ASSESSING THE EFFECTIVENESS OF PALLIATIVE CHEMOTHERAPY FOR NON-SMALL CELL LUNG CANCER: A PHASE IV STUDY OF PATIENTS TREATED AT ONTARIO'S CANCER CENTRES

by

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Abstract

Background: Randomized controlled trials (RCTs) are the gold standard for assessing the efficacy of a medical treatment. However, the efficacy demonstrated by trials does not automatically translate into a comparable level of effectiveness in the real world. RCTs may vary from routine clinical practice in several ways; the patients themselves, the delivery of the treatment, and the collateral care provided during treatment. Phase IV studies that assess outcomes of a treatment in the real-world provide a mechanism for assessing treatment effectiveness.

Objectives: The objectives of this study were to: describe the characteristics of patients receiving standard, first-line, palliative, platinum-doublet chemotherapy (PPDC) for non-small cell lung cancer (NSCLC) in routine care; describe the effectiveness of PPDC in terms of wellbeing and symptom control; identify patient characteristics associated with change in wellbeing with treatment; and compare reported treatment efficacy to the effectiveness observed in the current study.

Methods: This study was a retrospective cohort study of patients treated at Ontario's Regional Cancer Centres (RCCs). Patients' Edmonton Symptom Assessment System (ESAS) scores were used to describe patients' symptomatic status and wellbeing. The proportions of patients whose wellbeing improved, remained stable or deteriorated at two months were calculated. Using logistic regression, patient and disease characteristics were assessed for association with change in wellbeing at two months (dichotomized as improved/stable and deteriorated). In comparing trial results to this study, adjustments were made for differences in case mix.

Results: Patients' median age was 65, 55% were male and the majority had stage IV disease and adenocarcinoma histology. Patients' baseline wellbeing and symptomatic status varied widely. 61.3% (95% CI: 55.8 – 66.6%) of patients had improved or stable wellbeing at two months. Histology and baseline wellbeing score were associated with change in wellbeing at two months.

The case mix adjusted estimates of the proportion of improved/stable patients (60.0% (95% CI 54.5 – 65.3) and 60.5% (95% CI 54.9 – 65.6)) were consistent with the proportion of patients achieving general quality of life improvement or stabilization in RCTs (55% and 63%).

Conclusion: The effectiveness of PPDC delivered in Ontario's RCCs is consistent with that expected based on the results of RCTs.

Co-Authorship

This thesis represents the work of Lyndsay Harrison in collaboration with her supervisors Dr. William J. Mackillop and Ms. Jina Zhang-Salomons. The study was designed by Lyndsay Harrison, Dr. Mackillop and Ms. Zhang-Salomons. Data linkage and statistical analyses were performed by Lyndsay Harrison with input and guidance by Dr. Mackillop and Ms. Zhang-Salomons. This thesis was written by Lyndsay Harrison with supervision and editorial feedback from Dr. Mackillop and Ms. Zhang-Salomons.

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Table of Contents

List of Figures

List of Tables

List of Acronyms

CCO	Cancer Care Ontario
CIHI-DAD	Canadian Institute of Health Information – Discharge Abstract Database
CT	Chemotherapy
EDS	Edmonton Symptom Assessment System Distress Score
ESAS	Edmonton Symptom Assessment System
EORTC-QLQ	European Organization for Research and Treatment of Cancer – Quality of Life Questionnaire
FACT-G	Functional Assessment of Cancer Therapy - General
MSAS	Memorial Symptom Assessment Scale
NSCLC	Non-Small Cell Lung Cancer
OCR	Ontario Cancer Registry
PPDC	Palliative, Platinum Doublet Chemotherapy
PRO	Patient Reported Outcome
PS	Performance Status
QOL	Quality of Life
RCC	Regional Cancer Centre
RCT	Randomized Controlled Trial
RT	Radiotherapy
SCLC	Small Cell Lung Cancer
TX	Treatment
WHO	World Health Organization

Chapter 1

Introduction

1.1 Background and Rationale

Several decades of clinical randomized controlled trials (RCTs) of palliative chemotherapy have demonstrated small improvements in quality of life (QOL) for patients with advanced non-small cell lung cancer (NSCLC) with treatment. However, there is a concern that this effect, or *efficacy*, demonstrated by the trials may not translate into *effectiveness* in routine practice. Clinical trials may vary from 'everyday treatment' in several ways: the patients themselves may be different; the treatment may be delivered differently; and the collateral care patients receive during treatment may be different.

Phase IV studies that look at patients treated in routine practice rather than as part of a clinical trial provide a mechanism for assessing the real-world impact of a treatment. Phase IV studies are a natural follow-up to clinical RCTs and are necessary to ensure treatment programs are producing the intended results. To date, there have been no real-world studies of the effectiveness of palliative chemotherapy for advanced NSCLC in terms of subjective outcomes of patient quality of life, general wellbeing or symptomatic status. There is also a noticeable lack of descriptive information about the patients who undergo this treatment outside the confines of RCTs.

1.2 Overview of Study Design

To assess the effectiveness of standard first-line palliative platinum doublet chemotherapy (PPDC) for NSCLC in terms of patient wellbeing, a retrospective cohort study of all patients treated at Ontario's Regional Cancer Centres (RCCs) was conducted. This study

involved the linkage of several administrative and clinical treatment databases held by Cancer Care Ontario (CCO). The impact of treatment on patient quality of life was assessed using the Edmonton Symptom Assessment System (ESAS), a now widely used clinical tool designed for measuring key symptoms and the overall wellbeing of palliative cancer patients. ESAS was introduced into the RCCs in 2007 and patient ESAS records have been collected in a CCO database since April 2008. Consideration was given to the potential influence of differences in case mix on the comparison of efficacy and effectiveness results.

1.3 Thesis Objectives

The specific objectives of this thesis were:

1. *To describe the characteristics of patients who begin PPDC for advanced NSCLC, the chemotherapy they receive and their wellbeing and symptom scores prior to initiation of PPDC (baseline) as captured by the ESAS.*
2. a) *To describe patients' change in wellbeing (and symptom) scores from baseline to two months post-initiation of PPDC.*

   b) To investigate whether patient characteristics: sex, age, stage of disease, histology and baseline ESAS wellbeing score predict change in wellbeing at two months.
3. *To compare the proportion of patients whose wellbeing improved or remained stable to the proportion of patients whose general QOL improved or remained stable in clinical RCTs of PPDC.*

1.4 Thesis Organization

This thesis consists of five Chapters and seven Appendices. The second chapter consists of a literature review of lung cancer (specifically NSCLC), treatment options, the evidence for palliative chemotherapy in terms of both survival and quality of life outcomes, definitions of

palliative care and quality of life and the measurement of quality of life. The third chapter provides a description of the data linkage and data analysis strategies used in the thesis. The fourth chapter contains the results of these analyses. The fifth chapter is a discussion of the thesis findings and their implications as well as suggestions for future research.

Chapter 2

Literature Review

2.1 Lung Cancer Epidemiology

2.1.1 Incidence and Mortality

Lung cancer is the leading cause of cancer mortality across the globe. In Canada, lung cancer is the second most commonly diagnosed cancer, accounting for 14% of new cancer diagnoses and it is the leading cause of cancer death, accounting for 28% of cancer deaths in men and 27% of cancer deaths in women (1). This is despite the fact that incidence rates have been decreasing in men for the past two decades and now appear to be reaching a plateau in women (1). Half of all lung cancers are diagnosed in people over the age of 70. In Canada, there were approximately 25300 new cases of lung cancer diagnosed and an estimated 20600 deaths due to the disease in 2011 (1). In that year in Ontario alone, there was an estimated 8000 new cases of lung cancer diagnosed and an estimated 6700 deaths due to lung cancer (1).

2.1.2 Risk Factors and Incidence Trends

By far, the greatest risk factor for lung cancer is smoking. Studies of the population attributable risk of lung cancer in the United States have estimated that smoking accounts for 90% of lung cancers (2). Epidemiologic studies, of which the most famous is arguably the British Doctors' Study, had shown by the early 1950s that cigarette smoking was strongly associated with lung cancer (2;3). Global patterns of lung cancer incidence today reflect the smoking habits in decades past (4). In Canada, the decline in lung cancer incidence rates in men began in the mid-1980s, mirroring the decrease in tobacco use that began in the mid-1960s (1). The same appears to be holding true for Canadian women whose lung cancer incidence rates seem to be

plateauing now, approximately two decades after their tobacco use began to decrease (1). In fact, in many Western countries where smoking rates have declined, there has been a corresponding reduction in lung cancer incidence rates (2). However, this decline is expected to plateau in the next couple of decades if current smoking rates remain the same (4). In countries like China, which is home to one third of the world's smokers (2) and where cigarette smoking rates have increased in the past several decades, lung cancer deaths are expected to increase for many decades to come (4).

Other established risk factors for lung cancer are generally occupational and include exposure to radon, tar, soot, arsenic and chromium (2). These exposures are risk factors individually but can also work synergistically with smoking to further increase lung cancer risk (2).

2.2 Histological Subtypes and Stages of Lung Cancer

Lung cancers are divided into two main histological subtypes*: small cell* and *non-small cell* lung cancers. These two types represent cancers that grow and respond to treatment in very different ways and are studied and treated as separate diseases.

Small cell lung cancers (SCLCs) account for 15%-20% of lung cancers, tend to grow quickly and are classified simply as either limited or extensive stage (5). Non-small cell lung cancers (NSCLCs) are much more common and are the focus of this thesis.

NSCLC is a collection of several tumour histologies including: adenocarcinoma, squamous-cell carcinoma and large cell carcinoma (6). It accounts for approximately 80%-85% of all lung cancers and is characterized by slower growth and spread than SCLC (7). NSCLC is staged using the traditional TNM solid tumour staging system which is based on tumour size, nodal status and presence or absence of metastases (5). TNM staging is used to group NSCLCs more broadly into 4 stage categories: I, II, III and IV, the first three of which can be subdivided

into A and B subtypes. Stage I cancers are confined to the lung and are no larger than 5cm while stage II cancers may have some limited spread beyond the primary tumour and are no larger than 7cm (5). Stage IIIA cancers are characterized by greater spread within the lung itself or connected organs (excluding the opposite lung) or lymph nodes on the same side of the chest (5). Stage IIIB cancers are those which have greater spread into connecting organs and/or nymph nodes above the collar bone or on the contralateral side of the body (5). Stage IV consists of disease that has metastasized either to the opposite lung, the fluid surrounding the lungs or heart or to other more distant parts of the body including the brain, liver, and bones (5). Stages III (usually restricted to IIIB) and stage IV are frequently collectively referred to as 'advanced' stage disease. Approximately 34% of patients are diagnosed with stage I or II, 27% diagnosed with stage III, and 39% diagnosed with stage IV (8).

2.3 Treatment Options

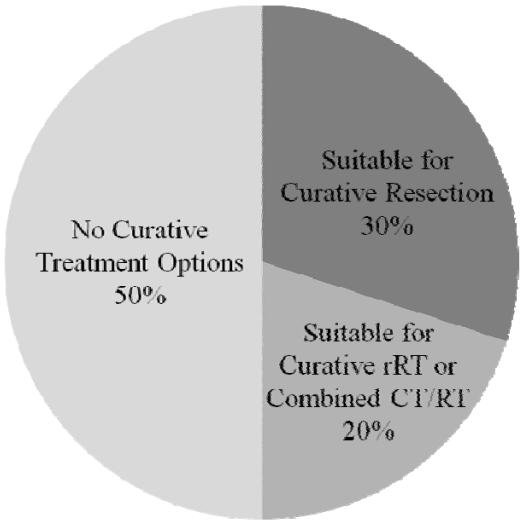
Treatment options for NSCLC depend on the extent of disease and can include: surgery, radiotherapy and chemotherapy in various combinations or alone. Several other treatment options including targeted therapy, photodynamic therapy and cryotherapy which have more limited applicability will not be discussed here.

Curative Treatment

Stages I and II and some stage IIIA NSCLCs can be cured and surgery is the gold standard treatment option whenever possible (4). Surgery may involve removal of a small portion of the lung, called a wedge resection or segmentectomy; removal of an entire lobe of the lung, called a lobectomy; or removal of the whole lung, called a pneumonectomy (4;6). This surgery may be accompanied by neoadjuvant or adjuvant chemotherapy. However, only about 30% of patients present with tumours suitable for resection (9) (Figure 1). An additional 20% receive radical radiotherapy or combined chemotherapy and radiotherapy (typically stage IIIA),

leaving 50% of patients diagnosed at stage IIIB or IV or earlier but with significant comorbidities such that their disease is no longer amenable to treatment with curative intent (8-10).

Figure 1 Proportions of patients eligible for different treatment options



rRT: radical radiotherapy; CT/RT: chemotherapy and radiotherapy

Palliative Treatment

For stage IIIB disease not amenable to curative treatment and all stage IV disease, treatment is palliative in nature and focuses on increasing survival time, controlling symptoms and improving or maintaining quality of life. Palliative treatment options include chemotherapy, radiotherapy and supportive care (11).

2.4 Survival in NSCLC

Despite survival gains made in many cancers over the past several decades, lung cancer remains an overwhelmingly fatal disease and most patients succumb to their disease in short order. The overall 5-year survival rate for lung cancer is 15% (12) but that number can be as low as 2% for those diagnosed with stage IV non-small cell disease (13;14). Median survival of patients with untreated metastatic lung cancer is only 4-5 months, and 1yr survival rates are around 10%-15% (4;15). The corollary of the 15% 5-year survival rate, is that more than 85% of

NSCLC patients at some point require palliative care for their disease, be it quickly following their diagnosis or after the failure of earlier curative interventions.

2.5 Palliative Care and Quality of Life

2.5.1 Definitions of Palliative Care, Quality of Life and Wellbeing

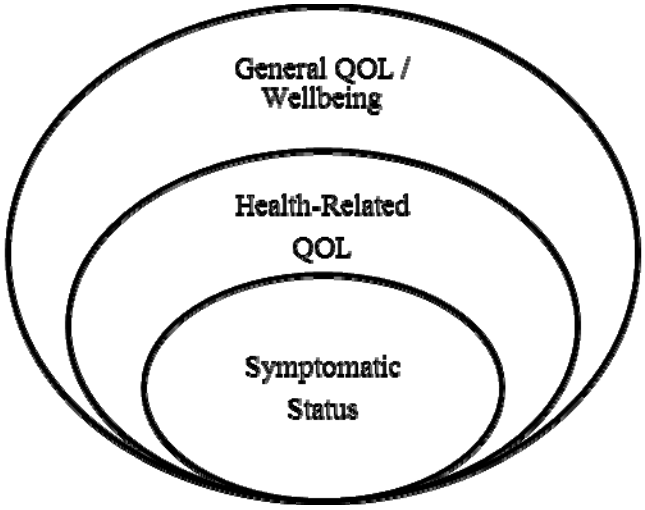
Palliative care can be broadly defined as care that aims to improve the quality of life (QOL) of people suffering from life-threatening illnesses (7). The World Health Organization (WHO) describes palliative care as "an approach that improves the quality of life of patients and their families facing the problems associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual" (16).

Quality of life is an broad, multi-dimensional concept itself. The WHO defines quality of life as: *"an individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns. It is a broad ranging concept affected in a complex way by the person's physical health, psychological state, personal beliefs, social relationships and their relationship to salient features of their environment*" (17).

A related concept is that of Wellbeing, which has been defined as 'a global assessment of a person's quality of life according to his own chosen criteria" (18).

In the medical context of incurable terminal disease, much emphasis is placed on preventing or relieving physical and psychological symptoms to improve patients' QOL (19). This more narrow focus is often described as health-related QOL or a person's perceived physical and psychological wellbeing or health status (20). In this context, symptomatic status can be thought of as a domain of health-related QOL, which is itself a component of the broader concept of general QOL (21) (Figure 2).

Figure 2 Conceptual relationship between QOL / wellbeing and symptomatic status



2.5.2 Symptoms Experienced by Patients with Advanced NSCLC

A 2002 systematic review of symptoms in adults with lung cancer synthesized the results of 18 previous studies (the majority of which were confined to advanced NSCLC, though the review noted symptoms were similar in both NSCLC and SCLC groups) (22). The studies included cross-sectional, longitudinal, and randomized controlled trial designs in single and multicentre settings. The most common symptoms reported in newly diagnosed patients were physical: fatigue, pain, loss of appetite and cough (22).

Another literature review reported estimates of the prevalence of specific symptoms in lung cancer patients (23). Fatigue was present in 47-82% and shortness of breath was present in 46-87% of patients (23). The range in estimates is likely explained by the fact that these estimates cover patients at all stages of disease and these symptoms increase in prevalence and severity as the disease progresses (23). A single institution study of newly diagnosed advanced NSCLC patients reported over 50% of patients present with dyspnea (shortness of breath), pain, appetite loss, cough, weight loss and tiredness and unclear thinking and over 20% of patients reported severe shortness of breath and appetite loss (24).

Psychological distress has also been noted to be high in lung cancer patients. This may be a result of self-blame for having caused their disease and/or may be reflective of pre-existing levels of distress that led to behaviours like smoking which put them at an elevated risk of developing cancer in the first place (23). One study reported anxiety and depression symptoms in 31% and 21% of patients (24).

2.5.3 Palliative Care for NSCLC

Palliative care for NSCLC can be broken down into two main categories: supportive (or patient-centred) care and tumour-directed therapy. Supportive care, which can include antibiotics, corticosteroids, analgesics, antiemetics, transfusions and psychosocial support (9), is targeted directly at improving the wellbeing of the patient. Tumour-directed therapy also aims to improve patient wellbeing but does so indirectly through targeting the cancer itself using strategies that decrease tumour burden, which in turn improves patient symptoms and wellbeing. Tumour-directed palliative treatment options for NSCLC include palliative chemotherapy and palliative radiotherapy.

2.5.4 Palliative Chemotherapy for NSCLC

For locally advanced unresectable and metastatic NSCLC (stages IIIB and IV, which are unsuitable for curative treatment options), the standard first-line palliative treatment is palliative chemotherapy with supportive care (25-27). Patients not well enough to undergo chemotherapy are offered supportive care alone. For patients with specific, localized symptoms care may also include a short course of radiotherapy which has been shown to alleviate symptoms and improve QOL (11;19).

2.6 Supporting Evidence for First-line Palliative Chemotherapy

2.6.1 Palliative Chemotherapy versus Supportive Care Alone

Clinical trials have shown a survival advantage of palliative chemotherapy compared to supportive care alone (9). A meta-analysis performed by the Cochrane Collaboration, which included 16 trials and represented over 84% of the patients from all known randomized trials (as of November 2009) reported an absolute median survival improvement of 1.5 months (from 4.5 to 6 months) resulting in an absolute improvement in the one year survival rate of 9% (from 20% to 29%; HR=0.77, 95%CI0.71-0.83, $p<0.0001$) for chemotherapy compared to supportive care alone (9). In patients fit enough to undergo modern, standard, platinum-based, two drug (platinum doublet) combination chemotherapy, reported median survival times range from 7.4 to 11.3 months (28).

2.6.2 Comparisons of Different Palliative Chemotherapy Regimens

A recent systematic review of first-line systemic chemotherapy for advanced NSCLC (26) included discussion of 10 previous systematic reviews (29-38) and concluded that platinum doublet chemotherapy is the standard of care for first-line chemotherapy, that platinum-based doublets are superior to non-platinum-based chemotherapies (30;35), platinum agents alone or other agents alone (37), and that no one of the standard platinum doublets is clearly superior to any other (26). Standard palliative, platinum-based, doublet chemotherapy (PPDC) regimens include cisplatin or carboplatin with one of: gemcitabine, vinorelbine, paclitaxel or docetaxel (39;40).

2.6.3 Patient Perspective on Survival Benefit of Palliative Chemotherapy

While the survival benefit is clear, the magnitude of that benefit is small (41), which begs the question: is such a small gain important from the patients' perspective? A study of patients previously treated with cisplatin-based chemotherapy for advanced NSCLC reported a median

survival threshold for accepting mildly toxic chemotherapy of 4.5 months and 9 months for accepting severely toxic chemotherapy (42). When given the choice between supportive care and chemotherapy, only 22% of those patients would choose chemotherapy for a 3 month survival advantage. In contrast, 68% would accept chemotherapy if it substantially reduced symptoms (42). The limited survival gains achieved and the relative importance patients place on quality over quantity of life underscores the need for data on the QOL and symptom implications of palliative chemotherapy (25) and supports the contention that QOL and symptomatic status are important endpoints in their own right when assessing palliative chemotherapy (41).

2.6.4 Impact of Palliative Chemotherapy on QOL and Symptom Levels

Traditionally, the primary endpoints in clinical RCTs of palliative chemotherapy for advanced NSCLC have been survival and objective tumour response while QOL and symptom control have been neglected or relegated to secondary objectives (21). Acceptance of QOL measures as important primary endpoints is growing and clinical trials of the past decade often report some QOL measurement. In the RCTs that have addressed QOL, a variety of study methods, chemotherapy regimens and measurement instruments have been employed and the ability of chemotherapy to improve QOL is still debated (41;43;44). However, the majority of studies using validated QOL tools have reported some QOL (45-49) and symptom benefit (45;48;50) in favour of chemotherapy over supportive care alone, or at minimum, no detrimental effect of chemotherapy compared to supportive care (51;52). Unfortunately, QOL results are usually confined to a few comments about whether there was a significant difference between treatment arms or from baseline and a corresponding p-value without any further detail on absolute changes or proportions of patients who obtained improvement or stabilization of their QOL or symptom levels. Often there is no statistically or clinically significant mean change in QOL from baseline (53-56). It should be noted that given the natural trajectory of NSCLC is for

QOL and symptoms to continually decline, a treatment that merely maintains current QOL and symptom levels and delays progression is considered successful.

A review of QOL across different chemotherapy regimens for advanced NSCLC concluded that there is little evidence to suggest a difference in global quality of life between standard chemotherapy regimens (56). The reviewers also noted that across studies, there was minimal to no mean change in QOL over time (56). Below (Table 1) is a summary of two trials that have provided more detailed QOL and symptom assessment data. They reported improved or stable general QOL in 55 and 63% of patients and improvement or stabilization in key symptoms including pain, shortness of breath and fatigue in one half to three quarters of patients.

Table 1 QOL and symptom impact of standard palliative chemotherapy regimens

Author	*Patient Characteristics*				CT Regimen	QOL Measure	QOL Timeframe	QOL Results % Improved or Stable
	Median Age (Range)	Sex %Male	Stage %	Histology %				
von Plessen et. al (54)	64 (34-84)	63	IIIB 24 IV 76	Ade 43 Squ 27 Oth 30	Carb + Vino	EORTC QLQ-C30, -LC13	Baseline to 9weeks	55% Global QoL 52% Pain 44% Shortness of Breath 34% Fatigue
Gridelli et. al (55)	62 (35-72)	81	IIIB 20 IV 80	Ade 42 Squ 34 Oth 24	Cisp+ Vino or Cisp+ Gemc	EORTC QLQ -C30, -LC13	Baseline to end of cycle 2	63% Global QoL 71% Pain 73% Shortness of Breath 52% Fatigue 49% Appetite

CT: Chemotherapy; Ade: Adenocarcinom; Squ: Squamous-Cell Carcinoma; Oth: Other NSCLC; Carb+Vino: Carboplatin + Vinorelbine; Cisp+Vino: Cisplatin + Vinorelbine; Cisp+Gemc: Cisplatin + Gemcitabine.

2.7 Practice Guidelines

The Cancer Care Ontario Program in Evidence-Based Care guideline, "First-line systemic chemotherapy in the treatment of advanced non-small cell lung cancer," recommends platinum doublet chemotherapy as the standard first-line treatment option (27). The drugs most commonly paired with the platinum agents are gemcitabine, vinorelbine, docetaxel, and paclitaxel. The recommendation for treatment duration is that treatment not continue beyond 4 to 6 cycles as there is no evidence of improved survival with prolonged treatment and toxicities increase the longer these drugs are administered (27).

These guidelines are consistent with other clinical practice guidelines including the American Society of Clinical Oncology Clinical Practice Guidelines for advanced non-small cell lung cancer (40;57) and the British Columbia Cancer Agency`s Cancer Management Guidelines (58).

2.8 Characteristics of the Patients Included in Randomized Controlled Trials

A recent systematic review of methodological issues of quality of life in NSCLC in randomized controlled trials summarized the demographic characteristics of patients who have been included in these types of trials (59). In the 53 trials identified, patient median age ranged from 60 to 76 with the majority falling in the early to mid-60s. Typical age ranges were from early 30s to mid-80s. Most studies consisted of more men than women with the proportion of male participants ranging from 50 to 88%. Most included patients diagnosed with either stage IIIB or stage IV NSCLC and some also included patients with recurrent disease.

2.9 Efficacy versus Effectiveness

While clinical RCTs remain the gold standard for determining the efficacy of a treatment, their participants do not represent a random sample of all patients and therefore their results may not translate into effectiveness in the general patient population. The way the treatment is delivered and the collateral care received during treatment may also differ between clinical trials and general practice and result in different levels of effectiveness. Phase IV studies provide a mechanism for assessing the benefits of a particular treatment in truly representative patients (60). To our knowledge, there have been no studies formally assessing the effectiveness of palliative chemotherapy for NSCLC patients treated in routine practice. Making use of newly available administrative data on patient QOL (Ontario Regional Cancer Centres collected patient symptom and wellbeing scores, see Section 2.10 below), this study will attempt to quantify the effectiveness of palliative chemotherapy in NSCLC patients and compare this to the efficacy demonstrated in clinical trials.

2.10 Quality of Life and Symptom Assessment of Palliative Interventions

Due to the subjective nature of the symptom experience and QOL, the gold standard for measurement is a patient's own opinion (61). Many questionnaires have been developed and validated for these purposes; two of the most well-known in cancer research are the European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC-QLQ-C30) (62) and its Lung Cancer modular supplement (EORCT-QLQ-LC13) (63), and the Functional Assessment of Cancer Therapy-General (FACT-G) (64). However, these tools, which are popular in clinical trials, are too long or burdensome for patients and the staff who administer them to be used in everyday clinical settings. As a result, short questionnaires have been developed specifically for use in clinical practice.

2.10.1 The Edmonton Symptom Assessment System

The Edmonton Symptom Assessment System (ESAS) (Appendix A) is a self-reported clinical tool developed for use in rapid assessment, screening and monitoring of palliative cancer patients' symptoms and overall wellbeing (61). It includes numerical rating scales for eight symptoms common to advanced cancer patients: pain, tiredness, nausea, depression, anxiety, drowsiness, appetite and shortness of breath and one more general scale for wellbeing. Thus, it covers symptoms common of local effects of the tumour (pain and shortness of breath), systemic symptoms (tiredness, appetite, nausea and drowsiness) and psychological symptoms (anxiety and depression). Since the focus of this instrument is on symptoms, it can be categorized as a symptom-based QOL measure (65). Previous work has described cut-off points of 4 and 7 to define moderate and severe levels of a symptom, that is 0-3 represents mild, 4-6 moderate, and 7-10 severe symptom levels, although these have not been validated (66).

Starting in 2007, Cancer Care Ontario began systematically collecting ESAS scores for patients treated at Ontario's 14 RCCs with the intention of having patients fill out the ESAS at every visit. ESAS is administered electronically or by paper at the Cancer Centres and scores have been collected in a central electronic database held by Cancer Care Ontario since April 2008.

2.10.2 Validity and Reliability of the ESAS

The ESAS has good face validity as it covers 8 symptoms commonly experienced by palliative cancer patients (61).

Concurrent validity of the ESAS is supported by good correlation in palliative cancer patient populations of the individual ESAS symptom items with the symptom measures of other well-established, validated tools. ESAS symptoms are correlated with items on the Memorial

Symptom Assessment Scale (MSAS) and the Functional Assessment of Cancer Therapy-General (FACT-G) in general cancer patient populations (67). Significant correlations between ESAS symptoms and MSAS symptoms include pain (0.85), shortness of breath (0.83), nausea (0.62) and appetite (0.75), with similar correlations observed for the ESAS and the FACT-G symptoms (67). ESAS symptoms are also correlated with corresponding measures on the Symptom Distress Scale (nausea, shortness of breath and pain all at 0.8 or greater, appetite at 0.74 and depression at 0.45) (68). Correlation between the Brief Pain Inventory and the ESAS pain score is 0.61 (69) and weighted kappas show moderate agreement between ESAS and the Rotterdam Symptom Checklist (ranging from 0.45 to 0.58 for shortness of breath, appetite, anxiety and depression) (69).

Much of the initial work around assessing the concurrent validity of the ESAS focused on correlations between the ESAS distress score (an equally weighted average of all 9 ESAS items) and other assessment tools. The ESAS distress score correlates most strongly with the MSAS global distress index (correlation coefficient 0.73) and physical symptom subscale (0.74) and the FACT-G physical well-being subscale (-0.75) (67). A smaller though still significant trend is seen in correlations between the ESAS distress score and the FACT-G emotional well-being and MSAS psychological subscales (67). This is not surprising given the greater number of physical (versus psychological) symptoms represented on the ESAS. It has been suggested that the distress score may represent the latent construct of physical symptom distress (65). Significantly greater ESAS distress scores ($p<0.01$) have been observed in inpatients compared to outpatients (67) supporting ESAS's discriminant validity, as one would expect patients requiring hospitalization to have greater levels of symptom burden than those treated as outpatients.

However, one might question the face validity of this summary measure. For one, it makes the inherent assumption that each component of the ESAS contributes equally to an individual patient's 'distress.' It also includes the wellbeing score, which is itself a summary

measure of how the patient is feeling (61). In terms of face validity, the single item wellbeing best matches the concept of general quality of life. In fact the ESAS measure of 'wellbeing' correlates significantly though modestly (Spearman correlation coefficient -0.48, $p<0.0001$) with the Functional Assessment of Cancer Therapy-General (FACT-G) total QOL score, a validated multidimensional QOL instrument (70).

Test-retest reliability of the ESAS is reportedly high (>0.8) for palliative patients within one day (67;71); however this is not the case over longer time frames than one day. This most likely indicates ESAS's responsiveness to the dynamic nature of the symptoms of palliative patients rather than a deficit in the reliability of this tool (65). For example, in a study of palliative care unit admissions, patients presenting with significant symptom burden saw a decrease in every symptom except fatigue within a few days of admission (71).

2.10.3 Defining Clinically Important Changes in ESAS Scores

In assessing the effect of a palliative intervention it is important not only to demonstrate statistical significance, but also to qualify the results with respect to the level of clinical significance. One way of operationalizing clinical significance is to define it as the minimally important or detectable difference as reported by the patient.

While there have been no studies formally identifying a degree of change in ESAS scores which would represent a clinically significant (i.e. detectable by the patient) difference, the body of evidence surrounding the interpretation of QOL measures in health research suggests that one half of the standard deviation (SD) of ESAS scores could serve a conservative estimate of a meaningful change (72).

Noting that many competing methods of quantifying a clinically significant difference converge around 0.5 of the test instrument's standard deviation, Sloan et al. propose using this 0.5 standard deviation, which they call the empirical rule of effect size, as an "estimate of a clinically meaningful difference, in the absence of further situationally-specific knowledge" (72).

A review of studies calculating minimally important differences (MID) for quality of life instruments in health research confirmed that over 80% of the calculated MIDs were close to 0.5 of a standard deviation (73).

A common competing method is to use a change that corresponds to 5% or 10% of the range to the measurement instrument to represent a clinically significant effect (72;74). For each ESAS item, a one point change on the 0–10 scale represents a 9% change and could also be used as an estimate of the minimally detectable and thus clinically significant effect.

2.11 Prognostic and Predictive Factors and Quality of Life

After determining whether a treatment is effective, the next logical step is to ask if there are any factors related to the patient or their disease that predict a more favourable response to treatment. That is to say, are there characteristics that identify certain subgroups of patients who achieve more or less benefit from a given treatment. A predictive factor is associated with a differential response to a particular therapy with respect to the levels of that factor (75;76). This differs from a prognostic factor which is a characteristic associated with a patient's disease trajectory or outcome *regardless* of the treatment undertaken (75;76), though a given factor may be both prognostic and predictive. Prognostic and predictive factors research in lung cancer has focused on the outcome of survival (even occasionally including QOL as a predictor (52)).

In patients with advanced NSCLC disease, earlier stage (stage III versus stage IV), less weight loss and good performance status are the strongest predictors of survival time after systemic chemotherapy (77). Female sex and better pre-treatment QOL were also noted as factors predicting longer survival time. Early studies of NSCLC identified old age (>70) as a negative prognostic factor (77), however this has not been supported by more recent studies. It now appears as though this effect of age may simply be reflection of a greater number of comorbidities in the elderly (78) and that old age alone is not associated with shorter survival

time in fit individuals (79). In fact, a Southwest Oncology Group analysis found older age to be a positive prognostic factor (80).

Histology has been frequently studied but not consistently described in the literature as either a predictive or prognostic factor with respect to survival or tumour response. A review of the topic concluded more research needed to be done as it is not clear whether either of the two main subtypes (adenocarcinoma or squamous-cell carcinoma) was more likely to respond to chemotherapy (81).

A review of prognostic factors in NSCLC concluded that research has focused almost exclusively on survival (77). The authors noted while it has been demonstrated that patients are interested in the likely impact of treatment endpoints beyond survival alone, such as QOL and symptoms (77), there is a paucity in the literature with respect to the impact of treatment on these alternative outcomes.

This study will examine some of these factors, which have been associated with survival after chemotherapy treatment, for an association with patients' change in wellbeing after initiating palliative chemotherapy. Due to the nature of the study design (that is to say there is no supportive care / no chemotherapy control group), it will not be possible to separate out which factors are purely predictive from those that are prognostic or represent some combination of the two. However, this study will begin to explore whether patient and disease characteristics are associated with wellbeing as an alternative treatment outcome to survival.

2.12 Summary

Palliative chemotherapy has been recommended as the standard of care for patients with advanced NSCLC based on the results of clinical RCTs completed over the past several decades. These trials have reported improvement or stabilization in quality of life in one half to one third of patients. However, no studies have investigated the effectiveness of this treatment in the real

world and it is uncertain whether the efficacy demonstrated in the trials has translated into similar levels of effectiveness in routine practice. There is also a lack of real-world data describing the patients who undergo this treatment, their pre-treatment symptomatic status and wellbeing, and what subgroups of patients may be most likely to experience a wellbeing benefit with treatment. This study aims to begin to fill these gaps in knowledge.

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Chapter 3

Methods

3.1 Study Objectives

The specific objectives of this study were:

1. *To describe the characteristics of patients who begin PPDC for advanced NSCLC, the chemotherapy they receive and their wellbeing and symptom scores prior to initiation of PPDC (baseline) as captured by the ESAS.*
2. a) *To describe patients' change in wellbeing (and symptom) scores from baseline to two months post-initiation of PPDC.*

   b) To investigate whether patient characteristics: sex, age, stage of disease, histology and baseline ESAS wellbeing score predict change in wellbeing at two months.
3. *To compare the proportion of patients whose wellbeing improved or remained stable to the proportion of patients whose general QOL improved or remained stable in clinical RCTs of PPDC.*

3.2 Study Design

This was a retrospective cohort study that involved linking multiple administrative and clinical databases.

3.3 Study Population

The target population was all NSCLC patients beginning first-line, palliative, platinum doublet chemotherapy (PPDC) in Ontario's Regional Cancer Centres between April 2008 and

November 2010. (A list of the 14 Centres is provided in Appendix B.) April 2008 was chosen as the start date to coincide with the availability of patient ESAS records. NSCLC patients were identified using the ICD-9 for lung cancer and ICD-O histology codes for NSCLC.

3.3.1 Inclusion Criteria

Patients must have initiated PPDC for NSCLC at an Ontario Regional Cancer Centre between April 2008 and November 2010. Patients had to have at least one valid baseline ESAS record to be included in the study.

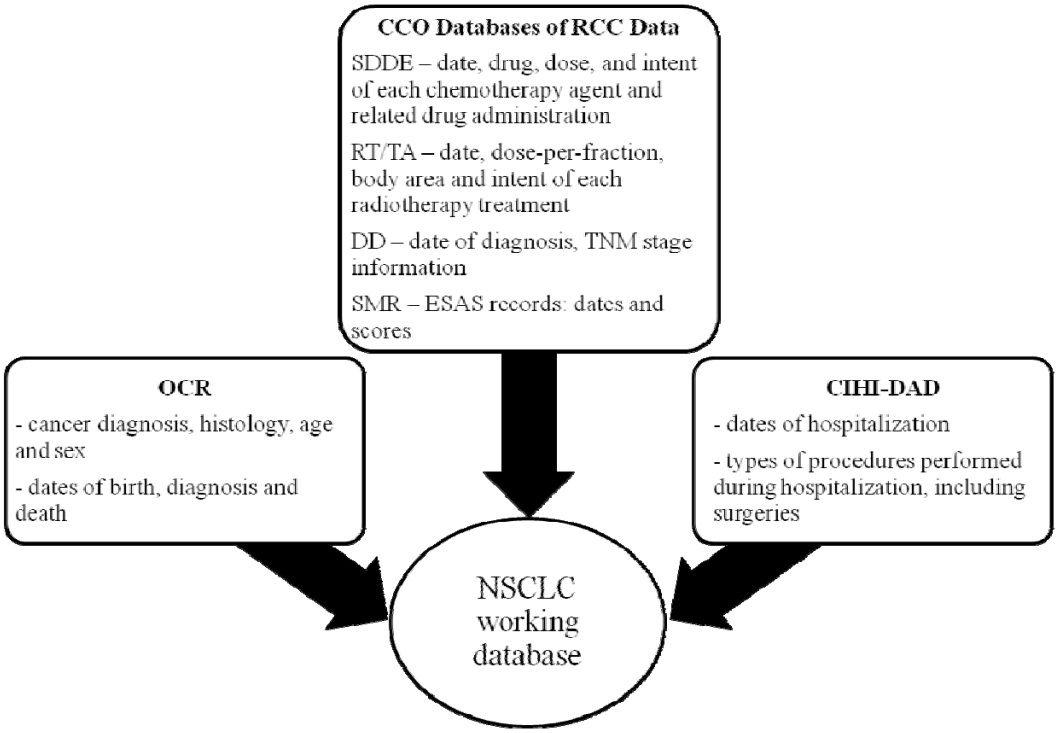
3.3.2 Exclusion Criteria

Patients with more than one primary cancer diagnosis were excluded to ensure any chemotherapy records for that patient were for NSCLC and to ensure the patient was truly chemotherapy naïve (i.e. had not had previous chemotherapy for another cancer). Patients who had prior curative adjuvant or neoadjuvant chemotherapy for NSCLC were excluded from the analysis. Patients who had curative surgery (segmentectomy, lobectomy or pneumonectomy) within the sixteen weeks prior to initiation of palliative chemotherapy were excluded as it was assumed their chemotherapy was adjuvant therapy misidentified as palliative. This cut-point has been used previously to identify adjuvant chemotherapy (1). Procedure codes used to identify lung surgeries are listed in Appendix C. Patients who received curative and/or palliative radiotherapy within the one month prior to initiation of PPDC were excluded as it would be impossible to determine which therapy was responsible for any observed HRQL changes. Patients who received palliative radiotherapy between the baseline ESAS assessment and the two-month assessment were included in the baseline descriptive analyses but excluded from analyses in objectives two and three.

3.4 Data Sources and Linkage

NSCLC patients were identified through the Ontario Cancer Registry (OCR) using the International Classification of Diseases code for lung cancer (2) and the International Classification of Diseases for Oncology histology codes for non-small cell lung cancer (3). (Appendix D contains a list of histology codes.) These records were then linked to several other databases to identify the study population receiving first-line PPDC at Ontario's RCCs and to ensure inclusion and exclusion criteria were met. Figure 3 below is a schematic illustrating from which databases the various data elements came. Linkage across databases was completed using unique patient identifiers (called Group Numbers). All required databases are held by Cancer Care Ontario (CCO) and are accessible on a secure server at the Queen's Cancer Research Institute's Division of Cancer Care and Epidemiology through a data sharing agreement with CCO.

Figure 3 Data sources



CCO: Cancer Care Ontario; OCR: Ontario Cancer Registry; CIHI-DAD: Canadian Institute for Health Information – Discharge Abstract Database; SDDE: Systemic Drug Delivery Event Database; RP/TA: Radiation Planning/Treatment Activity Database; DD: Disease Database; SMR: Symptom Management Reporting Database.

3.4.1 Ontario Cancer Registry (OCR)

The OCR is a database of all Ontario residences with respect to cancer incidence and mortality. The only cancer not included in the database is non-melanoma skin cancer. This passive, population-based registry captures a minimum of 98% of all new cases of cancer in the province (4;5). Records include cancer site and histology, date of diagnosis, patient age and sex, vital status and other demographic information (6).

3.4.2 CCO's Activity Level Reporting (ALR) Treatment Databases

The ALR includes the Systemic Drug Delivery Event database, the Radiation Planning/Treatment Activity database and the Disease database. The Systemic Drug Delivery Event database contains detailed information on all chemotherapy administered at Ontario's Regional Cancer Centres including treatment intent, type of drug, dose, date and time of drug administration (7). The database is of high quality as it is populated by CCO's automated drug prescribing system, the computerized physician order entry system (CPOE), which has 100% physician adoption at the cancer centres (8). It therefore covers all systemic treatments occurring at the centres.

The Radiation Planning/Treatment Activity database contains detailed information on all radiotherapy administered in Ontario including: date and time, dose per fraction, body region, and intent of radiation treatment (7). Previous versions of this database were shown to be at least 95% complete and 99% accurate (9). The current version of the database is thought to be even more complete as it is compiled from data pulled directly from the radiotherapy treatment machines.

The Disease database contains detailed information on patients' tumours including TNM staging information and histology (7). Stage capture for lung cancer is 90% complete for all cases diagnosed from 2008 on (10).

3.4.3 CCO's Symptom Management Reporting Database

This database includes all Edmonton Symptom Assessment System data for patients treated at Ontario's Regional Cancer Centres. Data are available across centres from April 2008-on. ESAS data is either entered directly by the patient into the system through a kiosk at the cancer centre or filled out on a paper form and then uploaded by clinic staff (7). By the end of 2007, 43% of lung cancer patient treated at the centres were screened with ESAS at least once a month (11) and by 2010 59% were screened at least once per month (12).

NB: ESAS data from Princess Margaret Hospital from 2008-2009 has been withheld because it was part of a clinical trial where patients were randomized to receive ESAS screening or not (6).

3.4.4 Canadian Institute for Health Information's Discharge Abstract Database

The Canadian Institute for Health Information's Discharge Abstract Database (CIHI-DAD) contains information on all hospital performed surgeries including: hospital location, date of admission to hospital, date of hospital discharge and type of surgery performed (7). The database is complete across Ontario institutions (13). CCO has a Cancer Surgery Agreement with hospitals for the hospitals to report cancer surgeries directly to CCO throughout the year which is then reconciled at year end with the final CIHI-DAD data for that year (7).

3.5 Assignment of Chemotherapy Regimens and Treatment Cycles

The CCO Systemic Drug Delivery Event database contains records for every drug administration for each patient treated in the RCCs. This includes chemotherapeutic and non-chemotherapeutic agents. The first step in identifying patients receiving PPDC regimens was to sort out the codes for chemotherapeutic agents and exclude any patients who received agents not identified as part of the standard platinum chemotherapy doublets. Then regimens were assigned

based on the drug codes recorded for each administration of chemotherapeutic agents to that patient. The chemotherapy doublets included in this study are listed in Table 2 and were chosen based on being the standard and most common chemotherapy doublets used for the palliative treatment of advanced NSCLC.

Table 2 Standard chemotherapy doublet regimens included in this study

Platinum Agent		Agent Paired with Platinum
Cisplatin *or* *Carboplatin*	with one of	*Gemcitabine* *Vinorelbine* *Docetaxel* *Paclitaxel*

The next step was to define the cycles of chemotherapy. Chemotherapy cycles are not identified in the Systemic Drug Delivery Event database and therefore had to be coded by hand for this study. In general, practice guidelines recommend 21 or 28 day cycles with the platinum agent delivered on day one of each cycle and sometimes additionally on other days (14;15). Cycles were defined based on the dates of administration of the platinum agent. See Table 3 below for examples.

Table 3 Examples of platinum chemotherapy administrations and cycles assignments

Cycle Assignments for Platinum Chemotherapy Administrations						
Patient	**Day in the cycle**	**Cycle 1**	**Cycle 2**	**Cycle 3**	**Cycle 4**	**Notes**
1	1 2 3	2009/11/09 2009/11/10 2009/11/11	2009/11/30 2009/12/01 2009/12/02	2009/12/21 2009/12/23	2010/01/11 2010/01/12 2010/01/13	Day 1,2,3 administration 21day cycle
2	1	2009/01/28	2009/02/18	2009/03/11	2009/04/01	Day 1 administration 21day cycle
3	1	2010/01/28	2010/04/07			Day 1 administration Long gap between cycles
4	1 8	2009/06/11 2009/06/18	2009/07/02 2009/07/09	2009/07/21 2009/07/28	2009/08/13 2009/08/20	Day 1,8 administration 21day cycle
5	1	2009/02/05	2009/03/05	2009/04/02	2009/04/30	Day 1 administration 28 day cycle

3.6 Outcome Variables

The primary outcome variable was the change in ESAS wellbeing score at two months post-initiation of PPDC. The two month time point was chosen as it approximates the end of two cycles of chemotherapy, is the time at which treatment benefit should manifest itself, and is a common assessment time in RCTs measuring QOL, aiding comparison with those studies. Change scores were calculated by subtracting the two-month score from the baseline score such that a positive change score represented improvement and a negative change score represented

deterioration. Patients who died before the two-month assessment were also classified as deteriorated.

Survival of the study population was calculated from the date of first chemotherapy treatment to date of death using the Kaplan-Meier method.

Additional secondary outcome variables were the changes in the eight individual ESAS symptoms (pain, shortness of breath, appetite, tiredness, nausea, drowsiness, anxiety and depression). The validity and reliability of the ESAS as a measurement tool are described in the Literature Review.

3.6.1 Definitions and Identification of Baseline and Two-Month ESAS Records

i) Baseline ESAS Record

An ESAS record was considered to be baseline if it was completed within the 30 days leading up to and including the date of the initiation of palliative chemotherapy. The date of the first chemotherapy treatment was included because the ESAS is completed at the beginning of each clinic visit, and thus an ESAS measurement on the same day as a chemotherapy treatment would still precede the chemotherapy administration. If there was more than one baseline ESAS record identified for an individual patient, the record closest to the date of the first chemotherapy treatment was chosen.

ii) Two Month ESAS Record

An ESAS record was considered to be a 'two month' record if it was taken within six to ten weeks of the first chemotherapy treatment date and met one of the following criteria:

a) If the patient received only one cycle of chemotherapy, no further criteria needed to be met. If there was more than one 'two-month' record available for an individual, the one closest to the end of the 6 – 10 week interval was chosen.

b) If the patient received two or more cycles of chemotherapy, the 'two month' assessment must have taken place more than 18 days after the second cycle's first treatment date and up to and including the first treatment date of the third cycle. If there was more than one 'two month' record available for an individual, the one closest to the start of the third cycle was chosen.

3.7 Patient Characteristics

Patient characteristics included: age, sex, stage, histology and baseline ESAS scores. Age was assessed as both a continuous variable and as a categorical variable with the categories '30-49 years', '50-70 years' and '70-90 years'. The other variables were categorical. Stage was classified as 'stage III', 'stage IV', 'recurrent' or unknown. Histology was classified as 'adenocarcinoma', 'squamous-cell carcinoma' or 'other' which included large cell, mixed type and NSCLC not otherwise specified. Baseline ESAS scores were also classified as 'mild' (0-4), 'moderate' (5-7), or 'severe' (8-10) using cut-points defined in previous work (16).

3.8 Data Analysis Plan: Objective One

Objective 1: *To describe the characteristics of patients who begin PPDC for advanced NSCLC, the chemotherapy they receive and their wellbeing and symptom scores prior to initiation of PPDC (baseline) as captured by the ESAS.*

To address the question of the representativeness of patients for whom a baseline ESAS record was available, a comparison of patient characteristics (including median survival) between patients with a baseline ESAS record and patients for whom a record was not available was performed. This included comparisons of age (t-test) and sex, histology, stage of disease (Chi square test) and survival from start of treatment (Kaplan-Meier survival curves, log-rank test).

Univariate analysis of the patient characteristics were performed to provide a descriptive overview of the study population. The proportion of patients at each of the RCCs with baseline ESAS records, the chemotherapy regimens used and the number of cycles completed were also described.

The distribution of baseline ESAS wellbeing scores was presented as well as the distributions of the individual symptom items. The proportions of patients whose symptoms fell into the categories of mild, moderate or severe were also reported.

3.9 Data Analysis Plan: Objective Two A

Objective 2 a) *To describe patients' change in wellbeing (and symptom) scores from baseline to two months post-initiation of PPDC.*

Frequency distributions of patients' wellbeing and individual symptoms change scores were generated and the proportions of patients who improved, deteriorated or remained stable with respect to their ESAS scores were calculated based on a chosen cut-point for defining clinically meaningful change (see Section 3.9.1 below).

3.9.1 Selection of a Cut-Point for Defining a Clinically Meaningful Change in Score

A change of one point on the scale was selected as the cut-point for a clinically meaningful change. Thus a decrease of 1 point or more was classified as improved, no change as stable, and an increase of 1 point or more as deteriorated.

The choice of one as the cut-point was assessed by comparing it to a distribution-based method for selecting cut-points for clinically meaningful change. The distribution-based method uses half of the standard deviation of the distribution of baseline scores as a cut-point (17). Provided the 0.5 standard deviation of the baseline score distribution was close to one, we were

satisfied with our choice of one as the cut-point. If the half standard deviations had been much different, other cut-points would have been considered.

3.9.2 Sensitivity Analysis to Assess the Influence of Missing Data

A sensitivity analysis was performed to assess the potential influence of missing data on the calculated proportions of wellbeing improvement, stabilization and deterioration at two months. All patients with a baseline ESAS wellbeing score were included in this analysis. If a patient was missing a two month ESAS record but had a later record, those who had improved or remained stable later were classified as improved/ stable at two months (i.e. their imputed change at two months was improved/stable). Patients who underwent palliative radiotherapy between baseline and their two month ESAS assessment were classified as unevaluable. All other patients missing a two month score were classified as unknown. The worst-case scenario of all unevaluable and unknown patients actually having deteriorated was used to recalculate the proportion of patients who achieved a wellbeing benefit. This is likely an overly pessimistic view, but it provides the most conservative estimate of benefit in wellbeing.

3.10 Data Analysis Plan: Objective Two B

Objective 2 b) *To investigate whether patient characteristics: sex, age, stage of disease, histology and baseline ESAS wellbeing score predict change in wellbeing at two months.*

Each variable was assessed bivariately for an association with wellbeing change. Any variables significantly associated at an alpha level of 0.2 were then assessed for joint predictive value in a multivariate model. A final predictive model was developed through backward selection until only variables significant at an alpha level of 0.05 remained.

Logistic regression was employed to develop the predictive model. The dependent variable (wellbeing change) was dichotomized as improved/stable (i.e. wellbeing benefit) and deteriorated. See Section 3.7 for the categorizations of the predictor variables.

3.11 Data Analysis Plan: Objective Three

Objective 3: *To compare the proportion of patients whose wellbeing improved or remained stable to the proportion of patients whose general QOL improved or remained stable in clinical RCTs of PPDC.*

The proportion of patients whose wellbeing improved or remained stable (considered wellbeing benefit), was compared to the proportion of patients whose general quality of life improved or remained stable in two relevant RCTs. As described in the Literature Review, wellbeing is closely aligned to the conceptual definition of QOL and as such was selected as the proxy measure of QOL for this study.

The 95% confidence intervals were calculated for the proportion of patients with improved or stable wellbeing in this study. The point estimate and surrounding confidence interval was compared to the estimates of improved/stable QOL in the RCTs to determine if there was any statistical difference between them.

In the event that the case mix of the current study varied from that of the clinical trials with respect to any of the predictive variables described above, the following was done to ensure the comparison across studies was appropriate and not confounded by the difference in case mix.

a) If the predictor variable was found to be a predictor of treatment benefit, then the results of the current study were standardized to the clinical trials based on that variable.
b) If the predictor variable was not associated with treatment benefit, no standardization was performed.

3.12 Ethical Considerations

The study proposal for this thesis received approval from the Queen's University Health Sciences Research Ethics Board, Study Code EPID-339-11 and access to the Cancer Care Ontario databases was approved by Cancer Care Ontario (Number 11-064) (Appendix E).

All analyses were undertaken using Statistical Analysis Software (SAS)® , version 9.2 (18).

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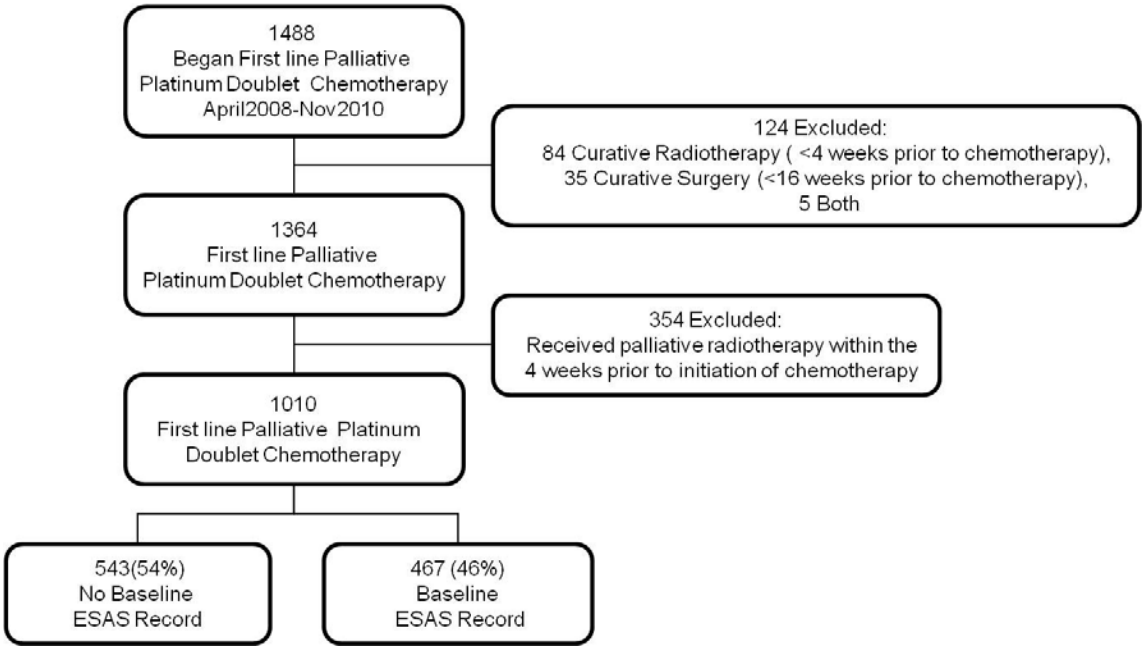
Chapter 4

Results

4.1 Identification of Study Population

Using the Ontario Cancer Registry (OCR), all cases of NSCLC diagnosed in the province after 2004 were identified. By linking OCR records to the RCCs' chemotherapy treatment records, 1488 NSCLC patients who began first-line PPDC between 1 April 2008 and 30 November 2010 were identified (Figure 4). Patients for whom it was likely their palliative chemotherapy was misidentified adjuvant chemotherapy were excluded (n=124). This was the case for patients who had undergone curative surgery within 16 weeks prior to starting their PPDC or who had undergone curative radiotherapy within 4 weeks prior to starting their PPCD. 354 patients were excluded for receiving palliative radiotherapy within 4 weeks prior to the initiation of chemotherapy as the close timing of the treatments would make it difficult to know which treatment (radiotherapy or chemotherapy) to attribute any observed change in ESAS scores. This left 1010 patients who met the inclusion criteria. Of the 1010, 467 (46%) patients had an ESAS record within the baseline window (30 days). The remaining 543 (54%) did not have a baseline ESAS record available. See section 4.2.1 for a comparison of characteristics of patients with a baseline ESAS record to patients without a baseline ESAS record.

Figure 4 Flow chart of study subject identification



4.2 Objective One: Describing Patients Who Receive First-line PPDC

4.2.1 Comparison of Patients with Baseline ESAS Records to Those Without

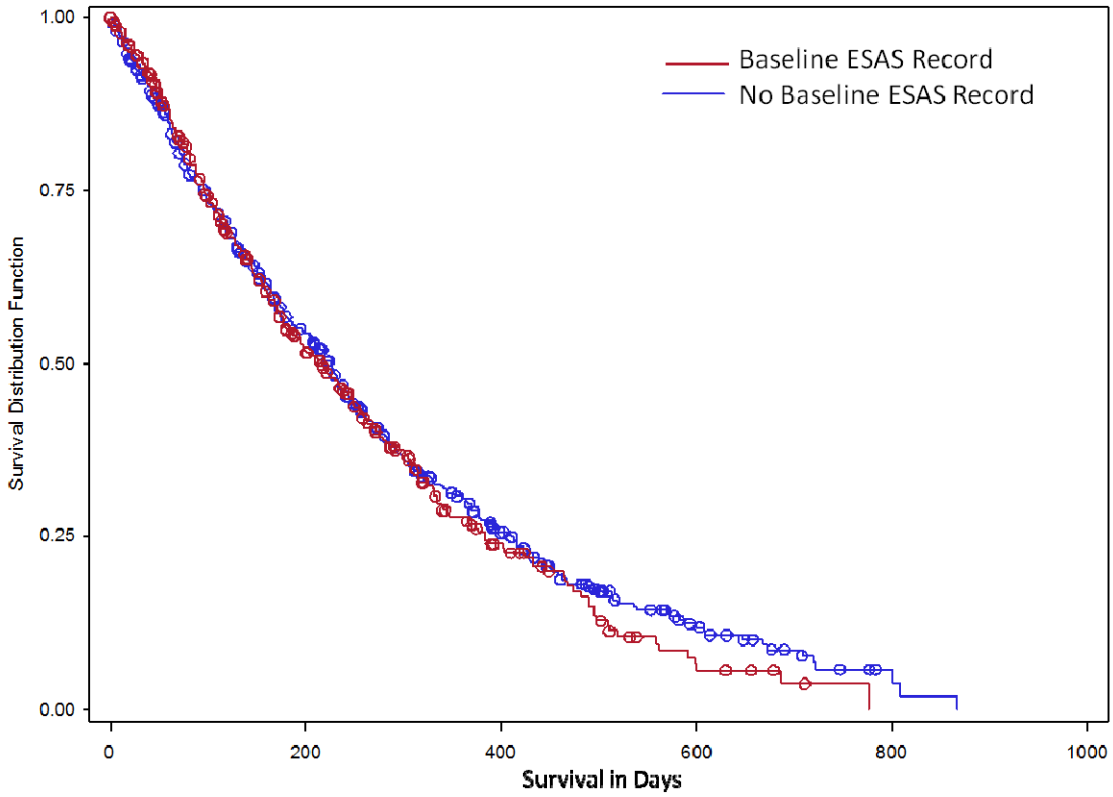
First, to assess whether the patients who had a baseline ESAS record were representative of all eligible patients undergoing PPDC, the patients with baseline ESAS records were compared to those without baseline records (Table 4). There were no statistically significant differences between the two groups with respect to patient characteristics including: age, sex, stage of disease at diagnosis and histology. The groups were also similar with respect to overall survival from the start of palliative chemotherapy. Below, Figure 5 displays the survival curves for the two groups. Median survival was 212 days (approximately 7 months) for patients with ESAS records and 231 days for patients without ESAS records (Log Rank χ^2= 1.44, 1DF, p=0.23). Therefore, we were confident the subset of patients who were evaluated with ESAS was representative of all patients undergoing first-line PPDC at Ontario's RCCs.

Table 4 Comparison of characteristics of patients with a baseline ESAS record and patients for whom a baseline ESAS record was not available

Variable, N (%)	Baseline ESAS record (N=467)	No baseline ESAS record (N=543)	p value*
Age, Years			
Mean	63.8	63.6	0.69
Range	37-88	35-86	
Sex			0.95
Male	253 (54.2)	293 (54.0)	
Female	214 (45.8)	250 (46.0)	
Histology			0.59
Adenocarcinoma	241 (51.6)	274 (50.5)	
Squamous-cell Carcinoma	72 (15.4)	75 (13.8)	
Other NSCLC	154 (33.0)	194 (35.7)	
Stage			0.38
Recurrent	34 (7.3)	42 (7.7)	
III	99 (21.2)	100 (18.4)	
IV	304 (65.1)	352 (64.8)	
Unknown	30 (6.4)	49 (9.0)	

*p values generated from a t-test for age and chi square tests for the remaining categorical variables.

Figure 5 Survival of patients with a baseline ESAS record and patients without a baseline ESAS record



The proportion of eligible patients who had a baseline ESAS record available varied substantially across the 14 RCCs (Table 5). Centres in Windsor, Kitchener, Barrie and Sudbury had baseline ESAS records for more than 70% of their PPDC patients, with Kitchener leading the group at 95%. Three more centres had baseline records for more than 50% of patients while five centres had records for between 30 and 50% of patients. Only two centres had records for less than 10% of patients. One of these was Princess Margaret Hospital in Toronto, which was expected to be low because their 2008-2009 ESAS data was withheld as part of a clinical trial (1). As a result of the differential availability of ESAS records across the centres, the majority of study patients (N=337, 72.2%) were treated at 6 of the RCCs (Windsor, London, Kitchener, Hamilton, Sudbury and Ottawa) while the remaining 27.8% were treated at the other 8 locations.

Table 5 Proportion of PPDC patients with a baseline ESAS record by Cancer Centre

Centre	City	Patients with Baseline ESAS Record (N=467)	All PPDC Patients (N=1010)	% of All PPDC with Baseline ESAS Record
Windsor Regional Cancer Program	Windsor	56	60	93.3
London Regional Cancer Program	London	37	89	41.6
Grand River Regional Cancer Centre	Kitchener	38	40	95.0
Juravinski Cancer Centre	Hamilton	78	172	45.4
Carlo Fidani Peel Regional Cancer Centre at Credit Valley Hospital	Mississauga	26	82	31.7
Odette Cancer Centre at Sunnybrook Health Sciences Centre	Toronto	18	48	37.5
Princess Margaret Hospital	Toronto	3	96	3.1
Stronach Regional Cancer Centre	Newmarket	24	44	54.6
RS McLauglin Durham Regional Cancer Centre	Oshawa	6	72	8.3
Cancer Centre of Southeastern Ontario	Kingston	22	37	59.5
The Ottawa Hospital Cancer Centre	Ottawa	94	165	57.0
Simcoe Muskoka Regional Cancer Centre	Barrie	19	27	70.4
Sudbury Regional Hospital Cancer Program	Sudbury	34	44	77.3
Regional Cancer Care - Northwest	Thunder Bay	12	34	35.3

Platinum-based doublet regimens that were included as PPDC for this study consisted of cisplatin or carboplatin with one of: gemcitabine, vinorelbine, paclitaxel, docetaxel. Most study patients (93.8%, N=438) were treated with one of the following four doublets: carboplatin-gemcitabine, carboplatin-paclitaxel, cisplatin-gemcitabine or cisplatin-vinorelbine (Table 6). The remaining 6.2% (N=39) received: carboplatin with vinorelbine or docetaxel; or cisplatin with paclitaxel or docetaxel.

Table 6 Proportion of PPDC patients with a baseline ESAS record by platinum doublet

Doublet, N (%)	Baseline ESAS Record (N=467)	All PPDC Patients (N=1010)	% of all PPDC with Baseline ESAS Record
Cisplatin & Gemcitabine	144	330	43.6
Cisplatin & Vinorelbine	39	95	41.1
Cisplatin & Paclitaxel	1	1	100.0
Cisplatin & Docetaxel	5	11	45.5
Carboplatin & Gemcitabine	138	291	47.4
Carboplatin & Vinorelbine	13	43	30.2
Carboplatin & Paclitaxel	117	222	52.7
Carboplatin & Docetaxel	10	17	58.8

4.2.2 Baseline Descriptive Analysis of Patient Characteristics

Of the 467 patients with baseline ESAS records, 34 were excluded from further analyses for having had palliative radiotherapy within the 4 weeks preceding the initiation of first-line PPDC, as per the study exclusion criteria, leaving 433 patients assessable at baseline

Of the 433 patients with baseline ESAS records, 237 (54.7%) patients were male and the mean age was 64.0 years. 277 (63.9%) patients had stage IV diseases, 94 (21.7%) had stage III disease, 33 (7.6%) had recurrent disease and 29 (6.7%) did not have their stage recorded.

For patients diagnosed with stage IV and stage III disease, the median time from diagnosis to the start of PPDC was 78.0 days and 83.5 days respectively. For patients with unknown stage, the median time was 58.0 days. This unknown stage group was therefore likely comprised of patients with stage IV disease who simply did not undergo detailed staging. For patients with recurrent disease (initially diagnosed as stage I or II), the median time was 386.0 days.

233 (53.8%) patients had adenocarcinoma, 65 (15.0%) had squamous-cell carcinoma, and 135 (31.2%) had another NSCLC histology including large-cell or NSCLC not otherwise specified.

97 (22.4%) patients received only one cycle of first-line PPDC, 69 (16.0%) received two cycles, 64 (14.9%) received three cycles, 85 (19.6%) received four cycles, 41 (9.5%) received five cycles, 74 (17.1%) received six cycles, and 3 (<1%) received more than six cycles.

In terms of previous curative interventions, 28 (6.5%) of patients had previous curative radiotherapy, and 38 (8.8%) had previous curative surgery. 139 (32.1%) of patients had palliative radiotherapy more than 4 weeks prior to their baseline ESAS assessment and 123 (28.4%) received palliative radiotherapy at some point after their two month ESAS assessment.

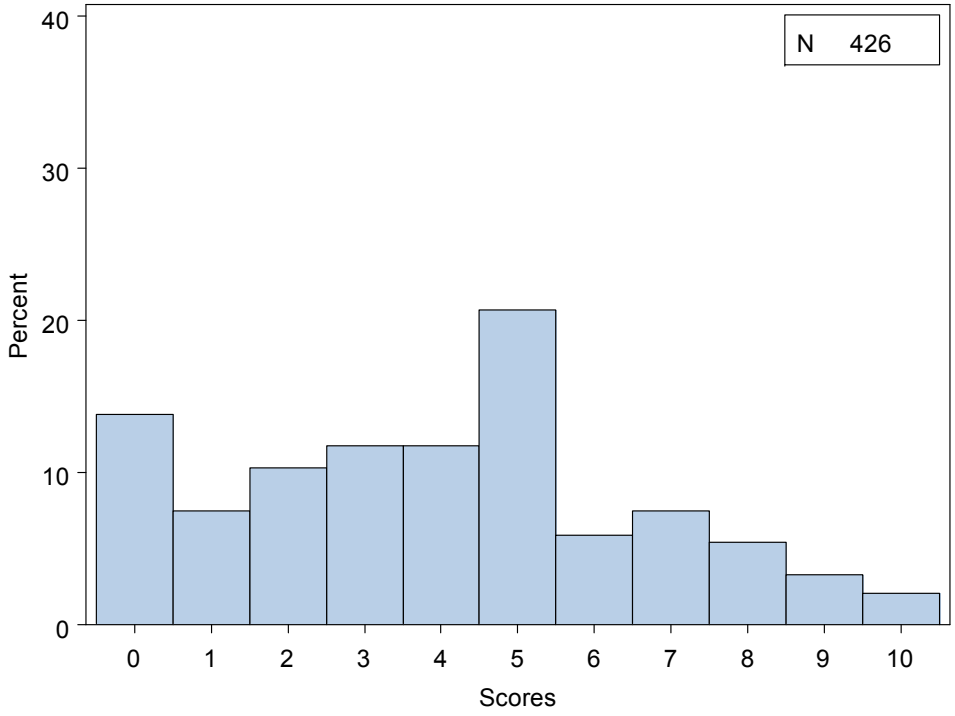
4.2.1 Baseline ESAS Scores

Occasionally a score was missing on an ESAS record and therefore the total number of subjects available for overall wellbeing and individual symptoms assessment varies slightly.

Wellbeing

Patients' baseline wellbeing scores were heterogeneous and covered the entire 11 point range of the rating scale. A minority of patients (<15%) rated their wellbeing at zero (best feeling of wellbeing) indicating most patients were experiencing a deficit in their wellbeing prior to beginning first-line PPDC. The frequency distribution for patient baseline wellbeing scores provided in Figure 6 illustrates this heterogeneity of scores.

Figure 6 Frequency distribution of baseline ESAS wellbeing scores



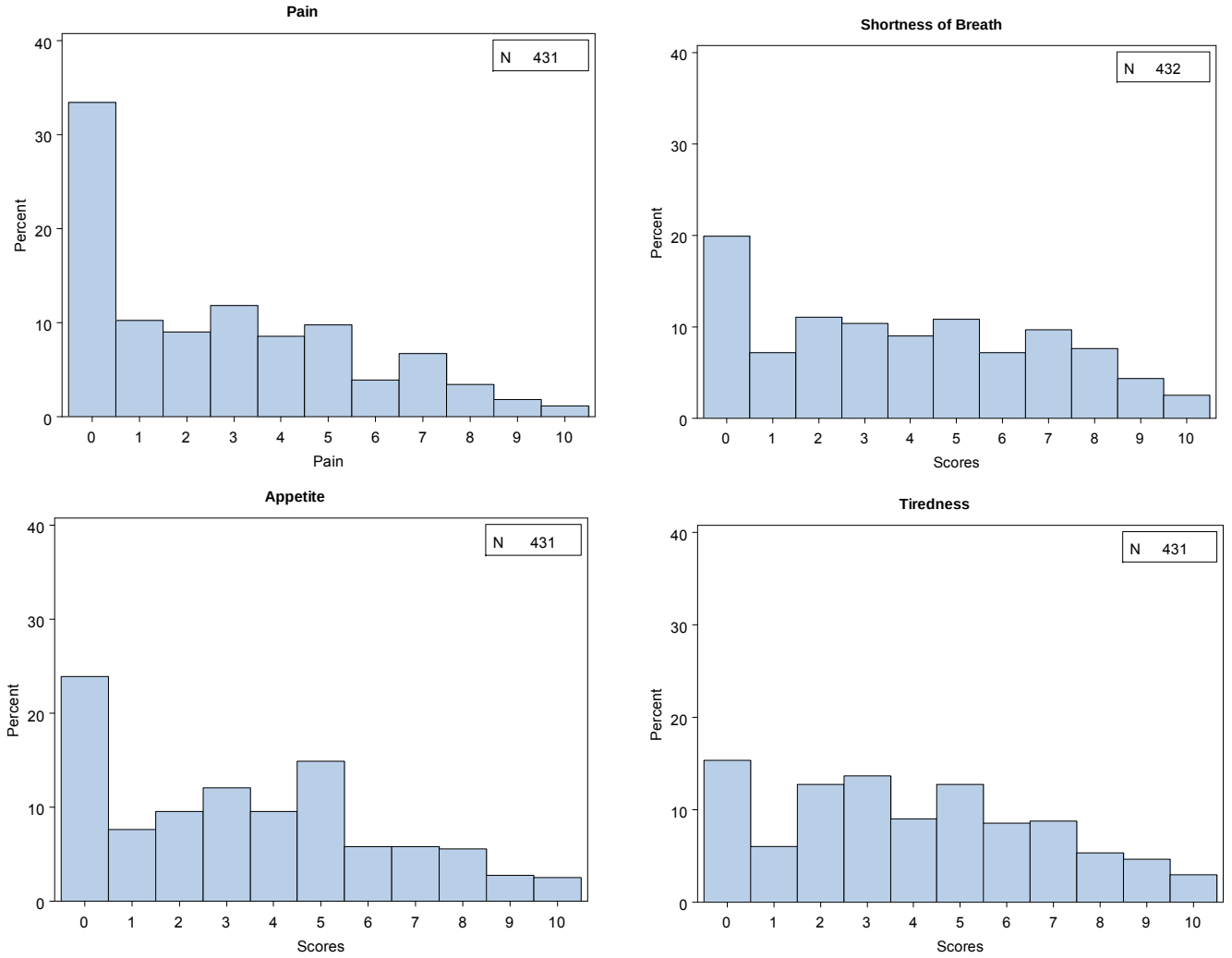
Wellbeing scores were then grouped into three symptom level categories: absent/mild, moderate and severe for the purpose of summarizing the results and for use in the logistic regression modeling described later in this chapter. Cut-points for defining these categories were 0-4 (mild), 5–7 (moderate) and 8-10 (severe) as described earlier (2). These categories are summarized in Table 7 along with the eight ESAS symptoms. Baseline wellbeing was scored high enough by 44.8% of patients to fall into the moderate to severe range, while 55% of patients' wellbeing scores fell into the absent/mild range.

Individual Symptoms

As with wellbeing, patients varied widely with respect to their baseline ratings of the 8 individual symptoms. Frequency distributions for baseline pain, shortness of breath, appetite and tiredness scores are provided in Figure 7. Frequency distributions for the remaining four symptoms can be found in Appendix F. Patients' ratings ranged across the entire 11 point scale

for each symptom. The most common symptoms were pain, shortness of breath, appetite problems, tiredness and anxiety, which is consistent with the literature on NSCLC symptoms (3;4). Each of these symptoms was reported as absent (rating = 0) in less than one third of patients. Drowsiness and depression were less common with only 37 and 41% of patients respectively reporting their absence. Nausea was by far the least common with 65% of patients reporting no nausea.

Figure 7 Frequency distributions for baseline scores for pain, shortness of breath, appetite, and tiredness



Patients' baseline symptoms were grouped into mild, moderate, or severe categories using the same cut-points described for wellbeing. These results are reported in Table 7. With respect to the physical symptoms, which are reflective of local effects of the tumour, 27% of patient's pain scores and 38% of patients' shortness of breath scores fell into the moderate to severe categories.

Systemic symptoms of appetite, tiredness, drowsiness and nausea were classified as moderate or severe in 38%, 43%, 27% and 10% respectively. This is consistent with the fact that appetite problems and tiredness (fatigue) are common in patients with advanced lung cancer while drowsiness and nausea are not as often associated with this disease. The latter two symptoms are more commonly observed as side effects of treatment.

Finally, the psychological symptoms, anxiety and depression, were categorized as moderate or severe in 33% and 21% of patients respectively.

Table 7 Baseline wellbeing and symptom severity categories

		Symptom Level		
Variable	N	Absent/Mild 0 – 4 N (%)	Moderate 5 – 7 N (%)	Severe 8 – 10 N (%)
Wellbeing	***426***	***235 (55.16)***	***145 (34.04)***	***46 (10.80)***
Pain	431	315 (73.09)	88 (20.42)	28 (6.50)
Shortness of Breath	432	249 (57.64)	120 (27.78)	63 (14.58)
Appetite	431	270 (62.65)	114 (26.45)	47 (10.90)
Tiredness	431	245 (56.84)	130 (30.16)	56 (12.99)
Nausea	430	385 (89.53)	36 (8.37)	9 (2.09)
Drowsiness	430	316 (73.49)	81 (18.84)	33 (7.67)
Anxiety	429	288 (67.13)	93 (21.68)	50 (11.19)
Depression	432	343 (79.40)	59 (13.66)	30 (6.94)

4.3 Assessing Selection of One as the Cut-point for Clinically Meaningful Change

To assess the choice of a one point change in score as representative of a clinically significant change, the standard deviations of baseline ESAS scores were calculated. As discussed in the Literature Review, different methods for assigning cut-points for defining clinically significant change in quality of life measures tend to converge around a half standard deviation of the range of baseline scores. In this study, the half standard deviations of scores ranged from 1.03 to 1.49 (Table 8). Thus, the only reasonable choices for a cut-point were one or two.

Since the half standard deviations were all close to one (and did not exceed two), a one point change was kept as the cut-point for defining a clinically significant change in score. Therefore, a decrease in score of one or more will be defined as an improvement, no change in score as stabilization and an increase of one or more as deterioration.

Two was also considered as a cut-point but ultimately rejected in the interest of being conservative in the estimate of the proportion a patients who achieved any wellbeing/symptom benefit with treatment. If two was used as the cut-point it would have increased the number of patients classified as stable (by including those whose score changed by ±1) and thus would increase the proportion ultimately classified as benefitting (improved and stable combined) from treatment.

Table 8 Standard deviations and half standard deviations for baseline ESAS scores

Variable	N	Standard Deviation	0.5 Standard Deviation
Wellbeing	426	2.65	1.33
Pain	431	2.73	1.37
Shortness of Breath	432	2.98	1.49
Appetite	431	2.85	1.43
Nausea	430	2.06	1.03
Tiredness	431	2.83	1.42
Drowsiness	430	2.78	1.39
Anxiety	429	2.92	1.46
Depression	432	2.71	1.36

4.4 Objective Two A: Describing Change in Wellbeing and Symptoms at Two Months

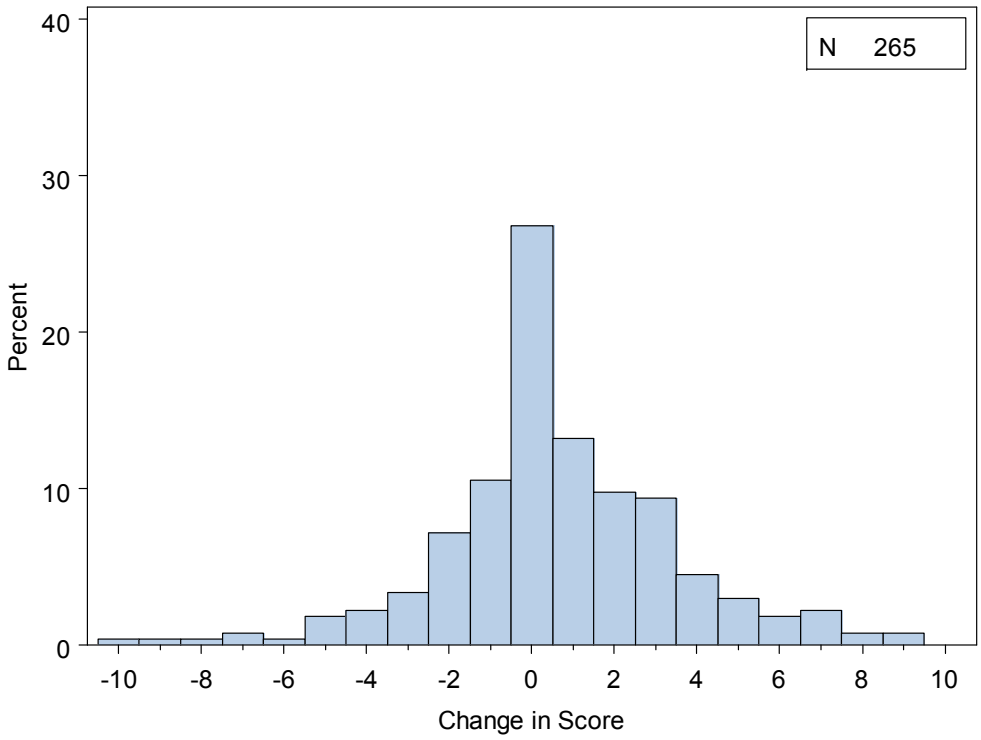
4.4.1 Change in Wellbeing and Symptom Levels at Two Months

Approximately 270 of the patients with a baseline ESAS record also had an ESAS record at two months and were thus assessable for changes in their scores at that time. An additional 48 patients had died and were classified as deteriorated for the assessment of change wellbeing. Those who died were not included in the reporting of changes in individual symptoms. Occasionally an ESAS score was missing for a particular item on the questionnaire; therefore, the exact number of patients assessable at two months varies slightly depending on which symptom is being considered (Range: 265-270).

Wellbeing

The frequency distribution for wellbeing change scores is provided in Figure 8 below. Of those patients accounted for at two months (those with a wellbeing score at two months and those who had died by that time, N=313), wellbeing improved in 121 (38.7%, 95% CI: 33.4-44.2%) and remained stable in 71 (22.7%, 95% CI: 18.4 – 27.6%) patients. Conversely, wellbeing deteriorated in 121 (38.7%, 95% CI: 33.4-44.2%) patients. In total, 192 (61.3%, 95% CI: 55.8 – 66.6%) patients were improved or stable at two months and could be said to have experienced wellbeing benefit with treatment.

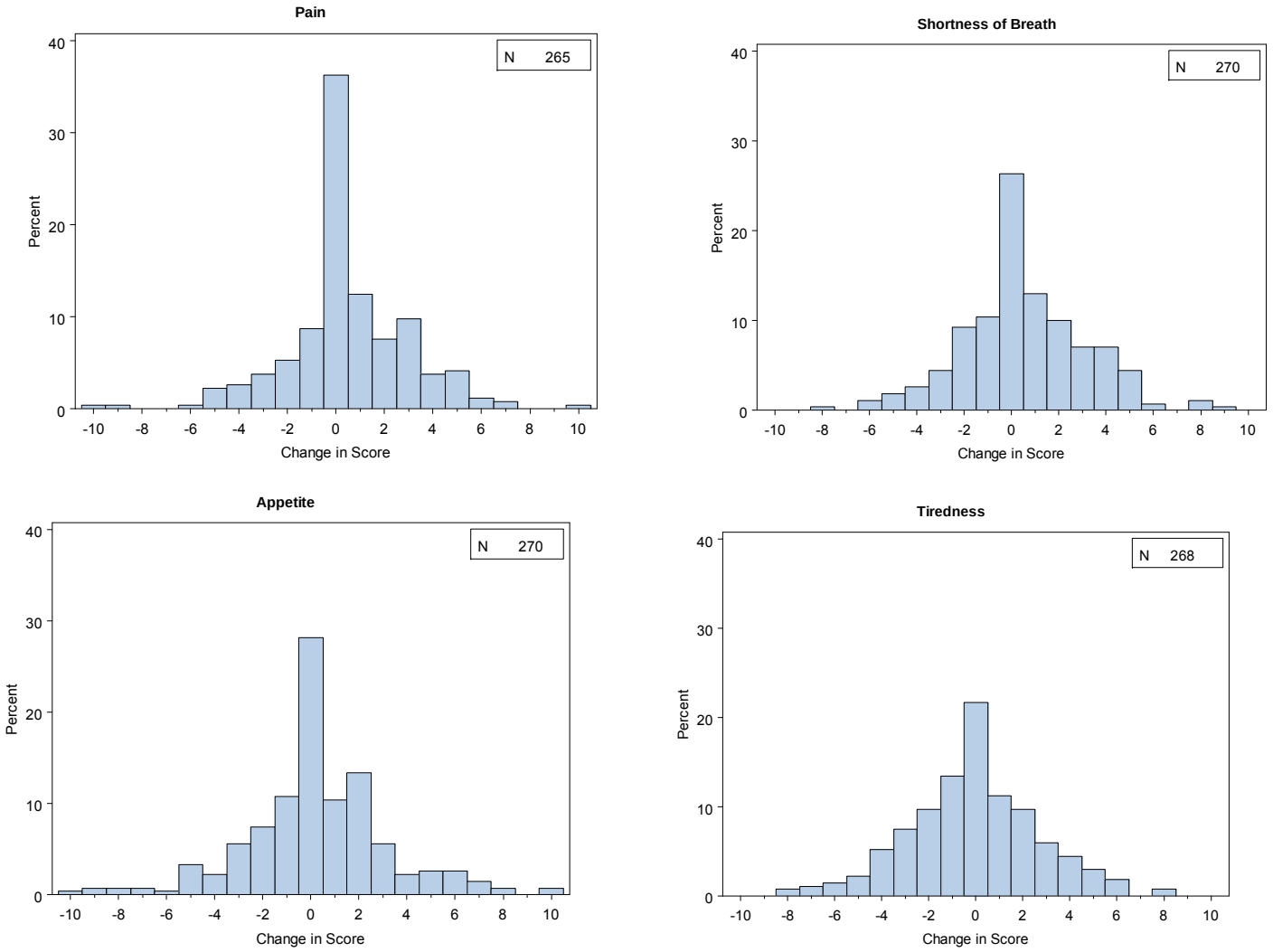
Figure 8 Frequency distribution of wellbeing change scores at two months



Symptoms

Frequency distributions for pain, shortness of breath, appetite and tiredness are presented in Figure 9. Frequency distributions for the other four symptoms can be found in Appendix G. As was the case for baseline scores, there was a high degree of variability in symptom change scores at two months. The frequency distributions show that for most symptoms, patients' change scores covered the entire possible range. The distributions were all approximately bell-shaped, but the peaks were too high for them to be normal. Based on their interquartile ranges (IQs), the symptoms with the most variability were tiredness (IQ = 4), followed by wellbeing, shortness of breath, appetite and drowsiness (all IQ=3). Pain, anxiety and depression (IQ =2) and tiredness (IQ =1) were less variable.

Figure 9 Frequency distributions of symptom change scores at two months



A summary of the proportions of patients who survived to two months who improved, remained stable or deteriorated with respect to each of the eight ESAS symptoms are reported in Table 9. The majority of symptoms were improved in roughly 40% of patients and only deteriorated in one quarter of patients.

Tiredness and drowsiness improved in 37% and 30% of patients. Anxiety improved in almost half (48%) of patients while depression, which was generally reported as less severe prior to treatment, improved in 36% of patients. Nausea, which was relatively mild prior to treatment but is also a common side effect of chemotherapy, improved in only 19%, remained stable in 52% and deteriorated in 30%.

Table 9 Change in symptoms at two months

Variable	Improved N (%)	Stable N (%)	Deteriorated N (%)	Total
Pain	106 (40.0)	96 (36.2)	63 (23.8)	265
Shortness of Breath	118 (43.7)	71 (26.3)	81 (30.0)	270
Appetite	112 (41.5)	76 (28.2)	87 (32.2)	270
Nausea	51 (19.0)	139 (51.7)	79 (29.4)	269
Tiredness	99 (36.9)	58 (21.6)	111 (41.4)	268
Drowsiness	80 (29.9)	85 (31.7)	103 (38.4)	268
Anxiety	127 (47.6)	78 (29.2)	62 (23.2)	267
Depression	97 (35.9)	101 (37.4)	72 (26.7)	270

4.4.2 Sensitivity Analysis of the Improved/Stable Wellbeing Proportion Estimate

Due to the fact that 115 (26.5%) of patients with baseline wellbeing scores were unaccounted for at two months (they did not have a wellbeing score at two months and had not died by that time), there was concern that the calculated proportion of patients with improved/stable wellbeing at that time may not be representative of the entire baseline group. Therefore, the proportions of improved/stable and deteriorated were recalculated for the entire baseline wellbeing group (N=426) to explore the effect of the missing data (Figure 10). This was done using the imputation rules described in the Methods chapter and illustrated in Figure 11. Patients who were missing a two-month ESAS wellbeing score but had a later score that indicated improvement or stabilization were classified as improved or stable. Patients who had received palliative radiotherapy between their baseline assessment and their two-month assessment were classified as unevaluable and all other patients with missing wellbeing scores at two months were classified as unknown.

Figure 10 Change in wellbeing for entire baseline wellbeing record group

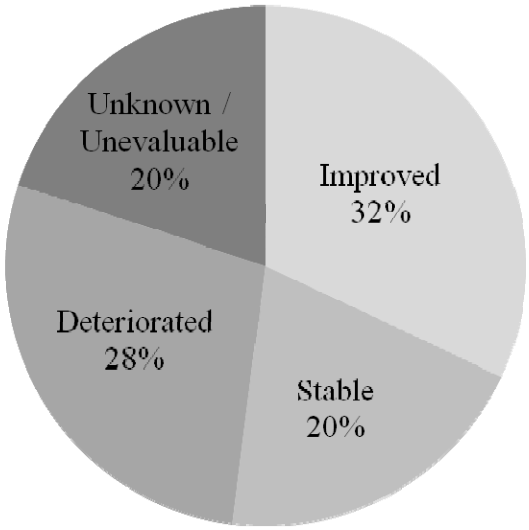
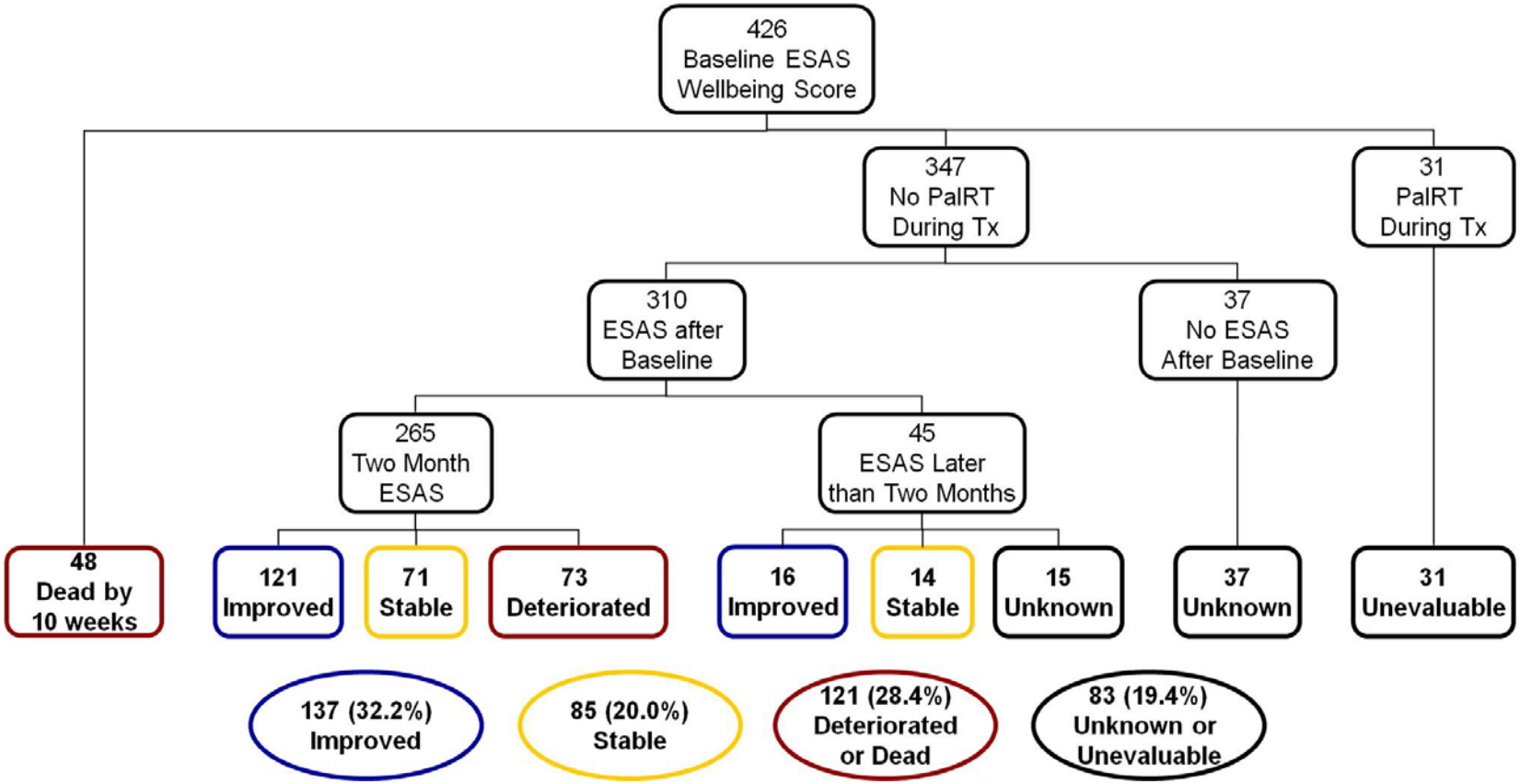


Figure 11 Change in wellbeing for the entire baseline ESAS wellbeing record group (N=426)



PalRT: palliative radiotherapy; Tx: treatment

Of the entire baseline group (N=426), 137 (32.2%, 95% CI 27.9 - 36.7%) had improved, 85 (20.0%, 95% CI: 16.4 - 23.0%) were stable and 121 (28.4%, 95% CI: 24.3 – 32.9%) had deteriorated or died. An additional 83 (19.5%, 95% CI: 16.0 – 23.5%) were unknown or were unevaluable due to having had palliative radiotherapy between the two assessment time points. The worst-case scenario of all unknown and unevaluable cases having deteriorated only reduced the estimate of wellbeing benefit to 52.1% (95% CI: 47.4 – 56.8%).

4.5 Objective Two B: Assessment of the Association between Patient Characteristics and Change in Wellbeing at Two Months

In addition to describing the wellbeing impact of PPDC, another goal of this study was to identify factors that may help to predict which patients are most likely to experience a wellbeing benefit with this treatment. Potential patient characteristics were assessed using bivariate and multivariate analyses for an association with wellbeing benefit (i.e. improvement or stabilization of wellbeing at two months).

4.5.1 Bivariate Analysis

Categorical patient characteristics (sex, age group, baseline wellbeing score, stage and histology) were assessed using bivariate analysis for association with wellbeing benefit (Table 10). Variables that were significant at an alpha level of 0.2 were retained for the multivariate analysis.

Table 10 Bivariate analysis of patient characteristics with wellbeing benefit

Variable	Odds Ratio	95% CI*
Age		
30-49	0.47	0.20 – 1.12
50-69*	1.00	
70-89	1.09	0.66 – 1.79
P trend	*0.19*	
Sex		
Male*	1.00	
Female	1.05	0.67 – 1.66
P value	*0.83*	
Histology		
Adenocarcinoma *	1.00	
Squamous-cell Carcinoma	0.49	0.25 – 0.95
Other NSCLC	0.72	0.43 – 1.20
P value	*0.08*	
Stage of Disease		
Recurrent	2.43	0.94 – 6.28
III	1.05	0.60 – 1.85
IV*	1.00	
Unknown	1.23	0.52 – 2.93
P value	*.28*	
Baseline Wellbeing		
Mild*	1.00	
Moderate	2.55	1.51 – 4.30
Severe	1.90	0.84 – 4.26
P value	*0.001*	

CI = confidence interval, *Reference group

Sex was not associated with wellbeing benefit. This suggests it was reasonable to compare the results of this study to those of the RCTs despite there being a large difference in the ratios of male and female patients.

Of particular note, the most senior age category (70-89) was similar to the average age category (50-69) and in fact the odds ratio for wellbeing benefit (OR = 1.09) favoured the senior

group. This suggests that the elderly were just as likely to achieve wellbeing benefit with this treatment as their younger counterparts.

The odds of wellbeing benefit was lower in squamous-cell carcinomas (OR = 0.49) and other histologies (OR = 0.72) than adenocarcinomas.

Stages III and IV had very similar odds of wellbeing benefit as did the Unknown stage category. This is likely due to the majority of the unknown group being stage IV disease that simply did not undergo any detailed staging investigation or the stage was not recorded in the patient record. The odds of wellbeing benefit was highest in the recurrent disease group (OR = 2.43), likely reflecting this group's slower progressing disease.

The odds of wellbeing benefit was higher in the moderate (OR = 2.55) and severe (OR = 1.90) baseline wellbeing categories compared to the mild category.

Sex was not significantly associated with wellbeing benefit (OR = 1.05, p value 0.83) and was not included in the multivariate modeling. Stage of disease was borderline significant (p value 0.28), and was therefore included in the multivariate analysis. All other variables were significant the 0.2 level and were included in the multivariate analysis.

4.5.2 Multivariate Analysis

Wellbeing benefit was then modeled using multiple logistic regression. Age group, stage, histology and baseline wellbeing category were all initially included in the model as potential predictors based on the results of the bivariate analyses. A process of backwards selection was employed to refine the model until only those variables significant at a p-value of 0.05 were left. In the final model (Table 11), only histology and baseline wellbeing category were associated with treatment benefit. The odds of wellbeing benefit were higher in those with

moderate or severe baseline wellbeing scores. The odds of wellbeing benefit were lower in those with squamous-cell carcinoma than in those with adenocarcinoma.

Table 11 Final multivariate model of factors associated with wellbeing benefit

Variable	Odd Ratio	95% CI*
Histology		
Adenocarcinoma *	1.00	
Squamous-cell Carcinoma	0.50	0.25 – 0.98
Other NSCLC	0.72	0.42 – 1.21
Baseline Wellbeing		
Mild*	1.00	
Moderate	2.53	1.50 – 4.29
Severe	1.86	0.82 – 4.22

Hosmer-Lemeshow test for goodness of fit: χ^2 (DF=6)=1.42, p=0.96.
CI = confidence interval, *Reference group

4.6 Objective Three: Comparison of the Results of this Study with the RCTs

Overall, the current study population was similar to the patients participating in the trials (5;6) with respect to patient characteristics (Table 12). There were, however, more female patients in this study than in the trials, likely reflecting the increase in lung cancer incidence among women from the time the trials were accruing patients. Even though the sex ratio in this study was noticeably different from the ratio in the trials, sex was not associated with change in wellbeing, the primary outcome of interest. Thus, sex was not considered as a confounder in the comparison of the results of this study with the RCTs. Histology, on the other hand, was different in this study and was significantly associated with change in wellbeing. Histology, therefore, was considered a potential confounder in comparing this study to the RCTs.

Table 12 Descriptive comparison of the current study with two key RCTs

Variable	Current Study	Gridelli, et al. *	von Plessen, et al. †
Age			
Median	65	62	64
Range	42 - 88	35 – 72	34 – 84
Sex, %			
Male	55	81	63
Female	45	19	37
Stage, %			
IV	62	80	76
III	22	20	24
Recurrent	9	0	0
Unknown	8	0	0
Histology, %			
Adenocarcinoma	54	42	43
Squamous-cell Carcinoma	14	34	27
Other	32	24	30

*Gridelli, et al. (5) results from the cisplatin-based arms only

†von Plessen, et al. (6) results from three cycle and six cycle arms combined

Below (Table 13), is a comparison of the wellbeing outcome of the current study to the QOL outcome of the two key trials (5;6) mentioned in the literature review and described above. Overall survival was included as well for comparison. A direct comparison of the proportion of patients reporting improved or stable wellbeing/QOL shows that the current study's estimate of 61.3% falls directly between the trial estimates of 55% and 63%.

Table 13 Comparison of outcomes in the current study to two key RCTs

Variable	Current Study	Gridelli, et al. *	von Plessen, et al. †
N for QOL assessment	321	111	208
Wellbeing/QOL Outcome, N(%)			
Improved	121 (38.7)	73 (38)	/
Stable	71 (22.1)	48 (25)	/
Improved + Stable	192 (61.3)	121 (63)	114 (55)
Deteriorated	121 (38.7)	71 (37)	94 (45)
Survival, weeks			
Median	32	38	28-32

*Gridelli, et al. (5) results from cisplatin-based arms only

†von Plessen, et al. (6) results from three cycle and 6 cycle arms combined

However, as noted above, the difference in histology between studies may be a source of confounding that would invalidate the direct comparison. To improve the comparability of this study to the trials, the wellbeing benefit estimate was standardized to the trials' histology composition. Interestingly, the standardization only altered the estimate by one percentage point. When standardized to the Gridelli trial, 60.0% (95% CI 54.5 – 65.3) of patients in the current study achieved wellbeing benefit, and when standardized to the von Plessen trial 60.5% (95% CI 54.9 – 65.6) of patients achieved wellbeing benefit. The 95% confidence intervals around these adjusted estimates contain the trials' point estimates and are therefore not significantly different. Thus, it was concluded that the proportion of patients who experienced wellbeing benefit with PPDC was consistent with the proportion reported to experience QOL benefit in the RCTs.

In addition, the median survival was similar (see Table 13), lending support to the comparability of the current study population to that of the trials.

4.7 Reference List

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Chapter 5

Discussion

The primary goal of this thesis was to describe the effectiveness of palliative chemotherapy for NSCLC with respect to patient wellbeing. This was a retrospective cohort study of patients undergoing standard first-line PPDC for NSCLC at Ontario's Regional Cancer Centres. This study was conducted using electronic administrative health databases.

This chapter will summarize and interpret the results of this work, discuss the methodological limitations and strengths and place the findings in the context of previous work. The contributions of this study and suggestions for future research will also be discussed.

5.1 Main Findings and Interpretations

5.1.1 Baseline Patient Characteristics

Patients about to begin PPDC varied widely with respect to their general wellbeing. As much as 85% of patients were burdened with reduced wellbeing and 45% of patients reported wellbeing scores in the moderately or severely impaired range, although a minority reported no problem with wellbeing. Patients' baseline symptomatic status was also highly variable. Almost half of patients' ratings of key lung cancer symptoms (shortness of breath, appetite problems and tiredness) were in the moderate to severe range. Again, there was a minority of patients who reported almost no symptoms.

The availability of ESAS records varied considerably across Ontario's RRCs but some centres had baseline records for more than 90% of their PPDC patients.

The patients who had baseline ESAS records were similar to those who did not have baseline records. The variability in location of records but not in the types of patients suggests there are no inherent barriers to the collection of ESAS in a higher proportion of patients in the future. The variation in availability of ESAS records is rather a reflection of the variation in the extent to which the individual RCCs have adopted the ESAS.

The patients in this study were also similar to the patients included in clinical RCTs with the exception of the proportion of women, which was considerably higher in this study and the representation of different histology subtypes, which was more dominated by adenocarcinoma in this study. The difference in the sex ratio is most likely a result of the changing ratio of male to female lung cancer diagnoses that has happened over the past couple of decades. While more men were being diagnosed when the clinical trials were accruing patients more than a decade ago, the past few years have seen more even proportions of men and women being diagnosed with the disease (1). This shift is a reflection of the later rise in smoking prevalence among women compared to men (1;2). The difference in the proportion of adenocarcinomas can likewise be explained by smoking habits changing the histopathological case mix of lung cancer diagnoses. The decrease in squamous cell carcinoma and corresponding increase in adenocarcinomas has been largely attributed to the increased use of filtered cigarettes which decrease exposure to tar (associated with squamous-cell carcinomas) but increase exposure to nitrates (associated with adenocarcinomas (3).

5.1.2 Proportion of Patients with Improved or Stable Wellbeing

This study found the proportion of patients treated with first-line PPDC at Ontario's RCCs whose wellbeing improved or remained stable with treatment was 61.3% (95% CI 55.8-66.6%). Additionally, the sensitivity analysis, which used a worst case scenario for assessing the effect of missing data, only reduced the wellbeing benefit estimate to 52.1% (95% CI: 47.4 – 56.8%). This is likely an overly pessimistic view with the true proportion falling somewhere between 52.1% and 61.3%.

5.1.3 Factors Associated with Improved or Stable Wellbeing

Histology was associated with wellbeing benefit and more patients who benefitted from treatment had adenocarcinomas than other histologies. Some previous work exploring the relationship between histology and the survival benefit of treatment has also favoured adenocarcinomas over other histologies, but the results have not been conclusive, with some reports favouring squamous-cell carcinomas (4). This is likely due to complicated relationships between histology and other factors like tumour genotype and the specific ability of individual chemotherapeutic agents to act on these combinations (4). This study was not large enough to explore the relationship between histology and individual chemotherapy regimens and genetic information was not available. However, as electronic health databases continue to improve in both their breadth and scope of data available, a clearer picture may emerge.

The odds of a patient's wellbeing improving or remaining stable at two months were higher if their baseline wellbeing score were in the moderate (OR 2.53, 95% CI 1.50 – 4.29) or severe (OR 1.86, 95% CI 0.82 – 4.22) range rather than mild. The odds of experiencing wellbeing benefit were also higher in patients with adenocarcinoma rather than squamous-cell

carcinoma (OR 0.50, 95% CI 0.25 – 0.98) or another type of NSCLC (OR 0.72, 95% CI 0.42 – 1.21).

It is not surprising that those who felt worse at the outset more often benefited from treatment than those who felt better. If a patient's wellbeing was quite compromised to begin with then the treatment would have a lot of room in which to improve how the patient feels, and these improvements could easily outweighed any treatment side-effects. However, if a patient's wellbeing was relatively good initially than the treatment would have little opportunity to improve upon it and side-effects could more easily outweigh any subtle treatment-related improvements.

The higher odds of wellbeing benefit in patients with moderate and severe baseline wellbeing scores could also be partially explained by floor and ceiling effects, where in patients who reported the lowest wellbeing scores prior to treatment had no space on the ESAS scales to report any improvement should they experience any, and those reporting the highest baseline wellbeing scores likewise had no room on the scale to report any worsening. Very few patients reported severe baseline wellbeing scores so any ceiling effect is likely not very strong.

A floor effect, on the other hand, could be present as more patients reported lower baseline wellbeing scores. Thus, there was less space for those patients to report any improvement if they experienced any (though arguably, by definition there should be little room for the improvement of a mild or absent problem). However, even if some patients were misclassified as stable rather than improved due to such a floor effect, this would not change the overall result or conclusion of this study. Both improvement and stabilization of wellbeing are considered treatment successes and were combined for analyses. Therefore, any improved patient

who was misclassified as stable would still have been in the same improved/stable category for the analyses.

It was not possible to standardize the results of this trial to patients' baseline QOL in the clinical trials as was done for histology; however there is no reason to suspect there would have been any significant differences because the stage mix in the trials was similar (Table 12).

5.1.4 Factors Not Associated with Improved or Stable Wellbeing

Sex was not associated with wellbeing benefit. As a result, the fact that the sex ratio in the current study was very different from that of the clinical trials did not impede a comparison with those studies.

Two other factors that were not statistically significantly associated with wellbeing benefit were patient age and stage of disease. Of note, the odds of wellbeing benefit in the 70+ age group was the same as in the 50-69 year age group (OR 1.11). This conclusion is in line with recent work that has found fit elderly NSCLC patients experience the same benefit in survival with adjuvant chemotherapy as their younger counterparts (5;6).

Stage was not associated with treatment benefit. It is likely that the majority of patients with unknown stage had stage IV disease but had not undergone detailed staging. Thus it is not surprising that this group of patients responded to treatment the same way as those with stage IV disease. Similarly, we suspect the majority of those classified as stage III were specifically stage IIIB, a subgroup which is often lumped together with stage IV for treatment planning. Therefore, the stage III, IV and unknown groups in this study are likely a rather homogeneous collection of stage IIIB and IV patients whose response to treatment would not be expected to vary widely. The group of patients who received PPDC for recurrence could be of potential interest. While it

was a very small group and did not reach the level of statistical significance, the odds of wellbeing benefit in the bivariate analysis was over two times higher for the recurrent group compared to the stage IV group. This may represent something akin to the length-time bias associated with screening programs in which slower progressing tumours are caught earlier and therefore appear to respond better to treatment. Patients whose NSCLC was caught early and are only coming to palliative chemotherapy after exploring other treatment options could very well have tumours which are naturally slower growing and more responsive to treatment.

5.1.5 Comparison of Study Results with Previous Clinical RCTs

This study found the proportion of patients treated with first-line PPDC at Ontario's RCCs who experienced wellbeing benefit with treatment was 61.3% (95% CI 55.8-66.6%). This study's estimate of the effectiveness of PPDC was compared to the results of RCTs (8;13) that evaluated the efficacy of this treatment. The two key trials this study was compared to reported QOL improvement or stabilization in 63% (13) and 55% (8) of patients, respectively. To ensure the comparison to the clinical trials was fair, the case mix in this study was first compared to that of the trials. Sex and histology were noticeably different but only histology was associated with treatment benefit in this study. Recognizing the risk of confounding due to this difference in histopathological case mix, the proportion of patients experiencing treatment benefit was standardized to the histology compositions of each of the RCTs. This external standardization shifted the estimate of treatment benefit to 60.0% (95% CI 54.5 – 65.3%) when standardized to Gridelli, et. al (13) and 60.5% (95% CI 54.9 – 65.6%) when standardized to von Plessen, et. al (8) Standardization decreased the estimate because there were fewer adenocarcinomas in the trial populations and this subtype had the highest odds of wellbeing benefit with treatment in this study. The confidence intervals around these standardized estimates contain the point estimates

of the trials and are thus not statistically significantly different. All of this points to the conclusion that PPDC has lived up to its promise with respect to patients' QOL in the real world. Also of note, although it was not the main objective of this study, it is reassuring that the median survival time achieved in this study was similar to what was achieved in the clinical trials.

5.2 Limitations and Strengths of the Study

5.2.1 Study Population

This study was not truly population-based as it was confined to patients treated at Ontario's RCCs, and it is possible the results may not be generalizable to patients treated elsewhere. The cancer centres represent collections of highly specialized healthcare providers including specialists in supportive and palliative care and therefore the collateral care received at the centres could reasonably be expected to be more sophisticated or more optimal than elsewhere and for this reason results may be different.

However, this study does represent a large, representative sample of patients who received PPDC in routine practice at the RCCs. The subset of patients receiving this treatment who were evaluable, based on the availability of their ESAS records, were similar to those patients who did not have ESAS records. This allowed for the examination of the real world impact of this therapy outside the confines of controlled clinical trials from which all past data has been obtained.

Additionally, the case mix treated at the centres would not be expected to differ greatly from that of patients treated elsewhere as the centres serve geographical regions. Also, platinum-based doublets are a standard therapy that has been available for many years and one would not expect their delivery to be very different outside of the cancer centres. Thus, the results of this

study are likely generalizable to patients receiving this treatment in other provinces and countries, provided the case mix is similar and similar collateral care is available.

5.2.2 The Edmonton Symptom Assessment System

While the ESAS contains many symptoms common to lung cancer patients, it does not provide any information about two other symptoms common in lung cancer: cough and hemoptysis. Having information on these symptoms would provide a more complete picture of the disease.

On the other hand, using the ESAS allowed for the assessment of wellbeing benefit in routine practice without imposing any additional burden onto patients beyond the normal requirements of treatment. Indeed, all of the information used in this study was collected during the course of regular patient treatment. This is not an insignificant fact in a population of palliative cancer patients.

It is also worth pointing out this study designated a QOL measure (ESAS wellbeing score) as the primary outcome and focus where most studies of PPDC have focused on survival. As improved QOL is one of the stated goals of palliative chemotherapy, it is equally deserving of primary attention. This study evaluated wellbeing and symptomatic status using patients' self-reported outcomes which are the gold standard in QOL assessment. These patient reported outcomes (PROs) provide a mechanism for quantifying information about patients' subjective experiences (9) that adds another level of detail on top of other traditional, objective measures of treatment-related outcomes such as survival.

5.2.3 Measurement Issues

Choice of Wellbeing as the QOL Proxy

As mentioned previously, the measure of wellbeing on the ESAS that was used in this study as a proxy for QOL was not the same measure of QOL employed in the RCTs (which used EORTC-QLQ) and therefore does not use the same operational definition of QOL. However, wellbeing has been defined as "a global assessment of a person's quality of life according to his own chosen criteria" (10) and thus matches the conceptual definition of QOL. The alternative choice for this study would have been to use the ESAS distress score (EDS) which is the mean of a patient's rating of all 9 items on the questionnaire. This approach lacks face validity by implying each of the symptoms contained in the ESAS contributes equally to how a patient feels. Additionally, the summary EDS contains the wellbeing score, which itself is a summary measure. Therefore, wellbeing was chosen as the best proxy for the global QOL measure of the EORTC-QLQ.

Finally, in light of the sensitivity analysis; the use of conservative cut-points to define improvement, stabilization and deterioration; and the external standardization to the RCTs case mix, it is highly unlikely that this study has over-estimated the benefit of PPDC in terms of patient wellbeing. If anything, it may represent an underestimation.

Choice of Cut-Point for Defining Clinically Significant Change in Wellbeing

Acknowledging that the selection of a cut-point for defining a clinically significant change in wellbeing score is somewhat arbitrary, the choice in this study of a one point change was made carefully. It was based on one point being consistent with an accepted statistical method of choosing a cut-point that corresponds to the half standard deviation of the measurement tool. The only other potentially reasonable choice would have been a change of

two points. As discussed in the Results, this would have moved patients whose wellbeing had deteriorated by one point into the improved/stable treatment outcome category. This would have resulted in a higher estimate of wellbeing benefit which may not have been warranted. The decision to use a change of one point was the more conservative choice.

5.2.4 Missing Data (Loss to Follow-Up)

Missing data is a ubiquitous problem in quality of life research, particularly in palliative care settings. In this study, 115 (26%) patients were not evaluable at two months. While the subset of patients with baseline ESAS records were representative of all patients undergoing first-line PPDC, the same cannot be said of the representativeness of those accounted for at two months to the complete baseline group. It would be unreasonable to consider their data missing at random as it is unlikely that a patient being lost was unrelated to that individual's response to treatment. The sensitivity analysis attempted to address this concern by re-calculating the wellbeing benefit of the entire baseline group under the assumption that almost all patients who were lost had in fact deteriorated. This is likely an overestimate of deterioration; however, even this pessimistic approach still suggests that at least 52% of patients' wellbeing benefitted with treatment.

5.2.5 Potential Impact of Other Treatments, Placebo Effect and Response Shift on Observed Wellbeing Benefit

It must be conceded that the observed benefit of PPDC may not be entirely due to the chemotherapy. Some of the benefit may be the result of other treatments, a placebo effect, response shift or some combination of the three.

Supportive care has the ability to act on some symptoms and improve patient wellbeing (i.e. analgesics for pain management). It was recently demonstrated that early palliative care has

an independent positive effect on patient QOL and survival time (11). A placebo effect is also possible; patients may feel better because they expected the chemotherapy to make them feel better. Additionally, response shift, wherein patients' ratings of their wellbeing improve not because their wellbeing improved but because their conceptualization of wellbeing has changed, may have contributed to the observed outcome. Patients' ideas of what wellbeing means to them may change as they adapt and come to terms with their illness.

However, each of these phenomena would also have affected the apparent efficacy of PPDC in the clinical trials upon which current practice guidelines are based and therefore does not invalidate the efficacy – effectiveness comparison.

5.2.6 Unmeasured Covariates

Performance status (PS) is a known predictor of survival in NSCLC patients undergoing palliative chemotherapy (12) and is of interest as a covariate for the multivariate assessment of factors associated with wellbeing benefit; however PS is very poorly reported in the administrative databases used for this study and not enough data were available to be included in the analyses.

However, since this study found that patients treated with PPDC in routine practice closely met the eligibility criteria of the clinical trials of the same treatment, it seems reasonable to assume that this would extend to patient PS. Trials typically restricted entry to patients with performance status 0 or 1 (8;13;14). If the same was true for this study population, there may not have been enough variation to observe an effect anyway.

5.3 Context of This Study

Lung cancer is the second most common cancer diagnosis and the most common cause of cancer death. Given that most of these patients require palliative interventions, studies of palliative treatment options for this disease have the opportunity to inform the treatment of a large segment of the cancer population and are thus of great public health importance.

This study provides the first real-world description of the symptomatic status and wellbeing of patients about to undergo PPDC and as such provides a snap-shot of current clinical practice. It is also the first study we are aware of to use data from routine clinical practice to assess the effectiveness of this treatment with respect to patients' wellbeing.

Phase IV studies have historically focused on monitoring the safety of new medications as they were introduced to the market (15). In the past decade, however, there has been a push towards making use of electronic health databases to perform phase IV studies to also look into adoption and practice patterns and outcomes of various treatments in the real world (15;16). These studies add to the knowledge-base physicians and patients may draw upon when making treatment decisions.

Phase IV studies can also been viewed as a sort of program evaluation, as they assess whether treatments are producing the outcomes which formed the rationale for their implementation in the first place. Common practice and clinical trials conducted in decades past should not be the extent of investigation into the effects treatments have on patients. There should be routine assessment of the performance of treatments in real clinical practice. Indeed, in these times of economic restraint, it will be increasingly important for health systems managers to confirm the effectiveness of the treatments they offer.

The current study follows a phase IV study of adjuvant chemotherapy treatment of NSCLC in Ontario, which encouragingly supported the conclusions of RCTs. The study looked at the survival of patients treated with adjuvant chemotherapy and found that patients in the general population were in fact achieving the survival benefit promised by the clinical trials without experiencing any greater levels of acute toxicity (17). Further analyses looked at the effect of age on the survival benefit and concluded that patients aged 70 years or older fared no worse than those who were younger and suffered no increase in acute toxicity (6).

Phase IV studies have also been informative outside the setting of cancer care (15). Importantly, these studies have not always been able to confirm that the effectiveness of a treatment was the same as its efficacy. A population-based study of a medication to reduce mortality from congestive heart failure found increased use of the medication in patients who would not have met the eligibility criteria of the clinical trials for that drug (15;18). The study also found that not only was there no mortality reduction at the population level, there was actually an increase in other adverse events which themselves led to a mortality increase.

The importance of investigating effectiveness versus efficacy has also been recognized in the field of health promotion (19). Clinical trials have reported life-style counseling to be an important intervention for preventing diabetes complications but population-based studies have demonstrated this counseling is poorly implemented in practice and has not produced the desired outcomes (19).

5.4 Implications and Contributions of This Study

This study was consistent with RCTs of the QOL effect of palliative chemotherapy for patients with NSCLC. This study is the first to provide clinicians with a real-world estimate of the QOL benefit of first-line PPDC with which to discuss this treatment option with their patients.

This study also provides information on practice patterns with respect to PPDC. Based on the similarity of study patients to those in the clinical trials, it appears clinicians are selecting patients for this treatment based closely on the inclusion criteria of the trials.

The fact that 61% of patients in this study had improved or stable wellbeing after two months of treatment is only one part of the picture. Palliative chemotherapy is given also with the intent of increasing survival time, if only by a couple of months. Patients may very well chose to enter treatment solely with the goal of living longer, and that is certainly their prerogative. However, for those who are on the fence, and place greater importance on the quality rather than quantity of the life they have left, information on alternative outcomes like those presented in this thesis, will be integral to enabling them to make informed decisions about treatment.

Although this study was time consuming, now that the methods and algorithms have been developed, it could be repeated at very little cost and could translate into a routine report that could be part of a regular program evaluation. In the context of a health care system under ever increasing financial pressure, there will be a need to demonstrate that the treatments we offer produce a benefit. Studies like this could be a starting point for cost effectiveness studies of the performance of this treatment in the real world.

The data analysis methods developed in this study could also easily be extended to different disease sites and treatment modalities and used as a component of program outcomes evaluation for many of the therapies provided by the regional cancer centres which are

administered with the goal of improving patient QOL. Analyses could be repeated simply as the use of ESAS within the centres increases and more data becomes available. These methods could also be used to compare the effectiveness of different treatments within the population, including comparing new treatments with current standards.

With the growing availability and accessibility of large administrative health databases, population-based research can be done quickly and relatively inexpensively. These databases could be an electronic gold-mine on information. While acknowledging the limitations inherent in using data collected for other purposes, these databases can be used to explore population health research questions which would not be feasible using a traditional prospective cohort study design.

5.5 Future Research Avenues

This is the first real-world assessment of the QOL impact of palliative chemotherapy for NSCLC. As more ESAS (or other QOL) data becomes available, larger studies can be done. Of particular interest will be subgroup analyses that clinical trials often are not powered to explore due to their smaller numbers. For example, exploring the relationship between histology and specific platinum-doublet regimens, which was not possible it this study due to sample size, will be important in teasing out the relationship between these factors. Investigating these types of relationships will be particularly important as we move into an era of personalized medicine and targeted therapies.

The fact that PPDC for NSCLC works in the real-world, as would be expected from reports of RCTs, does not necessarily mean the same would be true of other treatments or in other populations. Therefore, another avenue of research could be to extend the work done in this

study to other palliative interventions like radiotherapy and second- and third-line chemotherapy for NSCLC as well as to the treatment of other disease sites. Perhaps more directly, these methods could be employed to assess the effectiveness of palliative single-agent chemotherapy, the chemotherapeutic alternative for NSCLC patients not fit enough to receive the standard PPDC.

This work could also be extended by incorporating additional data such as patient use of home care and nursing services and hospitalizations to provide a more complete picture of what happens to patients receiving PPDC.

Future research might focus on adapting the ESAS or developing other QOL assessment tools that incorporate additional symptoms common to lung cancer, but still remain simple and fast enough to be feasible for routine clinical use. This would allow for a more complete picture of the patient experience for both researchers and the healthcare providers caring for these patients without placing undue burden on the patients themselves.

5.6 Conclusion

The ultimate goal of this study was to assess the impact of first-line, palliative, platinum doublet chemotherapy on patient wellbeing in the real world. In this respect, PPDC appears to have lived up to expectations with over half of patients' wellbeing improving or stabilizing with treatment. Findings also suggest that patients vary widely with respect to their symptomatic status and wellbeing before beginning treatment and that the odds of achieving a wellbeing benefit with treatment is higher in those with worse baseline wellbeing and adenocarcinoma histology.

5.7 Reference List

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Appendix A

Edmonton Symptom Assessment System

Edmonton Symptom Assessment System (ESAS)

Please circle the number that best describes:

No pain	0	1	2	3	4	5	6	7	8	9	10	Worst possible pain
Not tired	0	1	2	3	4	5	6	7	8	9	10	Worst possible tiredness
Not nauseated	0	1	2	3	4	5	6	7	8	9	10	Worst possible nausea
Not depressed	0	1	2	3	4	5	6	7	8	9	10	Worst possible depression
Not anxious	0	1	2	3	4	5	6	7	8	9	10	Worst possible anxiety
Not drowsy	0	1	2	3	4	5	6	7	8	9	10	Worst possible drowsiness
Best appetite	0	1	2	3	4	5	6	7	8	9	10	Worst possible appetite
Best feeling of wellbeing	0	1	2	3	4	5	6	7	8	9	10	Worst possible feeling of wellbeing
No shortness of breath	0	1	2	3	4	5	6	7	8	9	10	Worst possible shortness of breath
Other problem	0	1	2	3	4	5	6	7	8	9	10	

Alberta Health Services Regional Palliative Care Program. Edmonton Symptom Assessment System (ESAS).

The ESAS is used by Cancer Care Ontario and Ontario's Regional Cancer Centres with permission from the Regional Palliative Care Program, Edmonton, Alberta, 2006.

Appendix B

The 14 Regional Cancer Centres of Ontario

Centre	City	Address	LHIN
Windsor Regional Cancer Centre	Windsor	2220 Kildare Road Windsor, ON, N8W 2X3	Erie St. Clair
London Regional Cancer Program	London	790 Commissioners Road East London, ON, N6A 4L6	South West
Grand River Regional Cancer Centre	Kitchener	P.O. Box 9056 835 King Street West Kitchener, ON, N2G 1G3	Waterloo-Wellington
Juravinski Cancer Centre	Hamilton	699 Concession Street Hamilton, ON, L8V 5C2	Hamilton, Niagara, Haldimand, Brant
Carlo Fidani Peel Regional Cancer Centre	Mississauga	The Credit Valley Hospital 2200 Eglinton Avenue West Mississauga, ON, L5M 2N1	Central West, Mississauga, Halton
Odette Cancer Centre	Toronto	Sunnybrook Health Sciences Centre 2075 Bayview Avenue Toronto, ON, M4N 3M5	Toronto Central
Princess Margaret Hospital	Toronto	610 University Avenue Suite 16-609 Toronto, ON, M5G 2M9	Toronto Central

Regional Cancer Centres, continued

Centre	City	Address	LHIN
Stronach Regional Cancer Centre at Southlake	Newmarket	596 Davis Drive Newmarket, ON, L3Y 2P9	Central
R.S. McLaughlin Durham Regional Cancer Centre	Oshawa	1 Hospital Court Oshawa, ON, L1G 2B9	Central East
Cancer Centre of Southeastern Ontario	Kingston	25 King Street West Kingston, ON, K7L 5P9	South East
The Ottawa Hospital Cancer Centre	Ottawa	501 Smyth Road Ottawa, ON, K1H 8L6	Champlain
Simcoe Muskoka Regional Cancer Centre	Barrie	201 Georgian Drive Barrie, ON, L4M 6M2	North Simcoe Muskoka
Hôpital régional de Sudbury Regional Hospital - Regional Cancer Program	Sudbury	41 Ramsey Lake Road Sudbury, ON, P3E 5J1	North East
Regional Cancer Care – Northwest	Thunder Bay	980 Oliver Road Thunder Bay, ON, P7B 6V4	North West

Appendix C

Procedure Codes to Identify Lung Surgeries

Surgery	Surgical Procedure Codes
Pneumonectomy	1GT89QB, 1GT91QB, 1GT89NW, 1GT89DA, 1GT91NW
Lobar Resection (Lobectomy)	1GR89QB, 1GR91QB, 1GR89DA, 1GR89NW, 1GT87QB, 1GR91NWXXF, 1GT87NW, 1GT87DA
Sub-lobar Resection (Segmentectomy)	1GR87QB, 1GR87DA, 1GR87NW

Appendix D

ICD-O Histology Codes Used to Identify NSCLC Cases

Non-Small Cell : Adenocarcinoma	
81403	Adenocarcinoma, NOS
81413	Scirrhous adenocarcinoma: Scirrhous carcinoma; Carcinoma with productive fibrosis
81433	Superficial spreading adenocarcinoma
81443	Adenocarcinoma, intestinal type: Carcinoma, intestinal type `
81453	Carcinoma, diffuse type: Adenocarcinoma, diffuse type
81903	Trabecular adenocarcinoma: Trabecular carcinoma
82003	Adenoid cystic carcinoma: Adenocystic carcinoma; Cylindroma, NOS (except cylindroma of skin M-8200/0); Adenocarcinoma, cylindroid. Bronchial adenoma, cylindroid
82013	Cribriform carcinoma: Ductal carcinoma, cribriform type
82103	Adenocarcinoma in adenomatous polyp: Adenocarcinoma in tubular adenoma; Carcinoma in adenomatous polyp; Adenocarcinoma in polypoid adenoma; Adenocarcinoma in a polyp, NOS; Carcinoma in a polyp, NOS
82113	Tubular adenocarcinoma: Tubular carcinoma
82303	Solid carcinoma, NOS: Solid carcinoma with mucin formation; Solid adenocarcinoma with mucin formation
82313	Carcinoma simplex
82503	Bronchiolo-alveolar adenocarcinoma, NOS: Bronchiolo-alveolar carcinoma; Bronchiolar adenocarcinoma; Bronchiolar carcinoma; Alveolar cell carcinoma
82513	Alveolar adenocarcinoma: Alveolar carcinoma
82523	Bronchiolo-alveolar carcinoma, non-mucinous. Bronchiolo-alveolar carcinoma, Clara cell. Bronchiolo-alveolar carcinoma, type II pneumocyte
82533	Broncholo-alveolar carcinoma, mucinous. Bronchiolo-alveolar carcinoma, goblet cell type
82543	Bronchiolo-alveolar carcinoma, mixed mucinous and nonmucinous. Bronchiolo-alveolar carcinoma, Clara cell and goblet cell type. Bronchiolo-alveolar carcinoma, type II pneumocyte and goblet cell type. Bronchiolo-alveolar carcinoma, indeterminate type
82553	Adenocarcinoma with mixed subtypes
82603	Papillary adenocarcinoma, NOS. Papillary carcinoma of thyroid. Papillary renal cell carcinoma
82613	Adenocarcinoma in villous adenoma
82623	Villous adenocarcinoma
82633	Adenocarcinoma in tubulovillous adenoma. Papillotubular adenocarcinoma: Tubulopapillary adenocarcinoma

	Non-Small Cell : Adenocarcinoma (continued)
82903	Oxyphilic adenocarcinoma: Oncocytic carcinoma; Oncocytic adenocarcinoma. Hurthle cell carcinoma. Hurthle cell adenocarcinoma. Follicular carcinoma, oxyphilic cell
83003	Basophil carcinoma: Basophil adenocarcinoma; Mucoid cell adenocarcinoma
83103	Clear cell adenocarcinoma, NOS: Clear cell carcinoma. Clear cell adenocarcinoma, mesonephroid
83203	Granular cell carcinoma: Granular cell adenocarcinoma
83233	Mixed cell adenocarcinoma
83303	Follicular adenocarcinoma, NOS: Follicular carcinoma, NOS
83323	Follicular adenocarcinoma, trabecular: Follicular carcinoma, trabecular. Follicular adenocarcinoma, moderately differentiated: Follicular carcinoma, moderately differentiated
83403	Papillary carcinoma, follicular variant: Papillary adenocarcinoma, follicular variant; Papillary and follicular adenocarcinoma; Papillary and follicular carcinoma
83413	Papillary microcarcinoma
83803	Endometrioid adenocarcinoma, NOS: Endometrioid carcinoma, NOS. Endometrioid cystadenocarcinoma
84703	Mucinous cystadenocarcinoma, NOS: Pseudomucinous adenocarcinoma; Pseudomucinous cystadenocarcinoma, NOS
84803	Mucinous adenocarcinoma: Mucinous carcinoma; Colloid adenocarcinoma; Colloid carcinoma; Gelatinous adenocarcinoma; Gelatinous carcinoma; Mucoid adenocarcinoma; Mucoid carcinoma; Mucous adenocarcinoma; Mucous carcinoma. Pseudomyxoma peritonei with unknown primary site
84813	Mucin-producing adenocarcinoma: Mucin-producing carcinoma; Mucin-secreting adenocarcinoma; Mucin-secreting carcinoma
84903	Signet ring cell carcinoma: Signet ring cell adenocarcinoma
85003	Infiltrating duct carcinoma: Infiltrating duct adenocarcinoma; Duct adenocarcinoma, NOS; Duct carcinoma, NOS; Duct cell carcinoma; Ductal carcinoma, NOS
85103	Medullary carcinoma, NOS. Medullary adenocarcinoma
85503	Acinar cell carcinoma: Acinic cell adenocarcinoma; Acinar adenocarcinoma; Acinar carcinoma
85703	Adenocarcinoma with squamous metaplasia: Adenoacanthoma
85713	Adenocarcinoma with cartilaginous and osseous metaplasia: Adenocarcinoma with cartilaginous metaplasia; Adenocarcinoma with osseous metaplasia
85723	Adenocarcinoma with spindle cell metaplasia
85743	Adenocarcinoma

Non-Small Cell : Squamous-Cell Carcinoma	
80503	Papillary carcinoma, NOS
80513	Verrucous carcinoma, NOS: Condylomatous carcinoma; Verrucous squamous cell carcinoma; Verrucous epidermoid carcinoma; Warty carcinoma
80523	Papillary squamous cell carcinoma: Papillary epidermoid carcinoma
80703	Squamous cell carcinoma, NOS: Epidermoid carcinoma, NOS; Squamous carcinoma; Squamous cell epithelioma
80713	Squamous cell carcinoma, keratinizing, NOS: Squamous cell carcinoma, large cell, keratinizing; Epidermoid carcinoma, keratinizing
80723	Squamous cell carcinoma, large cell, nonkeratinizing, NOS: Squamous cell carcinoma, nonkeratinizing, NOS; Epidermoid carcinoma, large cell, nonkeratinizing
80743	Squamous cell carcinoma, spindle cell: Epidermoid carcinoma, spindle cell; Squamous cell carcinoma, sarcomatoid
80753	Squamous cell carcinoma, adenoid: Squamous cell carcinoma, pseudoglandular; Squamous cell carcinoma, acantholytic
80763	Squamous cell carcinoma, microinvasive
80823	Lymphoepithelial carcinoma: Lymphoepithelioma; Lymphoepithelioma-like carcinoma. Schmincke tumor
80833	Basaloid squamous cell carcinoma
80843	Squamous cell carcinoma, clear cell type
Non-Small Cell : Mixed Type	
84303	Mucoepidermoid carcinoma
85603	Adenosquamous carcinoma: Mixed adenocarcinoma and squamous cell carcinoma; Mixed adenocarcinoma and epidermoid carcinoma
Non-Small Cell : Large Cell Anaplastic	
80123	Large cell carcinoma, NOS
80223	Pleomorphic carcinoma
Non-Small Cell : Carcinoma NOS	
80003	Neoplasm, malignant: Tumor, malignant, NOS; Malignancy; Cancer; Unclassified tumor, malignant; Blastoma, NOS
80013	Tumor cells, malignant
80033	Malignant tumor, giant cell type
80043	Malignant tumor, spindle cell type: Malignant tumor, fusiform cell type
80103	Carcinoma, NOS: Epithelial tumor, malignant
80203	Carcinoma, undifferentiated, NOS
80213	Carcinoma, anaplastic, NOS
80343	Polygonal cell carcinoma
80403	Carcinoma, NOS

Non-Small Cell : Other NSCLC	
80303	Giant cell and spindle cell carcinoma
80113	Epithelioma, malignant: Epithelioma, NOS
80313	Giant cell carcinoma
80323	Spindle cell carcinoma, NOS
80333	Pseudosarcomatous carcinoma: Sarcomatoid carcinoma
80463	Non-small cell carcinoma, general term used to separate SC from NSC types of carcinomas. Only used when there is no other type of NSC carcinoma contained in source document
Small Cell (SCLC)	
80023	Malignant tumor, small cell type
80413	Small cell carcinoma, NOS: Reserve cell carcinoma; Round cell carcinoma. Small cell neuroendocrine carcinoma
80423	Oat cell carcinoma
80433	Small cell carcinoma, fusiform cell
80443	Small cell carcinoma, intermediate cell
80453	Combined small cell carcinoma: Mixed small cell carcinoma. Combined small cell-large cell carcinoma. Combined small cell-adenocarcinoma. Combined small cell-squamous cell carcinoma
80733	Squamous cell carcinoma, small cell, nonkeratinizing: Epidermoid carcinoma, small cell, nonkeratinizing

Appendix E
Ethics and Data Access Approvals

QUEEN'S UNIVERSITY HEALTH SCIENCES & AFFILIATED TEACHING HOSPITALS RESEARCH ETHICS BOARD

February 28, 2011

This Ethics Application was subject to:

☐ Full Board Review
Meeting Date:
☒ Expedited Review

Ms. Lyndsay Harrison
Department of Community Health and Epidemiology
Queen's University Cancer Research Institute
2nd Floor
10 Stuart Street
Queen's University

Dear Ms. Harrison,

Study Title: **Assessing the Effectiveness of Palliative Chemotherapy for Advanced Non-Small Cell Lung Cancer: A Phase IV Study in the Ontario Cancer Population**
Co-Investigators: **Dr. W. Mackillop and Mr. J. Zhang-Salomons**

I am writing to acknowledge receipt of your recent ethics submission. We have examined the protocol for your project (as stated above) and consider it to be ethically acceptable. This approval is valid for one year from the date of the Chair's signature below. This approval will be reported to the Research Ethics Board. Please attend carefully to the following list of ethics requirements you must fulfill over the course of your study:

- **Reporting of Amendments**: If there are any changes to your study (e.g. consent, protocol, study procedures, etc.), you must submit an amendment to the Research Ethics Board for approval. (see http://www.queensu.ca/vpr/reb.htm).

- **Reporting of Serious Adverse Events**: Any unexpected serious adverse event occurring locally must be reported within 2 working days or earlier if required by the study sponsor. All other serious adverse events must be reported within 15 days after becoming aware of the information.

- **Reporting of Complaints**: Any complaints made by participants or persons acting on behalf of participants must be reported to the Research Ethics Board within 7 days of becoming aware of the complaint. Note: All documents supplied to participants must have the contact information for the Research Ethics Board.

- **Annual Renewal**: Prior to the expiration of your approval (which is one year from the date of the Chair's signature below), you will be reminded to submit your renewal form along with any new changes or amendments you wish to make to your study. If there have been no major changes to your protocol, your approval may be renewed for another year.

Yours sincerely,

Allison Clark
Chair, Research Ethics Board

March 1, 2011
Date

ORIGINAL TO INVESTIGATOR - COPY TO DEPARTMENT HEAD- COPY TO HOSPITAL – BINDER COPY - FILE COPY

Study Code: EPID-339-11

- **Investigators please note that if your trial is registered by the sponsor, you must take responsibility to ensure that the registration information is accurate and complete**

QUEEN'S UNIVERSITY HEALTH SCIENCES AND AFFILIATED TEACHING HOSPITALS ANNUAL RENEWAL

Queen's University, in accordance with the "Tri-Council Policy Statement, 1998" prepared by the Medical Research Council, Natural Sciences and Engineering Research Council of Canada and Social Sciences and Humanities Research Council of Canada requires that research projects involving human subjects be reviewed annually to determine their acceptability on ethical grounds.

A Research Ethics Board composed of:

Dr. A.F. Clark, Emeritus Professor, Department of Biochemistry, Faculty of Health Sciences, Queen's University (Chair)
Dr. H. Abdollah, Professor, Department of Medicine, Queen's University
Dr. R. Brison, Professor, Department of Emergency Medicine, Queen's University
Dr. M. Evans, Community Member
Dr. S. Horgan, Manager, Program Evaluation & Health Services Development, Geriatric Psychiatry Service, Providence Care, Mental Health Services Assistant Professor, Department of Psychiatry
Ms. J. Hudacin, Community Member
Ms. D. Morales, Community Member
Ms. P. Newman, Pharmacist, Clinical Care Specialist and Clinical Lead, Quality and Safety, Pharmacy Services, Kingston General Hospital
Dr. W. Racz, Emeritus Professor, Department of Pharmacology & Toxicology, Queen's University
Ms. S. Rohland, Privacy Officer, ICES-Queen's Health Services Research Facility, Research Associate, Division of Cancer Care and Epidemiology, Queen's Cancer Research Institute
Dr. B. Simchison, Assistant Professor, Department of Anaesthesiology and Perioperative Medicine, Queen's University
Dr. A.N. Singh, WHO Professor in Psychosomatic Medicine and Psychopharmacology Professor of Psychiatry and Pharmacology Chair and Head, Division of Psychopharmacology, Queen's University Director & Chief of Psychiatry, Academic Unit, Quinte Health Care, Belleville General Hospital
Dr. E. Tsai, Associate Professor, Department of Paediatrics and Office of Bioethics, Queen's University
Dr. E. VanDenKerkhof, Professor,Â School of Nursing and Department ofÂ Anaesthesiology and Perioperative Medicine, Queen's University

has reviewed the request for renewal of Research Ethics Board approval for the project **Assessing the Effectiveness of Palliative Chemotherapy for Advanced Non-Small Cell Lung Cancer: A Phase IV Study in the Ontario Cancer Population** as proposed by **Ms. Lyndsay Harrison of the Department of Community Health and Epidemiology** , at Queen's University. The approval is renewed for one year, effective **March 01, 2012.** If there are any further amendments or changes to the protocol affecting the participants in this study, it is the responsibility of the principal investigator to notify the Research Ethics Board. Any unexpected serious adverse event occurring locally must be reported within 2 working days or earlier if required by the study sponsor. All other adverse events must be reported within 15 days after becoming aware of the information.

Albert F. Clark.

_____Date: February 16, 2012
Chair, Research Ethics Board
Renewal 1[X] Renewal 2 [ ] Extension [ ] **Code# EPID-339-11 Romeo file# 6005825**

cancer care ontario | action cancer ontario

Data Request for a Research Study

Request Number	11- 064
Requestor	Lyndsay Harrison
Role/Title	Graduate Student, supervised by Dr. William Mckillop
Organization	Queen's University
Request Date	Mar. 17, 2011
Short Title	Assessing the Effectiveness of Palliative Chemotherapy for Advanced Non-Small Cell Lung Cancer: A Phase IV Study in the Ontario Cancer Population.

Estimated Cost: 0 hours @ $50/hour

___ hours @ $100/hour

Total: 0

Statement: CCO has reviewed the request for access to records containing identifying information, and is of the opinion that:

i. the request is for a bona fide research or planning purpose,

ii. the disclosure is consistent with the conditions or reasonable expectations of disclosure under with the personal information was provided, collected or obtained,

iii. the terms and conditions related to security and confidentiality contained in the application by the person seeking access are appropriate and sufficient considering the nature of the personal information contained in the records.

Subject to receipt of signed confidentiality agreement from the requestor.

Required:

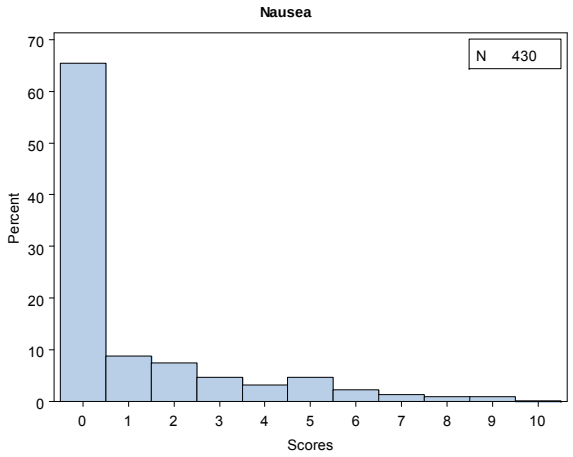
Matthew Hodge — 13 Apr 2011

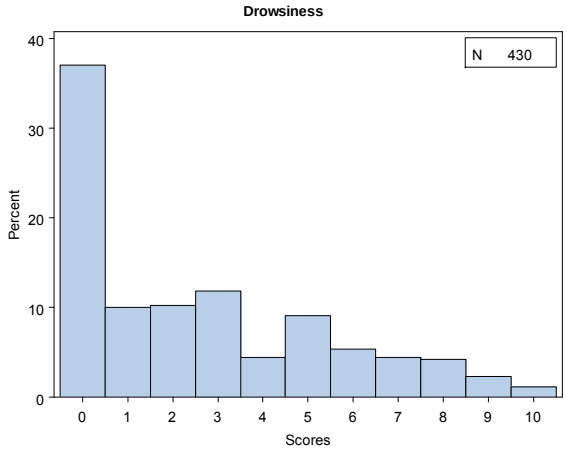
Signed: Dr. Matthew Hodge - Chief Medical Information Officer — Date

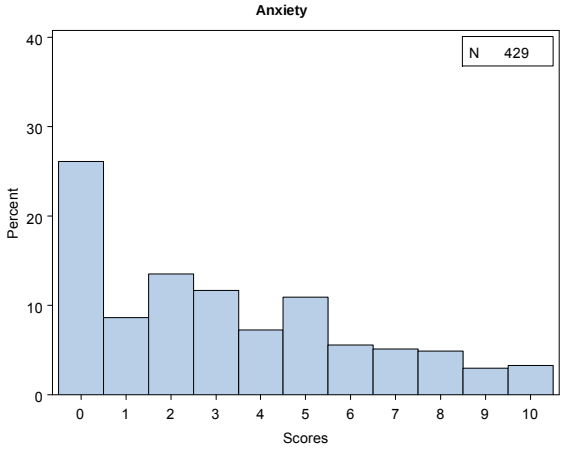
Per Pamela Spencer — 13 Apr 2011

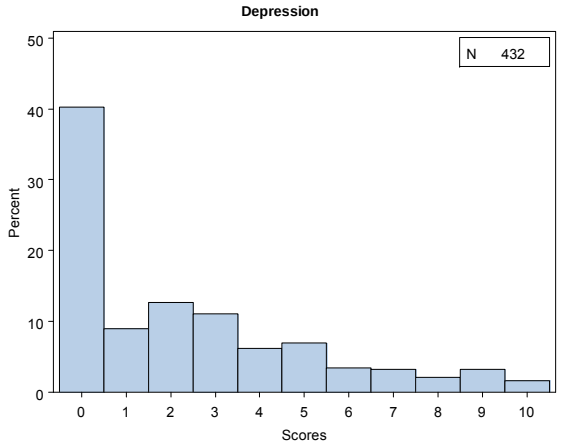
Signed: Pamela Spencer – Chief Privacy Officer — Date

Appendix F
Additional Frequency Distributions for ESAS Scores at Baseline









Appendix G
Additional Frequency Distributions for ESAS Change Scores at Two Months