Spring 5-5-2018

# The Survival and Treatment Refusal of Lung Cancer Patients: Analyses of National Cancer Registries

Poppy Deviany
*University of Nebraska Medicial Center*

# THE SURVIVAL AND TREATMENT REFUSAL OF LUNG CANCER PATIENTS: ANALYSES OF NATIONAL CANCER REGISTRIES

by

Poppy E. Deviany, MPH

A DISSERTATION

Presented to the Faculty of
the University of Nebraska Graduate College
in Partial Fulfillment of the Requirements
for the Degree of Doctor of Philosophy

Epidemiology Graduate Program

Under the Supervision of KM. Monirul Islam, MD, MPH, PhD

University of Nebraska Medical Center
Omaha, Nebraska

April, 2018

Supervisory Committee:

Shinobu Watanabe-Galloway, PhD  Gleb R. Haynatzki, PhD  Apar K. Ganti, MD, MS, FACP

# ACKNOWLEDGEMENTS

I would like to thank the many people that have supported me in the writing of this dissertation.

First, I would like to thank my supervisory committee members, Drs. KM Monirul Islam, Shinobu Watanabe-Galloway, Gleb R. Haynatzki and Apar K. Ganti, who have been supportive from the initiation phase until the final writing of this dissertation.

I would like to thank Dr. Deborah A. Levy and the faculties in Department of Epidemiology for all their supports during my time in the program.

Thank you to Drs. Veenu Minhas and Jennie L. Hill for the experiences as teaching assistant in the online and in-campus epidemiology classes.

To Dr. Ann Fetrick and Ms. June Ryan for the experience working together in the PCORI lung cancer grant lead by Dr. Islam.

Thanks to all of my colleague and friends in Jakarta (Center for Family Welfare - University of Indonesia), Omaha (Lata Nawal, Tran Vu Hoang, Hong Van Do, Nitin Fafat, Zijian "Egg" Qin, Kate Rieke, Zaeema Naveed, and many more that I am really grateful to know and consider them as family in the foreign land).

Very special thanks to my family in Medan and Depok, Indonesia for the continues understanding, supports, and sacrifice during my time to pursue my dreams in the United States.

To Trisari Anggondowati, a wonderful auntie to Divira and a bestie that I can always rely on.

To my Papa, alm. S. Damanik, who made me promise to pursue PhD in the US and to Mama Lina for her love, encouragement and trust in me.

To my dear husband, Dimas Her Prabowo, who always believe in me though out this time, we shared this 'degree' together.

Finally, this dissertation is dedicated to my dear daughter, Divira Merinska Prabowo (May 20$^{th}$ – June 25$^{th}$ 2017).

# TABLE OF CONTENTS

# LIST OF TABLES

# LIST OF FIGURES

# LIST OF ABBREVIATIONS

| | |
|---|---|
| ACS | American Cancer Society |
| ACoS | American College of Surgeons |
| AJCC | American Joint Committee on Cancer |
| AOR | Adjusted Odds Ratio |
| CDCC | Charlson/Deyo Comorbid Conditions |
| CoC | Commission on Cancer |
| CI | Confidence Interval |
| CT | Computed Tomography |
| ES-SCLC | Extensive Stage-Small Cell Lung Cancer |
| HR | Hazard Ratio |
| IARC | International Agency for Research on Cancer |
| IASLC | International Association for the Study of Lung Cancer |
| ICD-O-3 | International Classification of Disease for Oncology Third Edition |
| LS-SCLC | Limited Stage-Small Cell Lung Cancer |
| MRI | Magnetic Resonance Imaging |
| NSCLC | Non-Small Cell Lung Cancer |
| NCDB | National Cancer Database |
| PAH | Polycyclic Aromatic Hydrocarbon |
| PH | Proportional Hazards |
| OR | Odds Ratio |
| SCLC | Small Cell Lung Cancer |
| SEER | Surveillance Epidemiology and End Results |
| US | The United States |

| | |
|---|---|
| USCS | United States Cancer Statistics |
| VA | Veterans Affairs |
| VACCR | Veteran’s Affairs Central Cancer Registry |
| VHA | Veterans Health Administration |
| WHO | World Health Organization |

# ABSTRACT

## THE SURVIVAL AND TREATMENT REFUSAL OF LUNG CANCER PATIENTS: ANALYSES OF NATIONAL CANCER REGISTRIES

Poppy E. Deviany

University of Nebraska, 2018

Supervisor: KM. Monirul Islam, MD, MPH, PhD

Lung cancer is the second most commonly diagnosed cancer and the leading cause of cancer mortality of both genders in the United States. A recent report suggests that the relative five-year survival rate of lung cancer is only 18%. Studies indicate many factors are associated with the survival of lung cancer patients, including age at diagnosis. It is widely known as a disease of older people, but the literature shows a substantial number of young people have been diagnosed with lung cancer. The literature also indicates that the refusal of recommended treatment contributes to cancer-related death and poorer survival. The objectives of this dissertation were to estimate the survival of lung cancer patients, examine the effect of treatment refusal on survival, and investigate factors associated with treatment refusal. To address these objectives, we conducted our analyses using two large cancer databases: the Veterans Affairs Central Cancer Registry and the National Cancer Database. We performed statistical data analyses using logistic regression, the Kaplan–Meier survival estimator, and Cox regression (proportional hazards regression) method. The results indicate a better five-year survival among younger-onset patients compared with older-onset patients, particularly among early-stage cancer. In the multivariable analyses, treatment refusal was associated with higher mortality risk. Furthermore, our results suggested that patients of older age at diagnosis, female gender, with comorbid conditions, and uninsured status were more likely to refuse recommended lung cancer treatment. In this

dissertation, we could not analyze other relevant factors, such as types of comorbidity, patient's performance status, treatment side effects, family history of lung cancer, and cost of treatment, due to data limitation. Adjusting such factors in future studies will provide a more robust comparison of survival and genetic differences between younger- and older-onset lung cancer cases. Future studies should also examine patients' and clinical aspects of cancer education and patient–physician communication materials to improve patient acceptance of lung cancer treatment.

# CHAPTER 1

# INTRODUCTION

## Lung Cancer

Lung cancer begins with an abnormal growth of cells of the lung. The disease develops following a series of pathological changes in the respiratory epithelium.[1] In theory, lung cancer grows from a single malignant cell into a detectable lesion.[2] At the time of diagnosis, the majority of the lung cancer patients are symptomatic. The most common initial symptom is a cough, especially if the cancer grows in the central air-way.[1,2] When the cancer is located in the peripheral part, however, the cough may manifest as a late symptom. Other symptoms include bronchorrhea, fever, chills, purulent sputum production, dyspnea, chest pain, hemoptysis, wheeze, and stridor.[3] The literature suggests that the local tumor growth, regional extension, metastases, and a combination of mechanisms causes tumor-associated symptoms.[3]

## Epidemiology of Lung Cancer

Globally, lung cancer has had a significant impact on morbidity and mortality for decades. The disease has been reported as the most common cancer diagnosed worldwide since 1985.[4] The GLOBOCAN report by the International Agency for Research on Cancer (IARC) in 2002 indicated that lung cancer accounted for 12% (1.35 million people) of all invasive cancers diagnosed worldwide.[4] A decade later, the IARC report in 2012 on cancer status worldwide suggested an increase in the incidence of lung cancer to 1.8 million cases.[5] The last report also shows that in 2012 lung cancer was responsible for one in five cancer-related deaths in the world.[5]

Changes in the tobacco epidemic are thought to have affected the global differences in lung cancer rates and trends.[6,7] In countries such as the United States (US) and the United Kingdom, the tobacco epidemic peaked in the middle of the 20th century and the highest incidence of lung cancer rates was reported around that period.[6,8] Lung cancer incidence has declined since the mid-2000s, particularly among men.[8] The increase in lung cancer rates among women is considered to be the reflection of the increased frequency of smoking among women.[5,9,10] In countries where the number of smokers continues to increase, such as China, Indonesia, and countries in Africa, more cases of lung cancer are anticipated in the next few decades.[5,6]

A recent report by the American Cancer Society (ACS) suggests that 234,030 new cases of lung cancer will be diagnosed in 2018 in the US.[11] The estimation indicates that lung cancer contributes to one in seven cancer cases in the country. The report also points out that lung cancer-related deaths account for about 25% of all cancer mortality of both sexes.[11,12] Advancements in lung cancer care, such as the use of low-dose spiral computed tomography for screening and cancer-targeted therapy based on specific tumor molecular characteristics for a treatment option, have contributed to some reduction in disease morbidity and mortality.[5,11,13] However, lung cancer survival remains poor. The estimation made for the five-year relative survival of lung cancer cases in the US in 2018 is 18%.[12] The survival rate varies between early and advanced stages; the five-year survival of local and distant stages were 56% and 5%, respectively.[12] Many epidemiologic studies have suggested that multiple factors affect lung cancer mortality, including, patient characteristics, demographic, tumor clinical, geographic, environmental, and therapeutic factors.[8,14,15]

## Risk Factors of Lung Cancer

A number of risk factors have been associated with lung cancer. Tobacco smoking has been reported as the main risk factor.[16,17] Other risk factors, such as environmental exposures, family history of lung cancer, infection, and other substances exposures, have also suggested an increased risk of lung cancer.[14,16,17] In addition, the shift in smoking patterns has affected individual susceptibility to lung cancer. Evidence of changes in patient characteristics, such as age and gender, associated with the tobacco epidemic has been reported.[17,18] Details on the association of those risk factors and lung cancer are described in the following sections.

### *Cigarette Smoking*

Tobacco mainstream smoke contains a mixture of approximately 4,000 compounds. Of those compounds, studies have reported 60–70 carcinogens, such as polycyclic aromatic hydrocarbons (PAHs), heterocyclic hydrocarbons, *N*-nitrosamines, and *N*-heterocyclic amines.[19,20] Lung cancer involves interactions between carcinogens and lung tissue. For example, the incomplete combustion of tobacco during smoking will produce PAHs, and lung tissue metabolizes these components to form mutagenic DNA adducts.[2,21] The DNA adduct formation in lung tissue is considered the initiating phase of carcinogenesis that leads to lung cancer.[21,22] The risk of lung cancer among smokers was estimated as 20 times higher than never-smokers.[16] Furthermore, findings from case-control and cohort studies summarized in a paper by Alberg et al. indicate the risk of lung cancer increases with the duration of smoking and number of cigarettes smoked per day.[23]

Tobacco smoking is associated with more than 80% of lung cancer cases in the US.[16,17] In studies summarized by Cruz et al., four out of five adult smokers begin to smoke before the age of 18 years in the US.[17] The chronological trend suggests the average time lag between smoking initiation and lung cancer occurrence is approximately 20 years.[16,24] Considering the age of smoking initiation and the time lag for tobacco to cause lung cancer, more smokers who started

smoking as adolescents or young adults may be diagnosed with the disease at a younger age than the current average age of lung cancer cases, that is 70 years. Nevertheless, the number of cigarettes per day also affected this estimation.

*Environmental Exposures*

Occupational exposures have been reported as the second risk factor of lung cancer following cigarette smoking, particularly in industrial countries.[16] In many work settings, workers are exposed to carcinogens, such as asbestos fiber, silica dust, metals including arsenic and chromium, and radiation, which leads to an increased risk of lung cancer and other respiratory diseases.[5,23,25] Studies reviewed in an article by Alberg et al. indicate that asbestos exposure may increase the risk of lung cancer to more than five times higher than non-exposure.[16] The risk was even higher among smokers due to the synergistic effect between smoking and asbestos exposure.[17,26]

Similarly, an increased risk of lung cancer has been suggested due to exposure to high linear energy transfer, such as radon, which was frequently reported among uranium miners.[16,25] Studies reviewed in lung cancer literature suggest that approximately 9–15% of lung cancer cases were associated with radon exposure.[2,16] Radon, a natural soil-derived gas, is also found in residential settings, and its presence may be increasing due to the low ventilation rates in indoor air. A lack of association between indoor radon exposure and lung cancer was suggested by the World Health Organization (WHO) at an exposure level of less than 100 $Bq/m^3$, whereas the recommendation from the Environmental Protection Agency for radon exposure in the US was 148 $Bq/m^3$.[27,28] Studies indicate a significant positive linear trend of radon concentration were associated with the increasing risk of lung cancer.[28-30] For example, a nonsmoker exposed to 200 $Bq/m^3$ has a risk of developing lung cancer 1.5 times higher than those exposed to 100 $Bq/m^3$; an exposure of 400 $Bq/m^3$ would result in three times higher risk.[28] A synergistic effect on risk of lung cancer was also suggested between smoking and radon exposure.[16]

*Family History of Lung Cancer*

Individuals with a positive family history of lung cancer have a higher risk of lung cancer,[31,32] which may suggest the effect of both shared environmental factors and shared genetic factors among family members. Individual factors, such as differences in carcinogen metabolism and detoxification, DNA repair, cell cycle control, and inflammation pathways, have been suggested to modify susceptibility to lung cancer.[2] A meta-analysis of cohort and case-control studies reported that positive family history of lung cancer increased individual risk of lung cancer by 1.63 times; for those aged less than 50 years, the risk was even higher (odds ratio [OR] = 2.08; 95% confidence interval [95% CI]: 1.18–3.63).[31] Findings from other studies corroborate the results of the association between positive family history of lung cancer and lung cancer occurrence, particularly among the young.[32-34] Cote et al. reported that a first-degree relative of a lung cancer case had a 1.51 times higher risk of lung cancer after adjustment for smoking and other covariates (95% CI: 1.39–1.63).[35] The study also reported that the association was strongest when the lung cancer case is a sibling (OR = 1.82; 95% CI: 1.62–2.05).[35]

*Infection*

Studies reviewed in a paper by Cruz et al. suggest that inflammation caused by tuberculosis and tuberculosis-related scar contribute to lung cancer pathogenesis.[17] In addition, patients with HIV infection have been reported to experience a higher risk of lung cancer in comparison to non-HIV infected individuals.[16,36] As a potential explanation of this, Kirk et al. reported a higher proportion of smoking among HIV infected people.[37] This behavior combined with an immunosuppressed condition increased the relative risk of lung cancer 3.6 times among those with HIV infection as compared with those without HIV infection.[36]

*Other Substances*

A cumulative exposure of carcinogens from ambient outdoor air pollution, such as polycyclic aromatic hydrocarbon compound from fossil fuel, may cause inflammation in the respiratory system.[25] In urban or industrialized settings, a significant increase in lung cancer risk has been reported due to increased fine particle concentration from engine emissions.[38,39] Indoor air contamination resulting from cooking combustion and space heating also has been reported by studies, thereby increasing the risk of lung cancer.[16,17]

*Age at Diagnosis*

Diagnosis of lung cancer is common among individuals ages 65–74 years.[12] Currently, the median age at diagnosis of lung cancer in the US is 70 years.[12] Data from 22 population-based central cancer registries in the US over the period of 1995–1999 showed that lung cancer was among the five most common cancers, with a significant increase in the younger age group, particularly people aged 40–49 years.[40] Population-based data has reported around 10% of cases were diagnosed before age 55 years,[12] while facility-based studies reported 12–14% of lung cancer cases occurred before age 50 years.[41-43] The literature suggests that the changes to the median age at diagnosis in lung cancer cases of over 20 years earlier were associated with the smoking epidemic among the young people.[17,23,44]

Previous studies that used the cutoff age at diagnosis as 40–50 years to define younger-onset cases reported differences in patient and tumor characteristics between younger- and older-onset patients. Those diagnosed at less than 50 years of age had higher proportions of advanced stage at diagnosis,[44-46] adenocarcinoma histologic subtype,[47,48] and predisposing genetic factors.[33,49,50]

*Gender*

The association between gender and risk of lung cancer is closely related to cigarette smoking.[17,23] Although smoking prevalence was higher among men than women in the 1940s,[18] after 1950 there was an increase in cigarette smoking among women, leading to the increased incidence of lung cancer in women.[17,18] Studies reviewed by Cruz et al. suggest gender differences in the risk of lung cancer, indicating that a higher susceptibility among women may be due to differences in nicotine metabolism, metabolic activation of lung carcinogens, and hormonal factors between men and women.[17]

## Diagnosis of Lung Cancer

Lung cancer evaluation aims to efficiently and accurately establish the diagnosis and initial extent of the disease. The procedures include a check on medical history and physical examinations, followed by imaging tests and tests to obtain tissue diagnosis and measurement on the extent of disease.[3]

Smoking history, concurrent chronic obstructive pulmonary disease, and previous exposures to certain environmental and occupational carcinogens are obtained from the patient as part of individual medical history.[3] In physical examinations, the patient's general appearance may be normal or may show signs, such as lethargy, pallor, jaundice, or other significant comorbidities.[3] Respiratory examinations may reveal issues with different areas. For example, tachypnea (abnormally rapid breathing) may indicate pleural effusion, post-obstructive pneumonia, or rib metastases; neck palpation may indicate that the cancer has spread to supraclavicular lymph nodes; and bronchial breath sounds and increased fremitus indicate consolidation with patent proximal airways.[3]

The subsequent examination may utilize imaging procedures, including chest radiograph, computed tomography (CT) and magnetic resonance imaging (MRI). Posteroanterior and lateral chest radiograph is usually the first standard test to detect bronchogenic carcinoma.[3,51] The procedure also helps to assess the intrathoracic extent of the cancer, suggest subsequent work-up, and identify other thoracic disease. The literature suggests a wide spectrum of findings from this procedure, including a localized opacity (nodule or mass), pleural effusion, atelectasis, adenopathy, and possible histologic type of lung cancer.[3] A CT procedure has been suggested to greatly enhance the imaging of bronchogenic carcinoma.[17,51] The procedure can further define the primary lesion's appearance, detect simultaneous parenchymal or pleural disease, display lymphangitic spread of malignancy, guide diagnostic maneuvers, and evaluate lymph nodes metastases.[3] In lung cancer evaluation, an MRI is not a routine procedure, although it can detect vascular invasion better than a CT procedure.[3]

The accurate tissue diagnosis is important, not only to establish lung cancer diagnosis but also to develop a treatment plan. In most patients suspected of lung cancer, biopsy procedures are necessary because the clinical and radiographic procedures may not determine small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC).[3] The common techniques used to obtain tissue for cytologic and histopathologic analysis are sputum examinations, flexible fiberoptic bronchoscopy, transthoracic needle aspiration, endoscopic ultrasound, and thoracic surgery.[3]

**Treatment of Lung Cancer**

The treatment plan for lung cancer cases is defined mostly based on the type and stage of cancer.[13] The majority of recommendations are made for NSCLC and SCLC,[13,24] which comprise around 90–95% of total lung cancer cases.[5,7,24]

*Non-small Cell Lung Cancer*

For early-stage cancer (stages I and II) that is operable, surgery and resection are utilized as the primary treatment to provide increased longevity.[24,52] A complete surgical resection, including lobectomy or complete lymph node dissection, should be conducted, particularly when smaller tumors (< 1–2cm) are identified.[53] For patients with inoperable tumors, the options to consider would include radiotherapy and/or chemotherapy.[13,24,52] Durable results, including reduction of toxicity and increase of five-year survival up to 40%, have been reported among medically inoperable patients treated with advanced radiotherapy methods.[53] Promising evidence have been reported in the management of early-stage lung cancer, however, data from clinical observations and cancer registries suggest that the majority (more than 70%) of lung cancer cases are diagnosed at an advanced stage (stages III and IV).[13]

Lung cancer cases with operable stage III may receive multimodality therapy as a standard treatment, such as surgery followed by chemotherapy.[24,53] For inoperable stage III, the treatment recommendation may include a sequential or concurrent combination of chemotherapy and radiotherapy or external radiation alone.[24,52] As cancer progresses to advanced stages, such as stage IV, treatment options might include a combination of chemotherapy, palliative radiation, and targeted therapy.[13,52] Other factors, such as comorbidities, performance status, and genetic factors, are considered for treatment recommendations.[53]

*Small Cell Lung Cancer*

Although small percentages of lung cancer cases are classified as SCLC (13–15%), the disease has specific treatment recommendations as it is considered to be more aggressive and often at wide dissemination at the time of diagnosis than NSCLC.[24,54] Treatment for SCLC is defined according to disease stage, general health, and existing comorbidities.[24,53] The most common treatment option for limited-stage SCLC is a combination of chemotherapy and

radiation or chemotherapy alone; for extensive stage SCLC, the treatment recommendation includes the combination of chemotherapy regimens or chemotherapy alone.[55,56]

**Staging of Lung Cancer**

Cancer staging describes the occurrence or spread of cancer at diagnosis, which is essential in the diagnosis process and development of the treatment plan for lung cancer patients. Cancer staging may help clinicians to identify the appropriate treatment plan, understand disease prognosis, evaluate treatment results, etc.[13,24,25] The TNM system is the standard International Staging System for lung cancer administered by the Union for International Cancer Control.[13,57] The T category defines the size and extent of the primary tumor, the N category defines the absence or presence of regional lymph node involvement, and the M category defines the extent of distant metastases.[13,24] The tumor stage system used in cancer registries was based on TNM staging in defining the categories of local stage (cancer confined to the organ of origin), regional stage (cancer spread to nearby tissues or lymph nodes in the area of the organ of origin), and distant stage (cancer spread to distant organs or parts of the body).[11,13,57]

In clinical practice and specific cancer registry, the TNM subsets with similar prognosis and treatment option are combined into different stage groups. For NSCLC, the assigned stages are 0, I, II, III, or IV; stage 0 is described as an *in situ* stage and the following stages are invasive cancer.[13,24,25] Stage I represents the early-stage invasive cancer, while stage IV represents the most advanced stage. For SCLC, the combined staging group as applied in NSCLC is considered irrelevant. The International Association for the Study of Lung Cancer (IASLC) recommends different grouping of TNM staging system for SCLC by combining stages I–III into limited stage (LS) and renaming stage IV as the extensive stage (ES).[56,58] The limited stage (LS-SCLC) is defined as cancer confined to the hemithorax of origin, the mediastinum, or supraclavicular

lymph nodes, while the extensive stage (ES-SCLC) is defined as cancer that has spread beyond the supraclavicular areas.[24,56,58]

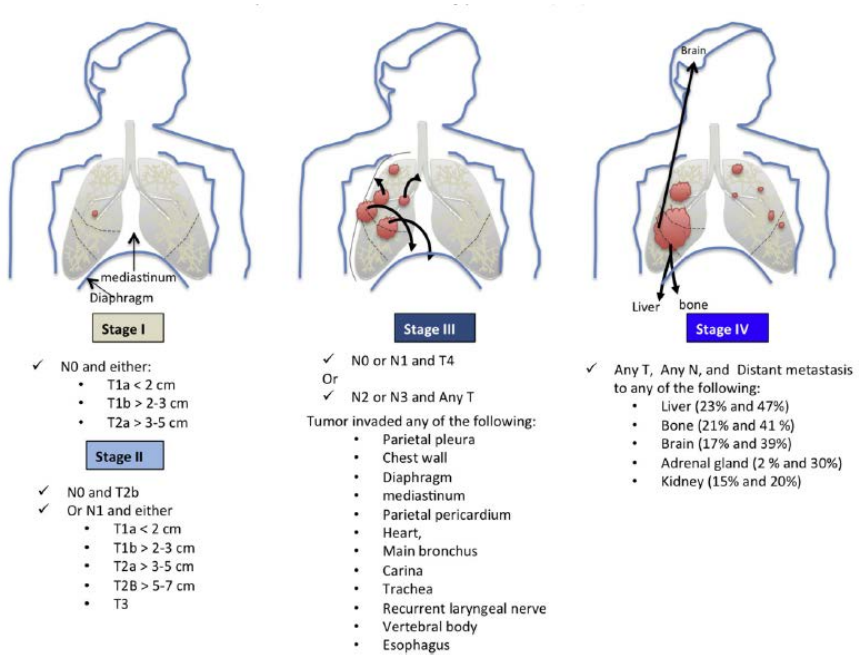



Figure 1. 1 The Schematic Illustration of Non-Small Cell Lung Cancer Staging.

Originally presented in Lemjabbar-Alaoui H, et al. (2015). "Lung cancer: Biology and treatment options." Biochim Biophys Acta. 2015;1856(2):189-210.[24] Reprinted with permission.

**Histopathology of Lung Cancer**

The international standard for histologic classification of lung tumors proposed by the WHO and the IASLC includes major histologic types of lung cancer, such as adenocarcinomas, squamous cell carcinomas, large cell carcinomas, and small cell carcinomas (SCLC).[59] These major types can be classified into many other subtypes based on the different clinical significance of the tumor.[59,60] The two most common histologic types are non-small cell lung cancer (NSCLC) and SCLC; their proportions of all lung cancer cases are approximately 80–83% and 10–13%, respectively.[11,12] Studies suggest these histologic types have differences in etiology, pathology, clinical features, and clinical management.[24,59]

Of the NSCLC, adenocarcinoma accounts for approximately 40–45%[12,61] and is commonly found in peripheral parts of the lung.[16,24] Adenocarcinoma occurs mainly in current or former smokers, but is also the most common type of lung cancer seen in nonsmokers.[62,63] In addition, adenocarcinomas are more likely to occur in younger people than other types of lung cancer.[31,49] The second most common histologic type of NSCLC is squamous cell carcinomas, which accounts for 25–30% of cases.[12,61] This subtype is often linked to a history of smoking and tends to be found in the central part of the lungs, near a major airway (bronchus).[23,64,65]

The SCLC tends to arise in the central mediastinum of the lung.[56] Compared with NSCLC, the SCLC is extremely aggressive and spreads rapidly to nearby tissues or lymph nodes in the area of the organ of origin and is strongly associated with tobacco smoking.[24,55,66] The SCLC is a malignant epithelial tumor consisting of small cells with scant cytoplasm, ill-defined cell borders, finely granular nuclear chromatin, and absent or inconspicuous nucleoli.[67]

**Survival of Lung Cancer Patients**

Analyses of lung cancer data from multiple countries indicate that lung cancer patients had poor survivals; the five-year relative survival were 6–14% among men and 7–18% among women.[6] In developing and less developed countries the number was even lower; the five-year relative survival of lung cancer cases was approximately around 9%.[4,6] In the US, despite the achievements in lung cancer care in previous years, improvements in the five-year survival of lung cancer is low. A recent report indicates in four decades the absolute improvement of five-year relative survival of lung cancer was only 6.5%; the five-year relative survival reported in 1975 and 2012 were 12.2% and 18.7%, respectively.[68]

The low survival rate of lung cancer patients has been reported to be associated greatly with an advanced cancer stage at diagnosis.[6,68] Studies suggest that due to the nonspecific nature

of lung cancer symptoms, the majority of lung cancer cases were diagnosed at advanced stages,[69,70] whereas available treatment options are most effective in early-stage cancer.[13,25] Studies have suggested many other factors that affect the survival of lung cancer patients, including patient characteristics such as age, gender, and race;[41,71-73] smoking and smoking-related comorbidities;[74-77] treatment factors and socioeconomic factors.[7,48,78-84]

Tumor biology and hormonal factors were suggested in studies to explain gender-related differences in the survival of lung cancer patients.[73,85] The estrogen mechanism, capacity to repair DNA damage, and PAH metabolism are some factors that differ between women and men.[2] A possible explanation for the effect of age is that young patients may have a better health condition due to fewer comorbidities, which subsequently allows them to receive more aggressive treatment and benefit the survival.[41,45,46] However, studies also suggest that young lung cancer patients may have a different character of disease that resulted in a worse prognosis. More of the young lung cancer patients were diagnosed at an advanced stage; young lung cancer cases also were suggested to have a different histologic type compared with older cases, which may indicate genetic variation.[45,48,86,87]

The histologic type and stage of cancer may explain differences associated with treatment. The NSCLC types of cancer are considered less aggressive,[24] and with the available treatment options the five-year relative survival of NSCLC was 23%; the survival of early-stage cases was 60% and advanced stage cases was 5%.[12] Whereas, for SCLC that has aggressive growth and wide infiltration, a recent data suggest the five-year survival of SCLC cases was only 6.3%.[12] The survival of SCLC has not significantly changed since the early 1990s.[12] A meta-analysis study suggests that due to the toxicity associated with chemoradiation, the survival benefit from treatment of LS-SCLC was limited to younger patients.[88] Whereas findings from other studies indicate a similar response to combined modality therapy were seen in older and younger patients.[89,90]

**Treatment Refusal by Lung Cancer Patients**

Patients with advanced chronic disease, such as lung cancer, are challenged with potential trade-offs between treatment benefits and burdens. For example, a study by Fried et al. indicated that for a low-burden treatment with restoration of current health, 98.7% of patients agreed to the treatment; however, when the outcome was survival but at the same time having severe functional impairment or cognitive impairment, more than 75% of patients decided to refuse the treatment.[91] Rothman et al. suggested that high proportions of treatment refusal may indicate insufficient patient-centered decision-making.[92] Patients were more likely to refuse treatments that do not meet their treatment goal, as also suggested in studies reviewed by Puts et al.[93] Many factors influence a patient's decision to receive or forgo the recommended treatment. It may range from individual factors (such as age, gender, and race) to culture, the burden of treatment (such as length of hospital stay), extent of diagnostic procedures, invasive interventions, and the likelihood of the outcome.[91,94]

A review of cancer studies by Ward et al. suggests that compared with other cancers, lung cancer patients have higher rates of treatment refusal.[95] The decline of recommended cancer treatment was not only associated with poor survival but also higher mortality risk.[63,96] In addition, studies have suggested that age is one of the important factors that greatly influence a cancer patient's decision regarding treatment.[94,97] Older lung cancer patients were more likely to forgo treatment than their younger counterparts. Studies among early-stage NSCLC patients reported a positive association between the increase of age and refusal of recommended surgical treatment.[98,99] However, due to data limitation, the studies were conducted only among early-stage lung cancer cases [98,99] or older lung cancer cases.[98] Not including advanced stage in the analysis of lung cancer is a disadvantage because majority of the cases diagnosed at advanced stage.

In terms of gender differences, studies reveal that women with lung cancer more likely believed the disease to be incurable and that the treatment was only for comfort care.[100,101] In addition, limited access to cancer care due to lack of medical insurance is another factor suggested by many studies to be associated with higher treatment refusal.[95,102] Previous studies indicate that the risk of being uninsured varies by age; young lung cancer patients were more likely to be uninsured or underinsured as compared with their older counterparts [102,103]

**Limitations of Previous Research**

Previous studies conducted to estimate the prognosis of lung cancer patients indicate that many factors predict survival, including age at diagnosis. The inconclusive findings regarding whether the diagnosis of lung cancer at a younger age benefits survival suggested the need to examine the characteristics of younger-onset lung cancer cases and determine its difference with older-onset cases, as well as investigate the survival of these groups. In addition, many studies used simplify age category that was not represented younger-onset lung cancer.

Other studies have suggested that patient acceptance of recommended treatment is another essential factor in survival and an important point to reduce lung cancer mortality.[12,63,104] However, many of previous studies examined treatment refusal among early-stage cancer, or limited their study population to those recommended for surgery in a single-site hospital, or included small number of cases in the analysis. These restrictions may not allow a representative estimate of treatment refusal among lung cancer cases because a higher proportion of lung cancer diagnosed at advanced stages and more treatment refusal are anticipated from them.

In addition to gaps in the literature regarding survival of the young-onset lung cancer patients, studies suggested many of the young lung cancer patients having issues with access to cancer care.[103,105,106] The Veterans Affairs Central Cancer Registry (VACCR) offers an

opportunity to examine survival of patients who have similar access to cancer care and included information such smoking history, family history, and chemotherapy, that are limited in other databases.

To better describe the patient characteristics and have robust analyses, we used different categories of age at diagnosis to address the younger-onset cases and included a larger sample of lung cancer cases. Firstly, our analyses examined the characteristics of lung cancer patients diagnosed at different categories of age and examined their survival. At the same time, we investigated factors associated with survival, including age at diagnosis and treatment refusal. Secondly, our analyses investigated factors associated with treatment refusal by patients. We used two large cancer databases for our analyses; the National Cancer Database (NCDB), which represents the general population, and the VACCR, which represents a unique veteran population.

**Specific Aims**

The burden of morbidity and mortality caused by lung cancer cases emphasize the urgent need to conduct more studies to suggest improvement in cancer care. The overall objective of this dissertation was to investigate survival and treatment refusal of lung cancer patients. We established three specific aims to address the study objective.

Specific aim 1: To describe the characteristics and examine survival of NSCLC patients by age at diagnosis

Specific aim 2: To investigate factors associated with treatment refusal and the impact of treatment refusal on the survival of SCLC patients

Specific aim 3: To investigate factors associated with treatment refusal by NSCLC patients

These specific aims are presented as chapters 2–4 in this dissertation.

## Data Sources

### *National Cancer Database*

The NCDB provides a clinical oncology database of hospital registry data collected from more than 1,500 Commission on Cancer (CoC)-accredited facilities.[107-109] The database included cancer cases diagnosed and or treated at the CoC-accredited facilities. It supports data for national cancer surveillance and resource for cancer quality improvement through a joint program of the American College of Surgeons and the ACS.[110] The database captures approximately 70% of newly diagnosed cancer cases nationwide and more than 34 million records with detailed information, including patient and tumor characteristics, treatments, and outcome.[111,112]

### *Veterans Affairs Central Cancer Registry*

The VACCR serves a shared comprehensive cancer database of the US veterans population from Veterans Affairs medical centers facilities.[113,114] The Veteran Affairs provides an integrated health care system access for veterans in a single payer system.[114,115] The VACCR uses standards established by institutions including the American College of Surgeons Commission on Cancer, the American Joint Commission on Cancer, and the North American Association of Central Cancer Registries, among others.[113] Data in VACCR, include extensive demographics, cancer identification, the extent of disease and staging, first course of treatment, and outcomes.[113]

## Conceptual Framework

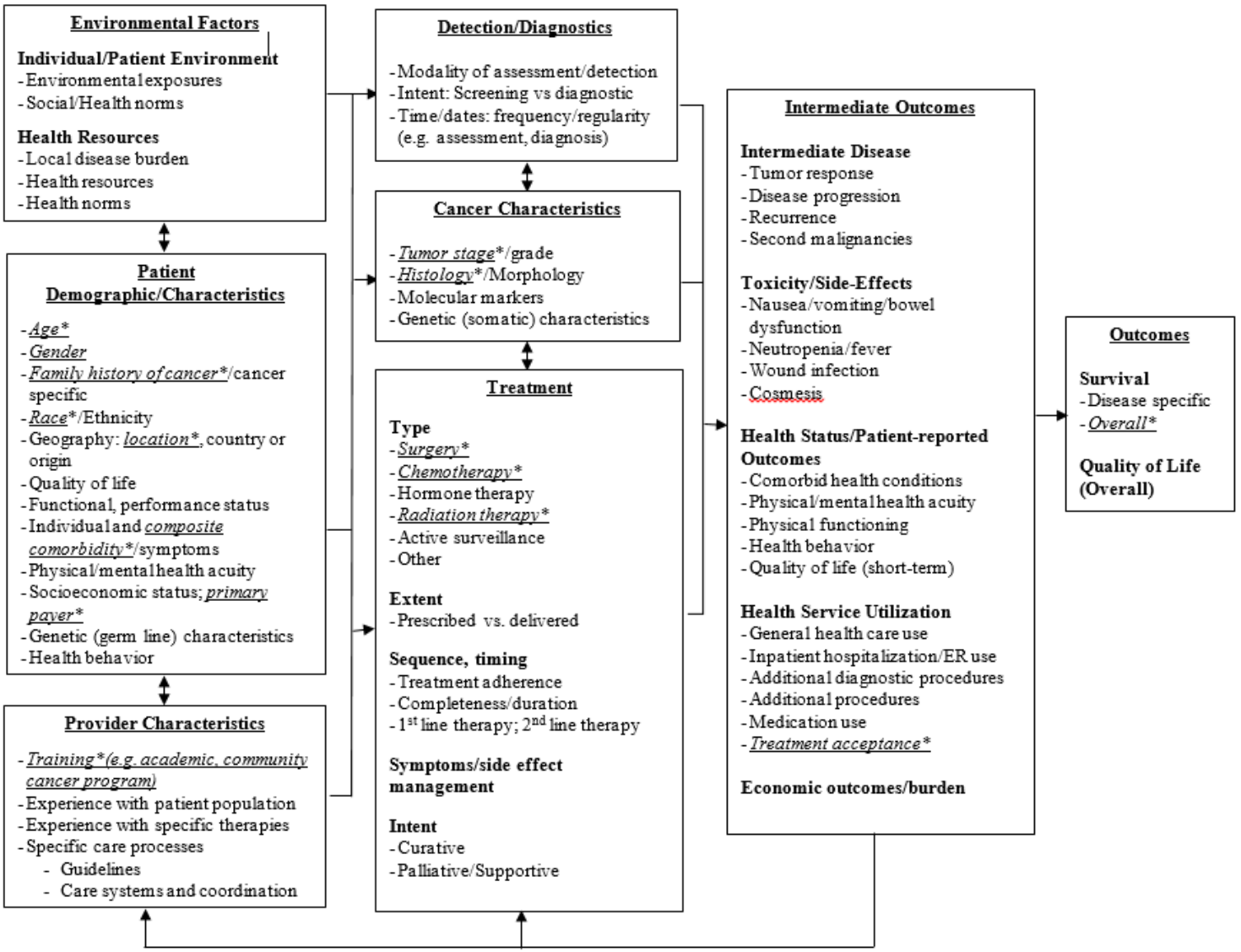
In this dissertation, we adapted the model on measures of patient-centered cancer outcomes research using observational data by Carpenter et al.[116] The model emphasizes the expanding repositories of secondary data, such as cancer registry, and electronic health records, and suggests the importance of presenting measures and outcomes in cancer care. Using the

model as a baseline, we identified measures and outcomes from variables in cancer registries that are relevant to our study objectives.

Figure 1.2 exhibits multiple factors relevant to factors associated with the survival of lung cancer care. One important factor that we added in the model is treatment acceptance as intermediate outcome. We view this model as a longitudinal process. For example, the improvement in lung cancer care will eventually increase patient's survival. However, prior to evaluate the survival it is important to see the acceptance towards treatment.

Many of the variables listed in the model are not available for inclusion in our analyses; however, it is helpful for future studies to include and adjust multiple factors, not only for cancer care evaluation but also to address challenges in the interpretation of findings from previous studies. Our analyses have included most components in the model, i.e., patient demographics (age, gender, family history of cancer, race, category of residence, composite comorbidity, primary payer/insurance status), provider characteristics (cancer care facility), cancer characteristics (stage, histology), treatment (surgery, chemotherapy, radiation, and combined therapies), intermediate outcome (treatment acceptance), and outcome (survival), these variables are marked in the model. Taking into account various components in our analyses ensured the reliability of our estimations and supported the interpretation of our findings.

Figure 1. 2 Conceptual Model of the Survival of Lung Cancer Patients.



# CHAPTER 2

# SURVIVAL OF NON-SMALL CELL LUNG CANCER PATIENTS IN THE UNITED STATES VETERANS AFFAIRS POPULATION BY AGE


## Abstract

**Background:** A significant number of young cases of non-small cell lung cancer (NSCLC) has been reported. This study compared the characteristics of younger-onset cases to older counterparts and examined their survival. **Methods:** We analyzed data from the Veterans Affairs Central Cancer Registry (VACCR) from 2001–2008. We estimated survival probability using the Kaplan–Meier method and compared survival of different age categories using Cox Proportional Hazards regression analysis. **Results:** Of the 48,899 NSCLC cases studied, 1,182 patients were diagnosed as younger-onset (< 50 years). The younger-onset group had high proportions of advanced stage at diagnosis, current smokers, positive family history of cancer, and adenocarcinoma histology. The five-year survival of younger-onset patients was 5.6% compared with 3.0% of older-onset patients (> 70 years). Of those with early-stage (I and II), younger-onset patients had a lower risk of mortality than intermediate-onset (50–70 years) (hazard ratio [HR] = 0.78; 95% CI: 0.62–0.98); the intermediate-onset patients had a lower risk than older-onset (HR = 0.66; 95% CI: 0.62–0.69). For advanced stage (III and IV), there was no difference in mortality risk between younger- and intermediate-onset patients, whereas those with older-onset had a 24% increased risk of mortality than intermediate-onset patients (HR = 1.24; 95% CI: 1.20-1.28). **Conclusions:** Younger-onset NSCLC patients have a better five-year survival than older-onset patients, although more of them were diagnosed at an advanced stage. Further investigations in genetic or tumor molecular are recommended as younger-onset patients present with more adenocarcinoma and positive family history than older counterparts.

**Introduction**

In the US, lung cancer is the leading cause of cancer-related death, with an estimated 154,050 deaths in 2018.[12] Of lung cancer subtypes, NSCLC accounts for 84% of the cases.[12] Historically, lung cancer has been predominately diagnosed among the older population, with a median age at diagnosis of 70 years. However, recent studies have reported a substantial proportion of patients developed NSCLC at younger age.[12,40,44,45]

Patients with younger-onset NSCLC, age at diagnosis between 40 and 50 years, have been reported to have distinct characteristics such as advanced stage at diagnosis,[44-46] high proportion of adenocarcinoma histologic subtype,[47,48] and predisposing genetic factors[33,49,50] in comparison to older-onset patients. Previous studies have reported higher proportions of tobacco use, a better performance status, and more aggressive treatment in younger-onset patients.[41,45,46] These factors have been suggested as contributing factors for the different prognoses between younger and older-onset NSCLC patients.

In previous studies, the influence of age at diagnosis on patient survival of NSCLC patients has been found to be inconclusive. Studies conducted using different cancer registries, i.e., Surveillance Epidemiology and End Results (SEER) and NCDB, have reported that young patients tend to have less comorbidity and better performance status, which enable them to receive more comprehensive treatment and results in better survival.[45,47,79] Findings from a study by Mauri et al. indicate no difference in overall survival between patients age < 45 and > 45 years.[117] A hospital-based study by Bryant et al. indicated that younger NSCLC patients have a significantly worse prognosis than older patients due to the aggressiveness of different cancer types among the younger patients.[48] Other than cancer aggressiveness, poorer survival among the younger patients appeared to be related to limited access to and use of care among younger patients. Insurance is a contributing factor related to issues in access to cancer care. Studies have reported that more of younger-onset lung cancer patients did not have insurance and experienced

delay in cancer diagnosis.[103,105] Findings from studies also indicate that younger patients often delayed visiting health care providers until they became symptomatic and thus were diagnosed at a more advanced stage.[42,43,48,86,118] Therefore, using a large cohort of patients, such as VA patients who have similar access to cancer care, would allow the evaluation for effect of age at diagnosis on patient survival.

The purpose of this study was to describe the characteristics of younger-onset NSCLC cases and to examine the survival based on age at diagnosis of patients treated within the VA health care system, which provides a more equitable access to health care.

## Materials and Methods

### *Study Population, Design, and Data Source*

The Veterans Affairs (VA) facilities maintain a shared comprehensive cancer database that covers 132 Veterans Affairs medical centers. In addition, the VACCR contains demographic and clinical information of cancer patients who have been diagnosed and/or treated at the VA medical centers.[113] The VACCR uses standards established by institutions including the American College of Surgeons Commission on Cancer, the American Joint Commission on Cancer, and the North American Association of Central Cancer Registries.[113]

In this retrospective cohort study, we analyzed data of patients with NSCLC of all histology subtypes included in the VACCR database between 2001 and 2008. Analyses were conducted utilizing data of those patients diagnosed with a primary invasive lung cancer with a defined cancer stage at diagnosis ($N$ = 48,899).

*Exposures and Outcomes*

We included data on patient age at diagnosis, race, gender, smoking history, family history of cancer, alcohol history, stage at diagnosis, histology type, and treatment received as predictor variables. The five-year overall mortality, the study outcome, was defined as the time from diagnosis of NSCLC to (a) the date of death (from any cause), (b) loss to follow-up, or (c) vital status up to 60 months (after diagnosis), whichever came first. Age at diagnosis of NSCLC was categorized as younger-onset (diagnosed before age 50 years), intermediate-onset (diagnosed at age 50–70 years), and older-onset (diagnosed at 70 years and after).

*Statistical Analysis*

We used the chi-square test to compare patient characteristics, the Kaplan–Meier method to estimate survival probabilities, and the log-rank test to assess survival differences. Multivariable Cox Proportional Hazards (PH) regression was performed to examine the association between age at diagnosis and overall survival, adjusting for other factors including smoking history, alcohol history, family history of cancer, clinical stage, and histology subtypes. The assumption of proportional hazards was tested using the log–log plots. Covariates with *p*-value > 0.25 were excluded in the final model. All data were analyzed using the SAS software version 9.4 (SAS Institute; Cary, NC).

*Confidentiality and Ethics*

The study used data from a de-identified VACCR database and was approved by the Institutional Review Board at the VA-Nebraska Western Iowa Health Care System. The views expressed in this publication are solely those of the authors, including the statements made in the discussion and conclusions drawn from the data. The VA has not verified, and is not responsible for, the analytic and/or statistical methods used in this study.

## Results

### *Demographic and Clinical Characteristics*

Analyses included 48,899 NSCLC cases recorded in the VA database between 2001 and 2008. Of these 1,182 patients were diagnosed as younger-onset lung cancer. Comparison of patient demographic and clinical characteristics by age categories are presented in Table 2.1.

Younger-onset patients were more likely to be diagnosed at an advanced stage (stages III and IV) than the older groups. A higher proportion of adenocarcinoma was present among the younger-onset patients, whereas more squamous cell carcinoma was observed among the older-onset patients. Higher proportions of younger-onset patients received combined cancer treatment than either of the intermediate-onset and older-onset patients.

We used family history of cancer as a surrogate of inherent factors for lung cancer in our analyses. A higher proportion of younger-onset patients had a positive family history of cancer (39%) than older-onset patients (30%). The proportion of current smokers was higher among the younger-onset patients (76%) in comparison to the intermediate-onset (62%), and older-onset patients (37%) as shown in Table 2.1.

### *The Survival of NSCLC Cases*

The younger-onset cohort had better median survival than older-onset patients (9 versus 7 months) as shown in Table 2.2. The five-year survival of patients diagnosed at the three age categories was significantly different (log-rank $p < 0.001$). A higher proportion of younger-onset patients (6%) survived to 60 months after diagnosis than intermediate-onset (5%) and older-onset (3%) patients.

The log–log tests indicated all predictors met the proportional hazards (PH) assumption. Therefore, we included age at diagnosis, smoking history, alcohol history, family history of cancer, clinical stage at diagnosis, and histology subtype in multivariable analyses. Results were

stratified by stage in Table 2.3 and indicated that among early-stage (stages I and II), younger-onset patients had a 22% lower risk of mortality than intermediate-onset patients (HR = 0.78; 95% CI: 0.62–0.98). No difference was found in the comparison of mortality risk between younger-onset and intermediate-onset patients among those with advanced stage; however, older-onset patients had a 24% (HR = 1.24; 95% CI: 1.20–1.28) increased risk of mortality than intermediate-onset patients.

**Discussion**

Our study results show that in the veteran population with NSCLC, overall survival is affected by various factors, including age at diagnosis, smoking history, alcohol history, family history of cancer, clinical stage at diagnosis, and histology. Of these factors, age at diagnosis and cancer stage are factors that strongly influence patient survival. Younger-onset NSCLC patients had a better five-year survival than patients diagnosed at an older age. Mortality risk stratified by cancer stage showed consistent patterns. The younger-onset lung cancer patients had a lower mortality risk than intermediate-onset, particularly among early-stage. Similarly, intermediate-onset patients also showed a lower risk of death than those with older-onset in both early and advanced stages of NSCLC.

As lung cancer has been widely regarded as a disease affecting older people, it is likely that younger people may pay less attention to respiratory symptoms and may not think that they could have developed NSCLC at a younger than typical age. In fact, some studies have suggested that younger people's decreased attention to their health leads to lower proportions of cancer screening, causing them to be symptomatic at the time of presentation.[41,119] Our findings were corroborated previous studies that observed more of the younger-onset patient diagnosed with NSCLC at stages III and IV.[47,48] Moreover, Bryant et al. suggested that clinically NSCLC appears

more aggressive among the young, which may be another reason the younger-onset group is frequently found at a more advanced stage.[48]

Overall survival of patients diagnosed at different age categories in the multivariable analyses showed that younger-onset patients had a lower risk of mortality than the older patients. Similar findings have been reported by previous studies suggesting lower mortality risk among younger-onset across cancer stages at diagnosis.[45,47,79] One posited explanation of this has been that younger-onset patients may have fewer comorbidities and are more likely to receive aggressive treatment than older counterparts.[41,46,71] Our analyses indicated that among the veterans population, that received equal access to health care, those with younger-onset had less mortality risk compared with those diagnosed in older groups, particularly among early-stage. One possible explanation is that the disease aggressiveness in advanced stages of NSCLC reduces the observed survival benefits in those with younger-onset.

An interesting finding in our analysis was the higher proportion of adenocarcinoma in younger patients, despite the high proportion of current smokers. Of all histologic subtypes, adenocarcinoma seems to have the least association with smoking, and is the most common subtype of lung cancer in never and light smokers.[63] Given the high proportion of a family history of cancer in the younger-onset cohort, it is likely that in a setting of increased susceptibility, a less cumulative smoking exposure may be needed to cause lung adenocarcinoma at a younger age. Moreover, the possibility of other exposures among the veteran population, such as asbestos and other chemicals components, could explain the increased risk of cancer among young adults.[120]

A strength of the present study was the ability to analyze smoking status among cancer patients, a variable that is not available in most of the cancer registries such as SEER and NCDB. In addition, the VA population has been known to have a higher proportion of smokers than the general population.[120,121] The increased proportion of NSCLC cases among the younger-onset patients has been suggested by some researchers due to smoking “dose,” which is the number of

cigarettes smoked, total pack-years, and age at smoking initiation.[122] Our findings among the veterans population were in agreement with previous studies[42,43] and demonstrated a higher proportion of current smokers among younger-onset patients. Bhat et al. suggested that current smokers were more likely to be diagnosed with NSCLC at a younger age.[62]

Our results also demonstrated that a higher proportion of younger-onset patients had a positive family history of cancer. This corroborates findings in other studies that have shown a positive association between genetic and NSCLC, especially among the younger-onset patients.[32,35,49,50] It appears that inherited risk factors in combination with tobacco smoking increases the risk of diagnosis with the disease at a younger age.[33,49,50] Our study showed that the median survival of patients with a positive family history of cancer was higher than those without.

Other studies among NSCLC patients in the veterans population have suggested similar findings, in that patients with a positive family history of cancer have a lower risk of mortality than those without.[62,123] This is possibly due to increased awareness among patients with a positive family history, which leads to earlier lung cancer screening. In addition, because of concern about military exposures and the accessible health care services provided by the VA health care system, more veterans may be screened for lung cancer[120] leading to earlier diagnosis and receipt of prompt treatment resulting in better survival.

We have found no study addressed the issue of survival among different age at diagnosis of NSCLC patients in the veteran population. The VACCR provided us with a large national cancer database of veterans in the US, with equal access to care and comprehensive medical insurance benefits available to all enrolled veterans.[124] In addition, the database included information on smoking history, family history of cancer, and treatment received including chemotherapy, which is frequently stated as a limitation in previous studies using cancer registry data.[45,47] We believe that in comparison to previous cancer registry-based studies, our analyses

demonstrate important findings on factors associated with survival of NSCLC patients, particularly among younger-onset NSCLC patients in the US veterans population.

Nevertheless, we acknowledge the following limitations in our study. First, we were unable to explain the variation in patient performance status and comorbidity on patient survival as the database we utilized did not capture this information. A study by De Rijke et al. suggests these two factors are important predictors of mortality and are correlated with increases in patient age.[125] Second, due to the characteristics of the veterans population, these findings may not be generalizable to other cohorts. Studies have reported a higher proportion of female patients among younger-onset,[45,47,79] however, most of the patients in our study were male, thus we could not explain variation according to gender. Nevertheless, it is unlikely that either of these factors would have detracted the interpretation of the present study results.

**Conclusions**

Younger-onset NSCLC patients have a better five-year survival than older-onset patients. The lower mortality risk observed in younger-onset NSCLC might indicate an area of improvements such as better access to cancer screening and cancer care, and recommendations on the use of aggressive treatments that will result in better patient survival. In addition, with more younger-onset patients presenting with advanced stage cancer, adenocarcinoma, and positive family history of cancer, further investigations into genetic or tumor molecular characteristics are needed. These will help to understand the associations between genetic susceptibility, environmental carcinogens including tobacco smoking, and treatment-specific factors on survival of young NSCLC patients.

Table 2. 1 Characteristics of Non-Small Cell Lung Cancer Patients by Age (N=48,899)

| Characteristics | <50 years (n = 1,182) | | 50–70 years (n = 26,787) | | >70 years (n = 20,930) | | *p* value |
|---|---|---|---|---|---|---|---|
| | n | % | n | % | n | % | |
| Gender | | | | | | | |
| Female | 101 | 8.54 | 528 | 1.97 | 240 | 1.15 | < 0.001 |
| Male | 1,081 | 91.46 | 26,259 | 98.03 | 20,690 | 98.85 | |
| Race | | | | | | | |
| White | 779 | 65.91 | 21,478 | 80.18 | 17,168 | 82.03 | |
| Black | 371 | 31.39 | 4,702 | 17.55 | 3,304 | 15.79 | < 0.001 |
| Others/unknown | 32 | 2.71 | 607 | 2.27 | 458 | 2.19 | |
| Smoking History | | | | | | | |
| Never smokers | 40 | 3.38 | 659 | 2.46 | 907 | 4.33 | |
| Former smokers | 149 | 12.61 | 7,618 | 28.44 | 10,438 | 49.87 | < 0.001 |
| Current smokers | 893 | 75.55 | 16,635 | 62.17 | 7,754 | 37.05 | |
| Unknown | 100 | 8.46 | 1,857 | 6.93 | 1,831 | 8.75 | |
| Alcohol History | | | | | | | |
| Never | 223 | 18.87 | 6,244 | 23.31 | 6,619 | 31.62 | |
| Former | 239 | 20.22 | 6,296 | 23.50 | 4,916 | 23.49 | < 0.001 |
| Current | 540 | 45.69 | 10,015 | 37.39 | 5,283 | 25.24 | |
| Unknown | 180 | 15.23 | 4,232 | 15.80 | 4,112 | 19.65 | |
| Family History of Cancer | | | | | | | |
| No | 413 | 34.94 | 9,727 | 36.31 | 8,210 | 39.23 | |
| Yes | 460 | 38.92 | 9,960 | 37.18 | 6,249 | 29.86 | < 0.001 |
| Unknown | 309 | 26.14 | 7,100 | 26.51 | 6,471 | 30.92 | |
| Clinical Stage (AJCC) | | | | | | | |
| I and II | 283 | 23.94 | 7,965 | 29.73 | 6,902 | 32.98 | |
| III | 358 | 30.29 | 7,426 | 27.72 | 5,790 | 27.66 | < 0.001 |
| IV | 541 | 45.77 | 11,396 | 42.54 | 8,238 | 39.36 | |
| Histology | | | | | | | |
| Adenocarcinoma | 456 | 38.58 | 8,927 | 33.33 | 5,784 | 27.63 | |
| Squamous cell carcinoma | 290 | 24.53 | 8,877 | 33.14 | 7,248 | 34.63 | |
| Large cell carcinoma | 53 | 4.48 | 870 | 3.25 | 518 | 2.47 | < 0.001 |
| NSCLC, NOS | 282 | 23.86 | 5,766 | 21.53 | 4,284 | 20.47 | |
| Others | 101 | 8.54 | 2,347 | 8.76 | 3,096 | 14.79 | |
| Type of Treatment | | | | | | | |
| Chemotherapy only | 160 | 13.54 | 3,662 | 13.67 | 2,278 | 10.88 | |
| Radiation only | 167 | 14.13 | 4,170 | 15.57 | 4,101 | 19.59 | |
| Surgery only | 170 | 14.38 | 4,840 | 18.07 | 3,244 | 15.50 | |
| Chemoradiation | 347 | 29.36 | 5,628 | 21.01 | 2,210 | 10.56 | |
| Surgery with chemotherapy with or without radiation | 128 | 10.83 | 2,135 | 7.97 | 679 | 3.24 | < 0.001 |
| No surgery or radiation or chemotherapy recorded/ unknown | 210 | 17.77 | 6,352 | 23.71 | 8,418 | 40.22 | |

*NSCLC* = non-small cell lung cancer; *NOS* = not otherwise specified

Table 2. 2 Median Survival and Bivariable Analyses

| Characteristics | | No. of patient* | Median survival (month) | 5-yr survival (%) | Log-rank test |
|---|---|---|---|---|---|
| Age | 50–70 years | 26,787 | 9 | 5.0 | < 0.001 |
| | < 50 | 1,182 | 9 | 5.6 | |
| | > 70 | 20,922 | 7 | 3.0 | |
| Gender | Female | 869 | 11 | 0.0 | < 0.001 |
| | Male | 48,022 | 8 | 4.1 | |
| Race | White | 39,420 | 8 | 4.2 | 0.546 |
| | Black | 8,374 | 8 | 3.7 | |
| | Others/unknown | 421 | 9 | 3.0 | |
| Smoking History | Never smokers | 1,606 | 8 | 0.0 | < 0.001 |
| | Former smokers | 18,204 | 9 | 4.4 | |
| | Current smokers | 25,297 | 8 | 4.1 | |
| Alcohol History | Never | 13,085 | 9 | 4.2 | < 0.001 |
| | Former | 11,450 | 8 | 3.1 | |
| | Current | 15,837 | 9 | 4.8 | |
| Family History of Cancer | No | 18,349 | 8 | 3.7 | < 0.001 |
| | Yes | 16,668 | 9 | 4.3 | |
| Clinical Stage (AJCC) | I and II | 15,149 | 20 | 11.7 | < 0.001 |
| | III | 13,573 | 9 | 2.6 | |
| | IV | 20,169 | 4 | 0.5 | |
| Histology | Squamous cell carcinoma | 16,411 | 10 | 4.9 | < 0.001 |
| | Adenocarcinoma | 15,165 | 10 | 5.8 | |
| | Large cell carcinoma | 1,441 | 8 | 4.2 | |
| | NSCLC, NOS | 10,331 | 7 | 1.8 | |
| | Others | 5,543 | 5 | 2.1 | |
| Treatment | No surgery or radiation or chemotherapy | 14,641 | 3 | 0.7 | < 0.001 |
| | Chemotherapy only | 6,099 | 9 | 1.0 | |
| | Radiation only | 8,437 | 5 | 1.1 | |
| | Surgery only | 8,253 | 28 | 18.7 | |
| | Chemoradiation | 8,184 | 11 | 2.8 | |
| | Surgery with chemotherapy with or without radiation | 2,941 | 23 | 1.2 | |

*NSCLC* = non-small cell lung cancer; *NOS* = not otherwise specified

*include number of patients with information on specific characteristics

Table 2. 3 Multivariable Cox Regression of Factors Associated with Survival of NSCLC Cases

| Characteristics | Stage I and II | | | Characteristics | Stage III and IV | | |
|---|---|---|---|---|---|---|---|
| | **AHR** | **95% CI** | ***p* value** | | **AHR** | **95% CI** | ***p* value** |
| Age | | | | Age | | | |
| 50–70 years | Ref | | | 50–70 | Ref | | |
| < 50 | 0.78 | 0.62-0.98 | 0.031 | < 50 | 0.96 | 0.88-1.04 | 0.298 |
| > 70 | 1.52 | 1.44-1.61 | < 0.001 | > 70 | 1.24 | 1.20-1.28 | < 0.001 |
| Smoking History | | | | Smoking History | | | |
| Never smokers | Ref | | | Never smokers | Ref | | |
| Former smokers | 1.01 | 0.88-1.17 | 0.842 | Former smokers | 1.06 | 0.99-1.15 | 0.095 |
| Current smokers | 1.14 | 0.99-1.31 | 0.069 | Current smokers | 1.12 | 1.04-1.21 | 0.002 |
| Alcohol History | | | | Alcohol History | | | |
| Never | Ref | | | Never | Ref | | |
| Former | 1.11 | 1.04-1.19 | 0.002 | Former | 1.06 | 1.02-1.10 | 0.002 |
| Current | 0.92 | 0.86-0.98 | 0.011 | Current | 0.98 | 0.95-1.01 | 0.252 |
| Family History | | | | Family History | | | |
| No | Ref | | | No | Ref | | |
| Yes | 0.94 | 0.89-0.99 | 0.018 | Yes | 0.92 | 0.89-0.94 | < 0.001 |
| Clinical Stage (AJCC) | | | | Clinical Stage (AJCC) | | | |
| I | Ref | | | III | Ref | | |
| II | 1.49 | 1.40-1.58 | < 0.001 | IV | 1.88 | 1.83-1.94 | < 0.001 |
| Histology | | | | Histology | | | |
| Squamous cell | Ref | | | Squamous cell | Ref | | |
| Adenocarcinoma | 0.78 | 0.73-0.83 | < 0.001 | Adenocarcinoma | 1.02 | 0.99-1.06 | 0.225 |
| Large cell | 1.04 | .88-1.23 | 0.614 | Large cell | 1.14 | 1.05-1.24 | 0.002 |
| NSCLC, NOS | 1.29 | 1.20-1.39 | < 0.001 | NSCLC, NOS | 1.10 | 1.06-1.14 | < 0.001 |
| Others | 1.24 | 1.13-1.36 | < 0.001 | Others | 1.40 | 1.33-1.47 | < 0.001 |

[+] Gender, race and treatment were not included in the multivariable analysis

AHR: Adjusted Hazard Ratio CI: Confidence Interval

# CHAPTER 3

# FACTORS ASSOCIATED WITH TREATMENT REFUSAL AND IMPACT OF TREATMENT REFUSAL ON SURVIVAL OF SMALL CELL LUNG CANCER PATIENTS


## Abstract

**Background:** With less than 7% of small cell lung cancer (SCLC) patients surviving five years after diagnosis, the receipt of recommended treatment is of utmost importance for patient survival. Nevertheless, treatment refusal of SCLC patients has not been studied well. Our study examined factors associated with treatment refusal and the effect of refusal on patient survival. **Methods:** We analyzed data of 107,988 SCLC patients diagnosed between 2003 and 2012 from the National Cancer Database. Treatment refusals were analyzed separately for chemoradiotherapy among limited stage (LS-SCLC) and chemotherapy among extensive stage (ES-SCLC) patients. We used logistic regression to investigate factors associated with treatment refusal. We estimated survival probability using the Kaplan–Meier method and compared survival of those who received and refused treatment using Cox Proportional Hazards regression analysis. **Results:** The refusals of chemoradiotherapy among LS-SCLC and chemotherapy among ES-SCLC patients were 1.34% and 4.70%, respectively. From 2003 to 2012, trends show an increase of refusals, especially among the ES-SCLC recommended chemotherapy. Multivariable analyses showed that in both SCLC groups, older age at diagnosis (> 70 years), female gender, uninsured status, and presence of comorbidities were associated with treatment refusals. LS-SCLC patients who refused chemoradiotherapy had a higher risk of mortality than those who received treatment (hazard ratio [HR] = 4.96; 95% CI: 4.45–5.53); the median survival of those who refused treatment was 3 months versus 18 months of those who received ($p < 0.001$).

Similarly, ES-SCLC patients who refused chemotherapy had a higher risk of mortality than those who received treatment (HR = 3.69; 95% CI: 3.48–3.92); the median survival was 1 month versus 7 months, respectively ($p < 0.001$). **Conclusions:** Treatment refusal among SCLC patients was associated with worse survival; therefore, strategies to increase patient acceptance of the recommended treatment need to be studied further.

## Introduction

Of the estimated 234,030 new lung cancer cases diagnosed in the United States (US) in 2018, more than 30,000 cases were identified as small cell lung cancer (SCLC).[12] Analyses of the surveillance, epidemiology, and end results reported the five-year survival rate of SCLC was less than 7%.[12] In addition, in the last two decades, the SCLC survival rate has shown little improvement.[83]

Therapeutic options for SCLC have not significantly changed within the last 30 years.[126,127] Concurrent chemoradiotherapy is typically recommended for patients diagnosed with limited stage (LS-SCLC); whereas those diagnosed with extensive stage (ES-SCLC) are predominantly treated with chemotherapy.[55,126,128] Lack of patient acceptance of recommended treatment has been implicated by previous studies as a key factor in SCLC survival.[126,127,129] Nonetheless, there is a lack of research concerning treatment refusal among SCLC patients.[127,130]

Our study addressed this gap by examining factors associated with treatment refusal by SCLC patients from a US national facility-based cancer registry. We also analyzed the trend of treatment refusal over time as well as the effect of treatment refusal on patient survival.

## Materials and Methods

### *Study Population, Design, and Data Source*

The National Cancer Database (NCDB) provides national cancer surveillance data through a joint program of the Commission on Cancer (CoC) of the American College of Surgeons and the American Cancer Society (ACS).[107] According to the United States Cancer Statistics, this database captures approximately 70% of newly diagnosed cancer cases.[107,112]

We used cross-sectional design in the analysis of factors associated with treatment refusal and retrospective cohort in the analysis of survival data. The sample for analysis were drew from

the 198,405 SCLC cases diagnosed between 2003 and 2012. Figure 4.1 shows the sample selection process. Criteria for data inclusion were: (1) confirmed diagnosis of primary invasive SCLC according to the International Classification of Disease for Oncology Third Edition (ICD-O-3) codes 8041-8045, (2) diagnosis established at a CoC-accredited facility and patient received all or part of their treatment from CoC facility/facilities, (3) diagnosis confirmed with cancer stage and patient treated at one or more of the following types of CoC facilities: community, comprehensive community, and academic cancer programs, (4) known insurance status, and (5) recommendation for first-course of treatment was either chemotherapy or radiation or combination of chemoradiotherapy. We utilized the data of 107,988 eligible patients in our analyses.

*Exposures and Outcomes*

We included sociodemographic and clinical characteristics as predictor variables. Information on cancer stage was taken from the NCDB analytic stage, which uses standards publicized by the American Joint Committee on Cancer (AJCC) 7$^{th}$ edition.[107] In the analysis, we followed the recommendation of the IASLC by grouping stages I–III as limited stage (LS-SCLC) and stage IV as extensive stage (ES-SCLC).[56] Comorbidity was recorded as Charlson/Deyo Comorbid Conditions (CDCC).[111] We used the NCDB definition of median income quartile according to the proportion of income range in the patient's area of residence for income categories. The category of residence is based on information established by the United States Department of Agriculture Economic Research Services.[107]

Our outcome variables were refusal of recommended treatment and five-year overall mortality. Refusal of recommended treatment was defined as standard therapies recommended by a physician(s) and refused by the patient. We analyzed data of those who were recommended chemoradiotherapy among LS-SCLC and chemotherapy among ES-SCLC patients. Our analysis focused particularly on treatment refusal by patients who were recommended the above therapies,

through the comparison of their median survival to those who accepted recommended treatment. In addition, we examined the effect of treatment refusal on patient survival in the multivariable model.

*Statistical Analysis*

The chi-square test was used to examine differences in demographic and clinical characteristics of patients with limited and extensive stages of SCLC who refused and received the recommended treatment. We used multivariable logistic regression to examine factors associated with refusal of chemoradiotherapy among patients with LS-SCLC and refusal of chemotherapy among patients with ES-SCLC. Backward selection was used to fit the multivariable logistic regression model. Changes in the proportion of treatment refusal over time for cases diagnosed between 2003 and 2012 are shown graphically in Figure 4.2. We used the Kaplan–Meier method to estimate survival probabilities and log-rank test to assess survival differences. We performed multivariable Cox Proportional Hazards (PH) regression to examine the effect of treatment refusal on the risk of mortality adjusted for other factors. The PH assumption was tested using the log–log plots; all predictors met the proportionality assumption. Analyses were performed using the SAS software version 9.4 (SAS Institute; Cary, NC).

*Confidentiality and Ethics*

We used data from a de-identified NCDB file. The ACS and CoC have not verified, and neither is responsible for the analytic and statistical methods utilized in this study. The statements made in the discussion and the conclusions drawn from these data are solely the authors' responsibility. This study has been classified as exempt by University of Nebraska Medical Center's Institutional Review Board due to the use of de-identified data.

## Results

### *Demographic and Clinical Characteristics*

Of the 107,988 SCLC cases included in the analysis, 40,432 cases were diagnosed with LS-SCLC and 67,556 cases with ES-SCLC. Comparison of characteristics of patients who received and refused treatment for LS-SCLC and ES-SCLC are presented in Table 3.1. Separate analyses among those LS-SCLC and ES-SCLC showed that a higher proportion of patients of older-onset age (> 70 years), female and treated at the comprehensive community cancer program refused the recommended treatment modalities ($p < 0.001$). Interestingly, those without comorbidity had a higher proportion of refusal than those with comorbidities.

For the first-course treatment (data not shown), of the LS-SCLC patients (n = 40,432) recommendation for chemoradiotherapy was given to 75% of the cases. Among patients diagnosed with ES-SCLC (n = 67,556), the majority of them were recommended either for chemotherapy (47%) or chemoradiotherapy (45%).

### *The Trend of Treatment Refusal*

In total, 1,898 cases declined the recommended chemoradiotherapy of LS-SCLC and the recommended chemotherapy of ES-SCLC. Figure 4.2 shows an increase in the proportion of refusal of each therapy over 10 years. Overall, refusal of the recommended chemoradiotherapy among patients diagnosed with LS-SCLC was 1.34% and refusal of the recommended chemotherapy among ES-SCLC patients was 4.7%. Analysis of 10 years' worth of data shows that the increase in refusal among those with ES-SCLC was higher (50%) than it was among those with LS-SCLC (34%).

### *Factors Associated with Treatment Refusal*

After adjusting for demographic and clinical characteristics, we found that age at diagnosis, gender, insurance status, and comorbidity score were associated with the refusal of

chemoradiotherapy among LS-SCLC patients (Table 3.2). Patients diagnosed at age > 70 years were more likely to refuse treatment than those aged 50–70 years; the adjusted odds ratio (AOR) for refusal of chemoradiotherapy was 3.50 (95% CI: 2.77–4.44). Women were more likely to refuse recommended chemoradiotherapy than men, AOR was 1.29 (95% CI: 1.05–1.58). Compared with those with private insurance, uninsured patients were more likely to refuse treatment (AOR = 3.61, 95% CI: 2.05–6.35). In addition, we found that patients with comorbid conditions were more likely to refuse recommended chemoradiotherapy than those without comorbidity, AOR was 2.54 (95% CI: 1.94–3.31).

The multivariable logistic regression analysis showed that similar factors, as those observed in the analysis of LS-SCLC, were associated with refusal of chemotherapy among ES-SCLC patients (Table 3.2). Patients diagnosed at age > 70 years were more likely to refuse chemotherapy than those age 50–70 years (AOR = 2.25; 95% CI: 1.99–2.55). Women were more likely to refuse recommended treatment than men (AOR = 1.42; 95% CI: 1.27–1.58). Uninsured patients were more likely to refuse chemotherapy than those with private insurance (AOR = 1.76; 95% CI: 1.29–2.40). ES-SCLC patients with comorbidities were more likely to refuse chemotherapy than patients without comorbidity, AOR was 1.43 (95% CI: 1.23–1.65). As previous studies had suggested,[131,132] interactions of race with variables including gender, insurance status, and comorbidity were examined separately for both LS-SCLC and ES-SCLC, but no significant association was found.

*The Survival of SCLC Cases*

The overall median survival for all SCLC patients included in the analysis was 9.4 months. Among LS-SCLC patients who were recommended chemoradiotherapy, the median survival of patients who refused and received the treatment were 3 and 18 months, respectively ($p < 0.001$) (Figure 4.3). For ES-SCLC patients, median survival of those who refused chemotherapy was 1 month compared with 7.5 months of patients who received treatment ($p <$

0.001). Within one year following the diagnosis (data not shown) among LS-SCLC patients who were recommended chemoradiotherapy, 67% of patients who received the treatment had survived, compared with 14% of those who declined. The five-year survival of LS-SCLC patients who received chemoradiotherapy was 17% compared with only 2% of those who refused (Figure 4.3). For ES-SCLC, the one-year survival of patients who received the recommended chemotherapy was 25%, compared with 3% of those who refused.

We included age, gender, primary payer, category of residence, presence of comorbidity, facility, and treatment status in multivariable analyses using Cox PH regression. Results are presented in Table 3.3 and indicate that among LS-SCLC patients recommended chemoradiotherapy, those who refused treatment had a higher risk of mortality than those who received treatment (hazard ratio [HR] = 4.96; 95% CI: 4.45–5.53). Similarly, among ES-SCLC patients who were recommended chemotherapy, patients who refused treatment had a higher risk of mortality than those who received (HR = 3.69; 95% CI: 3.48–3.92).

**Discussion**

Our study found that the majority of first-course treatments received by SCLC patients in the database met national clinical practice guidelines, which include a combination of chemoradiotherapy for LS-SCLC and chemotherapy alone for ES-SCLC.[55,133] Regarding survival among both LS-SCLC and ES-SCLC groups, patients who accepted recommended treatment had significantly higher survival than those who refused. The overall refusal of the recommended chemoradiotherapy among LS-SCLC patients was 1.34% and refusal of chemotherapy among ES-SCLC patients was 4.7%. These proportions are smaller than the overall treatment refusal reported by Ward et al., which was 9% from analysis of 11 cancer sites.[95] Our analyses indicated that over time there were increases in the proportions of treatment refusal of both LS and ES-SCLC patients. This was particularly so among ES-SCLC patients, where the refusal of treatment

increased by 50% in 10 years. The fact that three-fourths of SCLC cases are diagnosed with ES-SCLC suggests that our findings on treatment refusal deserve special attention. Aizer et al. indicate that compared with other cancers, refusal of treatment among SCLC patients was more likely to result in death due to cancer.[63]

Of factors associated with treatment refusal, age at diagnosis was significantly associated with refusal of both chemoradiotherapy for LS-SCLC and chemotherapy for ES-SCLC. After adjusting for other characteristics, patients diagnosed at a younger age were less likely to refuse treatment compared with older patients. A meta-analysis among LS-SCLC suggested that due to the toxicity associated with chemoradiotherapy, the survival benefit from treatment was limited to younger patients.[88]

However, other studies have shown that both older and younger patients respond just as well to a combined modality therapy.[89,90] A recent study using NCDB data suggested that older patients who received combined modality therapy had a better overall survival than for chemotherapy alone.[134] Younger patients are considered to have better performance status, less comorbid conditions, and increased life expectancy, which are all factors that support the decision to agree to cancer treatment.[135] Older patients, on the other hand, have increased concerns regarding the tolerability of chemotherapy, treatment duration and effectiveness, as well as comorbid conditions that affect the decision to decline the offered treatment.[93,135] Analyses of the population and facility-based data in previous studies have shown a continuous increase in the proportion of SCLC patients diagnosed who were over the age of 70 years.[136-138] If more SCLC patients are diagnosed at an older age, it may be reasonable to expect that the proportion of treatment refusal will continue to rise, due in part to the aforementioned array of concerns of older patients.

Regarding association with gender, previous studies have suggested an increased incidence of SCLC cases among women.[139,140] Women with SCLC were also shown to have better survival than men,[128,139] with gender differences in survival being linked to patients'

perceptions of cancer care.[100,101] A recent study by Lee et al. showed that more women did not receive active cancer therapy (no treatment) for their initial treatment modality of SCLC.[141] These findings are in agreement with our results, which suggested that women were more likely to refuse the recommended chemoradiotherapy for LS-SCLC and chemotherapy for ES-SCLC. Refusal linked to gender may occur because women with advanced cancer tend to value the quality of life more than just prolonging life.[142] As also indicated in other cancer studies, women seemed to be more vulnerable to treatment toxicities than men, and were more likely than men to plan for other things in their end-of-life rather than repeatedly visiting medical facilities to complete cancer treatment series.[100,143] These perceptions may affect women's decisions to decline recommended cancer treatment. Our findings suggest the need for future studies to investigate the perception of SCLC treatment and expectations regarding their cancer treatment among women.

Uninsured patients were 2–3 times more likely to decline chemoradiotherapy for LS-SCLC and to decline chemotherapy for ES-SCLC than those with private insurance. Other studies among lung cancer cases have been suggested that uninsured patients were more likely to refuse the offered cancer treatment.[103,144] In addition, Halpern et al. also suggested that the uninsured were more likely to be diagnosed with advanced stage disease.[103] The American Society of Clinical Oncology has raised concerns about inequities in cancer care due to insurance status.[145] A study by Duh et al. estimated that the average cost of IV chemotherapy for SCLC was $788 per visit or $9,449 per treatment course (three visits per cycle for four cycles).[146] For uninsured patients, these costs may affect their decision to accept or decline recommended cancer treatment. Furthermore, any factor that delays treatment, could result in a more advanced and aggressive disease. To ensure delivery of quality cancer treatment and optimize patient outcomes, it is important to identify and remove impediments related to the health payer.

Results of survival analysis in this study demonstrate that the one-year survival of LS-SCLC patients who received chemoradiotherapy was five times higher than those who refused.

Among ES-SCLC, those who received chemotherapy were eight times more likely to survive for one year compared with those who refused recommended treatment. Similar to our study, Lally et al. and Behera et al. have previously suggested better survival rates among SCLC patients who received treatment than those who did not.[136,147] Regardless of the benefit on survival of receiving treatment, patient autonomy and locus of control remain important aspects of care. Patient–provider communication and patient education are essential in decision-making to increase patient acceptance of standard recommended treatment.

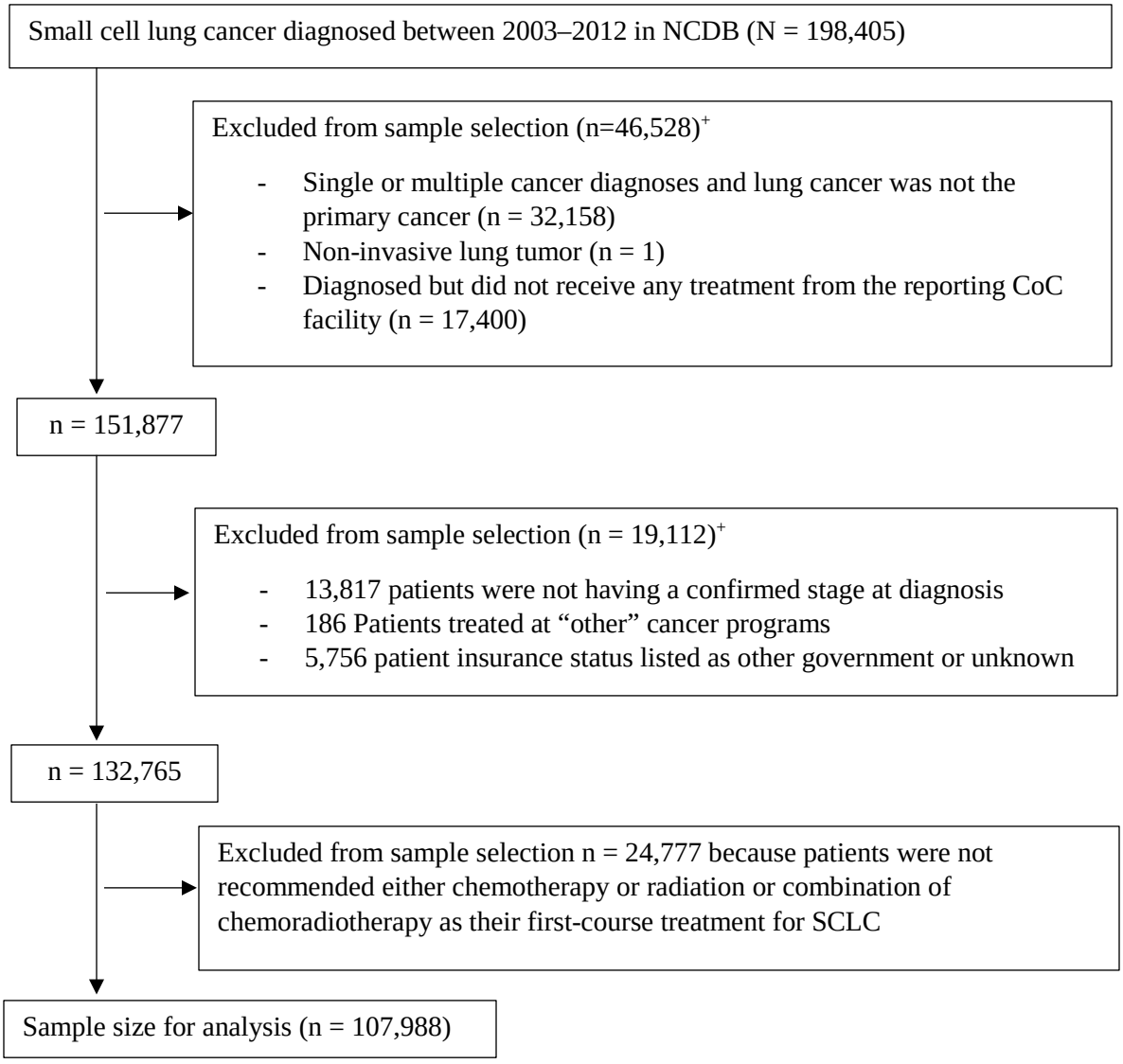
To our knowledge, our study is the most comprehensive one that has analyzed treatment refusal among SCLC patients using a national facility-based database. We specifically examined the treatment refusal of chemoradiotherapy for LS-SCLC and chemotherapy alone for ES-SCLC, as these have the strongest evidence bases as stage-specific recommended treatments modalities for SCLC patients. Our findings are relevant for patient management and future studies. The main strengths of our study are in the use of comprehensive clinical information including cancer stage and treatment recommendations, and a large sample size of SCLC cases included in our analyses. We used the database that includes approximately three-fourths of newly diagnosed cancer in the US population.[107,112]

The main limitations of our study are those seen with retrospective and database studies in general. Although the database covers a majority of cancer cases in the US, around 20% of newly diagnosed are not captured in the data.[103] However, only marginal differences between NCDB and the SEER data have been acknowledged and should not meaningfully affect our findings.[148] Our findings suggested the necessity for future studies to focus on factors that might contribute to treatment decision, for example patient–physician interactions, patient education regarding cancer treatment and care, and patient support networks.

## Conclusions

Although the proportion of patients refusing treatment for SCLC is relatively low, the increase in the treatment refusal over time is concerning. Older age at diagnosis, female gender, uninsured status, and comorbidities were associated with higher refusal of chemoradiotherapy among LS-SCLC and higher refusal of chemotherapy among ES-SCLC patients. It is important for health providers and policymakers to not only make good treatment recommendations but also consider the ways their recommendations are delivered to patients. Interventions targeting factors associated with higher treatment refusal may increase acceptance of recommended treatment and ultimately improve patient survival.

Figure 3. 1 Sample Selection




+ *Criteria are non-mutually exclusive*

Figure 3. 2 Refusal of Recommended SCLC Treatment by Stage at Diagnosis, NCDB 2003–2012

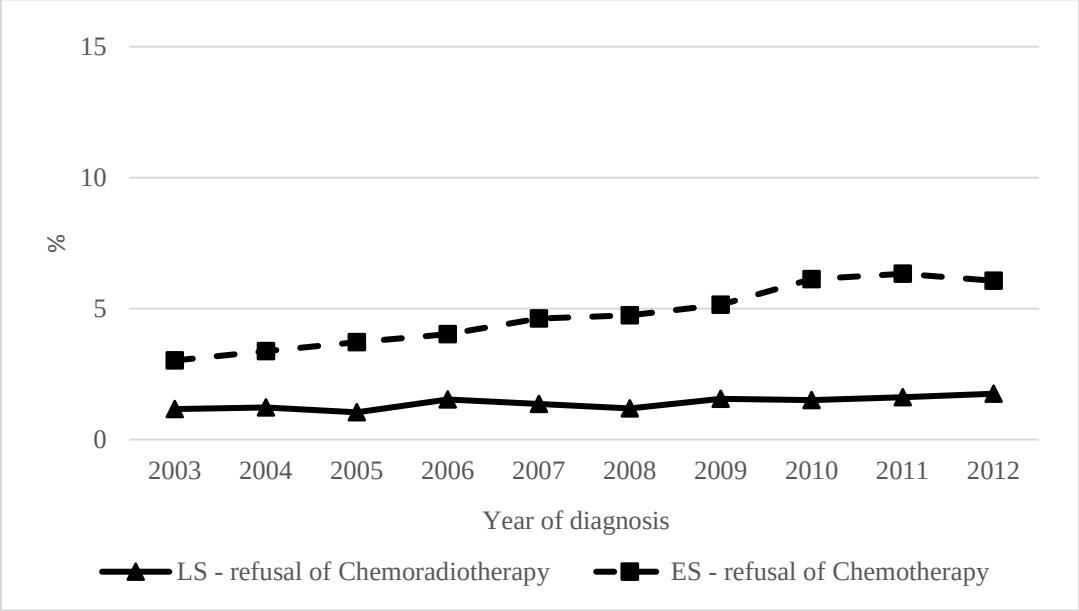
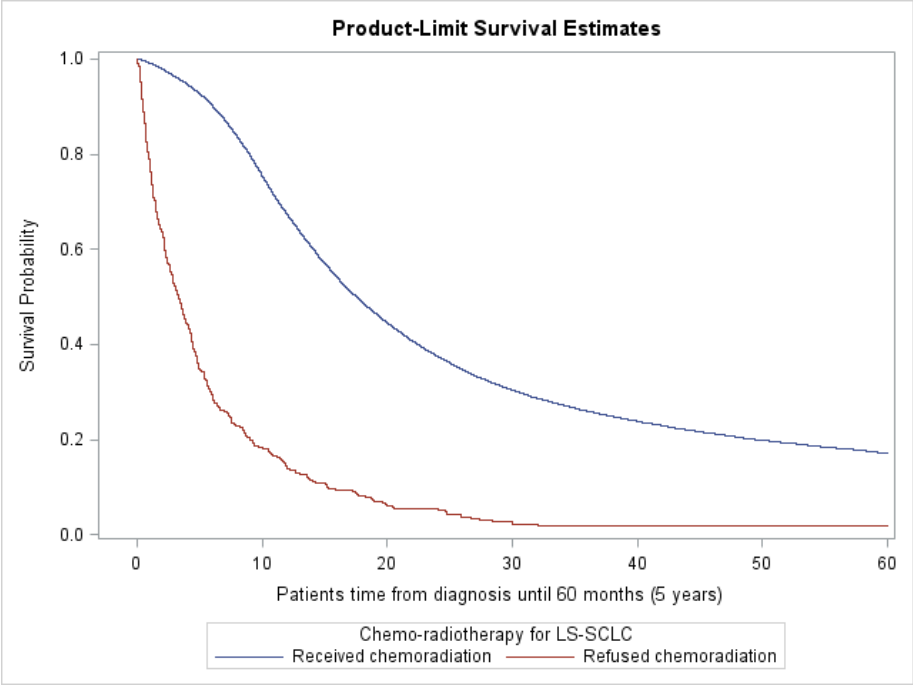


Figure 3. 3 Survival Plots of Chemoradiotherapy for LS-SCLC and Chemotherapy for ES-SCLC



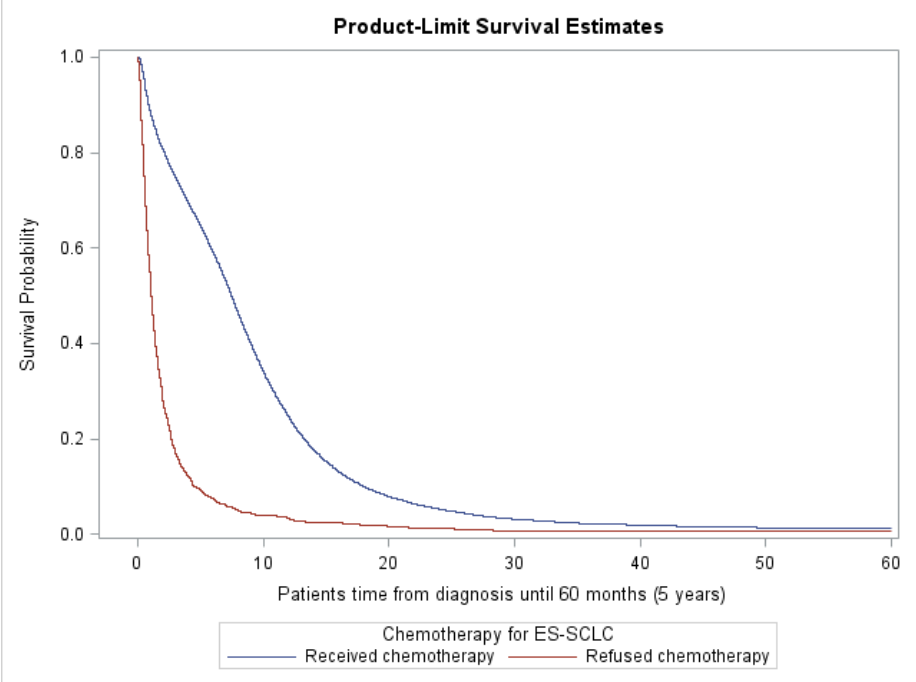



Table 3. 1 Characteristics of Small Cell Lung Cancer Cases Who Received and Refused Treatment

| Characteristics | Limited Stage+ (n = 30,585) | | | Extensive Stage++ (n = 31,679) | | |
|---|---|---|---|---|---|---|
| | Received n = 29,001 n (%) | Refused n = 409 n (%) | *p* value | Received n = 29,792 n (%) | Refused n = 1,489 n (%) | *p* value |
| Age at diagnosis (years) | | | | | | |
| < 50 | 2,280 (7.9) | 8 (2.0) | < 0.001 | 1,736 (5.8) | 34 (2.3) | < 0.001 |
| 50–70 | 18,950 (65.3) | 142 (34.7) | | 17,886 (60.0) | 573 (38.5) | |
| > 70 | 7,771 (26.8) | 259 (63.3) | | 10,170 (34.1) | 882 (59.2) | |
| Gender | | | | | | |
| Male | 12,816 (44.2) | 156 (38.1) | 0.014 | 15,566 (52.3) | 651 (43.7) | < 0.001 |
| Female | 16,185 (55.8) | 253 (61.9) | | 14,226 (47.8) | 838 (56.3) | |
| Race | | | | | | |
| White | 25,972 (89.6) | 362 (88.5) | 0.470 | 27,047 (90.8) | 1,358 (91.2) | 0.542 |
| Black | 2,370 (8.2) | 34 (8.3) | | 2,034 (6.8) | 92 (6.2) | |
| Others/unknown | 659 (2.3) | 13 (3.2) | | 711 (2.4) | 39 (2.6) | |
| Median Income Quartiles 2008–2012 | | | | | | |
| < $ 38,000 | 6,290 (21.7) | 100 (24.5) | 0.101 | 6,188 (20.8) | 317 (21.3) | 0.664 |
| $ 38,000–$ 47,999 | 8,116 (28.0) | 118 (28.9) | | 7,924 (26.6) | 398 (26.7) | |
| $ 48,000–$ 62,999 | 7,510 (25.9) | 100 (24.5) | | 7,784 (26.1) | 402 (27.0) | |
| $ 63,000 + | 6,298 (21.7) | 88 (21.5) | | 6,899 (23.2) | 330 (22.2) | |
| Unknown | 787 (2.7) | 3 (0.7) | | 997 (3.4) | 42 (2.8) | |
| Category Residence | | | | | | |
| Metro counties | 21,633 (74.6) | 310 (75.8) | 0.228 | 22,293 (74.8) | 1,119 (75.2) | 0.681 |
| Urban counties | 5,428 (18.7) | 81 (19.8) | | 5,275 (17.7) | 264 (17.7) | |
| Rural counties | 723 (2.5) | 9 (2.2) | | 781 (2.6) | 43 (2.9) | |
| Unknown | 1,217 (4.2) | 9 (2.2) | | 1,443 (4.8) | 63 (4.2) | |
| Insurance status | | | | | | |
| Uninsured | 1,262 (4.4) | 17 (4.2) | < 0.001 | 1,436 (4.8) | 57 (3.8) | < 0.001 |
| Private insurance | 10,661 (36.8) | 46 (11.3) | | 9,056 (30.4) | 222 (14.9) | |
| Medicaid | 2,416 (8.3) | 24 (5.9) | | 2,421 (8.1) | 75 (5.0) | |
| Medicare | 14,662 (50.6) | 322 (78.7) | | 16,879 (56.7) | 1,135 (76.2) | |
| Charlson/Deyo Comorbid Conditions (CDCC) | | | | | | |
| No comorbid condition | 18,058 (62.3) | 169 (41.3) | < 0.001 | 16,269 (54.6) | 664 (44.6) | < 0.001 |
| Score 1 | 7,974 (27.5) | 154 (37.7) | | 9,193 (30.9) | 530 (35.6) | |
| Score 2 | 2,969 (10.2) | 86 (21.0) | | 4,330 (14.5) | 295 (19.8) | |
| CoC Facility | | | | | | |
| Community Cancer Program | 4,323 (14.9) | 75 (18.3) | 0.036 | 4,438 (14.9) | 218 (14.6) | 0.002 |
| Comprehensive Community Cancer Program | 17,704 (61.1) | 254 (62.1) | | 17,941 (60.2) | 959 (64.4) | |
| Academic/Research Program | 6,974 (24.1) | 80 (19.6) | | 7,413 (24.9) | 312 (21.0) | |

+ LS-SCLC patients who were recommended chemoradiotherapy, including those who did not receive for unknown reason

++ ES-SCLC patients who were recommended chemotherapy, including those who did not receive for unknown reason

Table 3. 2 Multivariable Logistic Regression of Factors Associated with Refusal of Small Cell Lung Cancer Treatment

| Characteristics | | AOR | 95% CI | *p* value |
|---|---|---|---|---|
| ***Limited Stage – SCLC*** | | | | |
| Age at diagnosis (years) | 50–70 | Ref | | < 0.001 |
| | < 50 | 0.47 | 0.22–1.01 | |
| | > 70 | 3.50 | 2.77–4.44 | |
| Gender | Male | Ref | | 0.016 |
| | Female | 1.29 | 1.05–1.58 | |
| Primary Payer | Private insurance | Ref | | < 0.001 |
| | No insurance | 3.61 | 2.05–6.35 | |
| | Medicaid | 2.50 | 1.51–4.12 | |
| | Medicare | 2.41 | 1.72–3.38 | |
| CDCC | No comorbid | Ref | | < 0.001 |
| | Score 1 | 1.86 | 1.49–2.33 | |
| | Score 2 | 2.54 | 1.94–3.31 | |
| ***Extended Stage – SCLC*** | | | | |
| Age at diagnosis (years) | 50–70 | Ref | | < 0.001 |
| | < 50 | 0.73 | 0.51–1.04 | |
| | > 70 | 2.25 | 1.99–2.55 | |
| Gender | Male | Ref | | < 0.001 |
| | Female | 1.42 | 1.27–1.58 | |
| Primary Payer | Private insurance | Ref | | < 0.001 |
| | No insurance | 1.76 | 1.29–2.40 | |
| | Medicaid | 1.32 | 1.01–1.74 | |
| | Medicare | 1.72 | 1.46–2.02 | |
| CDCC | No comorbid | Ref | | < 0.001 |
| | Score 1 | 1.29 | 1.15–1.46 | |
| | Score 2 | 1.43 | 1.23–1.65 | |

AOR = Adjusted odds ratio CI: Confidence interval

Note: In the final model variables **race, category of residence, and facility** were not significantly associated with treatment refusal among LS-SCLC and ES-SCLC.

Table 3. 3 Multivariable Cox Regression of Factors Associated with Survival of SCLC Cases

| Characteristics | | AHR | 95% CI | *p* value |
|---|---|---|---|---|
| ***Limited Stage – SCLC***$^{+}$ | | | | |
| Age at diagnosis (years) | 50–70 | Ref | | < 0.001 |
| | < 50 | 0.91 | 0.86–0.97 | |
| | > 70 | 1.27 | 1.23–1.32 | |
| Gender | Male | Ref | | < 0.001 |
| | Female | 0.82 | 0.79– 0.84 | |
| Primary Payer | Private insurance | Ref | | < 0.001 |
| | No insurance | 1.17 | 1.09–1.26 | |
| | Medicaid | 1.20 | 1.14–1.27 | |
| | Medicare | 1.18 | 1.14–1.23 | |
| CDCC | No comorbid | Ref | | < 0.001 |
| | Score 1 | 1.18 | 1.14–1.21 | |
| | Score 2 | 1.36 | 1.30–1.43 | |
| Facility | Community | Ref | | < 0.001 |
| | Comprehensive Community | 0.95 | 0.91–0.98 | |
| | Academic/Research | 0.91 | 0.87–0.95 | |
| Combination of chemoradiation | Received | Ref | | < 0.001 |
| | Refused | 4.96 | 4.45–5.53 | |
| ***Extended Stage – SCLC***$^{++}$ | | | | |
| Age at diagnosis (years) | 50–70 | Ref | | < 0.001 |
| | < 50 | 0.95 | 0.90–1.00 | |
| | > 70 | 1.17 | 1.13–1.20 | |
| Gender | Male | Ref | | < 0.001 |
| | Female | 0.85 | 0.83–0.87 | |
| Race | White | Ref | | 0.012 |
| | Black | 0.93 | 0.89–0.98 | |
| | Others/unknown | 0.95 | 0.87–1.03 | |
| Primary Payer | Private insurance | Ref | | < 0.001 |
| | No insurance | 1.17 | 1.10–1.25 | |
| | Medicaid | 1.11 | 1.06–1.17 | |
| | Medicare | 1.12 | 1.09–1.16 | |
| CDCC | No comorbid | Ref | | < 0.001 |
| | Score 1 | 1.16 | 1.13–1.20 | |
| | Score 2 | 1.41 | 1.36–1.47 | |
| Facility | Community | Ref | | 0.005 |
| | Comprehensive Community | 1.01 | 0.98–1.05 | |
| | Academic/Research | 0.96 | 0.93–1.00 | |

| Characteristics | | AHR | 95% CI | *p* value |
|---|---|---|---|---|
| Combination of chemotherapy | Received | Ref | | < 0.001 |
| | Refused | 3.69 | 3.48–3.92 | |

AHR = Adjusted hazard ratio CI: Confidence interval
+ LS-SCLC patients who were recommended chemoradiotherapy
++ ES-SCLC patients who were recommended chemotherapy
Note: In the final model variables **category of residence** was not significantly associated with survival among LS-SCLC and ES-SCLC.

# CHAPTER 4

# FACTORS ASSOCIATED WITH REFUSAL OF RECOMMENDED TREATMENT BY PATIENTS WITH NON-SMALL CELL LUNG CANCER: AN ANALYSIS OF NATIONAL CANCER DATABASE 2003–2012


## Abstract

**Objectives:** Refusal of recommended treatment contributes to a higher number of cancer-related deaths. Our study aimed to analyze factors associated with treatment refusal among non-small cell lung cancer (NSCLC) patients. **Materials and Methods:** We analyzed data on 884,817 NSCLC patients from the National Cancer Database diagnosed between 2003 and 2012. The analysis of treatment refusal was carried out for surgery (stages I and II) and chemotherapy (stages III and IV). Logistic regression was used to investigate factors associated with treatment refusal. **Results:** Patients diagnosed at age < 50 years were less likely to refuse treatment than those age 50–70 years; the adjusted odds ratio (AOR) of treatment refusal comparing these two groups was 0.37 for surgery and 0.58 for chemotherapy. Compared with patients with private insurance, uninsured patients were more likely to refuse surgery (AOR = 2.47) and chemotherapy for stage III (AOR = 2.56) and IV (AOR = 2.50). Patients with comorbid conditions were less likely to refuse surgery for stage I and II (AOR = 0.87) but more likely to refuse chemotherapy for stage III (AOR = 1.94) and stage IV (AOR = 1.99). In comparison with those treated at community facilities, patients treated at academic facilities were less likely to refuse surgery (AOR = 0.45) and chemotherapy for stage III (AOR = 0.78), and stage IV (AOR = 0.68). **Conclusions:** Multiple patient and system-related factors, such as older age at diagnosis, comorbid conditions, and uninsured status, were associated with higher treatment refusal. Consideration of these factors is essential in patient education and patient–provider

communication to increase patient acceptance of the recommended treatment that may improve patient outcomes.

## Introduction

An estimated 234,030 new cases of lung cancer will be diagnosed in the US in 2018.[12] The disease is responsible for one in four cancer deaths; more than any other cancer in the US.[12] Many studies have reported the underuse of treatment modalities recommended to cancer patients, with lung cancer having higher treatment refusal rates in comparison to other cancers.[63,95,97] Refusal of recommended cancer treatment is a contributing factor to cancer-related death and could be a potential cause for failure to achieve a significant reduction in lung cancer mortality.[12,63,104]

Previous studies that used cancer registry data have provided important insights; however, because of data limitations, they have not typically examined refusal of chemotherapy.[45,71,148] The exclusion of chemotherapy is problematic as it is currently considered the most important treatment modality for advanced non-small cell lung cancer (NSCLC) and forms an integral part of care for patients with early and locally advanced disease.[24,149] Although surgery provides an opportunity to cure nonmetastatic cancer, patient responses to this radical treatment are complex and need to be studied further.[63] The primary purpose of our study was to examine factors associated with treatment refusal of surgery and chemotherapy by NSCLC patients.

## Materials and Methods

### *Study Population, Design, and Data Source*

Our study utilized the National Cancer Database (NCDB), a joint project of the American Cancer Society (ACS) and the Commission on Cancer (CoC) of the American College of Surgeons (ACoS). It serves as a nationwide cancer surveillance program that captures approximately 70% of newly diagnosed cancers in the US.[107,112]

In this cross-sectional study, all patients diagnosed with NSCLC between 2003 and 2012 were eligible for inclusion in the analysis, with 1,237,129 NSCLC cases recorded in the database. We used the following eligibility criteria for sample selection: (1) diagnosed with a primary invasive lung cancer and (2) diagnosed at CoC-accredited facilities and received all/part of the treatment from CoC facilities. Figure 3.1 shows a flow chart of sample selection, with a final sample size of 884,817 after the application of inclusion criteria.

*Exposures and Outcomes*

We included information on patient demographic and clinical characteristics as predictor variables and examined refusal of recommended treatment as the study outcome. The NCDB defines treatment refusal as a condition when patients refuse the standard therapy recommended by their physician. Patient responses were recorded for each therapy, e.g., surgery and chemotherapy, separately.[111] If patients refused the recommended therapy, they were included in the refusal group; if there was no contraindication recorded, all others were included in the acceptance group. It should be noted that the NCDB does not record information regarding patients' follow-up for a second opinion. The standard quality measures for evaluation of lung cancer directed-therapy in NSCLC used by the Veteran Health Administration include recommendations of curative surgery for stages I and II and recommendations for chemotherapy for stages III and IV.[132] Therefore, we focused the treatment refusal analysis on these therapies for these respective stages.

*Statistical Analysis*

We compared demographic and clinical characteristics of patients who refused to those who accepted the recommended therapy. A bivariate analysis was conducted to examine potential association of predictor variables with an outcome, i.e., refusal of surgery or refusal of chemotherapy. Predictor variables that showed statistically significant association with outcome

in the bivariate analysis or variables that are important from a clinical or biological standpoint were included in multivariable analyses.

Predictors included in multivariable logistic regression analysis were: age at diagnosis, gender, race, primary payer, residence category, histologic type, tumor size, comorbid conditions, and facility type. The dataset was partitioned into three parts according to cancer stage: refusal of surgery for stages I and II, refusal of chemotherapy for stage III, and for refusal of chemotherapy for stage IV. All tests were two-sided, with a $p$-value $< 0.05$ considered statistically significant. All analyses were conducted using the SAS software version 9.4 (SAS Institute; Cary, NC).

*Confidentiality and Ethics*

The data used in the present study were derived from a de-identified NCDB file. Results reported in this study are in compliance with the privacy requirements of the Health Insurance Portability and Accountability Act of 1996. The ACS and CoC have not verified, and neither is responsible for the analytic and statistical methods utilized in this study. The statements made in the discussion and the conclusions drawn from these data are solely those of the investigators. Given that it uses existing and de-identified data, this study has been classified as exempt by the Institutional Review Board of University of Nebraska Medical Center.

**Results**

Demographic and clinical characteristics of NSCLC patients are presented in Table 4.1. The cohort included predominantly White patients (85%). There was a male preponderance (53%), and 51% of patients were diagnosed between 50 and 70 years of age. The majority of patients were covered by Medicare (57%) and private insurance (29%), while approximately 4% were uninsured. More than half of patients were diagnosed with advanced stages, specifically stage III (23%) and stage IV (40%).

Of the 257,811 patients diagnosed with stages I and II, surgery was recommended for 73%. There were 199,166 patients diagnosed with stage III and 354,892 diagnosed with stage IV. Chemotherapy was recommended for 69% and 57% of these patients, respectively (data not shown). Figure 3.2 shows a higher proportion of treatment refusal as the stage increased; the proportion of patients who refused treatments ranged from 2–9%.

Among patients diagnosed with stages I and II, and for whom surgery was recommended, a higher percentage of older-onset patients (age > 70 years) refused treatment (71%) (Table 4.2). A higher proportion of those who were covered by private insurance agreed to undergo surgery, while a lower proportion of patients with Medicare agreed ($p < 0.001$). Interestingly, patients with no comorbid conditions were more likely to refuse surgery. Patients without comorbidity were more likely to agree to the recommended chemotherapy than those with comorbid conditions ($p < 0.001$).

Results of the multivariable analysis are presented in Table 4.3. Compared with intermediate-onset patients (age 50–70 years), patients diagnosed at younger-onset (age < 50 years) were less likely to refuse treatment, while older-onset patients were more likely to refuse treatment. The adjusted odds ratio (AOR) was 0.37 for refusal of surgery (95% CI: 0.28–0.49) and AOR = 0.58 for refusal of chemotherapy for stage III (95% CI: 0.49–0.68). Uninsured patients were more likely to refuse treatment than those with private insurance, with the AOR being 2.47 for refusal of surgery (95% CI: 1.89–3.20) and AOR = 2.56 for refusal of chemotherapy for stage III (95% CI: 2.19–2.98) and AOR = 2.50 for stage IV (95% CI: 2.27–2.75).

Patients with comorbid conditions were less likely to refuse surgery, but more likely to refuse chemotherapy. In addition, we found that patients treated at academic facilities were less likely to refuse surgery (AOR = 0.45; 95% CI: 0.40–0.50) or chemotherapy (for stage III AOR =

0.78; 95% CI: 0.72–0.86; and for stage IV AOR = 0.68; 95% CI: 0.64–0.73). Potential interaction of race with insurance status was examined, and we found no significant association.

**Discussion**

This study is one of a very limited number of studies that have examined the association of various factors related to treatment refusal among NSCLC patients. The analysis of refusal of surgery and chemotherapy in this study delineate comprehensive care of patients with early and advanced stages of lung cancer. Using similar category of treatment refusal, analyses of 11 cancer sites, including lung cancer by Ward et al., suggested that surgery and chemotherapy were the most commonly refused treatment modality.[95] Our results showed that the proportion of treatment refusal ranged from 2–9%. Use of a national facility-based cancer registry enabled us to analyze more clinical data than previous studies.

We found that older-onset patients were three times more likely to refuse surgery or chemotherapy than intermediate-onset patients. Similar findings were reported in studies of early-stage NSCLC patients.[97,99,132] De Rijke et al. reported that older age (75+ years) was the most important factor for patients not to receive standard treatment.[125] Among the older-onset patients, treatment refusal was frequently affected by fear of toxicity or treatment side effects, treatment duration, and patient beliefs about the effectiveness of the treatment offered.[92,93,99,150] A systematic review of patients' decisions in cancer treatment showed that older adults might choose the quality of life over survival prolongation.[93] In addition, older patients might have other diseases in addition to cancer that could affect treatment tolerability, effectiveness, and life expectancy.[93,99] Differences in priorities and comorbidities among older patients influence their decision to decline treatment offered.

Findings on the effect of gender have been mixed. Our analysis found no difference in surgical refusal between males and females with early-stage cancer. Similar findings have been reported in previous studies.[99,131] However, among patients diagnosed with stage III and stage IV and recommended chemotherapy, we observed that women were more likely to refuse treatment than men. Findings from a multisite cohort study among patients with advanced cancer also reported that women were less likely than men to agree to aggressive end-of-life treatments.[142] Explanations of the differences among patients with advanced cancer stages seem related to the individual patient's view of life, their values, and personal judgment. Women appeared more likely to understand that they had an incurable disease, which influenced their decision to forgo the treatment.[100] A different study among severely ill patients, including some cancer patients, suggested that women were more likely to believe that medical recommendations were only for comfort care rather than intended to prolong life.[101]

The American Society of Clinical Oncology has highlighted the issue of significant inequities in cancer care related to insurance status.[145] Previous studies have reported that lung cancer was among cancers with a high prevalence of uninsured cases in the US.[103,144] Our study found that 55,465 patients were on Medicaid and 33,254 patients were uninsured. Our analysis further revealed that patients without insurance and those on Medicaid were 2–3 times more likely to refuse surgery or chemotherapy than those with private insurance.

A national study of pathology and patterns of NSCLC care suggested that recommendation for surgery was determined more by cancer stage and patients' age than by comorbidity.[151] Conversely, other studies found that comorbid conditions were associated with a higher surgical refusal.[99,132,152] Our study found that patients without comorbidity were more likely to refuse surgery than those with comorbidity. It is possible that patients without comorbidity believe they are healthier and, therefore, choose to seek a second opinion before deciding to accept recommended surgery.[153] because surgery is considered a radical treatment, the

decision to have it might be affected by other nonclinical factors such as access to medical care, patient–physician interactions, and patient perception of the necessity of surgery.[99,132,153,154] As reported by Bradley et al., the length of stay and cost of inpatient care influence patients' decisions concerning whether or not to accept surgery, especially for those who are uninsured and underinsured.[155] The influence of these factors on patients' decisions to decline recommended treatment requires further investigation in future studies.

Finally, previous studies in lung cancer have reported that due to problems in accessing health facilities, those living in rural areas were more likely to refuse the treatment options than patients residing in urban area.[132,154] However, our study did not find this association, possibly due to a small proportion of patients coming from rural areas.

A few limitations of the study should be considered for interpretation of the study findings. About 20–25% of newly diagnosed cancer patients are treated at non-CoC facilities that are not part of the NCDB data.[103] However, Mettlin et al. reported marginal differences in patient and treatment characteristics between Surveillance, Epidemiology and End Results (SEER) and the NCDB.[148] The wide coverage and diverse nature of the CoC facilities, as well as the small differences, contribute to our confidence in the generalizability of the study findings. Another limitation of the NCDB data was that factors that may contribute to treatment refusal, such as patient's social support, patient–physician interactions, and level and type of psychological stressors were not measured. These important factors need to be examined further in future studies.

**Conclusions**

Multiple patient and system-related factors, such as older age at diagnosis, comorbid conditions, and uninsured status, were associated with higher treatment refusal. Consideration of

these factors is essential to develop strategies for patient education and patient–provider communication. Further investigations are needed to identify the beneficial treatments that cover both clinical and patient aspects.

Table 4. 1 Patient Demographic and Clinical Characteristics

| Characteristics | Total NSCLC cases N = 884,817 | % |
|---|---|---|
| Age at diagnosis (years) | | |
| < 50 | 57,674 | 6.5 |
| 50–70 | 449,339 | 50.8 |
| > 70 | 377,804 | 42.7 |
| Gender | | |
| Male | 471,891 | 53.3 |
| Female | 412,926 | 46.7 |
| Race | | |
| White | 750,676 | 84.8 |
| Black | 101,436 | 11.5 |
| Others/unknown | 32,705 | 3.7 |
| Primary Payer | | |
| Uninsured | 33,254 | 3.8 |
| Private insurance | 255,058 | 28.8 |
| Medicaid | 55,465 | 6.3 |
| Medicare | 506,989 | 57.3 |
| Other government | 11,278 | 1.3 |
| Unknown | 22,773 | 2.6 |
| Median Income Quartiles 2008–2012 | | |
| < $ 38,000 | 185,912 | 21.0 |
| $ 38,000–$ 47,999 | 222,090 | 25.1 |
| $ 48,000–$ 62,999 | 226,808 | 25.6 |
| $ 63,000 + | 224,291 | 25.4 |
| Unknown | 25,716 | 2.9 |
| Category Residence | | |
| Metro counties | 691,638 | 78.2 |
| Urban counties | 135,567 | 15.3 |
| Rural counties | 18,489 | 2.1 |
| Unknown | 39,123 | 4.4 |
| AJCC analytic stage | | |
| Stage I | 193,098 | 21.8 |
| Stage II | 64,713 | 7.3 |
| Stage III | 199,166 | 22.5 |
| Stage IV | 354,892 | 40.1 |
| *Missing*[+] | 72,948 | 8.2 |

[+]Missing include AJCC staging not applicable/unknown

| Characteristics | Total NSCLC cases N = 884,817 | % |
|---|---|---|
| Tumor size (cm) | | |
| ≤ 3 | 285,149 | 32.2 |
| 3–7 | 309,134 | 34.9 |
| > 7 | 85,714 | 9.7 |
| Tumor involvement at lung | 1,591 | 0.2 |
| Unknown | 203,229 | 23.0 |
| Charlson/Deyo Comorbid Conditions (CDCC)[$] | | |
| No comorbid condition | 524,606 | 59.3 |
| Score 1 | 248,723 | 28.1 |
| Score 2 | 111,488 | 12.6 |
| Histology | | |
| Non-small cell carcinoma | 150,323 | 17.0 |
| Squamous cell carcinoma | 214,879 | 24.3 |
| Adenocarcinoma | 368,423 | 41.6 |
| Large cell carcinoma | 30,363 | 3.4 |
| Others | 120,829 | 13.7 |
| CoC Facility | | |
| Community | 106,766 | 12.1 |
| Comprehensive Community | 499,651 | 56.5 |
| Academic/Research | 277,276 | 31.3 |
| Other cancer programs | 1,124 | 0.1 |
| First course treatment | | |
| Surgery | 167,109 | 18.9 |
| Radiotherapy | 126,556 | 14.3 |
| Chemotherapy | 108,457 | 12.3 |
| Surgery and chemo and/or radiotherapy | 80,520 | 9.1 |
| Chemotherapy and radiotherapy | 196,902 | 22.3 |
| No surgical, chemo or radiotherapy received | 196,022 | 22.2 |
| Unknown | 9,251 | 1.1 |

Table 4. 2 Characteristics of Patients Who Accepted vs. Refused Recommended Treatment: Surgery for Stage I-II, and Chemotherapy for Stage III-IV

| Characteristics | **Stage I and II – recommended surgery** | | | | *p* value | **Stage III and IV – recommended chemotherapy** | | | | *p* value |
|---|---|---|---|---|---|---|---|---|---|---|
| | Accepted | | Refused | | | Accepted | | Refused | | |
| | n = 181,721 | % | n = 4,313 | % | | n = 300,519 | % | n = 27,452 | % | |
| Age at diagnosis (years) | | | | | | | | | | |
| < 50 | 10,540 | 5.8 | 60 | 1.4 | < 0.001 | 28,982 | 9.6 | 886 | 3.2 | < 0.001 |
| 50–70 | 100,293 | 55.2 | 1,174 | 27.2 | | 183,158 | 61.0 | 10,207 | 37.2 | |
| > 70 | 70,888 | 39.0 | 3,079 | 71.4 | | 88,379 | 29.4 | 16,359 | 59.6 | |
| Gender | | | | | | | | | | |
| Male | 88,514 | 48.7 | 2,089 | 48.4 | 0.722 | 167,820 | 55.8 | 13,779 | 50.2 | < 0.001 |
| Female | 93,207 | 51.3 | 2,224 | 51.6 | | 132,699 | 44.2 | 13,673 | 49.8 | |
| Race | | | | | | | | | | |
| White | 160,718 | 88.4 | 3,569 | 82.8 | < 0.001 | 251,503 | 83.7 | 23,518 | 85.7 | < 0.001 |
| Black | 14,821 | 8.2 | 575 | 13.3 | | 37,138 | 12.4 | 2,899 | 10.6 | |
| Others/unknown | 6,182 | 3.4 | 169 | 3.9 | | 11,878 | 4.0 | 1,035 | 3.8 | |
| Primary Payer | | | | | | | | | | |
| Uninsured | 3,498 | 1.9 | 76 | 1.8 | < 0.001 | 13,659 | 4.6 | 1,237 | 4.5 | < 0.001 |
| Private insurance | 60,227 | 33.1 | 527 | 12.2 | | 110,836 | 36.9 | 4,521 | 16.5 | |
| Medicaid | 7,737 | 4.3 | 211 | 4.9 | | 22,961 | 7.6 | 1,935 | 7.1 | |
| Medicare | 104,808 | 57.7 | 3,388 | 78.6 | | 141,223 | 47.0 | 19,015 | 69.3 | |
| Other government | 1,632 | 0.9 | 45 | 1.0 | | 4,058 | 1.4 | 271 | 1.0 | |
| Unknown | 3,819 | 2.1 | 66 | 1.5 | | 7,782 | 2.6 | 473 | 1.7 | |
| Median Income Quartiles 2008–2012 | | | | | | | | | | |
| < $ 38,000 | 33,416 | 18.4 | 999 | 23.2 | < 0.001 | 60,778 | 20.2 | 6,194 | 22.6 | < 0.001 |
| $ 38,000–$ 47,999 | 44,258 | 24.4 | 1,120 | 26.0 | | 74,523 | 24.8 | 7,279 | 26.5 | |
| $ 48,000–$ 62,999 | 47,772 | 26.3 | 1,110 | 25.7 | | 77,712 | 25.9 | 6,970 | 25.4 | |
| $ 63,000 + | 52,117 | 28.7 | 1,016 | 23.6 | | 78,092 | 26.0 | 6,325 | 23.0 | |
| Unknown | 4,158 | 2.3 | 68 | 1.6 | | 9,414 | 3.1 | 684 | 2.5 | |
| Category Residence | | | | | | | | | | |
| Metro counties | 142,594 | 78.5 | 3,406 | 79.0 | 0.066 | 233,671 | 77.8 | 21,470 | 78.2 | < 0.001 |
| Urban counties | 28,246 | 15.5 | 690 | 16.0 | | 46,515 | 15.5 | 4,359 | 15.9 | |
| Rural counties | 3,722 | 2.1 | 76 | 1.8 | | 6,463 | 2.2 | 594 | 2.2 | |
| Unknown | 7,159 | 3.9 | 141 | 3.3 | | 13,870 | 4.6 | 1,029 | 3.8 | |

| Characteristics | Stage I and II – recommended surgery | | | | *p* value | Stage III and IV – recommended chemotherapy | | | | *p* value |
|---|---|---|---|---|---|---|---|---|---|---|
| | Accepted | | Refused | | | Accepted | | Refused | | |
| | n = 181,721 | % | n = 4,313 | % | | n = 300,519 | % | n = 27,452 | % | |
| Tumor size (cm) | | | | | | | | | | |
| < 3 | 112,687 | 62.0 | 2,202 | 51.1 | < 0.001 | 67,966 | 22.6 | 5,737 | 20.9 | < 0.001 |
| 3–7 | 58,503 | 32.2 | 1,629 | 37.8 | | 116,028 | 38.6 | 10,614 | 38.7 | |
| > 7 | 8,325 | 4.6 | 186 | 4.3 | | 37,415 | 12.5 | 3,533 | 12.9 | |
| Tumor involvement at lung | 9 | 0.0 | 0 | 0.0 | | 683 | 0.2 | 92 | 0.3 | |
| Unknown | 2,197 | 1.2 | 296 | 6.9 | | 78,427 | 26.1 | 7,476 | 27.2 | |
| CDCC | | | | | | | | | | |
| No comorbid condition | 93,470 | 51.4 | 2,477 | 57.4 | < 0.001 | 202,250 | 67.3 | 14,430 | 52.6 | < 0.001 |
| Score 1 | 64,179 | 35.3 | 1,185 | 27.5 | | 72,208 | 24.0 | 8,467 | 30.8 | |
| Score 2 | 24,072 | 13.3 | 651 | 15.1 | | 26,061 | 8.7 | 4,555 | 16.6 | |
| Histology | | | | | | | | | | |
| Non-small cell carcinoma | 8,439 | 4.6 | 660 | 15.3 | < 0.001 | 65,275 | 21.7 | 4,833 | 17.6 | < 0.001 |
| Squamous cell carcinoma | 53,797 | 29.6 | 1,119 | 25.9 | | 69,056 | 23.0 | 5,998 | 21.9 | |
| Adenocarcinoma | 97,382 | 53.6 | 1,213 | 28.1 | | 133,709 | 44.5 | 9,722 | 35.4 | |
| Large cell carcinoma | 6,148 | 3.4 | 78 | 1.8 | | 11,427 | 3.8 | 862 | 3.1 | |
| Others | 15,955 | 8.8 | 1,243 | 28.8 | | 21,052 | 7.0 | 6,037 | 22.0 | |
| CoC Facility | | | | | | | | | | |
| Community | 15,050 | 8.3 | 659 | 15.3 | < 0.001 | 37,828 | 12.6 | 4,226 | 15.4 | < 0.001 |
| Comprehensive Community | 101,367 | 55.8 | 2,474 | 57.4 | | 166,419 | 55.4 | 16,686 | 60.8 | |
| Academic/Research | 64,942 | 35.7 | 1,173 | 27.2 | | 95,898 | 31.9 | 6,495 | 23.7 | |
| Other cancer programs | 362 | 0.2 | 7 | 0.2 | | 374 | 0.1 | 45 | 0.2 | |

Table 4. 3 Multivariable Logistic Regression of Factors Associated with Treatment Refusal

| Characteristics | Refusal of Surgery (stage I and II) | | Refusal of Chemotherapy (stage III) | | Refusal of Chemotherapy (stage IV) | |
|---|---|---|---|---|---|---|
| | AOR | 95% CI | AOR | 95% CI | AOR | 95% CI |
| Age at diagnosis (years) | | $p < 0.001$ | | $p < 0.001$ | | $p < 0.001$ |
| 50–70 | Ref | | Ref | | Ref | |
| < 50 | 0.37 | 0.28 - 0.49 | 0.58 | 0.49 - 0.68 | 0.58 | 0.52 - 0.64 |
| > 70 | 3.42 | 3.15 - 3.71 | 3.16 | 2.97 - 3.37 | 2.68 | 2.56 - 2.81 |
| Gender | | $p = 0.056$ | | $p < 0.001$ | | $p < 0.001$ |
| Male | Ref | | Ref | | Ref | |
| Female | 1.07 | 1.00 - 1.14 | 1.31 | 1.24 - 1.38 | 1.25 | 1.20 - 1.30 |
| Race | | $p < 0.001$ | | $p = 0.019$ | | $p = 0.192$ |
| White | Ref | | Ref | | Ref | |
| Black | 2.25 | 2.04 - 2.49 | 1.06 | 0.98 - 1.15 | 0.99 | 0.93 - 1.05 |
| Others/unknown | 1.42 | 1.19 - 1.68 | 1.20 | 1.04 - 1.38 | 1.09 | 0.99 - 1.21 |
| Primary Payer | | $p < 0.001$ | | $p < 0.001$ | | $p < 0.001$ |
| Private insurance | Ref | | Ref | | Ref | |
| No insurance | 2.47 | 1.89 - 3.20 | 2.56 | 2.19 - 2.98 | 2.50 | 2.27 - 2.75 |
| Medicaid | 3.09 | 2.59 - 3.69 | 2.26 | 2.00 - 2.56 | 2.12 | 1.96 - 2.31 |
| Medicare | 2.04 | 1.84 - 2.27 | 1.75 | 1.61 - 1.89 | 1.69 | 1.60 - 1.79 |
| Other government | 2.92 | 2.10 - 4.04 | 1.55 | 1.21 - 1.98 | 1.48 | 1.20 - 1.82 |
| Category Residence | | $p = 0.249$ | | $p = 0.797$ | | $p = 0.455$ |
| Metro counties | Ref | | Ref | | Ref | |
| Urban counties | 0.99 | 0.90 - 1.08 | 0.98 | 0.91 - 1.05 | 0.98 | 0.93 - 1.03 |
| Rural counties | 0.81 | 0.63 - 1.04 | 0.96 | 0.81 - 1.14 | 0.94 | 0.82 - 1.07 |
| Histology | | $p < 0.001$ | | $p < 0.001$ | | $p < 0.001$ |
| Adenocarcinoma | Ref | | Ref | | Ref | |
| Non-small cell carcinoma | 6.16 | 5.54 - 6.85 | 1.12 | 1.04 - 1.21 | 1.05 | 1.00 - 1.11 |
| Squamous cell carcinoma | 1.43 | 1.31 - 1.57 | 1.22 | 1.14 - 1.31 | 1.21 | 1.15 - 1.28 |
| Large cell carcinoma | 1.08 | 0.84 - 1.37 | 0.96 | 0.82 - 1.12 | 1.18 | 1.06 - 1.32 |
| Others | 7.44 | 6.82 - 8.12 | 3.90 | 3.59 - 4.23 | 4.16 | 3.95 - 4.39 |
| Tumor size (cm) | | $p < 0.001$ | | $p = 0.015$ | | $p < 0.001$ |
| < 3 | Ref | | Ref | | Ref | |
| 3–7 | 1.33 | 1.24 - 1.42 | 1.06 | 1.00 - 1.13 | 1.06 | 1.01 - 1.11 |
| > 7 | 1.19 | 1.02 - 1.40 | 1.12 | 1.03 - 1.21 | 1.24 | 1.17 - 1.31 |

| Characteristics | Refusal of Surgery (stage I and II) | | Refusal of Chemotherapy (stage III) | | Refusal of Chemotherapy (stage IV) | |
|---|---|---|---|---|---|---|
| | AOR | 95% CI | AOR | 95% CI | AOR | 95% CI |
| Tumor involvement at the lung | < 0.001 | < 0.001 - ∞ | 1.90 | 0.93 - 3.89 | 1.53 | 1.19 - 1.96 |
| CDCC | | $p < 0.001$ | | $p < 0.001$ | | $p < 0.001$ |
| No comorbid | Ref | | Ref | | Ref | |
| Score 1 | 0.64 | 0.59 - 0.69 | 1.42 | 1.34 - 1.51 | 1.48 | 1.42 - 1.55 |
| Score 2 | 0.87 | 0.79 - 0.96 | 1.94 | 1.81 - 2.09 | 1.99 | 1.88 - 2.11 |
| Facility | | $p < 0.001$ | | $p < 0.001$ | | $p < 0.001$ |
| Community | Ref | | Ref | | Ref | |
| Comprehensive Community | 0.57 | 0.52 - 0.63 | 0.97 | 0.90 - 1.05 | 0.91 | 0.86 - 0.96 |
| Academic/Research | 0.45 | 0.40 - 0.50 | 0.78 | 0.72 - 0.86 | 0.68 | 0.64 - 0.73 |
| Other cancer programs | 0.75 | 0.35 - 1.62 | 1.18 | 0.62 - 2.26 | 1.04 | 0.65 - 1.66 |

AOR = *Adjusted Odds Ratio* CI = *Confidence Interval*

Figure 4. 1 Sample Selection

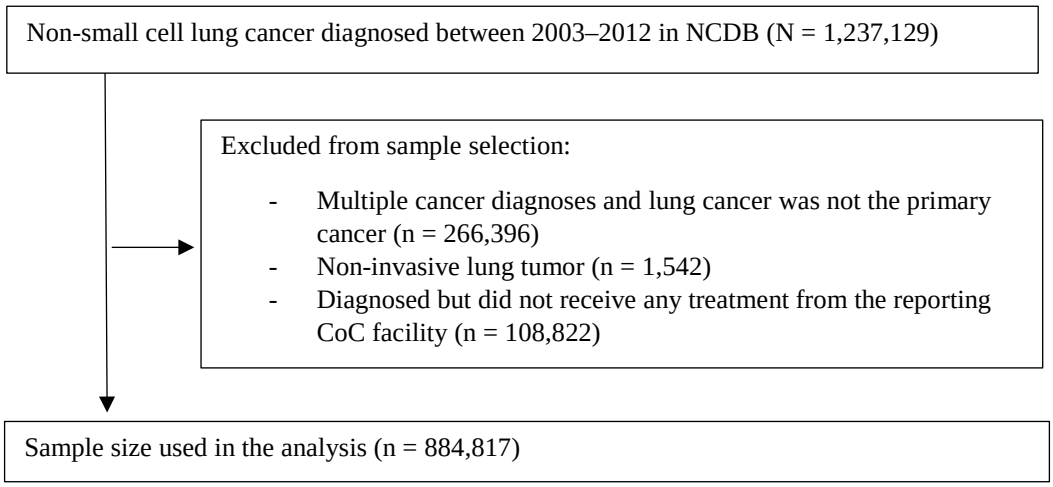
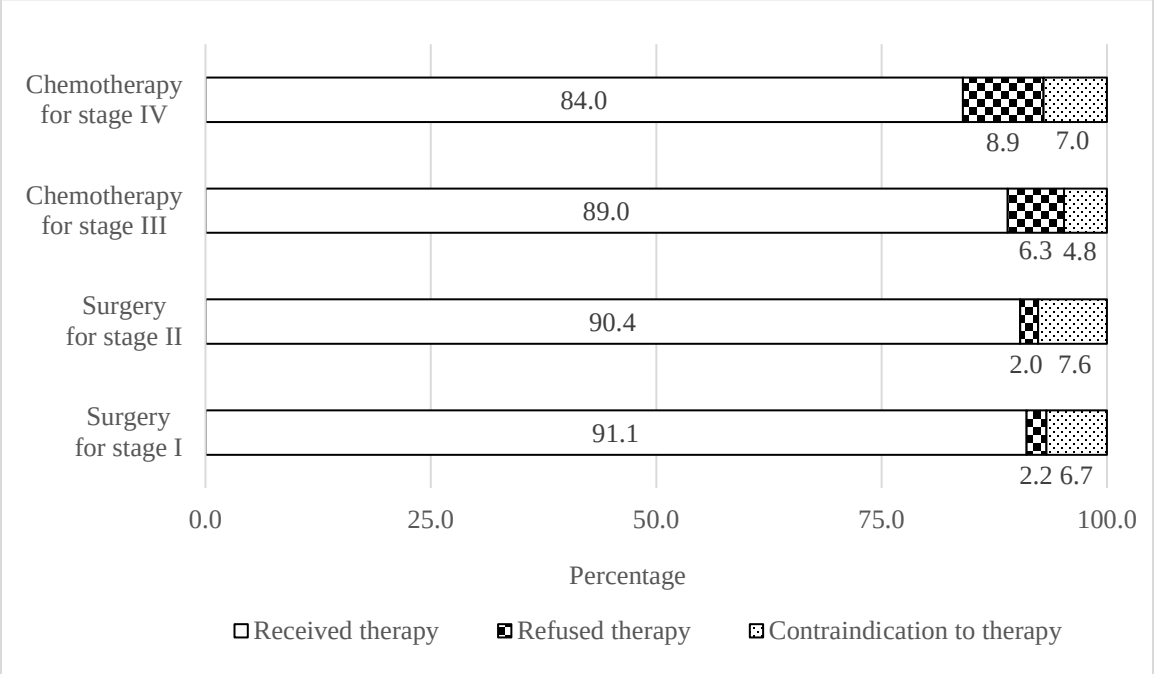


Figure 4. 2 Treatment Recommendations and Patient Response



# CHAPTER 5

# DISCUSSION AND CONCLUSIONS

Lung cancer is a major cause of cancer morbidity and mortality in the US. The estimation made in 2018 suggests that lung cancer diagnosis is the second most commonly diagnosed cancer in both genders.[11] Although many improvements in diagnosis and treatments have been achieved,[5,11,13] the number of deaths due to lung cancer is still high. For both genders, lung cancer is causing 25% of all cancer-related deaths.[11,12] Recent report indicate the relative five-year survival rate of lung cancer is only 18%.[11] Because of the great burden of lung cancer, investigating and examining factors associated with survival are essential to suggest areas of improvement in lung cancer care.

This dissertation focused on investigating factors associated with the survival of lung cancer patients through three specific aims. First, we examined the survival of NSCLC patients and analyzed factors associated with the survival. Second, we investigated the effect of treatment refusal on the survival of SCLC patients and factors associated with treatment refusal by patients. Lastly, we investigated factors associated with treatment refusal of NSCLC patients.

## Study Findings and Its Relevance to Literature

Earlier findings suggest that individuals with different age at diagnosis of lung cancer have different characteristics, such as cancer stage, type of tumor, and genetic susceptibility.[44,45,47] Our results included in Chapter 2 demonstrate that a higher proportion of patients among the younger-onset patients were diagnosed at advanced stages, had a positive family history of cancer, were current smokers, and had adenocarcinoma histology than the older-onset cases. Other studies have observed similar findings on characteristics of the younger-onset lung cancer

patients from the analyses of population and facility-based data.[45,47,79] Patients diagnosed with lung cancer at different age have different characteristics.[44,45,47]

Studies reported that many of the younger-onset lung cancer patients were typically symptomatic and diagnosed at an advanced stage.[42,48,86] One explanation may be that a younger patient is less likely to think that he or she could have developed lung cancer at a younger than typical age. These young people perhaps pay less attention to the respiratory symptoms and present later to their providers. In addition, a general practitioner may suspect less about a younger patient to have lung cancer than an older patient with similar symptoms. This condition may delay the health provider in ordering diagnostic tests to detect lung cancer.

Previous studies also indicate that the late diagnosis among young lung cancer patients was due to issues with not having insurance, being underinsured, and having limited access to cancer care.[103,105,106] It is also possible that because of the social perception that lung cancer is a self-inflicted disease, it may hinder young patients to take a lung cancer screening. Consequently, these young patients ended up being diagnosed with lung cancer at an advanced stage. Lung cancer is mostly known as a disease of older people, but the literature suggests that a substantial number of lung cancer cases occur before the age of 50 years.[12,17,41,42] Studies defined this group of patients as younger-onset lung cancer cases.[17,31,34] The observed proportion of younger-onset lung cancer in the databases that we used, the VACCR and the NCDB data, were 2.4% and 6.5%, respectively. Those proportions we observed were relatively similar to previous studies.[47,79]

The survival of lung cancer patients has been examined in previous studies and results suggest multiple factors were associated with survival including age at diagnosis.[45,47,48,79] However, the direction of the association between age at diagnosis and patients' survival has been inconclusive. Among the veterans population, our results show that the overall five-year survival of younger-onset patients was 5.6% compared with 3.0% of older-onset patients (> 70 years).

These results corroborate findings from earlier studies suggesting a higher survival among younger-onset patients than older-onset patients.[45,47,79]

While multiple factors were associated with overall survival, our results indicate that age at diagnosis and cancer stage were factors that strongly influenced patients' survival. Notable differences in clinical and statistical results that suggest a better five-year survival among the younger-onset were shown among early-stage (I and II) patients, whereas among advanced stage (III and IV) patients, only a marginal difference in survival was seen between the younger- and older-onset. It is likely that the disease aggressiveness at advanced stages of NSCLC lowers the overall survival of both younger-and older-onset patients.

Previous studies also suggest that the fewer comorbidities and a better performance status among younger-onset patients were contributed to a better survival.[41,45,46] Younger patients are typically healthier; thus, physicians were more likely to recommend them for an aggressive treatment, including surgery than older patients. In addition, it is likely that comorbidities associated with increasing age lead to lower survival in the older patients. Unfortunately, the VACCR database that we analyzed does not capture clinical information such as comorbid conditions and patient performance status. The availability of more comprehensive information will enable us to better explain the higher survival among younger-onset patients.

Treatment decline was another factor suggested as being directly associated with cancer-related deaths.[63,104] However, that information is still not convincing enough for lung cancer patients to take the recommended treatment. Of all lung cancer cases, the SCLC patients are well known to have the least five-year survival rates. A recent report indicates the five-year survival rate of SCLC was less than 7%.[12]

In Chapter 3, we present our results on survival analyses according to typical recommended therapies for patients diagnosed at different cancer stages for SCLC: LS-SCLC and ES-SCLC. The common recommended therapy for LS-SCLC patients is concurrent

chemoradiotherapy; whereas, ES-SCLC cases are predominantly treated with chemotherapy.[55,126,128] The results of our analyses among SCLC patients suggest that patients who received the recommended treatment had a significantly higher survival than those who declined the treatment, both in LS-SCLC and ES-SCLC. The overall median survival of SCLC patients was 9.4 months. Our results show that among LS-SCLC patients who were recommended chemoradiotherapy, the median survival of patients who refused and received the treatment was 3 and 18 months, respectively. For ES-SCLC patients, the median survival of those who refused chemotherapy was 1 month compared with 7.5 months of patients who received therapy.

Our findings were consistent with previous studies that suggested better survival rates among SCLC patients who received treatment than those who declined.[136,147] In multivariable analyses using the Cox PH regression, our results show that younger age, female gender, private insurance, no comorbid conditions, and acceptance of cancer treatment were associated with lower risk of mortality. Of those factors, treatment refusal demonstrates a profound effect. Of LS-SCLC patients who were recommended chemoradiotherapy, those who declined treatment had five times higher risk of mortality than those who received treatment. Similarly, among ES-SCLC patients who were recommended chemotherapy, patients who refused treatment had about four times higher risk of mortality than those who received treatment. A better survival may have resulted from a combination of multiple factors, however, it is likely that acceptance of treatment may increase patient life expectancy. Nevertheless, we have to acknowledge that the existence of barriers in the use of optimal lung cancer care is a complex condition. Many factors may play a role in the final decision for lung cancer care including diagnostic tests, patient preference, cultural aspects, and provider judgment.

Studies have reported a higher rate in underuse of treatment modalities among lung cancer patients than other cancers.[63,95,97] Treatment refusal is an important reason for underutilization of recommended treatment among lung cancer patients. However, evidence of

factors associated with treatment refusal among lung cancer patients are lacking. Our results showed factors that associated with treatment refusal among the early and advanced stages lung cancer patients and those factors can suggest areas of improvement in lung cancer care.

In Chapter 3, our results show that a majority of first-course treatments received by SCLC patients were according to the clinical practice guidelines. The overall refusal of recommended chemoradiotherapy among LS-SCLC patients was 1.34% and the refusal of chemotherapy among ES-SCLC patients was 4.7%. Over 10 years of data, we observed an increase in proportions of treatment refusal among SCLC cases, especially ES-SCLC patients. With approximately 75% of SCLC cases diagnosed with ES-SCLC, issues associated with treatment refusal deserve attention in regard to the lethality of this type of cancer.

For NSCLC, the current guidelines indicate surgery as the primary treatment for operable early-stage cancer (stages I and II).[156] For advanced stage cancer, treatment options may include a combination of chemotherapy, palliative radiation, and targeted therapy.[13,52] The results presented in Chapter 4 suggest that 2% to 9% of NSCLC patients refused the recommended treatment and a higher proportion of refusal was seen among patients with advanced stages. Furthermore, we observed multiple patient and system-related factors that were associated with patient decision to refuse recommended treatment. Of those factors, older age at diagnosis, female gender, comorbid conditions, and uninsured status were strongly associated with higher treatment refusal. We could not explore more about the aforementioned factors in this study as the variables in the database are limited; however, our literature review may suggest possible reasons for the factors we observed. Another limitation, because the data do not have follow up information for treatment refusal, we cannot assessed if the patient made changes in their decision.

Despite the fact that previous studies have shown both older and younger patients respond just as well to combined modality therapy,[89,90] older-onset lung cancer patients were more likely to refuse treatment than younger patients. Studies suggest that factors that may

support young patients to agree to cancer treatment were their overall health status and less comorbid conditions.[135] In contrast, older-onset patients have increased concerns regarding their tolerability to treatment, duration and effectiveness of treatment, and comorbid conditions that eventually influenced their decision to decline the offered treatment.[93,135] Other studies also suggest that older-onset patients might not see their chance to be curable, thus they opt out of the recommended treatment.[93] It has also been reported that older patients may not receive enough information about treatment options and its benefits that discourage them from taking treatment.[157,158] Statistics have been shown demographic shift toward an older population and with majority of lung cancer cases diagnosed at older age, it may explain the increase pattern of treatment refusal.

Results of our analyses suggest that women, especially those with advanced stage lung cancer, were more likely to refuse the recommended therapies. Differences according to gender may be related to patients' perceptions of cancer care.[100,101] Previous studies suggest that women with advanced stages cancer tend to refuse the treatment options due to nonclinical reasons such as they prefer the quality of life more than prolonging life[142] and tend to plan for other things in their end-of-life rather than to complete cancer treatment series.[100,143] In addition, earlier studies reported that women were clinically more vulnerable to treatment toxicities than men.[100,143] Understanding concerns associated with treatment refusal among women is important in regard to incidence rates of lung cancer among women.[12]

From the analyses of NCDB data on treatment refusal, we observed an interesting finding that patients without comorbidity were more likely to decline surgery than those with comorbidity among early-stage cancer. We cannot further analyze the comorbid conditions that were associated with the refusal because the database only included information about comorbidity scores. Literature suggests that patients were considering surgery as a radical treatment, and their decision to take it was strongly affected by other factors such as access to medical care, patient–

physician interactions, and patient perception of the necessity of surgery.[99,132,153,154] A qualitative study by George et al. suggested that following the surgical recommendation, lung cancer patients usually searched for a second opinion before making a plan to take the option.[153] The length of stay and cost of inpatient care associated with surgery were some of the factors that concerned patients, particularly for patients without an insurance plan.[155]

In regard to insurance, our results suggest that uninsured and Medicaid patients were two to three times more likely to refuse either surgery or chemotherapy than those with private insurance. Similar findings to our results have been reported by previous studies.[159] Concerns about treatment cost and limited insurance coverage were indicated by different studies resulting in a lack of diagnostic and therapeutic cancer care received by uninsured and underinsured patients.[103,160] The issue for non-optimal cancer care associated with insurance status has caused a substantial concern that the American Society of Clinical Oncology highlighted it as the issue of significant inequities in cancer care.[145] To achieve equity in health care, approaches to remove the barriers such as access to lung cancer screening and treatment need to be addressed.

**Implication of Current Research**

Findings from this dissertation emphasize the importance of understanding factors associated with survival and patient decision for lung cancer treatment. Our focus on age at diagnosis would not only explain the influences over disease prognosis but also offer explanations related to the patient's view of life, their values, and personal judgment.

Our results demonstrated that more of the younger-onset group patients were diagnosed at advanced stages. The results may indicate issues on access to lung cancer screening, especially among young patients. Improvements, such as providing a better access for lung cancer screening among young patients with symptoms, may prevent cases being diagnosed at an advanced stage.

In addition, a higher survival observed among younger-onset patients could be a point of interest for health providers and health system. The possibilities that younger-onset patients have better health performance, fewer comorbidities, and higher acceptance to treatment may enable health providers to recommend more diverse treatment options. Identifying and treating younger-onset lung cancer patients may be a point to improve the survival and to reduce mortality rates of lung cancer.

To improve patients' survival in relation to treatment refusal, our results in Chapters 3 and 4 may suggest points to enhance in patient education and patient–provider communication. Our data indicate that older-onset patients, having comorbid conditions, and being uninsured were more likely to refuse recommended treatment. Thus, it is important to inform patients with these characteristics about treatment options and its benefits including palliative treatment that essential for patients in making their decision. Although the majority of patients with advanced stage lung cancer cannot be cured, they can still make plans of their interest in end-of-life. Options for less toxic treatment regimens or palliative care that may improve patient quality of life should work better than having no treatment.

**Suggested Future Research**

Findings presented in this dissertation are expected to add more information to the existing body of literature on lung cancer research. With the higher burden of morbidity and mortality of lung cancer, more research should be directed to address gaps in identifying and treating patients. We have included some suggestions that may be focused in future studies.

The results indicate that younger-onset patients were more likely diagnosed at advanced stages. It is possible because the lack of attention to their health caused these younger people to present later at their health provider. However, earlier studies suggest that genetic susceptibility

related to detoxifying reactive metabolites of tobacco smoke procarcinogens among young patients with genetic polymorphisms of glutathione S-transferases exposed them to a higher risk of developing cancer.[34] Different studies indicate that lung cancer patients diagnosed at less than 50 years of age have predisposing genetic factors.[33,49,50] To better understand the risk for younger-onset lung cancer, future research should try to identify genetic features that are more prevalent among the younger-onset than the older-onset. In addition, results also showed that younger-onset patients presented more with adenocarcinoma histology and positive family history of cancer. Further investigations into tumor molecular characteristics or genetic mutations are needed to explain lung cancer at a younger age and potential targeted therapies.

In our discussion of factors associated with survival, databases that we used for this dissertation do not include comprehensive information that may better explain the findings. Further research should include factors such as types of comorbidities, patient performance status, exposures from smoking, amount of smoking, and other environmental factors to present a more comprehensive understanding on profound factors associated with the survival of lung cancer patients.

The current research found that younger-onset lung cancer patients obtained the greatest benefits of treatment because they are relatively eligible for aggressive treatment and are less likely to refuse treatment in comparison to the older patients. Future research needs to evaluate this further and see if improvement in survival could also be achieved by increasing awareness about lung cancer risk factors and improving access to screening and treatment of lung cancer. For the older-onset group, more work should see if by improving patient education and patient–physician communication, more patients are taking the recommended treatment. In addition, future studies should aim to identify the most beneficial treatment for lung cancer that addresses both clinical and patient aspects.

## Conclusions

The results of this dissertation suggest that multiple factors were associated with patients' survival including age at diagnosis and treatment refusal. The younger-onset patients had a better survival and were less likely to refuse recommended treatments than the older-onset patients. Our findings support the notion of better access for lung cancer screening, patient education, and patient–provider communication, as well as genetic studies to improve the survival of lung cancer patients.

## BIBLIOGRAPHY


1. Bruske-Hohfeld I. Environmental and Occupational Risk Factors for Lung Cancer. In: Verma M, ed. *Cancer Epidemiology*. New York, USA: Humana Press; 2009:3-23.
2. Haugen A, Mollerup, S. Etiology of Lung Cancer. In: Hansen H, ed. *Textbook of Lung Cancer*. London, United Kingdom: Informa Healthcare; 2008:1-9.
3. Mullon JJ, Olson, E.J. Clinical Diagnosis and Basic Evaluation. In: Hansen H, ed. *Textbook of Lung Cancer*. London, United Kingdom: Informa Healthcare; 2008:75-96.
4. Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. *CA: a cancer journal for clinicians.* 2005;55(2):74-108.
5. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. *CA: a cancer journal for clinicians.* 2015;65(2):87-108.
6. Youlden DR, Cramb SM, Baade PD. The International Epidemiology of Lung Cancer: geographical distribution and secular trends. *J Thorac Oncol.* 2008;3(8):819-831.
7. Cheng TY, Cramb SM, Baade PD, Youlden DR, Nwogu C, Reid ME. The International Epidemiology of Lung Cancer: Latest Trends, Disparities, and Tumor Characteristics. *J Thorac Oncol.* 2016;11(10):1653-1671.
8. Jemal A, Center MM, DeSantis C, Ward EM. Global patterns of cancer incidence and mortality rates and trends. *Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology.* 2010;19(8):1893-1907.
9. Torre LA, Siegel RL, Ward EM, Jemal A. International variation in lung cancer mortality rates and trends among women. *Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology.* 2014;23(6):1025-1036.

10. Boyle P, Gandini, S., Gray, N. Epidemiology of lung cancer: a century of great success and ignominious failure. In: Hansen H, ed. *Textbook of Lung Cancer*. London, United Kingdom: Informa Healthcare; 2008:10-19.

11. American Cancer Society. *Cancer Facts & Figures 2018*. Atlanta: American Cancer Society. 2018.

12. Howlader N, Noone AM, Krapcho M, Miller D, Bishop K, Kosary CL, Yu M, Ruhl J, Tatalovich Z, Mariotto A, Lewis DR, Chen HS, Feuer EJ, Cronin KA (eds). SEER Cancer Statistics Review, 1975-2014, National Cancer Institute. Bethesda, MD https://seer.cancer.gov/csr/1975_2014/. 2017(based on November 2016 SEER data submission, posted to the SEER web site, April 2017).

13. Miller KD, Siegel RL, Lin CC, et al. Cancer treatment and survivorship statistics, 2016. *CA: a cancer journal for clinicians.* 2016;66(4):271-289.

14. Alberg AJ, Brock MV, Samet JM. Epidemiology of lung cancer: looking to the future. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2005;23(14):3175-3185.

15. Dubey AK, Gupta U, Jain S. Epidemiology of lung cancer and approaches for its prediction: a systematic review and analysis. *Chin J Cancer*. 2016;35(1):71.

16. Alberg AJ, Brock MV, Ford JG, Samet JM, Spivack SD. Epidemiology of lung cancer: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest.* 2013;143(5 Suppl):e1S-29S.

17. Dela Cruz CS, Tanoue LT, Matthay RA. Lung cancer: epidemiology, etiology, and prevention. *Clin Chest Med.* 2011;32(4):605-644.

18. Jemal A, Travis WD, Tarone RE, Travis L, Devesa SS. Lung cancer rates convergence in young men and women in the United States: analysis by birth cohort and histologic type. *International journal of cancer Journal international du cancer*. 2003;105(1):101-107.

19. Tobacco smoke and involuntary smoking. *IARC Monogr Eval Carcinog Risks Hum.* 2004; 83:1-1438.

20. Swauger JE, Steichen TJ, Murphy PA, Kinsler S. An analysis of the mainstream smoke chemistry of samples of the U.S. cigarette market acquired between 1995 and 2000. *Regul Toxicol Pharmacol.* 2002;35(2 Pt 1):142-156.

21. Phillips DH. Smoking-related DNA and protein adducts in human tissues. *Carcinogenesis.* 2002;23(12):1979-2004.

22. Vineis P, Perera F. DNA adducts as markers of exposure to carcinogens and risk of cancer. *International journal of cancer Journal international du cancer.* 2000; 88(3): 325-328.

23. Alberg AJ, Samet JM. Epidemiology of lung cancer. *Chest.* 2003;123(1 Suppl):21S-49S.

24. Lemjabbar-Alaoui H, Hassan OU, Yang YW, Buchanan P. Lung cancer: Biology and treatment options. *Biochim Biophys Acta.* 2015;1856(2):189-210.

25. Molina JR, Yang P, Cassivi SD, Schild SE, Adjei AA. Non-small cell lung cancer: epidemiology, risk factors, treatment, and survivorship. *Mayo Clin Proc.* 2008; 83(5):584-594.

26. Frost G, Darnton A, Harding AH. The effect of smoking on the risk of lung cancer mortality for asbestos workers in Great Britain (1971-2005). *Ann Occup Hyg.* 2011;55(3):239-247.

27. World Health Organization. WHO Handbook on Indoor Radon*: A Public Health Perspective*. Geneva. 2009.

28. Torres-Duran M, Barros-Dios JM, Fernandez-Villar A, Ruano-Ravina A. Residential radon and lung cancer in never smokers. A systematic review. *Cancer Lett.* 2014;345(1):21-26.

29. Zhang ZL, Sun J, Dong JY, et al. Residential radon and lung cancer risk: an updated meta- analysis of case-control studies. *Asian Pac J Cancer Prev.* 2012;13(6):2459-2465.

30. Krewski D, Lubin JH, Zielinski JM, et al. Residential radon and risk of lung cancer: a combined analysis of 7 North American case-control studies. *Epidemiology.* 2005;16(2):137-145.

31. Lissowska J, Foretova L, Dabek J, et al. Family history and lung cancer risk: international multicentre case-control study in Eastern and Central Europe and meta-analyses. *Cancer causes & control : CCC.* 2010;21(7):1091-1104.

32. Matakidou A, Eisen T, Houlston RS. Systematic review of the relationship between family history and lung cancer risk. *British journal of cancer.* 2005;93(7):825-833.

33. Cassidy A, Myles JP, Duffy SW, Liloglou T, Field JK. Family history and risk of lung cancer: age-at-diagnosis in cases and first-degree relatives. *British journal of cancer.* 2006;95(9):1288-1290.

34. Cote ML, Kardia SL, Wenzlaff AS, Ruckdeschel JC, Schwartz AG. Risk of lung cancer among white and black relatives of individuals with early-onset lung cancer. *Jama.* 2005;293(24):3036-3042.

35. Cote ML, Liu M, Bonassi S, et al. Increased risk of lung cancer in individuals with a family history of the disease: a pooled analysis from the International Lung Cancer Consortium. *European journal of cancer.* 2012;48(13):1957-1968.

36. Kirk GD, Merlo C, P OD, et al. HIV infection is associated with an increased risk for lung cancer, independent of smoking. *Clin Infect Dis.* 2007;45(1):103-110.

37. Kirk GD, Merlo CA, Lung HIVS. HIV infection in the etiology of lung cancer: confounding, causality, and consequences. *Proc Am Thorac Soc.* 2011;8(3):326-332.

38. Pope CA, 3rd, Burnett RT, Turner MC, et al. Lung cancer and cardiovascular disease mortality associated with ambient air pollution and cigarette smoke: shape of the exposure-response relationships. *Environ Health Perspect.* 2011;119(11):1616-1621.

39. Turner MC, Cohen A, Jerrett M, et al. Interactions between cigarette smoking and fine particulate matter in the Risk of Lung Cancer Mortality in Cancer Prevention Study II. *American journal of epidemiology.* 2014;180(12):1145-1149.

40. Wu X, Groves FD, McLaughlin CC, Jemal A, Martin J, Chen VW. Cancer incidence patterns among adolescents and young adults in the United States. *Cancer causes & control : CCC.* 2005;16(3):309-320.

41. Gadgeel SM, Ramalingam S, Cummings G, et al. Lung cancer in patients < 50 years of age: the experience of an academic multidisciplinary program. *Chest.* 1999;115(5):1232-1236.

42. Etzel CJ, Lu M, Merriman K, Liu M, Vaporciyan A, Spitz MR. An epidemiologic study of early onset lung cancer. *Lung cancer.* 2006;52(2):129-134.

43. Ak G, Metintas M, Metintas S, Yildirim H, Erginel S, Alatas F. Lung cancer in individuals less than 50 years of age. *Lung.* 2007;185(5):279-286.

44. Thomas A, Chen Y, Yu T, Jakopovic M, Giaccone G. Trends and Characteristics of Young Non-Small Cell Lung Cancer Patients in the United States. *Front Oncol.* 2015;5:113.

45. Subramanian J, Morgensztern D, Goodgame B, et al. Distinctive characteristics of non-small cell lung cancer (NSCLC) in the young: a surveillance, epidemiology, and end results (SEER) analysis. *J Thorac Oncol.* 2010;5(1):23-28.

46. Radzikowska E, Roszkowski K, Glaz P. Lung cancer in patients under 50 years old. *Lung cancer.* 2001;33(2-3):203-211.

47. Lara MS, Brunson A, Wun T, et al. Predictors of survival for younger patients less than 50 years of age with non-small cell lung cancer (NSCLC): a California Cancer Registry analysis. *Lung cancer.* 2014;85(2):264-269.

48. Bryant AS, Cerfolio RJ. Differences in outcomes between younger and older patients with non-small cell lung cancer. *Ann Thorac Surg.* 2008;85(5):1735-1739; discussion 1739.

49. Gemignani F, Landi S, Szeszenia-Dabrowska N, et al. Development of lung cancer before the age of 50: the role of xenobiotic metabolizing genes. *Carcinogenesis.* 2007;28(6):1287-1293.

50. Chen LS, Baker T, Hung RJ, et al. Genetic Risk Can Be Decreased: Quitting Smoking Decreases and Delays Lung Cancer for Smokers With High and Low CHRNA5 Risk Genotypes - A Meta-Analysis. *EBioMedicine.* 2016;11:219-226.

51. Mulshine JL. Current Status of Lung Cancer Screening. In: Hansen H, ed. *Textbook of Lung Cancer*. London, United Kingdom: Informa Healthcare; 2008:53-60.

52. Ettinger DS, Wood DE, Akerley W, et al. NCCN Guidelines Insights: Non-Small Cell Lung Cancer, Version 4.2016. *J Natl Compr Canc Netw.* 2016;14(3):255-264.

53. Hansen HH. Summary of Treatment. In: Hansen H, ed. *Textbook of Lung Cancer*. London, United Kingdom: Informa Healthcare; 2008:207-209.

54. Ettinger D, Johnson B. Update: NCCN small cell and non-small cell lung cancer Clinical Practice Guidelines. *J Natl Compr Canc Netw.* 2005;3 Suppl 1:S17-21.

55. Jett JR, Schild SE, Kesler KA, Kalemkerian GP. Treatment of small cell lung cancer: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest.* 2013;143(5 Suppl):e400S-419S.

56. Carter BW, Glisson BS, Truong MT, Erasmus JJ. Small cell lung carcinoma: staging, imaging, and treatment considerations. *Radiographics.* 2014;34(6):1707-1721.

57. Dusmet M, Goldstraw, P. Staging, Classification, and Prognosis. In: Hansen H, ed. *Textbook of Lung Cancer*. London, United Kingdom: Informa Healthcare; 2008:97-122.

58. Shepherd FA, Crowley J, Van Houtte P, et al. The International Association for the Study of Lung Cancer lung cancer staging project: proposals regarding the clinical staging of small cell lung cancer in the forthcoming (seventh) edition of the tumor, node, metastasis classification for lung cancer. *J Thorac Oncol.* 2007;2(12):1067-1077.

59. Travis WD, Brambilla E, Nicholson AG, et al. The 2015 World Health Organization Classification of Lung Tumors: Impact of Genetic, Clinical and Radiologic Advances Since the 2004 Classification. *J Thorac Oncol.* 2015;10(9):1243-1260.

60. Meza R, Meernik C, Jeon J, Cote ML. Lung cancer incidence trends by gender, race and histology in the United States, 1973-2010. *PLoS One.* 2015;10(3):e0121323.

61. Lewis DR, Check DP, Caporaso NE, Travis WD, Devesa SS. US lung cancer trends by histologic type. *Cancer.* 2014;120(18):2883-2892.

62. Bhatt VR, Batra R, Silberstein PT, Loberiza FR, Jr., Ganti AK. Effect of smoking on survival from non-small cell lung cancer: a retrospective Veterans' Affairs Central Cancer Registry (VACCR) cohort analysis. *Med Oncol.* 2015;32(1):339.

63. Aizer AA, Chen MH, Parekh A, et al. Refusal of curative radiation therapy and surgery among patients with cancer. *Int J Radiat Oncol Biol Phys.* 2014;89(4):756-764.

64. Khuder SA. Effect of cigarette smoking on major histological types of lung cancer: a meta-analysis. *Lung cancer.* 2001;31(2-3):139-148.

65. Pinsky PF, Church TR, Izmirlian G, Kramer BS. The National Lung Screening Trial: results stratified by demographics, smoking history, and lung cancer histology. *Cancer.* 2013;119(22):3976-3983.

66. Foster NR, Mandrekar SJ, Schild SE, et al. Prognostic factors differ by tumor stage for small cell lung cancer: a pooled analysis of North Central Cancer Treatment Group trials. *Cancer.* 2009;115(12):2721-2731.

67. Brambilla E, Lantuejoul, S. Histopathology of Lung Tumors. In: Hansen H, ed. *Textbook of Lung Cancer*. London, United Kingdom: Informa Healthcare; 2008:61-74.

68. Jemal A, Ward EM, Johnson CJ, et al. Annual Report to the Nation on the Status of Cancer, 1975-2014, Featuring Survival. *Journal of the National Cancer Institute.* 2017;109(9).

69. Salomaa ER, Sallinen S, Hiekkanen H, Liippo K. Delays in the diagnosis and treatment of lung cancer. *Chest.* 2005;128(4):2282-2288.

70. Birring SS, Peake MD. Symptoms and the early diagnosis of lung cancer. *Thorax.* 2005;60(4):268-269.

71. Ramalingam S, Pawlish K, Gadgeel S, Demers R, Kalemkerian GP. Lung cancer in young patients: analysis of a Surveillance, Epidemiology, and End Results database. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 1998;16(2):651-657.

72. Brundage MD, Davies D, Mackillop WJ. Prognostic factors in non-small cell lung cancer: a decade of progress. *Chest.* 2002;122(3):1037-1057.

73. Visbal AL, Williams BA, Nichols FC, 3rd, et al. Gender differences in non-small-cell lung cancer survival: an analysis of 4,618 patients diagnosed between 1997 and 2002. *Ann Thorac Surg.* 2004;78(1):209-215; discussion 215.

74. Tammemagi CM, Neslund-Dudas C, Simoff M, Kvale P. In lung cancer patients, age, race-ethnicity, gender and smoking predict adverse comorbidity, which in turn predicts treatment and survival. *J Clin Epidemiol.* 2004;57(6):597-609.

75. Tsao AS, Liu D, Lee JJ, Spitz M, Hong WK. Smoking affects treatment outcome in patients with advanced nonsmall cell lung cancer. *Cancer.* 2006;106(11):2428-2436.

76. Ryu JS, Lee HJ. Effects of comorbidity and smoking on the survival of lung cancer patients. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2006;24(34):5468-5469; author reply 5469.

77. Bryant A, Cerfolio RJ. Differences in epidemiology, histology, and survival between cigarette smokers and never-smokers who develop non-small cell lung cancer. *Chest.* 2007;132(1):185-192.

78. American Cancer Society. *Cancer Treatment & Survivorship Facts & Figures 2016-2017.* Atlanta: American Cancer Society; 2016.

79. Arnold BN, Thomas DC, Rosen JE, et al. Lung Cancer in the Very Young: Treatment and Survival in the National Cancer Data Base. *J Thorac Oncol.* 2016;11(7):1121-1131.

80. Asmis TR, Ding K, Seymour L, et al. Age and comorbidity as independent prognostic factors in the treatment of non small-cell lung cancer: a review of National Cancer Institute of Canada Clinical Trials Group trials. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2008;26(1):54-59.

81. Carrato A, Vergnenegre A, Thomas M, McBride K, Medina J, Cruciani G. Clinical management patterns and treatment outcomes in patients with non-small cell lung cancer (NSCLC) across Europe: EPICLIN-Lung study. *Curr Med Res Opin.* 2014;30(3):447-461.

82. Chen J, Jiang R, Garces YI, et al. Prognostic factors for limited-stage small cell lung cancer: a study of 284 patients. *Lung cancer.* 2010;67(2):221-226.

83. Gaspar LE, McNamara EJ, Gay EG, et al. Small-cell lung cancer: prognostic factors and changing treatment over 15 years. *Clin Lung Cancer.* 2012;13(2):115-122.

84. Hua X, Ward KC, Gillespie TW, Lipscomb J, Goodman M. Non-small cell lung cancer treatment receipt and survival among African-Americans and whites in a rural area. *J Community Health.* 2014;39(4):696-705.

85. Cerfolio RJ, Bryant AS, Scott E, et al. Women with pathologic stage I, II, and III non-small cell lung cancer have better survival than men. *Chest.* 2006;130(6):1796-1802.

86. Cornere MM, Fergusson W, Kolbe J, Christmas TI. Characteristics of patients with lung cancer under the age of 45 years: a case control study. *Respirology.* 2001;6(4):293-296.

87. Mittelstrass K, Sauter W, Rosenberger A, et al. Early onset lung cancer, cigarette smoking and the SNP309 of the murine double minute-2 (MDM2) gene. *BMC Cancer.* 2008;8:113.

88. Pignon JP, Arriagada R, Ihde DC, et al. A meta-analysis of thoracic radiotherapy for small-cell lung cancer. *N Engl J Med.* 1992;327(23):1618-1624.

89. Yuen AR, Zou G, Turrisi AT, et al. Similar outcome of elderly patients in intergroup trial 0096: Cisplatin, etoposide, and thoracic radiotherapy administered once or twice daily in limited stage small cell lung carcinoma. *Cancer.* 2000;89(9):1953-1960.

90. Schild SE, Stella PJ, Brooks BJ, et al. Results of combined-modality therapy for limited-stage small cell lung carcinoma in the elderly. *Cancer.* 2005;103(11):2349-2354.

91. Fried TR, Bradley EH, Towle VR, Allore H. Understanding the treatment preferences of seriously ill patients. *N Engl J Med.* 2002;346(14):1061-1066.

92. Rothman MD, Van Ness PH, O'Leary JR, Fried TR. Refusal of medical and surgical interventions by older persons with advanced chronic disease. *J Gen Intern Med.* 2007;22(7):982-987.

93. Puts MT, Tapscott B, Fitch M, et al. A systematic review of factors influencing older adults' decision to accept or decline cancer treatment. *Cancer Treat Rev.* 2015;41(2):197-215.

94. Blank T, Graves K, Sepucha K, Llewellyn-Thomas H. Understanding treatment decision making: contexts, commonalities, complexities, and challenges. *Ann Behav Med.* 2006;32(3):211-217.

95. Ward MM, Ullrich F, Matthews K, et al. Who does not receive treatment for cancer? *Journal of oncology practice / American Society of Clinical Oncology.* 2013;9(1):20-26.

96. Stavas MJ, Arneson KO, Ning MS, et al. The Refusal of Palliative Radiation in Metastatic Non-Small Cell Lung Cancer and Its Prognostic Implications. *J Pain Symptom Manage.* 2015;49(6):1081-1087 e1084.

97. Landrum MB, Keating NL, Lamont EB, Bozeman SR, McNeil BJ. Reasons for underuse of recommended therapies for colorectal and lung cancer in the Veterans Health Administration. *Cancer.* 2012;118(13):3345-3355.

98. Mehta RS, Lenzner D, Argiris A. Race and health disparities in patient refusal of surgery for early-stage non-small cell lung cancer: a SEER cohort study. *Annals of surgical oncology.* 2012;19(3):722-727.

99. Cykert S, Dilworth-Anderson P, Monroe MH, et al. Factors associated with decisions to undergo surgery among patients with newly diagnosed early-stage lung cancer. *Jama.* 2010;303(23):2368-2376.

100. Fletcher K, Prigerson HG, Paulk E, et al. Gender differences in the evolution of illness understanding among patients with advanced cancer. *J Support Oncol.* 2013;11(3):126-132.

101. Johnson MF, Lin M, Mangalik S, Murphy DJ, Kramer AM. Patients' perceptions of physicians' recommendations for comfort care differ by patient age and gender. *J Gen Intern Med.* 2000;15(4):248-255.

102. Ward E, Halpern M, Schrag N, et al. Association of insurance with cancer care utilization and outcomes. *CA: a cancer journal for clinicians.* 2008;58(1):9-31.

103. Halpern MT, Ward EM, Pavluck AL, Schrag NM, Bian J, Chen AY. Association of insurance status and ethnicity with cancer stage at diagnosis for 12 cancer sites: a retrospective analysis. *The Lancet Oncology.* 2008;9(3):222-231.

104. Huang HL, Kung PT, Chiu CF, Wang YH, Tsai WC. Factors associated with lung cancer patients refusing treatment and their survival: a national cohort study under a universal health insurance in Taiwan. *PLoS One.* 2014;9(7):e101731.

105. Robbins AS, Lerro CC, Barr RD. Insurance status and distant-stage disease at diagnosis among adolescent and young adult patients with cancer aged 15 to 39 years: National Cancer Data Base, 2004 through 2010. *Cancer.* 2014;120(8):1212-1219.

106. Bradley CJ, Given CW, Roberts C. Late stage cancers in a Medicaid-insured population. *Medical care.* 2003;41(6):722-728.

107. American College of Surgeons: About the National Cancer Data Base. *https://wwwfacsorg/quality%20programs/cancer/ncdb/about.* 2015.

108. Winchester DP, Stewart AK, Bura C, Jones RS. The National Cancer Data Base: a clinical surveillance and quality improvement tool. *Journal of surgical oncology.* 2004;85(1):1-3.

109. Mohanty S, Bilimoria KY. Comparing national cancer registries: The National Cancer Data Base (NCDB) and the Surveillance, Epidemiology, and End Results (SEER) program. *Journal of surgical oncology.* 2014;109(7):629-630.

110. Bilimoria KY, Stewart AK, Winchester DP, Ko CY. The National Cancer Data Base: a powerful initiative to improve cancer care in the United States. *Annals of surgical oncology.* 2008;15(3):683-690.

111. American College of Surgeons, National Cancer Data Base - Data Dictionary PUF 2014. *http://ncdbpuffacsorg/node/259.* 2015.

112. Lerro CC, Robbins AS, Phillips JL, Stewart AK. Comparison of cases captured in the national cancer data base with those in population-based central cancer registries. *Annals of surgical oncology.* 2013;20(6):1759-1765.

113. Administration DoVA-VVH. Veteran Affairs Central Cancer Registry (VACCR).

114. Zullig LL, Goldstein KM, Bosworth HB. Changes in the Delivery of Veterans Affairs Cancer Care: Ensuring Delivery of Coordinated, Quality Cancer Care in a Time of Uncertainty. *Journal of oncology practice / American Society of Clinical Oncology.* 2017;13(11):709-711.

115. Zullig LL, Sims KJ, McNeil R, et al. Cancer Incidence Among Patients of the U.S. Veterans Affairs Health Care System: 2010 Update. *Mil Med.* 2017;182(7):e1883-e1891.

116. Carpenter WR, Meyer AM, Abernethy AP, Sturmer T, Kosorok MR. A framework for understanding cancer comparative effectiveness research data needs. *J Clin Epidemiol.* 2012;65(11):1150-1158.

117. Mauri D, Pentheroudakis G, Bafaloukos D, et al. Non-small cell lung cancer in the young: a retrospective analysis of diagnosis, management and outcome data. *Anticancer Res.* 2006;26(4B):3175-3181.

118. Maruyama R, Yoshino I, Yohena T, et al. Lung cancer in patients younger than 40 years of age. *Journal of surgical oncology.* 2001;77(3):208-212.

119. Karami S, Young HA, Henson DE. Earlier age at diagnosis: another dimension in cancer disparity? *Cancer detection and prevention.* 2007;31(1):29-34.

120. Tanner NT, Egede LE, Shamblin C, Gebregziabher M, Silvestri GA. Attitudes and beliefs toward lung cancer screening among US Veterans. *Chest.* 2013;144(6):1783-1787.

121. Zullig LL, Williams CD, Fortune-Britt AG. Lung and colorectal cancer treatment and outcomes in the Veterans Affairs health care system. *Cancer Manag Res.* 2015;7:19-35.

122. Kreuzer M, Kreienbrock L, Muller KM, Gerken M, Wichmann E. Histologic types of lung carcinoma and age at onset. *Cancer.* 1999;85(9):1958-1965.

123. Ganti AK, Subbiah SP, Kessinger A, Gonsalves WI, Silberstein PT, Loberiza FR, Jr. Association between race and survival of patients with non--small-cell lung cancer in the United States veterans affairs population. *Clin Lung Cancer.* 2014;15(2):152-158.

124. Cohen RA, Makuc DM, Bernstein AB, Bilheimer LT, Powell-Griner E. Health insurance coverage trends, 1959-2007: estimates from the National Health Interview Survey. *Natl Health Stat Report.* 2009(17):1-25.

125. de Rijke JM, Schouten LJ, ten Velde GP, et al. Influence of age, comorbidity and performance status on the choice of treatment for patients with non-small cell lung cancer; results of a population-based study. *Lung cancer.* 2004;46(2):233-245.

126. Byers LA, Rudin CM. Small cell lung cancer: where do we go from here? *Cancer.* 2015;121(5):664-672.

127. Pietanza MC, Byers LA, Minna JD, Rudin CM. Small cell lung cancer: will recent progress lead to improved outcomes? *Clin Cancer Res.* 2015;21(10):2244-2255.

128. Ganti AK, West WW, Zhen W. Current concepts in the management of small cell lung cancer. *Indian J Med Res.* 2013;137(6):1043-1051.

129. Parsons HM, Harlan LC, Stevens JL, Ullmann CD. Treatment of small cell lung cancer in academic and community settings: factors associated with receiving standard therapy and survival. *Cancer J.* 2014;20(2):97-104.

130. Recalcitrant Cancer Research Act of 2012, Pub L. No. 112-176, 112 Stat. 733. September 20, 2012.

131. Esnaola NF, Gebregziabher M, Knott K, et al. Underuse of surgical resection for localized, non-small cell lung cancer among whites and African Americans in South Carolina. *Ann Thorac Surg.* 2008;86(1):220-226; discussion 227.

132. Ryoo JJ, Ordin DL, Antonio AL, et al. Patient preference and contraindications in measuring quality of care: what do administrative data miss? *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2013;31(21):2716-2723.

133. National Comprehensive Cancer Network (NCCN) Guidelines - Small Cell Lung Cancer. *NCCNorg.* 2014.

134. Corso CD, Rutter CE, Park HS, et al. Role of Chemoradiotherapy in Elderly Patients With Limited-Stage Small-Cell Lung Cancer. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2015;33(36):4240-4246.

135. Ludbrook JJ, Truong PT, MacNeil MV, et al. Do age and comorbidity impact treatment allocation and outcomes in limited stage small-cell lung cancer? a community-based population analysis. *Int J Radiat Oncol Biol Phys.* 2003;55(5):1321-1330.

136. Lally BE, Geiger AM, Urbanic JJ, et al. Trends in the outcomes for patients with limited stage small cell lung cancer: An analysis of the Surveillance, Epidemiology, and End Results database. *Lung cancer.* 2009;64(2):226-231.

137. Dores GM, Qubaiah O, Mody A, Ghabach B, Devesa SS. A population-based study of incidence and patient survival of small cell carcinoma in the United States, 1992-2010. *BMC Cancer.* 2015;15:185.

138. Schabath MB, Nguyen A, Wilson P, Sommerer KR, Thompson ZJ, Chiappori AA. Temporal trends from 1986 to 2008 in overall survival of small cell lung cancer patients. *Lung cancer.* 2014;86(1):14-21.

139. Govindan R, Page N, Morgensztern D, et al. Changing epidemiology of small-cell lung cancer in the United States over the last 30 years: analysis of the surveillance, epidemiologic, and end results database. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2006;24(28):4539-4544.

140. Osann KE, Lowery JT, Schell MJ. Small cell lung cancer in women: risk associated with smoking, prior respiratory disease, and occupation. *Lung cancer.* 2000;28(1):1-10.

141. Lee K, Kloecker G, Pan J, Rai S, Dunlap NE. The Integration of Multimodality Care for the Treatment of Small Cell Lung Cancer in a Rural Population and Its Impact on Survival. *Am J Clin Oncol.* 2015;38(5):448-456.

142. Sharma RK, Prigerson HG, Penedo FJ, Maciejewski PK. Male-female patient differences in the association between end-of-life discussions and receipt of intensive care near death. *Cancer.* 2015;121(16):2814-2820.

143. Citrin DL, Bloom DL, Grutsch JF, Mortensen SJ, Lis CG. Beliefs and perceptions of women with newly diagnosed breast cancer who refused conventional treatment in favor of alternative therapies. *The oncologist.* 2012;17(5):607-612.

144. Grant SR, Walker GV, Guadagnolo BA, Koshy M, Allen PK, Mahmood U. Variation in insurance status by patient demographics and tumor site among nonelderly adult patients with cancer. *Cancer.* 2015;121(12):2020-2028.

145. American Society of Clinical Oncology - The State of Cancer Care in America 2015. *http://wwwascoorg/sites/wwwascoorg/files/2015ascostateofcancercarepdf.* 2015.

146. Duh MS, Reynolds Weiner J, Lefebvre P, Neary M, Skarin AT. Costs associated with intravenous chemotherapy administration in patients with small cell lung cancer: a retrospective claims database analysis. *Curr Med Res Opin.* 2008;24(4):967-974.

147. Behera M, Ragin C, Kim S, et al. Trends, predictors, and impact of systemic chemotherapy in small cell lung cancer patients between 1985 and 2005. *Cancer.* 2016;122(1):50-60.

148. Mettlin CJ, Menck HR, Winchester DP, Murphy GP. A comparison of breast, colorectal, lung, and prostate cancers reported to the National Cancer Data Base and the Surveillance, Epidemiology, and End Results Program. *Cancer.* 1997;79(10):2052-2061.

149. National Comprehensive Cancer Network (NCCN) Guidelines - Non-small Cell Lung Cancer *NCCNorg.* 2013(2013).

150. Jin J, Sklar GE, Min Sen Oh V, Chuen Li S. Factors affecting therapeutic compliance: A review from the patient's perspective. *Ther Clin Risk Manag.* 2008;4(1):269-286.

151. Little AG, Gay EG, Gaspar LE, Stewart AK. National survey of non-small cell lung cancer in the United States: epidemiology, pathology and patterns of care. *Lung cancer.* 2007;57(3):253-260.

152. Williams CD, Stechuchak KM, Zullig LL, Provenzale D, Kelley MJ. Influence of comorbidity on racial differences in receipt of surgery among US veterans with early-stage non-small-cell lung cancer. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2013;31(4):475-481.

153. George M, Margolis ML. Race and lung cancer surgery--a qualitative analysis of relevant beliefs and management preferences. *Oncol Nurs Forum.* 2010;37(6):740-748.

154. Margolis ML, Christie JD, Silvestri GA, Kaiser L, Santiago S, Hansen-Flaschen J. Racial differences pertaining to a belief about lung cancer surgery: results of a multicenter survey. *Ann Intern Med.* 2003;139(7):558-563.

155. Bradley CJ, Dahman B, Bear HD. Insurance and inpatient care: differences in length of stay and costs between surgically treated cancer patients. *Cancer.* 2012;118(20):5084-5091.

156. Ettinger DS, Wood DE, Aisner DL, et al. Non-Small Cell Lung Cancer, Version 5.2017, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw.* 2017;15(4):504-535.

157. Lynch CM, Abdollahi B, Fuqua JD, et al. Prediction of lung cancer patient survival via supervised machine learning classification techniques. *Int J Med Inform.* 2017;108:1-8.

158. Aumann I, Kreis K, Damm K, Golpon H, Welte T, Graf von der Schulenburg JM. Treatment-related experiences and preferences of patients with lung cancer: a qualitative analysis. *Health Expect.* 2016;19(6):1226-1236.

159. Groth SS, Al-Refaie WB, Zhong W, et al. Effect of insurance status on the surgical treatment of early-stage non-small cell lung cancer. *Ann Thorac Surg.* 2013;95(4):1221-1226.

160. Slatore CG, Au DH, Gould MK, American Thoracic Society Disparities in Healthcare G. An official American Thoracic Society systematic review: insurance status and disparities in lung cancer practices and outcomes. *Am J Respir Crit Care Med.* 2010;182(9):1195-1205.