# Alterations in Nutritional Status during Cancer Treatment

by

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## Abstract

Patients with cancers of the head and neck or lung are at high risk for malnutrition during cancer treatment. Malnutrition is associated with poor response to chemotherapy and decreased survival. Therefore, this research was conducted to assess nutritional alterations that occur during cancer treatment. Secondly, this research aimed to investigate if optimizing protein intake using dairy products attenuates loss of muscle in patients with lung cancer. The first objective was to determine the changes that occur with respect to dietary intake and micronutrient status of cancer patients undergoing treatment in relation to body composition alterations and treatment-related toxicities. Dietary intake was assessed by three-day food records occurring at the time of diagnosis and again at the end of treatment and beyond. Body composition was determined using computed tomography (CT) imaging. Poor micronutrient intake and status was prevalent among head and neck cancer (HNC) patients. The proportion of calories from milk, soup, and oral nutritional supplements (ONS) significantly increased by the time treatment ended, while consumption of other food groups such as meat decreased and consequently lower calorie and protein intake were observed during treatment. Considerable loss of weight, muscle and adipose tissue occurred during treatment. Greater weight loss was experienced by patients who consumed higher intakes of ONS compared with patients with lower ONS consumption at an equal level of energy and protein intake. A negative correlation was observed between muscle loss and energy intake. These findings highlight the importance of providing positive energy balance as the first nutritional strategy to maintain muscle mass in patients with cancer. Assessing plasma levels of vitamins in both HNC and lung cancer patients, revealed a high prevalence of vitamin D deficiency which was correlated with developing mucositis in HNC patients and dose limiting toxicity (DLT) in women with lung cancer. The correlation observed between vitamin D deficiency and muscle loss in each of these cohorts warrant further investigation. The last objective was to determine if optimizing protein intake based on counselling to increase intake of dairy products during chemotherapy treatment is effective to maintain skeletal muscle mass in

lung cancer patients. Patients with good adherence to the intervention maintained or gained muscle mass compared to those with poor adherence. However, this effect was attenuated by the presence of inflammation. Patients maintained their physical function and QOL over the course of treatment. This study contributes to gaps in knowledge around micronutrient status and its relation with oncological outcomes. Also, these results demonstrate the potential of food-based intervention to address limiting nutrients to support the maintenance of muscle mass and improve outcomes of cancer patients.

## Preface

This thesis is an original work by Sara Nejatinamini and consists of eight chapters: **Chapter 1**. Part of this chapter has been published as a systematic review as *"Sensory preferences of supplemented food products among cancer patients: a systematic review",* Blanca Enriquez-Fernández, Sara Nejatinamini, Sandra Campbell, Vera Mazurak, Wendy Wismer. Support Care Cancer (2018). In collaboration with Blanca Enriquez-Fernández, we were both responsible for critically reviewing the papers, compiling data tables, and drafting of the manuscript. Sandra Campbell helped perform the comprehensive literature search and edited the manuscript. Dr. Vera C. Mazurak and Dr. Wendy Wismer guided the process, provided input on selected papers and themes and contributed to the editing of the manuscript.

**Chapter 3.** This chapter was prepared in paper format and was published as *"Head and Neck Cancer Patients Do Not Meet Recommended Intakes of Micronutrients without Consuming Fortified Products"* Sara Nejatinamini, Catherine Kubrak, Mirey Álvarez-Camacho, Vickie E. Baracos, Sunita Ghosh, Wendy V. Wismer & Vera C. Mazurak , Nutrition and Cancer (2018) 70:3, 474-482. I was responsible for the data analysis, interpretation of the results, and writing of the manuscript. Dr. Catherine Kubrak and Dr. Mirey Álvarez-Camacho completed subject recruitment and data collection, and Dr. Sunita Ghosh assisted with statistical analysis. Dr. Vickie E. Baracos, Dr. Wendy V. Wismer & Dr. Vera C. Mazurak designed the study and assisted in the interpretation of the data, consultation and writing of the manuscript. This study is a secondary data analysis of studies which were approved by the Health Research Ethics Board of Alberta- Cancer Committee (ethics numbers: 25818, 23028). **Chapter 4.** This chapter is written in a manuscript format for submission to *Nutrients* The paper is entitled *"Correlation of dietary energy and protein intake with body composition alteration during cancer treatment in HNC patients" by* Benjamin McCurdy, Sara Nejatinamini and Vera C. Mazurak. I conceived the study, recruited patients,

performed data collection, compiled and analyzed the data and revised the manuscript; Benjamin McCurdy performed the analysis of the CT scans, compiled the data, performed statistical analysis and drafted the paper; Dr. Vera C. Mazurak assisted with study conception, compilation of data and writing of manuscript. This study is a secondary data analysis of studies which were approved by the Health Research Ethics Board of Alberta- Cancer Committee (ethics numbers: 25852, 25818, 23028). **Chapter 5.** This chapter was prepared in paper format and was published as *"Poor Vitamin Status is Associated with Skeletal Muscle Loss and Mucositis in Head and Neck Cancer Patients"*, Sara Nejatinamini, Brock J. Debenham, Robin D. Clugston, Asifa Mawani, Matthew Parliament, Wendy V. Wismer, Vera C. Mazurak, *Nutrients* (2018) *10*, 1236. I was responsible for the subject recruitment, data analysis, interpretation of the results, and writing of the manuscript; Dr. Brock J. Debenham and Dr. Matthew Parliament contributed to conception of study, study design and patient recruitment; Asifa Mawani completed subject recruitment and data collection; Dr. Robin D. Clugston assisted with laboratory analysis and interpretation; Dr. Wendy V. Wismer assisted with study design and provided significant advice all through the study; Dr. Vera C. Mazurak assisted with the study design, compilation of data and writing of the manuscript. The study was approved by the Health Research Ethics Board of Alberta- Cancer Committee (ethics number: 25852). **Chapter 6.** This chapter is written in a manuscript format and it will be submitted to the Nutrition and Cancer. I was responsible for compiling data, statistical analysis, and drafting the manuscript. Dr. Seyyed Mohammad Reza Kazemi-Bajestani and Dr. Rachel Murphy completed subject recruitment and data collection. Liquid chromatography-mass spectrometry was conducted by Dr. Vathany Kulasingam at University of Toronto. Dr. Vickie E. Baracos provided critical input. Dr. Vera C. Mazurak was the supervisory author and assisted with study conception, compilation of data and writing of manuscript. The study protocol was approved by Health Research Ethics Board of Alberta-Cancer Committee (reference number: HREBA.CC-18-0067). **Chapter 7.** This chapter is written in a manuscript format and it will be prepared for submission to the Clinical Nutrition. I was responsible for patient recruitment, data collection, and

analysis as well as the manuscript composition. Asifa Mawani assisted with patients' recruitment. Abha Dunichand-Hoedl assisted with CT scan analysis and blood analysis. Seyedeh Zeinab Taheri Rouhi contributed with dietary intake data analysis. Dr. Brock J. Debenham and Dr. Quincy Chu contributed to the conception of the study and patient recruitment. Dr. Wendy Wismer assisted with interpretation and manuscript edits. Dr. Vera C. Mazurak was the supervisory author and was involved with concept formation and manuscript composition. The study was approved by the Health Research Ethics Board of Alberta-Cancer Committee (ethics number: HREBA CC-16-0851) and registered with ClinicalTrials.gov (NCT03010657).

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## List of abbreviations

| | |
|---|---|
| **Alb** | Albumin |
| **BIA** | Bioelectrical impedance analysis |
| **BMI** | Body mass index |
| **BW** | Body weight |
| **Cal** | Calorie |
| **$cm^2$** | Centimeter squared |
| **CRP** | C-reactive protein |
| **CT** | Computed tomography |
| **DLT** | Dose limiting toxicity |
| **DXA** | Dual-energy X-ray Absorptiometry |
| **ECOG** | Eastern Cooperative Oncology Group |
| **ESPEN** | European Society for Clinical Nutrition and Metabolism |
| **FFM** | Fat free mass |
| **FFQ** | Food frequency questionnaire |
| **FM** | Fat mass |
| **GI** | Gastrointestinal |
| **HNC** | Head and neck cancer |
| **L** | Liter |
| **L3** | Third lumbar vertebra |
| **$m^2$** | Meter(s) squared |
| **µg** | Microgram |
| **mL** | Milliliter |
| **MNA** | Mini Nutritional Assessment |
| **MST** | Malnutrition screening tool |
| **MUST** | Malnutrition Universal Screening Tool |

| | |
|---|---|
| **PUFA** | polyunsaturated fatty acids |
| **NLR** | Neutrophil/lymphocyte ratio |
| **NIS** | Nutrition impact symptoms |
| **NRS-2002** | Nutrition Risk Screening 2002 |
| **NSCLC** | Non small cell lung cancer |
| **ONS** | Oral nutritional supplements |
| **QOL** | Quality of life |
| **PG-SGA** | Patient-Generated Subjective Global Assessment |
| **Pro** | Protein |
| **REE** | Resting energy expenditure |
| **ROS** | Reactive oxygen species |
| **RT** | Radiation therapy |
| **SAT** | Subcutaneous adipose tissue |
| **SATI** | subcutaneous adipose tissue index |
| **SD** | Standard deviation |
| **SM** | Skeletal muscle |
| **SMI** | Skeletal muscle index |
| **SPPBT** | Short physical performance battery test |
| **TAT** | Total adipose tissue |
| **TATI** | Total adipose tissue index |
| **VAT** | Visceral adipose tissue |
| **VATI** | Visceral adipose tissue index |
| **25(OH)D** | 25-hydroxy vitamin D |

## Chapter 1: Introduction and literature review

### 1.1 Malnutrition during cancer trajectory

Cancer survival rates are improving with advances in cancer treatment. The cancer continuum include diagnosis, treatment, recovery, living after recovery, and, for some, palliative treatment. Patients in each of these phases have different requirements and challenges in terms of nutrition. All of the major therapeutic modalities, including surgery, radiation, and chemotherapy, significantly influence metabolism and nutritional needs, change regular dietary habits, and negatively impact how the body digests, absorbs, and uses food (McMahon et al., 2000). The majority of cancer patients undergoing treatment experience malnutrition which reduces responses to the treatment, requires reduction of treatment dose and even treatment withdrawal (Andreyev et al., 1998; Pressoir et a., 2010). During active cancer treatment, the overall goals of nutritional support should be to prevent or reverse nutrient deficiencies, to preserve skeletal muscle mass and muscle strength, to improve immune function, to minimize nutrition impact symptoms (NIS), and to maximize quality of life (Doyle et al., 2006).

The aims of this literature review were to evaluate the effects of anticancer therapies on (i) malnutrition prevalence, (ii) body composition (iii) dietary intake, and (iv) biological measurement of nutrients in blood.

### 1.2 Prevalence of malnutrition in cancer patients undergoing anticancer treatment

Patients with cancer are at high risk for malnutrition which is associated with poor prognosis. Unlike starvation-related malnutrition, cancer-related malnutrition consists of both reduced dietary intake provoked by tumor and treatment induced NIS in combination with metabolic alterations such as increased resting metabolic rate, insulin resistance and muscle loss which are aggravated by systemic inflammation (Jensen et al., 2010).

There is a high prevalence of malnutrition at diagnosis in patients scheduled for cancer treatment. Cancer treatment subsequently aggravates preexisting nutrition problems by

increasing prevalence of malnutrition to 40 to 98% at the end of treatment (Attar et al., 2012; Hébuterne et al., 2014; Planas M et al., 2016). The large variability reported is due partly to the lack of universally accepted definitions for malnutrition in the oncology setting which could lead to misclassification of malnutrition. Criteria used to assess nutritional status vary between studies, including nutritional screening tools and nutritional assessment tools. Screening and assessment are completely different processes, though nutritional screening utilizes risk factors to identify at-risk patients whereas nutritional assessment helps make a nutrition diagnosis. A screening tool should be short and have good sensitivity and specificity. Frequently used screening tools include Nutrition Risk Screening 2002 (NRS-2002), Malnutrition Universal Screening Tool (MUST), Malnutrition Screening Tool (MST), Mini Nutritional Assessment Short Form Revised (Isenring et al., 2015). For nutritional assessment, in both clinical practice and in research, different tools have been used such as Subjective Global Assessment (SGA), Patient-Generated Subjective Global Assessment (PG-SGA) and Mini Nutritional Assessment (MNA) (Detsky et al., 1987; Bauer et al., 2002; Gabrielson et al., 2013).

Regardless of the tools used to assess malnutrition, it is well established that nutritional status deteriorates during cancer treatment. Nutritional status of patients with acute leukaemia worsened after chemotherapy treatment; at baseline all patients were moderately malnourished while after treatment 97% of patients were diagnosed with severe malnutrition (PG-SGA score of ≥9) (Malihi et al., 2015). Similarly, in advanced head and neck cancer patients 30% of patients were malnourished (PG-SGA B or C) at diagnosis, while after induction chemotherapy (iCT) followed by radiotherapy, 95% of patients were diagnosed as malnourished (Arribas et al., 2017). In geriatric patients with gastrointestinal cancer, 38% of patients were found to be malnourished at the time of the first visit; however after a single course of chemotherapy the rate of malnutrition significantly increased to 46% (Bicakli et al., 2018). In the latter study, nutritional status was assessed by MNA, which is the recommended tool for screening of nutritional status in elderly patients. When nutritional Risk Screening 2002 (NRS-2002) tool was applied in colorectal cancer

as well as mixed tumor types of cancer patients a significant increase in percent of patients at risk of malnutrition was reported (Fu et al., 2017; Pan et al., 2014). Likewise, both studies reported significant increase in malnourished patients after treatment using BMI<18.5 kg/m2 and serum Albumin level<35 g/L.

The main limitation in these studies is that confounding factors that influence cancer patients' nutritional status such as age, stage of disease, tumor site and treatment modalities, are not considered. Older patients (> 65 years) are at higher nutritional risk compared to younger patients (Fu et al., 2017). Malnutrition is more frequent in HNC patients compared to other tumor groups (Unsal et al., 2006). Furthermore, there is very low level of evidence regarding the relationship between nutritional alterations during cancer treatment and clinical outcomes of patients (Ghadjar et al., 2015, Sanders et al., 20146). Most studies assess clinical outcomes in relation to nutritional status at one time point, typically at diagnosis and prior to starting treatment.

Several studies have reported early integration of nutritional support with oncological treatment to reduce morbidity and mortality (Bakitas et al., 2015; Cox et al., 2016). In light of this, to prevent treatment related malnutrition and improve oncological outcome, nutritional screening and nutritional assessment in at risk patients should be initiated when the cancer is diagnosed, followed by simultaneous initiation of nutritional intervention and oncologic therapy (Figure 1.1). Moreover, the emerging understanding of pathology of cancer related malnutrition proposes to expand nutritional assessment to include malnutrition symptoms such as metabolic derangements, systemic inflammation and body composition changes (Arends et al., 2017). Currently available tools lack these components. Developing a comprehensive tool to assess malnutrition by using both subjective (patients' NIS, weight history, dietary intake) and objective (muscle mass, physical performance and the degree of systemic inflammation) assessment is suggested.

### 1.3 Effect of cancer treatment on nutritional status

#### 1.3.1 Cancer treatment and body composition

##### 1.3.1.1 Methods of body composition assessment

Body composition has been assessed by different methods including CT scan (Kakinuma et al., 2018; Aahlin et al., 2017; Eriksson et al., 2017; Nattenmuller et al., 2017; Blauwhoff-Buskermolen et al., 2016; Heus et al., 2016; Stene et al., 2015; Cooper et al., 2014; Yip et al., 2014; Awad et al., 2012; Prado et al., 2012; Dalal et al., 2012; Murphy et al., 2010), BIA (Tang et al., 2018; Arribas et al., 2017; Aoyama et al., 2016; Ida et al., 2014; Frenzel et al., 2013, Stanisavljevic et al., 2010, Gil et al., 2006), DXA (Jager-Wittenaarl et al., 2011, Silver et al., 2007), Skinfold method (Harvie et al., 2003) and air displacement plethysmography (Freedman et al., 2004). CT, MRI (magnetic resonance imaging) and Dual-energy X-ray absorptiometry (DXA) are the current reference method in body composition evaluation in patients with cancer (Prado et al., 2013). DXA has been regarded as a safe, convenient, and noninvasive method which provides estimates of three components: bone mineral, fat mass (FM) and lean body mass (LBM). Furthermore, as well as evaluating body composition at a whole body level, DXA also provides the quantification of regional estimates such as abdominal, lower versus upper limb as well as appendicular skeletal muscle (Svendsen et al., 1993). The major limitations of DXA, specifically in the oncology setting, is the poor differentiation of water and bone-free lean tissue, not being readily available for cancer patients and the controversial reproducibility between different types of DXA machines. While DXA is currently unable to distinguish between subcutaneous adipose tissue, visceral adipose tissue and intramuscular adipose tissue, CT is able to differentiate between these adipose tissues (Svendsen et al., 1993).The CT imaging is an opportunistic method to assess body composition in cancer patients since almost every cancer patient routinely undergoes a CT scan during cancer staging and follow-up. The L3 lumbar vertebra landmark is widely used in cross sectional body composition analysis and is found to be correlated to the

whole-body tissue measurements (Mourtzakis et al., 2008). Muscle area and density at this vertebral level includes the psoas, paraspinal muscles (erector spinae, quadratus lumborum) and abdominal wall muscles (transversus abdominus, external and internal obliques, rectus abdominus), thus making it an optimal level for skeletal muscle quantification. Currently, no standardized method has been defined on the CT image parameters that are required for the purpose of body composition analysis. Thus, for abdominopelvic CT as part routine diagnostic or follow up algorithm, the following CT acquisition parameters are appropriate: 120 kV, variable mA with dose modulation, soft tissue reconstruction algorithm, matrix of 512×512, field of view (FOV) of 30-35 cm and reconstructed slice thickness 5 mm (Thibault et al., 2012). BIA technique has been validated in cancer patients (Fredrix et al., 1990). BIA is inexpensive, portable and has no radiation exposure, however it can be affected by extreme BMI values and hydration status (Thompson et al., 1991) and thus BIA should be performed under standard conditions to minimise the measurement variation. Anthropometric methods (e.g skin fold thickness, mid arm and calf circumferences) are prone to measurement error with significant interobserver variability and are not recommended to assess muscle mass (Cruz-Jentoft et al., 2010).

#### 1.3.1.2 Effects of cancer treatment on body composition

Long-term changes of body composition in patients with cancer are influenced by the response to treatment and disease progression. However, there is evidence that treatment for cancer is associated with short-term changes in body composition particularly skeletal muscle mass which are endured throughout survivorship. Given the importance of association between muscles loss during cancer treatment and oncological outcomes, the changes in skeletal muscle as an adverse effects of anticancer treatment are of emerging interest.

Seventeen studies have revealed significant decrease of lean mass or skeletal muscle mass over the course of anti-cancer treatment (Kakinuma et al., 2018, Tang et al., 2018, Aahlin et al., 2017, Arribas et al., 2017, Eriksson et al., 2017, Nattenmuller et al., 2017, Blauwhoff-

Buskermolen et al., 2016, Aoyama et al., 2016, Stene et al., 2015,Cooper et al., 2014 , Yip et al., 2014, Awad et al., 2012, Dalal et al., 2012, Jager-Wittenaarl et al., 2011, Murphy et al., 2010, Silver et al., 2007, Freedman et al., 2004) (Table 1.3). It is critical to note that the rate of muscle loss reported during cancer treatment in these studies compared with muscle loss that occurs in normal aging (1%/year), were about 10-fold more rapid. One study found no significant changes but a trend toward a decreased lean mass after chemotherapy in non-Hodgkin lymphoma cancer patients (Stanisavljevic et al 2010). In contrast, two studies observed an increase in lean mass and skeletal muscle mass in cancer patients (Frenzel et al., 2013; Heus et al 2016). Lean body mass was assessed by bioelectrical impedance analysis (BIA) in the Frenzel 2013 study which is poorly correlated to skeletal muscle mass in oncology setting (Isenring et al., 2004) because it estimates lean mass by measuring body water. Patients who experienced alteration in their hydration status during BIA may have had their fat free mass (FFM) overestimated. Furthermore, enlargement of organs that is known to occur in advanced cancer patients interpret as lean mass (Lieffers et al., 2009). Heus et al 2016, reported increased skeletal muscle mass during treatment as an unprecedented finding with no clear explanation. It is also noteworthy that in the study by Prado (2012), patients receiving selumetinib (targeted agent) showed an increase of muscle mass compared to standard therapy group.

The current European Society for Clinical Nutrition and Metabolism (ESPEN) emphasizes the measurement of muscle mass in nutritional assessment of cancer patients (Arends et al., 2017). Indeed, muscle tissue is a major protein reserve as it contains about 60% of protein in the human body. Low muscle mass is associated with dose-limiting toxicity in several anticancer treatments (Prado et al., 2016). Likewise, cancer treatment, particularly chemotherapy, could have a detrimental effect on body composition by enhancing loss of muscle mass (Table 1.1). Cancer therapies like sorafenib provoke muscle wasting by targeting major muscle synthesis pathways (e.g. PI3K/AKT/mTOR) (Antoun 2010). Biopsies taken before and after chemotherapy with doxorubicin or melphalan in patients with melanoma or sarcoma revealed severe reductions

in myofiber size and mitochondria-dysfunction (Bonifati et al., 2000). Likewise, preclinical studies show that cisplatin is able to activate NF-κB signaling pathway in both mouse muscles and myotube cultures that could explain muscle wasting caused by this treatment (Damrauer et al., 2008). In addition to chemotherapy agents and physical inactivity, corticosteroids, given during chemotherapy treatment, also influence the body composition of cancer patients and induce muscle wasting.

Short-term evolution of fat mass through anti-cancer therapies has been shown to be very heterogeneous, depending mainly on the type of cancer and type of treatment. Five studies reported a decrease of fat mass during and after anti-cancer treatment (Cooper et al., 2014,Yip et al., 2014, Awad et al., 2012, Dalal et al., 2012, Silver et al., 2007) (Table 1.3). Additional studies revealed increase or no changes of fat mass after anti-cancer treatment (Nattenmuller et al., 2017, Stanisavljevic et al., 2010, Gil et al., 2006, Freedman et al., 2004, Aahlin et al., 2017, Arribas et al., 2017, Stene et al., 2015, Frenzel et al., 2013, Jager-Wittenaarl et al., 2011). Previous studies reported chemotherapy agents such as cisplatin and doxorubicin decrease de novo lipogenesis and increase lipolysis contributing to fat loss (Garcia et al., 2013, Biondo et al., 2016). On the other hand, weight gain associated with adjuvant chemotherapy for breast cancer is primarily due to an increase in fat (Aslani et al., 1999). Fat gain during chemotherapy has been attributed to decreased activity of brown adipose tissue (Gadea et al., 2014) and is associated with decreased survival (Atalay et al., 2015).

Seven studies reported results based on different characteristics of patients. Patients with esophageal cancer who experienced surgical complications lost more lean mass than similar patients without complications (Ida et al., 2014). Patients on targeted therapies showed a significant gain of muscle mass or attenuated skeletal muscle loss compared to those who received cytotoxic chemotherapy, although fat tissue decreased in both group regardless of treatment type (Prado et al., 2012; Kakinuma et al., 2018). In some types of tumor, molecular targeted therapy is more effective and less toxic than traditional cytotoxic chemotherapy (Russo

A., 2015); therefore, the differences in toxic adverse events during treatment may relate to the skeletal muscle loss. Changes in body composition during cancer treatment could be sex dependent, since male patients frequently experience a greater decline in muscle mass during cancer treatment compared to female patients (Nattenmuller 2017, Harvie et al., 2003). One study has specifically assessed the effect of radiotherapy on body composition based on cancer type (Tang et al., 2018). In this study HNC patients and patients with abdominal or pelvic cancer lost their lean mass however, no significant changes were observed in lean mass of patients with lung or breast cancer. Fat mass reduced significantly just in chest or breast cancer patients. A wide range of cofactors such as sex, age, treatment modalities, tumor type and comorbidities (e.g. diabetes) influence body composition alterations during treatment, which few studies consider in their analysis. For future studies, these key confounding variables should be measured and adjusted statistically for their impact on the relationship between cancer treatment and body composition changes.

Nutritional status is not effectively monitored by merely measuring weight and BMI in cancer patients. Given the exponential increases in the size of liver, hepatic metastasis and spleen and concurrent muscle loss with or without fat loss during disease progression, applying a method enabling discrimination between different fat free mass components and regional adipose tissue is highly important (Lieffers et al., 2009). Imaging techniques such as CT images and MRI are routinely used for cancer diagnosis and staging. Application of these techniques are becoming increasingly common for body composition assessment in patients with cancer by detecting loss of muscle mass and regional fat reserves. However, there is a paucity of knowledge regarding the association between body composition alterations during cancer treatment and health clinical outcomes. In patients with metastatic colorectal cancer, reduced muscle mass during chemotherapy was independently associated with survival (Blauwhoff-Buskermolen et al., 2016). There are many potential future areas of research to measure the longitudinal changes in body composition during different cancer treatment in relation to oncological outcomes.

### 1.3.2 The effects of anticancer treatment on dietary intake

Cancer treatment often causes nutrition impact symptoms (NIS) which refers to any impediment to oral dietary intake (Khalid et al., 2007; Kubrak et al., 2010). NIS occur frequently in the oncology setting with highest prevalence in HNC patients (Gellrich et al., 2015), include taste and smell alterations, mucositis, nausea, constipation, pain, or shortness of breath (Kubrak et al., 2010). Concurrent chemotherapy and radiation therapy is associated with higher rates of NIS compared to other treatment modalities such as surgery or radiation alone (Couch et al., 2007). Previous studies have reported the relationship of NIS to weight loss in patients with cancer (Jager-Wittenaar et al., 2007). An evaluation of the NIS showed symptoms such as anorexia, mucositis, or dysphagia are significant predictors of reduced oral dietary intake in head and neck cancer patients (Kubrak et al., 2010).

Changes in dietary patterns evoked by NIS may interfere with quality of dietary intake. However, there is limited information in terms of typical dietary pattern and food choices during cancer treatment. The majority of studies investigate food choices at one time point at diagnosis or during cancer trajectory regardless of treatment status, with only two studies evaluating changes during cancer treatment. In a cohort study, diet quality of women with breast cancer was assessed using the Brazilian Healthy Eating Index Revised (BHEI-R) during and after completion of chemotherapy. The results showed that the diet quality of the majority of patients worsened following the chemotherapy since fruit, vegetable and legume consumption decreased significantly during treatment (Custodio et al., 2016). Evaluating acceptance of the diet by patients with haematological cancers throughout chemotherapy treatment showed some food items were rejected more frequently, such as meat, rice, pasta, beans, vegetable soup and salad. In this study, milk and sweets were accepted by all patients (Prockmann et al., 2015). Information on food choices is valuable for developing dietary recommendations based on food preferences (Table 1.4).

Dietary changes that occur during cancer treatment may interfere with adequate dietary intake. High prevalence of inadequacy was identified for calories, protein, calcium, iron, phosphorus, magnesium, niacin, riboflavin, thiamin, vitamin B6, vitamin C and zinc during chemotherapy (Custodio et al., 2016). Assessing food records (3-day food records) in 47 HNC patients during treatment and after completion of treatment showed overall energy intake decreased from baseline through treatment, followed by a significant increase in energy intake during follow up. Those receiving chemoradiotherapy consumed the lowest calorie intake during treatment (about 1000 kcal/ day less than other treatment modalities). Those who had lowest energy intake experienced the greatest weight loss (about 10%) from baseline through treatment, however during the follow up period, weight continued to decline despite an increase in energy intake (Van der Berg 2006, Giles et al., 2016). Progressive weight loss could be explained by elevated resting energy expenditure (REE) in these patients following cancer treatment, since chemotherapy treatment may have an influence on the energy requirements of the patients and put them in a catabolic state (Kenway et al., 2004, Bosaeus et al., 2001). In a prospective study including 63 patients with acute leukemia, a significant reduction in macronutrient and micronutrients intake was observed across chemotherapy treatments (Malihi et al., 2015). In most cases, chemotherapy is associated with dietary intake impairment, however three studies showed no changes in dietary intake of patients through cancer treatment (Silver et al., 2007; Jeger-Wittenaar et al., 2010; Arribas et al., 2017). In the studies conducted by Arribas (2017) and Silver (2007), all patients received dietetic counseling and nutritional support from the diagnosis as a part of standard care which could partly explain maintaining the dietary intake during active treatment. Dietary intakes assessed at follow up period (one month after treatment completion) which may not represent dietary intake of patients during cancer treatment. While Van der Berg (2006) reported an increase in dietary intake during the follow up period (Van der Berg et al., 2006). Also, dietary intake during cancer treatment could be affected by type of treatment and

cancer, as patients with breast cancer and melanoma increased dietary intake but dietary intake of NSCLC patients did not change during treatment (Harvie et al., 2005).

Severity of NIS, such as taste and smell alterations, appetite loss, and feeling full is maximum during the immediate days of chemotherapy particularly over the first week of each cycle (Ijpma et al., 2017). Dietary intake varies depending on the cycle of chemotherapy, with the lowest intake on the first day of treatment and the highest before the next cycle of chemotherapy. Because of these observed variations in dietary intake between treatment time points, further studies evaluating dietary intake should report the time point of dietary assessment in their study protocol (Mardas et al., 2016).

Dietary intake changes during anticancer treatment is heterogeneous due to distinct effects of the types of cancer and treatment on the burden of NIS and dietary intake and also using different assessment time points in studies. There is paucity of knowledge regarding the effects of dietary intake during cancer treatment on treatment-related toxicities and oncological outcomes. Head and neck cancer patients with higher calorie and protein intake (>35 kcal/kg and >1.5 grams protein/kg body weight) lost significantly less weight and lean mass compared to patients with lower dietary intake during treatment (Jager-Wittenaar et al., 2010; Giles et al., 2016). Furthermore, in patients with advanced tumor disease undergoing chemotherapy treatment, low protein intake was associated with a more than twofold increased risk of cancer treatment-related fatigue and mortality (Stobaus et al., 2015). Available evidence suggesting every effort should be taken to guarantee adequate dietary intake in patients undergoing cancer treatment. Poor dietary intake should be recognized and addressed early by qualitative or if possible quantitative methods. Studies on dietary intake of cancer patients highlights several possible targets for dietary intervention.

### 1.3.3 Effects of anticancer treatment on plasma and tissue levels of nutrients

Poor dietary intake of patients during cancer treatment may cause nutrient depletion in serum and tissues. Cancer patients whose daily energy intake is less than 60% of their requirements for more than 7–10 days have an inadequate dietary intake including micronutrients (Arends et al., 2017). Moreover, patients undergoing chemotherapy or radiotherapy might not absorb micronutrients well due to gastrointestinal symptoms and mucositis (Fink et al., 2011). In addition, metabolic alterations and inflammatory processes induced by antineoplastic agents may alter micronutrient requirements. Therefore, although research around nutrient deficiencies that can occur during anticancer treatment is limited, it is highly likely that patients receiving cancer treatment would have certain nutrient deficiencies or insufficiencies. The European Society for Clinical Nutrition and Metabolism (ESPEN), the leading voice on nutrition for oncology patients, identified understanding micronutrient requirements for cancer patients as a major gap (Arends et al., 2017). The few studies that do exist have assessed micronutrient status at a single time point during the cancer trajectory, therefore alterations induced by treatment and whether micronutrient status recovers after treatment are not known. Single time measures of micronutrients may not be reflective of long-term status and could lead to an under- or over-estimation of adequacy. Six cohort studies have assessed plasma or serum levels of nutrients during cancer treatment with at least two time points. While the range of deficiencies could be numerous in cancer patients these studies only assessed selenium, water soluble vitamins (C, $B_6$, $B_{12}$, folate) and fat soluble vitamins (A, D and E) (Table 1.5).

A lower concentration of selenium was reported in the serum of breast cancer patients after radiotherapy compared to diagnosis (Franca et al., 2010). Selenium is an essential trace element, which has a crucial role in the most important endogenous antioxidative systems. Vitamin C deficiency, which is found particularly in patients with advanced cancer, may be exacerbated by anticancer treatment (Mayland et al., 2005). In a study conducted by Weij 1998

plasma levels of vitamin C decreased significantly during cisplatin treatment. Low plasma vitamin C levels are associated with increased CRP and albumin levels, and a shorter survival time. There is some evidence that vitamin C enhances the cytostatic effects of certain chemotherapy agents and, at the same time, reduces their toxic effects (Hoffer et al., 2015).

Vitamin D has been found to be deficient in cancer patients during chemotherapy treatment (Teleni et al., 2013, Kim et al., 2014, Iversen et al., 2010, Iversen et al., 2008). A retrospective study of 315 patients with colorectal cancer reported patients receiving chemotherapy were fourfold more likely to have severe vitamin D deficiency than non-chemotherapy patients (Fakih et al., 2009). Low serum 25OHD concentrations during chemotherapy could be partially explained by lifestyle changes such as limited number of dietary vitamin D sources or less participation in outdoor activities and thus have less sunlight exposure. Moreover, chemotherapy could active CYP3A4 or other metabolizing enzymes and convert 25OHD to inactive compounds such as 24, 25OHD (Fakih et al., 2009). Low serum vitamin D level is a risk factor for sarcopenia in older adults (Kuwabara et al., 2017) but there is a major lack of evidence on possible effects of vitamin D level on muscle condition in cancer patients. In addition to effects of vitamin D on muscle health, there is limited data suggesting that vitamin D deficiency may has a role in chemotherapy-induced toxicity , survival and prognosis of cancer, but conflicting findings have been reported (Fink et al., 2011).

Vitamins A and E are fat soluble vitamins with antioxidant properties which are required for a wide variety of physiological functions. Three studies reported a significant reduction of Vitamin E during cancer treatment (Iversen et al., 2010; Iversen et al., 2008; Melichar et al., 2010) however in two of them plasma levels of vitamin E restored six months after start of treatment (Iversen et al., 2010, Iversen et al., 2008). Vitamin A has been found to be diminished in patients with acute myeloid leukemia after chemotherapy (Iversen et al., 2008) however two other studies observed no changes in plasma vitamin A levels after treatment (Iversen et al., 2010; Melichar et al., 2010).

The effectiveness of chemotherapy and radiotherapy treatment are largely dependent on the formation of reactive oxygen species (ROS) and consequently on the increase of oxidative stress. Also, many toxic effects of chemotherapy and/or radiotherapy such as cardiotoxicity and nephrotoxicity are due to excess ROS generation in healthy tissues. Excessive ROS are diminished by enzymatic antioxidants such as superoxide dismutase, glutathione and nonenzymatic antioxidants such as antioxidant vitamins. Vitamins C, E and beta-carotene have several roles in antioxidant defense. The reduced concentration of antioxidant micronutrients during cancer treatment is reflected by the fact that oxidative stress markers are often increased (Chang et al., 2008, Tsao et al., 2007). Deficits in micronutrients with antioxidant functions caused by the cancer treatment is of importance in various aspects including compromised immune function (Carr A., 2017) and higher risk of treatment induced-toxicities. In head and neck cancer patients treated with radiotherapy, patients with higher plasma beta carotene had a significantly lower severe acute adverse effect and lower rate of local recurrence (Meyer et al., 2008). Further studies are required to investigate micronutrient status in relation to oncological outcome and treatment induced toxicities.

**1.4 Nutritional intervention**

In the light of the above, it appears clearly evident that all cancer patients undergoing cancer treatment need to complete nutritional screening before starting treatment so that the presence or risk of malnutrition can be detected and the most appropriate type of nutritional support determined. Early nutritional support and metabolic interventions aim to maintain or improve dietary intake, modulate metabolic alterations, maintain skeletal muscle mass and physical function, reduce the risk of treatment induced toxicities and treatment interruption, and improve quality of life. Based on a recent study in esophageal cancer patients receiving chemoradiotherapy, nutritional support initiated prior to treatment start improved survival. This study emphasizes the importance of early assessment and initiation of nutritional intervention (Cox et al., 2016). Data are still lacking in terms of the optimal time to initiate nutritional support.

The first step of nutrition support involves nutritional counselling by a health care professional, which aims to improve the food intake of patients through providing nutritional advice to create lasting changes in eating habits. In addition to health benefits, food and eating has important role in social integration which could impact patient's quality of life, so enhancing eating experience of patients should be considered. In patients with higher calorie and protein needs, considering food preferences of patients in the format of enriched foods or fortified foods is the preferred way to improve nutritional status.

In cancer patients who are unable to meet nutritional needs through food, oral nutritional supplements (ONS) are indicated. However, compliance with ONS intake is generally poor in cancer patients undergoing oncological treatment (Hubbard et al. 2012, Ravasco et al. 2005). In a study by Baldwin et al. 2011, compliance with high-energy ONS decreased after one week, and at the end of study (by week 6) only 19% of patients reported consuming all of the prescribed ONS. Effectiveness of ONS is dependent on the ability of the individual to intake sufficient quantities over an extended period of time. Palatability of the ONS was the main factor in long term compliance and successful use among a group of elderly patients (Lad et al. 2005). Supplement palatability can be affected by various factors including taste, color, flavor and texture. In addition, cancer patients often suffer from altered taste and smell perception that contributes to anorexia which may also influence long-term compliance to ONS. Another reason for low compliance to ONS is that socio-cultural aspects of food are not regarded. ONS provide little sensory pleasures, and ignore social and cultural habits associated with food and eating.

There is limited evidence regarding the efficacy of nutritional intervention during oncological treatment. A systematic review assessing the nutritional and clinical effectiveness of oral nutritional intervention during oncological treatment, showed an overall beneficial effect of nutritional interventions on body weight (van der Schueren et al., 2018). However, after subgroup analysis this finding was limited to high-protein and n-3 PUFA-enriched ONS intervention which highlighted the importance of targeting the metabolic alterations in cancer patients. Nutrition

counseling and/or high-energy density ONS showed no significant positive impact on body weight (van der Schueren et al., 2018). The inability to meet energy and protein targets due to poor compliance may partially explain the lack of significant effect on body weight. Strategies to increase compliance will improve the efficacy of nutritional interventions. For example; since sensory preferences are variable among patients, providing ONS and fortified foods that meet patients' sensory preference needs and expectations can improve intervention compliance and patient nutritional status. Also the opportunity to taste supplemented products and select the preferred one can increase compliance in a longitudinal evaluation (Enriquez-Fernández et al., 2018). Using more concentrated products by decreasing the volume to consume is another way to improve the compliance. Flexible meal planning allows lower food intake during treatment days with severe NIS and higher food intake to catch up the nutritional targets between treatment cycles.

Metabolic derangements (e.g. systemic inflammation, insulin resistance, anabolic resistance and muscle loss) which have been seen frequently in cancer patients may limit the positive effect of nutritional interventions. To the best of our knowledge, there is no study to consider the systemic inflammation status in their analysis in relation to the efficacy of nutritional interventions. Future studies are needed to include this aspect in their design. In addition, these metabolic abnormalities could increase protein turnover and catabolism, and finally muscle wasting. Muscle loss in cancer patients is an independent prognostic factor for treatment induced toxicities and response to treatment (Prado et al., 2016, Prado et al., 2009). Providing adequate energy and protein with increased amounts of high quality proteins and essential amino acids (overcoming anabolic resistance) and/or nutrients aimed at tempering the inflammatory response such as n-3 PUFA is the best effective way to ameliorate muscle wasting and malnutrition in cancer setting (Sanchez-Lara et al., 2014; Van der Meij et al., 2012; Engelen et al., 2015). It is in accordance with ESPEN recommendations which suggest the 1–1.5 g/kg/day protein intake and supplying n-3 PUFA during oncological treatment (Arends et al., 2017).

As cancer-related malnutrition is a syndrome with multifactorial origin, no single nutritional intervention alone will be sufficient, and patients would benefit from a multimodal approach (anabolic and anticatabolic therapies) that includes NIS management (MacDonald et al., 2003). Further research is required to improve efficacy of the nutritional intervention by early identification of patients at risk of malnutrition, optimal timing and duration of nutritional intervention, improving compliance to nutritional support and investigating ideal anabolic and anti-inflammatory components.

**1.5 Conclusion**

Despite remarkable advances in anticancer treatment, treatment induced malnutrition remains an unresolved issue. Cancer patients receiving anticancer treatment, particularly multimodal therapy, are at high risk of malnutrition. Further research is required to improve nutritional assessment tools to include new aspects of cancer-related malnutrition such as measures of body composition, insulin resistance and inflammatory biomarkers. It appears reasonable to start nutritional screening and assessment at diagnosis following simultaneous initiation of nutritional therapy and anticancer treatment.

During oncological treatment, muscle depletion increases considerably which could influence both compliance and response to the oncological therapy. Furthermore, there is limited evidence that dietary pattern and dietary intake of patients change during anticancer treatment, studies investigating the scope of these changes are urgently needed. Cancer patients may develop deficiencies in certain nutrients (e.g. nutrients with antioxidant properties) during treatment which could have detrimental effects on their oncological outcomes (treatment-induced toxicity, response to treatment and survival).

Treatments for cancer have progressed, moving from a simple antiproliferative approach to immunotherapy and molecular targeted therapies. Further research is required to ascertain possible nutritional insufficiencies and deficiencies caused by these new anticancer therapies that could contribute to poor oncological outcomes.

Tables

Table 1. 1 The effects of common chemotherapy agents on muscle mass

| Reference | Chemotherapy agent | Effect on muscle mass | Mechanism |
|---|---|---|---|
| Adegoke et al., 2012 | Targeted therapies (rapamycin derivatives): sirolimus, everolimus and ridaforolimus | ↓ | Interfere with the mTOR-dependent pathways |
| Cheregi et al., 2015 | Antimetabolites: 5-fluorouracil | ↓ | Mitochondrial dysfunction, oxidative damage, cellular energy depletion and apoptotic or necrotic cell death |
| Barreto et al., 2016 | Topoisomerase I inhibitors: irinotecan | ↓ | Mitochondrial dysfunction, reductions in myofiber size, oxidative damage |
| Damrauer et al., 2008 | Platinum based: cisplatin, carboplatin, oxaliplatin | ↓ | Mitochondrial dysfunction, NF-κB signaling pathway activation |
| Antoun et al., 2010 | Kinase inhibitor: Sorafenib | ↓ | Interfere with the mTOR-dependent pathways |
| Bonifati et al., 2000 | Anti-tumour antibiotics (Anthracyclines): Doxorubicin | ↓ | Mitochondrial dysfunction, reductions in myofiber size |
| Bonifati et al., 2000 | Alkylating agent: melphalan | ↓ | Mitochondria-dysfunction, reductions in myofiber size, suppresses protein synthesis and activates proteolytic and apoptotic signalling |
| Quan-Jun et al., 2017 | Selumetinib | ↑ | Decrease muscle atrophy by inhibition of ERK (extracellular signal–regulated kinase) activity, Increase protein synthesis by activation Akt (Protein Kinase B) pathway |

Table 1. 2 the effects of cancer treatment on malnutrition prevalence (n=6)

| Reference | Cancer population | Cancer treatment | Tools used to assess nutritional status | Time points of study | Prevalence of malnutrition | |
|---|---|---|---|---|---|---|
| | | | | | Baseline | Post-treatment |
| Bicakli et al., 2018 | GI cancer (n=, 153; age= 70.5 ± 5.6 y) | chemotherapy | MNA | before and after one cycle chemotherapy (min 4 wk and max 6 wk) | Patients at risk: 35%; malnourished: 38% | Patients at risk: 30%; malnourished: 46% |
| Arribas et al., 2017 | HNC patients (n=20; age=53± 7 y) | induction chemotherapy (iCT;taxanes and cisplatin) or radiotherapy plus cetuximab | PG-SGA | diagnosis (baseline); visit 1: after finishing iCT/prior to begin RT; visit 2: after finishing RT; visit 3: 1 month after RT; visit 4: 3 months after the end of treatment | moderately Malnourished: 15% ; malnourished: 15% | moderately Malnourished: 50% ; malnourished: 45% |
| Fu et al., 2017 | Colon and rectal (n=310; age=56.3 ± 17.2 y) | neoadjuvant chemotherapy (CapeOX-oxaliplatin and capecitabine) or radiochemotherapy (45 Gy plus CapeOX-oxaliplatin) | NRS-2002; Malnourishment:BMI<18.5 kg/m2 or serum Alb level<35 g/L. | 24 h of first admission and after completion of neoadjvant chemotherapy | Patients at medium and high risk: 37%; malnourished: 15% | Patients at medium and high risk: 61%; malnourished: 28% |
| Malihi et al., 2015 | Acute leukaemia patients (n=63) | Chemotherapy (For AML: Cytarabine plus either daunorubicin or idarubicin; For ALL: Cyclophosphaplus daunorubicin, vincristine, prednisolone) | PG-SGA | before starting chemotherapy and again after 1 month treatment completion | moderately malnourished: 100% | moderately malnourished: 3%; severely malnourished: 97% |
| Pan et al., 2013 | mixed tumor types (n=2248) | Chemotherapy, radiotherapy, surgery | NRS-2002; BMI, Alb (malnourished: BMI ≤18.5 | Baseline (24 h of admission), Post-treatment (surgery, 10th day after the operation; chemotherapies, after 2 | at nutritional risk:n 24.6%; malnourished: 19.7% | at nutritional risk:n 40%; malnourished: 27% |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | | kg/m2 and ALB <35 g/L) | Cycles; RT, after therapy) | | |
| Unsal et al., 2006 | mixed tumor types (n=207; age= 52.31± 0.84 y ) | radiotherapy (45–50 Gy) | SGA (A, B C) | at the onset, at the end of RT, and 3 and 6 months after irradiation | malnourished (total patients): 31% ; malnourished (HNC patients): 24% | malnourished (total patients): 43% ; malnourished (HNC patients): 88% |

Alb: albumin; HNC: Head and Neck Cancer; GI: gastrointestinal; MNA: Mini Nutritional Assessment (At risk for malnutrition: scores 17-23.5; malnourished score <17); NRS-2002: Nutritional Risk Screening 2002 (a total score ≥3 was defined as a marker of nutritional risk); PG-SGA: Patient Generated-Subjective Global Assessment ((A) well nourished, (B) moderately malnourished or risk of malnutrition or (C) severely malnourished); RT: Radiation therapy; SGA: Subjective Global Assessment

Table 1. 3 Effects of cancer treatment on body composition (n=24)

| Authors | Study population | Type of treatment | Method used for BC assessment | Duration of observation (week) | Findings |
|---|---|---|---|---|---|
| Kakinuma et al., 2018 | NSCLC (n=65; age=66.0± 10.5y) | cytotoxic chemotherapy (platinum based agent) *vs*. molecular targeted (EGFR and ALK TKI) | CT | ~ 19 | SMI ↓ by 8%; loss of SMM was greater in cytotoxic chemotherapy than in the targeted therapy. |
| Tang et al., 2018 | Mixed group tumor (n=101; age=52.83±11.06 y ; 32 HNC;; 45 chest or breast cancer; 24 abdominal or pelvic cancer) | Radiotherapy | BIA | ~ 6 | HNC patients: lost LBM (12.8%) but no changes in FM.<br>Chest or breast cancer patients:LBM did not change, FM ↓ (13%).<br>Abdominal or pelvic cancer patients: LBM ↓by 14.4%. |
| Aahlin et al., 2017 | Gastric adenocarcinoma (n=45) | neoadjuvant chemotherapy | CT | ~ 13 | SMI ↓ by 3%; No significant loss of fat tissue |
| Arribas et al., 2017 | HNC (n=20; age=53.7± 7.11) | induction chemotherapy (iCT) followed by chemoradiotherapy or bioradiotherapy | BIA | NC | FFM ↓ by 4%, FM did not change. |
| Eriksson et al., 2017 | Colorectal cancer (n=225) | neoadjuvant chemotherapy | CT | ~ 8 | SMI ↓ by 5.5 % |
| Nattenmuller et al., 2017 | Lung cancer (n=200; age= 62.3 ± 9.5y) | first-line-chemotherapy | CT | ~ 19 | SMM ↓ by 3%, while the TAT ↑ by 5.9% |
| Blauwhoff-Buskermolen et al., 2016 | Metastatic colorectal cancer (n=67; age= 66.4± 10.6 y) | Chemotherapy | CT | ~ 13 | SMM ↓ by 6.1% |
| Aoyama et al., 2016 | Gastric cancer (n=485) | gastrectomy | BIA | ~2 | LBM ↓ by 3.2 %,<br>The loss of LBM was significantly greater than the loss of FM. |
| Heus et al., 2016 | Rectal carcinoma (n=74; age=64±10y) | chemoradiation | CT | ~ 14 | SMM ↑ by 3.7%; AT showed no change. |
| Stene et al., 2015 | NSCLC (n=35; age=67.1±6.8y) | palliative chemotherapy (carboplatin plus | CT | ~ 12 | SMM ↓ by 3.8%; FM showed no change |

| | | | | | |
|---|---|---|---|---|---|
| | | vinorelbine or carboplatin plus gemcitabine) | | | |
| Ida et al., 2014 | Esophagus cancer (n=30; age=65 (53-75)y) | Neoadjuvant chemotherapy (Doxetaxel/ cisplatin/5-FU) | BIA | NC | Patients with surgical complications has ↓ in FFM compared to patients without surgical complications (-1.4±1.4 vs 4.3 ±2.3 kg). |
| Cooper et al., 2014 | Pancreatic cancer (n=82; age=63 (38-79)y) | Neoadjuvant chemotherapy (gemicitabine and cisplatin) | CT | ~16 | Significant ↓ in SMI (2.5%), VATI (8.8%) and SATI (7.9%) |
| Yip et al., 2014 | Esophagus cancer (n=35; age= 63(34-78y)) | Neoadjuvant chemotherapy (ECX/ECF or platinum/5-FU or 5-FU) | CT | ~ 5 | Significant ↓ in FFMI (4.6%) and FMI (1.7%) |
| Frenzel et al., 2013 | Breast cancer (n=70; age=55.6± 11.3y) | Adjuvant chemotherapy | BIA | NC | Significant ↑in FFMI (0.36 kg/m2) and no change in FMI |
| Awad et al., 2012 | Esophagus cancer (n=47; age=63±12y) | Chemotherapy (Platinum, capecitabine, epirubicin) | CT | ~15 | Significant ↓ in both SMM (7%) and AT (11%) |
| Prado et al., 2012 | Cholangiocarcinoma (n=50; 20 Selumetinib;age=54.5±14.4y, 30 standard treatment; age= 58.6±12.2y) | Targeted therapy (Selumetinib) *vs.* standard treatment | CT | ~ 13 vs ~12 | Selumetinib group gained SMM vs SMM loss in standard group (2.3 kg vs. -1.2kg); Both selumetinib and standard group lost fat tissue (-6.6 kg -3.8 kg; respectively) |
| Dalal et al., 2012 | Pancreatic cancer (n=41; age= 58.9 (41.7-81)y) | Chemoradiation therapy | CT | ~ 15 | Significant ↓ in SMM (4%), VAT (13%), and SAT (11%). |
| Jager-Wittenaarl et al., 2011 | HNC (n=29; age=60.6 ±10y) | radiotherapy, either alone or combined with chemotherapy or surgery | DXA | NC | LBM index ↓ by 4%, but FM did not change |
| Stanisavljevic et al., 2010 | Non-Hodgkin lymphoma (n=30;age=56 (20-82)y) | Chemotherapy (R-CHOP) | BIA | NC | Trend to lose FFM by 2.8% (not significant); ↑ in FM by 7.3% |
| Murphy et al., 2010 | NSCLC (n=41; age=62±1.4) | Chemotherapy | CT | ~ 14 | Whole body skeletal muscle ↓by 4.5% |
| Silver et al., 2007 | HNC (n=17; age=58.9 ± 5.4) | Concurrent chemoradiation | DXA | ~11 | FM and LBM ↓ by 12.5% and 10.7%; respectively. |

| | | | | | |
|---|---|---|---|---|---|
| Gil et al., 2006 | Ovarian cancer (n=12; age=59(35-79)y) | Surgery with Adjuvant chemotherapy (taxane and platinium based agent) | BIA | ~48 | No changes in LBM; FM ↑ significantly by 2.2%; Early stage patients: gain of FM; advanced stage patients: loss of FM |
| Freedman et al., 2004 | Breast cancer (n=26; age=48.2± 8.8 y) | adjuvant chemotherapy (AC/Docetaxelin and AC | ADP | ~16 | FFM ↓ by 2.3%;<br>FM ↑ by 2.5% |
| Harvie et al., 2003 | NSCLC (n=50; male: n=15; age=58.6±6.2y; female:n=5; age=59±8.1y ) | Chemotherapy | Skinfold | NC | FFM ↓ in male by 3.4%; but no significant change in FFM reported in female |

Table 1. 4 The effects of cancer treatment on dietary intake and dietary pattern of cancer patients (n=9)

| Reference | Study population | Treatment | Measurements | Time points | Results |
|---|---|---|---|---|---|
| Arribas et al., 2017 | HNC patients (n=20; age=53±7 y) | induction chemotherapy (iCT;taxanes and cisplatin) followed by chemoradiotherapy or radiotherapy plus cetuximab | Dietary intake (24-h recall) | diagnosis (baseline); visit 1: after finishing iCT/prior to begin RT; visit 2: after finishing RT; visit 3: 1 month after RT; visit 4: 3 months after the end of treatment | No changes in calorie and protein intake |
| Custódio et al., 2016 | breast cancer patients (n=55; age=51.5±10.1y) | chemotherapy | Dietary intake: 24h dietary recalls | T0, after the first cycle of chemotherapy; T1, after the intermediate cycle; and T2, after the last cycle of chemotherapy | ↓ macronutrients and micronutrients intake |
| Malihi et al., 2015 | acute leukaemia patients (n=63) | Chemotherapy (For AML: Cytarabine plus either daunorubicin or idarubicin; For ALL: Cyclophosphaplus daunorubicin, vincristine, prednisolone) | Dietary intake (24-h recall and a 136-item food frequency questionnaire) | before starting chemotherapy and again after 1 month treatment completion | ↓ macronutrients and micronutrients intake |
| Jager-Wittenaar et al., 2010 | HNC patients (n=29; age= ) | radiotherapy or chemoradiation | dietary intake (dietary history) | T0, one week before start the treatment; T1, 1 month after the end of treatment; T2, 4 months after the end of treatment | No changes in calorie and protein intake |
| Silver HJ et al., 2007 | HNC (n=17) | concurrent chemoradiation | energy intake (Random 24-hour telephone diet recalls ) | before and 1 month after CCR completion | No changes in calorie intake |
| Van der Berg et al., 2006 | HNC patients (n=47; age=60.07± 9.0y) | surgery, radiotherapy, combined surgery- radiotherapy and concomitant radiochemotherapy | FFQ | at diagnosis, the end of treatment and 6 months after treatment (follow up) | ↓ in calorie intake |

| | | | | | |
|---|---|---|---|---|---|
| Harvie MN et al., 2005 | patients with advanced melanoma, breast or lung cancer (n=41) | chemotherapy | four-day weighed food diaries | before starting chemotherapy, prior to the second chemotherapy cycle, and 1-month post completion of chemotherapy (4–6 cycles). | Patients with melanoma and breast cancer: ↑ in calorie and protein intake ; NSCLC: No changes in calorie intake |
| Food choices and dietary pattern | | | | | |
| Custódio et al., 2016 | breast cancer patients (n=55; age=51.5±10.1y) | chemotherapy | Dietary pattern (BHEI-R) | T0, after the first cycle of chemotherapy; T1, after the intermediate cycle; and T2, after the last cycle of chemotherapy | Diet quality of the majority of patients worsened following the chemotherapy |
| Prockmann et al., 2015 | lymphoma and leukaemia (n=32 patients age= 42 ± 11 y) | chemotherapy | Daily Food records | During chemotherapy treatment | Some food items were rejected more frequently, such as meat, rice, pasta, beans, vegetable soup and salad; lunch and dinner were the most frequently rejected meals |

BHEI-R: Brazilian Healthy Eating Index Revised; FFQ: Food Frequency Questionnaire; HNC: Head and neck cancer; NSCLC: Non-small cell lung cancer

Table 1. 5 Effects of cancer treatment on serum/plasma levels of nutrients (n=6)

| References | Study population | Treatment | Measured Nutrients | Timepoints | Findings |
|---|---|---|---|---|---|
| Kim et al., 2014 | Non-metastatic breast cancer (n=483; age=43 (24-54)y) | chemotherapy, anti-hormone therapy or radiotherapy | Serum hydroxyvitamin D | at diagnosis and 6 and 12 months after surgery | ↓ serum hydroxyvitamin D levels |
| Melichar et al., 2010 | Metastatic colorectal carcinoma (n=25; age=60±13y) | chemotherapy (irinotecan, leucovorin, 5-fluorouracil) and cetuximab | Serum retinol and alpha-tocopherol | before and after first month of treatment | ↓ serum alpha-tocopherol; Serum retinol level did not change. |
| Franca et al., 2010 | Breast cancer (n=209; age=61(59-62)y) | external beam radiotherapy (equal to 50 Gy/25 fr/5 weeks ) | Plasma selenium | before and at the end of the radiotherapeutic treatment | ↓plasma levels of selenium |
| Iversen et al., 2010 | Multiple myeloma (n=15) | high-dose chemotherapy and autologous stem cell support | Plasma concentrations of vitamins A, D, E, albumin | before, during and after the treatment | ↓ plasma vitamins D and E; transferrin and vitamin A did not change |
| BYSTRO'M et al., 2009 | Advanced colorectal cancer (n=93;age=63 (42-76)y) | first-line chemotherapy treatment (fluorouracil (5-FU) in combination with irinotecan) | Serum cobalamin, folate | before and during the treatment | Cobalamin and folate did not change |
| Iversen et al., 2008 | Acute myeloid leukemia (n=45) | chemotherapy (cytosine arabinoside and daunorubicine) | Plasma water-soluble vitamins (B6, B12 and C) and fat-soluble vitamins (A, D and E) | before, during and after chemotherapy and 9 months after diagnosis | ↓ vitamins A, D, E; plasma concentrations of vitamins B6, B12 or C did not change. |

## Figures

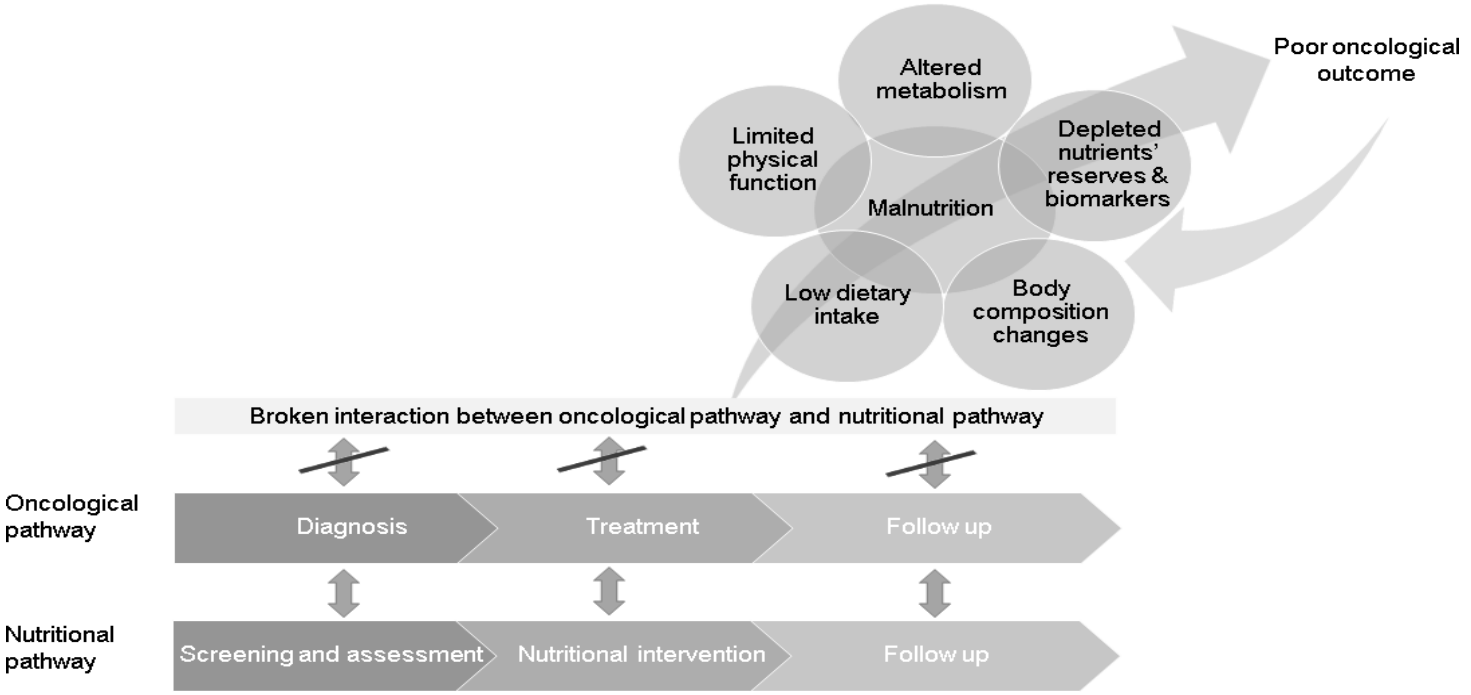



Figure 1.1 Parallel pathway of nutritional intervention during cancer trajectory and the vicious circle of malnutrition and poor oncological outcomes during cancer therapies in the absence of nutritional support

## Chapter 2: Research plan

### 2.1 Rationale

Malnutrition is a frequent complication in cancer patients that negatively affects the outcome of treatments. Consuming a balanced diet of adequate daily energy is difficult for cancer patients, especially during chemotherapy and/or radiotherapy because of the experience of frequent nutritional impact symptoms such as nausea, vomiting, dysphagia that interfere with food intake. Characterizing nutrients that may become limited during cancer treatment is important emerging research area with few trials performed in humans. Identifying these limited nutrients is of importance in various aspects including compromised immune function, higher risk of treatment induced-toxicities and decreased survival (Carr A et al., 2017, Meyer et al., 2008)

Muscle wasting is a consequence of malnutrition frequently observed in cancer patients particularly during cancer treatment (Baracos et al., 2010). Low skeletal muscle mass has been identified as an independent predictor of reduced survival, tolerance to chemotherapy and higher rates of toxicity in patients with different type of cancer (Anton et al., 2013; Martin et al., 2013). Therefore, a strong focus on nutritional interventions for the maintenance of muscle mass, particularly during chemotherapy treatment, would benefit people with cancer and ultimately improve patient outcomes (Paccagnella et al., 2011). Determining nutrients with a potential to influence muscle mass and applying them in nutritional intervention would be helpful to maintain skeletal muscle (Deutz et al., 2011).

The overall objective of this research is to enhance understanding of nutritional alterations that occur during cancer treatment and their relation with clinical outcomes of patients including muscle wasting and treatment induced toxicities in two unique cohorts of patients. The findings of our research were applied to design an intervention study to maintain muscle mass in cancer patients undergoing chemotherapy treatment.

## 2.2 Objectives and hypothesis

### 2.2.1 Changes in dietary intake during treatment for head and neck cancer (HNC)

Objectives:

i) To determine dietary macronutrient and micronutrient intake of head and neck cancer (HNC) patients in relation to body weight at key points in the disease trajectory (i.e. baseline, post-treatment, and follow-up)

ii) To evaluate the contribution of oral nutritional supplements (ONS) to total nutrient intake at each of study time points.

Hypothesis:

It was hypothesized that dietary macronutrient and micronutrient intake of HNC patients are low at diagnosis, decrease further during treatment and do not recover after treatment. Secondly, it was hypothesized that ONS consumption improves nutrient intake in HNC patients during cancer treatment and could prevent weight loss.

These objectives were investigated in chapter 3.

### 2.2.2 Correlation of dietary energy and protein intake with body composition alteration during treatment for HNC

Objectives:

i) To quantify the changes in skeletal muscle mass and adipose tissue as contributors to body weight over treatment in relation to energy and protein intake.

ii) To explore whether meeting current ESPEN guidelines for energy and protein protects against loss of skeletal muscle mass.

Hypothesis:

It was hypothesized that loss of muscle and adipose tissue is associated with energy and protein intake during treatment and would be greater in patients who do not meet ESPEN guideline for energy and protein intake.

These objectives were investigated in chapter 4.

### 2.2.3 The association of plasma vitamin status with skeletal muscle loss and mucositis in HNC patients undergoing cancer treatment

Objectives:

i) To determine the dietary intake and plasma levels of vitamin A, E, D, B12, folate during cancer treatment

ii) To investigate the relationship between vitamin status with body composition and mucositis among HNC patients undergoing cancer treatment.

Hypothesis:

It was hypothesized that plasma levels of vitamins will be lower after cancer treatment compared to baseline in patients with HNC and patients with poor vitamin status will experience a greater loss of muscle and increased severity of mucositis compared to those with normal levels.

These objectives were investigated in chapter 5.

### 2.2.4 The relationship between vitamin D status and changes in body composition and chemotherapy toxicity in lung cancer patients receiving platinum-based chemotherapy

Objectives:

i) To determine the association between plasma level of vitamin D and loss of skeletal muscle mass in lung cancer patients.

ii) To identify the association between plasma levels of vitamin D and treatment induced toxicities in lung cancer patients.

Hypothesis:

It was hypothesized that patients with insufficient levels of plasma vitamin D will experience a higher severity of toxicities and muscle loss.

These objectives were investigated in chapter 6.

### 2.2.5. Eating strategies for prevention of muscle loss during cancer treatment in lung cancer patients

Objectives:

To evaluate the changes in muscle mass that occur during treatment of lung cancer patients who habitually have low protein intake and switched to an optimized protein diet rich in dairy products. Our secondary objectives were to assess muscle strength and quality of life and inflammatory status.

Hypothesis:

It was hypothesized that a high protein diet rich in dairy products will support the maintenance of muscle mass, strength and inflammatory status, therefore improving outcomes for cancer patients undergoing chemotherapy treatment.

These objectives were investigated in chapter 7.

## Chapter 3. Changes in dietary intake during treatment for head and neck cancer (HNC) *

### 3.1 Introduction

Head and neck cancer (HNC) patients are at high risk for malnutrition, even long after completion of treatment. Several factors contribute to malnutrition in HNC patients including metabolic effects due to cancer and anti-cancer treatment, tumor location and nutrition impact symptoms (NIS) (De Luis O.; Aller, R 2007; Van Wayenburg CA van den Berg MG, Merkx MA, van Staveren WA, van Weel C, van Binsbergen JJ 2010). Radiation therapy, with or without chemotherapy, exacerbates NIS, further compromising dietary intake and increasing malnutrition risk (Brown et al. 2001). Malnutrition in HNC patients is associated with reduced quality of life, increased treatment toxicity and shorter survival.

Low dietary intake in HNC patients, particularly during treatment, may cause inadequate intake of certain micronutrients. Deficiency of micronutrients such as vitamins D, B12 and folate has been frequently reported among HNC cancer patients (Orell-Kotikangas et al. 2012). An optimal supply of micronutrients is important because of their role in immune defense, wound healing and energy metabolism. However, there is a paucity of knowledge regarding the micronutrient intake in this population. Moreover, little is known about the contribution of oral nutritional supplements (ONS) to overall micronutrient intake. ONS are commercially available, homogenous, generally nutritionally complete mixtures for oral consumption, and as such, are a fortified food product intended to supplement volitional food intake. The European Society for Parenteral and Enteral Nutrition (ESPEN) recommends ONS as well as counselling in cases where adequate intake of normal foods is difficult (Arends et al. 2017). For patients receiving radio-and/or chemotherapy this recommendation is aimed at preventing nutritional deterioration, but is not specific about the characteristics of ONS that are presumed to prevent deterioration of

* A version of this chapter has been published in the Nutrition and Cancer.

nutritional status. NIS caused by tumor and/or cancer treatment may alter food choices and dietary patterns of HNC patients especially during cancer treatment. In addition, cancer patients may change their dietary patterns during treatment and choose ONS to follow health care recommendations based on current guidelines (5). Knowledge of food preferences and dietary changes that occur at key time points of the treatment trajectory are essential to design interventions aimed at alleviating malnutrition among HNC patients. Compliance to nutritional care may be improved when food preferences of patients are taken into account (Moreira DCF Cerqueira IB, Oliveira APF, Morgano MA, Amaya-Farfan J, et al 2012; Feuz A 1994). Little is currently known about dietary patterns and patient selection of ONS for personal consumption during treatment.

The purpose of this study was to assess dietary intake of HNC patients at key points in the disease trajectory (i.e. baseline, post-treatment, and follow-up) with a focus on micronutrient intake from foods. We also aimed to evaluate the contribution of ONS to total micronutrient intake.

**3.2 Materials and methods**

This cohort study is an analysis of prospective data collected from two studies reporting on clinical determinants of weight loss (Kubrak et al. 2013) and taste and smell alterations among HNC patients (Álvarez-Camacho et al. 2016). Research procedures were approved by Health Research Ethics Board of Alberta Cancer Committee (HREBA-CC). Informed consent was obtained from all participants. Study inclusion criteria for newly diagnosed HNC patients were: 1) aged 18 years and above, 2) treatment involving radiation therapy with or without concurrent chemotherapy and/or surgery, and 3) maintaining oral intake during the study. Data were collected at baseline (at diagnosis and prior to starting treatment), post-treatment (after 4-6 weeks of radio- and/ or chemotherapy), and follow-up (approximately 8 to 10 weeks after completion of treatment). Only patients for whom there was a baseline measure were included in the study

(n=114) and remained in the study even if the three-day food record was missing for one of the other time points. The total number of patients at post-treatment was 79 and at follow up was 58.

Patients chose their own foods by personal preference; there was no intervention. ONS were selected by the patients according to personal preference and choice as part of a regular, orally consumed diet. At each time point, patients were categorized based on the proportion of calories from ONS. Patients were stratified by self-selected ONS consumption into either a low ONS group (<15% of total daily calories from ONS) or a high ONS group (≥15% of total daily calories from ONS) as per convention in the literature (Edington et al. 2004). Patients were treated according to standard protocols depending on disease stage, location, and general health.

### 3.2.1 Demographic and anthropometric data

Patient characteristics were obtained from medical records at the Cross Cancer Institute, Edmonton, Alberta, Canada. At each time point, body weight was measured with light clothes and without shoes using a calibrated digital platform scale, and recorded to the nearest 0.1 kg. Height was measured on a stadiometer and recorded to the nearest 0.1 cm at all three study time points. Body mass index (BMI; $kg/m^2$) was calculated at each time point. Weight loss during the study was calculated by determining the percent of weight loss at post-treatment and follow-up relative to baseline, and post-treatment to follow-up.

### 3.2.2 Dietary intake and nutrition impact symptoms

Trained research staff instructed patients on completion of the three-day dietary records collected at each of the three study time-points. The Canadian Nutrient File Database Analysis of the Food Processor II Nutrient Analysis Program™ (version 9: Esha Research, Salem, Oregon, USA) was used to analyze dietary records. Micronutrient intakes are presented as percent of Recommended Dietary Allowance (RDA), which covers nutrient requirements of nearly all (97%-98%) healthy individuals. Micronutrient intake was calculated from food items consumed. Only

dietary intake of alpha-tocopherol was calculated for vitamin E. The Head and Neck Patient Symptom Checklist© (HNSC©) (Kubrak, Olson, and Baracos 2013) was used to determine self-reported symptom interference with eating of 17 NIS (pain, anxiety, dry mouth, loss of appetite, constipation, feeling full, depression, thick saliva, diarrhea, sore mouth, lack of energy, nausea, difficulty chewing, altered smell, vomiting, difficulty swallowing and taste changes) on a five-point Likert scale ("1=not at all" to "5=a lot").

### 3.2.3 European Society of Parenteral and Enteral Nutrition recommendations

Recent ESPEN guidelines for cancer patients recommend that micronutrients be supplied in amounts equal to recommended daily allowance (RDA). ESPEN recommendations for energy intake are 25-30 kcal/kg BW/day, and 1-1.5 g/kg BW/day for protein. For this study, the minimum ESPEN recommendations were used as reference values for energy (25 kcal/kg/ day) and protein (1 g/kg BW/day) to understand whether patients are able to meet minimum recommended intake levels of macronutrients (5).

### 3.2.4 Definition of food categories

Food items were originally classified into 20 food categories as previously described by Hutton et al (Hutton et al. 2006) on the basis of similarities or differences in macronutrient content and their culinary role. The number of food categories were further combined to generate 14 food categories based on shared characteristics or roles in the diet (e.g. the grain group included rice, pasta, cereal, white bread and dark bread; Table 3.1).

### 3.2.5 Statistical analyses

Mean and standard deviation was reported for continuous data; frequency and proportions were reported for categorical data. Pearson's correlations were reported to relate food categories to calories, protein, ONS and micronutrient intakes. McNemars test with Bonferroni adjustment was used to compare the percentage of patients who met RDA for each micronutrient between study time points. Generalized Estimating Equation (GEE) method was used to analyze repeated

measures data. The GEE method accounts for within and between subject variability which arises due to repeated measurements on the same individual (Liang Zeger, S.L.. 1986), and was applied to determine differences in the change over time for calorie, macronutrient and micronutrient intake, percent of calories from different food categories, and NIS scores in total patients. A paired sample t-test was used to compare the percent of weight loss between post-treatment and follow-up. Differences between categorical variables of patients' characteristics in high and low ONS groups were determined by a chi square test. An independent sample t-test was used to compare differences in micronutrient intake and total NIS between the low and high ONS groups. All statistical analyses were performed using SPSS for WINDOWS software (version 20) and statistical significance was set at $P<0.05$ unless otherwise stated.

### 3.3 Results

#### 3.3.1 Patient characteristics

Baseline characteristics of the participants (n=114) are shown in Table 3.2. The majority were male (79%). Median age was 57 (24-84) years and mean BMI was 28.4±5.5 kg/$m^2$. The majority of patients had a locally advanced tumor in pharynx (54%) with classification stage of III and IV cancer (65%). Among all patients, 22% received radiotherapy only, 41% had chemo-radiotherapy (CRT), 21% underwent surgery + CRT and 16% received surgery + radiotherapy.

#### 3.3.2 Dietary intake and body weight in all patients

Body weight at baseline was 84.7 ± 18.7 kg. At the completion of treatment, patients had lost 8.4 ± 7.6% of baseline body weight and lost an additional 2.3 ± 5.1% of their body weight from the post-treatment time point until follow up. Patients had lower BMI at post-treatment and follow up compared to baseline (Figure 3.1). Energy and protein intake followed a similar pattern from baseline to post-treatment (Figure 1). Average daily energy (27.7 ± 9.4 kcal/kg BW/day) and protein intake (1.2 ± 0.6 g/kg BW/day) significantly decreased from baseline to post-treatment (21.8 ± 0.89 kcal/kg BW/day; $P<0.001$, 0.89 ± 0.5 g/kg BW/day; $P<0.001$, respectively). Energy

and protein intake were lower than ESPEN recommended levels for cancer patients at the post-treatment time point. At follow-up, energy and protein intake significantly recovered (30 ± 9.8 kcal/kg BW/day; P<0.001 and 1.4 ± 0.8 g/kg BW/day, P<0.001, respectively) to levels similar to baseline.

Micronutrient intake was compared to the RDA for each vitamin and mineral to determine the proportion of patients meeting recommended intakes (Figure 3.2). In general, a decline in micronutrient intake was observed at the post-treatment time point that was restored by the time of follow up. The majority of patients met the RDA levels for vitamins A, B2, B12, iron and zinc at all study time points. Inadequate intake of vitamins D, E, C, folate, calcium and magnesium was observed in the majority of patients over the study time points. In particular, about 90% of patients were not meeting the recommended levels for vitamin D at any time. At post-treatment, significantly more patients met the RDA level for vitamin E compared to baseline. The proportion of patients who met the RDA levels for vitamins A, B2, B6 and iron decreased from baseline to the post treatment time point.

### 3.3.3 Dietary changes

The average daily energy contributions from 14 defined food categories reveal that at baseline, the meat and grain food categories contributed the most to daily energy intake (19% and 17%, respectively; Figure 3.3). Percent of total daily calories from meat decreased by 74%, potato, oil and sugar each by 55%, grain by 50% and fruit by 38% at the post-treatment time point compared to baseline (P<0.002). Compared to baseline, consumption of foods from the milk and ONS categories increased 1.5-fold and 6-fold, respectively (P<0.006; Figure 3.1) at the post-treatment timepoint. Significantly fewer total daily calories were from the grain (12% *vs.* 17%, P<0.001), cheese (2.2% *vs.* 5.2%, P<0.001), and baked dessert (3.1% *vs.* 6.2%, P<0.001) food categories at follow up compared to baseline and significantly more energy came from the milk (14% *vs.* 7%, P<0.001) and ONS (17% *vs.* 7%, P=0.005) food categories.

Correlations were performed between specific food categories and calorie, protein and micronutrient intakes at each time point. At the post treatment time point, a negative correlation was observed between the percent of daily calories from Soup and total intake of calories (r= -0.29, P= 0.008), protein (r= -0.29, P= 0.009), vitamin B6 (r= -0.29, P= 0.01), vitamin B12 (r= -0.25, P=0.02), folate (r=-0.32, P=0.004), magnesium (r= -0.33, P=0.003) and zinc (r= -0.27, P=0.01). Conversely, positive correlations were observed between the percent of daily calories from the ONS food category and vitamin B1 (r= 0.32, P= 0.004), vitamin B6 (r= 0.34, P= 0.002), vitamin B12 (r=0.27, P=0.17), vitamin C (r=0.57, P<0.001), vitamin D (r=0.54, P<0.001), vitamin E (r=0.64, P<0.001), folate (r=0.53, P<0.001), and zinc (r=0.51 P<0.001). A positive correlation between ONS consumption and micronutrient intake was also observed at baseline and follow up.

### 3.3.4 Patients characteristics in the low and high ONS groups

The proportion of patients categorized into the high and low ONS groups changed over time. At baseline, 16% were categorized as high ONS, 63% at the post-treatment time point and 25% at follow up. There were no significant differences between sex and age between the two groups. (Table 3.3). Patients in the high ONS group had significantly lower BMI at baseline (P=0.02) and follow up (P=0.03) than patients in the low ONS group. There were more patients who underwent surgery + chemo-radiotherapy, had an advanced tumor stage and cancer of the pharynx in the high ONS groups at the post treatment and follow up time points (Table 3.3).

### 3.3.5 Dietary intake in low ONS and high ONS groups

When stratified according to low and high ONS consumption, energy intake was not significantly different between the two groups. Patients in the high ONS group experienced significantly greater weight loss at post-treatment (10.8 ± 6.4 *vs.* 4.1± 5.7; P<0.001) and follow up (14.8 ± 7.3 *vs.* 8.4 ± 8.2; P=0.01) relative to baseline. The high ONS group had significantly higher protein intake (P=0.02) at follow up (Table 3.4). Patients in high ONS group did not meet the

ESPEN recommendations for energy (20 ± 10 *vs.* 25 kcal/kg BW/day, P=0.002) nor protein (0.8 ± 0.4 vs. 1 g/kg BW/day, P=0.01) at the post treatment time point.

The specific micronutrients for which the majority of patients did not meet minimum recommended intakes in the low and high ONS groups was evaluated. At baseline and follow-up, the high ONS group had greater intakes of all assessed micronutrients compared to the low ONS group (Table 3.4). At post-treatment, the high ONS group consumed more vitamin D (P<0.001) and vitamin E (P<0.001), C (P=0.003) and folate (P=0.005) compared to the low ONS group (Table 3.4). Patients in the low ONS group failed to meet the RDAs of these micronutrients, meeting about 30% of the RDA for vitamins D and E at all three time points. Patients in the high ONS group exceeded 120% of the RDA for vitamin C at all time points. The RDA for vitamin E was exceeded at post-treatment and follow up, whereas and calcium exceeded the RDA at baseline and follow up (Table 3.4).

### 3.3.6 Nutrition impact symptoms

With the exception of anxiety, constipation and diarrhea, significant increases were observed in NIS interference scores for all symptoms (pain, dry mouth, loss of appetite, constipation, feeling full, depressed, thick saliva, sore mouth, lack of energy, nausea, difficulty chewing, smells bother me, vomiting, difficulty swallowing, taste changes) resulting in a higher total interference score at the post-treatment time point, compared to baseline, for all patients. At follow up, dry mouth (P<0.001), thick saliva (P=0.002), lack of energy (P=0.007), difficulty chewing (P=0.049), difficulty swallowing (P=0.002), and taste change (P<0.001) were higher than baseline. Overall, difficulty swallowing posed the greatest NIS interference (2.5±1.5 out of 5).

When patients were stratified according to ONS consumption, the high ONS group had greater total NIS interference scores at all three time points compared to the low ONS group (Table 3.3).

### 3.4 Discussion

This study provides information about the micronutrient intakes of patients with HNC at key time points in their treatment trajectory (baseline, post-treatment, and follow up) and reveals that it is difficult for cancer patients to meet recommended intakes for many of the micronutrients, unless they consume fortified foods. At the end of a course of treatment for head and neck cancer, calories, protein, vitamins A, B2, B6, B12 and iron are lower than at the time of diagnosis and at follow up. Furthermore, the majority of the patients did not meet the RDA for vitamins D, E, C, folate, calcium, and magnesium at any time point of the study. At the end of their treatment course and follow up, a greater percentage of energy was derived from food categories characterized as liquids, which may be related to a higher NIS burden experienced during and after treatment. Particularly remarkable was the proportion of patients selecting ONS as a major contributor to energy intake at post-treatment, with an average of 61% of calories coming from ONS in the diets of those patients. When patients were stratified according to ONS consumption, those with a higher consumption of ONS had a higher intake of micronutrients that exceeded RDA levels in a number of cases. Patients in the high ONS group lost more weight, despite having an equivalent energy intake to patients consuming more of their calories as food.

Low intakes of vitamin D, E, C, folate, calcium and magnesium even at diagnosis, were consistently observed in our study and revealed that HNC patients need fortified foods to meet the recommended levels for micronutrients. Intakes of the participants at baseline may represent the usual free-living Albertan with respect to food intakes and deficits in micronutrients as these nutrients are commonly described as nutrients of concern (Health Canada 2012). ESPEN recommends cancer patients consume micronutrients at the level of the RDA as part of a nutritionally adequate diet; however there exists a low level of evidence for this recommendation due to the lack of research directed at this topic (Arends et al. 2017).

The results of our study showed lower intake of calories, protein and several micronutrients at the time that treatment is completed compared to baseline. Food intake appears to be restored by eight weeks after treatment, yet patients did not achieve energy balance as evidenced by ongoing weight loss. Dietary intake and food choices may be affected by NIS in HNC patients (Feuz A 1994). Patients with head and neck cancer are known to follow specific food choice strategies to aid eating during and after therapy, such as changing food texture/consistency to soft or liquid (Wilson et al., 1991). NIS were highest at the post-treatment time point and a shift to liquid food categories (i.e. soup, milk and ONS) accompanied by lower intakes of foods with higher caloric density such as grain, meat and cheese was observed. The consumption of oral diets with modified texture among patients with difficulty swallowing has been associated with lower micronutrient intake (Moreno et al., 2006). Patients with advanced cancer who follow a dietary pattern consisting of milk and soup are at greater risk of malnutrition and weight loss (Hutton et al., 2006). Similarly, we observed that soup intake, which was significantly elevated post-treatment, was correlated with lower intakes of several nutrients.

ONS use among HNC patients, particularly during chemo- and/or radiotherapy, is recommended by ESPEN (Arends et al., 2017). However evidence is inconsistent whether ONS enable improvement of patient nutritional status in the absence of nutritional counselling (Langius et al. 2013). In our study, ONS provided about 60% of total calories in the high ONS *vs*. 3.5% in the low ONS group at the post-treatment time point. Those consuming a greater proportion of calories from ONS experienced the greatest amount of weight loss. After completion of treatment, energy and protein intakes were not different between high and low ONS groups, however, the high ONS group did not achieve energy and protein intake levels recommended by ESPEN (30 kcal/kg BW/day and 1.2 g/kg BW/day, respectively) for cancer patients. Patients in the high ONS group may have substituted ONS for foods with higher protein and energy content (i.e. meat category) as has been reported (20). Some studies have demonstrated a decrease in the consumption of usual foods when ONS are consumed (Wilson et al., 2002). As part of nutritional

support, patients should be encouraged to use ONS as a snack between meals and not as a food replacement at meal times. Moreover, significant differences in type of treatment, tumor site, stage of disease and NIS at post-treatment and follow up between the two groups may partly explain the higher weight loss in the high ONS group; as patients who are more nutritionally vulnerable because of advanced stage of disease or higher burden of NIS may be more likely to choose ONS.

The patients categorized in the low ONS group did not meet the RDA for any of the micronutrients while intake of most micronutrients met or exceeded the RDA by patients in the high ONS group at both the post-treatment and follow-up time points. Patients who consume food *vs.* ONS as their main nutrient source may be at elevated risk for not meeting micronutrient requirements. Standard ONS are fortified products and that are complete mixtures of macronutrients and micronutrients. Yet, low compliance, taste fatigue and high cost are common problems with ONS use in cancer patients (Barber et al., 1999; Matthew et al., 2001). Consumption of vitamin-mineral supplements as pills or tablets, a common strategy for providing micronutrients, may challenging for some cancer patients due to using multiple medications or difficulty swallowing. We were not able to accurately capture information on vitamin and mineral supplements which presents a limitation of our study; however, the objective was to evaluate the micronutrient intake from food as well as ONS.

Identification of foods desired by patients in accordance with their NIS experience during and after treatment is worthy of investigation. The longitudinal design of this study made it possible to assess dietary changes and NIS of HNC patients at critical points in the disease course. Given the low micronutrient intake and poor nutritional status of HNC cancer patients, particularly when their treatment ends, suggests strategies to improve micronutrient intake and prevent deficiency are needed. Fortifying foods desired by cancer patients who are deficient in micronutrients may be a better alternative to improve compliance and nutritional status than conventional ONS. Enhancing the energy and protein content of foods for hospitalized elderly and critically ill patients

is a recognized method to prevent malnutrition; however, less attention has been paid to the micronutrient content of foods. Lack of knowledge of micronutrient requirements in oncology patients has been identified as a gap and this research contributes to the body of evidence that it is difficult for cancer patients to achieve RDAs for micronutrients without consuming fortified foods. Future studies to compare foods fortified with deficient micronutrients against standard ONS, based on plasma levels of micronutrients, clinical outcomes and compliance of patients with cancer, are worthy of further evaluation.

### 3.5 Conclusion

Inadequate micronutrient intakes are common among HNC patients. While consuming more than 15% of calories from ONS improved micronutrient intake, greater weight loss occurred despite having similar total energy intakes as patients who consumed less than 15% of their intake from ONS. These findings address an important gap in the literature because understanding deficient nutrients and dietary changes of HNC patients through their disease trajectory is a critical first step in developing effective nutritional interventions.

## Tables

Table 3. 1 Definition of food categories

| Food Category | Examples of Food Items |
|---|---|
| Grain | Rice, pasta, cereal, white bread, dark bread |
| Meats | Beef roast, steak, beef stews, ground beef, mixed dishes with meat, chicken, turkey (all preparations), processed lunch meats, sausage, hot dogs, bacon, fish seafood |
| Meat alternatives | Beans, egg, nuts |
| Milk | Milk, yogurt, milk based beverage |
| Cheese | Cheese and cheese spread |
| Fruit | All fruit and juices |
| Vegetable | All vegetable and juices |
| Potato | All preparations of potato including baked, boiled, mashed, fried |
| Soups | Canned or fresh soups |
| Salty snacks | Chips, popcorn, cheese flavored snacks |
| Baked desserts | Doughnuts, cookies, cakes, pastries, pie |
| Ice cream | All ice creams and ice cream novelties |
| Oil and sugar | Butter, margarine, oils, sugar, soft drinks, hard candies |
| Oral nutritional supplements (ONS) | Ensure®, Boost®, Carnation Instant Breakfast®, other meal-replacement products that provide 1.0 to 2.4 kcal/mL |

Table 3. 2 Patient characteristics at baseline (n=114).

| Characteristic | Baseline |
|---|---|
| Sex, male, N (%) | 91 (79) |
| Age (years), median (min-max) | 57 (24-84) |
| BMI (kg/m$^2$), mean (SD) | 28.4 (5.5) |
| AJCC staging*, N (%) | |
| I and II | 28 (24) |
| III and IV | 86 (76) |
| Tumor site, N (%) | |
| Lip/oral cavity | 25 (22) |
| Pharynx | 61 (54) |
| Larynx | 22 (19) |
| Salivary gland | 6 (5) |
| Mode of treatment, N (%) | |
| Radiotherapy | 25 (22) |
| Chemoradiotherapy | 47 (41) |
| Surgery + chemoradiotherapy | 24 (21) |
| Surgery + Radiotherapy | 18 (16) |

* American Joint Committee on Cancer (AJCC) Staging 7th Edition 2010 (version 01.04.00)

Table 3. 3 Characteristics of patients in the high ONS and low ONS groups* at each study time point

| Characteristic | Baseline | | | Post-treatment | | | Follow up | | |
|---|---|---|---|---|---|---|---|---|---|
| | Low ONS N=96 | High ONS N=18 | *P-value* | Low ONS N=30 | High ONS N=52 | *P-value* | Low ONS N=44 | High ONS N=15 | *P-value* |
| Sex, male, N (%) | 75 (78) | 15 (83) | *0.61* | 23 (77) | 42 (81) | *0.65* | 30 (68) | 14 (93) | *0.06* |
| Age, mean (SD) | 58.3 ± 11.8 | 57.8 ± 11.4 | *0.87* | 59.5 ± 13.1 | 56.8 ± 11.2 | *0.32* | 57 ± 13.4 | 55 ± 9 | *0.52* |
| BMI (kg/m$^2$), mean (SD) | 28.9 ± 5.5 | 25.7 ± 5.1 | *0.02* | 26.4 ± 4.7 | 25 ± 4.7 | *0.2* | 25.5 ± 5.2 | 23.5 ±1.7 | *0.03* |
| AJCC staging** ,, N (%) | | | *0.61* | | | *0.03* | | | *0.06* |
| I and II | 24 (25) | 4 (22) | | 12 (40) | 7 (14) | | 17 (39) | 1 (7) | |
| III and IV | 72 (75) | 14 (78) | | 18 (60) | 45 (86) | | 27 (61) | 14 (93) | |
| Tumor site, N (%) | | | *0.65* | | | *0.005* | | | *0.03* |
| Lip/oral cavity | 20 (21) | 5 (28) | | 4 (13) | 12 (23) | | 8 (18) | 1 (7) | |
| Pharynx | 52 (54) | 9 (50) | | 12 (40) | 34 (65) | | 19 (43) | 13 (86) | |
| Larynx | 18 (19) | 4 (22) | | 10 (34) | 5 (10) | | 11 (25) | 1 (7) | |
| Salivary gland | 6 (6) | 0 | | 4 (13) | 1 (2) | | 6 (14) | 0 | |
| Mode of treatment, N (%) | | | *0.46* | | | *0.007* | | | *0.01* |
| Radiotherapy | 22 (23) | 3 (17) | | 12 (40) | 6 (11) | | 14 (32) | 1 (7) | |
| Chemoradiotherapy (CRT) | 41 (43) | 6 (33) | | 11 (36) | 24 (46) | | 14 (32) | 4 (27) | |
| Surgery + CRT | 20 (21) | 4 (22) | | 2 (7) | 15 (29) | | 8 (18) | 9 (60) | |
| Surgery + Radiotherapy | 13 (13) | 5 (28) | | 5 (17) | 7 (14) | | 8 (18) | 1 (6) | |
| total NIS interference scores | 19 (8) | 33 (19) | *0.003* | 33 (13) | 44 (11) | *0.005* | 26 (12) | 37 (10) | *0.005* |

P-value < 0.05 (Using chi-square test for categorical variables and Independent Samples *t* Test for numerical variables)

*At each time point, patients were categorized based on the proportion of calories from ONS. Low ONS group (<15% of total daily calories from ONS); high ONS group (≥15% of total daily calories from ONS)

**American Joint Committee on Cancer (AJCC) Staging 7th Edition 2010 (version 01.04.00)

Table 3. 4 Calorie, protein and micronutrient intake in the high ONS and low ONS groups* at each study time point

| Variable | Baseline | | | Post-treatment | | | Follow up | | |
|---|---|---|---|---|---|---|---|---|---|
| | Low ONS N=96 | High ONS N=18 | *P-value* | Low ONS N=29 | High ONS N=50 | *P-value* | Low ONS N=43 | High ONS N=15 | *P-value* |
| Calorie (kcal/kg BW/day) | 27 ± 9 | 29 ± 13 | *0.46* | 25 ± 17 | 20 ± 10 | *0.18* | 29 ± 9 | 33 ± 11 | *0.13* |
| Percent of calories from ONS | 1.3 ± 3.2 | 35.4 ± 25.7 | *<0.001* | 3.5 ± 5.1 | 60.9 ± 29.2 | *<0.001* | 3.7 ± 5.4 | 50.2 ± 23.8 | *<0.001* |
| Protein (g/ kg BW/day) | 1.2 ± 0.6 | 1.3 ± 0.6 | *0.68* | 1.0 ± 0.7 | 0.8 ±0.4 | *0.17* | 1.3 ± 0.5 | 1.8 ± 1.3 | *0.035* |
| Vitamin C (%RDA)** | 98 ± 81 | 159 ± 62 | *0.004* | 88 ± 98 | 187 ±158 | *0.001* | 95 ± 99 | 210 ± 128 | *0.001* |
| Vitamin D (%RDA) | 29 ± 25 | 63 ± 36 | *<0.001* | 30 ± 22 | 56 ± 30 | *<0.001* | 35 ± 27 | 82 ± 33 | *<0.001* |
| Vitamin E (%RDA) | 33 ± 43 | 94 ± 66 | *<0.001* | 30 ± 23 | 152 ± 145 | *<0.001* | 34 ± 42 | 192 ± 87 | *<0.001* |
| Folate (%RDA) | 70 ± 34 | 112 ± 49 | *<0.001* | 54 ± 30 | 81 ± 46 | *0.002* | 67 ± 34 | 104 ± 42 | *0.001* |
| Calcium (%RDA) | 85 ± 38 | 132 ± 63 | *<0.001* | 97 ± 57 | 95 ± 55 | *0.86* | 90 ± 52 | 142 ± 49 | *0.005* |
| Magnesium (%RDA) | 75 ± 31 | 101 ± 41 | *0.002* | 65 ± 40 | 78 ± 41 | *0.17* | 70 ± 28 | 107 ± 31 | *<0.001* |

P-value < 0.05 (calculated by Independent Samples *t* Test)

* At each time point, patients were categorized based on the proportion of calories from ONS. Low ONS group (<15% of total daily calories from ONS); high ONS group (≥15% of total daily calories from ONS).

** The proportion of the Canadian RDA (recommended daily allowance) that was met by patients on average.

## Figures

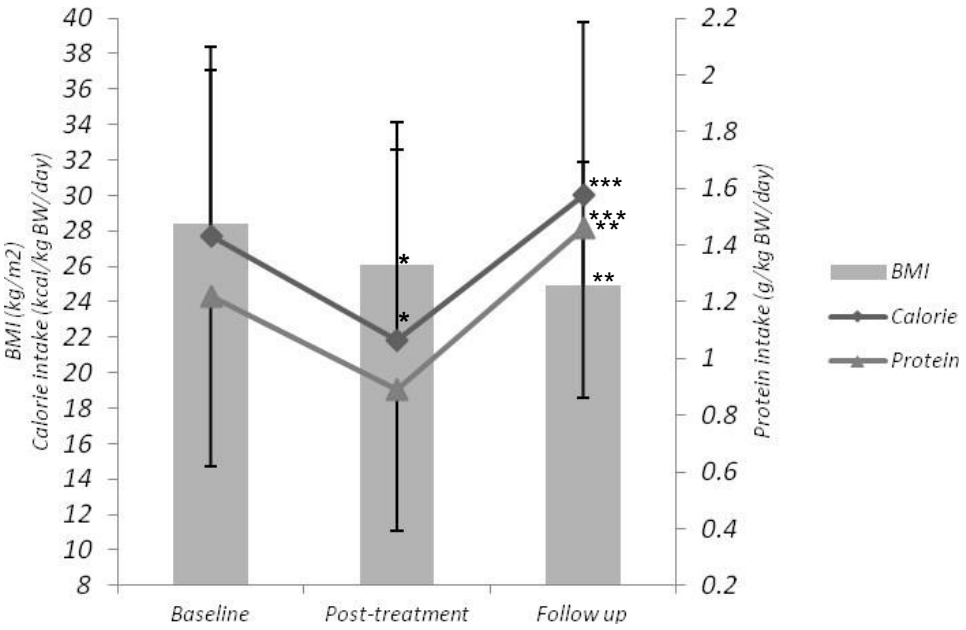



Figure 3. 1 Body mass index, energy and protein intake of patients at study time points

BMI: Body mass index; P-value < 0.05 (calculated by GEE); * baseline - post-treatment; ** baseline - follow up; *** post-treatment - follow up

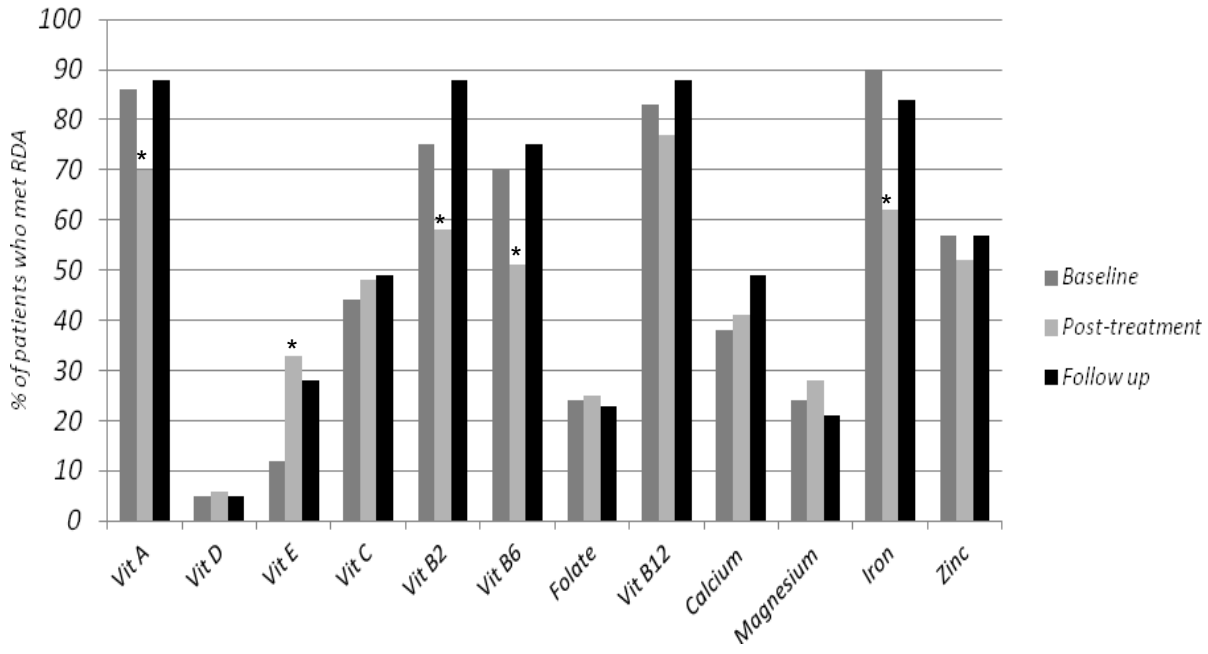



Figure 3. 2 Percent of patients meeting the Canadian Recommended Dietary Allowance (RDA) for micronutrients at three time points.

* P-value < 0.05 (calculated by McNemars test and controlled for multiple comparisons using Bonferroni adjustment)

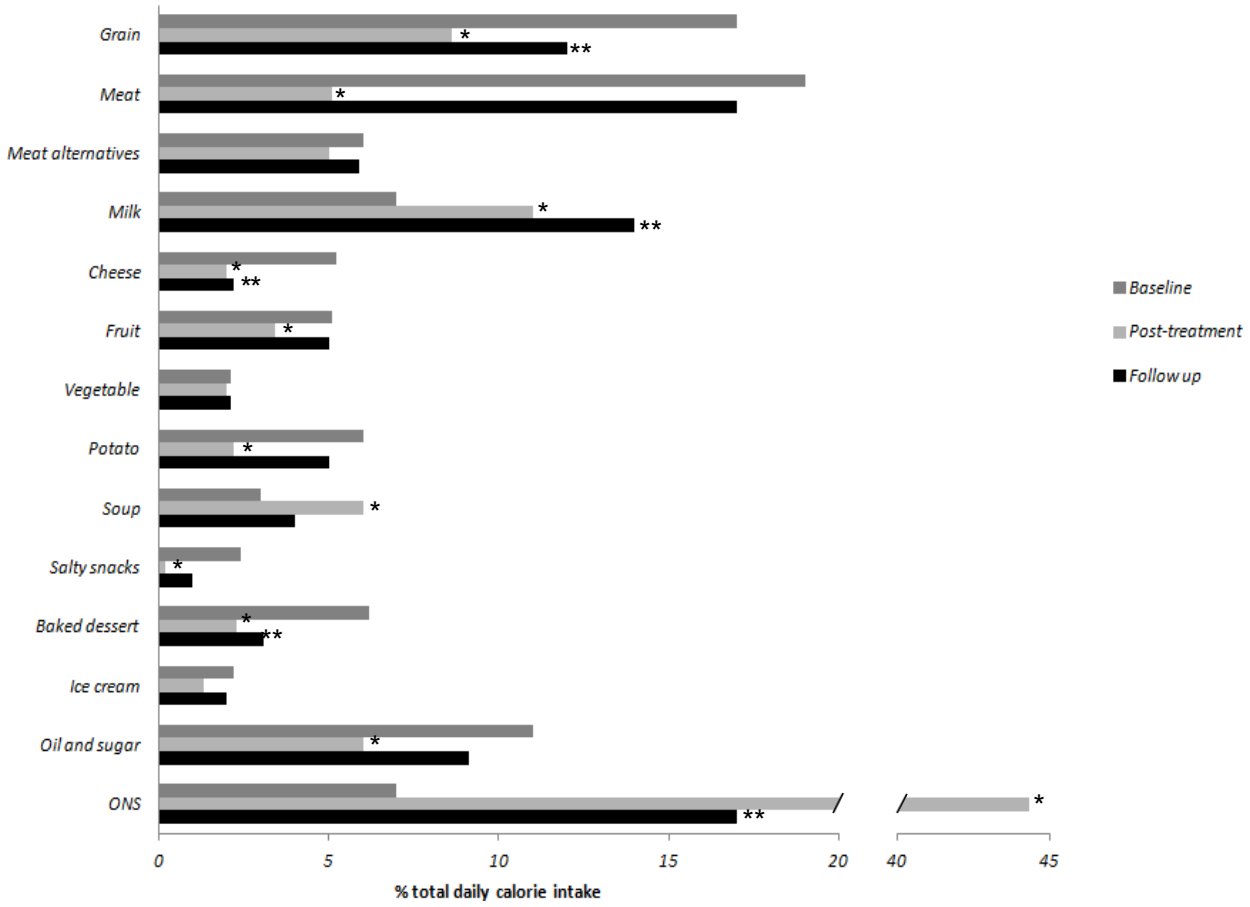



Figure 3. 3 Percentage of energy contribution from defined food categories at three time points.

*P-value < 0.05 (calculated by GEE); * baseline - post-treatment; ** baseline - follow up

# Chapter 4 Correlation of dietary energy and protein intake with body composition alteration during cancer treatment in HNC patients

## 4.1 Introduction

Head and Neck Cancer (HNC) patients experience a high degree of weight loss during treatment (Jager et al., 2010). Severe wasting in HNC is thought to be partly due to poor dietary intake (Kubrak et al., 2010). Many patients with HNC present with moderate-severe malnutrition at diagnosis, which is exacerbated during treatment (Baxi et al., 2016). Nutrition impact symptoms (NIS) arising from tumor location, radiation damage, and chemotoxicity are commonly experienced by HNC patients (Kubrak et al., 2013, Kubrak et al., 2010). Given many impediments in dietary intake, this cancer population illustrates how changes in dietary intake may drive alterations in body composition in cancer patients (Jager et al., 2010).

Cancer derived wasting has been linked to adverse clinical outcomes including poor prognosis, dose-limiting toxicities, impaired performance and immunity, and reduced quality of life (Kazemi et al., 2015, Baracos et al., 2013, Martin et al., 2013). Loss of both muscle and adipose tissue are experienced as a result of tumor-derived and/or systemic negative energy and nitrogen balance, hypoanabolism, and hypercatabolism (Sebast et al., 2013, Ebadi et al., 2014, Macdonald et al., 2003). Clinically, weight change is used to determine risk of malnutrition and prognosis, however lean mass is a better predictor of poor outcomes (Silver et al., 2007). Changes in body weight during treatment for HNC treatment has been previously documented (Giles et al., 2016), however, components of this weight loss remains uncharacterized in head and neck cancer patients. It has been established that conventional nutrition care is insufficient to combat cancer wasting, but anabolic potential does exist (Giles et al., 2016, Prado et al., 2013). Several studies have sought to determine the amount of energy that would be required to protect against weight loss

in HNC, but results have been inconclusive due to the heterogeneity of patients and treatment modalities (Jager et al., 2010, Zurlo et al., 1988, Bruning et al., 1988). The European Society for Parenteral and Enteral Nutrition (ESPEN) have established evidence-based guidelines for dietary intake for cancer patients, including guidelines for energy, protein, and micronutrient intake (Arends et al., 2017). ESPEN recommends energy intakes of 25-30 kcal/kg/d and protein intakes of 1.0-1.5 g/kg/d, however these guidelines are based on low and moderate evidence, respectively (Arends et al., 2017). Therefore, it remains largely unknown what intakes are adequate to ameliorate weight loss, and the effects on lean mass are even lesser known. Further evidence is needed to support these guidelines to optimize nutrition care and reduce malnutrition risk in the cancer population.

In this study, changes in muscle and adipose tissue over treatment specifically were identified using longitudinal computed tomography scans and associations with macronutrient intakes were explored. The secondary objective of this study was to explore whether meeting current ESPEN guidelines protects against loss of weight and skeletal muscle.

**4.2 Materials and Methods**

This cohort study is an analysis of prospective data collected from three studies reporting on clinical determinants of weight loss (Kubrak et al., 2013), taste and smell alterations among HNC patients (Alvarez et al, 2016) and micronutrient status over the course of treatment (data presented in chapter 5). Research procedures were approved by Health Research Ethics Board of Alberta Cancer Committee (HREBA-CC). Informed consent was obtained from all participants. Study inclusion criteria for newly diagnosed HNC patients were: 1) aged 18 years and above, 2) treatment involving radiation therapy with or without concurrent chemotherapy and/or surgery, and 3) maintaining oral intake during the study. Data were collected at diagnosis and prior to starting treatment (baseline) and after 6-8 weeks of radio- and/ or chemotherapy (post-treatment). Only patients with both dietary intake and body composition measures at baseline were included

in the study (n=42). Anthropometric data including weight and height was collected at baseline and follow-up. Tumor and treatment data were retrieved from patient file.

### 4.2.1 Dietary intake analysis

A trained researcher instructed patients on completion of the three-day dietary records collected at two study time-points. No intervention occurred; treatment and dietetic support was provided according to standard of care for all patients. The Canadian Nutrient File Database Analysis of the Food Processor II Nutrient Analysis Program™ (version 9: Esha Research, Salem, Oregon, USA) was used to analyze dietary records and calculate macronutrient and micronutrient intakes. Mean energy (kcal/kg/d), fat (g/kg/d), protein (g/kg/d) and carbohydrate (g/kg/d) intakes were expressed per kilogram of body weight.

### 4.2.2 European Society of Parenteral and Enteral Nutrition recommendations

Recent ESPEN guidelines for cancer patients recommend that micronutrients be supplied in amounts equal to the recommended daily allowance (RDA). ESPEN recommendations for energy intake are 25-30 kcal/kg BW/day, and 1.0-1.5 g/kg BW/day for protein (Arends et al., 2017). For this study, the minimum ESPEN recommendations were used as reference values for energy (25 kcal/kg/d) and protein (1.0 g/kg/d) to understand whether muscle loss during chemotherapy treatment could be influenced by meeting minimum recommended intake levels of macronutrients.

### 4.2.3 Body composition

Body composition was analyzed using computed tomography (CT) images taken for diagnostic purposes at baseline and after completion of the treatment. The 3rd lumbar vertebrae (L3) level was chosen as a standardized landmark because based on previous studies it is highly correlated to whole body muscle mass (Shen et al., 2004; Mourtzakis et al., 2008). CT images were assessed using Slice-O-Matic (Slice-O-Matic version 4.3, TomoVision, Montreal, QC, Canada) as previously described (Murphy et al., 2010). Cross-sectional areas of tissues ($cm^2$)

were calculated by using standard Hounsfield Unit (HU) thresholds of -29 to 150 HU for skeletal muscle (SM), - 150 to -50 HU for visceral adipose tissue (VAT) (Miller et al., 1998) and -190 to -30 HU for subcutaneous adipose tissue (SAT) (Mitsiopoulos et al., 1998). Mean tissue area was subsequently normalized by height to calculate indexes ($cm^2/m^2$) for skeletal muscle (SMI), total adipose tissue (TATI), visceral adipose tissue (VATI) and subcutaneous adipose tissue (SATI). Regression equations (Shen et al., 2004) was used to estimate whole body skeletal muscle in conventional units as follows: Whole body skeletal muscle mass = 0.166 * (total skeletal muscle at L3 ($cm^2$)) + 2.142; r2 = 0.855 (Shen et al., 2004).

Timing of CT scans was unique for each individual according to their evaluation and treatment schedule. To enable comparison between individuals, percent change in muscle and adipose tissue was divided by total days between the 2 CT images to calculate a daily rate of change. This value was multiplied by 100 to establish an index to express change in body components as a standard unit: %$\Delta$/100d.

**4.2.4 Statistical Analysis**

Results are stated as mean ± SD, unless otherwise stated. Changes in weight, body composition depot, and nutrient intake from baseline to after treatment were analyzed using a paired sample t test. Percentage changes in weight, SMI, TATI, SATI, and VATI were calculated. The Pearson correlation coefficient was used for the association between follow-up dietary intake and change in body composition depot. Multiple linear regression analysis was used to determine persistence of correlation significance when considering covariates. At the post-treatment time point, patients were stratified according to: (1) not meeting versus meeting or exceeding minimum ESPEN energy recommendations (25 kcal/kg/d); (2) not meeting versus meeting or exceeding minimum ESPEN energy recommendations (30 kcal/kg/d); (3) not meeting versus meeting or exceeding minimum ESPEN protein recommendations (1.0 kcal/kg/d); (4) not meeting versus meeting or exceeding minimum ESPEN protein recommendations (1.5 kcal/kg/d). Independent

t tests (2-tailed) were used to compare body composition depot change means between stratification groups. In all analysis statistical significance was set at $p < .05$. Statistical analyses were performed using SPSS (version 20, SPSS, Chicago, IL, 2016).

### 4.3 Results

#### 4.3.1 Patient Characteristics

Patient characteristics are summarized in Table 4.1. The majority of patients were men (n=32). Mean age was 58 ±11 years and mean BMI was 28.4 ± 5.1 kg/m$^2$. The pharynx (n=22; 52%) was the most common tumor site with most patients presenting with a tumor stage of three (n=28; 67%). The majority of patients received chemoradiotherapy with or without surgery. Eleven patients (26%) received radiotherapy without chemotherapy and thirty patients (71%) were treated with chemotherapy alone (Table 4.1).

#### 4.3.2 Changes in Body Composition and Dietary Intake

Body weight, SMI, TATI, SATI, and VATI significantly decreased during treatment ($p < .001$) (Table 4.2). Patients lost 8.1% of pretreatment body weight (6.9 ± 4.9 kg) during treatment on average. 11% of muscle lost during treatment which was estimated at -5.3 ± 2.2 kg using an approximate equation (Shen et al., 2004). is about and 28% of SMI and TATI, respectively. Muscle loss Loss of SATI and VATI were substantial and similar in magnitude to each other (-18.0cm²/m² and -18.1cm²/m², respectfully). IMAT nor muscle attenuation ($p = 0.069$) did not change over treatment.

Absolute amount of energy and protein intake decreased significantly over the course of treatment ($p=0.02$) however, after normalizing dietary intake for weight, no difference in energy or protein intake was observed between baseline and post-treatment. On average, ESPEN minimum energy and protein intake guidelines of 25 kcal/kg/d and 1.0 g/kg/d respectively, were achieved at baseline. At post treatment the minimum ESPEN energy intakes on average were not achieved, while 63% of participants failed to achieve intakes satisfying ESPEN energy

recommendations. Protein intakes ranged from between 0.3 g/kg/d to 2.2 g/kg/d and 52% of participants failed to achieve intakes satisfying ESPEN protein intake recommendations.

### 4.3.3 Correlations between Post-treatment Intakes and Skeletal Muscle

Energy intake normalized for weight was moderately positively correlated with percent SMI change per 100 days at end of treatment ($r = 0.62$; $p=0.004$) (Figure 4.1). Moreover, changes in energy intake was correlated with SMI changes during the study ($r=0.47$, $p= 0.04$) which remained significant after controlling for the covariates of age, sex, tumor stage, treatment modality, and protein intake (standardized coefficients Beta=0.65, $t=2.5$, $p=0.025$). In comparison, post-treatment protein intake demonstrated a weak positive correlation ($r=0.44$, $p=0.05$). The correlation between protein intake and SMI no longer approached significance when controlling against the covariates of age, sex, tumor stage, treatment modality, and energy intake. Changes in protein intake during treatment was not correlated with SMI changes ($r=0.21$; $p=0.38$).

### 4.3.4 Patient Skeletal Muscle Loss Based on Dietary Intake Stratifications

Patients were first categorized as meeting or not meeting the minimum recommendation for each of energy and protein by ESPEN (25 kcal/kg/day and 1 g/kg/day; respectively) on outcomes in body composition. Secondly, patients were stratified as meeting or exceeding the ESPEN recommended intakes. We explored whether the highest range of intakes was more effective at preventing muscle loss and to determine the proportion of patients who were losing or maintaining muscle at these levels of intakes.

No significant difference in percent muscle loss was observed when patients were categorized based on whether or not recommended intakes were being met [<25 kcal/kg/d versus ≥25 kcal/kg/d (Figure 4.2)]. However, when this stratification was increased to < and ≥30 kcal/kg/d, those patients with energy intakes <30 kcal/kg/d lost 7.7% SMI, while those with intakes >30 kcal/kg/d lost 1.0% SMI ($p<0.01$). The same analysis was performed for protein. Protein intake <1.0 g/kg/d showed an average loss of 8.3% SMI while intakes ≥1 g/kg/d showed an

average loss of 3.7% SMI which approached significance (p = .053). However, when the cut point of 1.5 g/kg/d was applied, there were no difference in percent SMI loss in those meeting or exceeding this cut point.

### 4.3.5 Patient Skeletal Muscle Loss Based on Baseline Adiposity

The amount of adipose tissue a patient had at the start of treatment was associated with change in SMI during treatment ($r = -0.75$; $p < .001$) (Figure 4.3). Even after controlling for confounding factors (age, sex, baseline SMI, stage of disease and type of treatment) this correlation remained significant ($r= -0.78$; $p<0.001$). When VATI and SATI were evaluated separately, SATI was strongly negatively correlated ($r = -0.741$; $p < 0.001$) whereas VATI showed a weak negative correlation, $r = -0.349$, which approached significance ($p=0.054$). When were considered, both VATI and SATI at baseline were significantly correlated with loss of SMI ($r=-0.57$, $p= 0.002$; $r=- 0.78$, $p<0.001$; respectively).

## 4.4 Discussion

This study further confirms that weight loss and muscle wasting occur at an unchecked rate in HNC patients undergoing treatment. An average weight loss of 8% bodyweight over 6-8 weeks well exceeds the ESPEN consensus criteria for diagnosis of malnutrition (Cederholm et al., 2015). By specifically quantifying muscle mass we demonstrate for the first time that muscle is lost at a considerable rate during treatment for HNC which is correlated with decreased energy intake. Loss of muscle persisted when the minimum recommended intakes for energy (25 kcal/kg/day) were met however were attenuated only when the highest range for energy intake was met or exceeded. There was a trend toward lower SMI loss in patients who were able to meet or exceed the minimum recommended intakes for protein (1 g/kg/day).

Skeletal muscle index decreased by 11% on average during treatment for HNC patients. Loss of this magnitude is not uncommon (Silver et al., 2014). ESPEN indicates that muscle protein depletion, with or without adipose tissue loss, is the principle aspect of cancer-associated

malnutrition (Arends et al., 2017). As the survival rate of HNC is increasing, loss of muscle of this magnitude (10 times faster than the normal aging process) is difficult to restore. Therefore, discovering ways to combat muscle protein depletion is paramount for survivorship.

The correlation between SMI loss and energy intake, while intuitive, was to our knowledge the first confirmation of such a relationship and suggests that energy balance plays a vital role in cancer muscle loss. Current consensus indicates that abundant protein intakes are required to overcome the anabolic resistance created by hypercatabolism and systemic inflammation experienced in the tumor-bearing state (Baracos et al., 2014, Bozzetti et al., 2013). In the present study, energy intake was found to have a stronger correlation with SM change than that of protein intake and a significant correlation between changes in dietary intake during treatment and SMI loss was observed only for energy intake not protein intake. This suggests that energy balance may have a greater implication for muscle protein depletion than nitrogen balance. Positive energy balance is mandatory for protein synthesis to occur whereas in negative energy balance, any additional protein will be used for energy rather than protein synthesis.

Current ESPEN guidelines indicate energy intakes and protein intakes between 25-30 kcal/kg/d and 1.0-1.5 g/kg/d, respectively. However, there is limited evidence supporting these recommendations. In our example where two different minimum cut points were applied to our data set, the results reveal that meeting the higher level of energy is more effective at preventing weight loss. First, those not meeting compared to those meeting or exceeding the minimum suggested energy intake of 25 kcal/kg/d were evaluated to reveal difference in SM loss which was reduced in both group. Intakes in excess of the ESPEN requirements were then investigated. A significant difference in SM loss was established when the high range of recommendation was applied. Patients consuming <30 kcal/kg/d group lost an average of 7.7% SM while those exceeding ≥30 kcal/kg/d group only lost an average of 1% SM ($p<0.01$). This suggests that intakes more than 30 kcal/kg/d may be required to achieve muscle stability in the HNC population. Similar to energy, protein intake was first explored by those failing to meet minimum ESPEN guidelines

of 1.0 g/kg/d compared to those meeting or exceeding the upper level of recommendations. Patients with intakes <1.0 g/kg/d protein lost an average of 8.3% SMI where patients with intakes ≥1.0 g/kg/d only lost an average of 3.7% SMI, a difference which approached significance ($p = 0.053$). When a similar stratification was made between 1.5 g/kg/day protein intake, no significant difference in SMI loss was observed. Only a small proportion of patients had protein intake higher than 1.5 g/kg/day, which could be a reason that we were unable to observe the effects of higher protein intake on SMI changes.

The obesity paradox, which remains controversial within the oncological population, suggests that although obesity is implicated in development of many chronic diseases, it may convey a survival effect in patients with some chronic diseases, including cancer (Gonzalez et al., 2014). Proponents of this theory would suggest that excess adiposity would convey a muscle-sparing effect in cancer patients (Gonzalez et al., 2014). High BMI has been linked to shorter survival in pancreatic and colorectal cancers (Kasenda et al., 2014, Vrieling et al., 2010), while also being linked to longer survival in gastrointestinal and lung cancers (Martin et al., 2013). Additionally, prognostic grading system, associates higher BMIs to better prognosis (Arends et al., 2017). In the present study, higher baseline adiposity correlated with greater loss of muscle even after controlling for confounding variables (baseline muscularity, sex, age, stage of disease and treatment). This finding is in line with previous studies (Koster et al., 2011; Dalal et al., 2012). Excess VAT may confer metabolic and endocrine abnormalities due to altered adipokine secretion resulting from macrophage infiltration (Ibrahim et al., 2010). When evaluating subcutaneous and visceral fat independently, subcutaneous appeared to more significant in muscle loss. However, in a mixed tumor group, SATI was associated with lower mortality risk (Ebadi et al., 2017). The effects of adiposity on skeletal muscle mass and its underlying mechanism remains to be fully elucidated.

Strengths of this study include the longitudinal design enabling assessment over total neoadjuvant treatment. Assessing body composition by CT imaging allowing discernments

between SM, TAT, SAT, and VAT and exploration of each depot individually. This study would have benefited from information pertaining to patient response to treatment, basal metabolic rate, tumor-based metabolic abnormalities, inflammation parameters, and levels of anabolic mediators.

Preservation of skeletal muscle mass remains a critical therapeutic challenge in the management of the cancer patients linked to clinical and functional outcomes (Tisdale et al., 2001; Fearon et al., 2003). These results suggest that meeting minimum energy recommendations (25 kcal/kg/day) may not be sufficient to attenuate loss of SM in HNC patients. It appears that the role and importance of positive energy balance in SM retention may have been previously overshadowed by proposed importance of nitrogen balance. Positive energy balance is required to effectively utilize protein for protein synthesis of muscle. Further research is required to elucidate energy and protein requirements in the oncology patients as the requirements for weight stability may differ between cancer types and treatment modalities. Cancer-associated malnutrition is a complex product of negative energy or protein balance, systemic inflammation syndrome, hypoanabolism, and tumor or inflammation derived hypercatabolism (Di Sebastiano et al., 2013, Ebadi et al., 2014, Macdonald et al., 2003, Arends et al., 2017). Therefore, a multifactorial approach is required to prevent malnutirition and muscle wasting during treatment. Findings of this study contribute to the evidence base for recommended energy and protein intakes for cancer patients.

Tables

Table 4. 1 Patient characteristics (n=42)

| Characteristics | Baseline |
|---|---|
| Age, y | |
| Mean ± SD | 58 ± 11 |
| Range | 41 – 84 |
| Sex | |
| Male n(%) | 32 (76) |
| BMI, (kg/m²) | |
| Mean ± SD | 28.4 ± 5.1 |
| Range | 19.1 – 43.6 |
| Tumor Stage n (%) | |
| T1 | 1 (2) |
| T2 | 5 (12) |
| T3 | 28 (67) |
| T4 | 7 (17) |
| Not Staged | 1 (2) |
| Tumor Site; n (%) | |
| Lip/oral cavity | 15 (36) |
| Pharynx | 22 (52) |
| Larynx | 2 (5) |
| Salivary gland | 2 (5) |
| Primary site unknown | 1 (2) |
| Mode of Treatment; n (%) | |
| RT | 6 (14) |
| Surgery RT | 5 (12) |
| Chemoradiotherapy | 25 (60) |
| Surgery chemoradiotherapy | 5 (12) |

BMI, body mass index; RT, radiotherapy.

Table 4. 2 Changes in weight, body composition, and dietary intake at baseline and post-treatment

| | Baseline | Post-Treatment | Mean Δ | *p*-value |
|---|---|---|---|---|
| Weight (kg) | 85.5 ± 16.4 | 78.5 ± 13.9 | -6.9 ± 4.9 | <0.001 |
| Skeletal Muscle Index (cm²/m²) | 52.2 ± 10.4 | 45.7 ± 8.6 | -5.9 ± 4.3 | <0.001 |
| Estimated skeletal muscle (kg) | 27.9 ± 6.1 | 24.8 ± 5.2 | 5.3 ± 2.2 | <0.001 |
| Total AT Index (cm²/m²) | 128.0 ± 56.3 | 92.2 ± 49.2 | -36.4 ± 38.4 | <0.001 |
| Subcutaneous AT Index (cm²/m²) | 67.1 ± 41.9 | 51.4 ± 32.9 | -18.0 ± 22.5 | <0.001 |
| Visceral AT Index (cm²/m²) | 57.7 ± 27.6 | 38.1 ± 23.5 | -18.1 ± 22.8 | <0.001 |
| Energy intake (g/day) | 2054 ± 720 | 1637 ± 599 | - 416 ± 933 | 0.029 |
| Energy Intake (kcal/kg/d) | 25.1 ± 7.9 | 22.2 ± 9.6 | - 2.8 ± 11 | NS |
| Proportion of patients with energy intake ≥25kcal/kg* | 47% | 37% | – | – |
| Proportion of patients with energy intake ≥30 kcal/kg** | 29% | 22% | – | – |
| Protein intake (g/day) | 91.7 ± 34 | 73.9 ± 33 | -17.8 ± 39.6 | 0.028 |
| Protein Intake (g/kg/d) | 1.1 ± 0.4 | 1.0 ± 0.5 | - 0.1 ± 0.4 | NS |
| Proportion of patients with protein intake ≥1.0 g/kg* | 63% | 48% | – | – |
| Proportion of patients with protein intake ≥1.5 g/kg** | 16% | 15% | – | – |

*Minimum ESPEN (European Society for Parenteral and Enteral Nutrition) intake guidelines: 25kcal/kg/d and 1.0g/kg/d protein. ** Optimal ESPEN intake guidelines: 30kcal/kg/d and 1.5g/kg/d protein. *AT, Adipose Tissue; IU, International Units.*

## Figures

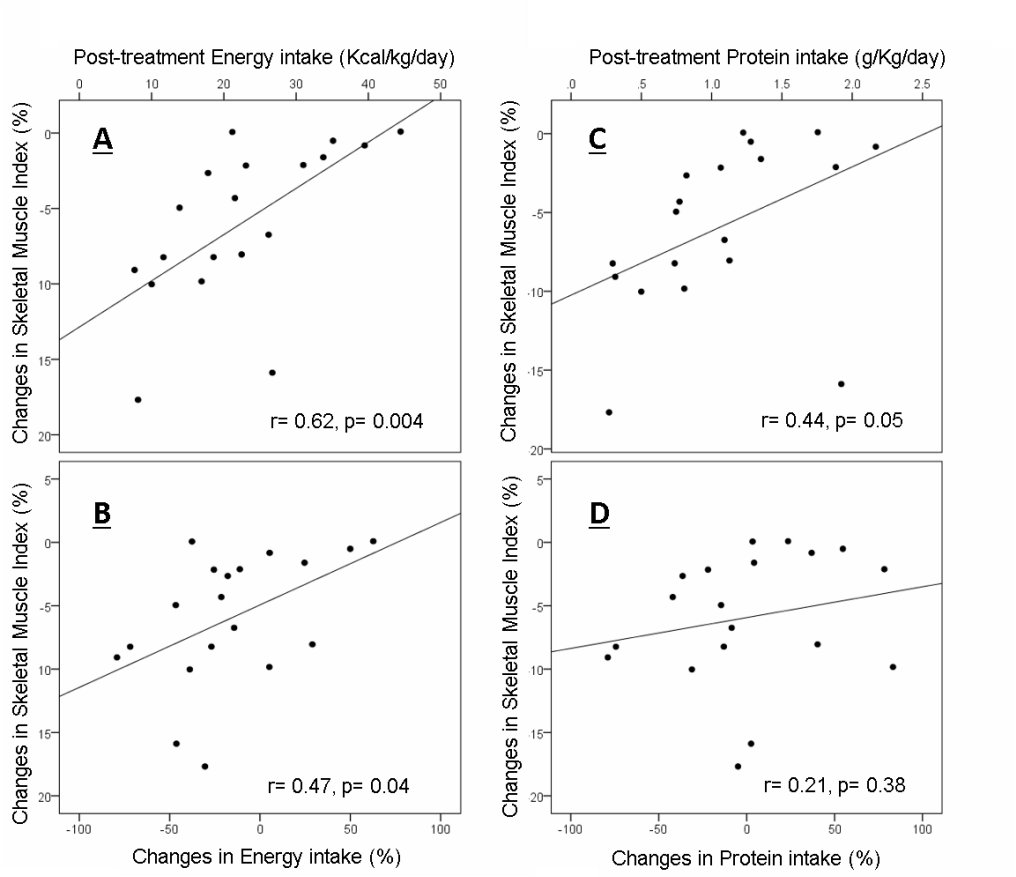



Figure 4. 1 Correlations of energy and protein intakes and changes in SM index

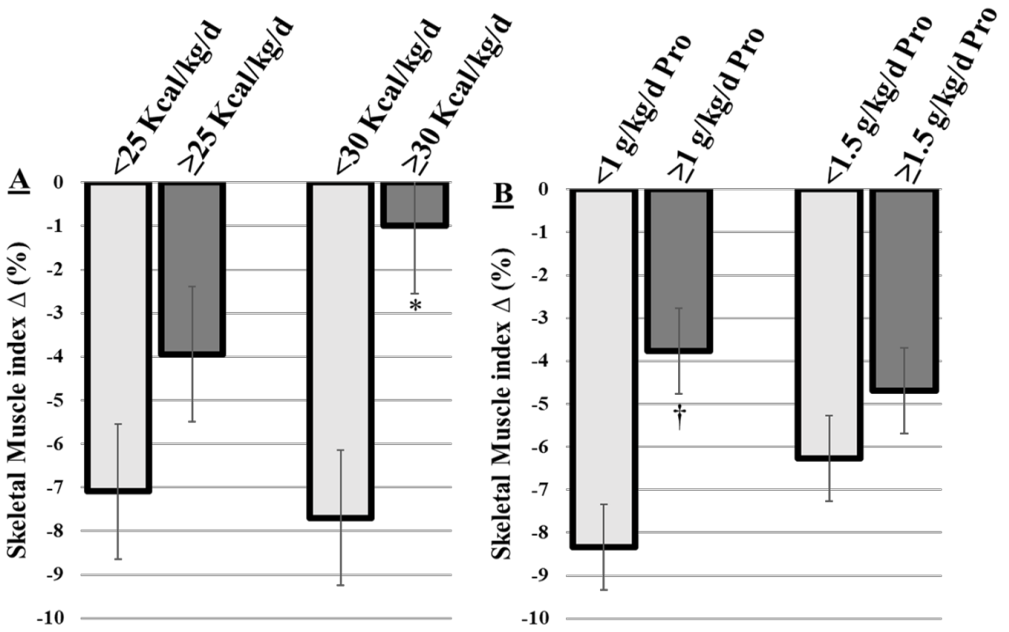



Figure 4.2 Percent changes in SMI based on post-treatment dietary intake stratifications

(A) percentage SMΔ/100d)/m² for 25kcal/kg/d and 30kcal/kg/d post-treatment energy intake stratifications; (B) percentage SMΔ/100d)/m² for 1 g/kg/d and 1.5 g/kg/d post-treatment protein intake stratifications. * p < .05; † p = .05-.06. Error bars denote standard error. Pro, protein.

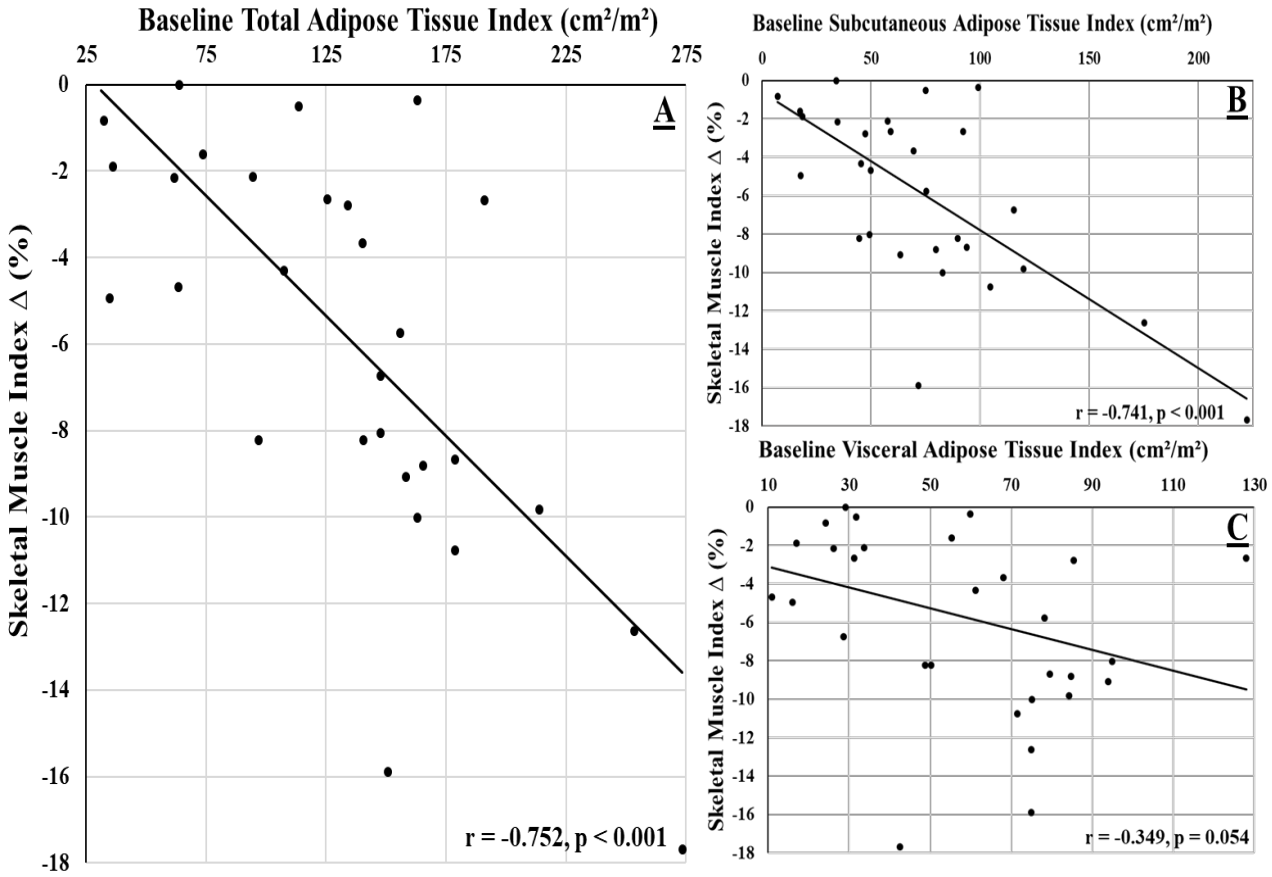



Figure 4. 3 Correlations between T1 adiposity index and percent SM index change per 100 days

(A) Correlation between T1 TATI (cm²/m²) and (%SMΔ/100d)/m²; (B) Correlation between T1 SATI (cm²/m²) and (%SMΔ/100d)/m²; (C) Correlation between T1 SATI (cm²/m²) and (%SMΔ/100d)/m². SAT, Subcutaneous Adipose Tissue; VAT, Visceral Adipose Tissue.

## Chapter 5 The association of plasma vitamin status with skeletal muscle loss and mucositis in HNC patients undergoing cancer treatment *

### 5.1 Introduction

The treatment of head and neck cancer (HNC) has evolved over the last several decades, with an increased emphasis placed on multimodality management. Despite advances in the management of HNC, treatment-induced toxicities that compromise dietary intake and nutritional status remain a common complication in HNC patients (Mason et al., 2016). Previous studies have suggested that at diagnosis, 42-77% of HNC cancer patients experience malnutrition which is exacerbated over the course of cancer treatment (Mulasi et al., 2016). This is clinically relevant, because poor nutritional status in cancer patients contributes to immune deficiency, increases treatment toxicities and diminishes the treatment response (Salas et al., 2008).

Weight loss during and after treatment is frequently noted among HNC patients. Traditionally, weight loss has been used to identify patients with cancer who are at risk for malnutrition (Jensen et al., 2012; Martin et al., 2015). However, in recently published study, muscle loss >5% was reported in 41% of patients with a weight loss<5%. Furthermore, new understanding of cancer related malnutrition aims to identify and measure metabolic derangements and muscle depletion. Low muscle mass prior to treatment and muscle loss that occurred during treatment is associated with poor outcomes including poorer response to treatment and decreased survival (Mulasi et al., 2016; Grossberg et al., 2016). Therefore, direct measures to quantify muscle loss and adipose tissue alterations are required; however only one study has precisely assessed body composition changes during treatment for head and neck cancer (Baxi et al., 2016).

Oral mucositis in HNC patients undergoing radiotherapy with or without chemotherapy represents one of the most debilitating toxicities that affects quality of life and results in a high rate of hospitalization and treatment interruptions. There is limited data regarding an association

* A version of this chapter has been published in the Nutrients.

between vitamin deficiencies and the development of mucositis (Fink et al., 2011). Poor vitamin status in people with cancer has several possible causes, including unbalanced dietary intake, altered metabolism, adverse effects of treatment and inflammation. Deficiencies in certain vitamins correlate with systemic inflammation assessed by C-reactive protein (CRP) in cancer patients (Melichar et al., 2010). Understanding the role of vitamin status in mucositis development and correcting vitamin deficiencies before starting cancer treatment may prevent mucositis while enabling patients to receive the most appropriate treatment for their cancer.

There is currently a low level of evidence regarding vitamin status in cancer patients and the European Society for Clinical Nutrition and Metabolism (ESPEN) recommends assessment of micronutrients in relation to oncological outcome as an understudied research area (Arends et al., 2017). While the number of vitamin deficiencies in the HNC cancer population may be numerous, the focus of this research was vitamins A, D, E, folate and B12 because we have previously reported low dietary intake of these vitamins (Chapter 3). It was hypothesized that patients with low intakes and plasma levels of vitamins would experience greater loss of muscle and be more likely to develop mucositis as toxicity events during treatment for head and neck cancer. The objective of the present study was to investigate how vitamin status prior to and after cancer treatment in patients with HNC relates to body composition, mucositis and systemic inflammation. Further we investigated whether baseline dietary intakes and plasma level of vitamins were related to the severity of mucositis and muscle loss.

## 5.2 Materials and Methods

### 5.2.1 Study population

This prospective cohort study was conducted at the Cross Cancer Institute, Edmonton, Canada. All subjects provided written informed consent prior to participation in the study. The study was conducted in accordance with the Declaration of Helsinki and the protocol was approved by the Health Research Ethics Board of Alberta- Cancer Committee (ethics number:

25852). Patients diagnosed with HNC that underwent radiation therapy, with or without chemotherapy, were invited to participate in the study. Eligibility criteria included pathologically confirmed squamous cell carcinoma of the oral cavity, pharynx, and larynx, with no history of a recurrent disease. Patients were excluded from the study if they were taking steroids or receiving palliative treatment. Patients who were unable to understand and speak English were excluded from the study. Thirty patients with HNC were enrolled in the study. Data were collected at diagnosis and prior to starting treatment (baseline) and at the completion of 4-6 weeks of radiotherapy with or without chemotherapy (post-treatment).

### 5.2.2 Dietary intake

A trained researcher instructed patients on completion of the three-day dietary records collected at both baseline and post-treatment. The Canadian Nutrient File Database Analysis of the Food Processor II Nutrient Analysis ProgramTM (version 9: Esha Research, Salem, Oregon, USA) was used to analyze dietary records and calculate the amount of calorie, protein and vitamin intake. Since vitamin intake at level of Canadian Recommended Dietary Allowance (RDA) is recommended by ESPEN for cancer patients, in this study vitamin intake was compared to the RDA for each vitamin to determine the degree to which the RDA that was met by patients on average. Participants were asked to complete a questionnaire about their micronutrient supplement intake.

### 5.2.3 Anthropometric and body composition measurement

At both time points, body weight was measured without shoes and with light clothes by using a calibrated digital scale and recorded to the nearest 0.1 kg. Height was measured on a stadiometer and recorded to the nearest 0.1 cm at both time points. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared at each time point (kg/m2). Body composition was assessed using computed tomography (CT) images taken for diagnostic purposes at baseline and after completion of the treatment (interval between 2 CT

scans ~ 6 months). Seventeen patients had CT images at both time points of study. The 3rd lumbar vertebrae (L3) level was chosen as a landmark because of its high correlation to whole body muscle mass (Shen et al., 2004; Mourtzakis et al., 2008). Images were analyzed using Slice-O-Matic software (V4.3; Tomo Vision) to determine the adipose tissue and skeletal muscle cross-sectional areas (cm2) and muscle attenuation at L3 as previously described (Murphy et al., 2010). Muscle and adipose areas were normalized for height in meters squared (m2) and reported as the skeletal muscle index, visceral adipose index and subcutaneous adipose index; (cm2 /m2). Whole body skeletal muscle and adipose tissue were calculated in conventional units using a regression formula: whole body skeletal muscle mass = 0.166 × [skeletal muscle > 5cm higher than L4 to L5 (cm2)] + 2.142; whole body adipose tissue mass = 0.068 × [adipose tissue > 5cm higher than L4 to L5 (cm2)] + 4.142 (Mourtzakis et al., 2008).

**5.2.4 Plasma vitamins and CRP measurement**

Blood samples were taken at baseline and post-treatment, plasma was separated by centrifugation and aliquots were stored at −80 °C. Plasma folate and plasma holotranscobalamin (holoTC; the metabolically active portion of vitamin B12) levels were assessed using the AXSYM analyzer as per manufacturer's instructions. For plasma folate level, we used a defined cutoff of <7 nmol/L for deficiency (Institute of medicine, 1998) and >46 nmol/L for above the normal range (Pfeiffer et al., 2007). The reference value used for normal holoTC was 35 to 140 pmol/L (Refsum et al., 2006). Quantification of plasma 25-hydroxy vitamin D (25-OHD) level was determined by liquid chromatography-tandem mass spectrometry (LC-MS/MS) (Adamec et al., 2011). The reference range for sufficient vitamin D status was determined as >75 nmol/L (Holick et al., 2012). All-trans retinol and α-tocopherol levels were analyzed by high-performance liquid chromatography (HPLC; Agilent 1200 HPLC system) following hexane extraction from plasma using established protocols (Kim et al., 2010; Redlich et al., 1996). Plasma levels of all-trans

retinol ≤0.70 μmol/L and α-tocopherol ≤12 μmol/L were used as deficiency cut off points (WHO, 1994).

CRP was determined using the CRPH enzyme-linked immunosorbent assay (Synchron LX system, Beckman Coulter). CRP assay functional sensitivity is estimated to be ≤ 0.18 mg/L which is defined by the lowest concentration that can be determined with CV=20%.

### 5.2.5 Mucositis

Information regarding mucositis of the upper aerodigestive tract caused by cancer treatment was collected from health records of patients. Mucositis was graded by a nurse using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE v3.0). These scales range from 1-5, which are defined as follows: grade 1 erythema of mucosa, grade 2 patchy ulcerations, grade 3 confluent ulcerations, grade 4 tissue necrosis, and grade 5 death. Patients with score of 1 or 0 were categorized as having no mucositis while patients with score 2 or higher were categorized as having mucositis. The most severe grade among several serial assessments was taken as final grade.

### 5.2.6 Statistical analyses

Mean ± standard deviation was reported for continuous data; frequency and proportions were reported for categorical data. A paired sample t-test was used to compare the dietary intake, plasma vitamin levels and body composition between baseline and post-treatment. Pearson's correlations were reported to assess the correlation of CRP level with skeletal muscle mass and plasma vitamin levels. Multiple linear regression analysis was performed to determine the correlation between skeletal muscle mass and possible independent variables. An independent sample t-test was used to compare differences in dietary intake and vitamin status between the mucositis and non-mucositis groups. Chi-square test used to compare mucositis prevalence in two cancer treatment arms (chemoradiotherapy vs radiotherapy alone or with surgery). All

statistical analyses were performed using SPSS software (version 20) and statistical significance was set at P<0.05 in 2-tailed tests.

## 5.3 Results

### 5.3.1 Participant characteristics

Baseline characteristics of the participants (n=28) are shown in Table 5.1. The majority of subjects were male (82%). Mean age was 60.3±10.8 years and mean BMI was 28.3±5.6 kg/m$^2$. The majority of patients had a locally advanced primary tumor in the pharynx (50%), and 82% had stage III or IV cancer.

### 5.3.2 Dietary intake and plasma level of vitamins

Analysis of dietary intake revealed no significant differences in energy and protein intakes from baseline to post-treatment (Table 5.2). However, both calorie and protein intakes were below the minimum range recommended by ESPEN at post-treatment. Patients failed to meet the RDAs for vitamins D, E, and folate at both time points of study. Dietary intakes of vitamin D increased from baseline to post-treatment (P=0.04), although this had little effect on measured plasma level which remained stable during the study. The majority of patients were vitamin D deficient (<50 nmol/L) or insufficient (50-75 nmol/L). Only 2 patients had a circulating 25-OHD level that would be considered sufficient (>75 nmol/L) at both time points. Although vitamin A intake was higher than recommendations at both baseline and post-treatment, mean plasma *all-trans* retinol concentrations decreased significantly from baseline to post-treatment (P=0.008) as the percent of patients with an insufficient level of retinol (<0.7 umol/L) increased from 4% at baseline to 46% at post-treatment. There were no significant changes in plasma concentrations of α-tocopherol nor folate during the cancer treatment. During the course of treatment, plasma level of active vitamin $B_{12}$ increased significantly (P=0.004).

### 5.3.3 Body composition and related factors

Body weight declined considerably over the course of treatment with an average percent weight loss of -7.1 ± 3.9 (ranging from 1.7 to -14.2). Approximately half of this loss was attributed specifically to muscle loss (3.4 kg) with an average loss of 12.6 ± 8.7 % of their muscle volume and the other half could be explained by 3.6 kg fat loss. Patients experienced a significant decrease in both visceral and subcutaneous adipose tissue. Muscle attenuation decreased significantly over the course of treatment (P=0.004). Patients with higher BMI at baseline lost more weight (r = -0.43, P= 0.02) and skeletal muscle mass (r = -0.53, P= 0.02) during treatment.

There was a trend toward greater muscle loss in patients with 25-OHD <50 nmol/L compared to patients with 25-OHD ≥ 50 nmol/L (-15.4% vs. -7.6%; P= 0.07). After controlling for age and sex, higher plasma 25-OHD was associated with greater muscle cross-sectional area at baseline and post-treatment (Table 5.4). This correlation remained significant after considering CRP, stage of disease and type of treatment in the regression model.

### 5.3.4 Plasma CRP levels

There was a significant increase in CRP over the course of treatment for all patients (6.7 ± 9.9 and 15.3 ± 16.7 mg/L; P= 0.01). Plasma *all-trans* retinol level was negatively correlated with CRP level (r=-0.57, P value=0.03) at the post-treatment time point. Patients with higher level of CRP had lower skeletal muscle mass at baseline and post-treatment (r= -0.5, P =0.01; r= -0.51, P =0.04, respectively).

### 5.3.5 Mucositis

The occurrence of moderate to severe mucositis (score 2 or higher) was observed in 52% patients at some point during the treatment. Patients with mucositis compared to those without mucositis had lower dietary intakes of vitamins D, E, folate, and $B_{12}$ at baseline (Table 5.5). Patients with mucositis had significantly lower plasma *all-trans* retinol and 25-OHD at baseline compared to patients without mucositis (Table 5.5).

Patients with mucositis compared to those without mucositis had higher BMI (30.3 ± 6.6 vs. 26.2 ± 3.6 kg/ $m^2$; P= 0.04) at baseline. Patients who received chemoradiotherapy had significantly higher prevalence of mucositis compared to patients who underwent radiotherapy alone or with surgery (P=0.001). Weight loss during the course of treatment was higher in those who developed mucositis compared to those without mucositis (9.0 ± 3.2 and 5.1 ± 3.7 %, P= 0.009, respectively) even though there were no significant differences in energy and protein intake between groups. Moreover, there was a trend toward higher skeletal muscle loss in patients with mucositis (-14.7 ± 8.2 vs. -7.5 ± 8.6 %, P= 0.07).

**5.4 Discussion**

This study reveals an association between vitamin status, muscle mass and mucositis in HNC patients undergoing treatment. Over the course of treatment, HNC patients lose a considerable amount of weight, which is explained by equal losses of muscle and fat. We also report a high prevalence of Vitamin D deficiency and insufficiency among HNC cancer patients. Patients who developed mucositis had poor micronutrient intake at baseline and lower plasma vitamin D and all-trans retinol level compared to patients without mucositis over the study time points. The decline in plasma concentration of all-trans retinol over the course of treatment related to elevated plasma CRP level.

Negative energy and protein balance are important factors that contribute to loss of body weight and lean mass in patients with cancer. The patients in this study lost 7.1 kg of weight and 3.4 kg skeletal muscle during cancer treatment. Low dietary intake due to treatment-related nutrition impact symptoms may have been one of the main contributing factors for muscle loss in HNC patients. Dietary intake of our patients was markedly lower than the ESPEN recommendations of 25 to 30 kcal/kg and 1 to 1.5-gram protein/kg body weight by the end of treatment. However, the actual intake of calorie and protein required to prevent muscle loss in HNC patients has not yet been determined. In a study by Jager-Wittenaar et al., 2011, protein

intake >1.7gram protein/kg body weight was suggested as the optimal protein intake to reduce weight and muscle loss in HNC patients during cancer treatment (Jager-Wittenaar et al., 2011). In addition to low dietary intake, inflammation could exacerbate muscle loss during cancer treatment. The negative correlation between CRP and muscle mass was observed in the current study at both baseline and post-treatment. Similarly, in a study of 471 cancer patients with solid tumors, those with CRP >10 mg/L had less muscle and lost more muscle during the disease trajectory (Wallengren et al.,2015). Understanding this association might provide a better illustration of the mechanism of muscle loss in HNC patients, therefore interventions that target inflammation may provide a benefit to attenuate muscle loss during treatment for HNC.

Our results suggest that HNC patients are not meeting recommended intakes for vitamin D, E, and folate at diagnosis, nor after completion of cancer treatment. Furthermore, we observed that habitual diets of poor vitamin intake may increase risk for toxicities during cancer treatment. There are few studies which have evaluated vitamin intakes in relation to the development of chemotherapy toxicities in cancer patients (Kennedy et al., 2004; Meyer et al., 2012). Our study suggests development of mucositis may relate to plasma levels of 25-OHD and all-trans retinol in patients with HNC. A prospective observational study in cancer patients reported that vitamin D deficiency was associated with a higher severity of treatment-related toxicities in patients receiving pelvic radiotherapy (Chorbanzadeh-Moghadam et al., 2015). However, in another study by Kitchen et al., 2015 in a mixed group of cancer patients, no relationship was observed between 25-OHD level and toxicities (Kitchen et al., 2012). This discrepancy may be the result of including a heterogeneous group of cancer patients undergoing different types of treatment and experiencing a variety of symptoms in the latter study. The involvement of vitamin D in development of mucositis could be explained by its crucial role in maintaining mucosal barrier homeostasis and modulation of immune responses.

This study is the first that we know of to prospectively evaluate the relationship between circulating 25-OHD concentrations and longitudinal changes in muscle mass in HNC cancer

patients. The current study revealed that plasma 25-OHD level was related to skeletal muscle mass even after considering confounding factors in the multiple regression model. Patients with 25-OHD levels < 50 nmol/l lost twice the amount of skeletal muscle during cancer treatment but this trend did not reach statistical significance. A larger sample size is required to determine this in future studies. Our results are in line with the findings from other studies in which poor vitamin D status was prospectively associated with greater appendicular skeletal muscle mass loss in older adults (Liu et al., 2014; Visser et al., 2003). The underlying mechanisms include both an indirect role of vitamin D through calcium and phosphate and a direct role via vitamin D receptor activation and regulation of the transcription of several genes involved in protein synthesis, differentiation and proliferation of muscle cells (Capiati et al., 2002).

Plasma levels of all-trans retinol decreased significantly over the course of treatment, which is in agreement with other studies reporting low circulating concentrations of retinol in patients with cancer (Melichar et al., 2010). Retinyl esters serve as a hepatic storage form of retinol to provide requirements over a long period of time. Intake of retinol by patients was higher than the recommended levels at baseline and post-treatment so the acute reduction in circulating retinol during cancer treatment is not likely due to low retinol intake in the diet. Decreased synthesis of proteins involved in retinol transport, retinol binding protein, and transthyretin, in response to the acute-phase reaction to inflammation could collectively contribute to this (Rosales et al., 1996). The results of our study are in accordance with other studies, where lower serum retinol was associated with plasma level of CRP in HNC patients (Melichar et al., 2010). The clinical relevance of this finding may reflect severity of acute phase reaction in HNC patients.

Our study has a number of strengths including a prospective study design, assessing vitamin status through both dietary intake and plasma level, using CT scan images to assess body composition as a gold standard method in homogenous group of patients. Limitations of this study included the small sample size and the lack of data regarding smoking and alcohol intake

of patients which may affect the circulating level of vitamins. Moreover, plasma levels of vitamins may not be the most reliable measure of certain vitamins status such as vitamin B12.

### 5.5 Conclusions

In conclusion, patients who have diets containing low vitamin content, low plasma levels of 25-OHD and/or all-trans retinol are more likely to experience mucositis during cancer treatment. Therefore, measurement of plasma levels of all-trans retinol and 25-OHD at baseline could be a possible biomarker of mucositis development in HNC patients, which needs further investigation. Our study confirms a correlation between plasma 25-OHD level with skeletal muscle mass as well as a tendency to lose more muscle in patients with lower 25-OHD concentration. Plasma all-trans retinol decreased significantly during cancer treatment which could be an indicator of the severity of inflammation during cancer treatment. Further research is needed to fully characterize the effects of vitamin status on treatment-induced toxicities in homogenous groups of patients with cancer.

**Tables**

Table 5. 1 Baseline characteristics of patients (n=28).

| Characteristics | Value |
|---|---|
| Sex, male, N (%) | 23 (82) |
| Age (years), mean (SD) | 60.3 (10.8) |
| BMI (kg/m$^2$), mean (SD) | 28.3 (5.6) |
| Tumor classification*, N (%) | |
| I | 1 (4) |
| II | 4 (14) |
| III | 19 (68) |
| IV | 4 (14) |
| Mode of treatment, N (%) | |
| Radiotherapy | 6 (22) |
| Chemo-radiotherapy | 20 (71) |
| Radiotherapy + Surgery | 2(7) |
| Tumor site, N (%) | |
| Lip/oral cavity | 11 (39) |
| Pharynx | 14 (50) |
| Larynx | 3 (11) |

* American Joint Committee on Cancer (AJCC) Staging 7th Edition 2010 (version 01.04.00)

Table 5. 2 Dietary intake and plasma level of vitamins at baseline and post-treatment

| | Baseline | Post-treatment | P-value |
|---|---|---|---|
| Calories, kcal/kg BW*/day | 23.1 ± 8.3 | 19.7 ± 9.8 | 0.17 |
| Protein, g/kg BW/day | 1.0 ± 0.4 | 0.8 ± 0.4 | 0.10 |
| ***Dietary intake of vitamins*** | | | |
| Vitamin A, (%RDA)** | 158 ± 32 | 124 ± 14 | 0.32 |
| Vitamin D, (%RDA) | 36 ± 5.6 | 53 ± 6.1 | 0.04 |
| Vitamin E, (%RDA) | 41 ± 7.0 | 74 ± 19.0 | 0.11 |
| Folate, (%RDA) | 72 ± 9.4 | 75 ± 10.0 | 0.80 |
| Vitamin B12, (%RDA) | 255 ± 50 | 234 ± 25 | 0.72 |
| ***Plasma level of vitamins*** | | | |
| *All-trans* retinol, μmol/l | 0.86 ± 0.2 | 0.69 ± 0.2 | 0.008 |
| 25-OHD, nmol/l | 55.1 ± 17.7 | 54.5 ± 18.9 | 0.78 |
| $\alpha$-tocopherol, μmol/l | 9.5 ± 2.8 | 9.9 ± 4.0 | 0.78 |
| Folate, nmol/l | 31.2 ± 14.0 | 27.8 ± 8.3 | 0.19 |
| HoloTC*** , pmol/l | 53.9 ± 14.0 | 74.7 ± 8.3 | 0.004 |

Data was presented as mean ± SD

* BW: body weight; ** the proportion of the Canadian RDA (Recommended Dietary Allowance) that was met by patients on average; *** HoloTC: Holotranscobalamin

Table 5. 3 Anthropometric variables of patients at baseline and post-treatment

| Variables | Baseline | Post-treatment | P-value |
|---|---|---|---|
| Body weight, kg | 87.2 ± 3.3 | 80.7 ± 2.8 | <0.001 |
| Muscle area ($cm^2$) | 159.2 ± 41.7 | 137.8 ± 34.7 | <0.001 |
| Skeletal Muscle index ($cm^2/m^2$) | 52.6 ± 11.1 | 45.5 ± 9.1 | <0.001 |
| Estimated whole body muscle (kg) | 28.5 ± 5.4 | 25 ± 6.3 | 0.002 |
| Muscle attenuation (HU)* | 31.6 ± 9.0 | 26.1 ± 6.9 | 0.004 |
| Visceral adipose tissue ($cm^2$) | 169.6 ± 74.9 | 131.9 ± 77.7 | 0.001 |
| Visceral adipose index ($cm^2/m^2$) | 57.3 ± 25.9 | 44.8 ± 27.5 | 0.001 |
| Subcutaneous adipose tissue ($cm^2$) | 226.8 ± 153 | 170.1 ± 112.1 | 0.01 |
| Subcutaneous adipose index($cm^2/m^2$) | 77.7 ± 54.8 | 58.6 ± 40.9 | 0.01 |
| Total adipose tissue ($cm^2$) | 408 ± 194.4 | 313.3 ± 165.9 | 0.002 |
| Estimated whole body fat mass (kg) | 28.3 ± 8.1 | 24.7 ± 6.9 | 0.002 |

Data was presented as mean ± SD
* HU: Hounsfield unit

Table 5. 4 Multiple regression analysis with skeletal muscle mass as the dependent variable and sex, age, 25-OHD as independent variables

| Time point | Variable | β | Standard error | P value |
|---|---|---|---|---|
| Baseline* | | | | |
| | Sex | 64.1 | 0.70 | <0.0001 |
| | Age | -1.4 | -0.39 | 0.01 |
| | 25-OHD (nmol/L) | 0.74 | 0.36 | 0.01 |
| Post-treatment** | | | | |
| | Sex | 57.8 | 0.78 | <0.0001 |
| | Age | -0.84 | -0.28 | 0.07 |
| | 25-OHD (nmol/L) | 0.63 | 0.37 | 0.02 |

*Baseline regression equation: $F(3,18)=14.76$, $P<0.0001$, with an $R^2$ of 0.711

**Post-treatment regression equation: $F(3,12)=14.28$, $P<0.0001$, with an $R^2$ of 0.781

Table 5. 5 Baseline dietary intake and plasma level of vitamins in patients based on mucositis status

| | No mucositis | Mucositis | P value |
|---|---|---|---|
| Calorie, kcal/kg BW*/day | 24.2 ± 5.6 | 21.7 ± 9.7 | 0.43 |
| Protein, g/kg BW/day | 1.05 ± 0.28 | 0.98 ± 0.46 | 0.63 |
| ***Dietary intake of vitamins*** | | | |
| Vitamin A, IU/day | 5403 ± 672 | 3635 ± 1056 | 0.16 |
| Vitamin D, IU/day | 339 ± 184 | 140 ± 89 | 0.002 |
| Vitamin E, mg/day | 10.7 ± 7.9 | 4.7 ± 2.8 | 0.013 |
| Folate, mcg/day | 368 ± 190 | 231 ± 147 | 0.04 |
| Vitamin B12, mcg/day | 6.3 ± 2.5 | 3.5 ± 2.2 | 0.01 |
| ***Plasma level of vitamins*** | | | |
| *All-trans* retinol, umol/l | 0.95 ± 0.15 | 0.77 ± 0.19 | 0.023 |
| 25-OHD, nmol/l | 62.3 ± 14.0 | 47.2 ± 17.9 | 0.025 |
| $\alpha$-tocopherol, umol/l | 9.5 ± 2.6 | 9.2 ± 2.9 | 0.78 |
| Folate, nmol/l | 34.5 ± 16.9 | 26.8 ± 8.3 | 0.16 |
| HoloTC** pmol/l | 52.5 ± 19.7 | 54 ± 28.9 | 0.87 |

Data was presented as mean ± SD

* BW: body weight; ** HoloTC: Holotranscobalamin

# Chapter 6. The relationship between plasma vitamin D levels and changes in body composition and toxicity in non-small cell lung cancer patients receiving platinum based chemotherapy

## 6.1 Introduction

Vitamin D is a fat-soluble steroid hormone. The critical roles of vitamin D on calcium homeostasis and bone health are well established. However, in recent years there has been considerable interest in potential roles of vitamin D on other functions such as immunity and muscle function (Girgis et al., 2013). The vitamin D receptor (VDR) is expressed in almost every tissue, enabling effects in variety of body systems (Bikle et al., 2014). Vitamin D deficiency has been reported in the majority of lung cancer patients (Hoffer. 2016) and may be particularly prevalent in patients receiving cancer treatment (Fakih et al., 2009). However, the clinical consequences of vitamin D deficiency in lung cancer patients are unknown.

Treatment by cytotoxic therapies improves overall survival in lung cancer patients but can induce severe toxic events. Chemotherapy-induced toxicities in advanced lung cancer patients have been associated with treatment interruptions and poor survival (Cherif et al., 2016). Therefore, a need to identify factors that might explain interpatient variation in developing toxicities. Limited evidence suggests that vitamin D deficiency in patients with advanced cancer could exacerbate toxicities induced by chemotherapy (Fink et al., 2011), since vitamin D has important functions in maintaining mucosal barrier homeostasis and modulation of immune responses (Xie et al., 2017; Kong et al., 2008).

In patients with cancer, weight loss occurs frequently during chemotherapy and is a poor prognostic factor (Murphy et al., 2010; Ross et al., 2004). Although weight loss is commonly used to assess nutritional status, a more specific assessment of body components may offer a better prognostic tool as weight loss contributed by loss of fat and/or skeletal muscle may have different effects on clinical outcome. There is an emerging body of evidence suggesting that muscle loss

during chemotherapy is an independent predictor of toxicities and survival (Blauwhoff-Buskermolen et al., 2016; Anandavadivelan et al., 2016; Prado et al., 2007; Prado et al., 2016). Low concentrations of plasma 25-hydroxy Vitamin D (25(OH)D) have been associated with muscle weakness, higher fat mass percentage and lower muscle mass among elderly and non-cancer subjects (Earthman et al., 2012; Seo et al., 2012). Furthermore, Inflammation is one of the underlying cause of muscle loss during treatment, however its correlation with vitamin D status is not known in this context.

Although muscle loss with or without fat loss are frequently found among cancer patients particularly during chemotherapy, no data exists on the association between vitamin D status and body composition changes that occur in these patients in relation to chemotherapy toxicities. The aim of this study was to evaluate vitamin D status in patients undergoing first line chemotherapy for non-small cell lung cancer (NSCLC) at diagnosis and after chemotherapy completion. Second, we evaluated whether plasma concentrations of vitamin D is related to body composition changes and toxicities during chemotherapy treatment.

**6.2 Methods**

This study is a secondary data analysis of data collected from previously published prospective studies which were designed to determine (i) relationship among muscle changes and plasma phospholipid fatty acid concentrations (Murphy 2010) and (ii) association between loss of heart muscle with functional and clinical outcomes in NSCLC patients (Kazemi-bajestani 2018, submitted). The study was carried out in 97 histologically proven stage II, III and IV NSCLC patients. All patients received platinum-based doublet therapy every 3 weeks for four to six cycles. Patients with missing information on 25(OH)D value and dose limiting toxicity (n = 27) were excluded, leaving a final sample of 70 patients. The study protocol was approved by Health Research Ethics Board of Alberta-Cancer Committee (reference number: HREBA.CC-18-0067).

Patients were evaluated at two time points, prior to first chemotherapy cycle and after 4 cycles of chemotherapy (3 months). Patients 18–80 y of age were included if they were eligible for platinum-based chemotherapy with/without radiotherapy and if their life expectancy was more than 3 months. Season of blood draw was categorized according to June through November and December through May.

### 6.2.1 Toxicity assessment

Toxicity data were collected from the medical records of patients. Toxicity was graded by a nurse according to the National Cancer Institute Common Toxicity Criteria, version 3.0. Dose limiting toxicity (DLT) was defined as a combination of any grade 3 or 4 toxicity, dose delays or dose reductions during treatment.

### 6.2.2 Body Composition

Computed tomography (CT) was used to assess body composition. Body composition assessment method was described in details in chapter 4 (section 4.2.3). The sex and age specific cutoff values was used to define sarcopenia (Kazemi-bajestani et al., 2016). The rate of muscle and adipose tissue change within a defined time interval was determined using two CT images from the same patient. Timing of CT scans was unique for each individual according to their evaluation and treatment schedule. To enable comparison between individuals, percent change in muscle and adipose tissue was divided by total days between the 2 CT images to calculate a daily rate of change. This value was multiplied by 100 to establish an index to express change in body components as a standard unit: %$\Delta$/100d. Follow-up CT scans after completion of chemotherapy were available in a subset of 64 patients which were used to perform a longitudinal analysis of body composition over time. The mean interval (± standard deviation [SD]) between CT scans was 100 (± 39) days.

### 6.2.3 Plasma 25-hydroxyvitamin D (25OHD) and C-reactive protein (CRP)

Plasma samples were collected at baseline and post-treatment time points and stored at –80°C. Plasma concentrations of C-reactive protein (CRP) was measured using the CRPH enzyme-linked immunosorbent assay (Synchron LX system; Beckman Coulter, Inc., Fullerton, CA, USA). Plasma 25(OH)D concentration was measured using liquid chromatography tandem mass spectrometry (LC-MS/MS). Levels of 25OHD were defined as (i) deficient (<50 nmol/L), (ii) insufficient (50–74.9 nmol/L), and (iii) sufficient (≥75 nmol/L) according to the Endocrine Society (Holick 2012).

### 6.2.4 Statistical analysis

Mean and standard deviation (SD) were reported for continuous data; frequency and proportions were reported for categorical data. For normally distributed continuous variables, an independent sample t-test was used to compare intergroup differences. Mann-Whitney U test or Kruskal-Wallis H test with a paired comparison method were conducted for intergroup comparison for non-normally distributed continuous data. Differences between categorical variables of patients' characteristics based on gender and vitamin D categories were determined by a chi-square test. Partial correlations were reported to relate % total adipose tissue index changes/100 days to plasma levels of 25OHD. All statistical analyses were performed using SPSS for WINDOWS software (version 24) and statistical significance was set at $P < 0.05$ unless otherwise stated.

## 6.3 Results

Characteristics of the patients enrolled in the study are summarized in Table 6.1. The mean age was 63.7 ± 8.2 years (range, 41-79 years). The majority of patients were female (n = 54, 59%) with stage IV tumor (n=60, 86%). As expected, men and women showed different characteristics in terms of body composition (Table 6.1). BMI, SM index, TAT index, VAT index

were significantly higher in men (p<0.001). Men had a significant higher IMAT index (p<0.001) that corresponded with a lower muscle attenuation (p= 0.004). Plasma vitamin D levels were similar between male and female. When patients were categorized based on vitamin D levels (25(OH)D <50 nmol/l vs. 25(OH)D ≥50 nmol/L), there were no significant differences in demographic and clinical characteristics between groups (Appendix 1).

### 6.3.1 Vitamin D status

The average 25(OH)D levels in the overall NSCLC population were 58.8 ± 31.8 nmol/L. Fifty three (76%) patients had 25(OH)D levels <75 nmol/l while nearly half of them (47%) had levels <50 nmol/L. No significant change of 25(OH)D was observed from baseline to after treatment completion (p=0.98). The season of blood draw did not affect 25(OH)D levels (p=0.10). There was a positive correlation between baseline CRP levels and decline in 25(OH)D during treatment (r= 0.37, p=0.02).

### 6.3.2 Changes in body composition from baseline to post-treatment

There was a significant loss of muscle mass (p<0.001) and fat mass (p=0.006) during the study period, with mean loss of 4.2 ± 7.9% and 3.8 ± 19.9%; respectively. A higher proportion of women were sarcopenic at baseline (70% vs 22%, p < 0.001). However, men lost significantly more muscle during treatment than women (-6.2 ± 6.9% vs -2.05 ± 8.3%, p=0.03).

### 6.3.3 Dose limiting toxicity

DLT was observed in 37% of patients. Patients who developed DLT had significantly greater TAT index (121.2 ± 73.1 vs 91.9 ± 53.3 $cm^2/m^2$; p= 0.04) and IMAT index (6.0 ± 3.8 vs 4.2 ± 2.8 $cm^2/m^2$; p= 0.03) at baseline compared with those who did not experienced DLT (Table 6.2). SMI, muscle attenuation and sarcopenic status was not different between groups at baseline.

Men with DLT had significantly higher BMI, TATI, SATI, VATI and IMAT at baseline compared to those who did not experience DLT. However, women with DLT had greater skeletal

muscle loss, adipose tissue loss and lower plasma 25(OH)D levels compared with women with no toxicity (Table 6. 2). On univariate logistic regression analysis, those with higher baseline IMAT levels were 25% more likely to develop DLT than those with lower levels. A trend toward significance was observed for TATI as an independent predictor for increasing the risk of DLT (p=0.05). However, in multivariate analysis, plasma CRP concentrations were associated with DLT (Table 6.3).

### 6.3.4 Plasma 25(OH) D levels and body composition

Skeletal muscle loss was not related to plasma 25(OH)D either when applied as a continuous variable or as category of adequacy (dichotomous). Loss of adipose tissue was significantly lower in the 25(OH)D > 50 nmol/L group (Figure 6.2). 25(OH)D was correlated with percent adipose tissue loss after controlling for sex, age, type of treatment, tumor stages, CRP, and season of blood draw (r=0.42, p=0.012) (Figure 6.3). In regression analysis, both plasma CRP and 25(OH)D levels were independent predictors of adipose tissue loss (p=0.01 and p=0.02; respectively).

## 6.4 Discussion

Given the role of vitamin D in influencing a wide variety of health outcomes, we aimed to characterize, for the first time, vitamin D status and its relationship with body composition changes and DLT in NSCLC patients. The majority of cancer patients presented with vitamin D deficiency and insufficiency. Patients who developed DLT had greater adiposity, including more fat with in muscle compared to those who did not experience toxicity. Body composition of male and females behave differently during cancer treatment in relation to DLT. Male patients experiencing DLT were more likely to be obese and all compartments of adipose tissue were higher at baseline. However, women developed DLT had greater loss of both adipose tissue and skeletal muscle mass during chemotherapy. In addition, women with DLT had lower 25(OH)D, determined at

diagnosis and before treatment initiation, compared with those who did not have toxicity. However, there was no difference in 25(OH)D among men with and without DLT. A negative correlation between 25(OH)D level and adipose tissue loss was observed even after controlling for confounding factors.

Plasma 25(OH)D levels in this lung cancer cohort was low; only about one quarter of our lung cancer population had levels above adequacy threshold of 75 nmol/L and severe vitamin D deficiency was seen in 17% of patients. These findings confirm previous reports that vitamin D deficiency is prevalent in patients being treated for advanced cancer (Vashi et al., 2010; Hoffer et al., 2016). Emerging evidence suggests that vitamin D has a critical role in the clinical outcomes and prognosis of cancer. In advanced cancer patients, there is a positive correlation between vitamin D status and the absence of fatigue and improved quality of life physical and functional well-being (Martínez-Alonso et al., 2016). Two studies with NSCLC patients reported that higher levels of circulating 25(OH)D was associated with improved survival (Ma et al., 2017; Zhu et al., 2007).

Our study revealed that obesity is correlated with higher risk of developing DLT in NSCLC patients. This is consistent with previous studies, which showed patients with higher fat mass more frequently had DLT (Gouerant et al., 2013; Wong et al., 2014). Carboplatin and cisplatin exhibit a hydrophilic pharmacokinetic profile in patients. The excess fat in patients with high adiposity is not available for the distribution of hydrophilic agents, so dosing of chemotherapy agents based on body surface (BSA) area leads to reduction in the volume of distribution, causing greater toxicities (Zuckerman et al., 2015; Prado et al., 2016). The same mechanism may be relevant for higher amount of intramuscular adipose tissue by limiting the distribution of chemotherapy agents into muscle and predisposing to greater toxicities.

Several studies related reduced muscle mass before and during treatment to the prevalence of DLT or severe toxicity (Barret et al., 2014; Prado et al., 2007), however three recent studies reported no relation between skeletal muscle mass and adverse effects in either study

(Awad et al., 2012; Yip et al., 2014; Blauwhoff-Buskermolen et al., 2016). Similarly, we did not observe this association. This discrepancy could be explained by either heterogeneity in chemotherapy drug pharmacokinetics or tumor type. There is no study specifically measuring the body composition in relation to DLT in NSCLC patients treated with platinum-based chemotherapy and the majority of available evidence regarding body composition and DLT is based on gastrointestinal or breast cancer with variety of treatment. The optimal parameter of body composition for dosing of platinum-based chemotherapy in NSCLC patients has yet to be determined and is an issue which warrants further evaluation in subsequent studies.

Data are lacking regarding sex differences in developing dose limiting toxicity in patients with cancer. We found different body composition phenotypes in men and women who experienced DLT toxicity during chemotherapy. This is aligned with a study in patients with stage II/III colon cancer who exhibited distinct gender effect in 5-Fluorouracil toxicity relating to differences in body composition in men and women (Prado et al., 2007). Sexual dimorphism is an emerging topic in cancer literature but much is still unknown in this regard.

Several studies have reported that low concentrations of serum 25(OH)D are associated with a higher body fat percentage in elderly (Vitezova et al., 2017). However, in our study we did not find a consistent association between plasma 25(OH)D and absolute amount of adipose tissue but we did find an association between 25(OH)D and loss of fat even after controlling for confounding factors. Studies suggest that vitamin D could be involved in adipogenesis in adipose tissue. However, the relation between vitamin D status and adipose tissue may be complicated by the presence of systemic inflammation observed in cancer patients. Inflammation may affect both vitamin D levels and influence changes in body composition. In our study, both loss of adipose tissue and plasma levels of 25(OH)D were correlated with plasma CRP concentrations, however the correlation between 25(OH)D and adipose tissue loss remained significant even after adjusting for CRP.

High prevalence of 25(OH)D deficiency in NSCLC patients and its correlation with DLT in female and adipose tissue alteration during chemotherapy is a novel finding suggesting that vitamin D status may be of significant importance in cancer outcome. Further intervention studies are necessary to evaluate the possible role of vitamin D in body composition alterations and DLT in cancer patients. Our findings demonstrated that adipose tissue, particularly intermuscular adipose tissue measured by CT analysis, was correlated with higher DLT whereas muscle volume were not. Our study supports the emerging role of body composition in chemotherapy dosing, and may in part explain the greater susceptibility of obese patients to DLT. In addition, we showed differences in body composition phenotype in men and women who developed DLT which needs further investigation.

## Tables

Table 6. 1 Patient characteristic for the overall population as well as stratified by gender (N=70)

| Variables | | Overall population (n =70) | Men (n=33) | Women (n=37) |
|---|---|---|---|---|
| Age, years | | 63.7 ± 8.2 | 65.5 ± 7.5 | 62.0 ± 8.5 |
| Stage of tumor, | II | 2 (3) | 1 | 1 |
| n (%) | III | 8 (11) | 3 | 5 |
| | IV | 60 (86) | 29 | 31 |
| Treatment | Carboplatin | 65 (93) | 31 | 34 |
| modalities | Cisplatin | 5 (7) | 2 | 3 |
| BMI, kg/m$^2$ | | 25.7 ± 5.1 | 28.2 ± 4.7 | 23.4 ± 4.5* |
| TATI, (cm$^2$/m$^2$) | | 102.9 ± 62.6 | 128.9 ± 80.5 | 80.5 ± 56.7* |
| SATI, (cm$^2$/m$^2$) | | 55.9 ± 32.5 | 56.3 ± 25.2 | 55.6 ± 38.0 |
| VATI, (cm$^2$/m$^2$) | | 42.06 ± 38.3 | 66.5 ± 39.2 | 20.9 ± 21.3* |
| IMATI, (cm$^2$/m$^2$) | | 4.9 ± 3.3 | 6.4 ± 3.7 | 3.6 ± 2.3* |
| Muscle attenuation (HU) | | 32.2 ±8.5 | 29.2 ± 7.1 | 34.9 ± 8.9* |
| SMI, (cm$^2$/m$^2$) | | 46.5 ± 10.1 | 54.4 ± 7.8 | 39.7 ± 6.2* |
| Sarcopenic, n (%) | | 33 (48) | 7 (22) | 26 (70)* |
| Sarcopenic obesity, n (%) | | 12 (17) | 6 (19) | 6 (16) |
| 25(OH)D, nmol/L | | 58.8 ± 31.8 | 55.4 ± 28.9 | 61.8 ± 34.4 |
| CRP, mg/L | | 23.5 ± 34.5 | 29.9 ± 38.5 | 17.7 ± 30.2 |

*P<0.05 comparison between male and female; CRP: C-reactive protein; TATI: total adipose tissue index; SATI: subcutaneous adipose tissue index; VATI: visceral adipose tissue index; IMATI: intramuscular adipose tissue index; SMI: skeletal muscle index; 25OHD: 25-hydroxyvitamin D

Table 6.2 Characteristics of patients in total population and according to the presence/absence of dose limiting toxicity

| Variables | | Overall population (n =70) | | Male(n=33) | | Female (n=37) | |
|---|---|---|---|---|---|---|---|
| | | No toxicity (n=44) | Dose limiting toxicity (n=26) | No toxicity (n= 21) | Dose limiting toxicity (n=12) | No toxicity (n=23) | Dose limiting toxicity (n=14) |
| Age, years | | 63.9 ± 8.0 | 63.3 ± 8.6 | 63.9 ± 6.9 | 68.4 ± 7.9 | 63.8 ± 9.1 | 59.0 ± 6.7 |
| Treatment | Carboplatin | 41 (59) | 24 (34) | 20 (61) | 11 (33) | 21 (57) | 13 (35) |
| regimen | Cisplatin | 3 (4) | 2 (3) | 1 (3) | 1 (3) | 2 (5) | 1 (3) |
| Stage of | II | 1 (1) | 1 (1) | 1 (3) | 0 | 0 | 1 (3) |
| tumor, n | III | 5 (7) | 3 (4) | 2 (6) | 1 (3) | 3 (8) | 2 (5) |
| (%) | IV | 38 (54) | 22 (31) | 18 (55) | 11 (33) | 20 (54) | 11 (30) |
| BMI ($kg/m^2$) | | 25.3 ± 4.3 | 26.4 ± 6.3 | 26.8 ± 3.8 | 30.6 ± 5.2* | 23.8 ± 4.3 | 22.8 ± 4.9 |
| TATI ($cm^2/m^2$) | | 91.9 ± 53.3 | 121.2 ± 73.1* | 103.4 ± 42.9 | 171.2 ± 61.4* | 81.8 ± 60 | 78.3 ± 53.0 |
| SATI ($cm^2/m^2$) | | 50.4 ± 29.6 | 65.1 ± 35.4 | 47.4 ± 18.0 | 71.9 ± 29.0* | 53.0 ± 37.2 | 60.0 ± 40.4 |
| VATI ($cm^2/m^2$) | | 36.9 ± 29.7 | 50.4 ± 48.8 | 51 ± 29.2 | 92.3 ± 41.2* | 24.7 ± 24.7 | 14.5 ± 12.1 |
| SMI (cm2/m2) | | 46.1 ± 10.3 | 47.2 ± 10.0 | 54.7 ± 6.9 | 53.9 ± 9.4 | 38.6 ± 5.9 | 41.6 ± 6.4 |
| IMATI ($cm^2/m^2$) | | 4.2 ± 2.8 | 6.0 ± 3.8* | 5.0 ± 3.2 | 9.0 ± 3.2* | 3.6 ± 2.4 | 3.7 ± 2.3 |
| Muscle attenuation (HU) | | 31.3 ± 9.0 | 33.7 ± 7.8 | 29.9 ± 7.9 | 28.0 ± 5.6 | 32.6 ± 9.9 | 38.6 ± 9.9* |
| Sarcopenic, n (%) | | 20 (46.5) | 13 (50) | 3 (15) | 4 (33) | 17 (74) | 9 (64) |
| Sarcopenic obesity, n (%) | | 8 (19) | 4 (15) | 3 (15) | 3 (25) | 5 (22) | 1 (7) |
| % SM loss/ 100 days | | -3.6 ± 6.8 | -5.4 ± 10.1 | -7.5 ± 5.4 | -4.0 ± 8.9 | -0.3 ± 6.2 | -7.6 ± 12.1* |
| % TAT loss/ 100 days | | -1.9 ± 22.3 | -8.3 ± 12.3 | -4.4 ± 22.9 | -5.1 ± 11.9 | 0.4 ±22.0 | -13.4 ±11.9* |
| 25(OH)D, nmol/L | | 63.1 ± 35.4 | 51.6 ± 23.5 | 56.0 ± 31.3 | 54.4 ± 25.4 | 69.6 ± 38.4 | 49.2 ± 22.4* |
| CRP, mg/L | | 18.9 ± 27.1 | 40.4 ± 52.5 | 24.1 ± 33.6 | 53.1 ± 53.2 | 14.0 ± 19.0 | 30.2 ± 55.6 |

*P<0.05 comparison between no toxicity and DLT group

BMI: body mass index; CRP: C-reactive protein; DLT: dose limiting toxicity; TATI: total adipose tissue index; SATI: subcutaneous adipose tissue index; VATI: visceral adipose tissue index; IMATI: intramuscular adipose tissue index; SMI: skeletal muscle index; 25OHD: 25-hydroxyvitamin D

Table 6. 3 Univariate and multivariate logistic regression analysis assessing the OR of dose limiting toxicity associated with clinical variables and body composition components in patients with NSCLC

| Variables | Univariate* | | | Multivariate* | | |
|---|---|---|---|---|---|---|
| | Exp (B) | 95% CI Lower-Upper | P value | Exp (B) | 95% CI Lower-Upper | P value |
| Baseline 25(OH)D, nmol/L | 0.99 | 0.97-1.00 | 0.16 | - | - | - |
| Baseline CRP, mg/L | 1.01 | 0.99-1.04 | 0.08 | 1.024 | 1.00-1.04 | 0.04 |
| Baseline SMI, ($cm^2/m^2$) | 1.01 | 0.94-1.09 | 0.63 | - | - | - |
| % $\Delta$muscle/100 days | 0.98 | .093-1.06 | 0.66 | - | - | - |
| Baseline muscle attenuation, HU | 1.03 | 0.96-1.1 | 0.33 | - | - | - |
| Baseline TATI, ($cm^2/m^2$) | 1.009 | 1.00-1.01 | 0.05 | 1.01 | 0.96-1.05 | 0.63 |
| Baseline SATI, ($cm^2/m^2$) | 1.01 | 0.99-1.03 | 0.08 | 0.99 | 0.92-1.07 | 0.89 |
| Baseline VATI, ($cm^2/m^2$) | 1.01 | 0.99-1.03 | 0.08 | 1.00 | 0.93-1.08 | 0.89 |
| Baseline IMATI, ($cm^2/m^2$) | 1.25 | 1.04-1.50 | 0.01 | 1.07 | 0.75-1.5 | 0.68 |
| % $\Delta$total adipose tissue/100 days | 0.98 | 0.95-1.01 | 0.32 | - | - | - |

*Adjusted for age, sex, treatment type, stage category
CRP: C-reactive protein; TATI: total adipose tissue index; SATI: subcutaneous adipose tissue index; VATI: visceral adipose tissue index; IMATI: intramuscular adipose tissue index; SMI: skeletal muscle index; 25OHD: 25-hydroxyvitamin D

**Figures**

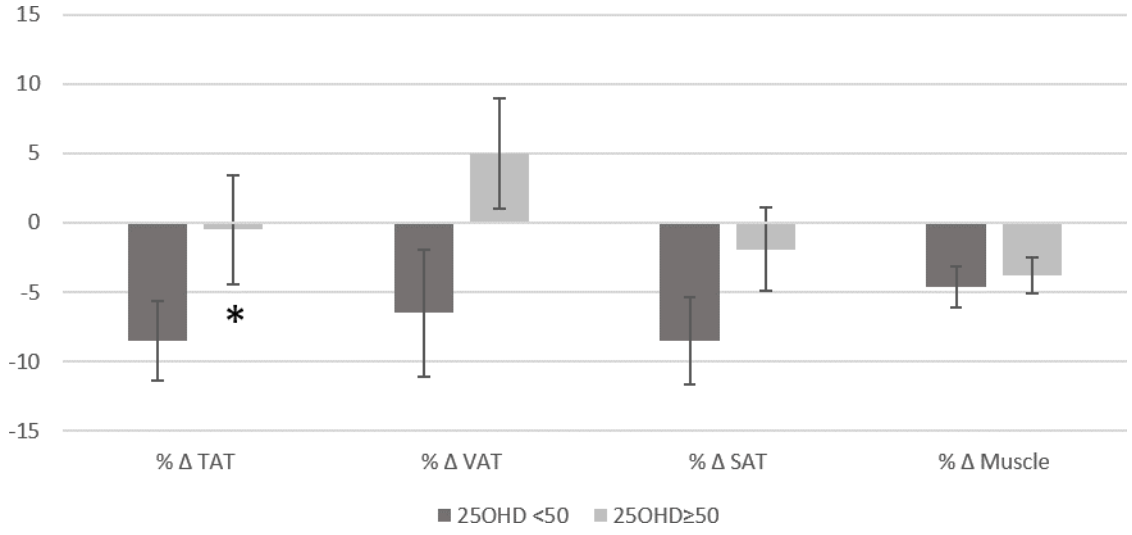



Figure 6.1 Body composition changes during chemotherapy in patients with NSCLC stratified by plasma vitamin D levels

TAT: total adipose tissue; VAT: visceral adipose tissue; SAT: Subcutaneous adipose tissue

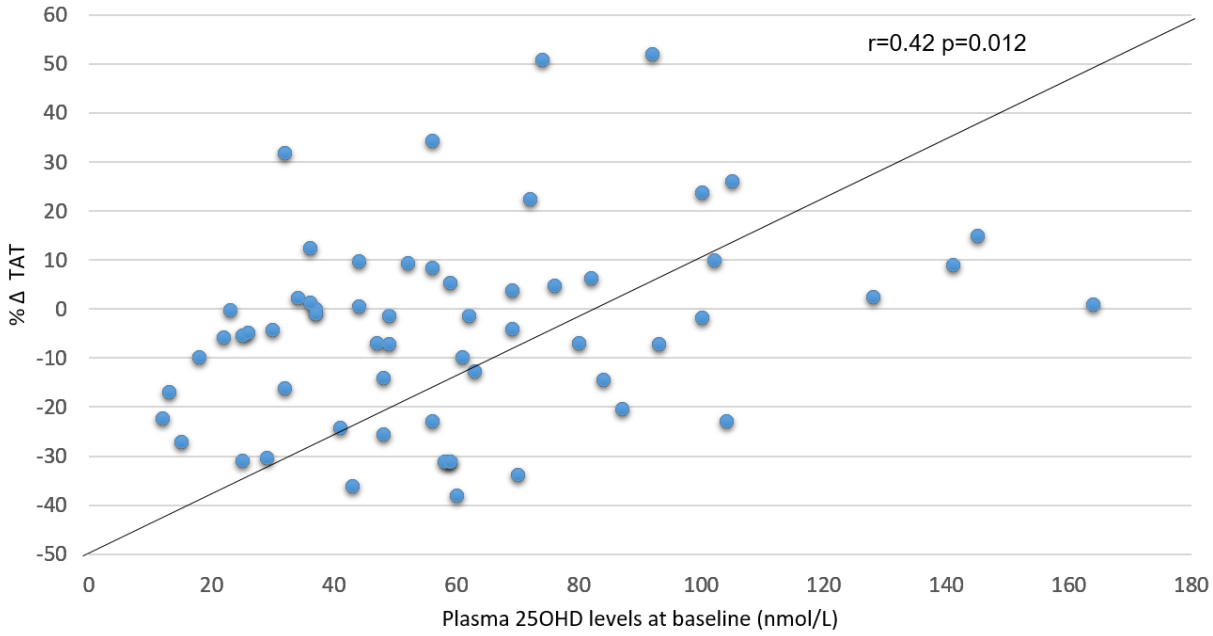



Figure 6.2 Partial correlation between plasma 25(OH)D levels and % ΔTAT (total adipose tissue changes/100 days) after controlling for age, sex, type of treatment, tumor stage, CRP and season of blood draw.

**Appendix 1**

Patient characteristics categorized based on vitamin D levels (25(OH)D <50 nmol/l vs. 25(OH)D ≥50 nmol/L)

| Variables | | 25OHD ≥50 nmol/L (n=37) | 25OHD <50 nmol/L (n=33) |
|---|---|---|---|
| Age, years | | 63.8 ± 8.6 | 63.4 ± 7.9 |
| Stage of tumor, n (%) | II | 0 | 2 |
| | III | 5 | 3 |
| | IV | 32 | 28 |
| Treatment modalities | Carboplatin | 36 | 29 |
| | Cisplatin | 1 | 4 |
| BMI, kg/m$^2$ | | 25.7 ± 5.2 | 25.7 ± 5.2 |
| TATI, (cm$^2$/m$^2$) | | 99.7 ± 64.1 | 107.9 ± 61.2 |
| SATI, (cm$^2$/m$^2$) | | 51.02 ± 29.2 | 61.4 ± 35.3 |
| VATI, (cm$^2$/m$^2$) | | 42.6 ± 40.7 | 41.4 ± 36.1 |
| IMATI, (cm$^2$/m$^2$) | | 4.6 ± 3.4 | 5.2 ± 3.2 |
| Muscle attenuation (HU) | | 33.2 ± 8.9 | 31.2 ± 8.1 |
| SMI, (cm$^2$/m$^2$) | | 47.3 ± 9.9 | 45.7 ± 10.4 |
| 25OHD, nmol/L | | 80.9 ± 27.7 | 34.0 ± 11.2 |
| CRP, mg/L | | 23.9 ± 33.4 | 23.0 ± 36.7 |

BMI: body mass index; CRP: C-reactive protein; TATI: total adipose tissue index; SATI: subcutaneous adipose tissue index; VATI: visceral adipose tissue index; IMATI: intramuscular adipose tissue index; SMI: skeletal muscle index; 25OHD: 25-hydroxyvitamin D

## Chapter 7. Dairy products to maintain muscle mass in people undergoing treatment for lung cancer: a pilot study

### 7.1 Introduction

Lung cancer is the most commonly diagnosed cancer worldwide and in Canada, and the leading cause of cancer-related death for both men and women (Canadian Cancer Statistics, 2017). Malnutrition affects between 45% and 65% of patients at time of diagnosis for lung cancer (Lemarie 2007, Read 2006). Furthermore, skeletal muscle wasting is frequently observed in this population despite having a normal or high body mass index (BMI) (Baracos et al., 2010; Murphy et al., 2012), and negatively affects the tolerance and tumor response to chemotherapy, performance status, quality of life (QOL) and survival (Bye et al., 2017; Harimoto et al., 2013; Lieffers et al., 2012; Prado et al., 2009; Prado et al., 2008). Therefore, a strong focus on nutritional interventions for the maintenance of muscle mass, particularly during chemotherapy treatment, would benefit people with cancer and would be expected to ultimately improve patient outcomes.

Although it remains to be fully elucidated as to whether increased protein breakdown or decreased synthesis primarily contribute to cancer-related muscle loss, it appears that stimulating muscle protein anabolism is crucial, which can be optimally achieved with nutritional interventions with high protein and essential amino acid content (Winter et al., 2012; Engelen et al., 2015; Deutz et al., 2011). Dairy products contain high-quality complete proteins (FAO Expert Consultation, 2013), which can stimulate increases in muscle protein synthesis in cancer patients to the same level as healthy controls (Engelen et al., 2015). A smaller volume of dairy foods compared with foods that contain lower quality proteins may stimulate muscle protein synthesis. This is of particular importance because cancer patients often experience reduced food intake during chemotherapy treatment. Our work has identified that dairy products are a preferred food choice for cancer patients undergoing treatment (Chapter 3). Collectively, it appears that increasing dairy

products may be an ideal intervention strategy for maintenance of muscle mass during chemotherapy treatment.

The current European Society for Clinical Nutrition and Metabolism (ESPEN) dietary protein recommendations for cancer patients (Arends et al., 2017) and protein intervention studies reveal that achieving an optimal total daily intake of high-quality proteins (1.0-1.5 g/kg body weight /day) along with achieving a threshold amount of protein (30 g) consumed at a single meal may be the ideal strategy to support the maintenance of muscle mass (Aleman-Mateo et al., 2014; Bouillanne et al., 2013). Collectively, given that dairy products are a preferred food choice during cancer treatment, the nutritional profile of dairy products can be exploited for availability of substrates used for muscle anabolism. The aim of present study was to evaluate the changes in skeletal muscle mass that occur during treatment of lung cancer patients who habitually have low protein intake (<1.2 g/kg body weight /day), and switched to an optimized protein diet rich in dairy products. Our secondary objectives were to assess muscle strength and quality of life (QOL) in this population.

## 7.2 Methods

### 7.2.1 Patients

This study was a clinical trial of an approximate 12-week intervention with a protein diet rich in dairy products in patients with a confirmed diagnosis of non-small cell lung cancer (NSCLC) scheduled for platinum-based chemotherapy and/or immunotherapy at the Cross Cancer Institute (Edmonton, AB). All patients had available CT images taken within 45 days before initiation of treatment. Patients were able to maintain oral intake during treatment and had Eastern Cooperative Oncology Group (ECOG) Performance Status ≤2. Exclusion criteria for this study were neuromuscular diseases, long-term consumption of drugs or supplements that modify muscle metabolism (e.g. corticosteroids, anti-androgens, omega-3 fatty acids), life expectancy <3 months, severe food restriction (e.g. food allergy, intolerance or dietary pattern), an inability to

comply with study instructions, patients engaged in a total of ≥50 minutes of moderate-to-vigorous cardiovascular exercise per week and/or structured resistance exercise occurring ≥2 times per week. All subjects signed a written informed consent form. The study was approved by the Health Research Ethics Board of Alberta-Cancer Committee (ethics number: HREBA CC-16-0851) and registered with ClinicalTrials.gov (NCT03010657).

### 7.2.2 Study design

This study was designed as an RCT. Patients with NSCLC scheduled for platinum-based chemotherapy from a single center from June 2017 to Aug 2018 from the population from which participants were accrued. However, significant delays were experienced, and recruitment targets within our specified time periods were challenging to meet. Subsequently, the design of the study was changed from a randomized controlled trial (RCT) to an open label clinical trial with accrual to the control arm proceeding subsequent to the intervention arm. Furthermore, the trial was extended to patients receiving immunotherapy as an increasing number of patients who were formerly eligible for cisplatin were routinely being treated with immunotherapy agents. Recruiting of control group is still on progress. Hence, in this chapter, the findings from the intervention group are presented. Patients presented in chapter 6 are similar to this cohort in tumor type, tumor stage as well as treatment (platinum-based chemotherapy), therefore, those patients serve as the reference group for comparison of changes in body composition analyzed by CT as well as CRP. As no data were available for the dietary intake of patients presented in chapter 6, published literature was used for the comparison of dietary data for dietary intake, QOL and physical function.

### 7.2.3 Study intervention

After entry into the study, baseline measurements were collected to assess habitual dietary intake of protein and physical activity level (Block 2014 Food and Activity Questionnaire), muscle mass (CT scan), physical function (the short physical performance battery test, SPPBT),

muscle strength (hand grip strength test), QOL (EORTC questionnaire), and systemic inflammation (plasma CRP) (Figure 7.1). After evaluation of the food frequency questionnaire, participants with a habitual protein intake <1.2 g/kg body weight/day were approached about participation in the study. Participants received individual dietary instruction on how to achieve at least 1.2 grams of high quality protein / kg of body weight / day (Arends et al., 2017), 50% from dairy products, and bolus protein intake (at least one meal per day consisting of a minimum of 30 g of high quality protein; ~14 g of essential amino acids) (appendix 1). In patients with a BMI of > 30 kg/m$^2$, protein requirements adjusted to a BMI of 27.5 kg/m$^2$ (Van der Werf et al., 2015). Participants began consuming their diets after all baseline measurements were collected and the dietary consultation has been performed. Diets were continued through chemotherapy treatment (at least 10 weeks), until endpoint measurements were performed (post-treatment). For all participants, endpoint measurements occurred, when possible, at the time of the participant's follow-up CT scan, which is approximately 21±5 days after the last day of chemotherapy. These CT scans were evaluated to determine changes in skeletal muscle mass compared with the baseline CT scan. Other information collected from the charts include routine clinical blood work, demographic and anthropometric information and clinical information (cancer stage, use of concomitant medications, comorbid condition burden).

At the end of the study, measurements were collected to assess changes in muscle mass (review of standard practice CT scans, along with height and weight), muscle strength (the short physical performance battery test and handgrip strength test), outcomes (EORTC QLQ questionnaire, and systemic inflammation (plasma CRP) (Figure 7.1).

### 7.2.4 Measurements and Assessments

#### 7.2.4.1 Food record assessments and compliance with nutritional interventions

Participants completed a food frequency questionnaire (FFQ) at the beginning of the study to determine their protein intake. The Block FFQ (2014 full length FFQ+ physical activity screener)

was used for this study which is a 127 items, plus additional questions to adjust for fat, protein, carbohydrate, sugar, and whole grain content. Additional adherence measures included weekly 24-hour food recalls conducted by phone by the study investigators.

Compliance with dietary intervention consisted of four main principles including: ability to achieve at least 1.2 grams of protein/ kg of body weight, ability to achieve 70% of recommended dairy serving, ability to achieve 70% of the recommended meat serving, and ability to consume at least one meal per day consisting of a minimum of 30 g of protein. The compliance of each patient was graded based on achieving these principles and scored from 0 to 4. Patients with a score of 0 to 2 were categorized as having poor adherence group while patients with a score of 3 and 4 were categorized as having good adherence. Completely adherent means that they were able to comply with all dietary components. Considering the degree of comorbid disease and poor overall health status of patients with NSCLC cancer, we proposed an adherence rate of 70% to be an acceptable goal (Temel et al., 2009).

#### 7.2.4.2 Quality of life questionnaire

Participants completed the European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire (EORTC-QLQ 30) which is a valid and reliable tool to assess QOL in the cancer setting and has a lung cancer disease-specific module to supplement each of the core measurements (EORTC-QLQ LC13) (Jacobsen et al., 2002). Six functional scales (physical, role, emotional, cognitive, social, global health status) and several questions relating to a range of physical symptoms were assessed by using this 30-item questionnaire (Aaronson et al, 1993). Patients marked to what extent each statement applied to them.

#### 7.2.4.3 Body Composition assessment

Body composition measures were conducted as reported in Chapter 4 (section 4.2.3).

#### 7.2.4.4 Physical performance and muscle strength

Currently, there is a gap in the literature regarding the best analytical instruments for measuring muscle strength in cancer patients. With that in mind, these tests were specifically chosen based on current best-evidence from systematic reviews of physical performance (Verweij et al., 2016) and muscle strength (Granger et al., 2013) instruments in cancer patients.

The short physical performance battery test (SPPBT) used to test physical performance. The SPPBT measures lower extremity function using tasks that mimic daily activities and were performed in the following sequence: a) standing balance tests, b) gait test, and c) chair stand test (Guralnik et al., 1994). The sum of the three tests comprised the final SPPB score, with a range from 0 to 12. A score of 12 indicated the highest level of lower extremity function. Handgrip strength used to test muscle strength and was measured to the nearest kilogram (kg) three times on each hand using a dynamometer. The highest value attained were considered the grip strength score (Roberts et al., 2011).

#### 7.2.4.5 Inflammatory status

Information regarding neutrophil and lymphocyte counts were extracted from the personal electronic medical records of patients as complete blood count is performed as part of the standard of care. Neutrophil/lymphocyte ratio (NLR) was calculated as the absolute neutrophil count divided by the absolute lymphocyte count. Also for the purpose of this study, venous blood samples were drawn from patients at the beginning and end of the study, arranged to coincide, wherever possible, with standard blood collection occurring as part of the standard of care to reduce patient burden. Serum C-reactive protein (CRP) was measured as an indicator of systemic inflammation using an enzyme-linked immunosorbent assay as per kit instructions (Sigma Aldrich, St. Louis, MO, USA). Plasma albumin levels were measured by the bromocresol green (BCG) assay (Abbott Laboratories, Abbott Park, IL 60064, USA) according to the manufacturer's

instruction. The CRP/Alb ratio was calculated by dividing the plasma CRP level by the plasma albumin level (Ranzani et al., 2013).

### 7.2.5 Statistics

Mean ± standard deviation was reported for continuous data; frequency and proportions were reported for categorical data. For normally distributed continuous variables, an independent sample t-test was used to compare the changes in all variables between baseline and post-treatment. Mann-Whitney U test or Kruskal-Wallis H test with a paired comparison method were conducted for intergroup comparison for non-normally distributed continuous data. An independent sample *t*-test was used to compare differences in body composition changes between the intervention group and reference group and also good adherence and poor adherence group. Pearson's correlations were reported to assess the correlation of NLR with skeletal muscle loss. All statistical analyses were performed using SPSS software (version 20 for Windows, IBM Corp., Armonk, NY, USA) and statistical significance was set at $p < 0.05$ in 2-tailed tests.

## 7.3 Results

This pilot study reports on the feasibility, acceptability, and effectiveness of an intervention with an optimal protein diet rich in dairy products for NSCLC patients. The median follow up was 85 days with a range of 61-137 days. We included 22 eligible patients with stage III and IV NSCLC, 10 men and 12 women, with a median age of 63 y (range 55–76 y). Three patients were excluded as they declined to receive chemotherapy after consent was obtained. Six patients had no follow-up because of early death (3 patients), treatment interruptions (2 patients) and withdrawal from the trial (1 patient) leaving 14 patients who completed study assessments (Figure 7.2).

### 7.3.1 Dietary intake and compliance

Energy intake was maintained over the study time points (p=0.29). Protein intake increased from baseline to post-treatment (from 0.9 ± 0.2 g/kg BW/day to 1.4 ± 0.3 g/kg BW/day,

p<0.001) (Table 7.2). Dairy intake increased significantly between baseline and post treatment time points (p<0.001; Figure 7.3). However, patients consumed fewer servings of meat at the post-treatment time point compared to baseline (p=<0.001). Compliance with the prescription of increasing total protein intake to ≥1.2 g/kg BW/day was excellent, as all patients except one met the prescribed levels for daily total protein intake. Seventy-one percent of patients were able to meet recommended intake for dairy, while fifty-seven percent of patients met recommended prescription for intake from the meat and alternates food group. Forty-three per cent of patients were able to consume at least one meal with 30-gram protein during a day (Figure7.4). Collectively, half of the patients (n=7) had good adherence (score 3 and 4) and twenty-nine per cent (n=4) had complete adherence (score 4). Two patients were unable to comply with any study instructions, and two other patients did not comply due to disease progression (n=1) and development of grade 4 toxicity (severe diarrhea; n=1) prior to collection of the end point of the study, those patients were not included in body composition analysis.

### 7.3.2 Body weight and body composition compartments

Changes from baseline to post-treatment: Patients maintained their body weight and SMI during treatment (p=0.33, p=0.19; respectively). There were no changes in TATI nor any of the depots between baseline to post-treatment, however SATI showed a trend toward being higher at the post treatment time point (p=0.07; Table 7.3).

Changes between intervention group and reference group: In the absence of an intervention, marked losses of weight, muscle and adipose tissues occur during treatment (p<0.009) (chapter 6, section 6-3, table 6.1). Changes in weight (-1.4 ± 3.9 % vs. -2.6 ± 6.1 %; p= 0.55), SM (-2.7 ± 8.8 % vs. -4.2 ±7.9 %; p=0.59) and VAT (3.0 ± 6.8 % vs. -0.3 ± 30.1 % p=0.73) were similar in these patients compared to the reference group. While patients in the current study showed an increase in TAT and SAT during treatment compared to the reference group (3.3 ±

6.5 % vs -3.8 ± 19.9 %; p=0.03 and 4.1 % ± 8.8 vs. -4.9 ± 18.5 %; p=0.008, respectively) (Figure 7.5).

Changes based on adherence: Patients with complete adherence (score 4; n=4) gained muscle whereas those with a score of 0-3 lost muscle (3.4 ± 7.8%/100 days vs. -10.3 ± 8.9%/100 days; p=0.025; Figure 7.6). Patients categorized as having good adherence (score 3-4) maintained their weight and muscle while the patients with poor adherence (score 0-2) lost weight and muscle mass (p= 0.04 and p= 0.007, respectively; Figure 7.7).

### 7.3.3 Quality of life, physical performance and hand grip strength

All six functional scales in the QOL measurement tool were maintained from baseline to post-treatment in the intervention group. Physical performance score and hand grip strength were maintained from baseline to post-treatment (data not shown). There was a positive correlation between handgrip strength and SMI at baseline (r= 0.6, p= 0.03) and post-treatment (r= 0.72, p= 0.007) (Table 7.4).

### 7.3.4 Inflammation

A significant reduction in serum CRP (p=0.005), CRP/Alb ratio (p=0.006) and neutrophils (p=0.005) was observed from baseline to post-treatment. There was a trend toward lower lymphocytes and NLR (p=0.06) at post-treatment compared to baseline. The higher NLR at baseline was associated with greater loss of muscle (r = −0.59, p = 0.04). Among seven patients with highest tertile of NLR at baseline (NLR>7.6), three completed the study, but experienced considerable muscle loss (-13±6.9 %/100 days). The patient with the highest NLR who was able to consume protein and energy within the range recommended by ESPEN (protein 1.53 g/kg BW, calorie 28.7 kcal/kg BW energy) lost 27.5% of muscle. Three other patients in the high NLR tertile died before treatment completion, and the other one experienced severe toxicity after the first session of chemotherapy causing a treatment interruption.

## 7.4 Discussion

This study demonstrated the feasibility and potential benefit of optimizing protein intake using foods commonly consumed by cancer patients undergoing treatment in a cohort of NSCLC patients receiving treatment. There are no previously published studies of individualized nutritional intervention for the management of muscle loss measured by CT analysis in cancer patients. Half of the patients had good adherence to all aspects of the nutritional intervention, demonstrating a significant increase in protein and dairy intake over treatment. On the other hand, protein intake from meat sources declined. Those who had complete adherence to intervention components gained a significant amount of muscle compared to patients who did not completely comply with the study recommendations. Notably, participants maintained their QOL, physical function and muscle strength over the cancer treatment. An improvement in the inflammatory status of patients was observed.

Without nutritional intervention, protein intakes of NSCLC patients decrease during chemotherapy (Sánchez-Lara et al., 2014). In the present study patients achieved protein intakes of 110 gram/day, which is markedly higher than baseline intakes. Other studies with cancer patients have reported a significant increase in protein intake by nutrition counselling (Bourdel-Marchasson et al., 2014; Ovesen et al., 1993). Adherence with the nutritional intervention was moderate in our study as only fifty per cent of patients were able to achieve the target adherence score (score 3 and 4). The majority of patients achieved at least 1.2-gram protein/Kg BW/day and recommended servings of the dairy product showing that these two targets are feasible in NSCLC patients. However, patients had a problem with achieving recommended number of serving from meat group and bolus protein intake (30 gram protein intake in one meal). Increasing meat group intake during cancer treatment maybe challenging due to taste and smell alterations caused by treatment in NSCLC patients (Belqaid et al., 2018).

There was no significant differences in weight loss between intervention and reference group, however patients in intervention group maintained their weight during treatment. This observation is aligned with findings from two RCTs in cancer patients undergoing chemotherapy, who reported no difference in weight loss between groups receiving a nutritional intervention with counselling and control groups (Ovesen et al., 1993; Baldwin et al., 2011). Although changes in weight are traditionally used to assess the effectiveness of the nutritional intervention, more specific measurements of body components may offer a better assessment of nutritional status, studies employing precise measure of body compartments are limited.

Normally, patients lose both muscle and fat during cytotoxic treatment (chapter 6, section 6.3.2); however, muscle and fat remained stable during the intervention. Patients who were compliant to the high protein dairy-based intervention gained muscle. Ovesen et al reported no effect of dietary counselling on preventing fat-free mass loss measured using triceps skinfold measurement (Ovesen et al., 1993), whereas intervention with high-energy ONS containing high protein levels and n-3 polyunsaturated fatty acids (PUFA) showed improvements in muscle mass during chemotherapy compared with isocaloric controls (Breitkreutz et al. 2005; Van der Meij et al., 2010; Sanchez-Lara et al. 2014). The positive effect of nutritional interventions during treatment on muscle mass was mostly driven by protein containing oral nutritional supplements with added n-3 PUFA, suggesting the benefit of targeting metabolic alterations while supporting energy and protein intakes.

Our findings demonstrate that increasing total protein intake rich in dairy proteins and optimizing it by bolus protein intake enables gains in muscle mass. It has been suggested that a blunted muscle protein synthesis response observed in cancer patients can be overcome by consuming higher amounts of protein containing essential amino acids. Winter et al. (2012) revealed whole body protein synthesis to be normal in NSCLC patients when exposed to high levels of essential amino acids (Winter et al., 2012). Dairy products could be an ideal nutritional

intervention choice for the maintenance of muscle mass in cancer patients for a number of reasons including being a complete protein source with a high content of whey, casein and leucine (Devries et al., 2015; Wolfe et al., 2015). In addition, the findings of our research presented in chapter 3, revealed that as patients with head and neck cancers progress through chemotherapy treatment, consumption of other protein-containing foods such as meat declines whereas dairy products are the only food group that increases during this time period. A study by Alemán-Mateo et al., showed the addition of 210 g of ricotta cheese daily to the habitual diet of older subjects improved appendicular skeletal muscle mass (Alemán-Mateo et al., 2014). Besides protein quantity, the nutritional intervention in our study had a unique focus on bolus protein intake because a threshold of high-quality protein intake must be reached at each meal to stimulate protein anabolism. In patients with mixed tumor types and stages, including non-small cell lung cancer, oral consumption of a high-protein nutritional supplement (40 g of protein containing ~22 g of essential amino acids) significantly increased the fractional rate of muscle protein synthesis, while consumption of a conventional nutritional supplement (24 g of protein containing ~9 g of essential amino acids) was ineffective (Deutz et al., 2011). Collectively, it appears that to prevent muscle loss and associated deleterious effects, stimulating muscle protein anabolism is crucial, which can be optimally achieved with nutritional interventions containing a high protein/essential amino acid content in people with cancer.

QOL was maintained from baseline to post-treatment in our patients. In the study by Baldwin et al., no differences in QOL between the groups who received the nutritional intervention (dietary counselling/ONS) or those who received no nutritional intervention were found for any parameter of QOL (Baldwin et al., 2011). Unexpectedly, a study in mixed tumor group, showed the patients in the usual care group performed better in terms of QoL compared with patients who received nutrition counseling (Uster et al., 2013). It may be possible that the nutritional therapy itself decreased QoL in cancer patients due to the pressure to fulfill the aims of the nutritional

intervention. Although, high-protein, n-3 PUFA-enriched ONS were reported to improve some aspects of QoL using the EORTC C-30 questionnaire, evidence remains limited (Van der Meij et al., 2013; Sanchez-Lara et al., 2014).

Inflammation is a known underlying cause of muscle loss in cancer patients. The patients in this study had a significant improvement in inflammatory status demonstrated by a reduction in CRP, CRP/Alb ratio and neutrophil counts at the end of the study. CRP has been shown to decrease in response to oral nutritional supplements containing eicosapentaenoic acid, with no apparent benefit in the control groups in two separate studies (Guarcello et al., 2007; Sa´nchez-Lara et al., 2014). Notably, patients with the highest NLR lost a significant amount of muscle despite meeting targets of protein and calorie intakes. Malnutrition in cancer patients is frequently associated with metabolic alterations and muscle wasting induced by systemic inflammation (Arends et al., 2017). This systemic inflammation and metabolic derangements will interfere with nutritional interventions and may limit the efficacy of feeding in patients with cancer, regardless of the intervention proposed (Haran et al., 2012). Biomarkers of systemic inflammation such as NLR could be a good indicator of who does or does not benefit from an anti-inflammatory to accompany nutritional interventions.

There is no approved and standardized method for the assessment of adherence to dietary interventions. Different methods have been used in other studies, including prescription charts, supplement consumption records and diaries, and counting of cans or packs of supplement, are all known to be inaccurate (Lawson et al., 2000; Fearon et al., 2003; Bruce et al., 2003; Gosney, 2003). In the present study, information regarding adherence was obtained by a weekly phone call and 24-recall. Studies of adherence with nutritional intervention have focused on whether patients are adherent or not (Bruce et al., 2003; Gosney, 2003), rather than exploring the factors contributing to adherence. Future qualitative research to gain a deeper understanding

of exploring the factors influencing adherence in cancer patients and to suggest strategies to improve adherence to nutritional intervention is worthy of further investigation.

This study is subject to certain limitations. Several patients dropped out due to death and progressive medical complications, resulting in a final completion rate of 64%. Also, the preliminary results of this study should be interpreted cautiously given the single-arm nature of this study, small sample size, and use of reference groups for multiple comparisons for outcome variables. Confidence in these results will be enhanced when the study is complete.

Outcomes in the present study have been impacted by moderate compliance to the nutritional intervention. Hence, categorizing patients based on adherence demonstrated that individualized nutrition counselling by recommending a high protein diet rich in dairy products taken in bolus can improve skeletal muscle mass. Our results suggest that adding dairy products to the habitual diet may be a promising dietetic strategy for improving skeletal muscle mass in patients undergoing treatment. There is an urgent need for well-designed RCT to investigate the impact of individualized nutrition counselling with focus on preferred food of patients with high quality protein combining with anti-inflammatory components on body composition changes and clinical outcomes such as physical function and QOL during cancer treatment.

## Tables

Table 7. 1 Baseline characteristics of patients with NSCLC in the intervention group and reference group

| Variables | Intervention group (n=14) | Reference group (n =70)φ |
|---|---|---|
| Age, years | 64.9 ± 5.9 (55-76) | 63.7 ± 8.2 (41-79) |
| Male, n (%) | 8 (57) | 33 (47) |
| Stage of tumor, n (%) | | |
| II | - | 2 (3) |
| III | 3 (21) | 8 (11) |
| IV | 11 (79) | 60 (86) |
| Chemotherapy agents | | |
| Carboplatin | 8 (57) | 65 (93) |
| Cisplatin | 3 (21) | 5 (7) |
| Immunotherapy | 3 (21) | - |
| BMI, $kg/m^2$ | 29.8 ± 6.7 (19.8-43.7) | 25.7 ± 5.1 (16.3-39.0) |
| TATI, ($cm^2/m^2$) | 138.9 ± 84.4 | 102.9 ± 62.6 |
| SATI, ($cm^2/m^2$) | 86.2 ± 51.5 | 55.9 ± 32.5 |
| VATI, ($cm^2/m^2$) | 49.3 ± 38.4 | 42.06 ± 38.3 |
| SMI, ($cm^2/m^2$) | 47.9 ± 9.9 | 46.5 ± 10.1 |
| CRP, mg/L | 16.5 ± 16.4 | 23.5 ± 34.5 |

φ Reference group from chapter 6 (section 6-3, table 1)

BMI: body mass index; CRP: C-reactive protein; SATI: subcutaneous adipose tissue index; SMI: skeletal muscle index; TATI: total adipose tissue index; VATI: visceral adipose tissue index

Table 7. 2 Dietary intake of 14 patients with NSCLC at baseline and post-treatment

| Dietary intake | Baseline φ | Post-treatment Ψ |
|---|---|---|
| Calorie, kcal/day | 1791 ± 597 | 2000 ± 450 |
| Calorie, kcal/kg BW/day | 24.1 ± 7.1 | 26.1 ± 6.2 |
| Protein, g/day | 71.5 ± 20.0 | 110.8 ± 23.4* |
| Protein, g/kg BW/day | 0.9 ± 0.2 | 1.46 ± 0.31* |
| Protein, % of kcal | 16.7 ± 4.1 | 23.9 ± 4.3* |
| Carbohydrate, g/day | 216.2 ± 87.2 | 224.0 ± 84.4 |
| Carbohydrate, % of kcal | 47.6 ± 7.3 | 45.8 ± 11.3 |
| Fat, g/day | 70.2 ± 30.9 | 71.1 ± 28.4 |
| Fat, % of calorie | 35.7 ± 6.9 | 29.9 ± 11.7 |

*P value<0.05

φ Dietary intake was assessed using food frequency questionnaire at baseline

Ψ Dietary intake was assessed using 24 hour recall by phone during treatment

Table 7. 3 Weight and body composition of patients in the intervention group and reference control group at baseline and post-treatment (n=10)

| | Intervention group | | Reference group ᵠ | |
|---|---|---|---|---|
| Variables | Baseline | Post-treatment | Baseline | Post-treatment |
| Weight (kg) | 88.1 ± 18.8 | 87.2 ± 20.6 | 71.8 ± 19.0 | 69.7 ± 18.0* |
| SMI ($cm^2/m^2$) | 49.4 ± 10.9 | 47.1 ± 11.0 | 47.2 ± 10.3 | 44.5 ± 8.8* |
| TATI ($cm^2/m^2$) | 158.4 ± 89.4 | 162.3 ± 86.3 | 108.1 ± 62.4 | 101.1 ± 57* |
| SATI ($cm^2/m^2$) | 95.2 ± 54.8 | 98.2 ± 53.6 | 57.1 ± 32.6 | 52.8 ± 28.6* |
| VATI ($cm^2/m^2$) | 59.0 ± 41.5 | 60.5 ± 41.0 | 45.2 ± 38.5 | 42.1 ± 35.0 |

*P value<0.05 *vs.* baseline; ᵠ Reference group from chapter 6 (section 6-3, table 1)

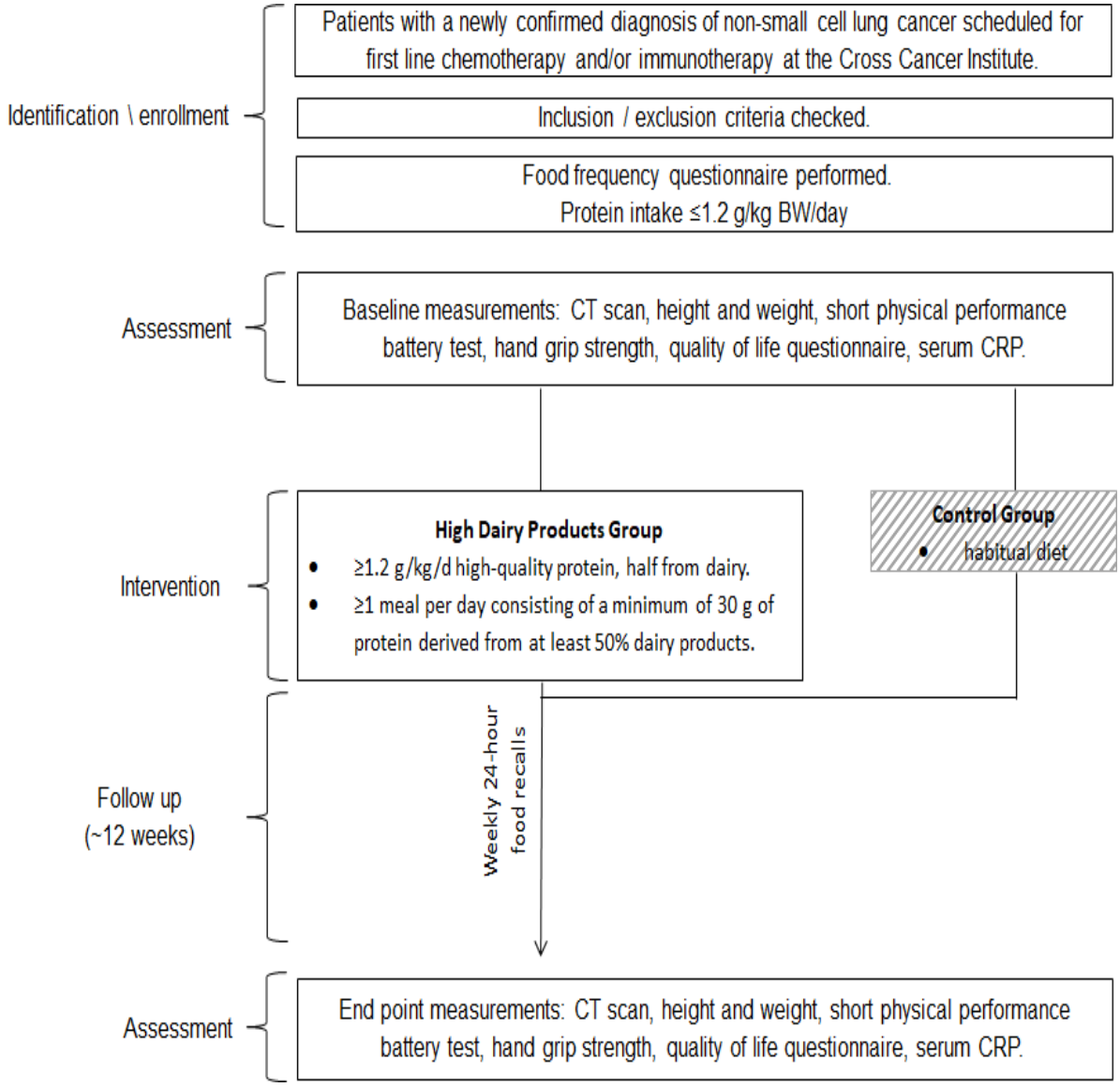
SATI: subcutaneous adipose tissue index; SMI: skeletal muscle index; TATI: total adipose tissue index; VATI: visceral adipose tissue index

Table 7. 4 Quality of life, physical function and inflammation measures of patients at baseline and post-treatment

| Variables | Baseline | Post-treatment |
|---|---|---|
| QOL- Physical function | 73.3 ± 18.8 | 72.9 ± 21.6 |
| QOL- Role functioning | 65.5 ± 28.8 | 72.6 ± 26.6 |
| QOL-Emotional functioning | 80.4 ± 18.3 | 83.3 ± 21.6 |
| QOL-Cognitive functioning | 85.7 ± 18.3 | 89.3 ± 15.4 |
| QOL-Social functioning | 67.9 ± 32.3 | 73.8 ± 23.3 |
| QOL-Global health | 40.5 ± 18.1 | 39.3 ± 19.1 |
| Handgrip strength (kg) | 36.9 ± 14.3 | 36.0 ± 12.8 |
| SPPBT score | 8.9 ± 2.2 | 8.8 ± 3.2 |
| Timed walk (4 m; second) | 4.8 ± 1.7 | 4.3 ± 1.1 |
| Repeated chair sit-stand test (second) | 16.2 ± 5.3 | 14.4 ± 6.2 |
| CRP | 17.2 ± 15.9 | 5.9 ± 7.4* |
| Neutrophil | 6.9 ± 3.1 | 3.9 ± 2.2* |
| Lymphocyte | 1.6 ± 0.7 | 1.2 ± 0.5 |
| NLR | 6.3 ± 6.8 | 3.7 ± 2.1 |
| CRP/Alb ratio | 0.4 ± 0.4 | 0.1 ± 0.1* |

QOL: quality of life; SPPBT: short physical performance battery test; CRP: C reactive protein; NLR: neutrophil to lymphocyte ration; Alb: albumin

**Figures**




Control group is in progress and not presented in this chapter.

Figure 7. 1 Participant flow diagram

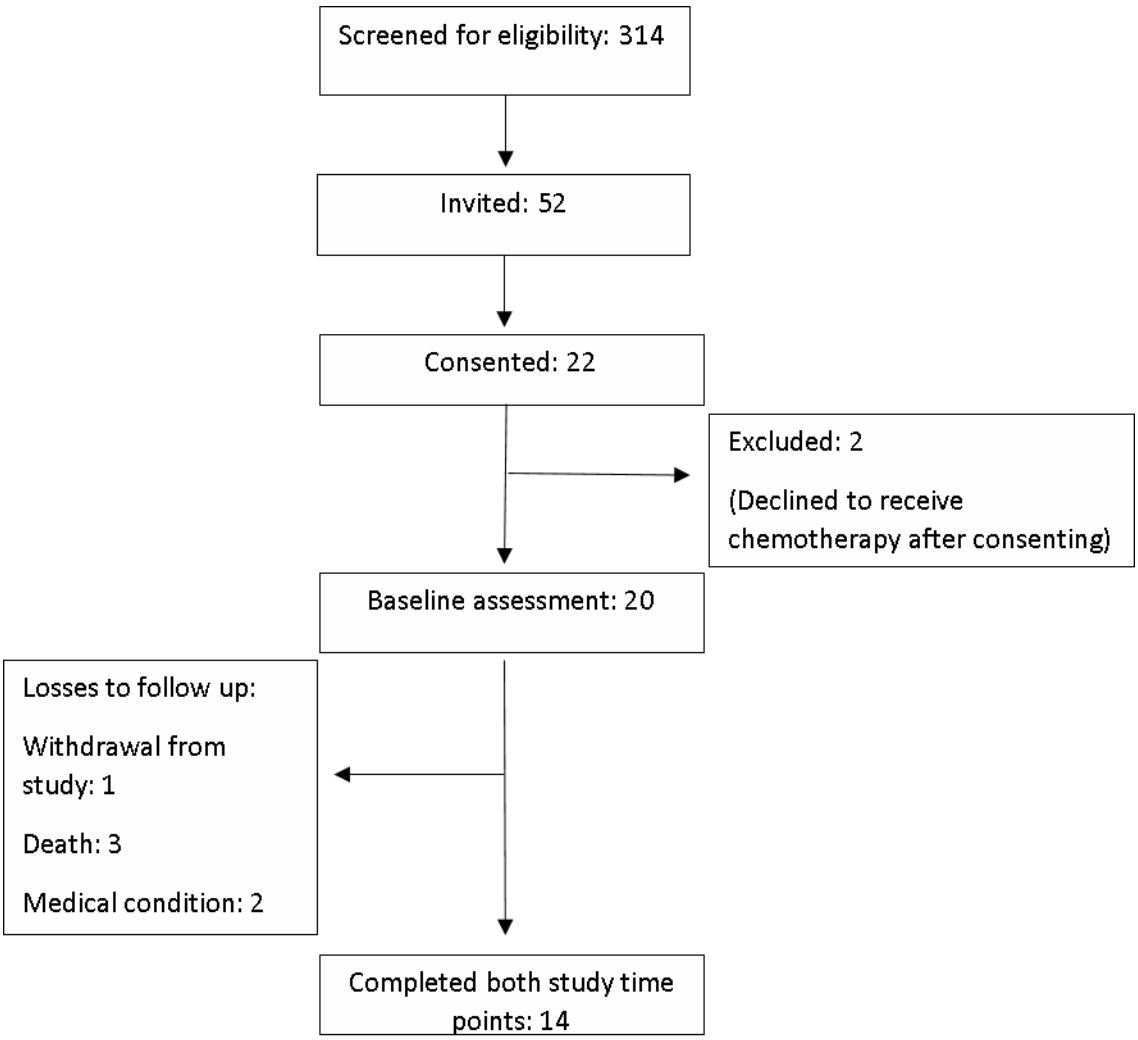



Figure 7. 2 Consort flowchart of Study participants

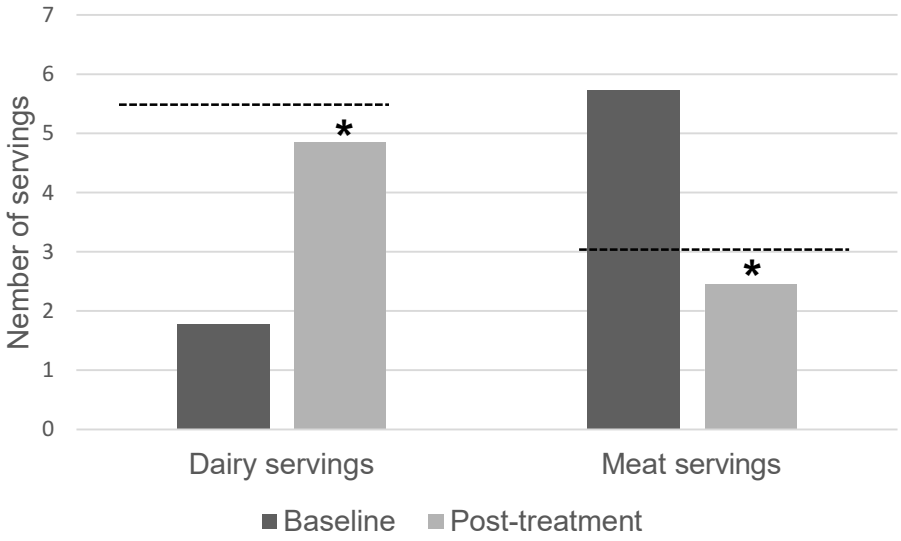



Figure 7. 3 Median intake per day of dairy and meat servings at baseline and post-treatment

Dashed lines are showing recommended servings for dairy and meat intake as prescribed during dietitian consultation

*P value<0.05 vs. baseline

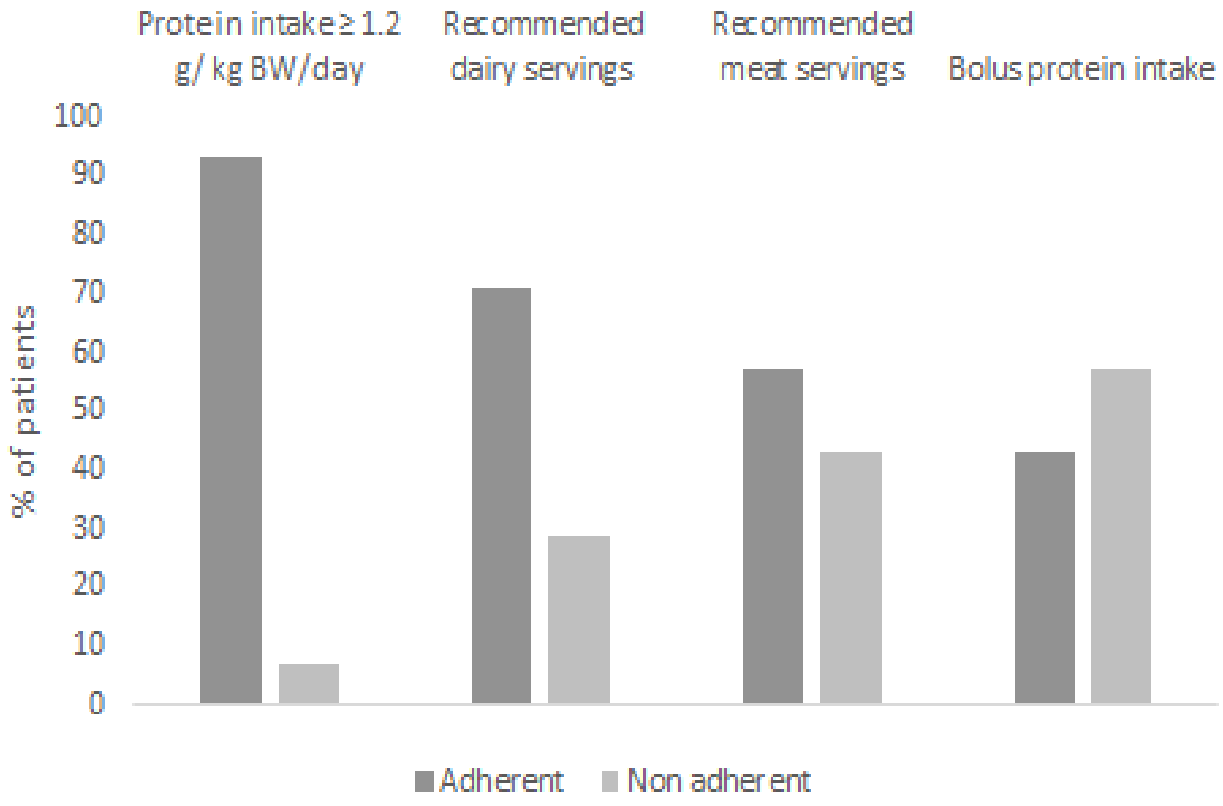



Figure 7. 4 Percent of patients who met the recommendations for each component of the prescribed

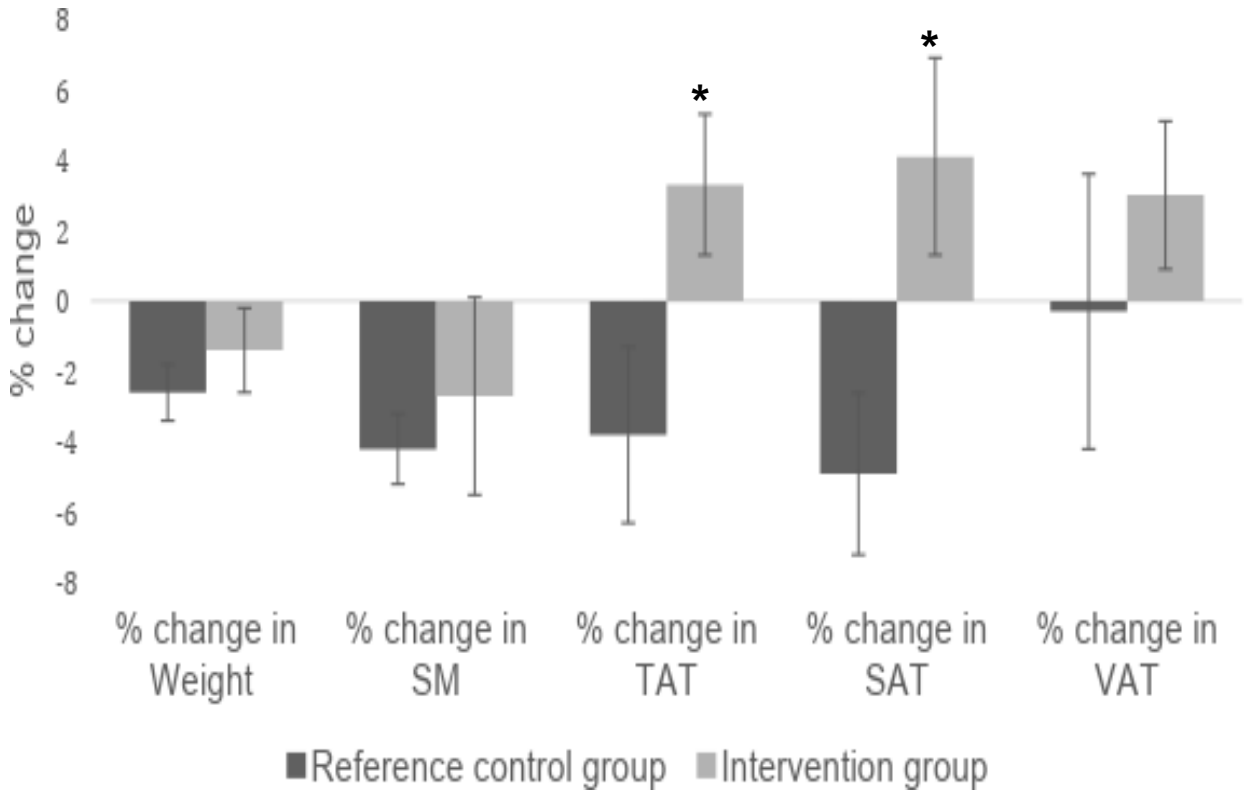



Figure 7. 5 Changes in weight and body composition compartments in intervention group compared with reference group

All the % changes in body composition components were normalized per 100 days; SAT: subcutaneous adipose tissue; SM: skeletal muscle; TAT: total adipose tissue; VAT: visceral adipose tissue

*P value<0.05

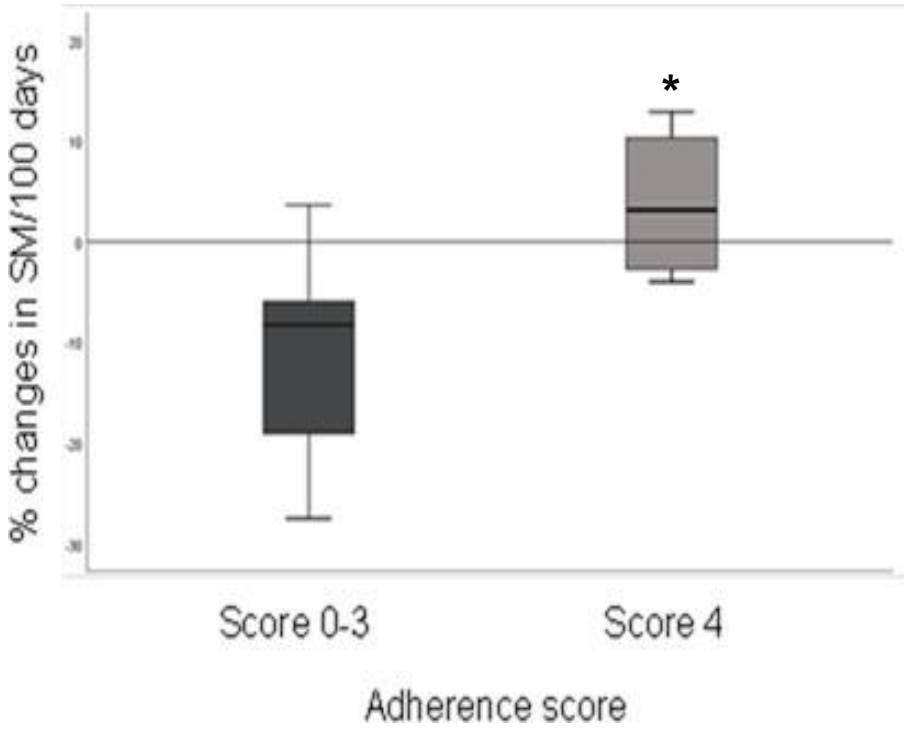



Figure 7. 6 Changes in skeletal muscle mass in patients with score 4 (complete adherence) vs. score 0-3 during treatment

*P value<0.05 vs. baseline

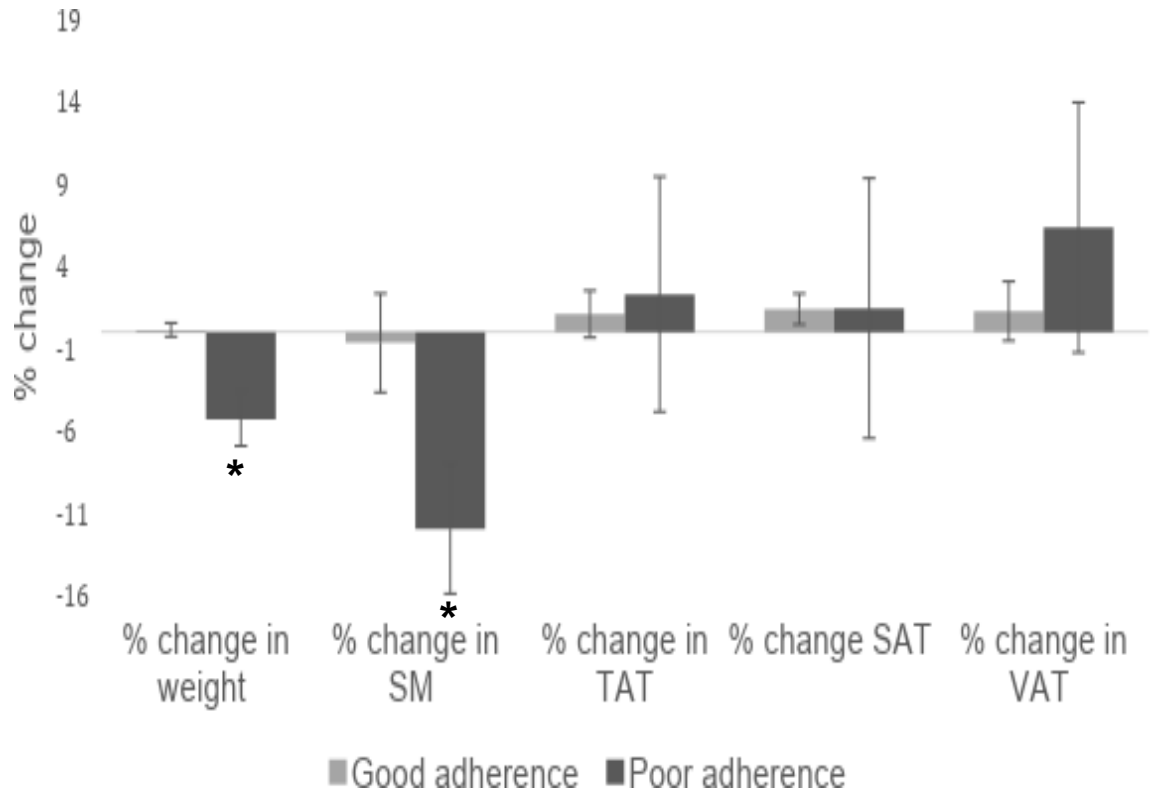



Figure 7. 7 Changes in weight and body composition components in patients with good vs. poor adherence during treatment

Good adherence: adherence score 3-4; Poor adherence: adherence score 0-2 All the % changes in body composition components were normalized per 100 days; SAT: subcutaneous adipose tissue; SM: skeletal muscle; TAT: total adipose tissue; VAT: visceral adipose tissue

*P value<0.05

Appendix 1

Eating Strategies for Treatment

Participant Study ID: _____

UNIVERSITY OF ALBERTA
DEPARTMENT OF AGRICULTURE, FOOD AND NUTRITIONAL STUDIES
DIVISION OF HUMAN NUTRITION

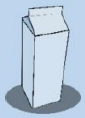
Alberta Health Services

## Eating Plan

- You need _____ choices from the meat group per day.

| Meat Group | Food | Choice Size |
|---|---|---|
|  | Beef, cooked | 75 g (1/2 cup) |
| | Fish, cooked or canned | 75 g (1/2 cup) |
|  | Lunch meat (cold cuts, deli meat) | 4 slices |
| | Pork, cooked | 75 g (1/2 cup) |
|  | Poultry, cooked | 75 g (1/2 cup) |
| | Eggs, whites | 125 mL (1/2 cup) |
|  | Eggs, whole large | 2 |

- You need _____ choices from the dairy group per day.

| Dairy Group | Food | Choice Size |
|---|---|---|
|  | Cheese, block (brie, cheddar, mozzarella, parmesan, swiss) | 30 g / 1 slice |
|  | Cottage or ricotta cheese | 60 g (1/4 cup) |
| | Milk | 250 mL (1 cup) |
| | Milk powder | 30 g (1/4 cup) |
|  | Yogurt, Greek | 165 mL (2/3 cup) |
| | Yogurt, regular | 250 mL (1 cup) |

- You need <u>one meal</u> with one of the below choice combinations per day.
  - 2 meat choices **OR** 1 meat + 2 dairy choices **OR** 4 dairy choices

| Food Group | Breakfast | Snack | Lunch | Snack | Dinner | Snack |
|---|---|---|---|---|---|---|
| **Meat** | | | | | | |
| **Dairy** | | | | | | |

## Chapter 8: Final discussion

### 8.1 Introduction

Recent advances in cancer treatment improve outcomes in patients with cancer. However, the efficacy of cancer treatments is impeded by the frequent development of malnutrition, induced by a tumor or its treatment. Malnutrition during cancer treatment occurs because of the combination of inadequate food intake, and various metabolic derangements. Malnutrition has been shown to be a common problem in many tumor types with a high prevalence in cancers of the lung and head and neck. The overall objective of this research was to explore the nutritional alterations that occur during treatment in these populations in relation to muscle loss and toxicities and determine the similarities and differences in types of nutrients deficits that occur during treatment. Subsequently, the findings of this research were applied to design a nutritional intervention to investigate the effects of optimized protein intake rich in dairy products on muscle mass of lung cancer patients.

### 8.2 Changes in dietary intake during treatment for head and neck cancer (HNC)

The first approach of this body of work was to characterize the nutrients and food choices that are affected by oncological treatment in HNC patients. In Chapter 3, we aimed to determine dietary intake changes with a focus on micronutrient intake that occur during and up to 3 months after the end of the treatment. We were also interested in the contribution of ONS to the total nutrient intake. It was hypothesized that dietary macronutrient and micronutrient intake of HNC patients would be low at diagnosis, decrease further during treatment and would not recover following completion of treatment. Secondly, it was hypothesized that ONS consumption enhances nutrient intake in HNC patients during cancer treatment and could prevent weight loss.

The majority of patients with a diagnosis of HNC did not meet recommended dietary intakes for vitamins D, E, C, folate, and magnesium at any point in the study. Relative to baseline, the proportion of calories from milk, soup, and ONS significantly increased at the end of treatment,

while grain, meat, potato, baked dessert, and oil and sugar decreased. At all study time points, patients categorized as high ONS consumers (>15% of total daily calories from ONS) had higher intakes of micronutrients. They also had more NIS and experienced greater weight loss during the study, despite having similar energy intake to patients consuming <15% kcal from ONS.

### 8.3 Correlation of dietary energy and protein intake with body composition alteration during cancer treatment in HNC patients

Weight loss is commonly used to assess nutritional status, however, a more specific assessment of body components may offer a better prognostic tool as muscle loss occurs in patients who may not be losing weight. In chapter 4, the changes in skeletal muscle mass and adipose tissue over treatment in relation to energy and protein intake were determined. Secondly, we aimed to explore whether meeting current ESPEN guidelines protects against loss of skeletal muscle mass in HNC patients. It was hypothesized that loss of muscle and adipose tissue is associated with energy and protein intake during treatment and would be greater in patients who do not meet ESPEN guidelines for energy and protein intake.

Our data confirmed that weight loss and muscle wasting occur at a remarkable rate in HNC patients undergoing treatment (8% and 11%; respectively). Loss of SM was negatively correlated with energy and carbohydrate intake but not protein intake. Meeting minimum ESPEN energy guidelines (25-30 kcal/kg BW/d) did not attenuate SM loss, where intakes >30 kcal/kg BW/d (above the upper range of the recommended intake) resulted in fewer participants losing muscle. Loss of muscle was experienced by all patients meeting the minimum recommended protein intakes (1.0 g/kg/d). Greater adiposity at baseline correlated with greater SM loss.

### 8.4 The association of plasma vitamin status with skeletal muscle loss and mucositis among HNC patients undergoing cancer treatment

While HNC patients have poor intake of vitamins compared to recommended dietary allowance (RDA), whether this translates into low plasma levels of vitamins has not been

characterized. In chapter 5, the plasma levels of vitamin A, E, D, B12, folate during cancer treatment were determined at the time of diagnosis and when treatment was complete. Secondly, the relationship between vitamin status with body composition and mucositis among HNC patients undergoing cancer treatment were investigated. It was hypothesized that plasma levels of vitamins would be lower after cancer treatment compared to baseline among patients with HNC and patients with poor vitamin status would experience greater loss of muscle and increased severity of mucositis compared to those with normal plasma levels.

Mean plasma *all-trans* retinol concentrations decreased significantly from baseline to post-treatment while plasma levels of active vitamin $B_{12}$ increased over the same time period. There were no significant changes in plasma concentrations of vitamin D, α-tocopherol nor folate during cancer treatment. Patients who developed mucositis had significantly lower dietary intake of all vitamins assessed and lower plasma 25-OHD and *all-trans* retinol levels. Patients lost a considerable amount of muscle mass (3.4 kg) and fat mass (3.6 kg) over the course of treatment. Greater muscle loss in patients with 25-OHD < 50 nmol/L was observed compared to patients with 25-OHD ≥ 50 nmol/L. A significant negative correlation was found between plasma *all-trans* retinol and CRP level at the end of treatment. Poor vitamin status could be a contributing factor in developing treatment-induced toxicities.

### 8.5 The relationship between vitamin D status and changes in body composition and chemotherapy toxicity in lung cancer patients receiving platinum-based chemotherapy

Our research showed deficits in 25-OHD was related to body composition and toxicity in the HNC cancer population and we aimed to extend these investigations to the lung cancer population. In chapter 6, the association between plasma level of vitamin D and loss of skeletal muscle mass in lung cancer patients was determined. Secondly, the association between plasma levels of vitamin D and treatment-induced toxicities in lung cancer patients were determined. It

was hypothesized that patients with insufficient levels of plasma vitamin D would experience a greater severity of toxicities and muscle loss.

The majority of cancer patients presented with vitamin D deficiency and insufficiency. Women with DLT had lower 25(OH)D levels, determined at diagnosis and before treatment initiation, compared with those who did not have toxicity. However, there was no difference in 25(OH)D among men with and without DLT.

### 8.6 Eating strategies for prevention of muscle loss during cancer treatment in lung cancer patients

For the last objective in this body of work, a nutritional intervention was designed to attenuate loss of muscle that occurs during cancer treatment. In chapter 7 we determined, the CT-derived change in muscle mass of lung cancer patients whose habitual protein intake was below 1.2 g/kg body weight /day, and changes to a high protein diet rich in dairy products. Secondly, muscle strength, quality of life and inflammatory status were assessed. It was hypothesized that a high protein diet rich in dairy products would support the maintenance of muscle mass and strength, and reduce inflammation, therefore improving outcomes for cancer patients undergoing chemotherapy treatment.

Half of the patients had good adherence to all aspects of the nutritional intervention, increasing their intake of protein and dairy products over treatment. On the other hand, protein intake from meat sources declined. Those patients who had complete adherence to the intervention gained muscle compared to patients whose compliance with the study recommendations was incomplete. Moreover, participants maintained their QOL, physical function and muscle strength over the cancer treatment and an improvement in inflammatory status was observed.

Achieving intervention targets is clearly difficult during oncological treatment. In our study, NSCLC patients receiving treatment had moderate compliance with the nutritional intervention.

However, they were able to increase their dairy intake significantly during treatment which confirmed our findings from chapter 4 that dairy products are a preferred food choice during treatment. In our study, the difficulty in reaching all intervention components, particularly meat servings and bolus intake of protein, explain the lack of significant effect on muscle mass among patients on average. However, patients with complete adherence with intervention components were able to gain muscle mass. Our results suggest that adding dairy products to the habitual diet could be a feasible strategy for improving high-quality protein intake and maintaining muscle mass.

### 8.7 Interpretation and application of results for future studies

Cancer treatment, particularly chemoradiotherapy is associated with impairments in macronutrient and micronutrient intake. ONS are frequently indicated for cancer patients with impaired dietary intake. However, in our study patients with higher consumption of ONS had higher micronutrient intake, and experienced greater weight loss. A study by Ravasco et al. in HNC receiving radiation therapy, revealed that adding ONS alone to a patient's diet was not as effective as dietary counselling. Concurrent individualized dietary counselling, based on regular foods, is the most effective strategy to improve patients' dietary intake, and QOL (Ravasco et al., 2005). This approach was adopted in the nutritional intervention trial presented in chapter 7. In addition, compliance with ONS intake is generally poor in cancer patients undergoing oncological treatment (Hubbard et al. 2012, Ravasco et al. 2005). One possible way to increase compliance to a nutritional intervention is the identification and incorporation of foods desired by patients in accordance with their NIS experience. Dairy products are not only a preferred food choice by cancer patients, but also are nutrient dense and provide high-quality protein and a variety of micronutrients (FAO, WHO 2006). Moreover, dairy products are considered a suitable food vehicle for nutrient fortification (FAO, WHO 2006). These findings address an important gap in

the literature because understanding deficient nutrients and preferred foods of cancer patients propose several possible targets for dietary intervention.

Positive energy balance is crucial for maintaining muscle mass whereas during energy deficit excess nitrogen will alternatively be metabolized for energy rather than protein synthesis. In negative energy balance, muscle protein synthesis is down-regulated, reflecting the loss of skeletal muscle mass (Bolster et al., 2002). Similarly, HNC patients with higher calorie and protein intake (above the upper range of recommended intake) lost significantly less weight and lean mass compared to those with lower dietary intake during treatment (chapter 4; Jager-Wittenaar et al., 2010; Giles et al., 2016). HNC patients are a unique cancer population, as malnutrition is mainly driven by reduced food intake due to NIS as a major driver of malnutrition (Ravasco et al., 2005; Couch et al., 2007). Nutritional interventions must first promote positive energy balance to be able to maintain muscle mass in the presence of anabolic amino acids for protein synthesis. However, in patients with NSCLC the ability to meet energy requirements led to gains in body fat (Harvie et al., 2005). In GI cancer patients, relations between energy intake and energy balance (FM and FFM calculated by DXA) are affected by systemic inflammation (Wallengren et al., 2013). Based on available evidence and findings from chapter 7, the presence of inflammation impedes the ability to gain muscle. Dampening an inflammatory response would provide a permissive environment for muscle to be anabolic when presented with sufficient nutrients.

In this study, the comparison between two different energy intake cutoffs (25 kcal/kg BW/d vs. 30 kcal/kg/d) revealed that meeting the higher level of energy is more effective at preventing muscle loss. Current ESPEN guidelines recommend energy intakes between 25-30 kcal/kg BW/d, however, there is a low level of evidence available for this recommendation because only a few studies with small numbers of patients have assessed total energy expenditure in cancer patients using direct measures. These findings indicate that current guidelines may be inadequate to attenuate SM loss in HNC patients. However, by comparing different cutoffs of protein intake (1.0 g/kg BW/d vs. 1.5 g/kg BW/d), no significant difference in SMI loss was observed. Little data exists

on measured energy expenditure in HNC patients. Further research is required to elucidate energy and protein requirements in the oncology patients as the requirements for weight and muscle stability may differ between cancer types and treatment modalities.

There is a major gap in the literature regarding micronutrient requirements for cancer patients (Arends et al., 2017). It is not known whether recommending intakes at the current RDA is sufficient in people with cancer who are undergoing treatment. High prevalence of vitamin D deficiency and insufficiency was observed among HNC (chapter 5) and lung cancer patients (chapter 6). In addition, vitamin A decreased significantly during treatment which was correlated with the severity of systemic inflammation (chapter 5). These findings confirm previous reports that patients receiving cancer treatment experience certain nutrient deficiencies or insufficiencies (Vashi et al., 2010; Hoffer et al., 2016). Moreover, our findings demonstrate that HNC patients and women with NSCLC who developed toxicity during oncological treatment had lower levels of some vitamins particularly vitamin D. These results align with a study in which vitamin D supplementation significantly reduced therapy-related toxicities among oral cancer patients (Anand et al., 2017). Since deficits in certain micronutrients may expose patients with cancer to increased risk of treatment-related toxicity, close attention should be paid to correction of vitamin deficits before treatment, especially vitamin D deficiency. Most vitamins are available as a supplement which could be used to easily correct deficiencies. Further studies are required to investigate micronutrient status in relation to oncological outcome and treatment induced toxicities.

There is a paucity of knowledge regarding the effects of individualized nutritional intervention during cancer treatment on body composition alterations. This subject was investigated in chapter 7. The research presented supports that systemic inflammation was correlated with muscle loss and adequate nutritional intake alone may not be sufficient to prevent muscle loss. However, in patients with low NLR, meeting the intervention recommendations translated to maintaining or even gaining muscle mass. Our findings suggest that muscle wasting

may be attenuated by addressing the inflammation concurrent with adding preferred foods containing high-quality protein to the diet of patients in order to minimize the caloric and protein gaps. In the light of these findings, future controlled clinical trials should investigate the effects of preferred foods of patients fortified with vitamin D and anti-inflammatory nutrients (such as n-3 fatty acids) on muscle mass and treatment-related toxicities during oncological treatment.

**8.8 Methodological consideration**

The intervention study described in Chapter 7 was conceived as an RCT, however, the design of the study was changed to an open label study design because of slow accrual (Chapter 7). While this study design can reduce the problem of low enrollment and high withdrawal rates, variation in individual characteristics (genetic, cultural differences, quality of life, physical activity level, and stage of disease) among patients of each group could have affected our results.

Due to small sample size, we are not able to draw conclusions about the differences in body composition alterations associated with different oncologic therapies, including immunotherapy and chemotherapy. Each of them may affect results and should be explored in future studies with a larger sample size.

Aligned with the bulk of literature, strategies to improve adherence to the nutritional intervention might be investigated in future studies by conducting qualitative research. Flexible nutritional intervention goals during the chemotherapy could allow for lower intake during treatment days, and higher nutritional goals to catch up between cycles could help to improve adherence. In addition, adherence might be improved by strategies to manage NIS and support patients' preferences, such as more concentrated foods for decreased appetite or improved palatability and increased flavour varieties of supplements for taste and smell alterations which are often experienced during chemotherapy (Cohen et al., 2016; IJpma et al., 2016; Enriques Fernandes et al., 2018).

## 8.9 Conclusion

Over the duration of this research, new information regarding dietary intake, nutritional status and micronutrient deficits in relation to body composition and treatment toxicities have been revealed. This research provides new information regarding micronutrient status and its relation to clinical outcomes in cancer patients undergoing oncological treatment. Micronutrient intake of HNC patients undergoing cancer treatment is impaired. Assessing plasma levels of vitamins showed a high prevalence of vitamin D deficiency even before starting treatment and decreased levels of vitamin A after treatment completion. While causality cannot be inferred, the correlation was observed between vitamin D status and treatment-related toxicity and body composition alterations which are a novel aspect of this research.

Food choices of patients are affected by the severity of NIS induced by treatment and suggest dairy products as preferred food choice of patients over the course of treatment. Given the high-quality protein and nutrient density of dairy products, this research revealed for the first time that optimizing protein intake using dairy products is an effective dietetic strategy to maintain skeletal muscle mass in cancer patients with good adherence. However, the beneficial effects of this intervention would be expected to be even greater in those whose inflammatory responses are attenuated.

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