Population-based evaluation of disparities in survival of lung cancer patients in Alberta, Canada

by

Mohammad Kaviul Anam Khan

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Department of Public Health Sciences
University of Alberta

Abstract

Lung cancer patients of Alberta have lower relative survival compared to their counterparts in Manitoba, British Columbia and Ontario. We conducted two population-based cancer mortality studies to explore the underlying reasons.

The first study assessed disparities in mortality across five zones of Alberta and compared them to the level of disparities between blacks and whites in the US cancer registries. The degree of the two disparities were similar, but more advanced stages at diagnosis, presumably due to diagnosis delays, was partly responsible for the disparities in the US but not in Alberta.

The second study assessed geographical disparity in mortality among non-small-cell lung cancer patients across five zones of Alberta, with and without taking treatment effects into consideration, and estimated variation by oncologist. Treatment variation across zones was observed and this variation was associated with differences in mortality. Patient mortality varied greatly by oncologist.

Preface

This thesis is an original work of Mohammad Kaviul Anam Khan (student ID: 1300404). No part of this thesis has been published previously. The research project, of which this thesis is a part, received research ethics approval from the University of Alberta Research Ethics Board, Project Name "Population based evaluation of quality and timeliness of lung cancer care", No. Pro00031009_AME2, Date: 09/18/2012.

TABLES OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

List of symbols, nomenclatures and abbreviations

AHS:	Alberta Health Services
AJCC:	American Joint Committee on Cancer
CI:	Confidence Interval
ASMR:	Age standardized Mortality Rate
ICD-O:	International Classification of Disease for Oncology
MRR:	Mortality Rate Ratio
NSCLC:	Non Small-Cell Lung Cancer
SCLC:	Small-Cell Lung Cancer
SEER:	Surveillance, Epidemiology and End Result
TNM:	Tumour, Node, Metastasis
US:	United States

Chapter 1 : Introduction

This is a paper-format thesis prepared in accordance with the guideline of the Faculty of Graduate Studies and Research, University of Alberta. The thesis is organized as follows:

Chapter 1 The introductory chapter for the full thesis, providing background, objectives, and significance of the work.

Chapter 2 The first manuscript is assessing disparity in mortality of lung cancer patients across zones of Alberta under the publicly funded healthcare compared to the level of disparity in the US in which the healthcare system is largely private.

Chapter 3 The second manuscript assessed geographical variation in the mortality of non-small cell lung cancer (NSCLC) patients across the zones of Alberta, with and without taking the received treatment into consideration and the degree of variation in mortality rates of NSCLC patients by oncologist.

Chapter 4 The concluding chapter summarizes the findings, their implications, and future directions of research.

Each chapter is presented with its own set of references.

1.1 Preamble

This thesis is a part of a larger research project that was conducted by Cancer Care, Alberta Health Services, under the leadership of Dr. Marcy Winget. The broad objectives of the larger research project were to address: the quality and timeliness of lung cancer care in Alberta and identification of major cancer care trajectories for lung cancer by developing a framework,

thereby, identifying priority areas for system improvement and to enable routine evaluation of patient care.

Data sources for this thesis work include Alberta Cancer Registry and Surveillance, Epidemiology and End Results (SEER) from the National Cancer Institute of the United States (US).

By linking various data sources, previous projects have evaluated: 1) uptake and tolerance of adjuvant chemotherapy in early stage non-small cell lung cancer (NSCLC) patients in Alberta, Canada[1]; 2) predictors of surgery and effect of consultation with an oncologist for adjuvant chemotherapy in early stage NSCLC patients in Alberta, Canada[2]; 3) comparison of oncology services and receipt of treatment between patients with breast, colon, rectal, or lung cancer[3]; and 4) uptake and tolerance of chemotherapy in elderly patients with small cell lung cancer (SCLC) and its impact on survival[4].

This thesis aims to: 1) examine geographical disparity in the mortality among lung cancer patients in Alberta and compare that with the levels of disparity in the US; 2) assess geographical variation in the mortality of NSCLC patients across zones of Alberta, with and without taking the received treatment into consideration; 3) assess degree of variation in mortality rates of NSCLC patients by oncologist.

1.2 Background

Lung cancer is the second most common cancer and a leading cause of death from cancer in the developed countries[5]. According to the statistics provided by the Canadian Cancer Society, 25,500 Canadians were estimated to be diagnosed with lung cancer, representing 14% of all new cancer cases in 2013[6]. Approximately 20,200 Canadians were estimated to have died from lung

cancer, representing 27% of all cancer deaths in 2013. On average, 70 Canadians were estimated to be diagnosed with lung cancer every day and 55 Canadians were estimated to die from lung cancer every day[7]. The factors that have been identified to greatly alter the risk of developing lung cancer include smoking and exposures to radon and asbestos[7].

The surveillance report published[8] by Alberta Health Services (AHS) gives the following lung cancer facts of Alberta.

- Approximately 4,150 Albertans who had been previously diagnosed with lung cancer were alive as of December 31, 2010.
- The age-standardized mortality rates (ASMR) were 51 per 100,000 male population and 32 per 100,000 female population in 2010.
- In 2010, 21,160 potential years of life were lost due to lung cancer, which constitutes about 25% of the potential years of life lost by all cancers, making lung cancer the largest single site contributor to the potential years of life lost by cancer in Alberta.
- In 2010, there were 1,839 new cases of lung cancer in Alberta and 1,445 deaths due to the disease.
- Approximately 2,250 cases of lung cancer are expected to be diagnosed in 2015.
- Risk of lung cancer increases by age. Annually for people aged less than 30, the risk of developing lung cancer is approximately 1 out of 10,000 people in both males and females of Alberta. In the group of age above 70, the risk of developing lung cancer is currently 1 out of 25 people in males and 1 out of 35 people in females, annually in Alberta.

- In 1990, there were 320 new cases in females and 677 new cases in males. In 2015, approximately 1,150 new cases are projected to develop in females and 1,100 cases in males.

Lung cancer patients have very low survival probability compared to patients of most of the other cancer types. There is no effective screening system to diagnose lung cancer: this often leads to a diagnosis at a late stage[9]. One-year age standardized relative survival[*1] of lung cancer patients diagnosed between 2008 and 2010 in Alberta was approximately 38%[8]. The 5-year age standardized relative survival was approximately 15%[8], indicating that out of all individuals diagnosed with this cancer between 2008 and 2010, only 15% are likely to be alive five years after diagnosis even if their cancer was the only cause of death.

A key international study, conducted using the data from population-based cancer registries in 12 jurisdictions in six countries from 1995-2007, was published in Lancet in 2011. This paper by Coleman *et al.*[10] showed that lung cancer patients, along with some other types of cancer patients, in Alberta had a lower relative survival than the same cancer patients in Manitoba, Ontario and British Columbia. The results of this paper were consistent with the reports from the Alberta Health Services[8], British Columbia Cancer Agency[11], Cancer Care Ontario[12] and Cancer care Manitoba[13]. In addition, during this 12-year time period, relative survival of all the provinces increased; however, the increment was the lowest in Alberta. These disparities were particularly concerning for Alberta since Canada has a publicly funded healthcare system and there is no apparent reason for cancer patients of Alberta to survive less than their counterparts in

[*] Relative survival is defined as the ratio of the proportion of observed survivors in a cohort of cancer patients to the proportion of expected survivors in a comparable set of cancer free individuals.

other provinces. To gain further insights following the paper of Coleman *et al*., we conducted this study to look at variations of survival by specific factors that underlie the observed poorer survival of lung cancer patients in Alberta. For this investigation we evaluated several factors described in the following subsections.

1.2.1 Geographical Zones of Alberta

One of the primary sources of our interest was geographical disparity in the mortality rates of the lung cancer patients. Alberta Health Services (AHS), the organization responsible for provision of healthcare services in the province, divides Alberta into five geographical zones[8]: North; Edmonton; Central; Calgary; and South. The zones of Calgary and Edmonton include the two biggest cities in the province, Calgary and Edmonton, each with a population of approximately 1.28 million and 1.08 million, respectively, in 2008[14]. North, Central and South zones mostly contain rural areas and a few small cities, with approximate population sizes of 412,000, 430,000, and 271,000, respectively[14].

1.2.2 Cancer Health Care System of Alberta

In Alberta, Canada, medical care including cancer care is publicly funded. Standard cancer treatments are free for Alberta residents through the provincial healthcare system eliminating access barriers due to costs. In the US, there exist disparities in lung cancer survival between black and white patients[15-19]. Healthcare is not publicly funded in the US and variation in socio-economic status has been shown to be strongly associated with differences in patient care and survival[15-19]. As the socio-economic factors differ overall between black and white patients in the US, a large part of the existing disparity is explained by the socio-economic disparity[16,18].

1.2.3 Types and Stages of Lung Cancer

A very important issue to account for while investigating survival of lung cancer patients is the subtype of lung cancer. In general lung cancer is divided into two categories, non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC). According to the ICD-O-3 coding[20], lung cancer cases are grouped by the following main histology types: NSCLC carcinoma (8011-8015, 8046, 8050-8084, 8140-8384, 8440-8490, 8560), SCLC carcinoma (8041-8045), and epithelial carcinoma, NOS (8010, 8016-8040). NSCLC is further categorized into squamous cell carcinoma (8050-8084), adenocarcinoma (8140-8384, 8440-8490, 8560), large cell carcinoma (8011-8015), and non-small-cell carcinoma, NOS (8046). Approximately 85% of the lung cancer patients are diagnosed with NSCLC and 15% are diagnosed with SCLC[21-23]. The characteristics (*i.e.*, tumor size and growth, staging systems and patient survival) of NSCLC and SCLC are appreciably different[1-4,21-23].

In addition to subtypes, it is also important to consider the stage of the lung cancer patients while evaluating patient survival and evaluating effect of treatments. According to the most commonly used staging system, American Joint Committee on Cancer (AJCC) 6th edition[22], lung cancer is classified into six groups: stage 0, I (IA and IB), II (IIA and IIB), III (IIIA and IIIB), IV and occult. This AJCC staging system is also referred to as TNM (Tumor, Node, Metastasis) staging system. Stage 0 refers to the earliest stage disease, cancer *in situ* (*i.e.*, abnormal cells that have not invaded other tissue, sometimes called pre-cancerous). In stage I, the cancer is confined to the lung. The stage is defined as stage IA if the tumor is ≤ 3 cm diameter without invasion more proximal than lobar bronchus (T1) with no regional lymph node (N0) and no distant metastasis (M0). If the tumor size is > 3 cm diameter; tumor with pleural invasion; partial lung atelectasis; proximal extent is < 2 cm from the carina (T2) with no regional

lymph node (N0) and no distant metastasis (M0) then it is defined as stage IB. In stages II, the cancer is confined to the chest. The stage is defined as stage IIA when the diagnosed tumor is T1 with ipsilateral hilar and/or ipsilateral peribronchial nodal involvement (N1) and no distant metastasis (M0), and, the stage is defined as IIB when the diagnosed tumor is T2 with ipsilateral hilar and/or ipsilateral peribronchial nodal involvement (N1) and no distant metastasis (M0). Stage IIIA is defined in two ways. When the tumor is of any size with chest wall invasion; diaphragm, pericardium, or diaphragm involvement; complete lung atelectasis; proximal extent is < 2 cm from the carina along with N1 nodal involvement and no distant metastasis. Another way of defining stage IIIA is where tumor size is any of T1-T3 with ipsilateral mediastinal and/or subcarinal nodal involvement (N2) with no distant metastasis. Like stage IIIA stage IIIB is also defined in two ways. When the tumor is of any size between T1-T3 with contralateral mediastinal or hilar nodal involvement; supraclavicular nodal involvement (N3) and with no distant metastasis the stage is defined as stage IIIB. Again if the tumor is of any size with: mediastinal, great vessel, trachea, esophageal, carinal or vertebral body invasion; malignant pleural or pericardial effusion; same lobe satellite nodule (T4) with any nodal involvement with no distant metastasis then it is also defined as stage IIIB. Stage IV refers to the most advanced disease in which cancer has spread from the primary site to distant organs (distant metastasis M1) with any tumor size and with any nodal involvement. In occult (hidden) stage, cancer cannot be seen by imaging or bronchoscopy. Cancer cells are found in sputum (mucus coughed up from the lungs) or bronchial washing (a sample of cells taken from inside the airways that lead to the lung). It is difficult to confirm the AJCC staging of SCLC patients, since, AJCC staging system requires surgical confirmation[4], which may not be applicable to the patients due to the fast growing nature of SCLC. SCLC is categorized as limited and extensive stage of

disease[24,25] in clinical studies. Limited SCLC is generally described as disease limited to one hemithorax, regional mediastinal lymph nodes, and ipsilateral supraclavicular lymph nodes[25]. Extensive SCLC is described as disease present in both hemithoraxes and/or metastasized to more distant areas of the body[26]. Those with limited stage SCLC have a better prognosis than those with extensive stage disease[24,25]. However, in population-based studies, the AJCC staging system is used to evaluate relative survival or all-cause mortality rates of both NSCLC and SCLC patients.

1.2.4 Treatments for lung cancer

The choice of treatment depends on age, stage of cancer, comorbidities and performance status, which is needed to be considered during analysis of survival of lung cancer patients[26-29]. Depending on these factors, any one of or any combination of surgery, chemotherapy, and radiotherapy are used. Treatment guidelines by histology and lung cancer stages are described below.

Surgery plays a significant role in the survival of early stage (stage I and II) NSCLC patients[26]. The probability of long-term survival without surgical resection is very low; a recent study conducted in the US reported that patients with untreated stage I disease had only 22 percent overall five-year survival [26]. In contrast, the five-year survival for patients with stage IA or IB disease who underwent surgical resection was approximately 60 to 80 percent[30]. The treatment guidelines of Alberta Health Services state that surgery is recommended as the primary treatment for stage I and II patients[26,27]. To improve survival and prevent recurrence, chemotherapy and radiotherapy are recommended after surgery for stage I-II lung cancer patients[23]. In the case of stage I patients who are medically inoperable or refuse surgery,

radiotherapy is recommended[26]. Medically inoperable stage II patients are treated with radiotherapy, neoadjuvant chemotherapy or combination of both[26,27].

For stage III NSCLC patients surgical resection is the primary recommendation for the patients who are medically operable along with adjuvant chemotherapy[28]. It has been shown in clinical trials that overall survival rate of patients were 5%-7% higher in the patients who received cisplatin based chemotherapy after surgery compared to the patients who did not[31]. However, when the patients have medical contraindication then surgical resection is not recommended[23]. Results of several clinical trials and meta-analyses have shown that the use of chemotherapy and radiotherapy prolongs five-year survival (3%-5%) among stage III NSCLC patients[32-35]. Stage IV NSCLC patients with solitary metastasis and good performance status can benefit from surgical resection[29]. However, most of the patients (approximately 90%) are not able to go through surgical resection[23]. The patients who are not able to go through surgical resection are treated with either a combination chemotherapy or palliative radiotherapy[29]. However, clinical trials have shown that none of these treatments can clinically significantly improve survival of stage IV patients[36].

For SCLC patients, surgery is recommended when the cancer is found in a lung or in nearby lymph nodes[23]. In most SCLC cases cancer is found in both lungs and thus, if surgery is recommended, then adjuvant chemotherapy and/or adjuvant radiotherapy should also be given[23]. The standard of care for patients with limited stage SCLC is combined concurrent chemotherapy and radiotherapy[24]. Patients with extensive stage SCLC are recommended to receive chemotherapy alone[25], which includes etoposide plus cisplatin. Patients who are unable to tolerate cisplatin are recommended etoposide plus carboplatin, which is an acceptable alternative.

1.3 SEER (Surveillance, Epidemiology and End Results) Registry Data

The US data we utilized were obtained from the SEER registry. SEER is a program run by the US National Cancer Institute, which covers about 10% of the US population in a population-based manner in specific localities[37]. SEER started in 1973 with seven registries. Later it expanded to nine registries in 1974-75. Currently the number of registries is up to 18. The SEER Program registries routinely collect data on patient demographics, primary tumor site, tumor morphology and stage at diagnosis, first course of treatment, and follow-up for vital status every year. The registry programs also make data of incidence and mortality rates publicly available.

1.4 Objectives

The major objectives of our study can be summarized as follows.

a) Assess disparities of mortality rates across the healthcare zones in Alberta under the publicly funded healthcare system and compare it to the levels of disparity across geographical locations and races in the US where the healthcare system is largely private. Specifically, the objectives are to calculate geographical-zone-specific mortality rates in Alberta and race/cancer-registry-specific mortality rates in the US and compare the variation across Alberta and the US registries.
b) Investigate geographical disparities in the mortality rates of NSCLC patients of Alberta with and without taking treatment effect into consideration.
c) Assess the effect of oncologist on NSCLC mortality rates.

1.5 Significance

This thesis consists of two population-level studies that address two distinct and important issues of lung cancer care in Alberta. Study 1 is the first study to formally assess variation in mortality rates of Alberta lung cancer patients across the geographical healthcare zones of Alberta and compare them with the race-registry level disparities in the US. Study 2 is the first attempt to identify the potential sources of geographical disparity found in the mortality rates of lung cancer patients taking treatment effects and oncologist effects into consideration. Findings from this work could provide important information for healthcare professionals and policy makers to identify and implement interventions that address barriers to optimal care as well as motivate further research to investigate and improve the quality of the lung cancer care system in Alberta.

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Chapter 2 : Population-based evaluation of disparities in survival of lung cancer patients in Alberta, Canada, and in the United States SEER registries

2.1 Introduction

Lung cancer is the leading cause of cancer related deaths in developed nations[1]. It was estimated that more than 25,000 Canadians would be diagnosed with this disease in 2013 and more than 20,000 deaths will occur, accounting for more than a quarter of all deaths from cancer across the country[2]. The estimated number of deaths in Canada this year as a result of lung cancer is approximately equal to the estimated number of deaths caused by prostate, breast and colorectal cancers combined[2]. Results published in one recent international study[3] showed disparities in lung cancer survival across four provinces of Canada with patients in Alberta having the lowest 5-year relative survival (15.1%) compared to Manitoba (20.1%), Ontario (19.1%) and British Columbia (17.7%). The results published in that report[3] are consistent with the results published in provincial cancer reports[4-7].

To gain further insights on this observation, we assessed variation in lung cancer survival across the five geographical healthcare zones of Alberta defined by Alberta Health Services (AHS), the organization responsible for delivering healthcare for the province[7]. In Alberta, Canada, medical care including cancer care is publicly funded[8], unlike the United States[9-11]. Standard cancer treatments are free to Alberta residents through the provincial health care insurance system eliminating barriers due to costs.

In the US, large disparities in lung cancer survival exist between black and white patients[12-16], largely attributable to socioeconomic differences[12-16]. The second objective of this study was, therefore, to compare the degree of geographical variation of lung cancer survival in Alberta to the degree of variation between the black and white populations in the US that is largely attributable to socioeconomic differences.

The specific objectives of the study were, therefore, to:

- Assess the disparity across the healthcare zones of Alberta under the publicly funded health care; and
- Compare it to the level of variation in the US where health care is largely private

2.2 Methods

2.2.1 Data sources

This was a population-based study of all lung cancer patients in the province of Alberta, Canada, and the US Surveillance, Epidemiology and End Results (SEER) registries diagnosed in 2004-2010. Information of the Alberta patients was obtained from the Alberta Cancer Registry. The information of the SEER patients was obtained from the SEER registries[17] of Atlanta, Connecticut, Detroit, Hawaii, Iowa, New Mexico, San Francisco, Seattle and Utah. The study was approved by the University of Alberta Health Research Ethics Board.

2.2.2 Inclusion criteria

Patients diagnosed with small cell lung cancer (SCLC) or non-small cell lung cancer (NSCLC) identified from the Alberta Cancer Registry or SEER registries who satisfied the following criteria were included: 1) diagnosed with malignant lung cancer (ICD-O-3[18] topology code

c34.0-c34.9 and ICD-O-3 behavior code "3") in 2004-2010 (excluding December 2010); and 2) survived more than 30 days after the diagnosis of lung cancer. Cases with AJCC stages I-IV, occult and unknown stages were included. Histologies of mesothelioma, melanoma, lymphoma, sarcoma, soft tissue and carcinoids were excluded. Non-white, non-black US SEER patients were excluded from the race-specific analysis. Black patients of any US SEER registries in which the number of patients was less than 300 were also excluded.

2.2.3 Data analysis

The ages of the patients were divided into five categories: 15-44, 45-54, 55-64, 65-74, and 75 or more to keep consistency with the paper published by Coleman *et al*.[3]. Cancer staging was based on the American Joint Committee on Cancer (AJCC) *Cancer Staging Manual (version 6)*[19]. For analysis purposes, stage unknown and occult were combined as "stage unknown/occult". The five geographical zones of AHS (North, Edmonton, Central, Calgary and South) were used. Given that the characteristics of NSCLC and SCLC are appreciably different[20-25], the analysis was performed separately for the two types of lung cancer. The frequency and percentage of patient characteristics were tabulated for NSCLC and SCLC patients separately and in total along with median survival time in months since diagnosis. The frequencies and proportion of stage at diagnosis were also tabulated for each zone of Alberta and each registry-race combination for the US SEER registries.

To investigate patients mortality we used the piecewise exponential model[26], where the follow-up period was grouped into every three months in the first year post-diagnosis, due to large changes in the rate of death in the first year, and annually afterwards. The piecewise exponential model is analogous to a Poisson regression where the count of death for a specific

time period is modeled as the outcome instead of the survival time and the survival time is used as an offset. This Poisson regression was used to model lung cancer mortality rates across zones/race-registry groups, adjusting for age, sex, and follow up period to evaluate disparities in lung cancer mortality across zones/race-registry groups. The follow up period was grouped by three-month periods in the first year post diagnosis, due to large changes in the rate of death in the first year, and annually afterwards. Adjusted mortality rate ratios (MRR) were estimated, along with 95% confidence intervals, using the following reference groups: age = 75 or older; sex = female; zone = Calgary; and follow-up period = 1-3 months. The same regression analysis was repeated adjusting for stage at diagnosis (Stage I as reference). The purpose of the additional adjustment was to evaluate disparities in mortality across zones/race-registry groups after controlling for differential distributions of stage at diagnosis.

The same regression analysis was also conducted excluding stage IV lung cancer patients to assess the disparities among those with non-metastasized lung cancer among whom the post-diagnosis influence of the healthcare system on patient survival may be appreciable. All analyses were conducted with R (version 3.0.2)[27].

2.3 Results

There were a total of 129,268 malignant lung cancer patients diagnosed in 2004-2010, 11,608 in Alberta and 117,660 in the US SEER registries. Information of 132 patients in the US and 251 patients in Alberta were excluded from the study as their cancer type was neither NSCLC nor SCLC (i.e., lymphoma, melanoma, mesotheliomas, soft tissue, sarcoma and carcinoid cases) or their diagnosis date and zones were missing or there age was less than 15 years. From the remaining patients in the US, information of 9,163 non-white or non-black patients were

excluded due to small sample sizes per registry. Among the remaining patients (black and white) information of 515 black patients were excluded from the analysis as their registries had less than 300 black patients (Hawaii, Iowa, New Mexico, and Utah). Further 1,510 (13%) patients from Alberta and 16,576 (15%) patients from the US were excluded as they died within the first 30 days of diagnosis or diagnosed in December 2010. After applying these exclusions, a total of 101,214 (9,847 from Alberta and 91,367 from US SEER) patients were included in the study. At baseline, median age was 71 years for NSCLC patients and 68 years for SCLC patients in the US. In Alberta the median age was 70 years and 68 years, respectively, for NSCLC and SCLC patients. Table 2.1 and Table 2.2 shows the proportion of NSCLC and SCLC patients by zone/race-registry and other characteristics along with median survival time.

Figure 2.1 shows the distribution of stage at diagnosis by zone/race-registry. In Alberta the proportion of patients diagnosed with stage I and II was from 21%-24% and proportion of patients diagnosed with stage III and IV were between 72%-74%. In the US, however, there was a higher proportion of stage IV patients in the black patient population than white patient population (40-48% vs. 38-43%, respectively) in most of the cancer registries. Conversely, the proportion of stage I patients was higher in the white patient populations than the black patient populations (17-25% vs.15-21%, respectively) in all SEER cancer registries. The proportion of unknown/occult stage was comparatively higher (5-18%) in some of the US registries than Alberta (2-4%).

Figure 2.2 and Figure 2.3 show the adjusted MRRs and 95% confidence intervals obtained from Poisson regression adjusting for age, sex and follow-up time (months) for NSCLC patients and SCLC patients, respectively (the exact values of the adjusted MRR are given in the appendix), and an adjacent figure also adjusted for stage at diagnosis. Adjusting for stage did not

significantly alter the zone-specific MRRs for either NSCLC for SCLC patients in Alberta, however, adjusting for stage made a difference in MRR estimates for the SEER race/regions. Among NSCLC patients in Alberta, unadjusted for stage, the adjusted mortality rates were higher in the North (adjusted MRR= 1.16; 95% CI= 1.07, 1.27; p<0.001), Edmonton (adjusted MRR= 1.06; 95% CI=1.00, 1.13; p=0.06), Central (adjusted MRR=1.14; 95% CI=1.05, 1.23; p=0.002) and South (adjusted MRR=1.20; 95% CI = (1.09, 1.33), p<0.001) zones compared to Calgary. For SCLC patients, the adjusted MRR is the highest in the Central zone (1.22; 95% CI = 1.00-1.50; p=0.05) compared to Calgary, unadjusted for stage, but the mortality rate of the North, Edmonton and South are not statistically significantly different from Calgary.

In all the US registries where the comparison of black vs. white patients was possible, the adjusted MRR was higher in black patients than white patients, for both types of lung cancer. The black-white disparity was smaller after adjusting for stage at diagnosis. For NSCLC, stage-unadjusted mortality rates for black patients were statistically significantly higher than Calgary for every registry except Connecticut and Seattle. The highest MRR was observed in Atlanta black patients (1.18; 95% CI = 1.10-1.26; p<0.001). Among white patients, the stage-unadjusted MRR was the lowest in Connecticut (0.86; 95% CI = 0.82-0.90; p<0.001) and the highest in Utah (1.10; 95% CI = 1.03-1.17; p<0.001). After adjusting for stage, in all registries, MRRs of the black patient population attenuated and did not differ statistically from Calgary. In the white SEER patient population, most of the MRRs did not change after adjusting for stage except three went from being statistically higher than Calgary to not differing statistically: Atlanta (MRR= 0.95; 95% CI = (0.89-1.00); p=0.06); New-Mexico (MRR = 1.02; 95% CI = 0.96-1.08; p=0.51); and Utah (MRR= 1.07; 95% CI = (1.00, 1.14); p=0.05). The MRR for San Francisco became

significantly lower than Calgary's after adjusting for stage (MRR= 0.93; 95% CI = 0.88-0.98; p=0.007).

For SCLC patients, none of the US race-registry subgroups had statistically significantly different mortality rate from Calgary unadjusted for stage. After adjusting for stage, Connecticut white patients had statistically significantly lower mortality rate (0.87; 95% CI = 0.76-0.99; p = 0.032) than the Calgary patients.

Table 2.2 shows the results of the second regression analysis, which includes only the patients who were diagnosed with stage I-III lung cancer. As previously, MRRs for the zones and race-registry groups were estimated adjusting for age, sex, stage, and follow up time. Among NSCLC patients in Alberta, adjusted for stage, mortality rates were higher in the North (adjusted MRR= 1.22; 95% CI= 1.06, 1.40; p=0.006), Edmonton (adjusted MRR= 1.05; 95% CI=0.95, 1.15; p=0.33), Central (adjusted MRR=1.21, 95% CI=1.07, 1.36; p=0.002 or 0.003 depending on the decimals) and South (adjusted MRR=1.28; 95% CI = 1.10, 1.49; p< 0.001) zones compared to Calgary. For SCLC patients, adjusted mortality rates did not differ significantly across the healthcare zones in Alberta.

In the US, restricting to stage I-III, black patient populations had higher adjusted mortality rates than the white patient populations in the same registry in all SEER registries. Mortality rates for white patient populations with NSCLC in most of the US registries were not statistically significantly different from Calgary: the only exceptions were Connecticut white patients (adjusted MRR=0.91; 95% CI=0.84; 0.99, p=0.02) which had a lower mortality rate and New-Mexico white patients (adjusted MRR=1.15; 95% CI=1.05, 1.27; p=0.002) who had a significantly higher adjusted MRR than Calgary. MRR estimates for NSCLC SEER black

patients of most of the SEER registries had statistically significantly higher adjusted mortality rates than Calgary, except for the Connecticut and San Francisco SEER black patients, which did not differ significantly from Calgary. Among SCLC patients, however, only white patients in the Utah SEER registry had statistically significantly higher mortality rate (adjusted MRR=1.36; 95% CI=1.03, 1.79; p=0.03) than Calgary patients. None of the other MRR race-registry subgroup estimates of the US SEER SCLC patients differed significantly from those of Calgary.

2.4 Discussion

The purpose of this study was to investigate the degree of geographical disparities in all-cause mortality rates of Alberta lung cancer patients and compare that with the degree of geographical and racial disparities in all-cause mortality rates of the US SEER lung cancer patients. The NSCLC patients in the North, Edmonton, Central and South healthcare zones of Alberta had higher mortality rates than their counterparts in Calgary, unadjusted for stage. The disparity pattern and degree did not change after adjusting for stage. This indicates that early or late diagnosis is not the reason of the existing disparity in the survival of lung cancer patients across the zones of Alberta.

The survival patterns within Alberta indicate that there is a clear disparity between the two big cities and other areas in the province. For example the stage adjusted MRR was 1.24 in the South NSCLC patients compared to Calgary. In a large review by the LACE Collaborative Group[28] which was a meta-analysis based on individual patient data, the investigators used pooled data from five clinical trials representing 4,584 patients to check the effect of adjuvant chemotherapy using the cisplatin drug on death of stage II patients. They found that the hazard ratio (analogous to mortality rate ratios that we have obtained) for death was 0.83, which is

inversely 1.20 (HR of patients who did not get chemotherapy in reference to patients who got chemotherapy). These results indicate that the difference in mortality between the South and Calgary NSCLC patients is higher than the difference in mortality of stage II NSCLC patients who did and did not receive cisplatin.

This study also found that all-cause mortality rates of the US white patients of most of the SEER registries did not differ from those of the Calgary patients. Stage-unadjusted mortality rates of the US black patients, however, were higher than those of the white patients in the same registry for both SCLC and NSCLC. This disparity decreased after stage adjustment indicating that delayed diagnosis and advanced stages in blacks explains part of the reason for the disparity in survival between the two races in the US. The degree of disparities in stage-unadjusted mortality rates between blacks and whites was similar to the corresponding degree of disparities across Alberta zones. After adjusting for stage, disparities across the zones of Alberta were higher than the disparities across the race registries in the US SEER. These results indicate that the disparity of mortality rates in Alberta lung cancer patients is greater than the black-white disparity in the US SEER lung cancer patients excluding delayed-diagnosis/advanced-stage effects.

Among patients diagnosed with stage I-III lung cancer in Alberta, Calgary patients had a lower all-cause mortality rate than patients of the other zones. The variation in MRR estimates of the patients across the zones Alberta was almost the same as the variation in estimates between the black and white patient populations in the US SEER registries.

In the US, differences in lung cancer mortality and incidence rates by race exist, especially between blacks and whites[12-16]. Studies using patient populations in the US military health system indicate there were no differences in survival of black and white patients since everybody received equal health care system.[29] This is expected since the US black-white differences are attributable largely to socioeconomic differences[12-16]. In our study we have observed that in the zones across Alberta, the stage distribution was nearly the same. In the US, however, black patients had higher proportions of stage IV than white patients in most of the cancer registries. The proportion of stage I cases was higher in the white patient populations in all the SEER cancer registries. This indicates that the white patients have a better chance of an early diagnosis compared to the black patients and thus a better survival probability. The disparity in the stage at diagnosis is, therefore, largely responsible for the observed survival difference in the black and white patient SEER populations. Since the stage distributions of Alberta lung cancer patients across the zones were similar, delayed diagnosis is not a reason for the disparity of mortality rates.

In the paper that reported international comparisons of cancer patients' survival[3], Alberta was reported to have the poorest survival of lung cancer patients among the four provinces of Canada (Ontario, Manitoba, Alberta, and BC) included in the study. This study shows disparities in survival exist within Alberta across its healthcare zones and elimination of these disparities will likely diminish the differences observed with other provinces of Canada. Unlike the US SEER registries, the survival disparity across the zones of Alberta was not attributable even partly to delayed diagnosis/advanced stages. In Alberta and other provinces in Canada, the health care system is publicly funded and should provide its population equitable healthcare. The existing disparity across the zones of Alberta is concerning. Further investigations should

investigate indicators of Alberta's lung cancer care system such as treatment modalities and time between diagnosis and treatment to pinpoint more specific reasons of the existing disparity in mortality rates of lung cancer patients across the zones of Alberta.

Table 2.1: Patient characteristics and median survival time in Alberta from 2004-2009

Variable		NSCLC		SCLC		Total	
		Number (%)	Median survival	Number (%)	Median survival	Number	Median survival
Overall		8,934 (88%)	8.0	1,213(12%)	7.0	9847	8.0
Age at diagnosis							
	15-44	112 (1%)	11.0	16 (1%)	9.5	128	11.0
	45-54	831 (10%)	9.0	126 (10%)	10.0	957	9.0
	55-64	1,976 (23%)	9.0	346 (29%)	8.5	2,322	9.0
	65-74	2,818 (33%)	8.0	441 (36%)	7.0	3,259	8.0
	75+	2,897 (34%)	7.0	284 (23%)	6.0	3,181	7.0
Sex							
	Female	4,133 (48%)	9.0	596 (49%)	7.0	4,729	9.0
	Male	4,501 (52%)	7.0	617 (51%)	7.0	5,118	7.0
Alberta Zones							
	Calgary	2,671 (31%)	9.0	360 (30%)	8.0	3,031	9.0
	Edmonton	3,153 (37%)	8.0	419 (35%)	7.0	3,572	8.0
	North	905 (10%)	7.0	165 (14%)	7.0	1,070	7.0
	Central	1,245 (14%)	8.0	164 (14%)	6.0	1,409	8.0
	South	660 (8%)	7.0	105 (9%)	9.0	765	7.0
Stage							
	I	1,853 (21%)	25.0	39 (3%)	16.0	1,892	25.0
	II	411 (5%)	20.0	21 (2%)	12.0	432	20.0
	III	2,254 (26%)	10.0	423 (35%)	10.0	2,677	10.0
	IV	3,868 (45%)	4.0	715 (59%)	6.0	4,583	4.0

Unknown/occult	248 (3%)	6.5	15 (1%)	9.0	263	7.0
Follow up time						
1- 3 Months	1,835 (21%)	-	245 (20%)	-	2,080	-
3-6 Months	1,538 (18%)	-	210 (17%)	-	1,748	-
6-9 Months	1,035 (12%)	-	230 (19%)	-	1,265	-
9-12 Months	715 (8%)	-	152 (13%)	-	867	-
>12 Months	3,511 (41%)	-	376 (31%)	-	3,887	-

Table 2.2: Patient characteristics and median survival time Surveillance, Epidemiology and End Results (SEER) registries from 2004-2009

Variable	NSCLC		SCLC		Total	
	Number (%)	Median survival	Number (%)	Median survival	Number	Median survival
Overall	79,941 (87%)	9.0	11,426 (13%)	8.0	91,367	9.0
Age at diagnosis						
15-44	1,267 (2%)	11	160 (1%)	10	1,427	11
45-54	7,259 (9%)	10	1,288 (11%)	10	8,547	10
55-64	16,903 (21%)	11	3,033 (27%)	9	19,936	10
65-74	24,762 (31%)	10	3,830 (34%)	8	28,592	10
75+	29,750 (37%)	8	3,115 (27%)	6	32,865	7
Sex						
Female	38,168 (48%)	10	5,858 (51%)	9	44,026	10
Male	41,773 (52%)	9	5,568 (49%)	7	47,341	8
SEER Race-registry						
Atlanta (Black)	2,427 (3%)	8	262 (2%)	7	2,689	8
Atlanta (White)	4,703 (6%)	10	641 (6%)	8	5,344	9
Connecticut (Black)	917 (1%)	10	75 (1%)	6	992	10
Connecticut (White)	12,699 (16%)	11	1,773 (16%)	9	14,472	10
Detroit (Black)	4,074 (5%)	9	439 (4%)	8	4,513	8
Detroit (White)	12,629 (16%)	10	2,082 (18%)	8	14,711	9
Hawaii (White)	1,110 (1%)	9	160 (1%)	7	1,270	9
Iowa (White)	11,545 (14%)	9	2,020 (18%)	8	13,565	9
New-Mexico (White)	4,247 (5%)	8	653 (6%)	7	4,900	8
San Francisco (Black)	1,481 (2%)	8	148 (1%)	7	1,629	8
San Francisco (White)	7,757 (10%)	9	841 (7%)	8	8,598	9
Seattle (Black)	508 (1%)	9	61 (1%)	6	569	8

	Seattle (White)	13,203 (17%)	9	1,908 (17%)	8	15,111	9
	Utah (White)	2641 (3%)	8	363 (3%)	7	3,004	8
Stage							
	I	19,192 (24%)	23	580 (5%)	16	19,772	22
	II	4,048 (5%)	18	245 (2%)	14	4,293	17
	III	18,823 (24%)	10	3,255 (28%)	11	22,078	10
	IV	30,936 (39%)	5	6,614 (58%)	6	37,550	5
	Unknown/occult	6,942 (9%)	8	732 (6%)	9	7,674	8
Follow up time							
	1- 3 Months	15,102 (19%)	-	2,268 (20%)	-	17,370	-
	3-6 Months	13,316 (17%)	-	1,863 (16%)	-	15,179	-
	6-9 Months	9,320 (12%)	-	1,908 (17%)	-	11,228	-
	9-12 Months	7,065 (9%)	-	1,517 (13%)	-	8,582	-
	>12 Months	35,138 (44%)	-	3,870 (34%)	-	39,008	-

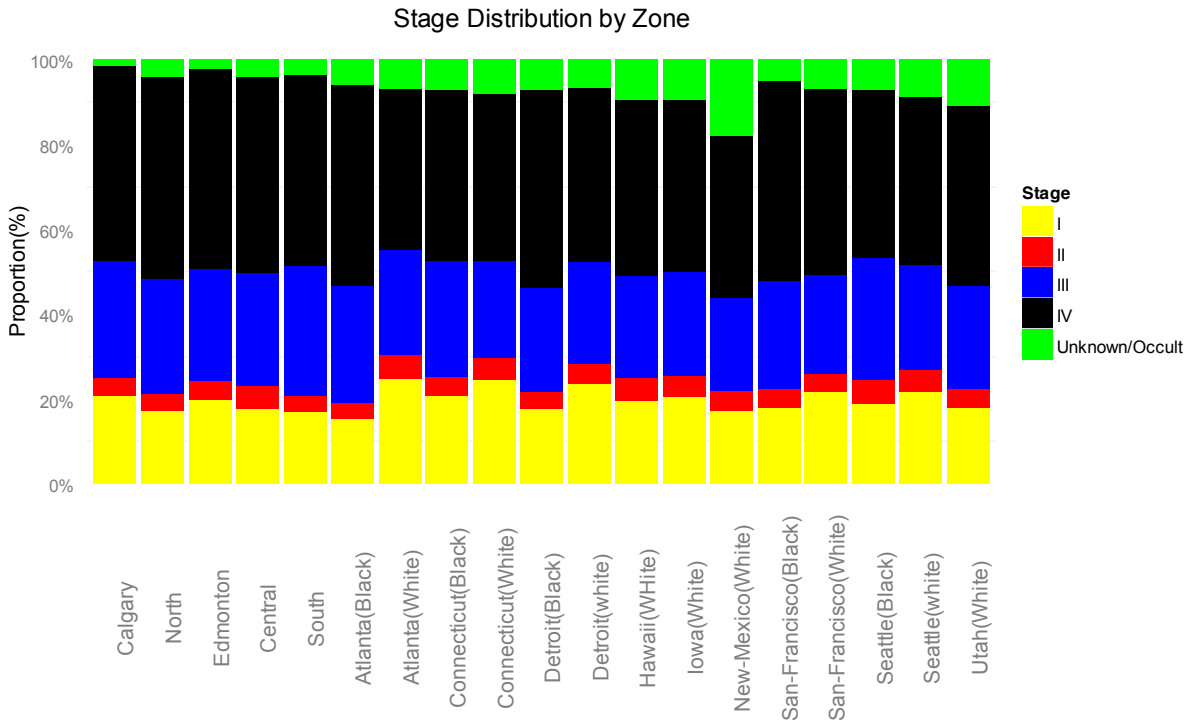

Figure 2.1: Stage distribution by zones of Alberta and United States Surveillance, Epidemiology and End Results (SEER) race/registry

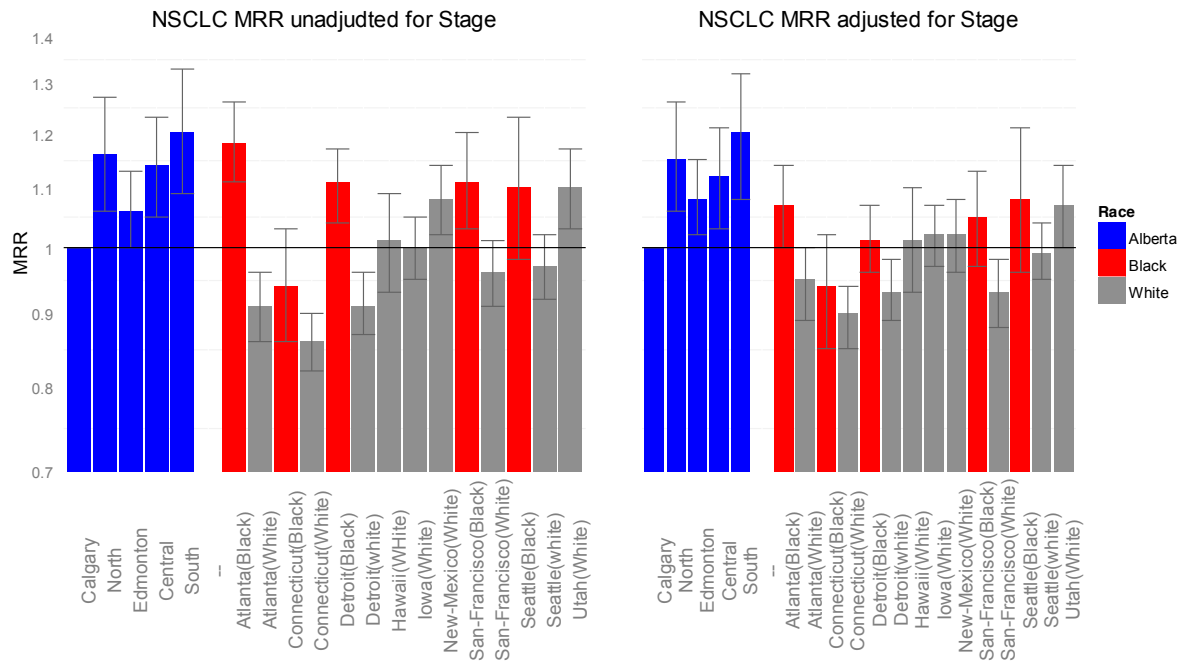

Figure 2.2: Adjusted mortality rate ratios of non-small cell lung cancer patients with 95% confidence intervals, adjusting for age, sex, and follow-up time (left panel), and adjusting for age, sex, follow-up time and stage at diagnosis (right panel)

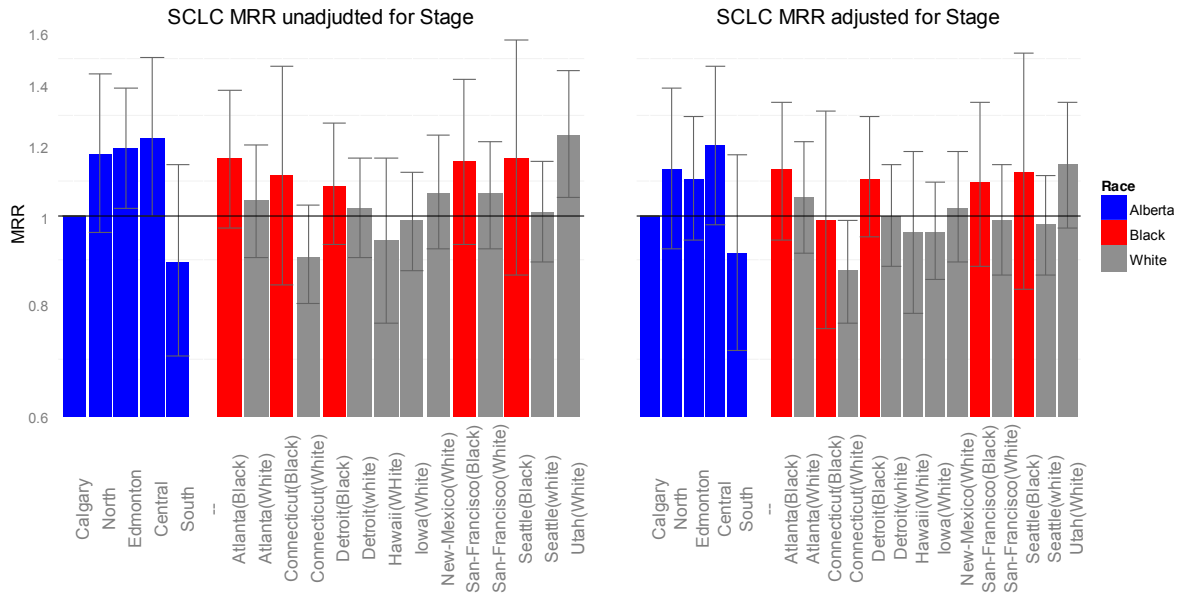

Figure 2.3: Adjusted mortality rate ratios of small cell lung cancer patients with 95% confidence intervals, adjusting for age, sex, and follow-up time (left panel), and adjusting for age, sex, follow-up time and stage at diagnosis (right panel)

Table 2.3: Adjusted mortality rate ratios from Poisson regression including patients with stage I-III lung cancer in Alberta and in the US Surveillance, Epidemiology and End Results (SEER) between 2004-2010

Covariates	NSCLC		SCLC	
	MRR [95% CI]	p	MRR [95% CI]	p
Age at diagnosis				
15-44	0.43 (0.38, 0.49)	<0.001	0.36 (0.25, 0.51)	<0.001
45-54	0.47 (0.45, 0.50)	<0.001	0.46 (0.41, 0.52)	<0.001
55-64	0.51 (0.49, 0.52)	<0.001	0.49 (0.44, 0.53)	<0.001
65-74	0.65 (0.63, 0.67)	<0.001	0.65 (0.60, 0.71)	<0.001
75+ (Ref)	1.00	-	1.00	-
Sex				
Female (Ref)	1.00	-	1.00	-
Male	1.24 (1.21, 1.27)	<0.001	1.2 (1.12, 1.29)	<0.001
Zones				
Calgary (Ref)	1.00	-	1.00	-
Edmonton	1.06 (0.96, 1.16)	0.25	1.28 (0.99, 1.66)	0.06
North	1.20 (1.04, 1.38)	0.01	1.24 (0.88, 1.75)	0.21
Central	1.18 (1.05, 1.34)	0.01	1.22 (0.87, 1.71)	0.25
South	1.24 (1.06, 1.44)	0.01	0.72 (0.48, 1.09)	0.12
Atlanta (Black)	1.27 (1.15, 1.41)	<0.001	1.24 (0.93, 1.67)	0.15
Atlanta (White)	1.08 (0.99, 1.17)	0.10	1.06 (0.84, 1.34)	0.61
Connecticut (Black)	0.99 (0.86, 1.14)	0.94	1.21 (0.72, 2.05)	0.47
Connecticut (White)	0.92 (0.85, 0.99)	0.03	0.91 (0.74, 1.12)	0.37
Detroit (Black)	1.20 (1.09, 1.31)	<0.001	0.95 (0.74, 1.24)	0.72
Detroit (White)	1.00 (0.93, 1.08)	0.94	1.03 (0.84, 1.26)	0.80
Hawaii (White)	1.06 (0.93, 1.20)	0.40	0.75 (0.52, 1.08)	0.12
Iowa (White)	1.08 (1.00, 1.16)	0.06	0.92 (0.75, 1.14)	0.45
New-Mexico (White)	1.16 (1.06, 1.27)	<0.001	1.11 (0.87, 1.42)	0.39
San Francisco (Black)	1.11 (0.98, 1.25)	0.10	1.26 (0.88, 1.79)	0.21
San Francisco (White)	1.01 (0.93, 1.09)	0.90	1.00 (0.79, 1.26)	0.99
Seattle (Black)	1.34 (1.13, 1.58)	<0.001	1.18 (0.71, 1.97)	0.52
Seattle (White)	1.03 (0.96, 1.12)	0.41	0.96 (0.78, 1.18)	0.69
Utah (White)	1.09 (0.98, 1.20)	0.11	1.35 (1.03, 1.77)	0.03
Stage				
I (Ref)	1.00	-	1.00	-
II	1.73 (1.66, 1.82)	<0.001	1.37 (1.14, 1.64)	<0.001
III	3.25 (3.16, 3.34)	<0.001	1.87 (1.68, 2.09)	<0.001
Follow up Time				
1- 3 Months (Ref)	1.00	-	1.00	-

3-6 Months	0.89 (0.85, 0.93)	<0.001	0.95 (0.84, 1.07)	0.41
6-9 Months	0.90 (0.86, 0.94)	<0.001	1.19 (1.06, 1.34)	<0.001
9-12 Months	0.86 (0.82, 0.91)	<0.001	1.45 (1.28, 1.63)	<0.001
12-24 Months	0.78 (0.75, 0.81)	<0.001	1.20 (1.08, 1.33)	<0.001
24-36 Months	0.61 (0.58, 0.64)	<0.001	0.75 (0.65, 0.87)	<0.001
36-48 Months	0.53 (0.50, 0.56)	<0.001	0.53 (0.43, 0.66)	<0.001
48-60 Months	0.45 (0.41, 0.49)	<0.001	0.44 (0.32, 0.59)	<0.001
60-72 Months	0.43 (0.39, 0.49)	<0.001	0.51 (0.34, 0.77)	<0.001
72-84 Months	0.42 (0.34, 0.52)	<0.001	0.29 (0.11, 0.78)	0.01

2.5 Appendix

Table 2.4: Mortality rate ratios from Poisson regression including patients of all stages adjusted for stage in Alberta and in the US Surveillance, Epidemiology and End Results (SEER) between 2004-2010

Covariates	Overall MRR (95% CI)	p	NSCLC MRR (95% CI)	p	SCLC MRR (95% CI)	p
Age at diagnosis						
15-44	0.56 (0.53, 0.60)	<0.01	0.56 (0.52, 0.61)	<0.01	0.56 (0.46, 0.67)	<0.01
45-54	0.63 (0.61, 0.65)	<0.01	0.63 (0.61, 0.66)	<0.01	0.59 (0.54, 0.63)	<0.01
55-64	0.65 (0.63, 0.66)	<0.01	0.65 (0.63, 0.66)	<0.01	0.61 (0.57, 0.64)	<0.01
65-74	0.75 (0.74, 0.77)	<0.01	0.75 (0.73, 0.77)	<0.01	0.74 (0.70, 0.78)	<0.01
75+ (Reference)	1.00	---	1.00	----	1.00	---
Sex						
Female (Ref)	1.00	---	1.00	----	1.00	---
Male	1.19 (1.17, 1.21)	<0.01	1.19 (1.17, 1.21)	<0.01	1.21 (1.15, 1.26)	<0.01
Zones						
Calgary (Ref)	1.00	---	1.00	----	1.00	---
Edmonton	1.06 (0.99, 1.13)	0.09	1.06 (0.99, 1.14)	0.11	1.05 (0.87, 1.26)	0.59
North	1.19 (1.08, 1.30)	<0.01	1.19 (1.07, 1.32)	<0.01	1.18 (0.93, 1.50)	0.17
Central	1.09 (1.00, 1.19)	0.06	1.09 (0.99, 1.19)	0.08	1.12 (0.88, 1.43)	0.36
South	1.09 (0.98, 1.22)	0.12	1.12 (0.99, 1.26)	0.07	0.94 (0.70, 1.26)	0.67
Atlanta (Black)	1.09 (1.01, 1.17)	0.02	1.09 (1.01, 1.18)	0.02	1.10 (0.90, 1.34)	0.37
Atlanta (White)	0.95 (0.89, 1.01)	0.12	0.95 (0.88, 1.01)	0.1	0.97 (0.82, 1.15)	0.73
Connecticut (Black)	0.94 (0.85, 1.04)	0.22	0.95 (0.85, 1.05)	0.32	0.93 (0.66, 1.30)	0.66
Connecticut (White)	0.90 (0.85, 0.95)	<0.01	0.91 (0.86, 0.96)	<0.01	0.84 (0.72, 0.97)	0.02
Detroit (Black)	1.02 (0.96, 1.08)	0.59	1.02 (0.95, 1.09)	0.66	1.05 (0.88, 1.25)	0.61
Detroit (White)	0.94 (0.89, 1.00)	0.03	0.93 (0.88, 0.99)	0.02	0.96 (0.83, 1.11)	0.57
Hawaii (White)	1.00 (0.92, 1.10)	0.95	1.01 (0.91, 1.11)	0.9	0.95 (0.75, 1.21)	0.69
Iowa (White)	1.02 (0.96, 1.08)	0.51	1.02 (0.97, 1.09)	0.42	0.95 (0.82, 1.10)	0.47
New-Mexico (White)	1.02 (0.96, 1.08)	0.56	1.03 (0.96, 1.10)	0.4	0.93 (0.79, 1.10)	0.40

San Francisco (Black)	1.04 (0.96, 1.13)	0.36	1.03 (0.94, 1.12)	0.52	1.14 (0.90, 1.45)	0.27
San Francisco (White)	0.93 (0.88, 0.99)	0.02	0.93 (0.87, 0.99)	0.02	0.94 (0.80, 1.10)	0.44
Seattle (Black)	1.10 (0.97, 1.24)	0.12	1.10 (0.97, 1.25)	0.13	1.07 (0.76, 1.51)	0.7
Seattle (White)	1.00 (0.95, 1.05)	0.95	1.00 (0.94, 1.06)	0.96	0.95 (0.82, 1.11)	0.54
Utah (White)	1.07 (1.00, 1.15)	0.05	1.08 (1.00, 1.16)	0.05	1.03 (0.85, 1.24)	0.79
Stage						
I (Ref)	1.00	---	1.00	----	1.00	---
II	1.70 (1.61, 1.78)	<0.01	1.69 (1.61, 1.78)	<0.01	1.30 (1.07, 1.59)	0.01
III	3.13 (3.04, 3.23)	<0.01	3.15 (3.06, 3.25)	<0.01	1.73 (1.53, 1.95)	<0.01
IV	5.99 (5.82, 6.16)	<0.01	5.99 (5.82, 6.17)	<0.01	3.45 (3.07, 3.89)	<0.01
Unknown/occult	3.55 (3.42, 3.69)	<0.01	3.59 (3.45, 3.73)	<0.01	2.00 (1.73, 2.31)	<0.01
Follow up Time						
1- 3 Months (Ref)	1.00	---	1.00	----	1.00	---
3-6 Months	1.24 (1.21, 1.27)	<0.01	1.24 (1.20, 1.27)	<0.01	1.28 (1.19, 1.38)	<0.01
6-9 Months	1.23 (1.19, 1.26)	<0.01	1.14 (1.11, 1.18)	<0.01	1.82 (1.69, 1.95)	<0.01
9-12 Months	1.18 (1.15, 1.22)	<0.01	1.07 (1.04, 1.11)	<0.01	2.03 (1.88, 2.20)	<0.01
12-24 Months	0.98 (0.96, 1.01)	0.23	0.90 (0.88, 0.93)	<0.01	1.73 (1.62, 1.86)	<0.01
24-36 Months	0.71 (0.69, 0.74)	<0.01	0.68 (0.66, 0.71)	<0.01	0.99 (0.88, 1.11)	0.87
36-48 Months	0.59 (0.55, 0.62)	<0.01	0.57 (0.54, 0.61)	<0.01	0.65 (0.54, 0.79)	<0.01
48-60 Months	0.51 (0.47, 0.56)	<0.01	0.50 (0.46, 0.55)	<0.01	0.49 (0.35, 0.68)	<0.01

Table 2.5: Mortality rate ratios from Poisson regression including patients of all stages unadjusted for stage in Alberta and in the US Surveillance, Epidemiology and End Results (SEER) between 2004-2010

Covariates	Overall MRR (95% CI)	p	NSCLC MRR (95% CI)	p	SCLC MRR (95% CI)	p
Age at diagnosis						
15-44	0.74 (0.69, 0.79)	<0.01	0.74 (0.69, 0.80)	<0.01	0.60 (0.49, 0.72)	<0.01
45-54	0.76 (0.74, 0.79)	<0.01	0.76 (0.73, 0.78)	<0.01	0.62 (0.57, 0.67)	<0.01
55-64	0.73 (0.71, 0.75)	<0.01	0.72 (0.70, 0.74)	<0.01	0.64 (0.60, 0.68)	<0.01
65-74	0.78 (0.77, 0.80)	<0.01	0.77 (0.75, 0.78)	<0.01	0.75 (0.71, 0.80)	<0.01
75+ (ref)	1.00	---	1.00	---	1.00	---
Sex						
Female (ref)						
Male	1.20 (1.18, 1.22)	<0.01	1.21 (1.19, 1.23)	<0.01	1.23 (1.18, 1.29)	<0.01
Zone						
Calgary (ref)	1.00	---	1.00	---	1.00	---
Edmonton	1.04 (0.97, 1.11)	0.3	1.03 (0.96, 1.11)	0.47	1.13 (0.94, 1.36)	0.19
North	1.20 (1.09, 1.32)	<0.01	1.19 (1.07, 1.32)	<0.01	1.21 (0.95, 1.53)	0.12
Central	1.10 (1.01, 1.20)	0.03	1.11 (1.01, 1.22)	0.04	1.13 (0.88, 1.44)	0.33
South	1.11 (1.00, 1.25)	0.06	1.13 (1.00, 1.28)	0.04	0.92 (0.69, 1.23)	0.58
Atlanta (Black)	1.21 (1.13, 1.30)	<0.01	1.23 (1.14, 1.33)	<0.01	1.14 (0.93, 1.40)	0.2
Atlanta (White)	0.93 (0.87, 0.99)	0.02	0.92 (0.86, 0.98)	0.01	0.97 (0.82, 1.15)	0.71
Connecticut (Black)	0.95 (0.86, 1.05)	0.35	0.97 (0.87, 1.08)	0.58	1.06 (0.76, 1.50)	0.72
Connecticut (White)	0.89 (0.84, 0.94)	<0.01	0.89 (0.83, 0.94)	<0.01	0.87 (0.75, 1.01)	0.07
Detroit (Black)	1.11 (1.05, 1.19)	<0.01	1.13 (1.06, 1.21)	<0.01	1.02 (0.86, 1.22)	0.8
Detroit (White)	0.95 (0.90, 1.00)	0.04	0.93 (0.88, 0.99)	0.01	0.97 (0.84, 1.13)	0.72
Hawaii (White)	1.00 (0.92, 1.10)	0.91	1.01 (0.91, 1.11)	0.91	0.93 (0.74, 1.18)	0.56
Iowa (White)	1.04 (0.98, 1.10)	0.18	1.03 (0.97, 1.09)	0.36	0.98 (0.85, 1.14)	0.8
New-Mexico (White)	1.10 (1.03, 1.17)	<0.01	1.11 (1.03, 1.18)	<0.01	0.98 (0.83, 1.16)	0.81
San Francisco (Black)	1.12 (1.03, 1.22)	0.01	1.12 (1.03, 1.23)	0.01	1.20 (0.95, 1.52)	0.13

San Francisco (White)	0.98 (0.92, 1.04)	0.43	0.98 (0.92, 1.04)	0.46	1.01 (0.86, 1.18)	0.94
Seattle (Black)	1.15 (1.02, 1.29)	0.03	1.16 (1.02, 1.31)	0.03	1.12 (0.80, 1.58)	0.51
Seattle (White)	1.00 (0.95, 1.06)	0.88	1.00 (0.94, 1.06)	0.95	0.99 (0.86, 1.15)	0.91
Utah (White)	1.12 (1.05, 1.20)	<0.01	1.12 (1.04, 1.21)	<0.01	1.12 (0.93, 1.35)	0.24
Follow-up time						
1-3 Months (ref)	1.00	---	1.00	---	1.00	---
3-6 Months	1.15 (1.12, 1.18)	<0.01	1.14 (1.11, 1.17)	<0.01	1.25 (1.16, 1.34)	<0.01
6-9 Months	1.07 (1.04, 1.10)	<0.01	0.98 (0.95, 1.01)	0.25	1.71 (1.59, 1.84)	<0.01
9-12 Months	0.96 (0.93, 0.99)	0.01	0.86 (0.84, 0.89)	<0.01	1.83 (1.69, 1.97)	<0.01
12-24 Months	0.71 (0.69, 0.73)	<0.01	0.65 (0.63, 0.67)	<0.01	1.43 (1.33, 1.53)	<0.01
24-36 Months	0.44 (0.43, 0.46)	<0.01	0.43 (0.41, 0.44)	<0.01	0.73 (0.65, 0.83)	<0.01
36-48 Months	0.34 (0.32, 0.35)	<0.01	0.33 (0.31, 0.35)	<0.01	0.47 (0.39, 0.57)	<0.01
48-60 Months	0.28 (0.26, 0.30)	<0.01	0.28 (0.25, 0.30)	<0.01	0.34 (0.25, 0.48)	<0.01
60-72 Months	0.24 (0.20, 0.28)	<0.01	0.23 (0.20, 0.28)	<0.01	0.39 (0.21, 0.73)	<0.01

Table 2.6: Characteristics of the patients who did not survive up to thirty days of diagnosis of Alberta from 2004-2009

Variable	NSCLC	SCLC
Overall	1,209 (14%)	301 (25%)
Age at diagnosis		
15-44	12 (11%)	4 (25%)
45-54	67 (8%)	14 (11%)
55-64	222 (11%)	78 (23%)
65-74	384 (14%)	101 (23%)
75+	524 (18%)	104 (37%)
Sex		
Female	493 (12%)	126 (21%)
Male	716 (16%)	175 (28%)
Zones of Alberta		
Calgary	324 (12%)	86 (24%)
Edmonton	449 (14%)	113 (27%)
North	146 (16%)	29 (18%)
Central	194 (16%)	43 (26%)
South	96 (15%)	30 (29%)
Stage		
I	54 (3%)	0 (0%)
II	10 (2%)	2 (10%)
III	201 (9%)	46 (11%)
IV	861 (22%)	245 (34%)
Unknown/occult	83 (33%)	8 (53%)

* The percentages are calculated as the (number of patients in the group who did not survive 30 days/ total number of patients in the group) × 100

Table 2.7: Characteristics of the patients who did not survive up to thirty days of diagnosis of Surveillance, Epidemiology and End Results (SEER) registries from 2004-2009

Variable	NSCLC	SCLC
Overall	14,149 (18%)	2427 (21%)
Age at diagnosis		
15-44	112 (9%)	8 (5%)
45-54	677 (9%)	146 (11%)
55-64	1,984 (12%)	454 (15%)
65-74	3,522 (14%)	756 (20%)
75+	7,854 (26%)	1,063 (34%)
Sex		
Female	6,480 (17%)	1,200 (20%)
Male	7,669 (18%)	1,227 (22%)
SEER Race-registry		
Atlanta (Black)	389 (16%)	36 (14%)
Atlanta (White)	742 (16%)	137 (21%)
Connecticut (Black)	117 (13%)	10 (13%)
Connecticut (White)	2,012 (16%)	343 (19%)
Detroit (Black)	667 (16%)	100 (23%)
Detroit (White)	2,204 (17%)	493 (24%)
Hawaii (White)	237 (21%)	35 (22%)
Iowa (White)	2,086 (18%)	390 (19%)
New-Mexico (White)	1,148 (27%)	150 (23%)
San Francisco (Black)	268 (18%)	37 (25%)
San Francisco (White)	1,582 (20%)	216 (26%)
Seattle (Black)	67 (13%)	7 (11%)
Seattle (White)	2,124 (16%)	381 (20%)
Utah (White)	506 (19%)	92 (25%)
Stage		
I	691 (4%)	29 (5%)
II	180 (4%)	17 (7%)
III	2,339 (12%)	376 (12%)
IV	6,844 (22%)	1,820 (28%)
Unknown/occult	4,095 (59%)	185 (25%)

* The percentages are calculated as the (number of patients in the group who did not survive 30 days/ total number of patients in the group) × 100

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Chapter 3 : Population-based evaluation of disparities in mortality rate of lung cancer patients due to treatment received and by oncologists in Alberta, Canada

3.1 Introduction

Lung cancer is the second most common cancer diagnosed in both men and women and the leading cause of cancer related deaths in developed countries[1]. A study based on multiple population-based investigations[2] reported that the lung cancer patients in Alberta had an appreciably lower 5- year relative survival (15.1%) than the patients in Manitoba (20.1%), Ontario (19.1%) and British Columbia (17.7%) in 1995-2007. In addition, during the same period, relative survival of all the provinces increased; however, the increment was the lowest (1.3%) in Alberta, compared to British Columbia (3.8%), Manitoba (3.5%) and Ontario (2.5%). Reasons for the lower survival and less improvement of it among the patients in Alberta are unknown.

Survival of lung cancer patients is influenced by stage at diagnosis and treatment. In Canada, the 5-year relative survival is 17%[3] for patients of non-small-cell lung cancer (NSCLC), the dominant subtype of lung cancer (approximately 85% of all lung cancer patients). Five-year relative survival for early stage (stage I and II) NSCLC patients is between 30-50%,[3] however, only 25-30% of NSCLC patients are diagnosed at an early stage[4]. Surgery is the primary treatment for early stage (stage I and II) NSCLC patients;[5 6] adjuvant chemotherapy and/or adjuvant radiotherapy are also recommended after surgery for stage IB-II lung cancer patients[7]. For stage III NSCLC patients, surgical resection plus adjuvant chemotherapy with or without neoadjuvant chemotherapy is the primary recommendation for the patients who are medically

operable[7,8] Stage IV NSCLC patients with solitary metastasis and good performance status can benefit from surgical resection,[9] however, most stage IV patients (approximately 90%) are not eligible for surgical resection[10]. Patients who are not eligible for surgery should receive radiation therapy (stage I[5,7]), radiation, chemotherapy or both (stage II[6,7] and III[11-14]), or chemotherapy or palliative radiotherapy (stage IV[9]).

Although surgery provides the best survival advantage for NSCLC patients of all stages, the majority of patients do not have resectable disease[7]. Furthermore, a study in Alberta found that a higher proportion of stage IB-II NSCLC patients living north of Red Deer received surgery than those living south of Red Deer suggesting important differences in treatment patterns that could affect survival[15]. An extension of that study[16]and another study in Alberta both found variation in the proportion of eligible patients who receive consultations with an oncologist[17]. There is clear evidence for different treatment and referral patterns for lung cancer patients, which could translate into differences in survival across the province.

Based on the above, the first objective of this investigation was to assess geographical variation in the mortality of NSCLC patients across the healthcare zones of Alberta with and without accounting for treatment received. The second objective was to investigate whether the degree to which mortality rates of NSCLC patients vary by oncologists.

3.2 Methods

3.2.1 Data sources

This was a population-based study of all NSCLC patients in the province of Alberta, Canada, diagnosed in 2004-2010. Patients were identified from the Alberta Cancer Registry. Patient demographics, clinical characteristics and initial treatments received were obtained from the

cancer registry. Treatments included surgery, chemotherapy, radiotherapy and any combination of them. The cancer electronic medical record was used to obtain anonymized IDs of the oncologist for each patient that had an oncologist consultation. The study was approved by the University of Alberta Health Research Ethics Board.

3.2.2 Inclusion criteria

Patients diagnosed with NSCLC in Alberta between 2004-2010 were identified from the Alberta Cancer Registry. Cases were included in the study if they were: 1) diagnosed with malignant lung cancer (ICD-O-3[18] topology code c34.0-c34.9 and ICD-O-3 behavior code "3" in 2004 through Nov 30, 2010; 2) diagnosed with stage I-IV lung cancer; and 3) alive more than 30 days after diagnosis, since 85% of these patients did not receive any treatment and 90% of the patients were diagnosed with either stage IV or unknown stage and thus, providing difficulty to observe treatment effect on survival. We included patients who were diagnosed with NSCLC (histology: 8011-8015, 8046, 8050-8084, 8140-8384, 8440-8490, 8560). Cancer staging was based on the American Joint Committee on Cancer (AJCC) *Cancer Staging Manual (version 6)*[19]

3.2.3 Data analysis

For the analyses, patient age was divided into five categories: 15-44, 45-54, 55-64, 65-74, and 75 or more. Ages were grouped as this to maintain consistency with the paper published by Coleman et.al[2]. The five geographical zones of AHS (North, Edmonton, Central, Calgary and South) were used. The frequency and percentage of patient characteristics were tabulated overall and stratified by geographical healthcare zones of Alberta along with median survival time in months since diagnosis. Treatments received were tabulated by geographical zone stratified by stage at diagnosis.

To maintain statistical power the treatments were grouped in the following order: 1) "surgery and chemotherapy or radiotherapy", which included patients who received surgery along with chemotherapy and radiotherapy (0.4%), surgery and chemotherapy (5.1%), and surgery and radiotherapy (0.1%); 2) patients who received "surgery only" (15.7%); 3) patients who received "both chemotherapy and radiotherapy" (9.0%); 4) either chemotherapy or radiotherapy", which included patients who received one of chemotherapy (10.5%) and radiotherapy (26.6%) and 5) patients who received "no treatment" (32.6%).

To investigate mortality we used the piecewise exponential model[20], where the follow-up period was grouped into every three months in the first year post-diagnosis, due to large changes in the rate of death in the first year, and annually afterwards. The piecewise exponential model is analogous to a Poisson regression where the count of death for a specific time period is modeled as the outcome instead of the survival time, and the survival time is used as an offset. Two multivariable Poisson regression models were fitted to evaluate post-diagnosis mortality rates across geographical zones for each stage of diagnosis, adjusting for age and sex interaction (since previous studies have shown that women in the same age group have better survival then men[21]), and the follow-up period, adjusted and unadjusted for treatment effect, respectively. A multivariable mixed-effect Poisson regression (analogous to multivariable piecewise exponential regression) was also fitted including all stages, adjusting for age and sex interaction, zones of Alberta and stage at diagnosis, considering the oncologist-specific effect as random. In this specific model we excluded 1,388 patients who did not receive an oncologist consultation.

Adjusted mortality rate ratios (MRR) were estimated for fixed effect Poisson regressions, along with 95% confidence intervals, using the following reference groups: age = 75 or older; sex = female; zone = Calgary; follow-up period = 1-3 months and treatment = surgery with

chemotherapy or radiotherapy. For the mixed-effect Poisson regression, the reference group of age, sex, zone and follow-up period were the same as the fixed-effect Poisson regressions and the reference group for stage at diagnosis was stage I. All analyses were conducted with R (version 3.0.2)[22].

3.3 Results

There were 11,608 malignant lung cancer patients diagnosed between 2004-2010 in Alberta. Total 3,222 patients were excluded for the following reasons: 1) 1,503 patients for their cancer type was not NSCLC (i.e., SCLC, lymphoma, melanoma, mesotheliomas, soft tissue and sarcoma and carcinoid cases) 2) 1,507 patients because they did not survive more than 30 days and 3) 212 patients due to their unknown stage at diagnosis. A total of 8,386 patients were, therefore, included in the study. The median age at diagnosis was 69 years and median survival was 8.7 months. Table 3.1 shows the patients characteristics by zone along with median survival time. Most of the patients (72%-75%) in each healthcare zone were diagnosed with stage III or IV lung cancer.

Table 3.2 shows the proportions of patients receiving each treatment by zone stratified by stage at diagnosis. Stage I patients in North Zone and Edmonton had higher proportions (66% and 62%, respectively) of receiving ”only surgery” than other zones (51% - 53%): in contrast, Stage I patients in Calgary, Central and South Zones had higher proportions (19%, 16% and 19%, respectively) of receiving “either chemotherapy or radiotherapy” compared to the North Zone and Edmonton (4% and 8%, respectively). Proportions of the other treatments for stage I patients were similar across the zones. For stage II, Calgary patients had a higher proportion of receiving “both chemotherapy and radiotherapy” (10%), “either chemotherapy or radiotherapy”

(25%) and "surgery with chemotherapy or radiotherapy" (36%) than the other zones. The other zones had higher proportions of "only surgery" (22%-36%) than Calgary (16%). The proportion of stage II patients who did not receive any treatment was higher in the North (20%), Central (20%) and South (22%) zones than in Edmonton (12%) and Calgary (12%) zones. All zones had a very low proportion (7-15%) of stage III patients receiving "surgery with chemotherapy or radiotherapy" or "only surgery". Most of the stage III patients who received treatment were treated with either "both chemotherapy and radiotherapy"(16%-24%) or "either chemotherapy or radiotherapy" (38%-48%). The proportion of patients who did not receive any treatment was higher in the Central and South zones (both 32%) than the other zones (22% - 24%). Most of the stage IV patients either received "either chemotherapy or radiotherapy" (43%-50%) or did not receive any treatment (42%-47%).

For stage I patients, the treatments which included surgery provided the lowest mortality rates ("surgery with chemotherapy or radiotherapy" was the reference and "only surgery" had MRR = 1.0; 95% CI = 0.7, 1.3) among all the treatment modalities considered (Table 3.3). Patients who received "both chemotherapy and radiotherapy" (MRR = 4.5; 95% CI = 1.6, 12.7), "either chemotherapy or radiotherapy" (MRR = 3.8; 95% CI = 2.6, 5.5) had statistically significantly higher mortality rates compared to patients who received "surgery with chemotherapy or radiotherapy". Similar to stage I patients, the treatments that included surgery were also associated with the lowest mortality rates among stage II patients. (Table 3.4). Patients who received "both chemotherapy and radiotherapy" had a statistically significantly elevated MRR (2.5; 95% CI = 1.3, 4.7), relative to the reference. Patients who received "either chemotherapy or radiotherapy" had almost the same MRR (MRR = 4.6; 95% CI = 3.0, 7.1) as the patients who did not receive any treatment (MRR = 4.8; 95% CI = 3.0, 7.6).

For stage III patients, the MRRs were 1.2 (95% CI = 0.8, 1.8), 2.0 (95% CI = 1.5, 2.7), 4.4 (95% CI = 3.3, 5.8), 5.2 (95% CI = 3.9, 6.9) for patients who received "surgery only", "both chemotherapy and radiotherapy", "either chemotherapy or radiotherapy" and "no treatment", respectively, compared to "surgery with chemotherapy or radiotherapy" (Table 3.5). For the same treatment categories the MRRs were 0.9 (0.4, 2.1), 2.6 (95% CI = 1.4, 5.0), 4.1 (2.2, 7.7) and 5.4 (2.9, 10.1), respectively, for stage IV patients.

Figure 3.1 shows the adjusted MRRs obtained from the fixed-effect Poisson regression adjusting for age and sex interaction and follow-up time (months), for each stage, unadjusted and adjusted associations with treatment, along with 95% confidence intervals (the exact values of the adjusted MRR and 95% CIs are given in Table 3a – 3d). Calgary and Edmonton had lower unadjusted and adjusted mortality rates than the other zones for all stages. For stage I and II, Edmonton and Calgary had approximately equal mortality rates: the adjustment for treatments increased the MRR of Edmonton relative to Calgary for both stage I and II, but the difference was not statistically significant. For stage I, the North zone (MRR = 1.6; 95% CI = 1.2, 2.1) and Central (MRR = 1.4; 95% CI = 1.1, 1.8) had statistically significantly higher mortality rates than Calgary without adjusting for treatment. In the case of stage II patients, none of the zones of Alberta had significantly higher mortality rates compared to Calgary without adjusting for treatment ($p \geq 0.05$). For stage I and II patients, MRRs increased after adjusting for treatments in all zones compared to Calgary except the stage I patients in the South zone and stage II patients in the North zone. For stage III patients, however, the MRRs in every zone except the South zone decreased after adjusting for treatment and became insignificant. Similarly, mortality rates were similar for all the zones for stage IV patients with an exception of South zone (MRR = 1.2; 95% CI = 1.0, 1.4; after adjusting for treatments).

Variation among the oncologist-specific MRRs was large ranging from low MRRs around 0.60 to 0.75 to high MRRs around 1.36 to1.53. The stage and oncologist specific MRRs are reported in the appendix. Figure 3.2 shows the oncologist-specific MRRs adjusted for the age and sex interaction and stage.

3.4 Discussion

The rationale for this study was to assess within-province geographical disparity as a potential reason for the lower survival of lung cancer patients in Alberta relative to those in Ontario, Manitoba and British Columbia and to assess the impact of variation in treatment patterns and the oncologist specific effects on survival differences. To our knowledge there had been no other population-based study on NSCLC patients, which investigated geographical disparity in mortality rates of the patients considering treatment and oncologist specific effects. This study found that NSCLC mortality rates of patients diagnosed between 2004-2010 differ across the geographical zones of Alberta. Calgary patients had consistently lower mortality rates than the other zones of Alberta: if the mortality rates of the other zones of Alberta can be reduced to the level of Calgary, then the overall survival in Alberta would improve, which will minimize the difference in lung cancer survival between Alberta and other provinces.

By assessing the geographical variation in the NSCLC patients' mortality with and without taking the received treatment into consideration, we attempted to assess whether, and how much of, the disparity was due to treatment types that the patients received (or did not receive). Specifically, a decrease in MRR by the treatment adjustment for a zone can be explained by the fact that the patients of that zone received less effective treatment than those in Calgary. If the pattern of treatments received by the patients of the zone is consistent to the

observed change in MRR by the treatment adjustment, we can infer that the disparity for that zone is attributable, at least partially, to the treatment patterns of that zone relative to Calgary. For example, the MRRs of stage III patients of the North, Edmonton, Central and South zones decreased after adjusting for treatment effect. We know from the treatment guidelines that surgery is recommended only to patients whose tumor is medically operable. Although treatments which included surgery were the most effective treatments for stage III patients (Table 3.5), only 7%-15% patients received them: most of the stage III patients received either "both chemotherapy and radiotherapy" or "either chemotherapy or radiotherapy" or "no treatment". Among these treatments "both chemotherapy and radiotherapy" was the most effective treatment in reducing mortality, which is also the standard treatment for medically inoperable patients according to the guidelines. Calgary stage III patients received the highest proportion of "both chemotherapy and radiotherapy" (24%) among all the zones (other zones ranged 16%-23%). The fact that more patients of the other zones received less effective "either chemotherapy or radiotherapy" or "no treatment" (67%-72%) than Calgary patients (65%) contributed to the disparity of mortality rates of the stage III patients.

Unchanged MRR by the treatment adjustment for a zone may suggest types of treatment received by the patients of that zone were similar to, or similarly effective to reduce mortality rates as those received by the Calgary patients. For example, stage I patients in the South zone and stage II patients in the North zone had unchanged MRRs after adjusting for treatment. The proportions of treatments received by the South stage I patients were almost the same as the proportion of the treatments received by the Calgary stage I patients, which is consistent to the unchanged MRR. The North stage II patients, however, received different proportions of each treatment (53% of treatments which included surgery, 27% of chemotherapy and/or radiotherapy

and 20% no treatment) from the Calgary stage II patients (52% of treatments which included surgery, 35% of chemotherapy and/or radiotherapy and 12% no treatment). According to treatment guidelines treatments which include surgery are the standard choice of treatment for stage I patients who are medically operable. It appears that approximately the same proportion of patients in North and Calgary received the most effective treatments, which are the treatments involving surgery. At the same time more patients in North received no treatment, which was expected to increase the MRR of North patients but did not appear in the analysis possibly due to the fact that very small numbers of patients were diagnosed with stage II NSCLC in North. Overall, the treatments received by Calgary stage II NSCLC patients had the similar effect on mortality as the treatments received by their counterparts in North. Unchanged MRR was also observed for stage IV patients in all the zones: this was due to the fact that most of the stage IV patients did not receive any treatment or received "either chemotherapy or radiotherapy".

An increment in the zone specific MRRs may suggest that the treatments received by the patients in the zone were more effective to reduce mortality than those received by their counterparts in Calgary. In these situations, observed disparity in unadjusted MRRs was not attributable to treatments; instead disparity was not explained by treatment differences and treatment-adjusted disparity was larger. For example, for stage I and II Edmonton patients, the MRR increased after adjusting for treatment effect. For stage I and II patients, treatments involving surgery were the most effective treatments in reducing mortality, which are also recommended by the treatment guidelines. Edmonton stage I and II patients received 6%-13% higher proportion of treatments involving surgery than Calgary patients. After taking into account of this advantage of Edmonton patients, however, stage I and II patients in Edmonton seem at even higher risk of death than their counterparts in Calgary. However, there is no

apparent reason for this finding and thus further research is needed to identify the reason. The same interpretation applies to North and Central stage I patients and Central and South stage II patients.

In all the above analyses, a key assumption was that treatment effects were constant on mortality across the zones, adjusting for age and sex interaction, and follow-up time in each stage: i.e., no interaction between geographical zones and treatments. However, whether the assumption is true needs to be identified. For example, surgery on NSCLC patients is only provided in Calgary and Edmonton among the zones of Alberta. Patients from North, South or Central have to travel to either Calgary or Edmonton to receive surgery. This may increase their waiting time before receiving surgery compared to Calgary and Edmonton patients who may have been diagnosed with the same stage. This may cause different effect of surgery on patients from different zones. To assess whether this assumption was reasonable or not, we ran the fixed effect Poisson regression allowing the interaction of zones and treatments, adjusted for age and sex interaction, and follow up time. This analysis was performed for stage I-III because we had observed some large differences in MRR estimates before and after the adjusting for treatment effect for the stage I-III patients. Some of the estimated interaction terms (ratio of mortality rate ratios) departed largely from 1.0. For example, the mortality rate ratio of "both chemotherapy and radiotherapy" compared to "surgery and chemotherapy or radiotherapy" was 3.00 (95% CI = 0.24, 38.22) times higher in Edmonton stage I patients compared to Calgary stage I patients. However, none of the interaction terms were statistically significant (Appendix Table 3.7). Large values of interaction terms indicate that the effect of treatment may not have been the same across zones for a specific stage, however.

Based on the mixed effects analysis, there was clear evidence of huge variation in oncologist-specific mortality rates. The oncologist specific MRR ranged from 0.6 to 1.5. One of the possible reasons for this disparity is that some oncologists are more aggressive than others in providing treatments. Disparity in the oncologist-specific MRRs was also observed for each specific stage (appendix Figure 3.3).

It was reported by Coleman *et.al* [2] that Alberta lung cancer patients had the lowest survival among the Canadian provinces they studied. In this research work, we have advanced our understanding of mortality disparity among the NSCLC patients in Alberta. Specifically, for all stages, Calgary patients had lower mortality rates than the other zones of Alberta. In a publicly funded health care system this geographical disparity presents a concern. The limitation of this study was that we investigated on all-cause mortality rates instead of lung cancer specific death and did not include other comorbidities as a factor in the analyses, which may produce some biased estimate of MRRs. The disparity we observed across the zones of Alberta was partly attributable to patterns of treatment received by the patients: but the patterns of treatment alone did not account for the disparity we observed. We also observed an appreciable degree of mortality differences across patients of different oncologists. This also needs further investigations as to why mortality rates are consistently higher among patients of some oncologists than others. To ensure better treatment for lung cancer patients and increase their quality of life, sources of disparity need to be identified and addressed: this is crucial given the geographical disparity within Alberta we observed here.

Table 3.1: Characteristics of the non-small cell lung cancer patients across the zones of Alberta

Variable		Calgary (%+)	Edmonton (%)	North (%)	Central (%)	South (%)	Total	Median Survival (Months)
Total		2,623	3,076	866	1,191	630	8,386	8.71
Age at diagnosis								
	15-44	37 (1%)	42 (1%)	18 (2%)	10 (1%)	4 (1%)	111 (1%)	11.73
	45-54	253 (10%)	314 (10%)	99 (11%)	106 (9%)	51 (8%)	823 (10%)	8.97
	55-64	601 (23%)	691 (22%)	222 (26%)	287 (24%)	148 (23%)	1,949 (23%)	9.53
	65-74	825 (31%)	993 (32%)	295 (34%)	409 (34%)	230 (37%)	2,752 (33%)	9
	75+	907 (35%)	1,036 (34%)	232 (27%)	379 (32%)	197 (31%)	2,751 (33%)	7.92
Sex								
	Female	1304 (50%)	1,472 (48%)	408 (47%)	551 (46%)	286 (45%)	4,021 (48%)	9.73
	Male	1319 (50%)	1,604 (52%)	458 (53%)	640 (54%)	344 (55%)	4,365 (52%)	7.85
Stage at diagnosis								
	I	607 (23%)	694 (23%)	180 (21%)	245 (21%)	127 (20%)	1,853 (22%)	25.53
	II	118 (4%)	156 (5%)	41 (5%)	69 (6%)	27 (4%)	411 (5%)	20.37
	III	705 (27%)	808 (26%)	232 (27%)	319 (27%)	190 (30%)	2,254 (27%)	10.25
	IV	1193 (45%)	1,418 (46%)	413 (48%)	558 (47%)	286 (45%)	3,868 (46%)	4.53
Follow Up Time								
	1- 3 Months	504 (19%)	665 (22%)	189 (22%)	268 (23%)	154 (24%)	1,780 (21%)	-
	3-6 Months	478 (18%)	523 (17%)	161 (19%)	200 (17%)	123 (20%)	1,485 (18%)	-
	6-9 Months	300 (11%)	369 (12%)	118 (14%)	140 (12%)	76 (12%)	1,003 (12%)	-
	9-12 Months	227 (9%)	251 (8%)	65 (8%)	111 (9%)	46 (7%)	700 (8%)	-
	>12 Months	1114 (42%)	1,268 (41%)	333 (38%)	472 (40%)	231 (37%)	3,418 (41%)	-

+ The percentages are given by column variable

Table 3.2: Number (%) of treatment by zone and stage in non-small cell lung cancer patients of Alberta

	Calgary	Edmonton	North	Central	South
Total	2,623	3,076	866	1,191	630
Stage I					
Surgery with chemotherapy or radiotherapy	56 (9%)	64 (9%)	16 (9%)	25 (10%)	11 (9%)
Only Surgery	322 (53%)	433 (62%)	119 (66%)	126 (51%)	67 (53%)
Both chemotherapy and radio therapy	5 (1%)	2 (0%)	1 (1%)	1 (0%)	0 (0%)
Either Chemotherapy or radiotherapy	117 (19%)	56 (8%)	8 (4%)	38 (16%)	24 (19%)
No treatment	107 (18%)	139 (20%)	36 (20%)	55 (22%)	25 (20%)
Stage II					
Surgery with chemotherapy or radiotherapy	43 (36%)	51 (33%)	13 (32%)	19 (28%)	8 (30%)
Only Surgery	19 (16%)	56 (36%)	9 (22%)	24 (35%)	7 (26%)
Both chemotherapy and radio therapy	12 (10%)	6 (4%)	2 (5%)	4 (6%)	1 (4%)
Either Chemotherapy or radiotherapy	30 (25%)	25 (16%)	9 (22%)	8 (12%)	5 (19%)
No treatment	14 (12%)	18 (12%)	8 (20%)	14 (20%)	6 (22%)
Stage III					
Surgery with chemotherapy or radiotherapy	37 (5%)	54 (7%)	21 (9%)	18 (6%)	7 (4%)
Only Surgery	34 (5%)	40 (5%)	13 (6%)	9 (3%)	5 (3%)
Both chemotherapy and radio therapy	172 (24%)	132 (16%)	41 (18%)	69 (22%)	43 (23%)
Either Chemotherapy or radiotherapy	290 (41%)	386 (48%)	105 (45%)	120 (38%)	74 (39%)
No treatment	172 (24%)	196 (24%)	52 (22%)	103 (32%)	61 (32%)
Stage IV					
Surgery with chemotherapy or radiotherapy	10 (1%)	7 (0%)	3 (1%)	5 (1%)	0 (0%)
Only Surgery	11 (1%)	12 (1%)	5 (1%)	6 (1%)	2 (1%)
Both chemotherapy and radio therapy	67 (6%)	95 (7%)	34 (8%)	40 (7%)	26 (9%)
Either Chemotherapy or radiotherapy	559 (47%)	704 (50%)	179 (43%)	254 (46%)	124 (43%)
No treatment	546 (46%)	600 (42%)	192 (46%)	253 (45%)	134 (47%)

Table 3.3: Adjusted mortality rate ratios obtained from fixed effect Poisson regression for stage I patients

Covariates		MRR unadjusted for treatment (95% CI)	p	MRR adjusted for treatment (95% CI))	p
Age at diagnosis					
	15-44	0.14 (0.02, 0.99)	0.05	0.35 (0.05, 2.51)	0.30
	45-54	0.21 (0.11, 0.38)	<0.01	0.55 (0.29, 1.03)	0.06
	55-64	0.33 (0.24, 0.47)	<0.01	0.78 (0.54, 1.12)	0.18
	65-74	0.48 (0.37, 0.63)	<0.01	0.83 (0.63, 1.10)	0.19
	75+	1.0 (Reference)	---	1.0 (Reference)	---
Sex					
	Female	1.0 (Reference)	---	1.0 (Reference)	---
	Male	1.35 (1.08, 1.68)	0.01	1.48 (1.19, 1.85)	<0.01
Age at diagnosis × Sex					
	Male 15-44	5.57 (0.5, 62.16)	0.16	5.97 (0.53, 66.63)	0.15
	Male 45-54	1.22 (0.49, 3.03)	0.66	1.03 (0.42, 2.57)	0.94
	Male 55-64	1.25 (0.78, 2.00)	0.35	1.01 (0.63, 1.62)	0.97
	Male 65-74	1.25 (0.88, 1.78)	0.21	1.05 (0.73, 1.49)	0.80
Zone					
	Calgary	1.0 (Reference)	---	1.0 (Reference)	---
	Edmonton	0.97 (0.81, 1.17)	0.77	1.14 (0.94, 1.38)	0.19
	North	1.35 (1.03, 1.77)	0.03	1.58 (1.20, 2.08)	<0.01
	Central	1.31 (1.03, 1.66)	0.03	1.41 (1.11, 1.79)	0.01
	South	0.99 (0.70, 1.39)	0.94	1.01 (0.71, 1.42)	0.97
Treatment					
	Surgery and Chemotherapy or Radiotherapy	1.0 (Reference)	---		<0.01
	Only Surgery	---	---	0.95 (0.68, 1.34)	0.77
	Both Chemotherapy and Radiotherapy	---	---	4.49 (1.59, 12.65)	<0.01
	Either Chemotherapy or radiotherapy	---	---	3.78 (2.59, 5.51)	<0.01
	No treatment	---	---	6.02 (4.22, 8.60)	<0.01
Follow-up period					
	1-3 Months	1.0 (Reference)	---	1.0 (Reference)	---
	3-6 Months	1.87 (1.20, 2.90)	0.01	1.92 (1.23, 2.99)	<0.01
	6-9 Months	2.17 (1.40, 3.35)	<0.01	2.29 (1.48, 3.54)	<0.01
	9-12 Months	2.30 (1.48, 3.56)	<0.01	2.50 (1.61, 3.87)	<0.01
	12-24 Months	2.66 (1.82, 3.88)	<0.01	3.10 (2.12, 4.53)	<0.01
	24-36 Months	2.37 (1.59, 3.51)	<0.01	3.12 (2.10, 4.64)	<0.01
	36-48 Months	2.33 (1.53, 3.54)	<0.01	3.33 (2.18, 5.07)	<0.01
	48-60 Months	1.66 (1.01, 2.74)	0.05	2.50 (1.51, 4.13)	<0.01
	60-72 Months	1.54 (0.83, 2.86)	0.17	2.67 (1.43, 4.97)	<0.01
	72-84 Months	1.76 (0.68, 4.52)	0.24	3.14 (1.22, 8.12)	0.02

Table 3.4: Mortality rate ratios obtained from fixed effect Poisson regression for stage II patients

Covariates		MRR unadjusted for treatment (95% CI)	p	MRR adjusted for treatment (95% CI))	p
Age at diagnosis					
	15-44	0.28 (0.04, 2.07)	0.21	0.63 (0.08, 4.75)	0.66
	45-54	0.74 (0.36, 1.53)	0.42	1.55 (0.73, 3.30)	0.25
	55-64	0.31 (0.16, 0.58)	<0.01	0.65 (0.34, 1.27)	0.21
	65-74	0.70 (0.42, 1.17)	0.17	0.87 (0.51, 1.46)	0.59
	75+	1.0 (Reference)	---	1.0 (Reference)	---
Sex					
	Female	1.0 (Reference)	---	1.0 (Reference)	---
	Male	0.74 (0.44, 1.22)	0.23	0.88 (0.53, 1.45)	0.61
Age at diagnosis × Sex					
	Male 15-44	3.50 (0.21, 58.92)	0.38	3.53 (0.21, 59.94)	0.38
	Male 45-54	0.47 (0.14, 1.64)	0.24	0.42 (0.12, 1.47)	0.17
	Male 55-64	3.16 (1.44, 6.96)	<0.01	2.31 (1.04, 5.14)	0.04
	Male 65-74	1.26 (0.65, 2.47)	0.49	1.22 (0.63, 2.39)	0.56
Zone					
	Calgary	1.0 (Reference)	---	1.0 (Reference)	---
	Edmonton	1.00 (0.71, 1.42)	0.99	1.17 (0.82, 1.66)	0.39
	North	1.12 (0.67, 1.88)	0.65	1.12 (0.67, 1.87)	0.67
	Central	1.51 (1.00, 2.27)	0.05	1.58 (1.04, 2.39)	0.03
	South	1.56 (0.88, 2.75)	0.13	1.73 (0.98, 3.05)	0.06
Treatments					
	Surgery and Chemotherapy or Radiotherapy	1.0 (Reference)	---		<0.01
	Only Surgery	---	---	1.55 (1.02, 2.35)	0.04
	Both Chemotherapy and Radiotherapy	---	---	2.52 (1.34, 4.72)	<0.01
	Either Chemotherapy or radiotherapy	---	---	4.64 (3.02, 7.14)	<0.01
	No treatment	---	---	4.81 (3.03, 7.64)	<0.01
Follow-Up period					
	1-3 Months	1.0 (Reference)	---	1.0 (Reference)	---
	3-6 Months	1.29 (0.70, 2.38)	0.42	1.36 (0.74, 2.52)	0.32
	6-9 Months	1.52 (0.83, 2.79)	0.18	1.61 (0.88, 2.96)	0.12
	9-12 Months	1.42 (0.75, 2.68)	0.28	1.53 (0.81, 2.90)	0.19
	12-24 Months	1.69 (1.02, 2.82)	0.04	1.93 (1.16, 3.22)	0.01
	24-36 Months	1.52 (0.88, 2.65)	0.14	2.05 (1.17, 3.59)	0.01
	36-48 Months	1.12 (0.58, 2.16)	0.73	1.64 (0.85, 3.20)	0.14
	48-60 Months	1.15 (0.50, 2.64)	0.74	1.77 (0.76, 4.09)	0.18
	60-72 Months	0.69 (0.16, 2.98)	0.62	1.10 (0.25, 4.78)	0.90
	72-84 Months	1.13 (0.15, 8.52)	0.91	1.89 (0.25, 14.36)	0.54

Table 3.5: Mortality rate ratios obtained from fixed effect Poisson regression for stage III patients

Covariates		MRR unadjusted for treatment (95% CI)	p	MRR adjusted for treatment (95% CI))	p
Age at diagnosis					
	15-44	0.88 (0.45, 1.71)	0.71	1.40 (0.72, 2.75)	0.32
	45-54	0.64 (0.50, 0.83)	<0.01	1.07 (0.82, 1.39)	0.61
	55-64	0.58 (0.47, 0.70)	<0.01	0.94 (0.77, 1.15)	0.57
	65-74	0.73 (0.61, 0.87)	<0.01	0.97 (0.81, 1.17)	0.77
	75+	1.0 (Reference)	---	1.0 (Reference)	---
Sex					
	Female	1.0 (Reference)	---	1.0 (Reference)	---
	Male	1.32 (1.13, 1.54)	<0.01	1.37 (1.17, 1.60)	<0.01
Age at diagnosis × Sex					
	Male 15-44	0.55 (0.21, 1.45)	0.23	0.46 (0.17, 1.20)	0.11
	Male 45-54	1.13 (0.79, 1.62)	0.50	0.97 (0.68, 1.39)	0.87
	Male 55-64	1.07 (0.82, 1.40)	0.60	0.89 (0.68, 1.16)	0.38
	Male 65-74	0.91 (0.72, 1.15)	0.44	0.84 (0.67, 1.06)	0.15
Zone					
	Calgary	1.0 (Reference)	---	1.0 (Reference)	---
	Edmonton	1.10 (0.98, 1.24)	0.10	1.03 (0.91, 1.16)	0.66
	North	1.16 (0.98, 1.38)	0.09	1.11 (0.94, 1.32)	0.22
	Central	1.13 (0.97, 1.32)	0.11	1.06 (0.91, 1.24)	0.46
	South	1.33 (1.11, 1.59)	<0.01	1.28 (1.07, 1.53)	0.01
Treatments					
	Surgery and Chemotherapy or Radiotherapy	1.0 (Reference)	---		<0.01
	Only Surgery	---	---	1.22 (0.83, 1.81)	0.31
	Both Chemotherapy and Radiotherapy	---	---	1.99 (1.49, 2.66)	<0.01
	Either Chemotherapy or radiotherapy	---	---	4.37 (3.31, 5.77)	<0.01
	No treatment	---	---	5.16 (3.87, 6.87)	<0.01
Follow-Up period					
	1-3 Months	1.0 (Reference)	---	1.0 (Reference)	---
	3-6 Months	1.36 (1.16, 1.60)	<0.01	1.41 (1.20, 1.66)	<0.01
	6-9 Months	1.56 (1.32, 1.85)	<0.01	1.68 (1.42, 1.98)	<0.01
	9-12 Months	1.36 (1.13, 1.64)	<0.01	1.51 (1.26, 1.83)	<0.01
	12-24 Months	1.42 (1.22, 1.65)	<0.01	1.67 (1.44, 1.94)	<0.01
	24-36 Months	1.10 (0.90, 1.35)	0.34	1.39 (1.13, 1.70)	<0.01
	36-48 Months	0.73 (0.54, 0.99)	0.05	0.99 (0.73, 1.35)	0.95
	48-60 Months	0.75 (0.49, 1.14)	0.18	1.09 (0.72, 1.66)	0.68
	60-72 Months	0.60 (0.30, 1.22)	0.16	0.86 (0.43, 1.74)	0.68
	72-84 Months	0.37 (0.05, 2.64)	0.32	0.51 (0.07, 3.61)	0.50

Table 3.6: Mortality rate ratios obtained from fixed effect Poisson regression for stage IV patients

Covariates		MRR unadjusted for treatment (95% CI)	p	MRR adjusted for treatment (95% CI))	p
Age at diagnosis					
	15-44	0.75 (0.53, 1.06)	0.10	0.85 (0.60, 1.20)	0.35
	45-54	0.81 (0.69, 0.95)	0.01	0.99 (0.84, 1.17)	0.93
	55-64	0.78 (0.68, 0.89)	<0.01	0.94 (0.82, 1.08)	0.38
	65-74	0.91 (0.80, 1.03)	0.13	0.99 (0.87, 1.12)	0.82
	75+	1.0 (Reference)	---	1.0 (Reference)	---
Sex					
	Female	1.0 (Reference)	---	1.0 (Reference)	---
	Male	1.17 (1.04, 1.32)	0.01	1.22 (1.08, 1.38)	<0.01
Age at diagnosis × Sex					
	Male 15-44	0.72 (0.41, 1.25)	0.24	0.77 (0.44, 1.34)	0.35
	Male 45-54	0.99 (0.79, 1.26)	0.96	0.94 (0.74, 1.19)	0.61
	Male 55-64	1.13 (0.94, 1.36)	0.18	1.04 (0.87, 1.25)	0.64
	Male 65-74	1.04 (0.87, 1.23)	0.69	1.01 (0.85, 1.20)	0.90
Zone					
	Calgary	1.0 (Reference)	---	1.0 (Reference)	---
	Edmonton	1.09 (1.00, 1.18)	0.05	1.10 (1.01, 1.19)	0.02
	North	1.11 (0.99, 1.25)	0.08	1.12 (1.00, 1.27)	0.06
	Central	1.07 (0.96, 1.19)	0.21	1.08 (0.97, 1.20)	0.15
	South	1.17 (1.02, 1.34)	0.03	1.19 (1.03, 1.36)	0.01
Treatments					
	Surgery and Chemotherapy or Radiotherapy	1.0 (Reference)	---		<0.01
	Only Surgery	---	---	0.93 (0.42, 2.06)	0.87
	Both Chemotherapy and Radiotherapy	---	---	2.63 (1.39, 4.97)	<0.01
	Either Chemotherapy or radiotherapy	---	---	4.12 (2.21, 7.69)	<0.01
	No treatment	---	---	5.39 (2.89, 10.05)	<0.01
Follow-Up period					
	1-3 Months	1.0 (Reference)	---	1.0 (Reference)	---
	3-6 Months	1.20 (1.10, 1.31)	<0.01	1.25 (1.14, 1.36)	<0.01
	6-9 Months	0.94 (0.84, 1.05)	0.26	0.99 (0.89, 1.10)	0.81
	9-12 Months	0.86 (0.75, 0.98)	0.02	0.90 (0.79, 1.03)	0.13
	12-24 Months	0.62 (0.55, 0.70)	<0.01	0.66 (0.59, 0.74)	<0.01
	24-36 Months	0.37 (0.30, 0.46)	<0.01	0.41 (0.33, 0.51)	<0.01
	36-48 Months	0.26 (0.18, 0.38)	<0.01	0.29 (0.20, 0.42)	<0.01
	48-60 Months	0.31 (0.18, 0.53)	<0.01	0.34 (0.20, 0.58)	<0.01
	60-72 Months	0.19 (0.06, 0.58)	<0.01	0.23 (0.07, 0.71)	0.01
	72-84 Months	0 (0, 0)	<0.01	0 (0, 0)	<0.01

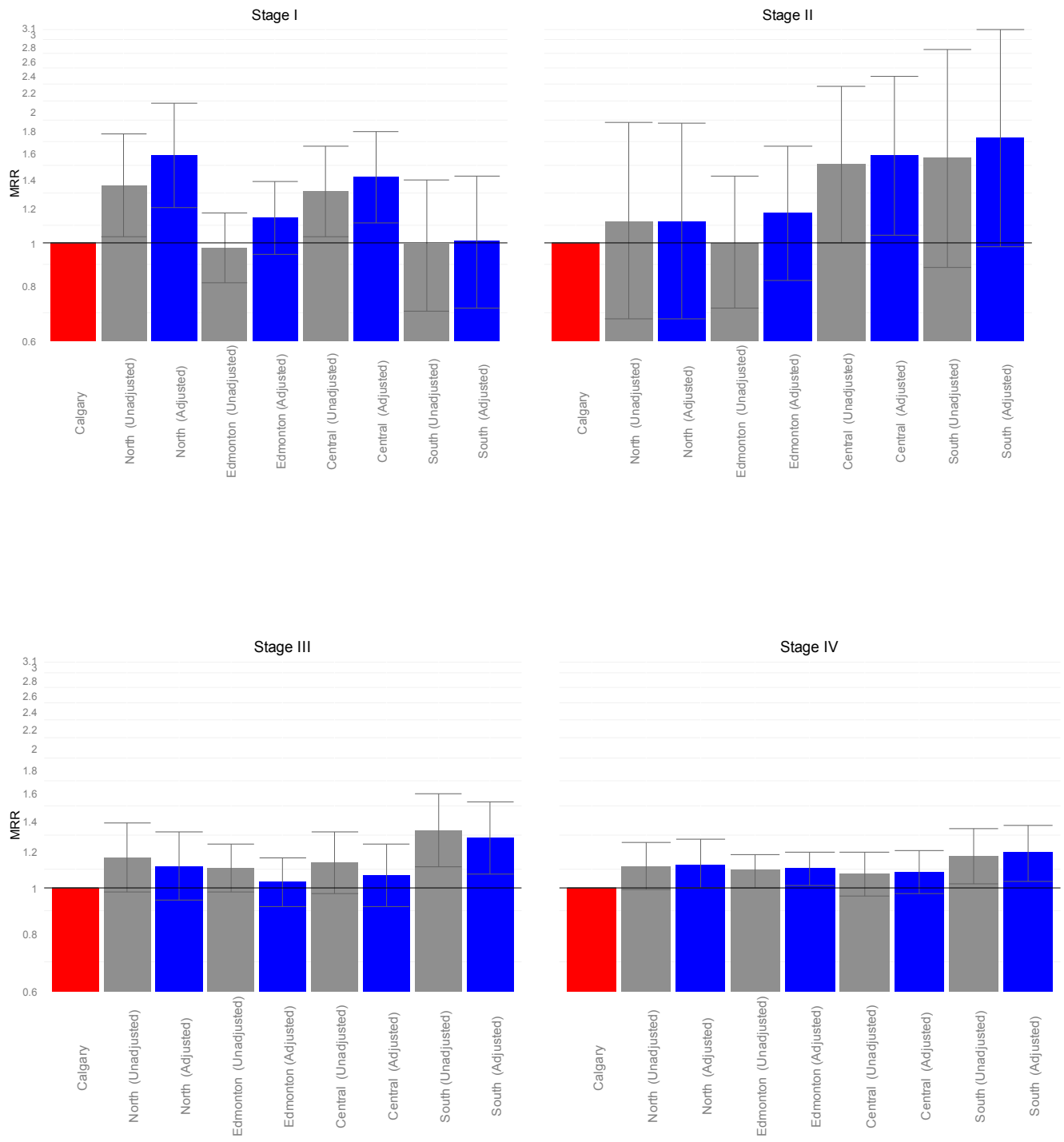

Figure 3.1: Adjusted mortality rate ratios of non-small cell lung cancer patients with 95% confidence intervals by stage, adjusted for age, sex, and follow-up time (grey bars) and also adjusted for treatment (blue bars)

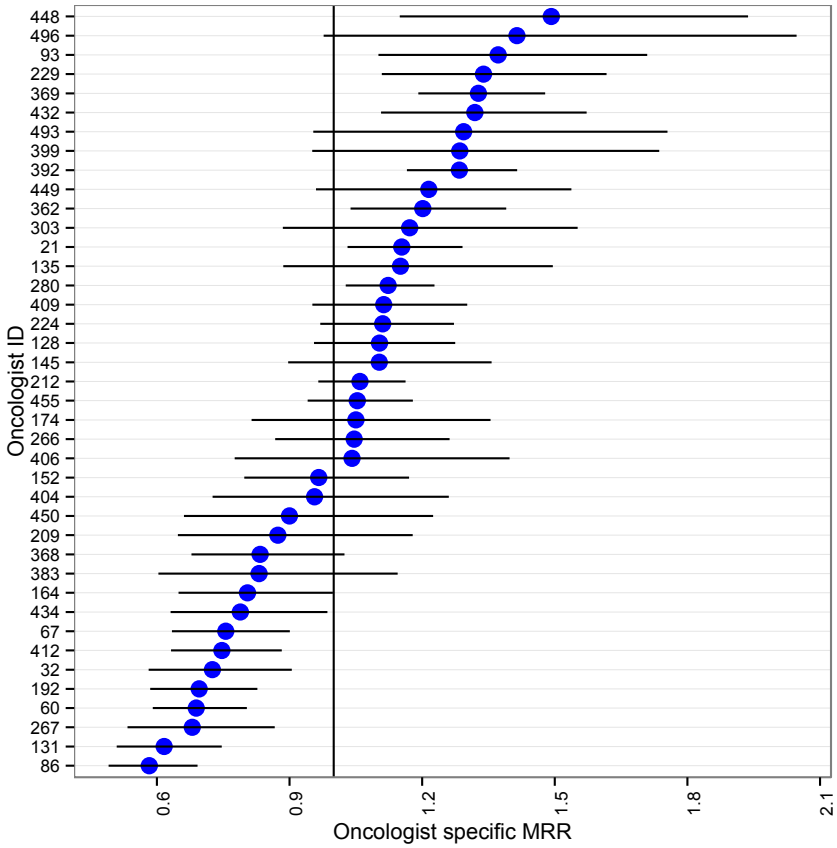

Figure 3.2: Mortality rate ratios and 95% confidence intervals by oncologist (with at least 10 patients per stage) adjusted for age and sex interaction, stage and follow-up time

3.5 Appendix

Table 3.7: Mortality rate ratios obtained from fixed effect Poisson regression for stage I-III patients with zone-treatment interaction

		Stage I (MRR)	P	Stage II (MRR)	P	Stage III (MRR)	P
Age at diagnosis							
	15-44	0.35 (0.05, 2.48)	0.29	0.43 (0.06, 3.35)	0.42	1.42 (0.72, 2.78)	0.31
	45-54	0.53 (0.28, 1.00)	0.05	1.79 (0.80, 3.97)	0.15	1.05 (0.81, 1.37)	0.70
	55-64	0.80 (0.55, 1.14)	0.22	0.65 (0.32, 1.30)	0.23	0.95 (0.77, 1.16)	0.60
	65-74	0.83 (0.63, 1.10)	0.19	0.92 (0.53, 1.59)	0.76	0.98 (0.82, 1.18)	0.84
	75+	1.00 (Reference)	--	1.00 (Reference)	--	1.00 (Reference)	--
Sex							
	Female	1.00 (Reference)	--	1.00 (Reference)	--	1.00 (Reference)	--
	Male	1.49 (1.20, 1.87)	<0.01	0.99 (0.58, 1.69)	0.98	1.38 (1.18, 1.61)	<0.01
Age at diagnosis × Sex							
	Male 15-44	6.17 (0.55, 69.28)	0.14	5.09 (0.28, 90.99)	0.27	0.43 (0.16, 1.13)	0.09
	Male 45-54	1.06 (0.43, 2.66)	0.89	0.44 (0.12, 1.61)	0.21	0.99 (0.69, 1.41)	0.94
	Male 55-64	0.98 (0.61, 1.57)	0.93	2.20 (0.95, 5.09)	0.07	0.89 (0.68, 1.16)	0.37
	Male 65-74	1.04 (0.73, 1.48)	0.84	1.14 (0.56, 2.30)	0.73	0.83 (0.66, 1.04)	0.11
Zone							
	Calgary	1.00 (Reference)	--	1.00 (Reference)	--	1.00 (Reference)	--
	Edmonton	0.95 (0.45, 2.00)	0.90	1.03 (0.49, 2.16)	0.95	2.06 (0.99, 4.27)	0.05
	North	1.42 (0.54, 3.71)	0.47	0.95 (0.31, 2.96)	0.93	1.12 (0.41, 3.09)	0.82
	Central	0.99 (0.40, 2.45)	0.98	2.11 (0.90, 4.95)	0.09	1.55 (0.59, 4.08)	0.37
	South	0.40 (0.05, 3.02)	0.37	1.23 (0.27, 5.60)	0.79	4.25 (1.54, 11.7)	0.01
Treatment							
	Surgery and Chemotherapy or Radiotherapy	1.00 (Reference)	--	1.00 (Reference)	--	1.00 (Reference)	--
	Both Chemotherapy and Radiotherapy	3.54 (0.80, 15.72)	0.10	1.92 (0.65, 5.64)	0.23	3.20 (1.67, 6.11)	<0.01
	Only Surgery	0.95 (0.53, 1.71)	0.87	1.47 (0.60, 3.61)	0.40	1.47 (0.65, 3.30)	0.36
	Either Chemotherapy or radiotherapy	2.89 (1.59, 5.27)	0.00	4.69 (2.28, 9.64)	<0.01	7.24 (3.83, 13.67)	<0.01
	No treatment	4.67 (2.59, 8.44)	0.00	5.23 (2.28, 12.00)	<0.01	7.48 (3.92, 14.27)	<0.01
Zone × Treatment							
	Edmonton & Both Chemotherapy and Radiotherapy	3.00 (0.24, 38.22)	0.40	4.78 (1.09, 20.95)	0.04	0.51 (0.23, 1.11)	0.09
	Edmonton and Only Surgery	0.86 (0.38, 1.95)	0.71	1.07 (0.35, 3.24)	0.91	0.50 (0.18, 1.41)	0.19

Edmonton & Either Chemotherapy or radiotherapy	1.71 (0.73, 3.98)	0.22	1.15 (0.44, 3.04)	0.77	0.47 (0.22, 0.99)	0.05
Edmonton & No treatment	1.34 (0.60, 2.98)	0.48	0.97 (0.32, 2.91)	0.96	0.52 (0.24, 1.11)	0.09
North & Both Chemotherapy and Radiotherapy	0.85 (0.06, 11.37)	0.91	0.88 (0.08, 10.25)	0.92	1.03 (0.34, 3.05)	0.96
North and Only Surgery	0.90 (0.31, 2.59)	0.84	1.98 (0.40, 9.83)	0.41	2.26 (0.61, 8.43)	0.22
North & Either Chemotherapy or radiotherapy	1.43 (0.43, 4.79)	0.56	0.82 (0.19, 3.55)	0.79	0.91 (0.32, 2.58)	0.86
North & No treatment	1.21 (0.42, 3.46)	0.73	1.68 (0.35, 8.03)	0.52	1.04 (0.36, 3.03)	0.94
Central & Both Chemotherapy and Radiotherapy	0 (0,INF)	0.98	0.27 (0.03, 2.89)	0.28	0.71 (0.25, 1.98)	0.51
Central and Only Surgery	1.35 (0.49, 3.69)	0.56	0.86 (0.25, 3.04)	0.82	2.05 (0.54, 7.75)	0.29
Central & Either Chemotherapy or radiotherapy	1.17 (0.41, 3.29)	0.77	0.82 (0.25, 2.75)	0.75	0.54 (0.20, 1.45)	0.22
Central & No treatment	1.75 (0.65, 4.71)	0.26	0.51 (0.15, 1.72)	0.28	0.84 (0.31, 2.29)	0.73
South & Both Chemotherapy and Radiotherapy	NA	NA	1.96 (0.14, 28.06)	0.62	0.18 (0.06, 0.56)	0.00
South and Only Surgery	2.14 (0.26, 17.87)	0.48	0.91 (0.12, 7.00)	0.93	0.42 (0.08, 2.11)	0.29
South & Either Chemotherapy or radiotherapy	3.73 (0.45, 31.17)	0.22	1.56 (0.26, 9.46)	0.63	0.30 (0.11, 0.87)	0.03
South & No treatment	2.43 (0.29, 20.01)	0.41	1.86 (0.29, 11.98)	0.51	0.35 (0.12, 1.01)	0.05
Follow-up period						
1-3 Months	1.00 (Reference)	--	1.00 (Reference)	--	1.00 (Reference)	--
3-6 Months	1.92 (1.23, 2.99)	<0.01	1.37 (0.74, 2.54)	0.31	1.42 (1.20, 1.67)	<0.01
6-9 Months	2.29 (1.48, 3.55)	<0.01	1.63 (0.89, 3.00)	0.12	1.69 (1.43, 1.99)	<0.01
9-12 Months	2.50 (1.61, 3.88)	<0.01	1.57 (0.83, 2.96)	0.17	1.52 (1.26, 1.83)	<0.01
12-24 Months	3.13 (2.14, 4.57)	<0.01	2.02 (1.21, 3.38)	0.01	1.68 (1.45, 1.96)	<0.01
24-36 Months	3.17 (2.13, 4.71)	<0.01	2.21 (1.25, 3.88)	0.01	1.40 (1.15, 1.72)	<0.01
36-48 Months	3.38 (2.22, 5.15)	<0.01	1.81 (0.92, 3.53)	0.08	1.00 (0.74, 1.37)	0.98
48-60 Months	2.55 (1.54, 4.21)	<0.01	1.92 (0.82, 4.47)	0.13	1.12 (0.73, 1.70)	0.61
60-72 Months	2.70 (1.45, 5.04)	<0.01	1.21 (0.28, 5.29)	0.80	0.89 (0.44, 1.81)	0.75
72-84 Months	3.14 (1.21, 8.11)	0.02	2.04 (0.27, 15.66)	0.49	0.56 (0.08, 4.01)	0.57

Table 3.8: Adjusted mortality rate ratios from Poisson regression from mixed effect model

Covariates	MRR (95% CI)	p
Age at diagnosis		
15-44	0.69 (0.51, 0.92)	0.01
45-54	0.69 (0.60, 0.78)	<0.01
55-64	0.67 (0.61, 0.75)	<0.01
65-74	0.81 (0.74, 0.90)	<0.01
75+	1.00 (Reference)	--
Sex		
Female	1.00 (Reference)	--
Male	1.21 (1.11, 1.32)	<0.01
Age at diagnosis × Sex		
Male 15-44	0.69 (0.44, 1.09)	0.11
Male 45-54	1.05 (0.87, 1.26)	0.77
Male 55-64	1.14 (0.99, 1.31)	0.07
Male 65-74	1.02 (0.90, 1.15)	0.94
Zone		
Calgary	1.00 (Reference)	--
Edmonton	1.07 (0.94, 1.22)	0.30
North	1.10 (0.99, 1.23)	0.08
Central	1.19 (0.98, 1.22)	0.11
South	1.16 (1.02, 1.31)	0.02
Stage at diagnosis		
Stage I	1.00 (Reference)	--
Stage II	1.89 (1.62, 2.21)	<0.01
Stage III	3.95 (3.59, 4.34)	<0.01
Stage IV	8.42 (7.69, 9.20)	<0.01
Follow-up period		
1-3 Months	1.00 (Reference)	--
3-6 Months	1.24 (1.15, 1.33)	<0.01
6-9 Months	1.12 (1.03, 1.21)	0.01
9-12 Months	1.01 (0.92, 1.12)	0.55
12-24 Months	0.95 (0.88, 1.03)	0.34
24-36 Months	0.76 (0.68, 0.85)	<0.01
36-48 Months	0.61 (0.52, 0.72)	<0.01
48-60 Months	0.56 (0.44, 0.70)	<0.01
60-72 Months	0.46 (0.32, 0.66)	<0.01
72-84 Months	0.43 (0.20, 0.90)	0.04

Table 3.9: Characteristics of patients who did not survive more than 30 days in Alberta from 2004-2010

Variable		Calgary (%[+])	Edmonton (%)	North (%)	Central (%)	South (%)
Age at diagnosis						
	15-44	4 (1%)	3 (1%)	2 (1%)	1 (1%)	2 (2%)
	45-54	20 (6%)	21 (5%)	6 (4%)	10 (5%)	10 (10%)
	55-64	53 (16%)	92 (20%)	39 (27%)	23 (12%)	15 (16%)
	65-74	102 (32%)	143 (32%)	49 (34%)	61 (31%)	29 (30%)
	75+	143 (44%)	190 (42%)	49 (34%)	99 (51%)	40 (42%)
Sex						
	Female	136 (42%)	173 (39%)	58 (40%)	89 (46%)	37 (39%)
	Male	186 (58%)	276 (61%)	87 (60%)	105 (54%)	59 (61%)
Stage at diagnosis						
	I	17 (5%)	18 (4%)	6 (4%)	7 (4%)	6 (6%)
	II	4 (1%)	1 (0%)	0 (0%)	3 (2%)	2 (2%)
	III	50 (16%)	80 (18%)	20 (14%)	34 (18%)	17 (18%)
	IV	230 (71%)	327 (73%)	112 (77%)	134 (69%)	58 (60%)
	Unknown/occult	21 (7%)	23 (5%)	7 (5%)	16 (8%)	13 (14%)
Treatments						
Surgery with chemotherapy or radiotherapy		1 (0%)	0 (0%)	0 (0%)	1 (1%)	1 (1%)
Only Surgery		8 (2%)	12 (3%)	6 (4%)	2 (1%)	3 (3%)
Both chemotherapy and radio therapy		4 (1%)	4 (1%)	1 (1%)	1 (1%)	1 (1%)
Either Chemotherapy or radiotherapy		38 (12%)	59 (13%)	17 (12%)	22 (11%)	8 (8%)
No treatment		271 (84%)	374 (83%)	121 (83%)	168 (87%)	83 (86%)

+ The percentages are given by column variable

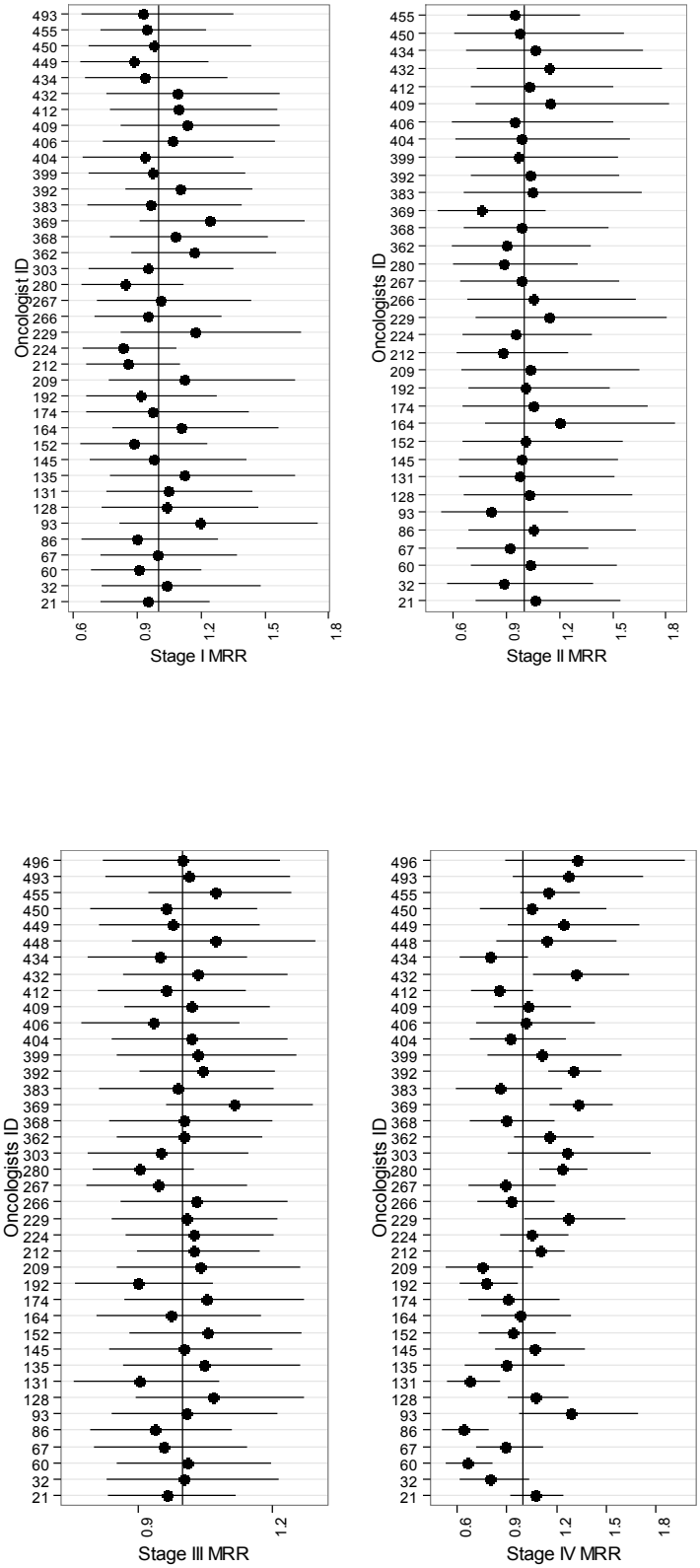

Figure 3.3: Stage-specific mortality rate ratios by oncologist with 95% confidence intervals

3.6 References

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Chapter 4 : Discussion and Conclusion

4.1 Discussion

4.1.1 Discussion of Chapter 2

Disparity in the survival of lung cancer patients across the provinces of Canada was reported by Coleman *et al.*[1]: Alberta lung cancer patients had lower survival than their counterparts in British Columbia, Ontario and Manitoba. In addition, the survival improvement was lowest in Alberta during 1995-2007[1]. To explore the causes of this, we conducted our first study. We evaluated the variation in mortality rates of lung cancer patients across the geographical zones of Alberta and compared it to the race-registry disparity found in the mortality rates of the US lung cancer patients diagnosed between 2004 and 2010.

At first, we investigated whether there was any disparity in the stages of diagnosis across all race-registry combinations of the US and the geographical zones of Alberta. The results showed that in the US registries the proportion of black patients diagnosed with stage III and IV (68%-75%) was higher than their white counterparts (60%-67%). In Alberta, however, stage at diagnosis of lung cancer patients did not differ across the geographical zones.

After adjusting for age, sex and follow-up time, including all stages but unadjusted for stage, patients of North, Edmonton, Central and South zones had higher mortality rates (MRR = 1.06 – 1.19) than Calgary patients: as expected, adjusting for stage did not change this result. White patients of all the registries except New Mexico (MRR = 1.10) and Utah (MRR = 1.12) had either lower or approximately the same (MRR = 0.89 - 1.04) mortality rates as Calgary patients, however black patients of most of the SEER registries had higher mortality rates (MRR

= 1.11 – 1.21); the only exception was black patients in Connecticut (MRR = 0.95). Black patients of all SEER registries had higher mortality rates than their white counterparts. The disparity between black and white patients reduced after the MRRs were additionally adjusted for stage, as expected given the stage differences between US SEER blacks and whites.

The degree of disparities in stage-unadjusted mortality rates between blacks and whites were similar to the degree of disparities across the Alberta zones. While the disparity of the mortality rates between black and white patients was reduced after adjusting for stage at diagnosis, the disparity pattern and degree did not change after adjusting for stage across the geographical zones of Alberta. These results indicate that the disparity of mortality rates in Alberta lung cancer patients that is not explained by delayed-diagnosis/advanced-stage effects is greater than the black-white disparity in the US SEER lung cancer patients that is not explained by delayed-diagnosis/advanced-stage effects. The disparity between blacks and whites in the US are often explained in relation to their socioeconomic differences[2-6]. Since, the US healthcare system is not publicly funded; disparities in access to healthcare by socioeconomic status exist. This disparity often appears in studies as differences between blacks and whites[2-6]. On the other hand, it has been shown that mortality risk due to lung cancer was approximately the same for black and white lung cancer patients in the US military health system (MHS), where everybody has equal access to the healthcare system[7]. These are consistent with the explanation that the observed disparity in the stage of diagnosis between US black and white patients, and its resulting disparity in their lung cancer mortality rates, is associated with socioeconomic disparity in the US. This explanation did not apply to the disparity across geographical zones of Alberta where the healthcare system is publicly funded and stage distribution is the same.

It was observed that mortality rates of lung cancer patients of North, Central and South zones were statistically significantly higher than the mortality rates of the Calgary patients for both adjusted and unadjusted for stage. However, patients from Edmonton did not have statistically significantly different mortality rates than those of Calgary in either analysis. The disparity in the MRRs across the zones of Alberta can be summarized as differences between the urban and rural zones. The explanation of this disparity is not as straightforward as the US since, unlike the US, Canada has a publicly funded healthcare system. Every patient included in this study from Alberta has the free access to the healthcare system. Delayed diagnosis for rural area patients was not observed relative to metropolitan area patients: the distributions of the stage of diagnosis were similar across the zones of Alberta.

The disparity in mortality rates of lung cancer patients across the zones of Alberta was similar to the disparity in mortality rates of black and white lung cancer patients in the US: the former was not due to delayed diagnosis. The disparity across the zones of Alberta is concerning. Since, delayed diagnosis did not explain the disparity, further investigations are needed to evaluate indicators of Alberta's lung cancer care system to pinpoint specific reasons of this disparity across the zones of Alberta. Proper steps need to be taken by decision makers, cancer health service providers and cancer researchers to identify and eliminate sources of disparity, and improve survival of lung cancer patients in Alberta.

4.1.2 Discussion of Chapter 3

The first objective of the second study was to assess geographical disparity in the mortality rates among non-small-cell lung cancer (NSCLC) patients across the zones of Alberta, with and without taking treatment effect into consideration. The second objective was to evaluate whether

the mortality rates of NSCLC patients vary by oncologist and if so to what degree. Patients diagnosed in Alberta between 2004-2010 with stage I-IV NSCLC were investigated.

First, geographical zone specific mortality rates adjusted and unadjusted for the combinations of treatment, controlling for age, sex and follow-up time were calculated; Calgary was the reference zone. We observed three scenarios: decrease, unchanged and increase in zone-specific MRRs before and after treatment adjustment. For example, MRRs of stage III patients of all zones decreased relative to Calgary after adjusting for treatment. These indicate that stage III patients in all zones except Calgary received less effective treatment (to reduce mortality rates) than the Calgary stage III patients. Also, compared to other zones, in Calgary a higher proportion of patients received treatments that are consistent with treatment guidelines. In these scenarios if the patients of the zones received similar treatment as the Calgary patients then the geographical disparity would reduce. Although treatments, which include surgery ("surgery with chemotherapy or radiotherapy" and "surgery only") were the most effective treatments to reduce mortality (MRR = 1.00 – 1.22) for stage III patients in Alberta, most patients in all the zones (85% - 93%) did not receive these treatments. Among the other treatments "both chemotherapy and radiotherapy" was the most effective (MRR = 1.99) and is standard treatment when surgery is not an option. Calgary stage III patients received the highest proportion of this treatment (24%) compared to the other zones (16% - 23%). Unchanged MRRs after adjusting for treatment in a zone suggests that the patients of that zone received similarly effective treatments to reduce mortality as the patients of Calgary. For example, stage I patients of the South and stage II patients of the North zones had unchanged MRRs after adjusting for treatment. An increase in MRR of a specific zone suggests that the patients of that zone received more effective treatment to reduce mortality than the Calgary patients. This scenario was observed in stage I and II

patients of Edmonton. For stage I and stage II patient treatments which included surgery (consistent with treatment guidelines) were the most effective in reducing mortality rates (MRR = 0.95 – 1.55) than the treatments that did not include surgery (MRR = 2.52- 6.02). Calgary stage I and II patients were less likely to receive surgery (62% and 52% respectively for stage I and II) compared to their counterparts in Edmonton (75% and 69% respectively for stage I and II). Although patients of Edmonton received treatment more consistent with guidelines than the Calgary patients, the patients of Edmonton have higher mortality rates than their counterparts in Calgary even after adjusting for many factors, for which there was no apparent reason found in this study.

In these analyses treatment effects were assumed to be constant across the zones, i.e., there was no interaction. To assess whether this assumption was reasonable or not, we ran the fixed effect Poisson regression allowing the interaction of zones and treatments, adjusted for age and sex interaction, and follow-up time for stage I-III. We did not detect statistically significant interaction, although the power was limited for this test.

Differences were observed in received treatments for the NSCLC patients across the zones of Alberta. The disparity in the mortality rates across zones is attributable partly to these differences of treatment received by the patients across zones but not entirely. Further investigations are needed to assess the underlying reasons for the disparity in receiving treatment.

To assess whether the mortality rates of NSCLC patients vary by oncologist we computed zone specific MRRs compared to Calgary, adjusting for age, sex, stage and follow-up time, considering oncologist-specific effect as random. There was a clear indication of

differences in oncologist-specific mortality rates. This disparity was also observed for each specific stage. The oncologist level disparity partially explained the geographical disparity, but not entirely. A possible reason could be that there existed disparity in receiving oncologist consultation for the patients of different zones; another possibility is that patients of different zones prefer different treatments. Given the treatment guidelines for NSCLC, little disparity in oncologist level MRRs is expected.

Results obtained from this study provide some valuable information to cancer care providers, decision makers, and researchers for removing the observed geographical disparity within Alberta, improving patients survival and reducing the discrepancy of lung cancer patients survival between Alberta and the other provinces of Canada. The analyses conducted in this study explained the geographical disparity across the zones of Alberta to some extent. Further investigations including interventions, however, are needed to explain the total disparity.

4.2 Recommendations and Future Research

- Further investigation is required to identify the other possible sources of disparity in the mortality of the lung cancer patients across the zones of Alberta. One of the sources could be the waiting time before receiving a treatment. For example, surgery is only provided in Calgary and Edmonton. Thus, patients from other zones need to travel to these cities. These distances may delay the time to receive the proper treatments compared to Edmonton and Calgary patients.

- Investigation of the socio economic status of the patients and life expectancy of the residents in the geographical zones are necessary.

- Clinical trials could be conducted to investigate and improve the existing treatment guidelines. Evaluation of more specific treatments for each specific stage (i.e., specific chemotherapies, surgeries and other treatments) could be one important objective.

4.3 Conclusion

Disparities in the mortality rates of NSCLC patients in Alberta exist across its zones. Addressing these disparities will likely diminish the differences with the other provinces of Canada.

The investigations in this study were conducted to identify the reasons behind the existing disparity in the lung cancer mortality rates of Alberta. Some of the sources of disparity were successfully identified, however, more investigations are needed to pinpoint the sources and diminish the disparities.

4.4 References

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