**Thesis:**

# Predictors of changes in health-related quality of life during chemotherapy in an advanced non-small cell lung cancer patient population

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**Abstract: Predictors of changes in health-related quality of life (HRQOL) during chemotherapy in an advanced non-small cell lung cancer (NSCLC) patient population**

*Objective:* To identify predictors of changes in physical and mental HRQOL after two chemotherapy cycles in patients with NSCLC

*Methods:* Forty-seven subjects with advanced NSCLC were evaluated before and after receiving two cycles of first-line chemotherapy. Predictors were pre-chemotherapy 6-Minute Walk Test distance (6MWT), grip strength, 1-minute chair rise repetitions, Schwartz Cancer Fatigue Scale scores (SCFS), Lung Cancer Subscale scores (LCS) and Patient-Generated Subjective Global Assessment scores (PG-SGA). Outcomes were change in physical and mental component summaries (PCS and MCS) of the 36-item Short-Form Health Survey (SF-36). Multiple linear regression analyses were performed.

*Results:* Adjusted for age, gender and chemotherapy combination, the SCFS scores and 6MWT distances explained 33% of the variance in MCS change ($p<0.01$). The PG-SGA scores explained 14% of the variance in PCS change ($p=0.12$).

*Conclusion:* Clinical management of fatigue symptoms and physical performance may be useful for HRQOL optimization in NSCLC patients undergoing chemotherapy.

**Abstrait: Facteurs prédisposant aux changements en qualité de vie (QV) pendant la chimiothérapie aux patients atteint de cancer du poumon de stade avancé (CPSA)**

*But:* Identifier les facteurs prédisposant aux changements en QV pendant la chimiothérapie aux patients atteints de CPSA

*Méthodologie:* Quarante-sept sujets avec le CPSA étaient évalués avant et après deux cycles de chimiothérapie. Les variables étaient le test de marche de 6-minutes (TM6), la force de préhension, les levés de la chaise, les scores Schwartz Cancer Fatigue Scale (SCFS), les scores Lung Cancer Subscale et les scores Patient-Generated Subjective Global Assessment (PG-SGA) avant chimiothérapie et les changements en scores résumés psychiques (MCS) et physiques (PCS) du SF-36 après chimiothérapie. Des analyses de régression linéaire multiple étaient exécutées.

*Résultats:* Ajustés pour l'âge, le sexe et la combinaison de chimiothérapie, les SCFS et TM6 ont expliqué 33% de la variance en changement de score MCS ($p<0.01$). Le PG-SGA a expliqué 14% du changement de score PCS ($p=0.12$).

*Conclusion:* La gestion clinique de la fatigue et la performance physique serait utile pour ces patients.

**Predictors of changes in health-related quality of life during chemotherapy in an advanced non-small cell lung cancer patient population**

## 1. Introduction

Chemotherapy can prolong survival for patients with advanced non-small cell lung cancer (NSCLC) and may also improve health-related quality of life (HRQOL). Many of the factors influencing HRQOL may potentially be better managed with non-invasive interventions. However, little is known about which factors contribute the most to changes in HRQOL during chemotherapy. This study will enable a better understanding of the primary factors influencing HRQOL in NSCLC patients undergoing chemotherapy and will allow for optimally targeted management. The goal of this study is to identify predictors of changes in physical and mental HRQOL during chemotherapy in individuals with advanced NSCLC, where predictors include baseline functional walking capacity, grip strength, chair rise performance, fatigue symptoms, lung cancer symptoms and nutritional status.

## 2. Health-related quality of life

**2.1 Definition:** The World Health Organization Quality of Life Group (1994) has defined quality of life as "the individual's perception of their position in the context of the culture in which they live and in relation to their goals, expectations, standards and experiences. It is a broad ranging concept affected in a complex way by the persons' physical health, psychological state, level of independence, social relationships and their relationship to salient features of their environment."[1] The concept of HRQOL refers to specific aspects of quality of life that are related to the health of the individual.[2,3]

**2.2 The model of patient outcomes by Wilson and Cleary:** Wilson and Cleary (1995) developed a model that describes five levels of patient outcomes (Figure 1).[4,5] The first level of the model addresses basic markers of health status: biological and physiological variables. The second level, symptom status,

includes physical, cognitive, and emotional symptoms. The third level is functional status and considers physical, psychological, social, and role functioning. The fourth level, general health perceptions, integrates all the previous levels to impact overall quality of life, the fifth level of the model. The model also considers characteristics related to the individual and the environment and their influence on the various levels related to quality of life. The framework for this study fits well under this model by studying various factors in NSCLC patients, including individual and disease characteristics (biological and physiological variables), nutritional, fatigue and other lung cancer symptoms (symptom status), as well as functional walking capacity, chair rise performance and grip strength (functional status), and their ability to predict changes in HRQOL.

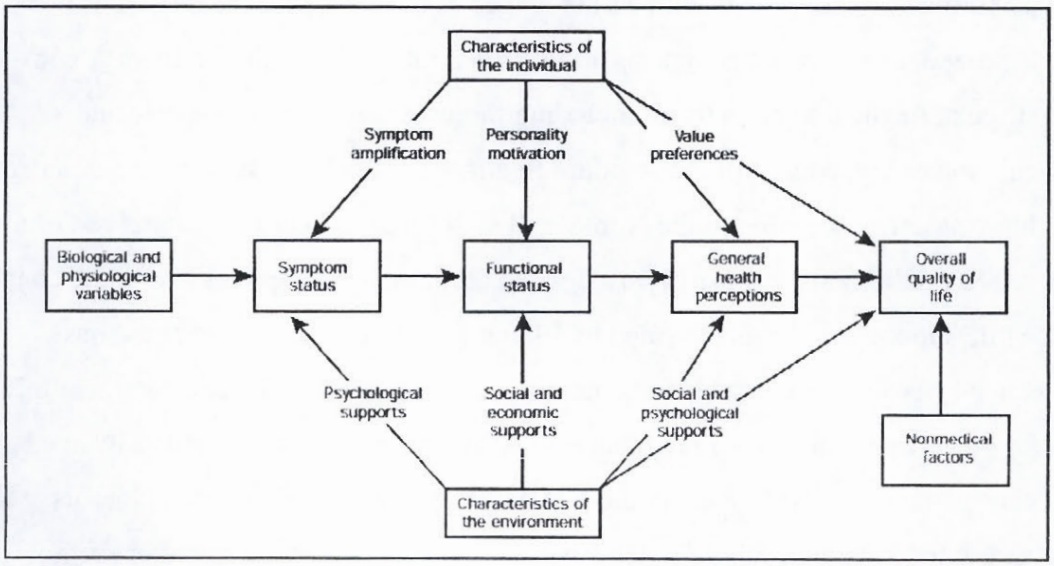


**Figure 1. Wilson and Cleary model of health-related quality of life**[4]

## 3. Background

**3.1 Lung cancer:** Statistics from the Canadian Cancer Society reveal that the estimated number of new cases for lung cancer in Canada is 23 400 for the year 2009.[6] Lung cancer is the leading cause of cancer death in both men and women

in Canada.[6,7] The average time of survival after diagnosis of lung cancer is one year and only about 15% of lung cancer patients survive five years after diagnosis.[6,7] Individuals with advanced stage lung cancer (stages IIIa, IIIb and IV) have a five-year survival rate of less than five percent.[7] During this time, people with lung cancer face multiple functional limitations and challenges due to the pathophysiological progression of the disease, the side effects of various medical treatments, and the physical and psychosocial consequences of having the disease.

**3.2 Lung cancer treatment:** Medical interventions for lung cancer include radiotherapy, chemotherapy and supportive care, whereas the only potentially curative treatment for lung cancer is surgical resection. While these surgical procedures may produce functional limitations, lung resection remains the most optimal treatment method for lung cancer. However, lung resection is often performed on individuals with earlier stages of cancer where the disease is localized, due to better prognosis and survival rates with such treatment.[8] Non-surgical medical interventions, including radiotherapy, supportive care and chemotherapy, consist of the standard treatment options for those with advanced lung cancer. According to the Non-Small Cell Lung Cancer Collaborative Group (2000), radiotherapy is usually used when the tumour has spread within the chest, while supportive care is provided to relieve symptoms when the disease has spread beyond the chest.[9] Chemotherapy can be given as adjuvant treatment (after surgical resection or with radiotherapy) or as first-line treatment (for advanced cancer stages) in NSCLC with the aim of providing modest survival benefits and additional symptom relief.[9-12] However, the role of chemotherapy after surgical resection remains a subject of ongoing discussion.[13]

*3.2.1 Chemotherapy treatment:* Commonly used in the medical treatment of patients with lung tumours, chemotherapy works by systemically killing malignant cells that are in process of proliferation and can help prolong survival in these individuals.[9] A number of randomized controlled trials have shown that

various types of chemotherapy, including docetaxel, carboplatin with etoposide, and other combination chemotherapies can provide survival benefits to patients with localized or advanced NSCLC.[14-16] Most research on chemotherapy in lung cancer has concentrated on identifying factors related to the treatment regimen, such as chemotherapy drug, dosage and duration, as well as patient characteristics, such as age, cancer type and stage, which predict the most beneficial effects on both survival and, more recently, HRQOL.

**3.3 Health-related quality of life in lung cancer:** Traditionally, lung cancer research has focused on determining the most effective treatments to increase survival rates. However, limited advances have been made in the treatment of lung cancer over the past few years. Due to the poor prognosis associated with lung cancer and the multiple side effects associated with its medical treatment, recent research has emphasized the importance of evaluating HRQOL in addition to survival for this patient population.[17] Lung cancer patients have generally been found to have poor HRQOL.[18]

*3.3.1 Effect of chemotherapy on HRQOL:* A descriptive study by Silvestri et al. (1998) revealed that many patients with advanced NSCLC would refuse chemotherapy for survival benefits of three months, but would accept it for improvement in HRQOL.[19] Several studies in the past have demonstrated that chemotherapy, when compared to standard treatment, improves HRQOL in advanced lung cancer patients, primarily through the palliation of lung cancer symptoms.[15,16,20-23] However, chemotherapy may lead to multiple acute and long-term side effects, such as fatigue, nausea and peripheral neuropathy, all of which may impact function and quality of life.[24,25] Other trials have shown that chemotherapy has no added benefit on HRQOL.[11,26] Some of these inconsistencies may be attributed to methodological differences. However, studies have demonstrated that factors, such as performance status and chemotherapy regimen, may affect the survival benefits obtained with chemotherapy in

advanced NSCLC patients.[23,27,28] Similarly, other factors may also play a role in how chemotherapy impacts HRQOL in such patients.

*3.3.2 Factors related to changes in HRQOL during chemotherapy*

*3.3.2 a) Patient and disease characteristics:* A number of individual characteristics, such as gender, age and cancer type, have been identified in the literature as potential factors influencing how lung cancer patients respond to chemotherapy, in terms of HRQOL. Billingham et al. (2001) and Agra et al. (2003) found similar effects of chemotherapy on survival and HRQOL in various subgroups of lung cancer patients.[29,30] Specific subgroups were created by age, sex, tumour stage, and histological cell type. However, survival differences according to performance status were found.[29] Cullen et al. (1999) conducted two randomized trials and showed that chemotherapy improves survival without negatively changing HRQOL in both young, ambulatory patients with localized lung cancer and patients with advanced stage lung cancer.[26]

*3.3.2 b) Chemotherapy treatment properties:* Various properties of chemotherapy treatment, including drug type, dosage, duration, frequency and the associated side effects, can potentially affect HRQOL. Ongoing research is being conducted to determine the most effective chemotherapy regimen to improve HRQOL, while maintaining survival benefits. Several studies and a recent systematic review on the topic have shown that different chemotherapy types and combinations provide similar benefits in HRQOL.[17,31,32] However, a randomized controlled trial by Belani et al. (2006) demonstrated that docetaxel-platinum regimens are superior to vinorelbine-cisplatin in improving HRQOL in advanced NSCLC patients.[33] Nonetheless, more studies are required in this fairly recent area of research to determine the role of treatment properties on HRQOL changes with chemotherapy.

*3.3.2 c) Other patient-related factors:* Additional patient-related factors which may predict the effect of chemotherapy on HRQOL include measures of physical performance, such as functional walking capacity, grip strength and chair rise performance, as well as patient-reported outcomes of symptom status, such as fatigue and lung cancer symptoms, and nutritional status. Their role in predicting HRQOL changes with chemotherapy has been much less researched in the advanced NSCLC population.

**Physical performance:** Physical performance refers to the execution of functional tasks and activities, such as walking, chair rise and grip strength.[34] These activities require several skills and functions, some of which may be impacted in the lung cancer population. For example, lower extremity strength is one of the various functions necessary for the ability to rise from a chair. [35,36] Cachexia, muscle wasting which occurs as a result of tumour-induced increases in protein catabolism, may produce skeletal muscle weakness in cancer.[37] Neurological changes due to chemotherapy-induced toxicity involve alterations to the sarcolemma, sarcoplasmic reticulum and mitochondrial membranes of muscle cells and can also result in reduced muscle force generation.[38] Chemotherapy-induced peripheral neuropathy can damage nerve fibers, axons and Schwann cells of motor neurons, causing muscle weakness, atrophy and hypotonia.[39] Additionally, several studies have documented a detrimental effect of lung cancer and treatment on pulmonary function and lung diffusing capacity.[40-45] Individuals with cancer, including cancer survivors, may also present with various symptoms, such as fatigue and pain, as well as depression.[46] Such findings can contribute to the reduced physical function that has been reported in individuals with advanced lung cancer.[47,48]

A number of cross-sectional studies have revealed that patients with advanced lung cancer have a lower measured walking performance, along with other physical activities, compared to healthy controls.[47,48] Self reports of lung cancer patients have also indicated that the greatest disruptions in physical activity

are in the performance of walking.[49] Various cross-sectional studies have revealed that the performance of several physical activities, including chair rise, chair transfers and dressing tasks, is significantly worse in advanced lung cancer patients than in healthy controls.[47,48,50,51]

Impaired physical performance due to the effects of lung cancer and its treatment has shown to bring about functional limitations in individuals with advanced lung cancer, which can contribute to changes in HRQOL. Self-reported physical function and role function have been found to be highly correlated in lung cancer patients prior to and after chemotherapy.[52] A recent cross-sectional study has demonstrated that functional walking capacity is positively correlated with global HRQOL in advanced NSCLC patients.[18] In lung cancer patients undergoing resection, better baseline functional walking capacity is shown to be associated with improved physical function and HRQOL post-operatively.[53] Kasymjanova et al. (2009) have demonstrated that baseline functional walking capacity may also be predictive of survival in advanced NSCLC patients undergoing chemotherapy.[54]

**Fatigue symptoms:** Fatigue refers to the subjective feeling of reduced energy and has both physical and psychological components to it. The biological mechanisms behind cancer-related fatigue are not clear and several hypothetical explanations related to the cancer diagnosis and cancer treatment have been identified by Morrow et al. (2002). These include: a) the exacerbation of anemia with certain cancer treatments (such as cisplatin); b) the abnormal generation or use of adenosine triphosphate (ATP), potentially related to reduced food intake, synthesis of depleted cellular ATP and altered muscle metabolism; c) the presence of vagal afferent activation as a response to pathogenic invasion and the release of pro-inflammatory mediators; and d) serotonin dysregulation due to the "cytokine cascade" due to elevated levels of tumour necrosis factor.[55] Other potential reasons for fatigue include the physical and emotional demands of cancer treatment, as well as psychological distress.

Okuyama et al. (2001) demonstrated that more than 80% of advanced lung cancer patients experience some degree of fatigue.[56] Data reported by Pater et al. (1997) from ten clinical trials with 2390 patients revealed that individuals with lung and ovarian cancer experience more fatigue than other types of cancer.[57] Forlenza et al. (2005) also found a high prevalence of fatigue in lung cancer patients, when compared to other cancers, in the Swedish Twin Registry.[58] Fatigue has been found to be the most common side effect of chemotherapy and radiotherapy in oncology patients and a high incidence of fatigue has been demonstrated in cancer patients undergoing chemotherapy as well as in those after treatment.[51,59-61]

Highly prevalent in advanced NSCLC, fatigue also has a major impact on daily function in this patient population.[50,51] A survey by Tanaka et al. (2002) on 171 ambulatory patients with advanced lung cancer revealed that fatigue significantly interferes with daily life activities, especially physical activities.[62] This symptom has been identified as the principal contributor to HRQOL in a study on lung and breast cancer patients prior to commencing radiotherapy.[63] Fatigue has been identified as an independent predictor of HRQOL in cancer patients.[64]

**Lung cancer symptoms:** Lung cancer symptoms comprise primarily of dyspnoea, coughing and chest pain and can lead to functional limitations. The presence of respiratory symptoms, including dyspnoea, cough, wheezing and haemoptysis, has been shown to be frequent and bothersome in lung cancer patients.[65,66] Dyspnoea in lung cancer is related to the presence of lung disease itself, but may also be related to systemic effects of chemotherapy on ventilatory muscle endurance.[67] Studies have also revealed a high occurrence of pain in lung cancer, with 69% of newly diagnosed lung cancer patients reporting some type of pain within 56 days of receiving chemotherapy.[68] However, evidence of symptom palliation with chemotherapy treatment has been found in advanced NSCLC patients.[16,22,69,70]

The symptoms associated with lung cancer can affect the performance of functional activities, leading to impaired HRQOL. Symptoms of dyspnoea and pain have also shown to negatively interfere with daily activities of ambulatory lung cancer patients.[62] Respiratory symptoms, especially dyspnoea, have been shown to contribute significantly to diminished HRQOL in lung cancer patients, including long-term survivors of lung cancer.[66,71]

**Nutritional status:** Cachexia, loss of weight (particularly skeletal muscle and adipose tissue), can occur in cancer patients as a result of tumour-related abnormalities in protein and fat metabolism.[72] Cancer-related anorexia, loss of appetite, is related to reduced taste and smell of food, early satiety, hypothalamic dysfunction, increased brain tryptophan and cytokine release.[72] A study on 104 newly diagnosed cancer patients found that many cancer patients do not have adequate food intake to maintain a healthy weight.[73] With chemotherapy treatment, malabsorption of nutrients, various mouth and throat problems, including sores, red areas and white patches, as well as symptoms of nausea and vomiting, are common and can also lead to changes in appetite and weight.[74]

Not unique to the lung cancer patient population, changes in nutritional status can produce reduced energy levels, changes in appearance and the presence of undesirable symptoms, all of which negatively affect HRQOL. Weight loss has been shown to be related to poorer HRQOL in a variety of cancer patients, including lung, ovarian and breast.[73] Symptoms of nausea and vomiting have been considered the most concerning side effect of chemotherapy and have also been shown to contribute to reduced HRQOL in oncology patients undergoing treatment.[75]

**3.4 Rationale:** These findings suggest that while chemotherapy may positively impact HRQOL through modest survival benefits and lung cancer symptom palliation, it may also negatively impact HRQOL through side effects related to its toxicities. HRQOL has been shown to be related to certain factors, including

physical performance, symptom status and nutritional status. Many of these factors may potentially be modified or better managed with various health interventions, including physical activity, nursing programs, cognitive-behavioural therapy, nutritional counselling and pharmacological treatment.[76] However, some of these forms of therapy are not traditionally part of the treatment regimen for this patient population. Little is known on which factors contribute the most to positive and negative changes in HRQOL during cancer treatment. Improving our knowledge on these factors can help us better prepare lung cancer patients prior to and during chemotherapy with the use of specific and focused non-invasive interventions. Essentially, this may promote a better response to chemotherapy amongst a larger proportion of advanced NSCLC patients, in terms of HRQOL and survival. To our knowledge, no study to date has identified the predictors of changes in HRQOL during chemotherapy treatment in patients with advanced NSCLC.

## 4. Objectives and hypotheses

**4.1 Objectives:** The primary objective of this study is to identify predictors of changes in physical and mental HRQOL after two cycles of chemotherapy in individuals with advanced NSCLC, where predictors include baseline functional walking capacity, grip strength, chair rise performance, fatigue symptoms, lung cancer symptoms and nutritional status. A secondary objective is to characterize physical performance, symptom status, nutritional status and HRQOL in NSCLC patients and estimate the extent to which they change after chemotherapy treatment. The third objective is to identify relationships between the variables under study and to analyze the strength of these relationships over time.

### 4.2 Hypotheses

*4.2.1* Baseline physical performance and symptom status will predict changes in physical and mental HRQOL, respectively, after two cycles of chemotherapy in patients with advanced NSCLC.

*4.2.2* Lung cancer symptoms will improve while physical performance, fatigue and nutritional status will remain unchanged after two cycles of chemotherapy.
*4.2.3* Physical and mental HRQOL will improve after two cycles of chemotherapy.
*4.2.4* Physical performance, lung cancer symptoms, fatigue symptoms and nutritional status will be moderately correlated with HRQOL both before and after chemotherapy treatment.

## 5. Methods

**5.1 Study design:** The data for this study was obtained from the Pulmonary Oncology Database created from 2004 to 2007 by the Pulmonary Division of the Sir Mortimer B. Davis (S.M.B.D.) Jewish General Hospital, a McGill University affiliated hospital. A longitudinal observational study design was used to collect various clinical data on sixty-four individuals with advanced NSCLC who underwent first-line chemotherapy at the Oncology Department of the S.M.B.D. Jewish General Hospital. Approvals were obtained from the Research Ethics Committee at the S.M.B.D. Jewish General Hospital for the primary study and this secondary analysis.

### 5.2 Study population

*5.2.1 Inclusion criteria:* The study population was chosen according to the following inclusion criteria: a) presence of advanced stage IIIa, IIIb or IV NSCLC with a pathologically confirmed diagnosis (histological or cytological); b) about to undergo chemotherapy as first-line treatment; c) Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2; d) expected life expectancy of greater than three months; e) aged 18 years or older; f) approved for participation by primary pulmonary oncologist; g) informed consent given.

*5.2.2 Exclusion criteria:* The following exclusion criteria were applied: a) contraindication to exercise; b) uncontrolled cardiac or musculoskeletal disease;

c) receiving treatment with steroids for metastases of the central nervous system; d) any erythropoietin or darbopoetin therapy prior to study entry; e) current or recent (in the last two months) participation in any exercise program or less; f) pregnant or breast-feeding mothers; g) prior chemotherapy treatment for NSCLC; h) prior chemotherapy treatment for other malignancy within six months of study entry; i) previous entry into this study.

**5.3 Subject recruitment:** The subjects were recruited from the Pulmonary Division of the S.M.B.D. Jewish General Hospital between 2004 and 2007. Potential subjects were referred by their pulmonary oncologist to the researchers involved in the study according to the specified eligibility criteria. A signed consent form was required prior to entry into the study.

**5.4 Data collection:** This study is a secondary analysis of the data from a study on functional capacity in advanced NSCLC patients undergoing chemotherapy. Each subject enrolled in the primary study was eligible to receive at least two chemotherapy cycles. Subjects were evaluated at three points in time; two evaluations were performed during the week prior to chemotherapy treatment and the third after two cycles of chemotherapy (42 to 56 days after administration of the first chemotherapy dose). Chemotherapy regimens were prescribed at the discretion of the treating physician and cycles mostly lasted 21 to 28 days each, depending on the agent. Data on patient characteristics that were collected include age, gender, ethnicity, height, weight, body mass index and smoking status. Disease and treatment characteristics assessed include diagnosis, disease stage, presence of metastases, concomitant medications, chemotherapy drug, dose and intensity, as well as TNM score. The TNM classification, provided by the International System for Staging Lung Cancer is a staging system where T refers to extent of primary tumour, N refers to spread to lymph nodes, and M refers to spread to distant metastases.[77] The evaluations also included the laboratory measurement of inflammatory markers (C-reactive protein), hemoglobin and

blood cell counts (white blood cell and neutrophil), the professional-rated assessment of functional walking capacity (6-Minute Walk Test), chair rise performance (chair rise repetitions in one minute) and grip strength (hand grip dynamometry), and the self-reported evaluation of HRQOL (36-item Short Form Health survey), functional capacity (Functional Assessment of Cancer Therapy-Lung and Functional Assessment of Cancer Therapy-Anemia), fatigue (Schwartz Cancer Fatigue Scale) and nutritional status (Patient-Generated Subjective Global Assessment). The evaluations were conducted by trained assessors, with standardized instructions, testing environments and rating guidelines for all types of measures.

## 6. Measurement of variables

### 6.1 Primary outcome variables

*6.1.1 Change in physical and mental HRQOL:* The 36-item Short-Form (SF-36) Health Survey is a generic questionnaire measuring the construct of HRQOL. The SF-36 has demonstrated adequate reliability, validity and responsiveness in a number of populations, including the general community, elderly individuals, patients with rheumatoid arthritis, coronary artery disease and traumatic brain injury, long-term survivors of childhood cancers, laryngeal cancer patients, as well as other various patient groups.[78-85] The questionnaire items are scored to produce eight subscale scores and two summary measures. The eight subscale scores, Physical Functioning (PF), Role-Physical (RP), Bodily Pain (BP), General Health (GH), Vitality (VT), Social Functioning (SF), Role-Emotional (RE) and Mental Health (MH), have values ranging from 0 to 100, where higher scores represent better HRQOL. Factor analysis, using norm-based scoring algorithms, is used to calculate the two composite summary measures, the Physical Component Summary (PCS) and the Mental Component Summary (MCS). Two studies have demonstrated that the factor structure for the SF-36 summary measures has been supported in adult survivors of childhood cancer as well as in a mixed cancer and HIV/AIDS patient population.[84,86] Norms for the SF-36 Health Survey in the

Canadian population were published in 2000 by Hopman et al. and were used to calculate the summary scores in this study.[87] The subjects completed the SF-36 Health Survey questionnaires before and after two cycles of chemotherapy. Absolute changes in the PCS and MCS scores were treated as continuous outcome variables for this study. A change of five units on the SF-36 Health Survey questionnaire has been considered clinically meaningful.[88,89]

*6.1.2 Measurement of HRQOL in lung cancer: generic vs. disease-specific*

There has been some concern regarding the use of generic HRQOL questionnaires, such as the SF-36 Health Survey, in cancer as they do not consider the impact of certain cancer-related issues and, therefore, may not be adequate to assess the impact of cancer on HRQOL or be sensitive to change in this patient population.[90] When comparing to population norms, some studies have found similar SF-36 scores between healthy populations and prostate cancer patients, women with endometrial cancer as well as long-term survivors of head and neck cancer and early stage ovarian cancer.[91-94] However, another study has shown that the SF-36 questionnaire can capture lower HRQOL levels in cancer patients when compared to individuals with no cancer.[95]

Despite potential similarities to population norms, the use of the SF-36 questionnaire to measure change in HRQOL in lung cancer patients can be justified. The purpose of this research study was to analyze changes in HRQOL with chemotherapy and predictors of these changes. The SF-36 has demonstrated good responsiveness to change in cancer. It has detected HRQOL changes in head and neck cancer patients and lung cancer patients undergoing treatment as well as HRQOL differences between prostate cancer patients undergoing radiation and surgery, between breast cancer patients undergoing different surgical procedures, and between lung cancer patients undergoing surgery and receiving chemotherapy or radiation.[96-99] In addition, the SF-36 has also been found to be a valid measure of HRQOL in some cancer populations, including patients with laryngeal cancer and adult survivors of childhood cancers, as well as in patients with chronic

obstructive pulmonary disease (COPD), who experience similar symptoms and functional limitations to lung cancer patients.[84,85,100,101] Finally, the SF-36 has demonstrated validity and responsiveness to change in NSCLC patients undergoing thoracic surgery.[102]

Disease-specific HRQOL questionnaires have also been found to be useful in cancer patients as they may be more sensitive to change. In this research study, both the SF-36 and the Functional Assessment of Cancer Therapy-Lung (FACT-L) questionnaires were completed by the subjects before and after two cycles of chemotherapy. The FACT-L, which is considered to be a lung cancer-specific HRQOL questionnaire, has demonstrated internal consistency, content validity and responsiveness to change in patients with lung cancer.[103,104] However, the Lung Cancer Subscale (LCS) of the FACT-L has been considered a good stand-alone indicator of clinical status, specifically lung cancer symptoms.[105] The LCS has demonstrated adequate reliability, criterion validity and responsiveness to change in the lung cancer patient population. Symptom status has consistently been found to be related to HRQOL and may be one of the strongest predictors of HRQOL. Using the LCS and the FACT-L to measure different variables (lung cancer symptoms and HRQOL, respectively) in the study would produce high correlations between these variables. Due to the strong measurement properties of the SF-36 and the usefulness of the LCS to measure lung cancer symptoms, the SF-36 was chosen to measure HRQOL and the LCS of the FACT-L to measure lung cancer symptoms in this study.

### 6.2 Independent variables

*6.2.1 Functional walking capacity:* The 6-Minute Walk Test (6MWT) has been used in many patient populations to assess functional walking capacity and measures the distance walked by the subject in six minutes. In cancer patients, it has been found to have excellent inter-tester reliability and good test-retest reliability. Also, it has good known groups validity using age and good convergent validity when comparing to healthy controls.[48] To minimize

measurement bias, assessors were trained to use standardized initial instructions and feedback throughout the test. The environment was kept consistent for each testing. The 6MWT provides measures of distance in metres and pre-chemotherapy 6MWT scores were treated as continuous variables for analysis. Norm 6MWT reference values for the elderly population have been generated.[106] Various studies have reported different values considered to be a clinically meaningful change on the 6MWT. Salzman (2009) recently reviewed the literature and reported changes ranging from 35 meters to 107 meters.[107] Perera et al. (2006) reported 50 meters as an estimate of substantial change on the 6MWT in a sample with community-dwelling older people and subacute stroke survivors and this was the value we chose for this study.[108]

*6.2.2 Chair rise performance:* The one-minute chair rise test is a measure of chair rise performance. The role of knee extensor strength in the chair rise movement has been recognized, especially in the functionally impaired elderly population.[35] Peak muscle power of the ankle dorsiflexors has also shown to correlate with time for ten chair rise repetitions.[109] The chair rise test measures the number of chair rise repetitions performed in one minute. This test has demonstrated excellent test-retest reliability and strong validity when compared with laboratory measures of one repetition maximum leg press.[110] To minimize measurement bias, standardized instructions and testing environments were used. The one-minute chair rise test provides a number of chair rise repetitions and test results were treated as continuous variables for analysis.

*6.2.3 Grip strength:* Hand grip strength was measured using dynamometry. Measurement of maximum grip strength has shown high inter-rater reliability and test-retest reliability when averages are used.[111] In this study, grip strength was tested using a Jamar dynamometer. The test was repeated three times each on both the dominant and non-dominant hands in a consistent testing environment and position and the mean average of the six scores was calculated to obtain a

measure of force in kilograms. Hand grip strength was treated as a continuous variable. Normative data for grip strength in adults have been established.[112]

*6.2.4 Fatigue symptoms:* The Schwartz Cancer Fatigue Scale (SCFS) is a self-reported measure of fatigue severity. It has demonstrated high reliability, content validity and construct validity.[113,114] The questionnaire has six items, each rated on a five-point scale, to generate a total score on 30, where higher scores represent worse fatigue symptoms. The SCFS scores were treated as continuous data during analysis. A five-unit change on SCFS has been considered clinically meaningful.[115]

*6.2.5 Lung cancer symptoms:* The Lung Cancer Subscale (LCS) of the Functional Assessment of Cancer Therapy-Lung (FACT-L) is a self-reported assessment of disease-related symptoms, such as dyspnoea, cough and chest tightness. The FACT-L has demonstrated good internal consistency and responsiveness to change.[103] The LCS includes seven items, with each item being rated on a five-point scale. A score on 28 is generated, with lower scores representing increased symptoms. The LCS has demonstrated adequate reliability and validity as an independent indicator of symptom status.[105] For the purpose of this study, LCS scores were treated as continuous data. Cella et al. (2002) estimated a two- to three-point difference on the LCS of the FACT-L to be clinically important in a randomized controlled trial comparing three chemotherapy regimens in advanced NSCLC patients.[104] More recent research has demonstrated that increasing the criterion for symptom improvement from a two-point change in LCS score to a three-point change barely affects calculated rates of symptom improvement.[116]

*6.2.6 Nutritional status:* Nutritional status refers to weight, food intake and nutrition-related symptoms (including nausea and vomiting). The Patient-Generated Subjective Global Assessment (PG-SGA) is a measure of nutritional status, with components of food intake, weight change, nutrition-related

symptoms and performance status. The PG-SGA has demonstrated moderate reliability, moderate concurrent validity and high sensitivity and specificity levels for the assessment of nutrition in patients with cancer.[117,118] The information obtained from the PG-SGA can be calculated to produce a continuous PG-SGA numerical score or classified into three Subjective Global Assessment SGA categories of nutritional status: well nourished (SGA-A), moderately malnourished (SGA-B), and severely malnourished (SGA-C). While the PG-SGA questionnaire includes a patient-reported component as well as a component completed by a health professional, only the first part was used for this study. Therefore, our modified PG-SGA numerical scores and SGA classifications are based on patient report only.

### 6.3 Confounding variables

Potential confounding variables which were measured included descriptive characteristics of age and gender. An additional component related to the chemotherapy treatment was also analyzed and this was type of chemotherapy drug. Chemotherapy drug combinations were divided into four categories: platinum/taxane-based (carboplatin-taxol or carboplatin-taxotere), platinum/gemcitabine (carboplatin-gemcitabine), gemcitabine/gemcitabine, and other. These variables were treated as categorical variables, with the exception of age, which was treated as continuous.

## 7. Statistical analysis

**7.1 Descriptive analysis:** The SAS statistical package (version 9.1) was used for all statistical analyses. Patient characteristics were analyzed with descriptive statistics through the calculation of means and standard deviations for quantitative data and relative frequencies for categorical data. Physical performance, symptom status, nutritional status and HRQOL of the subjects at baseline were also compared to age-related population norms or to other lung cancer patient samples. Descriptive variables were compared between subjects that remained in the study

and subjects that dropped out using independent t-tests (for means) and chi-square tests (for proportions). Descriptive statistics, through the calculation of means and standard deviations, were used to characterize changes in functional walking capacity, grip strength, chair rise performance, fatigue, lung cancer symptoms, nutritional status and HRQOL over time. Data imputation for missing item responses on self-reported questionnaires was performed using mean subscale scores (of non-missing item responses), when more than half of the subscale items were completed by the subject.

**7.2 Bivariate analysis:** Statistical comparison of mean baseline and post-chemotherapy scores for each of the variables were performed using paired t-tests. Relationships between the variables prior to and after chemotherapy, between changes in the variables under study, as well as between the variables at baseline and changes in the variables, were all analyzed using Pearson's correlations and correlation matrices. Minimum clinically important differences for HRQOL (SF-36), fatigue symptoms (SCFS), lung cancer symptoms (LCS) and functional walking capacity (6MWT) were used to identify percentages of subjects that improved or worsened after chemotherapy.

**7.3 Multivariate analysis:** Multiple linear regression analysis was used to identify predictors of changes in physical and mental HRQOL over chemotherapy. The primary outcome variables, change in physical HRQOL (SF-36 PCS score) and change in mental HRQOL (SF-36 MCS score), were treated as continuous variables. Separate regression analyses were performed for each outcome. Subjects with missing SF-36 scores pre- or post-chemotherapy were excluded from the analyses. Six independent variables, which were also treated as continuous, were initially chosen as potential predictors. Baseline (pre-chemotherapy) levels of the following variables were chosen: functional walking capacity (6MWT distance), chair rise performance (repetitions in one minute), hand grip strength, fatigue (SCFS score), lung cancer symptoms (LCS score) and

nutritional status (PG-SGA score). Subjects with missing scores for these variables at baseline were excluded from the analyses. The models were adjusted for age, gender and chemotherapy drug. Age was treated as a continuous variable while gender and chemotherapy drug were categorized with the use of dummy variables. The predictors were tested for collinearity to remove redundant independent variables from the models. Different methods of model selection, including forward, backward, stepwise and maximum adjusted R squared, were carried out to determine the most appropriate and consistent regression model. P-values and 95% confidence intervals of the regression coefficients for the final regression models were both analyzed for statistical significance and clinical relevance. The assumptions of multiple linear regression were verified for each chosen model. The assumptions of multiple linear regression are the following: normal distribution of dependent variable and residuals, linearity of relationships between each independent variable and dependent variable, homoscedasticity, and independence of observations and errors.

## 8. Results

### 8.1 Descriptive analysis

*8.1.1 Demographic and clinical characteristics:* Sixty-four subjects fulfilled the inclusion criteria and consented to participate in the study. Baseline demographic and clinical characteristics are presented in table 1. The subjects' mean age (and standard deviation) along with frequency data for gender, smoking status and cancer stage are included. Forty-seven subjects received two cycles of chemotherapy treatment and completed the study. Table 2 describes the type of chemotherapy given to the subjects who completed the study. Seventeen subjects were considered dropouts and were excluded from the analysis for reasons that included death before study completion, withdrawal from study and administrative reasons.

**Table 1. Baseline demographic and clinical characteristics of study sample**

| Descriptive variable | | |
|---|---|---|
| Age (years) | | 63.8 ± 11.9 |
| Gender (%) | Female | 53.1 (n=34) |
| | Male | 46.9 (n=30) |
| Smoking status (%)* | Current smoker | 36.7 (n=22) |
| | Ex-smoker | 50 (n=30) |
| | Never smoked | 13.3 (n=8) |
| Stage of cancer (%) | 4 | 60.9 (n=39) |
| | 3B+ | 17.2 (n=11) |
| | 3B | 17.2 (n=11) |
| | 3A | 4.7 (n=3) |

Data presented as means ± standard deviations (continuous data) or relative frequencies (categorical data);

* Smoking status data missing for 4 subjects (n=60)

**Table 2. Type of chemotherapy received by subjects who completed the study**

| Chemotherapy type | n (%) |
|---|---|
| Carboplatin-gemcitabine | 12 (25.5%) |
| Carboplatin-taxol | 14 (29.8%) |
| Carboplatin-taxotere | 10 (21.3%) |
| Gemcitabine-gemcitabine | 5 (10.6%) |
| Cisplatin-etoposide | 3 (6.4%) |
| Carboplatin-xyotax | 1 (2.1%) |
| Carboplatin-CT* | 1 (2.1%) |
| CT-CT* | 1 (2.1%) |
| **Total** | **47 (100%)** |

* CT: Investigational chemotherapy drug received by two patients, as part of another trial

*8.1.2 Baseline symptom and nutritional status:* Lung cancer symptoms, fatigue symptoms and nutritional status were analyzed in the 64 subjects prior to chemotherapy treatment. Means and standard deviations for the LCS scores, SCFS scores and PG-SGA scores are presented in table 3. Classification into PG-SGA categories is also presented. Analysis of specific lung cancer symptoms revealed that the symptoms reported most frequently by the subjects were shortness of breath (86%), difficulty breathing (83%), poor appetite (80%) and cough (75%). The most frequently reported severe symptoms were poor appetite (30%), cough (25%) and difficulty breathing (20%). Symptoms were considered severe if the patients rated the LCS item as 0 or 1 (after score reversal of four items). These findings are demonstrated in table 4. On the PG-SGA questionnaire, recent weight loss was reported by 25% of the subjects, while reduced nutritional intake was reported by 43%. In terms of activities and function, 51% rated their activity on the PG-SGA as "not my normal self, but able to be up and about with fairly normal activities", 16% as "not feeling up to most things, but in bed or chair less than half the day" and 11% as "able to do little activity and spend most of the day in bed or chair."[117] Frequency data for various nutritional symptoms are also demonstrated in table 5.

**Table 3. Baseline symptom status and nutritional status**

| Measure | |
|---|---|
| LCS score (0-28) | 18.9 ± 3.8 |
| SCFS score* (0-30) | 12.8 ± 4.9 |
| PG-SGA score†* | 5.4 ± 5.4 |
| SGA categories† (%) | |
| well nourished (A) | 16.4 (n=10) |
| moderately malnourished (B) | 55.7 (n=34) |
| severely malnourished (C) | 27.9 (n=17) |

Data presented as means ± standard deviations (continuous data) or relative frequencies (categorical data);

Lung Cancer Subscale (LCS) score, higher scores represent less severe lung cancer symptoms; Schwartz Cancer Fatigue Scale (SCFS) score, higher scores represent more severe fatigue symptoms; Patient-Generated Subjective Global Assessment (PG-SGA) score, higher scores represent worse nutritional status, and Subjective Global Assessment (SGA) categories: well nourished (SGA-A), moderately malnourished (SGA-B) and severely malnourished (SGA-C);

†Modified PG-SGA scores and SGA categories based on patient report only;

*SCFS data missing for 2 subjects (n=62); PG-SGA data missing for 3 subjects (n=61)

**Table 4. Frequency of subjects reporting lung cancer symptoms at baseline**

| LCS item | Symptomatic (%) | Severely symptomatic (%) |
|---|---|---|
| Shortness of breath* | 86 | 14 |
| Losing weight* | 56 | 9 |
| Unclear thinking | 59 | 8 |
| Coughing* | 75 | 25 |
| Poor appetite | 80 | 30 |
| Chest tightness* | 45 | 6 |
| Difficulty breathing | 83 | 20 |

Lung Cancer Subscale (LCS) items rated on 5-point Likert scale: 0=not at all; 1=a little bit; 2=somewhat; 3=quite a bit; and 4=very much; (n=64);

*LCS items reversed for scoring, so that higher scores represent better symptoms

**Table 5. Frequency of subjects reporting nutritional symptoms at baseline**

| PG-SGA item | Symptomatic (%) |
|---|---|
| No appetite | 39 |
| Nausea | 13 |
| Constipation | 11 |
| Things taste funny/have no taste | 11 |
| Vomiting | 7 |
| Diarrhea | 5 |
| Dry mouth | 16 |
| Smells bother me | 13 |
| Full quickly | 10 |
| Pain | 7 |

Patient-Generated Subjective Global Assessment (PG-SGA) items checked off as "problems that have kept me from eating enough during the past two weeks"; (n=61)

*8.1.3 Baseline physical performance:* Functional walking capacity, hand grip strength and chair rise performance were analyzed in the subjects prior to undergoing chemotherapy. Means and standard deviations for the 6MWT distances, grip strength measures and chair rise repetitions in one minute are presented in table 6.

**Table 6. Baseline physical performance**

| Measure | |
|---|---|
| 6MWT distance* (m) | 441.9 ± 103.8 |
| Grip strength* (kg) | 26.9 ± 11.1 |
| Chair rise repetitions* (in 1 min) | 20.8 ± 7.8 |

Data presented as means ± standard deviations;

6-Minute Walk Test (6MWT) distance in metres, longer distances represent increased walking capacity; Grip strength in kilograms, higher measures of force represent increased hand grip strength (average of three trials per hand); Chair rise repetitions performed in one minute, higher numbers represent better chair rise performance;

*6MWT data missing for 1 subject (n=63); Grip strength and chair rise data missing for 2 subjects (n=62)

*8.1.4 Baseline HRQOL:* Sixty-three subjects filled out the SF-36 questionnaire prior to commencing chemotherapy. One subject did not complete the Role-Emotional subscale, providing baseline PCS and MCS scores for 62 subjects only. Tables 7 and 8 present the eight SF-36 subscale and two summary scores of the subjects prior to commencing chemotherapy, as means and standard deviations.

**Table 7. Baseline health-related quality of life (SF-36 subscale scores)**

| SF-36 subscale | Score (0-100) |
|---|---|
| Physical Function | 59.5 ± 26.9 |
| Role-Physical | 31.3 ± 41.6 |
| Bodily Pain | 66.6 ± 29.8 |
| General Health | 55.2 ± 17.5 |
| Vitality | 52.6 ± 23.7 |
| Social Function | 61.7 ± 26.8 |
| Role-Emotional* | 50.0 ± 46.7 |
| Mental Health | 58.9 ± 22.2 |

Data presented as means ± standard deviations;

36-item Short-Form Health Survey (SF-36) subscale scores, higher scores represent better health-related quality of life; SF-36 data available for 63 subjects at baseline;

*SF-36 Role-Emotional subscale data missing for 2 subjects (n=62)

**Table 8. Baseline health-related quality of life (SF-36 summary scores)**

| SF-36 summary | Score |
|---|---|
| Physical Component Summary | 39.6 ± 11.6 |
| Mental Component Summary | 39.8 ± 14.4 |

Data presented as means ± standard deviations

36-item Short-Form Health Survey (SF-36) summary scores standardized using norm-based scoring (Canadian population norms used[87]), higher scores represent better HRQOL; SF-36 data available for 62 subjects at baseline

*8.1.5 Comparison of dropouts to completers at baseline:* When comparing dropouts to subjects that completed the study using independent t-tests for means and chi-square tests for proportions, no significant differences were found between the two groups in age, gender, cancer stage, symptom status, nutritional status, physical performance or HRQOL at baseline ($p > 0.01$). However, the dropout group tended to have a higher proportion of females, as well as have worse lung cancer symptoms and nutritional status than those that remained in the study ($p < 0.05$). These findings are presented in table 9.

**Table 9. Comparison of dropouts to completers at baseline**

| Measure | Dropouts (n=17*) | Completers (n=47*) | Between-group difference | p-value |
|---|---|---|---|---|
| Age (years) | 65.2 ± 11.3 | 63.3 ± 12.2 | 1.9 ± 12.0 | 0.57 |
| Gender (female, %) | 64.7 | 48.9 | N/A | 0.02 |
| Stage (4, %) | 58.8 | 61.7 | N/A | 0.69 |
| LCS (0-28) | 17.0 ± 3.8 | 19.5 ± 3.7 | 2.5 ± 3.7 | 0.02 |
| SCFS (0-30) | 14.3 ± 6.1 | 12.3 ± 4.4 | 2.0 ± 4.9 | 0.17 |
| PG-SGA† | 7.9 ± 6.6 | 4.6 ± 4.8 | 3.2 ± 5.3 | 0.04 |
| 6MWT (m) | 405.1 ± 100.9 | 454.5 ± 102.9 | 49.4 ± 102.4 | 0.10 |
| Grip strength (kg) | 25.4 ± 11.4 | 27.4 ± 11.1 | 1.9 ± 11.2 | 0.56 |
| Chair rise reps (in 1 min) | 18.9 ± 9.6 | 21.4 ± 7.2 | 2.5 ± 7.8 | 0.28 |
| SF-36 PCS | 36.0 ± 13.6 | 40.8 ± 10.7 | 4.8 ± 11.5 | 0.15 |
| SF-36 MCS | 35.8 ± 12.1 | 41.2 ± 15.0 | 5.4 ± 14.3 | 0.20 |

Data presented as means ± standard deviations (continuous data) or relative frequencies (categorical data); independent t-tests performed for comparison of means and chi-square tests for comparison of proportions;

Lung Cancer Subscale (LCS), higher scores represent less severe lung cancer symptoms; Schwartz Cancer Fatigue Scale (SCFS), higher scores represent more severe fatigue symptoms; Patient-Generated Subjective Global Assessment (PG-SGA), higher scores represent worse nutritional status; 6-Minute Walk Test (6MWT), longer distances represent increased walking capacity; Grip strength, higher measures of force represent increased grip strength; Chair rise repetitions performed in one minute, higher numbers represent better chair rise performance; 36-item Short-Form Health Survey (SF-36) Physical Component Summary (PCS) and Mental Component Summary (MCS), higher scores represent better health-related quality of life;

†Modified PG-SGA scores based on patient report only;

*Missing data ($n \leq 2$) for some measures in dropouts and completers

## 8.2 Bivariate analysis

*8.2.1. Relationships between variables prior to and after chemotherapy:*

Correlations between the variables under study were analyzed prior to and after chemotherapy. Pearson correlation coefficients are presented in table 10. Lung cancer symptoms, fatigue symptoms and nutritional status were all moderately correlated with each other in the subjects both pre- and post- chemotherapy ($r = -0.62$ to 0.38, range). Similarly, functional walking capacity, grip strength and chair rise performance were moderately correlated with each other prior to and after chemotherapy ($r \geq 0.4$). Fatigue symptoms and lung cancer symptoms were correlated with chair rise performance post-chemotherapy ($r = -0.40$ and $r = 0.33$, respectively). Nutritional status and functional walking capacity were correlated with physical HRQOL before chemotherapy, while lung cancer symptoms, fatigue symptoms and chair rise performance were moderately correlated with physical HRQOL both before and after chemotherapy. Fatigue and lung cancer symptoms correlated with mental HRQOL moderately to strongly both before and after chemotherapy (before: $r = -0.63$ and 0.31 for fatigue and lung cancer symptoms, respectively; after: $r = -0.60$ and 0.42). Nutritional status was moderately correlated with mental HRQOL only after chemotherapy.

**Table 10. Correlations between variables prior to and after chemotherapy**

| | Correlation coefficients | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | **LCS** | **SCFS** | **PG-SGA†** | **6MWT** | **GS** | **CRR** | **PCS** | **MCS** |
| **LCS** | | -0.57** | -0.53* | 0.29 | 0.27 | 0.33* | 0.47* | 0.42* |
| **SCFS** | **-0.52**** | | 0.31* | -0.09 | -0.29* | -0.40* | -0.43* | -0.60** |
| **PG-SGA†** | **-0.62**** | **0.38*** | | -0.15 | -0.07 | -0.18 | -0.21 | -0.47* |
| **6MWT** | 0.28* | -0.15 | -0.27* | | 0.43* | 0.53* | 0.16 | 0.29 |
| **GS** | 0.07 | -0.08 | -0.09 | **0.52**** | | 0.40* | 0.27 | 0.21 |
| **CRR** | 0.08 | -0.06 | -0.17 | **0.55**** | **0.42*** | | 0.43* | 0.19 |
| **PCS** | **0.56**** | **-0.31*** | **-0.42*** | **0.52**** | 0.14 | **0.31*** | | -0.02 |
| **MCS** | **0.31*** | **-0.63**** | -0.28* | 0.01 | 0.05 | -0.09 | 0.10 | |

Pre-chemotherapy  Post-chemotherapy  ** $p < 0.0001$  * $p < 0.05$

Lung Cancer Subscale (LCS), higher scores represent less severe lung cancer symptoms; Schwartz Cancer Fatigue Scale (SCFS), higher scores represent more severe fatigue symptoms; Patient-Generated Subjective Global Assessment (PG-SGA), higher scores represent worse nutritional status; 6-Minute Walk Test (6MWT), longer distances represent increased walking capacity; Grip strength (GS), higher measures of force represent increased grip strength; Chair rise repetitions (CRR) performed in one minute, higher numbers represent better chair rise performance; 36-item Short-Form Health Survey (SF-36) Physical Component Summary (PCS) and Mental Component Summary (MCS), higher scores represent better health-related quality of life;

†Modified PG-SGA scores based on patient report only

*8.2.2 Comparison of scores pre- and post-chemotherapy:* Subjects that completed the study were compared prior to and after two cycles of chemotherapy using paired t-tests. Lung cancer symptoms, fatigue symptoms, nutritional status, functional walking capacity, grip strength, chair rise performance and various domains of HRQOL were analyzed and the mean change scores with standard deviations are presented in table 11. Functional walking capacity, as measured by the 6MWT, decreased significantly after chemotherapy treatment ($p < 0.01$). On the SF-36 questionnaire, the Mental Health subscale improved significantly ($p < 0.01$). No other significant differences were found. However, trends towards a decline in grip strength, general health and physical HRQOL were shown, with lower grip strength measures, SF-36 General Health subscale scores and SF-36 PCS scores, respectively, after chemotherapy ($p < 0.05$).

**Table 11. Comparison of scores pre- and post-chemotherapy**

| Measure | Mean within-group difference (post – pre) | n | p-value |
|---|---|---|---|
| LCS (0-28) | 0.8 ± 3.4 | 46 | 0.13 |
| SCFS (0-30) | 0.02 ± 5.1 | 47 | 0.98 |
| PG-SGA† | 0.5 ± 6.3 | 45 | 0.57 |
| 6MWT (m) | -45.4 ± 106.6 | 44 | 0.0065** |
| Grip strength (kg) | -1.3 ± 3.9 | 46 | 0.03* |
| Chair rise reps (in 1 min) | -0.9 ± 5.4 | 46 | 0.25 |
| SF-36 PCS | -2.8 ± 8.2 | 46 | 0.02* |
| SF-36 MCS | 2.4 ± 12.8 | 46 | 0.2 |
| SF-36 PF (0-100) | -4.7 ± 23.2 | 47 | 0.17 |
| SF-36 RP (0-100) | -3.7 ± 38.3 | 47 | 0.51 |
| SF-36 BP (0-100) | 7.0 ± 25.2 | 47 | 0.06 |
| SF-36 GH (0-100) | -6.5 ± 16.7 | 47 | 0.01* |
| SF-36 VT (0-100) | -2.3 ± 20.2 | 47 | 0.43 |
| SF-36 SF (0-100) | -5.3 ± 24.7 | 47 | 0.15 |
| SF-36 RE (0-100) | -0.7 ± 51.8 | 46 | 0.92 |
| SF-36 MH (0-100) | 9.0 ± 18.9 | 47 | 0.002** |

** $p < 0.01$ * $p < 0.05$

Lung Cancer Subscale (LCS), higher scores represent less severe lung cancer symptoms; Schwartz Cancer Fatigue Scale (SCFS), higher scores represent more severe fatigue; Patient-Generated Subjective Global Assessment (PG-SGA), higher scores represent worse nutritional status; 6-Minute Walk Test (6MWT), longer distances represent increased walking capacity; Grip strength, higher measures represent increased grip strength; Chair rise repetitions performed in 1 minute, higher numbers represent better chair rise performance; 36-item Short-Form Health Survey (SF-36) Physical Function (PF), Role-Physical (RP), Bodily Pain (BP), General Health (GH), Vitality (VT), Social Function (SF), Role-Emotional (RE) and Mental Health (MH) subscales, Physical Component Summary (PCS) and Mental Component Summary (MCS), higher scores represent better status;

†Modified PG-SGA scores based on patient report only

*8.2.3 Clinically meaningful changes over time:* A change of five units was considered a clinically meaningful change in the SF-36 Physical Component and Mental Component Summaries. For the 46 subjects that completed the SF-36 at baseline and follow-up, 20% improved their physical HRQOL clinically meaningfully and 33% deteriorated after two cycles of chemotherapy. Similarly, 37% clinically improved in mental HRQOL while 26% deteriorated. For the LCS questionnaire, a change of three units was considered clinically meaningful. In this study, 33% of 46 subjects who provided LCS scores improved their lung cancer symptoms after chemotherapy while 17% worsened. On the SCFS, 15% of the 47 subjects worsened their fatigue, increasing their SCFS score by at least five units, while 15% improved after chemotherapy. On the 6MWT, a change of 50 meters in distance walked was considered clinically important. Of the 44 subjects that completed the 6MWT both before and after chemotherapy, 9% clinically improved their walking distance and 36% worsened.

*8.2.4 Relationships between variables at baseline and change in variables:* Correlations between baseline levels and changes in each variable after two cycles of chemotherapy were analyzed. Baseline levels of most of the variables were moderately correlated with change in those particular variables, except for measures of physical performance (chair rise, grip strength and 6MWT). Each baseline variable was negatively correlated with its change variable. In addition, baseline LCS scores were positively correlated with change in grip strength, while baseline chair rise repetitions were negatively correlated with change in 6MWT. Also, baseline physical HRQOL was correlated with change in fatigue symptoms ($r = -0.31$). These findings are presented in table 12. Correlations between changes in each of the variables studied were analyzed as well. The only moderate correlations found were between change in 6MWT distance and change in chair rise performance ($r = 0.51$) as well as between change in SCFS score and change in SF-36 MCS score ($r = -0.41$).

**Table 12. Correlations between baseline variables and change variables**

| | Correlation coefficients | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Baseline variables** | **Change variables (pre- to post-chemotherapy)** | | | | | | | |
| | **LCS** | **SCFS** | **PG-SGA†** | **6MWT** | **GS** | **CRR** | **PCS** | **MCS** |
| **LCS** | **-0.37*** | -0.09 | 0.04 | 0.16 | **0.35*** | 0.28 | -0.13 | -0.17 |
| **SCFS** | -0.02 | **-0.46*** | -0.04 | -0.04 | -0.09 | -0.17 | 0.02 | **0.41*** |
| **PG-SGA†** | 0.06 | -0.21 | **-0.54*** | -0.16 | -0.09 | -0.21 | 0.22 | 0.20 |
| **6MWT** | 0.04 | -0.13 | 0.02 | -0.25 | -0.11 | 0.29 | -0.10 | 0.29 |
| **GS** | 0.10 | -0.18 | 0.09 | -0.01 | -0.21 | 0.14 | 0.09 | 0.20 |
| **CRR** | 0.03 | -0.19 | -0.08 | **-0.30*** | 0.01 | -0.05 | 0.11 | 0.27 |
| **PCS** | 0.09 | **-0.31*** | -0.05 | -0.09 | 0.27 | 0.09 | **-0.36*** | 0.25 |
| **MCS** | -0.02 | 0.28 | -0.03 | 0.12 | 0.13 | 0.08 | -0.10 | **-0.59**** |

** $p < 0.0001$ * $p < 0.05$

Lung Cancer Subscale (LCS), higher scores represent less severe lung cancer symptoms; Schwartz Cancer Fatigue Scale (SCFS), higher scores represent more severe fatigue symptoms; Patient-Generated Subjective Global Assessment (PG-SGA), higher scores represent worse nutritional status; 6-Minute Walk Test (6MWT), longer distances represent increased walking capacity; Grip strength (GS), higher measures of force represent increased grip strength; Chair rise repetitions (CRR) performed in one minute, higher numbers represent better chair rise performance; 36-item Short-Form Health Survey (SF-36) Physical Component Summary (PCS) and Mental Component Summary (MCS), higher scores represent better health-related quality of life;

† Modified PG-SGA scores based on patient report only

**8.3 Multivariate analysis**

Of the forty-seven subjects that completed the study, one subject did not respond to the items of one SF-36 subscale and one subject did not complete the PGSGA questionnaire prior to receiving chemotherapy, resulting in final regression analyses on 45 subjects.

*8.3.1 Model selection:* The initial selection of the independent variables for the regression models was based on research findings that demonstrate relationships between the chosen predictors and the outcomes, change in physical and mental HRQOL. None of the six independent variables were found to be collinear (*Appendix 1*).

*8.3.2 Predictors of change in physical HRQOL:* The final regression model for PCS change included only nutritional status, adjusted for age, gender and chemotherapy drug combination. Baseline nutritional status, measured by the PG-SGA, explained 6% of the variance in the outcome, change in physical HRQOL after chemotherapy. The regression coefficient of 0.47 (95% CI: -0.14, 1.08) indicates that with a one-unit increase in the PG-SGA score prior to starting chemotherapy, the change in SF-36 PCS score with chemotherapy would differ by 0.47 units, keeping all other variables constant ($p = 0.12$). However, the high p-value and the inclusion of the value 0 in the 95% confidence interval of the regression coefficient for nutritional status indicate statistical and clinical insignificance. These findings are presented in table 13.

*8.3.2 Predictors of change in mental HRQOL:* The final regression model for MCS change included fatigue symptoms and functional walking capacity, adjusted for age, gender and chemotherapy drug combination. Baseline fatigue symptoms, measured by the SCFS, and functional walking capacity, measured by the 6MWT, both significantly predicted change in mental HRQOL with chemotherapy ($p = 0.0079$ and $p = 0.0496$, respectively). A regression coefficient

of 1.17 (95% CI: 0.32, 2.02) indicates that with a five-unit change on the SCFS questionnaire prior to starting chemotherapy, the change in SF-36 MCS score over chemotherapy would differ by about five to six points. Similarly, a regression coefficient of 0.02 (95% CI: -0.00, 0.08) indicates that an increase in the 6MWT distance walked before chemotherapy of 100 meters would increase the pre-post difference in MCS score by four points. The 95% confidence interval of the regression coefficient for fatigue symptoms does not contain the value 0, indicating both statistical significance and clinical relevance. For functional walking capacity, the 95% confidence interval indicates borderline clinical significance. Baseline fatigue symptoms explained 10% of the variance in the outcome, while baseline functional walking capacity explained an additional 8%. Table 13 demonstrates these findings. When chair rise performance was added to the model, chair rise performance and functional walking capacity both did not predict MCS change. When functional walking capacity was replaced with chair rise performance, chair rise repetitions in one minute at baseline also explained 7% of the variance in change in mental HRQOL. The regression coefficient for chair rise performance was 0.49 (95% CI: -0.01, 0.99) , indicating that an ability to perform ten additional chair rise repetitions in one minute at baseline would result in a five-point increase in MCS change score with chemotherapy ($p = 0.056$). The p-value and 95% confidence interval indicate borderline statistical and clinical significance for the role of chair rise performance in predicting MCS change.

**Table 13. Multiple linear regression models for predictors of changes in physical and mental HRQOL**

| Outcome | Predictors | Parameter estimate (β) | 95% CI (β) | p-value | Total $R^2$ |
|---|---|---|---|---|---|
| Physical HRQOL Δ (SF-36 PCS) | *Nutritional status* (PG-SGA†) | 0.47 | -0.14, 1.08 | 0.12 | 0.14 |
| Mental HRQOL Δ (SF-36 MCS) | *Fatigue* (SCFS) | 1.17 | 0.32, 2.02 | < 0.01 | 0.33 |
| | *Walking capacity* (6MWT) | 0.04 | -0.00, 0.08 | < 0.05 | |

Data presented as parameter estimates and 95% confidence intervals (CI) for regression coefficients (β) and total coefficients of determination ($R^2$) for regression models;
Regression models adjusted for age, gender and chemotherapy drug combination ($R^2$ = 0.08 and 0.15 for PCS change and MCS change, respectively);
Schwartz Cancer Fatigue Scale (SCFS), higher scores represent more severe fatigue symptoms; Patient-Generated Subjective Global Assessment (PG-SGA), higher scores represent worse nutritional status; 6-Minute Walk Test (6MWT), longer distances represent increased walking capacity; 36-item Short-Form Health Survey (SF-36) Physical Component Summary (PCS) and Mental Component Summary (MCS), higher scores represent better health-related quality of life;
†Modified PG-SGA scores based on patient report only

*8.3.3 Assumptions of multiple linear regression:* Histograms were constructed and Kolmogorov-Smirnov goodness-of-fit tests were performed to verify the normality of the distribution for the dependent variables, change in physical HRQOL and change in mental HRQOL (*Appendix 2*). Scatter plots were constructed to verify the linearity of the relationships between each independent and dependent variable (*Appendix 3*). Graphs and the Shapiro-Wilk tests were used to verify normality of the residuals of the two final regression models (*Appendix 4*). Homoscedasticity was verified using graphs of residuals plotted against predicted values and the White tests of specification (*Appendix 5*). As

demonstrated, the two final regression models used in this study satisfied the assumptions of multiple linear regression.

## 9. Discussion

Our findings show that pre-chemotherapy fatigue symptoms and 6MWT distances predict changes in mental HRQOL during chemotherapy in patients with advanced NSCLC. Due to the poor prognosis associated with the disease, one of the main focuses of lung cancer research has become the improvement of function and HRQOL. This study highlights the need for improved medical and non-medical management of physical performance and symptom status in order to promote optimal effects of chemotherapy on HRQOL in advanced NSCLC.

### Clinical profile

At baseline, the patients who participated in our study were mostly elderly ex-smokers with advanced stage NSCLC. Analysis of the SF-36 scores revealed high variability in the HRQOL status of our study sample. The subjects scored worst on the Role-Physical subscale, and best on the Bodily Pain and Social Function subscales. With the SF-36 composite summaries, it was found that the subjects in our study scored more than one standard deviation lower than the Canadian population for both physical and mental HRQOL, indicating poorer levels of HRQOL than the normal population. This is consistent with the study by Mohan et al. (2007), which demonstrated similar findings in this patient population despite using a different HRQOL questionnaire, the European Organisation for Research and Treatment of Cancer QLQ-C30.[18]

Analysis of symptom status demonstrated that the subjects in our study sample were mostly symptomatic and had mild to moderate levels of fatigue and other lung cancer symptoms. Not many previous studies have used the SCFS to measure fatigue symptoms in lung cancer. Recently though, Sarna et al. (2008) analyzed symptom severity in lung cancer patients immediately post-thoracotomy and found mean SCFS scores similar to ours.[119] A number of studies using other

fatigue questionnaires have also identified fatigue as a common problem in lung cancer patients.[56,57,120] In our study, the subjects had not undergone any previous treatment at the time of the initial evaluation, indicating that their fatigue was disease-related and not treatment-related. The phenomenon of fatigue has been identified as complex in the cancer population. Okuyama et al. (2001) found that fatigue in lung cancer was strongly related to depression, performance status as well as other symptoms, suggesting that fatigue can be attributed to both physical and psychological factors.[56]

For other lung cancer symptoms, our findings were similar to those found in previous studies of symptom status that used the LCS measure.[69,121,122] Mean LCS scores for our study's subjects were also similar to LCS normative data for the lung cancer patient population.[123] As expected, lung cancer symptoms reported most frequently by the subjects were respiratory in nature, including shortness of breath, difficulty breathing and cough. Interestingly, poor appetite was also a common issue and thirty percent of the subjects reported no or very little appetite prior to chemotherapy. In addition, more than half of the subjects were categorized as moderately malnourished on the SGA, while more than a quarter were classified as severely malnourished, indicating poor nutritional status in our study sample. Issues with appetite and nutritional status in this population are related to cancer cachexia, a complex syndrome associated with an imbalance of energy due to reduced nutritional intake and increased energy expenditure, as well as with metabolic abnormalities caused by tumour-catabolic factors.[124] Our PG-SGA proportions were similar to those reported by Bauer et al. (2002), who evaluated 71 hospitalized patients with mixed cancer types, but higher than those reported by Segura et al. (2005), who evaluated nutritional status in 781 subjects with advanced stage cancer of mixed types (23% lung cancer).[117,118] Similar to both studies, the subjects in our study also reported loss of appetite most frequently and diarrhoea less frequently for nutritional symptoms. However, the patients in our sample reported lower levels of nutrition-related pain than the other two studies.

In terms of physical performance, the subjects in our study had similar baseline functional walking capacity and hand grip strength to healthy controls. The subjects walked a mean 6MWT distance and scored a mean grip strength that was 83% and 92%, respectively, of age- and gender-matched population norm values.[106,112] The average 6MWT distance walked by the subjects in our study was higher than that reported in a study by Bruera et al. (2003) on 33 cancer patients (31 with lung).[125] However, one of the inclusion criteria for their study was an intensity score of 3 or more for dyspnoea at rest or with mild effort (on a scale of 0 to 10), which suggests lower walking capacity due to the presence of dyspnoea with exertion. In our study, not all of the subjects reported shortness of breath or difficulty breathing, which may explain the higher 6MWT distances. Compared to the patients in our study, lung cancer patients prior to undergoing resectional surgery have demonstrated similar 6MWT distances.[97,126] Grip strength measures of our study sample were higher than those found in a study on 12 patients with advanced cancer patients and lower than those found in 127 patients with untreated oral and maxillofacial cancer.[127,128] However, gender differences in grip strength have been demonstrated and the first study had a high proportion of female subjects, which may explain their findings of lower grip strength.[129] In addition, the second study used different measurement methods than our study (maximum vs. average).

Overall, the sample in our study demonstrated results similar to other studies on patients with advanced lung cancer or other cancer types. Based on these findings of clinical status, it can be presumed that our study sample is representative of the advanced NSCLC population and, therefore, our study's findings are generalizable to this population.

### Changes in patient-reported outcomes with chemotherapy

No significant changes were found in patient-reported outcomes, including physical and mental HRQOL, lung cancer symptoms, fatigue symptoms or nutritional status, after two cycles of chemotherapy. Our findings suggest that

chemotherapy does not improve HRQOL. This corresponds with some previous studies which demonstrated no effect of chemotherapy on HRQOL[11,26] but differs from others which reported significant improvement.[15,16,20] However, in our study, we observed trends towards declined physical HRQOL and general health on the SF-36 after chemotherapy. Interestingly, upon further analysis of the SF-36 subscale scores, a significant increase in the Mental Health subscale was found after chemotherapy, suggesting improved mental health status despite worsened physical health in the subjects.

Unlike what we expected, our findings also suggest that chemotherapy does not provide major symptom palliation, in terms of lung cancer symptoms. This study also adds to the ongoing debate regarding the effect of chemotherapy on tumour-related symptoms.[130] However, symptom palliation with chemotherapy has been demonstrated in many studies, including a number of randomized controlled trials.[16,22,69,70]

Finally, our study also suggests that chemotherapy does not worsen fatigue and nutritional symptoms of nausea and vomiting, unlike previously found in a longitudinal study by Wang et al. (2006) using chemo-radiation therapy in advanced NSCLC patients.[120] Other studies have also reported symptoms of fatigue, constipation, nausea and vomiting after chemotherapy treatment in advanced NSCLC lung cancer patients.[131,132] Chemotherapy-related toxicity, including symptoms of nausea and vomiting, has been reported with platinum-based chemotherapy.[133] This may indicate enhanced clinical management of side effects related to chemotherapy in advanced NSCLC patients.

Reasons for the lack of significant change found in HRQOL, symptom status and nutritional status may be related to a number of methodological differences. It is important to note that the dropouts from our study tended to have worse lung cancer symptoms and nutritional status at baseline and loss of their data at follow-up may have contributed to the lack of change found after chemotherapy. Also, most previous studies compared the effect of chemotherapy in two randomized groups, with one receiving chemotherapy, while ours analyzed

the extent of change in outcomes from baseline (randomized controlled trial vs. longitudinal study). However, the secondary objective of our study was to estimate the change that occurred from baseline in patients that completed two cycles of chemotherapy and, therefore, this study design can be considered appropriate.

The use of other questionnaires, treatment regimens and measurement end-points are other potential reasons for the lack of change found in patient-reported outcomes in our study. Regarding questionnaires, the LCS and the SCFS have both demonstrated responsiveness to change even in the short term, justifying their use in our study.[116,134] In addition, our study was one of the few in lung cancer that used the SF-36 questionnaire, which provides two measures of HRQOL, mental and physical, as well as multiple subscale scores. The ability to capture a trend towards worsened physical HRQOL after chemotherapy, despite improved mental health status demonstrates the value of using the SF-36 in the cancer population. This also reveals some of the potential issues with using patient-reported outcomes, such as response shift. A concept introduced by Sprangers and Schwartz (1999), response shift refers to "a change in the meaning of one's self-evaluation of a target construct" due to changes in internal standards of measurement, changes in values regarding the importance of various domains of the construct or redefinition of the construct through reconceptualization.[135] Response shift may be responsible for masking the effect of treatment on HRQOL and other patient-reported outcomes. Evidence of response shift has been found in individuals with advanced cancer and this concept has been used to explain lack of change or improvement in patient-reported health status in this patient population, despite deteriorating physical health.[136,137]

The administration of different treatment protocols may also explain the findings in our study. For example, the cancer treatment used in the study by Wang et al. (2006) was chemo-radiation therapy and fatigue has been identified as one of the most common side effects of radiation therapy.[120,138] Other studies on symptom status and HRQOL in advanced lung cancer patients have used different

types of chemotherapy, such as gefitinib, vinorelbine, topotecan and other combination chemotherapy regimens.[16,116,131,132]

Reasons for the lack of change found in patient-reported outcomes may also be related to the time of the measurement end-points. Our study measured symptoms after two cycles of chemotherapy, which may not have been adequate to produce substantial symptom changes. Some of the subjects in our study were recommended to continue with additional cycles of chemotherapy. Studies in advanced lung cancer have found that most symptom palliation occurs within the first three cycles of chemotherapy.[139,140] However, Cella et al. (2005) found in a clinical trial that improvement of lung cancer symptoms generally occurred within the first two weeks of treatment when gefitinib chemotherapy was given.[116] Also, a small study on the side effects of carboplatin chemotherapy in patients with ovarian cancer reported high incidences of fatigue and nausea after just one chemotherapy cycle.[141]

Finally, this study did not measure the long-term effects of chemotherapy treatment, which may also have demonstrated different effects, in terms of HRQOL, symptom status and nutritional status. However, considering the poor prognosis associated with lung cancer, symptom relief in the short term should also be considered clinically important in this patient population. Our study shows that while HRQOL and lung cancer symptoms do not improve immediately after two chemotherapy cycles, common side effects of chemotherapy, including fatigue and nutritional symptoms, do not worsen either, possibly due to improved clinical management. These findings can only be applied to the short term effect of two cycles of first-line chemotherapy for advanced NSCLC patients.

**Changes in professional-measured outcomes with chemotherapy**

Professional-rated measures of physical performance tended to worsen after chemotherapy, with declines demonstrated in functional walking capacity, as measured by the 6MWT, and hand grip strength. Platinum-based chemotherapy, received by the majority of our sample subjects during the first cycle, has been

associated with greater toxicity, especially nausea and vomiting, nephrotoxicity and hematologic toxicity, when compared to non-platinum-based chemotherapy.[133] Many of the subjects in our study also received taxane compounds (taxol and taxotere) which, unlike other chemotherapy compounds, have been found to have an acute effect on the excitability of human peripheral motor nerves, resulting in muscle weakness.[142] One study reveals that the only discouraging and worrisome concern for lung cancer patients pre-operatively is the potential for physical debility after resection surgery, demonstrating the importance of maintaining physical capacity after cancer treatment for patients.[143] In our study, both physical performance and physical HRQOL tended to worsen after chemotherapy, despite their change scores not being strongly correlated. Again, these findings can only be applied to the short term effect of two cycles of chemotherapy. However, the ability to capture declines in physical performance after chemotherapy despite the lack of change in patient-reported health status demonstrates the value of using both patient-reported and professional-measured outcomes in cancer research. In particular, regular administration of the 6MWT, which is already done in many other patient populations, would also be helpful in lung cancer patients to characterize physical status and predict response to treatment.[54]

**Relationships between variables**

As expected, the patient-reported measures of fatigue symptoms, lung cancer symptoms and nutritional status were correlated with each other prior to and after chemotherapy, while the professional-rated measures of physical performance, including functional walking capacity, grip strength, and chair rise performance, generally followed this pattern as well. This demonstrates consistency in the dataset, where measures of related constructs and with similar administration modes yield correlated scores.

Symptom status, including fatigue and lung cancer symptoms, tended to be moderately correlated with both physical and mental HRQOL prior to and after

chemotherapy treatment. This demonstrates the importance of symptom status, which has been highlighted in previous studies investigating fatigue and dyspnoea in the lung cancer patient population.[63,66] In particular, we found moderate to strong correlations between fatigue symptoms and mental HRQOL both before and after chemotherapy. The high prevalence of fatigue and its relationship with both physical function and psychological distress has been previously highlighted in a study on ambulatory patients with advanced lung cancer by Okuyama et al. (2002).[56] The relationship between fatigue symptoms and psychological distress has also been demonstrated before in a number of studies on cancer patients.[56,144,145]

Measures of physical performance, including chair rise performance and 6MWT, tended to be correlated with physical HRQOL. The relationship between walking capacity and HRQOL has been demonstrated before by Mohan et al. (2007).[18] Surprisingly, physical performance was not strongly related to symptom status prior to chemotherapy, indicating adequate physical performance in this patient population despite being symptomatic, in terms of fatigue and other lung cancer symptoms. However, after chemotherapy, physical performance tended to be more correlated with symptom status, suggesting that following the detrimental effects of chemotherapy on physical performance, symptom status contributes to reduced physical capacity. This further demonstrates the importance of better symptom management throughout chemotherapy, including after treatment, to improve physical performance and ultimately, HRQOL.

**Predictors of changes in HRQOL**

Pre-chemotherapy fatigue symptoms strongly predicted change in mental HRQOL with chemotherapy, when adjusted for confounding variables and 6MWT. Specifically, worse fatigue symptoms (SCFS score) at baseline predicted larger improvements in mental HRQOL (SF-36 MCS score) after two cycles of chemotherapy, while better fatigue predicted greater deteriorations. One reason for this may have been that subjects with worse fatigue symptoms tended to also

have worse mental HRQOL at baseline and, therefore, had more room for improvement (i.e. ceiling effects). Change in fatigue symptoms was also moderately correlated with change in mental HRQOL, indicating that those patients who had worse fatigue at baseline and improved their fatigue after chemotherapy tended to improve their mental HRQOL as well, while those patients who had better fatigue at baseline and had detrimental effects on fatigue with chemotherapy tended to worsen their mental HRQOL. While fatigue symptoms and mental HRQOL both did not change significantly with chemotherapy, these findings suggest that the management of fatigue symptoms during chemotherapy would result in improved mental HRQOL post-chemotherapy. An important relationship has been discovered between fatigue and mental HRQOL in this patient population. These findings demonstrate that clinical attention, in both practice and research, needs to be paid to symptom status, especially for fatigue symptoms, in advanced NSCLC patients during chemotherapy treatment.

Interestingly, functional walking capacity (6MWT distance) before chemotherapy also predicted change in mental HRQOL (SF-36 MCS score) with chemotherapy, when adjusted for confounders and fatigue. When walking capacity was replaced with chair rise performance in the regression model, chair rise repetitions in one minute predicted change in mental HRQOL. This demonstrates that patients with better physical performance at baseline would improve their mental HRQOL more after chemotherapy, while those with worse physical performance would deteriorate. In a study by Wall (2000), lung cancer patients participating in an exercise program before resection surgery demonstrated increased intensity of power immediately prior to and after surgery.[146] Power, defined as "the capacity to knowingly participate in change", is related to the awareness of options, choice and intention. The findings of Wall's study and our study may indicate the promotion of optimal changes in knowledge, empowerment and psychological well-being with increased physical capacity prior to treatment. Kasymjanova et al.'s (2009) recent work on the same dataset as

our study suggested that the 6MWT at baseline is also an independent predictor of response to chemotherapy, in terms of disease progression.[54] Eton et al. (2003) found that patient-reported physical well-being at baseline also predicted better response to treatment and survival after chemotherapy in advanced NSCLC patients.[147] Clinically, this shows the importance of improving and maintaining physical performance, prior to and during cancer treatment, respectively. Future research should study the role of exercise and physical therapy for lung cancer patients undergoing chemotherapy.

When adjusted for confounding variables, nutritional status (PG-SGA score) prior to chemotherapy accounted for a small amount of the variance in change in physical HRQOL (SF-36 PCS score) with chemotherapy. Similarly, subjects with better nutritional status at baseline also tended to have better physical HRQOL and may have had greater room for deterioration (i.e. floor effects). However, the predictive role of nutritional status in physical HRQOL change was insignificant both statistically and clinically.

**Clinical relevance**

While the potential for positive changes in HRQOL during cancer therapy may be enhanced by healthcare interventions, little was previously known about which areas needed to be emphasized on in the clinical setting. Improving our understanding of modifiable factors related to HRQOL during cancer treatment is essential to help guide health professionals providing rehabilitative interventions for the lung cancer patient population.[76] In this study, we found a close relationship between symptom status and HRQOL, particularly between fatigue symptoms and mental HRQOL, throughout the chemotherapy process in advanced NSCLC patients. Clinically, this demonstrates the potential value of better symptom management, especially for fatigue symptoms, during chemotherapy to optimize treatment effects on mental HRQOL. Various healthcare interventions, including aerobic exercise, behavioural therapy and pharmacological treatments, such as antiemetic therapy, can contribute to

minimizing fatigue, respiratory symptoms and chemotherapy-induced symptoms of nausea and vomiting in cancer patients undergoing chemotherapy.[59,65,75,148-152]

Secondly, we discovered the importance of baseline physical performance, in particular 6MWT distance, in predicting changes in mental HRQOL with chemotherapy in advanced NSCLC patients. Recent findings have also demonstrated the role of baseline 6MWT in predicting response to chemotherapy treatment and survival for this patient population.[54] In addition, we found that physical performance and physical HRQOL tended to worsen after chemotherapy. This demonstrates the clinical need to improve and maintain physical performance in lung cancer patients prior to and during chemotherapy treatment, respectively, in order to promote positive effects on HRQOL. Exercise training has shown to improve functional walking capacity, physical fitness and muscle strength in cancer patients after chemotherapy treatment.[149,151,153-155] Similar functional benefits have been found in allogenic stem-cell transplant patients with both supervised and self-directed exercise programs, suggesting that exercise guidance and education may be adequate to promote increased physical activity.[156]

Finally, an important finding of our study was the presence of issues with appetite in advanced NSCLC patients prior to cancer treatment. Increased clinical attention needs to be paid to this frequent and bothersome issue for this patient population. Physical exercise, dietary counselling and nutritional supplements have shown to improve symptoms of nausea, food intake and nutritional status in cancer patients, including NSCLC patients undergoing chemotherapy.[155,157]

### Study limitations

The presence of missing data due to the use of a dataset was one of the limitations of this study. Other limitations related to performing a secondary analysis of an existing dataset included the pre-selection of outcomes. This limited the collection of additional valuable information, such as other factors which may have predicted how HRQOL changes with chemotherapy. Some

examples included pulmonary function and mood state. The elimination of pulmonary function as a predictor does not seem to be a major issue, as pulmonary function has not been found to correlate well with HRQOL in studies on lung cancer survivors and COPD.[71,100] The role of mood state would have been useful to analyze due its close relationship with HRQOL in cancer.[64] In our regression analyses, we also did not control for the effects of other factors, including co-morbidities, such as COPD, or other medications, which may have impacted the role of chemotherapy on HRQOL. However, considering our small sample size, the set of predictors which were analyzed in our study was quite extensive and provided a valuable answer to the research question identified. More importantly, the predictors analyzed are factors potentially modifiable by healthcare interventions, demonstrating direct relevance to clinical practice. Another study limitation was related to the pre-selection of tests and questionnaires to measure the independent and outcome variables, as some of the measures used were not necessarily the best to measure those particular constructs. For example, the use of only the patient-reported component of the PG-SGA questionnaire limited the measurement of nutritional status in this study. The PG-SGA questionnaire for nutritional status aims to minimize issues with patient report by including both patient- and clinician-reported components. The clinician-reported component would have added information on disease, metabolic demand and findings of a physical examination related to fat stores, muscle status and fluid status.[117] Also, not much research exists on the chair rise test (repetitions in one minute) and a number of different versions of the test are used in the literature to measure chair rise performance (e.g. time for five or ten chair rises, chair repetitions in 30 seconds), making it difficult to compare study findings. This demonstrates the need to improve and standardize the measurement of functional status and physical performance, especially in the cancer patient population. Another limitation related to the study design was the time of the measurement end-points. In our study, outcomes were only measured after two cycles of chemotherapy despite the fact that advanced lung cancer patients often

undergo additional cycles. Also, no long term effects of chemotherapy were measured. Therefore, the findings of this study are only generalizable to the immediate effects of two cycles of first-line chemotherapy in advanced NSCLC cancer patients. A final limitation of this study is the small sample size. Future studies in this patient population should use larger sample sizes to measure the effects of non-pharmacological healthcare interventions, such as exercise therapy, on HRQOL during chemotherapy treatment.

## 10. Conclusion

Fatigue symptoms and 6MWT distances are predictors of change in mental HRQOL during chemotherapy in advanced NSCLC patients. Clinical management of fatigue symptoms and physical performance may be useful for HRQOL optimization in NSCLC patients undergoing chemotherapy.

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## 13. List of appendices

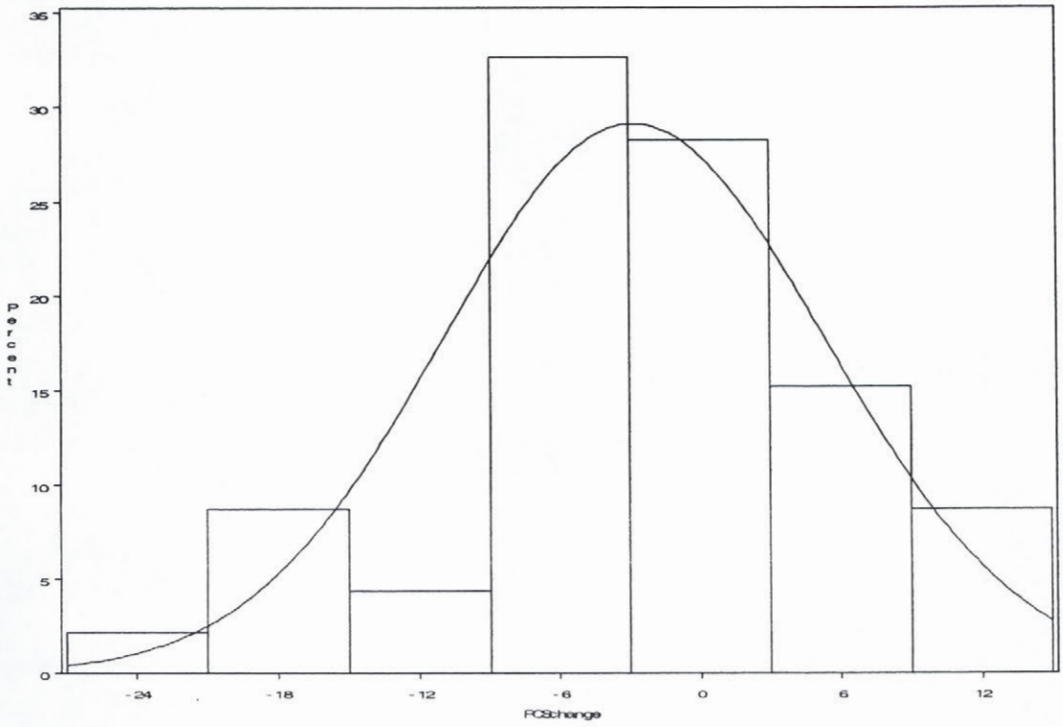
**Appendix 1: Collinearity testing between independent variables (r>0.8)**

| | LCS | SCFS | PG-SGA | 6MWT | Grip strength |
|---|---|---|---|---|---|
| **SCFS** | -0.52 | | | | |
| **PG-SGA** | -0.62 | 0.38 | | | |
| **6MWT** | 0.28 | -0.15 | -0.27 | | |
| **Grip strength** | 0.07 | -0.10 | -0.10 | 0.50 | |
| **Chair rise** | 0.08 | -0.06 | -0.17 | 0.55 | 0.42 |

## Appendix 2a: Distribution of dependent variable (SF-36 PCS change)

Goodness-of-Fit Tests for Normal Distribution (PCS change)

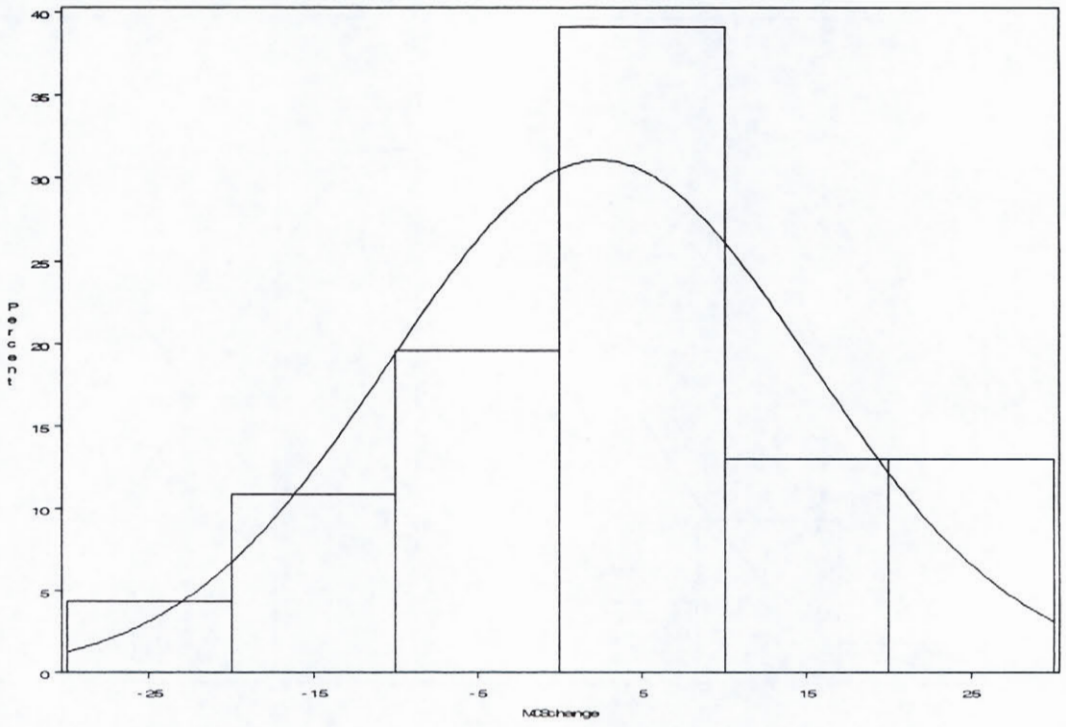
| Test | | ---Statistic---- | | -----p Value----- |
|---|---|---|---|---|
| Kolmogorov-Smirnov | D | 0.11919670 | Pr > D | 0.098 |
| Cramer-von Mises | W-Sq | 0.11365826 | Pr > W-Sq | 0.075 |
| Anderson-Darling | A-Sq | 0.67747789 | Pr > A-Sq | 0.076 |



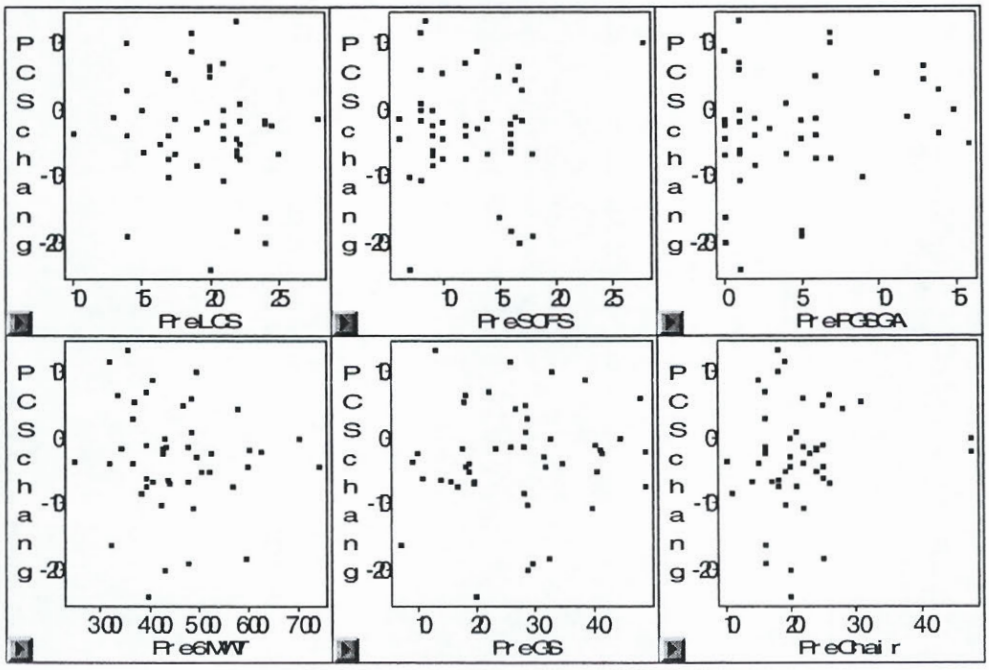
## Appendix 2b: Distribution of dependent variable (SF-36 MCS change)

Goodness-of-Fit Tests for Normal Distribution (MCS change)

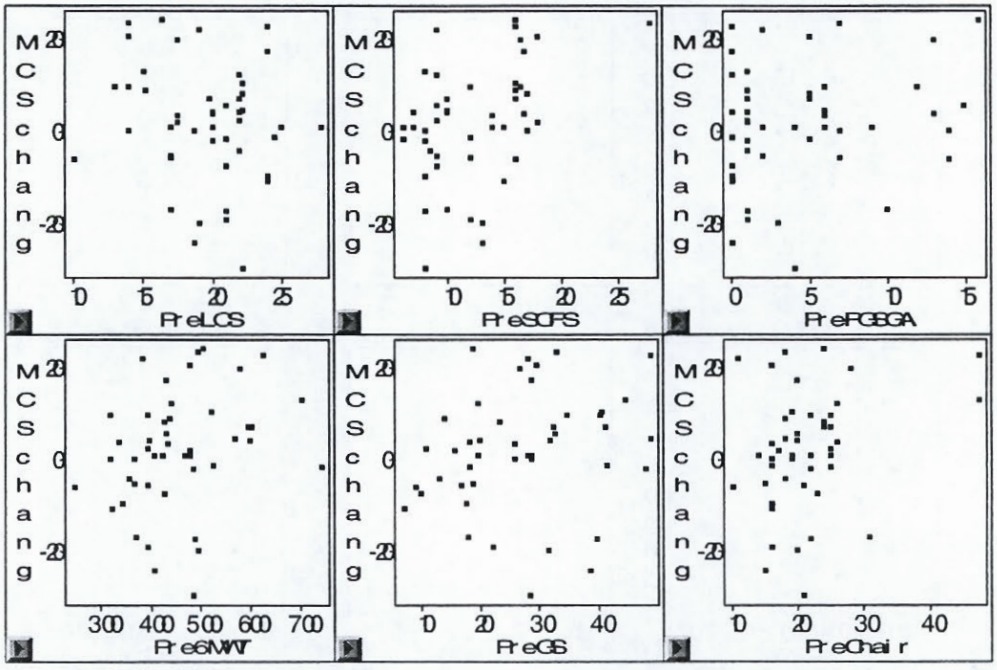
| Test | | ---Statistic---- | | -----p Value----- |
|---|---|---|---|---|
| Kolmogorov-Smirnov | D | 0.10162098 | Pr > D | >0.150 |
| Cramer-von Mises | W-Sq | 0.07046340 | Pr > W-Sq | >0.250 |
| Anderson-Darling | A-Sq | 0.44919170 | Pr > A-Sq | >0.250 |



**Appendix 3a: Linearity of relationships between independent variables and dependent variable (SF-36 PCS change)**



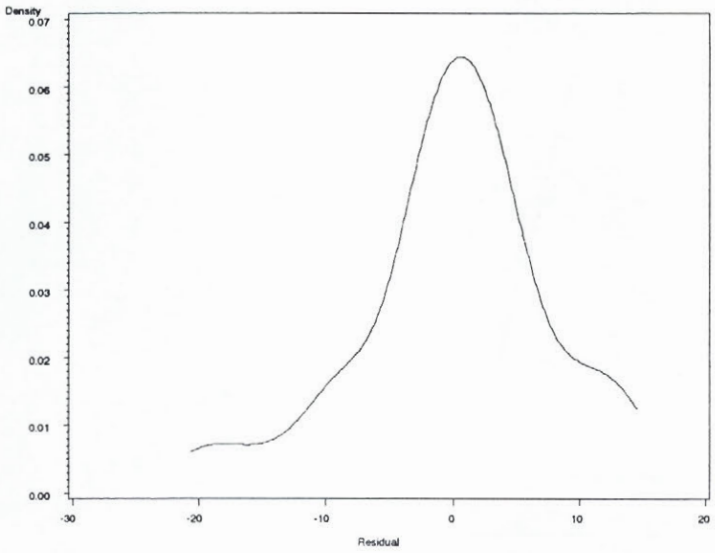
**Appendix 3b: Linearity of relationships between independent variables and dependent variable (SF-36 MCS change)**

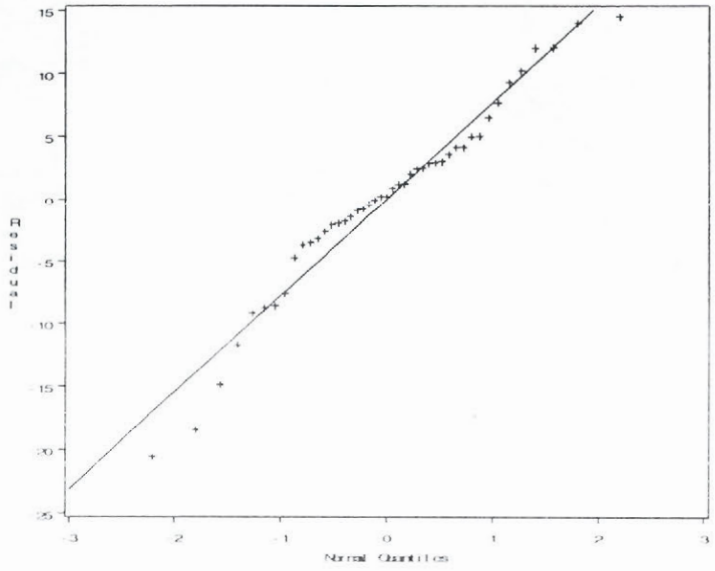


**Appendix 4a: Normality of residuals (model for predictors of SF-36 PCS change)**

Tests for Normality

| Test | --Statistic--- | | -----p Value------ | |
|---|---|---|---|---|
| Shapiro-Wilk | W | 0.96331 | Pr < W | 0.1632 |
| Kolmogorov-Smirnov | D | 0.116235 | Pr > D | 0.1292 |
| Cramer-von Mises | W-Sq | 0.100477 | Pr > W-Sq | 0.1093 |
| Anderson-Darling | A-Sq | 0.578427 | Pr > A-Sq | 0.1302 |

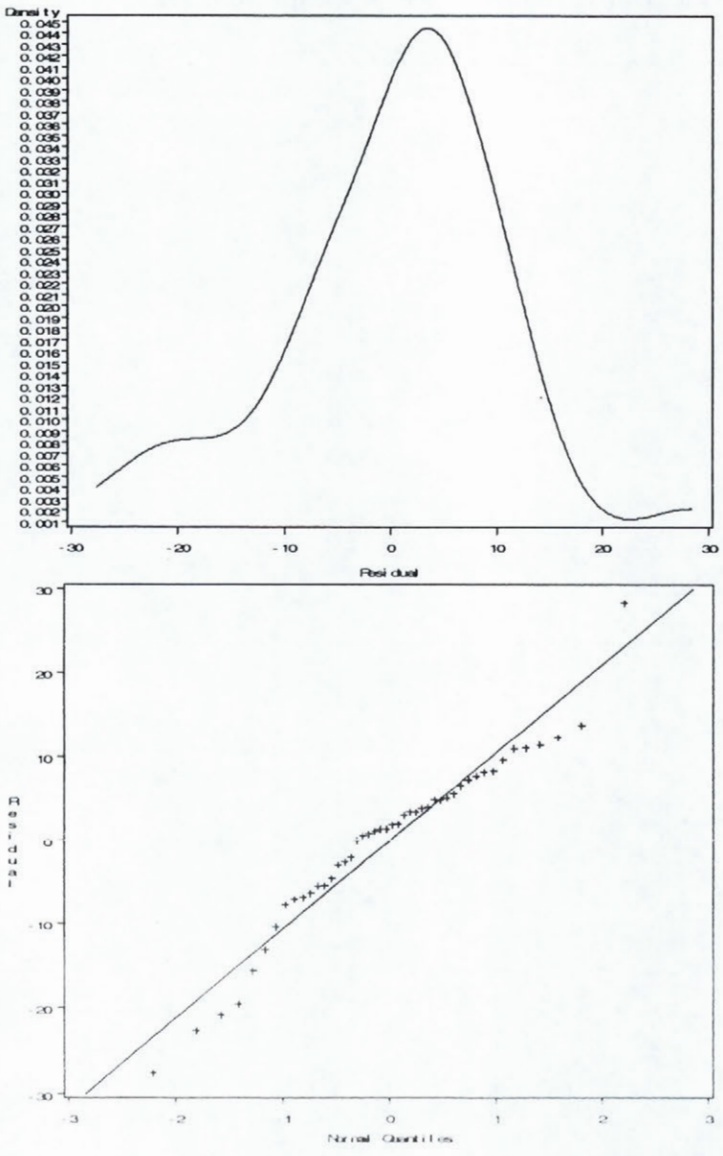


## Appendix 4b: Normality of residuals (model for predictors of SF-36 MCS change)

Tests for Normality

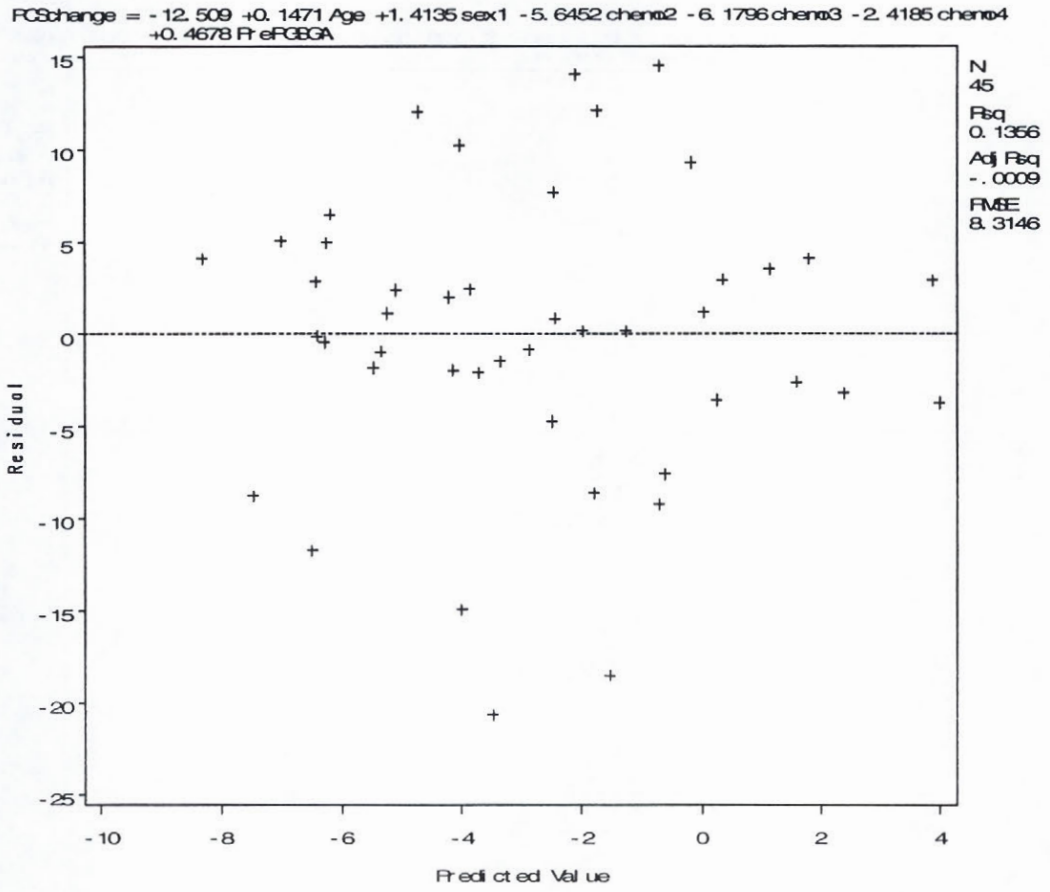
| Test | --Statistic--- | | -----p Value------ | |
|---|---|---|---|---|
| Shapiro-Wilk | W | 0.954813 | Pr < W | 0.0720 |
| Kolmogorov-Smirnov | D | 0.129713 | Pr > D | 0.0502 |
| Cramer-von Mises | W-Sq | 0.132605 | Pr > W-Sq | 0.0409 |
| Anderson-Darling | A-Sq | 0.818644 | Pr > A-Sq | 0.0333 |



## Appendix 5a: Homoscedasticity (model for predictors of SF-36 PCS change)

Test of First and Second Moment Specification

| DF | Chi-Square | Pr > ChiSq |
|---|---|---|
| 20 | 11.65 | 0.9275 |



## Appendix 5b: Homoscedasticity (model for predictors of SF-36 MCS change)

Test of First and Second Moment Specification

| DF | Chi-Square | Pr > ChiSq |
|---|---|---|
| 28 | 31.70 | 0.2870 |