dose banding. This method uses pre-defined ranges of BSA to calculate a dose. Research findings lack support for both alternative methods and continue to promote the use of BSA as the preferred method for dosing chemotherapy in obese patients (Lyman & Sparreboom, 2013).

Both the Griggs et al. (2012) and Lyman & Sparreboom (2013) articles found overwhelming support for the use of body surface area equations for chemotherapy dosing in overweight and obese patients. Griggs et al. article discussed the limitations of the BSA method but currently there are no other evidence-based guidelines for chemotherapy dosing in overweight and obese cancer patients. A major limitation of both these review articles is that there was no consideration for sarcopenic obesity as part of their systematic review. In fact, there most no mention at all of how body composition may affect the use of BSA for chemotherapy dosing in either of these articles. This is a crucial factor to examine considering the increasing amount of overweight and obese Americans being diagnosed with cancer and the significant potential for sarcopenia in this patient population during cancer treatment. This literature review will further examine research on body composition changes in the presence of cancer with special consideration to chemotherapy dosing, sarcopenic obesity and chemotherapy related toxicity.

Discrepancy between Body Surface Area and Body Composition

The body surface area (BSA) method for dosing chemotherapy has several limitations, such as it was not designed for obese patients. A study was designed to investigate the variability of body composition in cancer patients and compared to BSA in order to identify patients that were at risk for fat free mass changes and therefore may not receive optimal chemotherapy dosing (Stobaus, Kupferling, Lorenz, & Norman, 2013). Previous research has identified that patients with alterations to body composition, such as sarcopenia, are at increased risk for chemotherapy-related toxicity, experience more treatment complications and higher mortality (Prado et al., 2008). This has been attributed to changes in fat free mass (FFM), which includes skeletal muscle and metabolic tissue, such as the liver and kidneys (Stobaus et al., 2013). Fat-free mass is responsible for metabolizing certain chemotherapies, such as 5-fluorouracil (Stobaus et al., 2013). Thus, differences in FFM may affect the patient's ability to utilize chemotherapy. The investigators hypothesized that using BSA alone might lead to dosing inaccuracies and suggest that body composition, with specific consideration for FFM, be used along with BSA versus BSA alone.

The study included 630 patients recruited from the Department of Oncology and Hematology and the Department of Gastroenterology, Infectology and Rheumatology at the Charite University Medicine in Berlin, Germany. Patients were eligible to participate if they were 18 or older, had a malignant disease, and BMI between 16 and 34. The BMI criterion was set to ensure the validity of BIA calculations. Patients were ineligible if they had hyperhydration, such as ascites or edema, and/or a cardiac defibrillator because they would be unable to utilize the BIA.

Body composition was assessed using BIA. The Kyle et al. formula, which has been validated against DEXA in a population similar to the characteristics of this population, was used to calculate FFM (Kyle, Genton, Karsegard, Slosman & Pichard, 2001). BIA measurements were completed in the morning after an overnight fast in order to assure accuracy. BSA was calculated using the DuBois formula, which is one of the approved formulas according to the ASCO guidelines.

Functional status was determined using several components. Upper and lower body strength was evaluated using a hand grip strength test and a knee extension test. Fatigue was determined using a Quality of Life questionnaire from the European Organization for Research and Treatment of Cancer. Patients were also assessed using the Karnofsky performance status scale.

Mean standard deviation (SD) for FFM was calculated and participants were divided into 3 FFM groups accordingly. FFM ≥ 1 SD below the mean was the low FFM group. Patients with a mean FFM .99 above or below the mean were the normal group. High FFM group had a FFM ≥ 1 SD above the mean. T-test and chi-squared were used to compare the characteristics of the 3 FFM groups. A Kaplan-Meier analysis was utilized to compare 1 year survival amongst the 3 groups.

At the time of the study, 55.5% of patients had received chemotherapy, 6.2% had received chemo/radiation, and 4.5% had received radiation. 61.6% had experienced weight loss in the past 6 months with a mean weight loss of 9.7 kilograms. Of the 630 participants, 31.4% were overweight and 9.8% were obese. 15.7% of subjects were in the low FFM group, 69% in the normal FFM group and 15.2% in the high FFM group.

Characteristics of the 3 FFM groups were analyzed, it was found that men had significantly more FFM than women ($p < 0.001$). The low FFM group included significantly more women ($p < 0.0001$) and had significantly higher body mass indexes ($p < 0.05$) than the normal and high groups. The low FFM group also had significantly lower assessments for upper strength, lower strength, Karnofsky performance status and greater fatigue. These results strengthen the research discussed in the Kilgour et al. (2010) article, which stated that decreased skeletal muscle was associated with increased cancer related fatigue. In addition, low FFM was associated with a significant increase in 1 year mortality ($p=0.036$). 58.7% of low FFM patients died within 1 year of the follow up compared to 38.2% for normal FFM group and 42.9% in the high FFM group. There was no significant difference identified amongst the 3 groups for age, weight loss, or tumor stage. Overall, when analyzing the characteristics of the 3 FFM mass groups it was found that the low FFM group was primarily women and subjects in this group had higher body mass indexes. The low FFM group was also associated with overall poorer functional status.

Low FFM and high FFM groups, which accounted for roughly 30% of patients in this study, fell outside the mean. The 30% of patients that feel outside the mean would equate to patients receiving potentially inaccurate chemotherapy doses utilizing the BSA dosing method. The low FFM group would be overdosed and the high FFM group would be under dosed in comparison to their metabolically active tissue. Stobaus et al. suggested that those with relatively low FFM would be at increased risk for chemotherapy intolerance. The researchers concluded body composition should be considered due to the possible risk therapy intolerance and increased morbidity

Stobaus et al. identified some key flaws with the current practice guidelines for dosing chemotherapy. The DuBois formula used for BSA chemotherapy dosing in this study was developed using 9 individuals in 1916 and has never been validated since. Similar to the Griggs et al. article, they noted that BSA was not developed to be used in the obese and specifically does not account for conditions like sarcopenic obesity. In this study, obesity was twice as high in the low FFM group than the normal FFM and high FFM groups.

The results of the study supported the hypothesis that body composition should be considered as part of chemotherapy dosing by demonstrating the variation in actual FFM in comparison estimated FFM determined using a BSA chemotherapy dosing equation. This was demonstrated by approximately 30% of study subjects falling outside the normal range of FFM estimated using the BSA dosing equation, which translates to increased possibility of chemotherapy dosing discrepancy. The difference in body composition for women was especially notable. Women had significantly lower FFM but had significantly higher BSA. This supports the remark in the Griggs et al. (2012) article, that BSA does not consider gender differences. The researchers posed the question on whether women should receive lower doses of chemotherapy or should chemotherapy be based on body composition.

A strength of this study was the critical analysis of FFM and BSA. It would have been interesting if the researchers had additionally assessed chemotherapy related toxicities for the 3 FFM groups. A limitation of this study is that it did not investigate whether the various types of cancers contributed to variations in body composition. Also, there were additional treatment regimens besides solely chemotherapy that

patients had undergone prior to this study. There was no mention on how these variations in treatment may have contributed to FFM or functional status.

Body Composition, Chemotherapy Related Symptoms and Cancer Survival

A positive relationship between decreased muscle mass and decreased survival in cancer patients was described in the Thibault & Pichard article (2012). A prospective study at the University of Texas within the MD Anderson Cancer Department of Investigational Therapeutics set out to examine the relationships amongst body composition, the incidence and severity of cancer and chemo-related symptoms and survival in patients with advanced cancer (Parsons, Baracos, Dhillon, Hong & Kurzrock, 2012). The study included 104 patients with advanced cancer that were referred to the phase 1 clinic for clinical trials. In order to be eligible for the study patients had to be 18 or older and have advanced cancer. There was no exclusion criteria listed. Due to patients having advanced cancer and usually failing to respond to multiple treatment regimens prior to enrolling in clinical trials, survival is typically less than a 1 year.

Patients completed the MD Anderson Symptom Inventory, which has been validated in cancer patients (Cleeland et al., 2000). The symptom inventory assesses the intensity of 15 cancer and chemotherapy related symptoms that include pain, fatigue, nausea, sleep, distress, dyspnea, memory, appetite, drowsiness, xerostomia, sadness, vomiting, numbness, coughing and constipation. The survey also assesses how symptoms interfere with specific life domains, which include general activity, mood, normal work, ability to walk, interpersonal relations, and enjoyment of life. All questions are scored with a 0 to 10 scale.

Body composition was examined using CT images of the third lumbar vertebra cross-section. Utilizing this specific cross-section has been validated against DEXA and BIA in advance cancer (Mourtzakis et al., 2008). These images were obtained were for clinical purposes within 30 days of the symptom survey being completed.

Subjects were divided into 4 groups as part of the investigation based on their BMI and results of body composition testing. The 4 groups were BMI <25 without sarcopenia, BMI <25 with sarcopenia, BMI ≥25 without sarcopenia and BMI ≥25 with sarcopenia. Statistical analysis utilized a combination of parametric and nonparametric tests to analyze the data. Survival analysis was completed using Kaplan-Meier.

Overall there was minimal symptom burden and a low degree of interference with the 6 life domains reported regardless of BMI or the presence of sarcopenia. This was attributed to the strict criteria to qualify for phase 1 trial, such as minimal symptoms and good performance status. The only significant difference identified was patients with sarcopenic obesity reported greater interference with mood than those without sarcopenic obesity. Upon analyzing body composition via CT imaging, the study found that 51% of the participants had sarcopenia. The researchers identified that patients age 65 or greater were more likely to be sarcopenic than those less than 65 (71% versus 41%, p=0.003). Shorter median survival for patients with sarcopenia versus patients without sarcopenia was trending towards significance (304 days versus 474 days, p=0.151). The only group to reach statistical significance for shorter survival were subjects less than 65 years old with sarcopenia when compared to subjects in the same age category without sarcopenia (301 days versus 487 days, p=0.042). Sarcopenic obesity was trending towards significance, with a 6 month shorter average survival in

comparison to overweight and obese patients without sarcopenia. A multivariate analysis was completed controlling for age, gender, performance status, and fat index which found muscle index to be an independent prognostic factor for survival ($p=0.009$). The multivariate analysis indicated that decreased muscle index, such as sarcopenia, is associated with decreased survival.

The researchers concluded that patients 65 and older were more likely to have sarcopenia. That result was not surprising, because loss of muscle mass is associated with aging. The researchers also concluded that there is no relationship between symptom burden and sarcopenia. They suggested that results may have been skewed because in order to qualify for the clinical research clinic, where this study was conducted, patients had to have a higher functioning status and minimal symptom burden.

Other studies have found an association between decreased fat free mass and decreased functional status, like the Kilgour et al. study (2010), but have not analyzed how decreased muscle mass contributes to cancer related symptoms that may lead to dose limiting toxicities. Different results may have been seen in a more general cancer patient population. A strength was the examination of the survival rates for the BMI categories and sarcopenic obesity. As discussed by the authors, a weakness of the study was the skewed participant population due to the qualifications to enroll in a clinical trial. Therefore, the results of this study cannot be generalized to outpatient oncology patients.

Prevalence and Clinical Implications of Sarcopenic Obesity in Patients with Solid Tumors

A 2007 study by the National Cancer Institute using obesity prevalence data from the NHANES 2005–2006 database and number of new cancer cases in 2007 based on SEER registry data identified 84,500 new cases of cancer that were due to obesity (Bassen-Engquist-Chang, 2011). Being overweight or obese is a risk factor for a variety of cancers including gastrointestinal (GI) cancers. Prado et al. (2008) designed a study to further investigate sarcopenic obesity in patients with solid tumors of the respiratory and GI tracts. The primary hypothesis of the study was that sarcopenia in obese cancer patients is associated with low physical ability and mortality. A secondary hypothesis, which is more relevant to this literature review, was that patients with sarcopenic obesity receiving chemotherapy that is mainly distributed in lean body mass (LBM) would have a decreased volume of chemotherapy in relation to their bodyweight or body surface area.

Patients (n=2,114) with either respiratory or GI cancers were recruited from Cross Cancer Institute in Alberta, Canada. Anthropometric data was self-reported by patients and then verified by researchers in a sub group of 100 patients to assure accuracy of self-reporting. Patient reported height, weight, weight history and functional status were assessed using the Patient-Generated Subjective Global Assessment (PG-SGA). The PG-SGA has been validated for use in oncology patients (Bauer, Capra, & Ferguson, 2002).

Functional status was determined on the PG-SGA by patients choosing 1 of the 5 options that had scores associated with them. The 5 options included: normal with no limitations (0), not my normal self but able to be up and about with fairly normal activities (1), not feeling up to most things but in bed or chair less than half of the day (2), able to do little activity and spend most of the day in bed or chair (3), and pretty much bedridden/rarely out of bed (4). The scores 0 and 1 represent no physical disability, whereas scores 2-4 do indicate decreased functional status in patients.

Body composition was assessed using CT images that were completed within 30 days of the PG-SGA being administered. The CT images analyzed for body composition purposes were part of the normal diagnostic process. The researchers examined the third lumbar cross-section to determine body composition. Researchers used muscle indexes for the third lumber region to establish cut off limits for this study. BSA was calculated using the Mosteller formula. This is an approved equation for conducting BSA chemotherapy dosing per the ASCO guidelines. A Kaplan-Meier analysis was conducted to evaluate survival.

Based on self-reported anthropometrics, it was determined that 325 patients (15%) were obese. Patients were deemed obese if they had a BMI ≥ 30. 250 of the 325 patients had CT images within the 30 days of the PG-SGA assessment. Of the 250, 15% were determined to have sarcopenic obesity. Estimated FFM mass, which was calculated based on the third lumber cross section, was significantly less in patients with sarcopenia than patients without sarcopenia ($p < 0.0001$) Sarcopenic obesity was more prevalent in men than women ($p=0.013$) patients with colorectal cancer than other sites ($p=0.019$) and subjects age 65 or older when compared to younger subjects ($p=0.008$).

47% of patients with sarcopenic obesity reported poorer functional status, which was significantly greater than non-sarcopenic patients (p=0.009). The results of the Kaplan-Meier Survival Analysis found that patients with sarcopenic obesity had significantly shorter median survival than non-sarcopenic patients (11.3 months versus 21.6 months, p <0.0001). The portion of data supports the primary hypothesis that sarcopenic obesity in cancer patients is associated with increased mortality. The researchers postulated that this may be associated with increased inflammation which may lead to cancer cases that are less responsive to treatment or that this patient population has increased risk for other health complications which lead to mortality. Further research is needed to investigate these suggestions for the mechanism of increased mortality in sacropenic obese oncology patients.

An additional investigation was conducted to evaluate the relationship between body surface area and fat free mass. Researchers calculated hypothetical 5-FU doses using the BSA method and compared the dose to estimated FFM. Hypothetical doses were calculated at 425mg/m^2 of BSA. The hypothetical doses varied greatly from 11.3 mg per kilogram FFM to 31.3 mg per kilogram FFM. Women were more likely to have low FFM in comparison to BSA.

Researchers noted that average FFM in sarcopenic obesity patients was comparable to patients that are underweight and cachectic. This demonstrates that body weight and size are poor indicators of body composition. Based on the results of this study, Prado et al. urge the use of body composition analysis in oncology patients. The need for body composition analysis was supported in the demonstration using hypothetical chemotherapy doses to show the poor association between BSA and FFM.

The large variation in hypothetical doses may indicate that body composition is an important predictor of chemotherapy related toxicity due to relative overdosing of therapies metabolized in the FFM.

A strength of this study was the extensive multivariate statistical analysis to determine the independent effects of sarcopenia on functional status, survival and potential chemotherapy toxicity. However, this study had several limitations, such as relying on a large amount of self-reported data. The researchers did state that it would be beneficial to assess functional status with a validated strength assessment as opposed to using the PG-SGA. Another limitation was that the study was restricted to respiratory and GI cancers which can limit the generalizability of the results. Also, the article did not list any inclusion or exclusion criteria.

Relationship between Body Composition Parameters and Fluorouracil Parameters

Prado et al. (2008) used hypothetical doses to demonstrate the poor association between BSA and FFM and hypothesized that body composition may be a better predictor of chemotherapy tolerance. The aim of this study was to assess whether body composition parameters are correlated with fluorouracil (FU) clearance and volume distribution (Gusella, Toso, Ferrazzi, Ferrari & Padrini, 2002). In addition, the researchers wanted to examine if the correlation between body composition parameters better predicted FU pharmacokinetic factors than the standard methods of body weight and body surface area.

It is known that FU passes across biological membranes easily in order to reach the action and elimination sites (Gusella et al., 2002). It is thought that prolonged infusion of FU exceeds the ability of the liver, which is the primary site of metabolism. The remaining FU is then metabolized in other body compartments. Considering this, the researchers hypothesized that FU clearance and volume of distribution are related to body composition parameters- specifically, body cell mass, fat free mass and total body water.

Thirty-four patients (21 males and 13 females) between the ages of 45 and 80 were recruited for this study. Patients had normal hydration status, which is key factor in assuring accuracy of body composition analysis. All patients were diagnosed with colorectal cancer and were started on adjuvant chemotherapy after radical surgery. Patients received their dose of FU and leucovorin over the course of 5 days. This regimen was given for 6 consecutive cycles every 4-5 weeks. BSA was used to determine chemotherapy doses utilizing the Haycock formula. This is an approved BSA formula according to the ASCO guidelines.

Body composition was determined using BIA. Measurements were conducted 15 minutes before beginning treatment. These measurements were used to calculate total body water (TBW), fat free mass (FFM), and body cell mass (BCM). BIA has been previously validated in this patient population for these types of calculations (Kotler, Burastero, Wang & Pierson, 1996 and Deurenburg, van der Kooij, Evers, & Hulshof, 1990).

Pharmacokinetic factors were assessed by examining FU plasma concentrations. Plasma concentrations were measured at 0, 2.5, 5, 10, 15, 20, 30, 45, and 60 minutes after chemo administration. These measurements were analyzed and used to calculate clearance (CL) and distributions of volume steady state (Vss).

Means of patient characteristics and body composition analysis results were calculated and compared using a t-test. The study utilized multiple regression analysis to further compare CL and Vss to body composition parameters and sex. The analysis discovered that females had significantly lower body weight (BW), BSA, TBW and FFM when compared to males. There was no significant difference in mean age and BCM. TBW and FFM represented a significantly smaller percentage of BW in females versus males. TBW varied by 51.1 ± 4.5% versus 57.7 ± 3.9% ($p < 0.0001$) and FFM varied by 65.2 ± 5.6% versus 74.1 ± 6.8% ($p=0.0004$). Poor correlations between the pharmacokinetic parameters and body composition parameters were found when the whole population was considered. When multiple regression analysis was applied, findings indicated a significant relationship of FFM, sex and TBW with FU clearance and distribution volume of steady state.

Clearance was moderately correlated with sex and FFM ($r^2=.44$, $p<0.0001$) and distribution volume of steady state was moderately correlated with sex and TBW ($r^2=.36$, $p<0.0001$). This indicates that 44% of variation in CL and 36% of variation in Vss can be explained by sex, FFM, and TBW. BSA only had a weak correlation with CL ($r^2=.12$) and Vss ($r^2=.10$). The researchers concluded that the FFM and TBW were better predictors of pharmacokinetic parameters than BSA. Furthermore, the researchers stated the considering FFM, TBW and sex would likely lead to improved chemotherapy dosing.

The researchers noted several limitations to their study. One limitation was that the results of this study only apply to the specific chemotherapy regimen that was examined. They also noted that 56% of clearance and 64% of distribution volume of steady state remain unexplained. A strength of this study was that it provided new insight into the relationship of body composition parameters and FU pharmacokinetics.

Body Composition as a Determinant of Epirubicin Pharmacokinetics and Toxicity

The previous article by Gusella et al. (2002) indicated that body composition parameters, namely FFM and TBW, were better predictors of chemotherapy pharmacokinetic factors than BSA. It was concluded that body composition parameters along with sex would likely contribute to more accurate chemotherapy dosing. A 2011 study by Prado et al. was designed to investigate similar properties. The aim of Prado et al. (2011) study was to investigate the relationship of specific body composition parameters with pharmacokinetics and toxicity in breast cancer patients. It is thought that decreased lean body mass likely translates into poor chemotherapy tolerance due to excessive amounts of chemotherapy in the body relative to the metabolic tissues. A possible pharmacokinetics explanation is that due to reduced LBM, there is decreased volume distribution and clearance leading to greater chemotherapy related toxicity. The liver is responsible for the majority of metabolism for chemotherapies, including epirubicin which is the focus of this study. The ability of the liver to metabolize chemotherapy is related to the organ size and metabolic enzyme activity. Both of these factors can be reduced with age, chronic malnutrition and other disease related conditions. This study examined how LBM and functional liver volume related to epirubicin pharmacokinetics and chemotherapy related toxicity. Prior to this study being

conducted, variations in the pharmacokinetic parameters of epirubicin were poorly understood.

Patients were recruited from the Cross Cancer Institute in Alberta, Canada. Patients were diagnosed with either stage II or stage III breast cancer and were receiving adjuvant chemotherapy. The chemotherapy regimen in this study involved a combination of 5-FU, epirubicin, and cyclophosphamide. Patients were eligible if they were 18 or older, had no pre-existing liver disease, and had normal liver, cardiac and renal function. Patients were excluded if they had metastatic disease.

Body composition was analyzed using CT images that were obtained within 30 days of the assessment and treatment administration. Only CT images that were previously attained for diagnostic purposes were used. The third lumbar cross-section was used to calculate LBM. Liver volume was also determined from the CT images. Epirubicin plasma concentrations were drawn at about 1 hour and 24 hours post-chemotherapy infusion and pharmacokinetic factors were determined from the plasma concentrations. Toxicity was graded using the NCI-CTEP Common Toxicity Criteria, version 2.0. These criteria have been validated to assess chemotherapy related toxicity (Trotti et al., 2000). Patient toxicity assessments were done using a diary that was completed after each cycle of chemotherapy. Research nurses then reviewed the diaries with patients to determine the extent of chemotherapy related toxicity. This study only considered the toxicities reported after the first cycle due to possible dose reductions for the next cycle if toxicity was reported. T-tests were used to compare continuous variables and categorical variables were reported in frequency. A

multivariate analysis was used to further investigate potential confounders and clinically important variables that included BSA, LBM, and liver volume.

Of the 132 recruited patients, only 24 had CT images. 5 of the patients had stage II breast cancer and 19 had stage III breast cancer. There was a large variation in BMI (19.4-44.4). The mean BMI was 27.6 which falls into the overweight category. When patients with the same BSA were examined, a large variation in LBM and liver volume was observed. Toxicity was reported in most patients. Patients without toxicity had significantly greater mean LBM than patients with toxicity (56.2 kg vs 41.6 kg, p=0.002). There was a large variation in epirubicin dose per kilogram of LBM and cm^3 of liver volume. Once multivariate analysis was applied, it was determined that liver volume was strongly correlated with LBM (r=.87). A wide variation in epirubicin clearance was documented (33.3-107.9 per 1 hour). Examination of pharmacokinetic data found the LBM alone predicted 18% of variability. Based on the results of this study, the researchers concluded that LBM is a better predictor of drug efficacy and chemotherapy related toxicity than BSA, which was indicated by the large variation in LBM for patients with the same BSA.

To the researchers' knowledge, this is the first study to investigate the ability of LBM and liver volume to predict epirubicin pharmacokinetics. It was previously thought that correlations between hepatic clearance and LBM were attributed to LBM being a marker for liver volume. This study suggests that LBM not liver volume determines epirubicin clearance. Prado et al. noted that further investigation is needed.

Small sample size was noted as limitation of this study. Results may potentially be skewed since many of the patients had stage III breast cancer. Also, while researchers tried to control for the influence of the other chemotherapies that were part of the treatment regimen, some toxicity results may be due to the other treatments. However, research has identified similar results for FU (Prado et al., 2007). A strength of this study was that it further investigated the effect of LBM on chemotherapy clearance and also toxicity.

Summary

Cancer is a chronic disease associated with metabolic changes that lead to alterations in body composition. In recent years, the impact of sarcopenic obesity in oncology patients has been a trending topic, including how it affects functional status, chemotherapy tolerance and overall survival. The increased interest has been contributed to multiple factors including improved methods for analyzing body composition, recent research on the pharmacokinetics of chemotherapy and the growing number of oncology patients that are obese. This topic is especially important to examine due to the increasing amount of Americans that are classified as overweight or obese, which is a risk factor for developing cancer.

Body composition significantly contributes to patient quality of life and overall treatment tolerance. In the studies analyzed, there was significant data supporting the negative correlation between lean body mass and fat free mass and decreased functional status, cancer survival and treatment tolerance. The results of these studies indicate that LBM and FFM may be better predictors of chemotherapy tolerance and

cancer survival. Therefore, body composition analysis may lead to more concise chemotherapy dosing than the current dosing protocol.

The current doing protocol was reviewed in the Griggs et al. (2012) article which promoted the continuation of the BSA method for chemotherapy dosing. The article stated that there was no support for dosing chemotherapy differently in overweight and obese patients. However, it was noted that BSA was not developed for obese patients and currently there are ongoing efforts to improve the BSA method with special consideration for obesity. It is important to consider that the Griggs et al. article made no mention of how changes in body composition in overweight and obese patients may affect chemotherapy tolerance.

A 2013 study by Stobaus et al. investigated the discrepancy between BSA and body composition. The results identified significant variations in BSA and FFM. The researchers specifically noted that there twice as many obese patients in the low FFM group then the normal FFM and high FFM groups. It was stated that these patients would be at a higher risk for chemotherapy overdosing. These could lead to poor tolerance of chemotherapies, specifically those metabolized in FFM. While this study thoroughly investigated the limitations of BSA, especially in overweight and obese patients with decreased FFM, it failed to identify a link to chemotherapy tolerance.

The research studies by Parsons et al. (2012) and Prado et al. (2008) supported the claims that sarcopenic obesity is associated with decreased cancer survival and decreased functional status than non-sarcopenic obese patients. However, neither identified a link between sarcopenic obesity and decreased chemotherapy tolerance.

Parsons et al. specifically considered chemotherapy related toxicity and sarcopenic obesity but found no significant results. The researchers attributed the lack of findings to a skewed population and state that results would likely be different in a more general outpatient population versus the clinical trial population in the study. Prado et al. (2008) calculated hypothetical chemotherapy doses using BSA and identified a large variation in the doses per kilogram of FFM. The variation in doses demonstrated the poor association between BSA and FFM but researchers were limited to the conclusions that they could assume. Prado et al. stated that based on their findings decreased FFM may attribute to chemotherapy related toxicity for chemotherapy that is metabolized in FFM.

Gusella et al. (2002) and Prado et al. (2011) investigated the relationship between body composition and chemotherapy pharmacokinetics. Gusella et al. (2002) identified a moderate correlation between FFM and chemotherapy clearance while BSA had a much weaker correlation. The researchers concluded that body composition parameters were better predictors of pharmacokinetics parameters than BSA. Prado et al. (2011) identified similar findings. Similar to the hypothetical doses calculated in the Prado et al. (2008) article, the results of the Prado et al. (2011) study indicated a large variation in chemotherapy doses per kilogram of LBM. These doses had been calculated using BSA. Additionally, this study investigated chemotherapy related toxicity. Low LBM was significantly associated with increased chemotherapy toxicity. Like the Gusella et al. (2002) article, Prado et al. (2011) concluded that body composition was better at predicting drug efficacy and toxicity than BSA. Both studies identified limitations of their studies that restricted the generalizability of the results but

did urge that body composition analysis be considered in order to promote better chemotherapy tolerance.

In conclusion, sarcopenic obesity is associated with decreased functional status, decreased cancer survival and possibly poor chemotherapy tolerance. BSA dosing protocol does not consider variations in body composition and was not designed for obese patients. BSA has been shown to be poorly associated with LBM and FFM. Several chemotherapies are metabolized in the LBM and FFM, such FU and epirubicin which were discussed in the literature review. Patients with sarcopenic obesity are likely at increased risk for chemotherapy related toxicity for drugs that are metabolized in LBM and FFM due decreased metabolic capacity. This is due to receiving elevated doses of chemotherapy relative to their LBM and FFM when BSA is used to determine doses, since BSA is not correlated with LBM or FFM in the presence of sarcopenic obesity. The combination of reduced metabolic abilities and excessive chemotherapy likely leads to increased chemotherapy related toxicity.

CHAPTER 3: METHODS

This project is modeled after the Academy of Nutrition and Dietetics evidence analysis methodology for reviewing existing research. The purpose of the Academy of Nutrition and Dietetics Evidence Analysis Library is to provide access to systematic research reviews in order to assist dietetic practitioners in utilizing evidence-based practice (Academy of Nutrition and Dietetics, 2016). The Academy of Nutrition and Dietetics (AND) defines evidence-based practice as the use of systematically reviewed scientific evidence in making food and nutrition practice decisions by integrating best available evidence with professional expertise and client values to improve outcomes. Evidence-based practice translates research into everyday practice. Using evidence-based practice is part of the AND code of ethics for practitioners. This practice leads to improved quality of healthcare and decreased variations in care.

AND Evidence Analysis Process

The evidence analysis process is guide for systematically identifying, reviewing and summarizing research on a specific topic. The AND evidence analysis process involves 5 steps. The initial step of the process is to formulate a question. The question should be relevant to the practice of dietetics and be answerable. The PICO format should be adhered to when possible. PICO is an acronym for population, intervention, comparator, and outcome. The question should also be related to one of the steps of the nutrition care process, such as nutrition assessment.

After a question is formulated, research needs to be gathered and classified. The process involves reporting inclusion and exclusion criteria of the search for evidence.

Examples of inclusion criteria are: patient population characteristics (age, sex), clinical setting of the research, and sample size. The search plan is detailed in this step. This includes what databases are used to search for articles and the search terms. Both included and excluded articles are listed. All excluded articles should have a specific reason for why they were deemed inappropriate, such as insufficient sample size.

The third step of the analysis process is to critically appraise each article. The evidence worksheet from the AND is used as part of this step. The worksheet considers study design, research purpose, study inclusion and exclusion criteria, and sample size. Specific methods of the studies are described on the worksheet. The results of the study are summarized and the research conclusion is listed. The reviewer then includes their own remarks on the worksheet. In addition to the evidence worksheet, the AND quality criteria checklist is completed in order to determine a rating for article. Based on the results of the checklist, the article is given a rating of positive, neutral or negative.

After the research has been critically appraised, the evidence is summarized and displayed in an overview table. The evidence summary is a narrative discussing the overall findings of the evidence analysis. The overview table lists citations for the included articles and serves as an organized visual of the results from the evidence analysis. The table includes study design, quality rating, sample size, and interventions and outcomes. A benefit of the table is that practitioners can easily compare studies alongside each other.

The final step of the AND evidence analysis process is to develop a conclusion statement and to grade the strength of the supporting evidence. There are 5 grade

options. Grade I is the top and is described as good strength. To use this grade evidence must consist of results from studies with strong design which produce consistent results. The results can be generalized and the studies avoid bias and design flaws. Grade II is fair strength. There are 2 options for this grade. Results may be from strong design but contain some uncertainty and inconsistencies or results may be from weak design but have been previously verified in other studies. Grade III is limited strength which indicates that results are from a limited number of studies that have weak design. Grade IV is only an expert opinion based on clinical expertise and does not include any research results. Grade V has no evidence.

Evidence Analysis Project

Prior to developing the research question for the evidence analysis project, a search for existing research was conducted in order to assure that adequate evidence on the topic existed. The topic was further studied as part of the literature review process to gain a better understanding of the subject to assure the quality of the critical analysis. Currently oncology medical practice is striving for more individualized care. A possible consideration should be how to personalize chemotherapy dosing. The current protocol for dosing is to use body surface area (BSA), which has been shown to be poorly associated with lean body mass (LBM) and fat free mass (FFM). Many cancer patients will experience body composition changes, such as sarcopenic obesity, which increases the risk of chemotherapy related toxicity due to over dosing. The purpose of this evidence analysis project is to investigate the relationship between sarcopenic obesity and its effect on chemotherapy toxicity, functional status and overall survival. The results of this project would ideally translate into current dietetic oncology practice.

Search Plan

Question	Is lean body mass a better predictor of chemotherapy related toxicity than body surface area for cancer patients with sarcopenic obesity?
Date of Literature Review	2013-2015
Inclusion Criteria	• Adult gastrointestinal cancer patients • Overweight and/or obese cancer patient with sarcopenia • Primary research • Written in English
Exclusion Criteria	• Any studies including chemotherapy not metabolized in LBM or FFM
Search Terms	• Body composition and chemotherapy tolerance/chemotherapy toxicity • Sarcopenic obesity and chemotherapy tolerance/chemotherapy toxicity • Both lean body mass/FFM and chemotherapy tolerance/chemotherapy toxicity
Electronic Databases	• PubMed • Google Scholar
Inclusion List	• Anandavadivelan, P., Brismar, T., Nilsson, M., Johar, A. & Martin, L. (2015). Sarcopenic Obesity: A probable risk factor for dose limiting toxicity during neo-adjuvant chemotherapy in oesophageal cancer patients. *Clinical Nutrition,* 1-7 • Prado, C., Lieffers, J., McCargar, L., Reiman, T., Sawyer, M., Martin, L. & Baracos, V. (2008). Prevalence and clinical implications of sarcopenic obesity in patients with solid tumours of the respiratory and gastrointestinal tracts: a population-based study. *The Lancet Oncology, 9,* 629-635 • Rollins, K., Tewari, N., Ackner, A., Awwad, A., Madhusudan, S., Macdonald, I., Fearon, K. & Lobo, D. (2015). The impact of sarcopenia and myosteatosis on outcomes of unresectable pancreatic cancer and distal cholangiocarcinoma. *Clinical Nutrition,* 1-7 • Tan, B., Birdsell, L., Martin, L., Baracos, V. & Fearon, K. (2009). Sarcopenia in an Overweight or Obese Patient Is an Adverse Prognostic Factor in Pancreatic Cancer. *Clinical Cancer Research, 15,* 6973-6979
List of Articles Included from Handsearch or Other Means	n/a
List of Excluded Articles with Reason	n/a
Summary of Articles Identified to Review	4 primary research articles were identified and all were included

Results

Author, Year, Study Design, Class, Rating	Study Purpose	Study Population	Intervention	Outcomes	Limitations
Author: Prado et al. Year: 2008 Study Design: Prospective cohort study Class: B Rating: Neutral (ø)	To assess the prevalence and clinical implications of sarcopenic obesity in patients with cancer.	250 (136 men, 114 women) obese patients with cancer of the respiratory tract or gastrointestinal tract. Mean age: 63.9 +/- 10.4	The effect of sarcopenia was studied	Of the 250 obese subjects, 15 % had sarcopenia. 47% of sarcopenic obese patients reported poor functional status (p=0.009) Sarcopenic obese patients had statistically significant shorter median survival. (p<0.0001, HR 2.4, 95% CI 1.2-3.9) - Remained a significant independent predictor of survival once univariate and multivariate analysis was conducted	Utilized primarily patient reported data Limited generalizability: results limited to obese patients with these cancer types
Author: Tan et al. Year: 2009 Study Design: Cross-sectional study Class: D Rating: Neutral (ø)	Investigate if weight and body composition, specifically sarcopenia, is a prognostic value for patients with pancreatic cancer	111(52 males, 59 females) with pancreatic cancer entering a palliative care program Predominately stage IV pancreatic cancer Mean age: <u>BMI < 25</u> Non-sarcopenic: 60.7 +/- 7.5 Sarcopenic: 65.8 +/- 10.2 <u>BMI > 25</u> Not sarcopenic: 64.3 +/- 9.0 Sarcopenic: 66.0 +/- 9.3	Effect of body composition on survival was studied.	Sarcopenia and BMI ≥ 25 (overweight/obese) had a statistically shorter median survival 55 days vs 148 days for subjects without sarcopenia BMI ≥25 (overweight/obese) p=0.003. - This remained an independent prognostic value after multivariate analysis (HR= 2.07, 95% CI 1.23-3.50, p=0.006). Overweight/obese (p=0.071) and sarcopenia alone (p=0.217) were not statistically significant.	Anthropometric data was patient reported Limited generalizability: very specific patient population
Author: Anandavadivelan et al. Year: 2015	Are sarcopenia and/or sarcopenic obesity	72 (61 males, 11 females) with esophageal cancer or cancer	Patients received cisplatin (100 mg/m²) for 1 day and 5-FU (750 mg/m²) for 5	Subjects with sarcopenia and BMI ≥ 25 (overweight/obese) compared to non-sarcopenic and BMI ≥ 25 (overweight/obese) was the only subgroup to reach statistical	Researchers were reliant on previously collected data.

Study Design: Retrospective cohort study Class: B Rating: Neutral (ø)	associated with higher risk of dose-limiting toxicity during cycle 1 of neoadjuvant chemotherapy in reseceptable esophageal cancer patients?	of the gastric cardia. Tumor stage 3% stage 1 28% stage 2 69% stage 3 Mean age: 67 +/- 7	days. Oxalipltin (130 mg/m²) was substituted for cisplatin for patients with hearing impairment or decreased renal function. Carboplatin (AUC 5) was substituted for cisplatin for patients with squamous cell cancer. Dose-limiting toxicity was measured.	significance for increased risk of dose-limiting toxicity during cycle 1 of treatment (OR=5.54, 95% CI 1.12-27.44, p=0.04)	Limited generalizability: Specific patient population and treatment regimen.
Author: Rollings et al. Year: 2015 Study Design: Retrospective cohort study Class: B Rating: Minus/Negative (-)	What is the relationship between sarcopenia, myosteatosis, inflammation and survival?	228 patients with unresectable pancreatic cancer or distal cholangio carcinoma Mean age Underwent chemotherapy: 64.8 +/- 8.7 No chemotherapy: 72.9 +/- 11.1	Effect of body composition on survival was studied.	Subjects with sarcopenia and BMI ≥ 25 (overweight/obese) had a shorter median survival (p=0.013).	Poor description of statistical analysis Poor distribution of BMI and body composition factors Limited generalizability: specific patient population

CHAPTER 4: RESULTS

A total of four articles were included in the evidence analysis. The following results were found from the review.

Toxicity

Anandavadivelan, Brismar, Nilsson, Johar & Martin (2015) designed a retrospective study to investigate sarcopenic obesity as a risk factor for dose-limiting toxicity (DLT) during neo-adjuvant chemotherapy in esophageal cancer patients. The study received a neutral rating. This study defined DLT as any toxicity that resulted in a temporary reduction or delay or permanent discontinuation of treatment because of side effects or serious adverse events. Side effects and adverse events were assessed using the NCI Common Terminology Criteria for Adverse Events v3.0. The results of the study indicated an increased risk for DLT in patients with sarcopenia and a body mass index (BMI) ≥ 25 ($p=0.04$, OR 5.54, 95% CI 1.2-27.44). Patients with a BMI less than 25 and sarcopenia had no significant increased risk for DLT ($p=0.58$, OR 1.60, 95% CI 0.30-8.40).

Prado et al. (2008) analyzed hypothetical chemotherapy doses in obese cancer patients as a means to assess the potential for chemotherapy toxicity in their prospective study. This study received a neutral rating. A previous study by Prado et al. (2007), found that 93% of patients that received a 5-FU chemotherapy dose of ≥ 20 mg/kg of lean body mass experienced toxicity (OR=16.75, $p=0.013$). That result was contributed to the low proportion of LBM relative to BSA, which is used to dose chemotherapy agents. The Prado et al. (2008) study identified a large variation in fat

free mass (FFM) amongst obese cancer patients and wanted to investigate if there was a chemotherapy dose variation in this patient population. The researchers calculated hypothetical doses of 5-FU using 425 mg/m² of body surface area (BSA) and then compared the calculated dose to milligram 5-FU per kilogram of FFM. Results showed that doses ranged from 11.3 to 31.3 mg 5-FU/kg FFM. These findings suggested that patients with low FFM and relatively large BSA would be at increased risk for toxicity based on previous findings in the Prado et al. (2007) study.

Functional Status

Prado et al. (2008) used the Patient Generated Subjective Global Assessment (PG-SGA) as a tool in their prospective study of obese patients with cancer of the respiratory tract or gastrointestinal tract. A portion of that tool assessed functional status using phrases to describe the patient's physical ability. Those phrases had assigned points 0-4- 0 being "normal with no limitations" and 4 being "pretty much bedridden, rarely out of bed". The researchers found that 47% patients with sarcopenic obesity reported significantly poorer functional status, on the PG-SGA, when compared with non-sarcopenic obese patients (p=0.009).

Overall Survival

A cross-sectional study by Tan, Birdsell, Martin, Baracos & Fearon (2009) aimed to examine if sarcopenia in overweight and obese pancreatic cancer patients was an indicator of prognosis. This study received a neutral rating. Patients selected for this study were enrolled in a palliative program. Subjects were divided into four groups: BMI < 25 and not sarcopenic, overweight or obese, sarcopenic and BMI ≥ 25 and

sarcopenic. Overall median survival for all patients was 130 days. Patients with sarcopenia and a BMI ≥ 25 had a shorter median survival of 55 days which was statistically significant (p=0.003). Sarcopenia alone and overweight or obese alone had no significant effect on survival. After multivariate analysis, BMI ≥ 25 with sarcopenia was found to be an independent prognostic value for survival.

Rollins et al. (2015) studied the impact of sarcopenia in unresectable pancreatic cancer and distal cholangiocarcinoma in a retrospective study. This study received a negative rating. The investigators identified 228 patients with a CT scan that could be utilized for body composition analysis. Of those patients 58 were sarcopenic and had a BMI ≥ 25. Survival analysis was completed using Kaplan Meier survival curves. Results indicated significantly shorter survival in patients with sarcopenia and BMI ≥ 25 (p=0.013). Sarcopenia alone was not statistically significant (p=0.779).

Prado et al. (2008) included a survival analysis as part of their prospective study of obese cancer patients. Patients with sarcopenic obesity had a median survival of 11.3 months versus 21.6 months (p <0.0001, HR 2.4, 95% CI 1.5-3.9). After multivariate analysis, sarcopenic obesity remained an independent predictor of survival.

Conclusion Statement

Sarcopenia and a BMI ≥ 25 in adult patients with gastrointestinal cancers is associated with increased risk of chemotherapy toxicity, poor performance status and shorter overall survival.

This is a Grade III conclusion due to limited number of studies, lack of generalizability and flaws in study design.

CHAPTER 5: DISCUSSION

Body composition, including sarcopenic obesity, has been increasingly studied in oncology patients as a factor that affects treatment tolerance and quality life factors. A reason for growing interest in sarcopenic obesity can be attributed to the increasing number of individuals that are overweight and obese. Additionally, excessive body weight is a risk factor for cancers, including gastrointestinal cancers, which were studied in all of the articles included as part of this systematic review.

Overall Summary Statement

Sarcopenic obesity has significant effects on cancer patients, including decreased performance status, increased risk of dose-limiting toxicity and shortened overall survival. However, the results of the studies analyzed in this systematic review were limited by the types of cancers that the subjects had. The four studies included patients with gastrointestinal tract cancers, such as pancreatic cancer, colorectal cancer and esophageal cancer. Prado et al. (2008) had a few subjects with respiratory tract cancers, but they only accounted for 8% of the sarcopenic obese patients in this study.

At the time of this evidence analysis, there were no studies on sarcopenic obesity in subjects with other cancer types. It would be of interest to determine the effect of sarcopenic obesity on treatment tolerance and quality of life factors in the other cancer types that are common among obese individuals.

Comparison of Studies

Treatment tolerance

Ongoing analysis of different body composition changes in the oncology population has led to revelations about the limitations of the current method for chemotherapy dosing using body surface area. Several studies have demonstrated that presence of sarcopenia is predictor of poor chemotherapy tolerance (Fabro et al., 2012 and Prado et al., 2014).

Anandavadivelan et al. (2015) conducted one of the few existing studies to examine dose-limiting toxicity in overweight and obese patients with sarcopenia. While the study did not have enough sarcopenic patients to subdivide the BMI ≥ 25 group into overweight or obese, the results of the study indicating increased toxicity are still an important consideration in this patient population. The hypothetical dosing trial in Prado et al. (2008) discovered that patients with sarcopenic obesity were predicted to have an increased risk of dose-limiting toxicity. The researchers in both of these studies suggested that dose-limiting toxicity was due to poor chemotherapy distribution secondary to reduced LBM. LBM was responsible for metabolizing the treatments included in these studies. Similar results would then be expected for all chemotherapy treatments that are metabolized in LBM, however further research would need to be done in order to generalize this.

Chemotherapy Dosing Method

The limitations of the BSA method for chemotherapy dosing were discussed in the literature review. Anandavadivelan et al. (2015) found further support for the poor association between BSA and body composition. They compared subjects LBM to BSA and found a poor correlation (r=0.64) (no p-value listed). Prado et al. (2008) also

demonstrated a discrepancy between BSA and FFM in their hypothetical chemotherapy dosing exercise. This was demonstrated by a large variation in doses per kilogram of FFM. While there is plenty of existing evidence supporting the limitations of BSA, there are no alternative methods for dosing that have been studied.

Survival

Tan et al. (2009), Rollings et al. (2015) and Prado et al. (2008) all found statistically significant shorter survival, an average 47% reduction in time, in overweight and obese cancer patients with sarcopenia. There is no current evidence to explain the mechanism for this finding. Prado et al. proposed a possible explanation that the associated increased inflammation may cause a poorer response to chemotherapy; however this theory requires investigation. Shorter survival may be related to dose-limiting toxicity. Overweight and obese patients with sarcopenia are at increased risk for treatment delays or discontinuation, which may explain shorter survival if patients are not receiving the treatment intended to cure or delay progression of their cancer. Alternately, shorter survival may be a reflection of overall sicker patients. Tan et al. (2009) and Prado et al. (2008) predominately included stage III and IV cancer patients, which may skew results to shorter overall survival.

Tan et al. (2009) brought up an important consideration that should be discussed between patients and their healthcare providers. Their group questioned if treatment would be appropriate in advanced pancreatic cancer patients with sarcopenic obesity due to very short median survival (55 days). Of note, 93% of the subjects in the Tan et al. (2009) study had stage IV cancer, which likely was a contributing factor to survival

besides sarcopenia. However, this is still significantly shorter than the median survival of 130 days. This is an important ethical consideration for what is the best for the patient's quality of life. Especially considering that other studies have shown that patients with sarcopenic obesity are also at increased risk for chemotherapy toxicity and poorer functional status.

Limitations

Imaging

Currently DEXA, BIA and CT scans are all acceptable methods for determining the presence of sarcopenia. In this evidence analysis, all studies used CT scans as the diagnostic tool to determine the presence of sarcopenia. CT scans are routinely used for diagnostic purposes, such as disease staging, and therefore are a reasonable method for examining body composition in oncology patients (Anandavadivelan et al., 2015 and Prado et al., 2008). One limitation of this diagnostic method is if patients are too large fit into the CT machine. Patients then would be unable to undergo CT imaging or would have cutoff images. Prado et al. (2008) excluded 10 patients due to this limitation. With the increasing population of overweight and obese individuals, it is important to have improved access to equipment that can better accommodate this patient population.

Cancer Stage

Tan et al. (2009) and Prado et al. (2008) reported statistically shorter survival in overweight and obese patients with sarcopenia. However, the results of both studies could be skewed by advanced cancer. 93% of subjects in the Tan et al. (2009) study

had stage IV pancreatic cancer, which would likely equate to overall survival shorter due to the advanced diagnosis. Tan et al. (2009) controlled for tumor stage in the univariate analysis but it failed to meet statistical significance (p=0.09).

Similar to Tan et al. (2009), 47% of the sarcopenic obese subjects in the Prado et al. (2008) study had stage IV cancer, which could skew results especially considering that stage IV cancer patients had statistically shorter survival when compared to stage I, II and III ($p<0.001$). In comparison, 37% of non-sarcopenic obese patients had stage IV cancer.

Sample Size

A limitation of several studies was small sample sizes. Tan et al. (2009), Anandavadivelan et al. (2015) and Rollins et al. (2015) were unable to subdivide overweight and obese individuals with sarcopenia due to the small number of subjects in each group. It would be of interest if results would remain significant for both overweight and obese patients, or if one subgroup would no longer be a contributor to the overall outcome.

Future Research

Other Cancer Types

A general recommendation for future research would be to examine sarcopenic obesity in other cancer types. It is unknown if sarcopenic obesity would negatively impact treatment tolerance, survival, performance status or other quality of life factors in other cancer types.

Dosing Method

It has been noted that the BSA method for dosing chemotherapy is not appropriate for all patients. Anandavadivelan et al. (2015) and Prado et al. (2009) demonstrated increased risk for chemotherapy toxicity in overweight and obese cancer patients with sarcopenia. Both of studies utilized the BSA method to determine chemotherapy doses. However, there is no alternative method. A recommendation for future research would be to investigate if chemotherapy that is metabolized in LBM can be dosed per LBM versus BSA. This has the potential to improve tolerance and therefore decrease delays or discontinuation of treatment, which may in turn also improve overall survival.

Interventions to Treat Sarcopenic Obesity

While the mechanism of sarcopenic obesity is still not fully understood, there need to be methods to protect and improve LBM. Inflammation has been a proposed mechanism for causing sarcopenia in overweight and obese cancer patients. A future study could examine the role of anti-inflammatory diet, supplements and/or medications in sarcopenic obese cancer patients and observe the effect on LBM. A variety of nutrition interventions, such as varying levels of macronutrient distribution, as well as physical therapy interventions could be additional considerations for research on methods to improve LBM.

Individualized care

With growing interest in personalized cancer treatment, such as gene therapy and immunotherapy becoming more popular, there should be consideration for how the

differences in body composition among individuals may impact cancer outcomes. Tailoring cancer treatment to conditions such as sarcopenic obesity may lead to better quality of life for patients undergoing treatment as well as improved outcomes.

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Evidence Worksheet for Primary RESEARCH Article

Citation: *write it in AMA format as found in JADA.*	Anandavadivelan, P., Brismar, T., Nilsson, M., Johar, A. & Martin, L. (2015). Sarcopenic Obesity: A probable risk factor for dose limiting toxicity during neo-adjuvant chemotherapy in oesophageal cancer patients. *Clinical Nutrition.* 1-7
Study design: *Use algorithm – RCT, cohort, etc*	Retrospective cohort study
Study Class (A,B,C,D)	B
Research Quality Rating *This rating tells if the research design is good (+), bad (-) or neutral (∅)* *This is determined by the quality criteria list. Delete the ratings that do not apply (i.e. if positive, delete minus/negative and neutral).*	**NEUTRAL (ø)**
Purpose/Population Studied/Practice Studied	
Research purpose: *What is the research question being investigated in the study?)*	Are sarcopenia and/or sarcopenic obesity associated with higher risk of dose-limiting toxicity during cycle 1 of neoadjuvant chemotherapy in reseceptable esophageal cancer patients?
Inclusion criteria: *requirements for study eligibility*	- Diagnosed with esophageal cancer or cancer of the gastric cardia - Treated with neo-adjuvant therapy (radiotherapy and/or chemo radiotherapy) prior to surgery - Had CT scans available for analysis
Exclusion criteria (conditions that make individual ineligible)	- No exclusion criteria described
Recruitment	- Patient data was obtained from an ongoing two-arm multicenter randomized, open-label, Phase III controlled trial investigating chemotherapy versus radiochemotherapy for cancer of the esophagus or gastric cardia
Blinding used: *some of the persons involved are prevented from knowing certain information that might lead to conscious or unconscious bias on their part, invalidating the results*	No blinding used
Description of study protocol *What happened in the study?*	CT scans that had been obtained for diagnostic purposes were analyzed. This was done by looking at the L3 cross-section which was then used to estimate lean body mass. The investigators then used skeletal muscle index cut-offs, determined by Prado et al. (2008), to diagnosis sarcopenia. Dose-limiting

	toxicity was monitored using the NCI Common Terminology Criteria for Adverse Events v3.0. Statistical analysis was then conducted examining the characteristics that affect toxicity.
Intervention: *Describe interventions, regimens, risk factors, or procedures studied.*	Patients received cisplatin (100 mg/m²) for 1 day and 5-FU (750 mg/m²) for 5 days. Oxalipltin (130 mg/m²) was substituted for cisplatin for patients with hearing impairment or decreased renal function. Carboplatin (AUC 5) was substituted for cisplatin for patients with squamous cell cancer. There was no description of radiotherapy or mention that any patients that were included in this study were receiving radiotherapy.
Statistical analysis: *List tests, significance level set a priori (α=0.05; include intent to treat analysis if applicable; note if there is Power analysis.*	- Significance was set at $p < 0.05$ - Independent t-test - Pearson's correlation coefficient - Multivariable logistic regression
Timing of measurements: *when outcomes were measured; usually baseline and one or more later times*	- Toxicity was measured during cycle 1 of neoadjuvant chemotherapy - CT scans examined in this study were completed prior to starting treatment or as close to the start of treatment as possible.
Dependent variables: *outcomes that are measured or registered; variable whose change or different states the researcher wants to understand, explain, or predict*	- Presence of dose-limiting toxicity

Evidence Worksheet for Primary RESEARCH Article

Citation: *write it in AMA format as found in JADA.*	Prado, C., Lieffers, J., McCargar, L., Reiman, T., Sawyer, M., Martin, L. & Baracos, V.(2008). Prevalence and clinical implications of sarcopenic obesity in patients with solid tumours of the respiratory and gastrointestinal tracts: a population-based study. *The Lancet Oncology*. 9, 629-635
Study design: *Use algorithm – RCT, cohort, etc*	Prospective cohort study
Study Class (A,B,C,D)	B
Research Quality Rating *This rating tells if the research design is good (+), bad (-) or neutral (∅)* *This is determined by the quality criteria list. Delete the ratings that*	**NEUTRAL (ø)**

do not apply (i.e. if positive, delete minus/negative and neutral).	
Purpose/Population Studied/Practice Studied	
Research purpose: *What is the research question being investigated in the study?)*	To assess the prevalence and clinical implications of sarcopenic obesity in patients with cancer.
Inclusion criteria: *requirements for study eligibility*	- Undergoing treatment for cancer of the respiratory tract, colon or rectum or other gastrointestinal sites (anus, pancreas, stomach, esophagus) - Obese (classified as BMI ≥ 30) - CT scans within 30 days of BMI assessment
Exclusion criteria (conditions that make individual ineligible)	- Other cancer diagnoses - Other BMI categories
Recruitment	All new patient at the Cross Cancer Institute between January 13, 2004 and January 19, 2007 were considered.
Blinding used: *some of the persons involved are prevented from knowing certain information that might lead to conscious or unconscious bias on their part, invalidating the results*	No blinding used
Description of study protocol *What happened in the study?*	BMI was assessed during the first visit. Patients that were obese and had CT scans within 30 days of BMI being assessed were further examined. During this same visit, patients completed the Patient Generated Subjective Global Assessment, which provided data on weight, weight history and functional status. CT scans were used to examine fat free mass via the L3 cross-section which was used to determine the presence of sarcopenia. Researchers conducted log-rank tests to determine gender specific cutoffs. The cohort was prospectively followed until death.
Intervention: *Describe interventions, regimens, risk factors, or procedures studied.*	Effect of sarcopenic obesity
Statistical analysis: *List tests, significance level set a priori (α=0.05; include intent to treat analysis if applicable; note if there is Power analysis.*	Statistical significance was set at $p < 0.05$ - Log rank test - Fisher's exact test - Pearson's χ^2 test - Univariate and multivariate survival analysis - Kaplan-Meier Curves
Timing of measurements: *when outcomes were measured; usually baseline and one or more later times*	All data was collected during the initial visit and then followed until death.

Dependent variables: *outcomes that are measured or registered; variable whose change or different states the researcher wants to understand, explain, or predict*	- Functional status - Survival

Evidence Worksheet for Primary RESEARCH Article

Citation: *write it in AMA format as found in JADA.*	Tan, B., Birdsell, L., Martin, L., Baracos, V. & Fearon, K. (2009). Sarcopenia in an Overweight or Obese Patient Is an Adverse Prognostic Factor in Pancreatic Cancer. *Clinical Cancer Research. 15*, 6973-6979
Study design: *Use algorithm – RCT, cohort, etc*	Cross-sectional study
Study Class (A,B,C,D)	D
Research Quality Rating *This rating tells if the research design is good (+), bad (-) or neutral (∅)* *This is determined by the quality criteria list. Delete the ratings that do not apply (i.e. if positive, delete minus/negative and neutral).*	**NEUTRAL (ø)**
Purpose/Population Studied/Practice Studied	
Research purpose: *What is the research question being investigated in the study?)*	Is weight and body composition, specifically sarcopenia, a prognostic value for patients with pancreatic cancer?
Inclusion criteria: *requirements for study eligibility*	- Patients entering palliative program for pancreatic cancer - Had CT scan within 60 days of initial assessment
Exclusion criteria (conditions that make individual ineligible)	- Diagnosis of ampullary cancer, cholangiocarcinoma or neuroendocrine tumors
Recruitment	All patients referred to the regional cancer center from January 2004-October 2008 were considered.
Blinding used: *some of the persons involved are prevented from knowing certain information that might lead to conscious or unconscious bias on their part, invalidating the results*	No blinding used

Description of study protocol *What happened in the study?*	CT scans that had been obtained for diagnostic purposes were analyzed. This was done by looking at the L3 cross-section which was then used to estimate fat free mass. The investigators then used skeletal muscle index cut-offs, determined by Prado et al. (2008), to diagnosis sarcopenia. Investigators collected survival data for a time from of initial assessment until the censor date of January 5, 2009. Statistical analysis was then conducted to investigate the relationship between body composition and survival.
Intervention: *Describe interventions, regimens, risk factors, or procedures studied.*	Effect of body composition on survival was studied.
Statistical analysis: *List tests, significance level set a priori (α=0.05; include intent to treat analysis if applicable; note if there is Power analysis.*	- Statistical significance was set at $p < 0.05$ - Cox regression model for survival analysis - One-way ANOVA - Paired t-test - Pearson's χ^2 - Log-rank test - Kaplan-Meier for survival curves
Timing of measurements: *when outcomes were measured; usually baseline and one or more later times*	There was only an initial assessment. No follow up after besides monitoring for survival.
Dependent variables: *outcomes that are measured or registered; variable whose change or different states the researcher wants to understand, explain, or predict*	- Survival

Evidence Worksheet for Primary RESEARCH Article

Citation: *write it in AMA format as found in JADA.*	Rollins, K., Tewari, N., Ackner, A. Awwad, A., Nadhusudan, S., Macdonald, I., …Lobo, D.(2015) The impact of sarcopenia and myosteatosis on outcomes of unrescetable pancreatic cancer or distal cholangiocarcinoa. *Clinical Nutrition.* 1-7
Study design: *Use algorithm – RCT, cohort, etc*	Retrospective cohort study
Study Class (A,B,C,D)	B
Research Quality Rating *This rating tells if the research design is good (+), bad (-) or neutral (∅)* *This is determined by the quality criteria list. Delete the ratings that*	**MINUS/NEGATIVE (-)**

do not apply (i.e. if positive, delete minus/negative and neutral).	
Purpose/Population Studied/Practice Studied	
Research purpose: *What is the research question being investigated in the study?)*	What is the relationship between sarcopenia, myosteatosis, inflammation and survival?
Inclusion criteria: *requirements for study eligibility*	- Patients with unresectable pancreatic carcinoma or distal cholangiocarcinoma. - CT scan done at time of diagnosis
Exclusion criteria (conditions that make individual ineligible)	Ampullary and duodenal carcinoma, neuroendocrine tumors or gastrointestinal stromal tumors.
Recruitment	All patients presenting to Nottingham University Hospital that were diagnosed with unresectable pancreatic cancer and distal cholangiocarcinoma between 2006 and 2013 were considered.
Blinding used: *some of the persons involved are prevented from knowing certain information that might lead to conscious or unconscious bias on their part, invalidating the results*	No blinding used
Description of study protocol *What happened in the study?*	CT scans that had been obtained for diagnostic purposes were analyzed. This was done by looking at the L3 cross-section which was then used to estimate skeletal mass index and myosteatosis. The investigators then used skeletal muscle index cut-offs, determined by Birdsell et al. (2013, to diagnosis sarcopenia. Statistical analysis was then conducted to investigate the relationship between body composition and survival.
Intervention: *Describe interventions, regimens, risk factors, or procedures studied.*	Effect of body composition on survival was studied.
Statistical analysis: *List tests, significance level set a priori (α=0.05; include intent to treat analysis if applicable; note if there is Power analysis.*	Statistical significance was set at $p < 0.05$ - Paired t-test - Kaplan-Meier survival curves - Log-rank Mantel-Cox analysis - Cox regression - Pearson's correlation coefficient
Timing of measurements: *when outcomes were measured; usually baseline and one or more later times*	There was initial assessment for all patients. - For the group that underwent chemotherapy, there was a follow up CT scan approximately 60 days at the initial diagnostic scan

Dependent variables: *outcomes that are measured or registered; variable whose change or different states the researcher wants to understand, explain, or predict*	- Survival