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# Disparities in Non-Small Cell Lung Cancer in the United States: An Examination of Treatment, Survival, and Access to Care

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# DISPARITIES IN NON-SMALL CELL LUNG CANCER IN THE UNITED STATES: AN EXAMINATION OF TREATMENT, SURVIVAL, AND ACCESS TO CARE

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# DEDICATION

This work is dedicated to my best friend and husband, Peter. My accomplishments over the past ten years would not have been possible without for his constant reassurance and support. I also dedicate this to my parents who always stressed the importance of prioritizing my education. I am here because of their encouragement to always work hard and follow my dreams.

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# ABSTRACT

Lung cancer is the leading cause of cancer-related deaths in the United States with a 5-year survival rate of only 18%. Differences in access to care and treatment utilization may play a role in observed survival disparities among rural patient populations. This dissertation aimed to examine rural disparities in all-cause and lung-cancer specific survival, time to treatment initiation, and utilization of surgical treatment among non-small cell lung cancer cases.

We utilized comprehensive cancer registry data from the Surveillance, Epidemiology, and End Results program linked with Medicare billing claims (SEER-Medicare) for non-small cell lung cancer (NSCLC) patients diagnosed between 2003-2011. We compared differences in all-cause survival and lung cancer-specific survival based on urban and rural residence while controlling for demographic and clinical characteristics of patients. We examined differences in the time between diagnosis and treatment initiation for urban and rural NSCLC patients and furthermore the impact of time to treatment on survival. We also implemented multilevel modeling techniques to assess the associations of county-level neighborhood and patient-level demographic and clinical characteristics with utilization of surgical treatment in early-stage NSCLC patients.

Our results showed that rural NSCLC patients had worse all-cause and lung cancer-specific survival than their urban counterparts. Our adjusted Cox PH model results found that differences in the time between diagnosis and treatment initiation may not contribute to rural disparities in lung cancer survival. However, utilization of surgical treatment at any time point was related with high survival probability. More than 50% of the patients who received surgery survived longer than 5 years following diagnosis. When examining differences in surgical utilization, factors related to decreased likelihood of surgical treatment for lung cancer included living in higher poverty counties, enrollment in Medicaid, and black race. When controlling for county-level poverty and patient characteristics, rurality was not significantly related to differences in surgical utilization among NSCLC patients.

This dissertation identified persisting rural disparities in all-cause and lung cancer-specific survival in the United States. Observed rural disparities may be due to sociodemographic factors more common among rural cancer patients such as public insurance or being uninsured, and low incomes. In concordance with previous research, black NSCLC patients were also less likely than white patients to receive surgical treatment. Targeted interventions are needed to improve lung cancer survival in rural, low income, and black patient populations, particularly focusing on improving utilization of surgical treatment in early-stage cases among these groups.

Keywords: Non-small cell lung cancer, lung cancer survival, survival analysis, multilevel modeling, health disparities

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# LIST OF ABBREVIATIONS

ACA ..... Affordable Care Act

CHSDA ..... Contract Health Service Delivery Areas

CI ..... Confidence Interval

CMS ..... Centers for Medicare and Medicaid Services

CoC ..... Commission on Cancer

COPD ..... Chronic Obstructive Pulmonary Disorder

CPT ..... Carriage Paid To

EGFR ..... Epidermal Growth Factor Receptor

EPA ..... Environmental Protection Agency

ERS ..... Economic Research Service

ESRD ..... End Stage Renal Disease

FDA ..... United States Food and Drug Administration

FFS ..... Fee for Service

HCPCS ..... Healthcare Common Procedure Coding System

HR ..... Hazard Ratio

ICC ..... Intraclass Correlation Coefficient

ICD ..... International Classification of Diseases

IMRT ..... Intensity-Modulated Radiation Therapy

LDCT ..... Low Dose Computed Tomography

MA ..... Medicare Advantage

MITS ..... Minimally Invasive Thoracic Surgery

MOR ..... Median Odds Ratio

MUA .....Medically Underserved Areas

NCI..... National Cancer Institute

NIH ..... National Institutes of Health

NLST.....National Lung Screening Trial

NPCR ..... National Program of Cancer Registries

NSCLC.....Non-Small Cell Lung Cancer

OR ..... Odds Ratio

PH ..... Proportional Hazards

RUCC.....Rural Urban Continuum Codes

RVATS .....Robotic Video Assisted Thoracic Surgery

SBRT..... Stereotactic Body Radiation Therapy

SCLC.....Small Cell Lung Cancer

SEER..... Surveillance, Epidemiology, and End Results Program

SES..... Socioeconomic Status

TNM..... Tumor Node Metastasis

U.S. ..... United States

USDA.....Unites States Department of Agriculture

USPSTF .....United States Preventive Services Task Force

VATS ..... Video Assisted Thoracic Surgery

3D-CRT..... Three-Dimensional Conformal Radiation Therapy

# CHAPTER 1

# INTRODUCTION

Among all cancer types, lung cancer is the leading cause of cancer-related death in the United States (U.S.), for both men and women, killing approximately 156,000 people in 2017.[1] In comparison, an estimated 134,000 people died from the next three deadliest cancers combined (colorectal, pancreatic, breast) in the same year.[1] The American Cancer Society estimates that there will be 234,030 newly diagnosed cases of lung cancer in 2018, making up 13% of the total cancer cases in the U.S.,[2] creating a financial burden of over $12.12 billion for treatment costs.[3] Lung cancer survival varies depending on patient and environmental factors such as stage at diagnosis, smoking history, treatment approaches, and access to care. Such factors differ by racial and ethnic groups, sex, rurality, and geographic region, creating observed disparities in lung cancer survival.

Black and Native American populations have the highest lung cancer-specific mortality rates when compared to all other racial and ethnic groups.[4–7] The causes of these racial disparities are complex and multifactorial, including differences in access to care and risk factors for lung cancer. Existing data points to distrust of the medical community, perceived discrimination, and a predominately white medical workforce as possible contributing factors.[4,8,9] Black lung cancer cases are also diagnosed at later stages and less likely to receive surgery than white cases (even in early stages).[4–6,10–13]

Similarly, black and Native American cases are less likely to receive smoking cessation counseling (a crucial component of lung cancer prevention) and more likely to be diagnosed with lung cancer at late stages than whites.[7,14–18] In contrast, Hispanic and Asian American lung cancer patients have longer survival times that whites.[4]

A sex disparity in survival from lung cancer has been observed with men having shorter survival than women.[19–22] Historically, the population of lung cancer patients in the US has been predominately male, though the proportion of female cases has increased in recent years with incident cases in 2017 being 52.5% male and 47.5% female.[2,12] While the incidence of large cell and squamous cell lung cancers has decreased over time for both men and women, adenocarcinoma incidence rates in men have remained steady and increased among women.[12] In fact, higher overall lung cancer incidence rates among women than men were observed for those born between 1965-1980.[23] The smoking prevalence among women in this age group was higher than their predecessors but lower than the smoking prevalence in men of the same age and does not fully account for the observed increase in the incidence rates.[23] Sex differences in lung cancer incidence and survival need to be examined continuously in the future.

In the U.S., rural residents have a higher smoking prevalence, higher overall incidence rates of lung cancer, and higher rates of late-stage lung cancer diagnoses than urban residents.[24–27] When examining lung cancer mortality rates from 1999-2016 by region and rurality, the highest mortality rates existed in the rural South at 63.0 per 100,000 population.[28] Rural residents with lung cancer are also less likely to receive

treatment than urban residents with lung cancer.[29] Late-stage diagnoses and limited treatment options for late-stage cases are contributing factors to the higher observed mortality rates for rural Americans with lung cancer.[29] Combined with the sheer disease burden, rural residents also face higher poverty rates, lower education, and a higher proportion of uninsured and elderly adults than urban residents.[30,31]

Early detection is integral in improving survival from lung cancer.[32] Over 65% of lung cancer cases are diagnosed in stage III or IV.[33] When detected at stages I and II, the survival rate for lung cancer is 54%, and when detected after metastasis to other organs, the survival rate drops to 4%.[2,34] Annual screening by low-dose computed tomography (LDCT) for patients deemed high risk for lung cancer began being covered by most private health insurance providers and Medicare in 2015.[35] In randomized clinical trials, LDCT screening among high-risk individuals was shown to reduce the risk of lung cancer death by 20-40%, providing a promising avenue to improving survival rates for smoking-related lung cancers in the future.[36–38] Equal access to LDCT screening centers among rural residents of the screening-eligible population needs to be prioritized to close the gaps in disparities in early detection of lung cancer.[39,40]

Regional differences in lung cancer survival exist as well.[41–44] Southeastern states have the highest mortality-to-incidence ratios for lung cancer.[42] Disparities in accessing care for rural and black populations are most pronounced in the South where smoking prevalence, lung cancer incidence rates, and poverty are also the highest in the nation.[31,45]

The largest proportion of the lung cancer screening-eligible population also resides in the South.[39]

### 1.1 Statement of the Problem

First, the goal of this research was to identify existing disparities in lung cancer outcomes (i.e., survival and treatment utilization) among persons of different racial/ethnic backgrounds, sex, rurality, and geographic locations. Identifying persistent (or increasing) disparities may aid in the development of targeted public health interventions and policies for at-risk populations or regions. While lung cancer incidence and mortality rates among black and Native American races and rural residents are higher in comparison to their white and urban counterparts, estimates of these disparities need updating. The available data is largely based on non-generalizable datasets (e.g., single state cancer registries, single health care system), restricted to rare types of lung cancer (e.g., small cell lung cancer), data from the early 1990s to early 2000s, or survival not adjusted by race, sex, and/or rurality in modeling approaches.[11,46] Lung cancer survival data is highly cited in the field but is based on data from as far back as 1991 with the most recent publications utilizing data on non-small cell lung cancer only up to 2006.[6,47–53] We anticipate that our results will be highly cited data on lung cancer survival.

Second, significant changes have been made in the prevention and control of lung cancer in recent years with respect to lung cancer screening guidelines, tobacco control policies, declining smoking rates, genetic testing availability, oncology telemedicine (teleoncology), pharmaceutical development, and personalized/precision medicine.

Screening reduces mortality via early detection, while tobacco control and declining smoking prevalence have driven down lung cancer incidence.[54–56] Enhanced treatment approaches including genetic testing, teleoncology, evolving first-line drugs, and personalized medicine improve survival and expansion of these treatment approaches have the potential to change the disease progression.[57–59] Improved health insurance coverage through the Affordable Care Act (ACA) may also play a role in closing gaps in survival disparities between black and white populations. The percentage of black adults without health insurance decreased from 21% to 11% from 2010 to 2015.[60] A reference point for lung cancer survival among different racial groups is needed as we move into this new era to measure the impact, if any, that new screening and treatment efforts may have on the survival of lung cancer patients at the population-level.

Third, continuing expansion of rural oncology providers and early detection of lung cancer via annual LDCT screening provide possible avenues for reducing rural and racial disparities. The results of this project allow for monitoring of temporal changes in disparities when compared with results from earlier cohorts from SEER-Medicare data. Additionally, the National Cancer Institute's (NCI) stated research emphasis areas currently includes a focus on health disparities and rural cancer control current research.[61] This work contributes to their research agenda[61] by identifying geographic areas of high need or disparities among rural populations, providing formative data needed to develop and/or target future research projects.

### 1.2 Aims and Hypotheses

To address these known gaps in the field, we implemented a comprehensive registry and claims-based analysis of lung cancer patients in the U.S. using the existing 2003-2011 SEER-Medicare database for all aims. Specifically, we:

**Aim 1: Investigated disparities in lung cancer-specific and all cause survival by race/ethnicity, sex, and geography and identify patient-level and county-level factors associated with survival**

Hypothesis 1a: We hypothesized that lung cancer survival and overall survival would be lower among black and Native American races vs. whites, men vs. women, and rural vs. urban residence.

Hypothesis 1b: We further hypothesized that these disparities would be most pronounced in the South Census region (SEER locations in Louisiana, Kentucky, Georgia).

Methods: We used Cox Proportional Hazards models for primary lung cancer cases

**Aim 2: Examined differences in lung cancer-specific survival at differing thresholds of treatment initiation**

Hypothesis 2: We hypothesized that lung cancer survival would be highest among those initiating treatment within 4 weeks of diagnosis.

Methods: We used three time dependent and stratified Cox Proportional Hazards models, one for each treatment type (surgery, chemotherapy, radiation), comparing survival of those (with the same stage at diagnosis) initiating treatment after diagnosis at five

differing thresholds: 4 weeks or less, 5-6 weeks, 7-9 weeks, 9-12 weeks, greater than 12 weeks.

**Aim 3: Explored disparities in <u>utilization</u> of lung cancer surgical treatment and related patient and county predictors among lung cancer patients**

Hypothesis 3a: We hypothesized that county-level factors would impact surgical treatment utilization among lung cancer patients

Hypothesis 3b: We further hypothesized that Medicaid enrollees (low income) and black patients would be less likely to receive surgery when compared to those not on Medicaid and white patients

Methods: We performed a multilevel logistic regression examining patient factors nested within counties (and county-level factors) associated with utilization of surgical treatment for lung cancer

### 1.3 Significance and Rationale

The goals of this project were to identify potential disparities in lung cancer survival along with access, utilization, and timely receipt of treatment for lung cancer. There is currently no standard guideline for appropriate time intervals between the data of diagnosis and treatment initiation for the of lung cancer. Time may play a role in lung cancer survival as lung cancer is an aggressive disease that metastasizes to other organs. Differences in time to treatment initiation may be an important mechanism driving observed disparities in lung cancer mortality, especially among black and Native American races, and rural residents. Empirically based guidelines for timeliness of

treatment could provide a valuable measure for patients interested in seeking second opinions or for those concerned about time delays in scheduling required appointments following initial diagnosis.

A better understanding of disparities in survival and access to surgical cancer treatment is a crucial step in improving lung cancer survival. Patient race/ethnicity, sex, and residential location impacts the course of cancer treatment received.[4–6,11,13,62] Our results provide insight necessary to develop targeted interventions aimed at improving access to treatment and survival of lung cancer by identifying areas with the greatest need of expanded healthcare services, including but not limited to teleoncology, mobile LDCT screening units, and hospital partnerships (e.g., local tumor boards, physician sharing arrangements). This also lays the groundwork for potential interventions aimed at advancing patient navigation for racial minorities or rural patients, patient education initiatives improving surgical acceptance among black and Native American patients, as well as physician education on discrimination, bias, and cultivating trusting relationships with patients.

Race and ethnicity, rurality, and region may be social determinants of patient experience in navigating cancer care, influencing potential differences in survival rates. Residents of rural counties may have longer travel times to cancer treatment facilities and decreased likelihood of receiving care from specialist physicians, such as thoracic surgeons. This could contribute to differences observed in urban and rural outcomes as utilization of surgical treatment can greatly improve survival among early stage cases.

Our examination of urban-rural differences in timely treatment and lung cancer survival also provides insight into how space and place impact receipt of healthcare. Examining factors for potential intervention is imperative in addressing the multifaceted mechanisms driving healthcare decisions. The growing focus by federal agencies on multilevel intervention research points to the importance of researching various sources of impact on patient outcomes. Projects such as ours, which help pinpoint predictors of survival, the timeliness of cancer treatment, and the utilization of surgical treatment open the door for future changes to health care policy and interventions aimed at improving equity to access to care, and ultimately survival rates.

# CHAPTER 2

# LITERATURE REVIEW

This chapter provides a brief overview of the existing data related to lung cancer survival including environmental exposures, histology, disease staging, treatment types and timeliness, cancer treatment centers and patient characteristics (e.g., race/ethnicity, sex, rurality, and residential location). An understanding of lung cancer history, causes, treatment, and related disparities is crucial to comprehension of the evolving landscape of the disease.

## 2.1 Epidemiology of Lung Cancer

Several environmental exposures have been directly linked to lung cancer through epidemiologic research dating back to the 1950s.[56] Lung cancer incidence in the U.S. began increasing in the 20th century with increased popularity and mass production of cigarettes containing addictive materials, particularly nicotine. In the 1950s, U.S. and British researchers published numerous studies demonstrating a probable link between cigarette smoking and lung cancer.[63–73] Subsequently in 1964, the U.S. Surgeon General's Advisory committee released a report compiling the existing evidence warning that smoking causes lung cancer, citing retrospective studies with relative risks ranging in magnitude from 2.0 to 25.5 for the relationship of smoking and lung cancer. Since that report, tobacco smoke has emerged as the most profound factor impacting lung cancer incidence and premature death, with an estimated 80-90% of cases directly attributed to

active smoking and second-hand smoke exposure.[74] Despite this, approximately 40 million Americans currently smoke.[75] Time trends in the occurrence of lung cancer closely follow smoking prevalence rates. Lung cancer mortality peaked among men in approximately 1990 at 70 cases per 100,000 population and has since decreased every year, closely tracking with declining smoking prevalence.[55,56,76,77] Relatively high smoking prevalence among black adults, men, residents of rural areas, and in the South drive high lung cancer incidence and mortality in these populations.[60,75,78]

Approximately 10-20% of lung cancer cases are not linked to smoking.[79,80] Chemical exposures such as radon, asbestos, nickel, and chromates are also strongly linked to lung cancer.[56,81,82] In 1970, asbestos was recognized as a hazardous chemical and thus began being regulated by the Environmental Protection Agency (EPA). Radon, the second leading cause of lung cancer, was first linked to lung cancer in mine workers in 1989, the same year that the EPA issued a full ban on asbestos use.[56,82] Moreover, high levels of arsenic exposure are established as causing lung, liver, kidney, prostate, and bladder cancer.[82] Additional lung cancer risk factors include outdoor air pollution, occupational smoke inhalation (e.g., firefighters) and smoke inhalation from cooking on an open fire.[56,83] Rarely, lung cancer occurs in those with no smoking history and no known exposures to chemicals or smoke. These cases are often attributed to genetic mutations or possibly unidentified environmental exposures.[56,79,80]

**2.2 Low Dose Computed Tomography (LDCT) Screening**

Annual LDCT screening significantly reduces lung cancer mortality by 20-40%.[54] Following the National Lung Screening Trial in 2011, national organizations including

the U.S. Preventive Services Task Force (USPSTF) and the American Cancer Society released recommendations for annual LDCT screening to individuals at high risk for lung cancer.[54,84–86] Although eligibility criteria vary by organization, the USPSTF classifies high risk individuals as current and former smokers who quit within the last 15 years, persons aged 55 to 80 years, and those with 30+ pack-years smoking history.[35,84,87] Medicare began covering LDCT screening for high risk individuals (including a shared decision-making visit with a qualified health care provider) in 2015.[35] Although LDCT screening for lung cancer increased from 3.3% in 2010 to 3.9% in 2015 following the publication of the NLST results in 2011 and updated USPSTF recommendations in 2013, national LDCT screening rates remain very low.[88,89] Screening utilization significantly varies by region with the highest utilization in Northeast (10.1%) compared to the Midwest (2.2%), the South (3.5%), and the West (1.6%).[39] Utilization does not mirror the size of the LDCT screening eligible population, as the largest proportion of those eligible (40.3%) resides in the South.[39]

Many factors contribute to low screening rates. Screening eligible smokers are less likely to have a usual source of care than the general population and therefore less likely to be referred for LDCT screening.[90] However, eligible individuals who are identified as smokers and have a usual health care provider appear to miss opportunities to learn about LDCT screening from their healthcare providers. Previous research has reported both physician barriers,[91–93] and patient factors contribute to these missed opportunities. For example, patients who smoke have reported barriers in discussing lung cancer screening with their health care providers due to feelings of discrimination based

on their smoking history.[94,95] Furthermore, patients eligible for screening with comorbidities may experience more harm than benefit, thus motivating the patient and physician to decide against screening during a shared decision-making counseling session.[94] Screening among high-risk populations provides an opportunity to diagnosis more cases at early stages. More research is needed to understand and improve low screening utilization in an effort to further improve lung cancer survival.

### 2.3 Histology and Staging

Lung cancer histology and staging are associated with survival, as both play prominent roles in defining the clinical characteristics of a case and choosing the appropriate treatment approach following a lung cancer diagnosis. Lung cancer histology is divided into two categories: non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC). NSCLC accounts for 85-90% of all cases and includes three subtypes: large cell, adenocarcinomas and squamous cell carcinomas.[12] Adenocarcinoma is the most common histologic type and is the most common type among never smokers.[96] The remaining 10-15% are SCLC, which is almost exclusively observed among smokers and former smokers. SCLC is considered the most aggressive form of lung cancer since it is the least responsive to chemotherapy.[97] Small cell, squamous cell, and large cell incidence rates have decreased over time while the incidence of adenocarcinomas has increased in women and remained constant among men.[12,98]

The American Joint Committee on Cancer defines lung cancer stages 0-IV by three combined categories, referred to as TNM classifications, including: primary tumor

size (TX, T0-T4), regional lymph node involvement (NX, N0-N3), and distant metastasis (M0, M1, M1a, M1b).[99] Tumor size (T score) defines the greatest dimension in centimeters and the physical location of the primary tumor.[99] Determining the involvement of lymph nodes (N score) has been cited as the most important piece to staging the disease and determining the proper course of treatment.[100] Conversely, improper nodal detection can lead to treatment failure and decreased survival.[101] Nodal involvement can be determined through various methods (invasive/surgical approaches or non-invasive scans: CT or PET).[100] Surgical systematic nodal sampling is preferred by the American College of Chest Physicians, with a detection rate almost twice that of surgical selective sampling of lymph nodes and non-invasive scans.[102] Cases with metastasis (M1, M1a, M1b) are defined as Stage IV. Approximately 40% of lung cancer cases are diagnosed with stage IV disease, with a 5-year survival rate between 0-10%.[99,103]

**2.4 Treatment Options**

Treatment approaches for lung cancer are highly variable depending on histologic type, stage at diagnosis, genetic profile, overall health of a patient, and location of cancerous nodule(s). Cancer-directed treatment is defined as any treatment approach intended to control, remove, or destroy cancer cells in the body.[104] Cancer-directed treatment approaches may include surgery to resect the tumor, chemotherapy, radiation, immunotherapy, or a combination of all four. Non-cancer-directed therapies are given for clinical reasons such as pain management, nutrition supplementation, and diagnostic tests. Cancer registries are required to differentiate between cancer-directed and non-

cancer-directed treatments in patient records. For this project, we only considered the use of cancer-directed treatment.

In otherwise healthy adults diagnosed with lung cancer before metastasis, surgery is the most effective treatment approach to improve survival.[100] Staging, tumor size, tumor location(s), and patient comorbidities (i.e., medical operability) are collectively considered when determining if surgical resection is appropriate and is often reserved for patients diagnosed in early stages.[100,105] Surgery to remove tumors from the lungs can be complex, depending on the location of the nodules in proximity to crucial blood vessels and surrounding organs.[100]

Lung resection for the treatment of lung cancer may be performed in various ways (e.g., lobectomy, sleeve lobectomy, or pneumonectomy) through a traditional open approach or via minimally invasive thoracic surgery (MITS), which includes video-assisted thoracic surgery (VATS) or robotic VATS (RVATS).[100,106] Lobectomy (removal of a lobe of the lung) is the preferred surgical approach for the surgical management of lung cancer, recommended by the American College of Surgeons due to the lower rates of tumor recurrence and longer survival in comparison to the use of segmentectomy (removal of a segment of a lung lobe).[100] Patient outcomes further improve when lobectomy is performed by MITS rather than by an open surgical approach.[106–108] In fact, research has demonstrated increased 5-year survival, shorter hospital stays, better post-operative pulmonary function, and lower reported levels of pain in comparison to open surgical approaches.[106–108] Despite these advantages, MITS approaches have not been

adopted uniformly as the standard approach to lung resection.[109] Thoracic surgeons have been shown to adopt recommended surgical guidelines more readily than general surgeons and have better patient outcomes including improved survival.[110,111] However, thoracic surgeons are not widely accessible in rural areas, potentially resulting in unequal access to high-quality surgery for early-stage lung cancer cases.[112,113]

In late-stage cases and/or people with poor health, surgery may not be an option. Hence, chemotherapy and/or radiation is the next best treatment approach. Depending on the stage at diagnosis, chemotherapy for lung cancer can be given prior to surgery, after surgery (adjuvant therapy), or at the same time as radiation treatment (concurrent therapy). Most patients receive a combination of two chemotherapy drugs given in cycles lasting one to three days, with breaks in between over a three to four-week period.[87] All chemotherapy drugs recommended for use in the treatment of NSCLC are included in Appendix A of this document.[114]

In the same way as chemotherapy, radiation may be given before surgery, after surgery, and in some cases alone.[87] Radiation prior to surgery is often an attempt to shrink tumors to make them easier to remove. Radiation alone may be recommended for late-stage patients as a palliative care approach. The two main types of radiation for the treatment of NSCLC are external beam radiation therapy and brachytherapy (also referred to as internal radiation therapy). Subtypes of external beam radiation therapy are three-dimensional conformal radiation therapy (3D-CRT), intensity modulated radiation

therapy (IMRT), and stereotactic body radiation therapy (SBRT).[87,115] Radiation therapy is often given five days a week for up to seven weeks.

Lung cancer treatment is constantly evolving through the development of new medications, novel genetic testing techniques, and advanced treatment protocols from clinical trials. Immunotherapy drugs work to stimulate the immune system to destroy cancer cells and can be given along with, after, or in place of chemotherapy. The first immunotherapy drug for NSCLC, Opdivo, was approved in 2015 followed by Keytruda, Tecentriq, and Imfinzi.[116] Targeted therapy drugs are commonly used for late-stage patients and are coupled with genetic testing to pinpoint when they are appropriate for each patient. These drugs work to inhibit tumor development differently than chemotherapy drugs through processes such as altering proteins, hindering chemical signals, and blocking blood vessel production in tumors. In 2018 there were ten FDA approved targeted treatments.[114,117] Epidermal growth factor receptor (EGFR) mutation testing was the first approved in 2013 following recommendations by the National Comprehensive Cancer Network for EGRF testing for late-stage NSCLC patients in 2007.[118] However, disparities may exist in the use of targeted therapies. An examination of utilization of EGFR testing from 2011-2013 found it was being underutilized in all practice settings and most commonly performed in urban areas and among Asians. On the contrary, Medicaid recipients, Hispanics and black cases were the least likely groups to be tested, potentially leading to missed opportunities for use of targeted therapies and improved treatment outcomes for these populations.[118]

Clinical trials provide opportunities to understand the efficacy of new treatment approaches. Clinical trials are sometimes considered a last option in survival for late-stage lung cancer patients when approved treatment options have failed or are not considered appropriate. In December 2018, there were 149 NIH funded clinical trials active in the U.S. focusing on innovative approaches to lung cancer treatment.[119] However, it may be difficult for all eligible patients to access clinical trial locations. The NCI and FDA have acknowledged the underrepresentation of racial minorities and rural residents in past clinical trials.[120,121] New initiatives such as the National Community Oncology Research Program sponsored by NCI focus on bringing more clinical and intervention trials to diverse communities serving minority and rural patients at local community-based hospitals.[121]

**2.5 Time to treatment initiation**

Choosing the appropriate treatment approach varies depending on patient characteristics and provider tendencies, which can impact the time between diagnosis and treatment initiation. An appropriate time interval between diagnosis and treatment initiation is defined as *timely treatment* and is one of six domains of health care quality recommended by the Institute of Medicine.[122] However, optimal timing of treatment initiation and the impact of timely treatment on lung cancer survival is not well defined.[123–126] Recommendations from agencies such as the American Cancer Society and American Lung Association suggest starting treatment "very soon" or "within a few weeks" after a cancer diagnosis. These vague recommendations ideally could be more precise.[123] Because a cancer diagnosis can cause anxiety and depression that delay patient

action to seek immediate follow-up care and plan a course of treatment, clearly defined recommendations for timely treatment are needed to encourage prompt delivery of guideline-concordant treatment.

### 2.6 Factors driving treatment delays

Previous research has reported multiple factors driving delays in treatment including medical system processes, patient comorbidities, stage at diagnosis, and diagnostic testing approaches. Medical system processes, including long referral periods, have contributed to treatment delays in early-stage patients diagnosed in community settings[127] and time spent scheduling PET scans contributed to treatment delays in a diverse population of Medicare patients.[124] In a single health system in Texas, patients treated at public hospitals experienced longer delays in treatment than those treated in private hospitals (76 days vs. 45 days, $p<0.01$.[128] Among a sample of veterans, the median time to surgery was 98 days and waiting for smoking cessation significantly delayed treatment for almost a third of the study sample (29%).[125] In this same population, time spent on evaluation and staging (a median wait time of 71 days for scans) also contributed to delays in treatment.[125] Missed diagnoses was reported as causing delays in patient interviews from cancer centers, outpatient settings, and community treatment centers.[125,127,129] Late-stage diagnosis (versus early-stage) and treatment in non-academic settings versus a VA hospital have been associated with improved timely treatment in some studies.[130,131] However, treatment for late-stage disease at academic centers was associated with delays in a diverse population of patients from the National Cancer Data Base as were urban location, having an income less than

$35,000 and increasing Charlson comorbidity scores were all associated with delays in treatment.[132]

**2.7 Timely treatment and survival**

Timely treatment and its association with lung cancer survival is not well understood. Publications on the topic have used a range of definitions for treatment itself (surgery, chemotherapy, or radiation) and timely treatment (e.g., median time from study sample, arbitrarily 6 weeks). Few studies have identified a positive association between timely treatment and improved survival in lung cancer patients. A study of early-stage lung cancer patients at John Hopkins cancer center reported an average referral time of 61.2 days following diagnosis. They found that increasing weeks from diagnosis to first surgery (measured continuously) predicted worse survival (HR=1.04, 95%CI:1.00-1.09).[127] However, these results were not statistically significant after adjusting for patient demographics and clinical factors. Findings from a 12-year sample of stage I patients from the National Cancer Database found that surgery initiation before 8 weeks post-diagnosis resulted in significantly higher survival rates.[132] Similarly, a review among Medicare patients found a median time-to-treatment of 27 days. In early-stage cases, treatment initiation within 35 days was associated with improved survival. There was no association between treatment time and survival for distant-stage cases.[124]

Others have reported conflicting findings, showing worse survival or no association between timely treatment and lung cancer. In a small sample of veterans (n=129) from a single health care system, the median time to treatment was longer than

that reported in other settings at 84 days.[133] They defined timely treatment as less than the median, 84 days, and found that patients receiving timely treatment were more likely to die than patients receiving care after 84 days (HR=1.6, 95%CI: 1.3-1.9). After stratifying by severity, the results were not significantly different.[133] A study of privately insured lung cancer patients in South Carolina found patients who received treatment within 6 weeks of diagnosis had shorter median survival at all stages (36.9, 27.1, 12.4 months for localized, regional, and distant) when compared to cases who received treatment in more than 6 weeks (39.4, 33.8, 25.2 months for localized, regional, distant).[134] Likewise, an investigation of 482 stage I-III NSCLC patients in a single medical network in Texas from 2000-2005 found a median diagnosis to treatment time of 33 days.[128] They defined timely treatment as less than the median 33 days and reported no association between timely treatment and survival using Kaplan Meier survival analysis (p=0.42).[128] An examination of SEER-Medicare records from 2002-2007 showed a substantial proportion of patients waiting over 300 days to initiate treatment.[126] Timely treatment was defined using guidelines published by the RAND corporation and the British Thoracic Society: less than 8 weeks for surgery, 7 weeks for radiation, and 4 weeks for chemotherapy.[126,135] In their survival analysis among 16,747 patients diagnosed in 2003 or 2004, they found lower mortality risk for patients receiving delayed care (HR=0.68, 95%CI:0.66-0.71) compared to patients receiving more rapid care.[126]

### 2.8 Disparities in timely treatment

There are also conflicting findings related to disparities in the time to treatment initiation for lung cancer; however, overall studies found disparities relating to race, sex

and rurality. A study of the association between race and time to treatment initiation for lung cancer among veterans found only slight racial differences in time to treatment between black and white patients (72 days vs. 65 days, p=0.80).[53] Using a Cox PH model adjusting for patient and disease characteristics, black cases had significantly better survival than whites (HR=0.30, p<0.01).[53] A SEER-Medicare analysis of lung cancer patients from 2000-2002 reported black patients had 1.4 times the odds of treatment delays when compared with white patients (p<0.01).[136] Other factors associated with delays in treatment were Medicaid and Medicare dual enrollment (vs. Medicare alone), being divorced or widowed (vs. married), and late-stage diagnosis (vs. early stage).[136] A SEER analysis using records from 2002-2007 reported differences in timely treatment by race and sex where females were 25% less likely to receive timely treatment compared to men and black patients were 66% less likely to receive timely treatment compared to white patients.[47]

### 2.9 National Cancer Institute and Commission on Cancer Treatment Centers

Treatment center type is related to patient outcomes including survival.[137–140] National Cancer Institute (NCI) designation and Commission on Cancer (CoC) accreditation are two of the highest standards for cancer treatment centers. Patients treated at these centers have better survival than those treated at non-accredited centers.[137–140] A study of 69,579 cancer patients in Los Angeles County found lung cancer patients who did not receive their first treatment at a NCI-designated comprehensive cancer center had worse survival than those treated at other cancer centers after adjusting for demographic and clinical factors (HR=1.4, 95% CI, 1.3-1.6).[137] More

research is needed to understand the factors associated with patient utilization of these centers in comparison to non-accredited treatment centers. NCI designation results from a peer-review process through the National Cancer Institute. There are currently 14 NCI-Designated Cancer Centers and 49 NCI Comprehensive Cancer Centers located in 36 states, primarily in urban areas.[141] Most NCI centers are part of high-volume university medical centers. High patient volume and academic settings have been shown to have better survival in lung cancer patients where post operation morality was 3.2% in high-volume settings (more than 90 operations per year) compared to 4.8% in low-volume settings ($p < 0.01$)[142] and are the primary locations of clinical trials testing new cancer treatments.[141]

The Commission on Cancer (CoC), an accreditation program from the American College of Surgeons, provides accreditation to high-quality treatment centers. The proportion of hospitals with CoC accreditation changes per year and varies widely across states. For example, in 2009 the proportion of CoC-accredited hospitals in Wyoming was 0% and 100% in Delaware.[143] CoC accreditation requires treatment centers to meet standards on prevention, research, education, and quality care aimed at improving survival.[144] When compared with non-CoC-accredited hospitals, CoC hospitals are larger, more commonly in urban areas, and have more available services for cancer patients such as patient navigation, financial counselors, and advanced surgical approaches.[143,145]

## 2.10 Race and Ethnicity

Racial disparities in lung cancer incidence, treatment, and thus survival, particularly among black vs. white race, are well documented.[2,12,49,50,146–151] Observed racial disparities in lung cancer survival may be a complex function of socioeconomic differences, access to care, treatment disparities, comorbidities, smoking behavior, or other factors. Statistically controlling for covariates such as socioeconomic status (SES), stage at diagnosis, and comorbidities has been shown to reduce or remove survival differences in survival observed between black and white lung cancer patients.[146–149]

## 2.11 Racial Differences in Incidence and Survival

Lung cancer incidence is higher in black adults than any other racial/ethnic group in the U.S.[2,12,50,150,151] Smoking functions as major contributor to the observed incidence of lung cancer in black adults.[150] The 2017 smoking prevalence for black adults in the US was 14.9% compared to 15.2% among whites.[152] Furthermore, black smokers are less likely to use smoking cessation assistance and less likely to stop smoking than whites.[153,154] Even among never smokers, lung cancer incidence is higher in blacks than whites.[96,155] Black lung cancer patients also tend to be younger and diagnosed at a later stage than their white counterparts.[6,148]

Like the overall U.S. population, cancer is the second leading cause of death among Native Americans.[156] Lung cancer mortality from 2009-2013 for Native American men was lower than the incidence for white and black men but higher than Asian men.[77] However, Native Americans in Oklahoma experience higher lung cancer incidence rates

than whites.[157] Native American women had the highest lung cancer incidence as compared to white, black, and Asian women. Despite the higher incidence rates, Native American women had lower mortality rates than white and black women.[77]

Lung cancer mortality rates are also highest among black men, followed by white men, white women and black women, respectively.[2] Research on racial differences in lung cancer survival using small cohorts, state cancer registries, and SEER data similarly report worse survival among black lung cancer cases than all other race categories.[4,5,146,149,158,159] Conversely, Asians have better survival than whites.[4,155]

Lung cancer survival among Hispanics is not well understood. In some populations, the survival of Hispanics is cited as better than whites.[4,155,160] Researchers point to potential differences in histologic type, social support, or exposures (e.g., wood burning smoke) as reasons for better survival in Hispanics, while others argue that detection bias and diversity among Hispanics may play a role.[161–163] An examination of Florida and Texas cancer cases from 1995-2003 reported high missingness among foreign-born Hispanics in the sample that can explain the previous observed rates of high survival.[162,163] In a study among stage I SEER registry patients from 1991-2000, Hispanics had worse survival than whites.[164] However, after adjusting for surgery and stage at diagnosis, the difference was not statistically significant suggesting that differences in surgical resection by race may explain observed survival differences between Hispanics and whites.[164]

The data related to Native American disparities in lung cancer mortality and survival is sparse and presents conflicting results. An analysis of lung cancer cases between 1999-2009 recorded by Indian Health Services found death rates among Native Americans living in Contract Health Service Delivery Area (CHSDA) counties higher than whites in the same CHSDA counties, citing disparities in tobacco control and interventions as contributing factors.[165] Kaiser Permanente Northern California reported significantly higher comorbidities among Native American lung, breast, colorectal, and prostate cancer patients compared to whites.[156] However, after adjusting for comorbidities and disease characteristics, all-cause mortality and cancer-specific mortality were not significantly higher in Native Americans than whites.[156] Similarly, Indian Health Services records in Florida spanning 1996-2007 examining 148,140 patients found no difference in lung cancer survival between whites and Native Americans.[166]

**2.12 Racial differences in treatment**

Racial differences in lung cancer treatment are also well documented. Black lung cancer patients are less likely than white patients to receive timely treatment (within 6 weeks of diagnosis), receive radiation therapy, undergo surgical staging, and receive surgical resection.[8,10,11,13,47,155,164] When choosing to undergo surgical resection, black patients are less likely than white patients to use high-volume hospitals, a metric associated with better surgical outcomes such as survival.[167] Black patients are also more likely to refuse treatment all together, even when diagnosed at an early stage.[8] Treatment delays among Medicare beneficiaries were reported where Native Americans experienced

significantly longer treatment delays and lower receipt of treatment than whites.[168] Native Americans were less likely to receive guideline concordant treatment, less likely to have surgical resection, and had lower rates of follow-up surveillance than whites.[168] Survival was significantly lower among those who did not receive optimal treatment and surgery. Minority groups' potential distrust in medical providers, fatalism, and negative surgical beliefs have been cited as contributing factors to differences in lung cancer treatment utilization.[155,164,169,170]

**2.13 Sex**

More lung cancer cases are male than female, as the smoking prevalence among men has historically been much higher than that of females. However, the gap between males and females in lung cancer incidence is narrowing at 52.2% male and 47.5% female in 2017.[12,60,171,172] Of note, more lung cancer cases among never smokers are female than male.[22,23] and a higher proportion of adenocarcinoma lung cancer cases are female than male.[173–175] There is concern over biological differences, specifically higher susceptibility to cigarette carcinogens in women than in men.[173,176–178] Additionally, women have a harder time quitting smoking compared to men.[179]

Female lung cancer cases tend to be younger and have better survival than men even after controlling for age, stage, and treatment type.[19,21,23,173,180,181] A meta-analysis reported sex differences in targeted therapy and immunotherapy, where females benefited more than males from EGFR inhibitors.[182] Sex differences in histology and treatment

response may need to be considered with greater magnitude when choosing the treatment approach for lung cancer.[22,182]

### 2.14 Rurality

At least 46 million people live in rural areas of the U.S. and often face higher rates of poverty, smoking, and overall poor access to healthcare in comparison to urban areas.[48,183] Most rural areas have a smoking prevalence twice that of large urban areas contributing to higher lung cancer incidence and mortality rates in rural areas.[24,48,184] Rural areas also have 1.15 (95%CI: 1.15-1.16) times the risk of lung cancer diagnosed at late-stage compared to those in urban areas, making treatment decisions more complicated and limiting.[185] Even among stage I patients, rural residents have higher odds of receiving no treatment than their urban counterparts (RUCA 9 vs. RUCA 1 OR=1.40, 95%CI: 1.09-1.80).[48]

The rural population is dispersed over 97% of the nation's land area, often making it difficult for rural residents to access healthcare resources needed to diagnosis and treat lung cancer.[186] Rural residents must travel farther to access care, specifically to access specialty physicians.[187] Access to specialists is important as treatment by specialists is associated with receipt of cancer-directed therapy even among late-stage lung cancer patients and improved survival.[110,111,188,189] In a geographic analysis of drive times to cancer treatment centers, researchers found that 45.2% of the population live less than a one-hour drive to an NCI-designated center and 69.4% live within a one-hour drive to academic centers.[187] However, Native Americans, rural residents, and those living in the

South had the longest drive times to any cancer treatment centers.[187] When examining the association of the interaction between race and rurality on access to cancer care, urban black cancer patients had shorter travel times than urban white patients,[190] yet rural black patients had longer travel times than rural whites to NCI-designated Cancer Centers. Rural black patients were also 58% less likely than rural whites to receive care at an NCI-designated cancer center.[191] On the other hand, in an analysis of self-reported quality of care among rural breast, lung, colorectal, and prostate cancer patients, the rural cancer patients reported getting cancer care quickly more so than urban cancer patients.[192]

**2.15 Regional differences**

The South bears the burden of the highest smoking rates and lung cancer incidence in the country.[50,193] Kentucky has the highest incidence rate of lung cancer cases for both men and women.[193] In 2015, the age-adjusted lung cancer incidence rates in for men was 105.6 per 100,000 and 77.5 per 100,000 for women in Kentucky. In comparison, Utah had the lowest age-adjusted cancer incidence rates at 29.6 per 100,000 for men and 22.1 per 100,000 for women. In Kentucky, 24.5% of adults currently smoke, placing them the second highest in the nation in 2016 behind West Virginia at 24.8% of adults.[193] An examination of regional differences in racial disparities of lung cancer incidence in 2016 reported that lung cancer incidence among black men in Kentucky is twice that of Colorado, further illustrating the differences in the burden of lung cancer between the two populations.[150] A review of SEER and National Program of Cancer Registries (NPCR) lung cancer data from 2004-2006 also reported differences in lung cancer incidence by region where those living in the South had the highest lung cancer

incidence.[50] They also described racial differences in incidence by region; the highest lung cancer incidence rates among whites were in the South, among Asians in the West, among Hispanics in the Northeast and among blacks and Native Americans in the Midwest.[50] Based on these results, the authors recommended tailoring prevention messages to fit regional culture.[50]

### 2.16 Socioeconomic Status

Socioeconomic status (SES) is an important factors influencing survival, potentially working through mechanisms of low smoking rates, better access to care, improved health literacy, and overall better health among high SES populations when compared to low SES populations.[51,146,194–196] Among lung cancer patients, low SES is linked to lower likelihood of surgical resection, guideline-concordant treatment, and lower survival.[6,51,195,197,198] Even after adjusting for comorbidities, patients of the lowest SES continue to have worse survival outcomes compared to those of higher SES (HR=1.05, $p<0.01$).[6] Differences in SES may be a contributing factor to the observed cancer disparities among rural and black populations. While some have shown that adjusting for SES eliminates rural and racial disparities,[53,195] others have demonstrated that these disparities are reduced, but not eliminated, after adjusting for SES.[146,195,196]

### 2.17 Martial Status

Marital status has also been associated with cancer survival, perhaps functioning through improved SES and social support.[146,195,196] Married individuals are less likely to have late stage at diagnosis (OR=0.83, 95%CI:0.82-0.84), more likely to undergo cancer-

directed treatment (OR=1.53, 95%CI: 1.51-1.56), and experience improved survival when compared to non-married individuals (single, divorced, widowed) (HR=0.80, 95%CI: 0.79-0.80).[196] The protective result of marital status may be stronger for men than women.[146]

**2.18 Summary**

An understanding of disparities in survival and access/utilization of high-quality lung cancer treatment facilities is a crucial step in reducing lung cancer mortality. Patient race/ethnicity, sex, and location impacts cancer treatment and thus survival. The results of our proposed project add to existing data on lung cancer disparities and our results identifying barriers in surgical utilization among low income and black patient populations provide necessary insight for the development of future interventions. Further research aimed at improving surgical utilization among early stage cases may improve survival of lung cancer among low income and black patient populations.

# CHAPTER 3
# METHODS

To address the aforementioned gaps in the literature, we used the National Cancer Institute's Surveillance, Epidemiology and Ends Results (SEER) cancer registry data linked with fee-for-service Medicare billing data from the Centers for Medicare and Medicaid Services (CMS), referred to as SEER-Medicare.[199] We used the SEER-Medicare linked database to address all three of our research aims.

## 3.1 Description of SEER-Medicare Dataset

The SEER-Medicare data set provides population-based cancer registry data from the SEER program and comprehensive Medicare billing data for fee-for-service (FFS) Medicare beneficiaries. We utilized twelve years of linked SEER-Medicare claims data from 2003-2014. SEER-Medicare data is fitting for our population of interest because it covers nearly 26% of the U.S. population and two-thirds of lung cancer patients in the U.S. are over the age of 65 (the age at which most individuals qualify for Medicare coverage).[200] SEER provides cancer registry information on patient disease characteristics such as primary cancer site, stage at diagnosis, and tumor behavior. Medicare FFS billing data provides information on all procedures and visits billed to Medicare including the treatment(s) received and the associated dates and locations of treatment receipt.

The geographic coverage of the SEER-Medicare linked dataset is limited to that of SEER registry sites in the United States: New Jersey, Connecticut, Iowa, Wisconsin, Detroit, Michigan, Louisiana, Kentucky, Georgia, Seattle (Washington), California, Hawaii, Utah, Idaho, New Mexico,  Alaska Natives.

### 3.2 Description of the SEER Program

The main objective of SEER is to reduce the mortality of morbidity of cancer in the US through research using cancer registry data. SEER began collecting cancer registry data in 1973 in Connecticut, Hawaii, Iowa, New Mexico, Utah, Detroit, and San Francisco/Oakland and has since expanded to include twenty registries representing a diverse population of US residents.[201] In addition to clinical data, SEER also provides information on the cause of death, survival time, demographics, and county-level urban versus rural designation. To address generalizability, NCI has shown that the characteristics of the geographic areas covered by SEER registries are similar to that of the overall US population in terms of education and poverty. The SEER registry population does, however, have a higher proportion of foreign-born residents that the general US population (17.9% vs. 13.2%). The racial coverage of the registry is 31.9% of whites, 30.0% of blacks, 44.0% of Hispanics, 57.5% of Asians, 49.3% of American Indians or Alaskan Natives, and 68.5% of Hawaiians or Pacific Islanders.[201]

### 3.3 Description of Medicare Fee for Service Claims

The Medicare portion of the dataset provides health care billing claims for covered expenditures for enrollees in fee-for-service (FFS) Medicare. Those covered

under Medicare Advantage (MA) do not have detailed billing claims available in the data files, restricting analytic capabilities to the FFS population only. Medicare is limited to those age 65 and older, those with disabilities, and patients with End Stage Renal Disease.[202]

NCI and CMS perform the SEER-Medicare linkage process before releasing the data files to researchers. This process occurred every 4 years between 1991-2003, every 3 years from 2006-2012, and now biennially since 2014 with the most recent linkage available from 2016. The most recent files released in 2016 cover SEER data for patients diagnosed with cancer through December 31, 2013 and their accompanying Medicare billing claims through December 31, 2014. The linkage itself includes matching SEER registry patient identifiers with corresponding identifying variables in Medicare master enrollment files with a reported successful match rate of 93%.[200]

**3.4 Study Sample**

Our sample included subjects identified with a first primary diagnosis of non-small cell lung cancer lung cancer confirmed by a biopsy procedure on record. Receipt of treatment was identified in claims data using CPT and ICD9 codes for chemotherapy, radiation, and/or surgical resection. Our inclusion criteria are: 1) a first primary lung cancer tumor diagnosed between 2003-2011, 2) a diagnosis of non-small cell lung cancer (NSCLC) only, which accounts for approximately 85% of lung cancer cases, and 3) age 66 years and older. We excluded lung cancer patients who were diagnosed postmortem. Patients undergoing surgical resection of the lung for reasons not related to treatment of

lung cancer (e.g., to treat collapsed lung, removal of blood clots, removal of damaged tissue from emphysema) or with Kaposi's sarcoma of the lung (this disease has a unique prognosis/associated complications) were also excluded (ICD-9 Codes in Figure 3.1 and Appendix). Patients eligible for Medicare due to a diagnosis of End Stage Renal Disease (ESRD) and/or disability were excluded from our study sample. These patients are often younger and coping with complex medical conditions as compared with Medicare beneficiaries who have aged into eligibility (65 and older).

### 3.5 Independent Variables

Patient-level variables were drawn from the SEER component of the data base and included age of patient (66-69, 70-74, 75-79, 80-84, 85+), sex (male vs female), and race with categories white, black, Asian and Pacific Islander, Native American/Alaskan Native. SEER provides four different variables for patient rurality, also a main exposure of interest. We used county-level U.S. Department of Agriculture defined Rural-Urban Continuum Codes (RUCC) for all three aims.[203] RUCC codes are based on metropolitan population densities and adjacency to metro areas.[203] We used primary RUCC codes, nine whole number categories indicating population sizes, with three metro classifications and six nonmetro classifications: 1) Metro county of over 1,000,000 population, 2) Metro county of 250,000-1,000,000 population, 3) Metro county of under 250,000 population, 4)Nonmetro county of 20,000 or more population and adjacent to a metro area, 5) Nonmetro county of 20,000 or more population and not adjacent to a metro area 6)Nonmetro county of 2,500 to 19,999 population and adjacent to a metro county, 7) Nonmetro county of 2,500 to 19,999 population and not adjacent to a metro county, 8)

Completely rural or less than 2,500 population and adjacent to a metro area, 9) Completely rural or less than 2,500 population and not adjacent to a metro area.[203] We used SEER registry location to assign Census regions in the following four categories:

1. Northeast: New Jersey, Connecticut
2. Midwest: Iowa, Wisconsin, Detroit, Michigan
3. South: Louisiana, Kentucky, Georgia
4. West: Seattle, California, Utah, Idaho, New Mexico, Alaska Natives, Hawaii

Covariates included marital status, year of diagnosis, and Medicaid enrollment (as a patient level measure of low income). We used clinical data from SEER on data of diagnosis, cause of death, date of death, survival time, stage at diagnosis, and histology type (with NSCLC as an inclusion criteria)

All statistical analyses were conducted with SAS software, version 9.4 (SAS Institute Inc., Cary, NC). This research contained only deidentified secondary data analyses and was deemed exempt from IRB review at the University of South Carolina.

### 3.6 Paper 1 Methods

**Investigate disparities in lung cancer-specific and overall survival by race/ethnicity, sex, and geography and identify patient and geographic factors associated with survival**

Hypothesis: We hypothesized that lung cancer survival would be lowest among black, rural, and male cases. We further hypothesized that these disparities would be most pronounced in the South Census region.

#### 3.6.1 Measures

Lung cancer disease characteristics and patient demographics were derived from the SEER component of our SEER-Medicare data. Our main independent variable of interest was rurality. Patient residence at county-level at the time of diagnosis was used to assign levels of rurality using RUCC codes.[203] The USDA 2003 RUCC designation, based on 2000 Census data, were used for cases diagnosed between 2003-2009. The 2013 RUCC codes, based on 2010 Census data, were used to define rurality for cases diagnosed in 2010-2011. We collapsed RUCC codes into three categories as follows: 1) Large urban=Metro counties over 250,000 population, 2) Small urban =Metro counties under 250,000 population, 3) Rural=All Nonmetro counties

We controlled for race (white, black, Asian, Native American, other), sex (male or female), Census region (Northeast, Midwest, South, West) and stage at diagnosis (localized, regional, distant) in our model. Cause of death was used to define lung cancer-specific and overall survival. Our outcome variables, vital status and survival time in

months, are reported by SEER. The following covariates were also tested with the main variables of interest for model selection based on literature reviews: year of diagnosis, patient age at diagnosis, Charlson Comorbidity Index, treatment type (chemotherapy, radiation, surgery, combination, all of the above), marital status, and Medicaid enrollment (yes or no).

### 3.6.2 Analyses

We produced descriptive statistics for our study sample demographics and performed between-group comparisons by rurality and stage at diagnosis using t-tests for continuous variables and chi-square tests for categorical variables. We used the Kaplan Meier method and the Log-Rank test to examine the unadjusted differences of all-cause and lung cancer-specific survival by levels of rurality. We used the logrank trend test to investigate a possible trend in survival with increasing rurality. We implemented multivariable survival analyses through two Cox Proportional Hazards (PH) models, one for all-cause survival and one for lung cancer-specific survival, with rurality as our primary exposure of interest. Before performing model selection, we tested the Proportional Hazard (PH) assumption for our model variables using log-log plots and Schoenfeld residual plots across time with $\alpha$=0.05. Two of our variables violated the PH assumption, race and receipt of radiation therapy. Through Likelihood Ratio testing, we determined that the best approach was to use a stratified Cox PH model, stratified by race. After examining the interaction of time with the variable for radiation therapy, which also violated the proportional hazards assumption, we recognized a clear crossover in all-cause survival probability at 12 months post diagnosis. We implemented a time-

dependent model using a heavy side function at 12 months post diagnosis for the all-cause model. In the lung cancer-specific model, the crossover of survival curves occurred earlier at month 8, and a heavy side function was implemented at 8 months post diagnosis. We selected variables in our final model through backward selection with removal level of $p \leq 0.05$ and then examined potential significant interactions between 1) rurality and sex, 2) rurality and Census region by performing additional Likelihood Ratio Tests. Once our final models were selected, we produced hazard ratios with 95% confidence intervals. We produced Kaplan Meier curves for levels of rurality in each region since the use of time-dependent Cox Ph models does not allow for estimation of final adjusted survival curves.

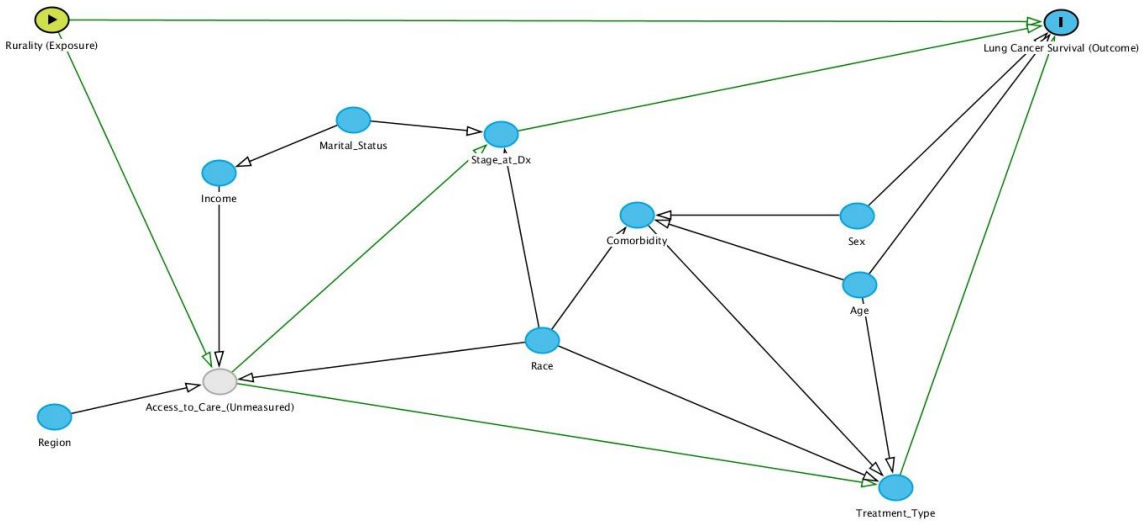



**Figure 3.1 Conceptual Framework of Paper 1 Survival Analysis**

**Table 3.1 Study Variable Definitions and Sources**

| Study Variable | Definition | Source | Aim(s) |
|---|---|---|---|
| **Patient characteristics** | | | |
| Age at diagnosis | 65-69, 70-74, 75-79, 80-84, 85+ | SEER | 1,2,3 |
| Race | White, Black, Native American, Asian, Other | SEER | 1,2,3 |
| Sex | Male or female | SEER | 1,2,3 |
| Marital status | Married, not married, unknown | SEER | 1,2,3 |
| Comorbidity | Charlson Index | Medicare | 1,2,3 |
| Income level | Low income (Yes or No) provided as Medicaid recipient or not | Medicare | 1,2,3 |
| End Stage Renal Disease | Yes or No (exclusion criteria) ICD9 585.6 | Medicare | 1,2,3 |
| Kaposi sarcoma | Yes or No (exclusion criteria) ICD9 176.4 | Medicare | 1,2,3 |
| Date of diagnosis | Month and year; first biopsy | SEER, Medicare | 2 |
| Vital status | Dead or alive | SEER | 1,2,3 |
| Cause of death | ICD codes | SEER | 1,2 |
| Date of death | Date of death agreement | SEER, Medicare | 1,2 |
| Survival time | Survival time in months (from date of diagnosis) | SEER | 1,2 |
| **Tumor factors** | | | |
| Stage at diagnosis | I, II, III, IV | SEER | 1,2,3 |
| Histology type | Non-small cell vs other (inclusion criteria) ICD-O-3 C34 | SEER | 1,2,3 |
| **Geographic factors** | | | |

| | | | |
|---|---|---|---|
| Patient location at diagnosis | State and county FIPS code | SEER | 1,2,3 |
| Rurality | County level Rural Urban Continuum Codes 2003 and 2013 | SEER | 1,2,3 |
| Census region | Northeast, South, Midwest, West (defined from patient registry location via SEER registry ID) | SEER, GIS | 1,2,3 |
| County Median Income | Continuous measure of median income of a county to gauge the socioeconomic status | Census | 3 |
| Medically Underserved Areas | County MUA designation (Yes or No) | HRSA | 3 |
| **Treatment factors** | | | |
| Surgery | Yes, No, Unknown | SEER, Medicare | 1,2,3 |
| Radiation therapy | Yes, No, Unknown | SEER, Medicare | 1,2,3 |
| Chemotherapy | Yes, No, Unknown | Medicare | 1,2,3 |
| Time to treatment | First surgery, chemotherapy, or radiation – date of diagnosis | SEER, Medicare | 2 |
| Thoracic surgeries other than removal of malignant neoplasms | Benign neoplasms ICD9 211.0-235.8<br>Cystic fibrosis IDC9 277.02<br>Primary pulmonary hypertension ICD9 416.0<br>Emphysema ICD9 492.0-494.1<br>COPD ICD9 496<br>Pneumonia ICD9 486, 513, 516<br>Pleurisy ICD9 511.0-511.9<br>Abscess of the lung ICD9 513.0-513.1 | Medicare | 1,2,3 |

### 3.7 Paper 2 Methods

**Examine differences in lung cancer-specific survival at differing thresholds of treatment initiation**

Hypothesis: We hypothesized that survival would be highest among those initiating treatment within 4 weeks of diagnosis

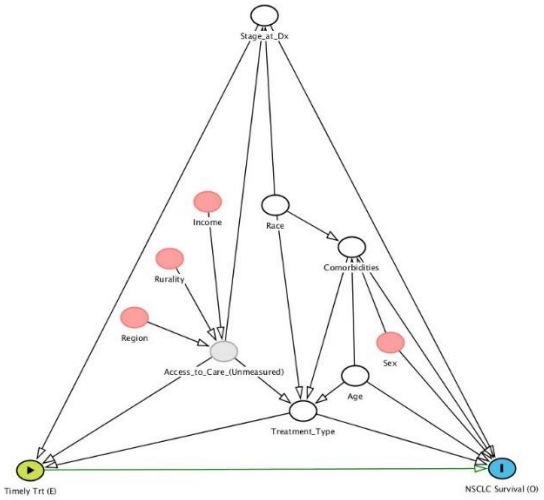



**Figure 3.2 Conceptual Framework of Paper 2 Survival Analysis**

#### 3.7.1 Measures

The outcome of lung cancer-specific survival time will be assessed from SEER data on vital status and survival time in months. Our main independent variable will be time from initial diagnosis to treatment defined at five differing thresholds: 4 weeks or less, 5-6 weeks, 7-9 weeks, 10-12 weeks, greater than 12 weeks. Time to treatment will be calculated by the weeks between the date of diagnosis (from SEER) to the time of the first treatment billing code in Medicare. Treatment is defined as first surgery, chemotherapy, or radiation and will be identified from Medicare billing codes using

HCPCS and CPT codes. A full list of the CPT, HCPCS, and ICD-9 codes for surgery and radiation are listed in the appendix.[204,205] To identify chemotherapy initiation, we will use codes associated with a comprehensive list of chemotherapy drugs approved by the Food and Drug Administration (FDA) for the treatment of NCSLC.[204] HCPCS codes for this list of drugs is available from the National Cancer Institute.[205] Since our data set does not include Medicare Part D (prescription drug billing codes), we will not be able to capture chemotherapy medications taken at home by prescription. We will control for age, stage at diagnosis, race/ethnicity, sex, rurality, and Census region. Rurality will be dichotomous (urban vs rural) based on rural urban continuum codes (RUCC).

### 3.7.2 Analyses

For each treatment type, we produced frequencies for all variables included in the model and performed between group comparisons by time to treatment using chi-square tests with $\alpha$=0.05. We tested the unadjusted relationship between time to treatment and lung cancer-specific survival with Kaplan Meier curves and the logrank test. We then tested the Proportional Hazards (PH) assumption using log-log of survival probability over time for all variables included in the model. We calculated univariate Hazards Ratios (HRs) for all variables tested for inclusion and performed a backwards selection with removal levels of 0.05 coupled with likelihood ratio tests to assess model fit. Using our final models, we produced hazards ratios with 95% confidence intervals for survival of NSCLC patients by categories of time to treatment.

For surgical treatment, two variables of interest violated the PH assumption: time to surgery initiation and radiation treatment. Time to surgery initiation showed a clear crossover in survival probability at 16 months post diagnosis. To account for these violations in our model, we incorporated a variable for the interaction between time to surgery initiation and survival time at 16 months post diagnosis and stratified by radiation treatment.

When stratifying by a radiation in survival analysis, the stratified Cox PH models constructs separate partial likelihood functions for each radiation group. The multiplies the two functions are multiplied together and use values of the coefficient that maximize the function. Therefore, the effect of radiation is absorbed into the time function and we can no longer make comparisons on this variable. Time-dependent Cox PH models allow us to account for the PH assumption of a variable, when deemed appropriate, and retain the ability to draw conclusions on that variable. Further explanations on time-dependent and stratified Cox PH models can be found elsewhere.[206,207]

For our sample of patients who received chemotherapy treatment, the variable for radiation treatment also violated the PH assumption; thus, we applied a time-dependent PH model. Specifically, we created and incorporated a time dependent variable into the Cox PH model representing radiation 12 months post diagnosis or not.

`For the model of time to radiation treatment initiation, Census region violated the PH assumption. We chose to use a stratified Cox PH model, stratified by region. As

described above, using a stratified Cox PH model accounts for the effect of region in the final model but does not allow for comparisons between regions.[206]

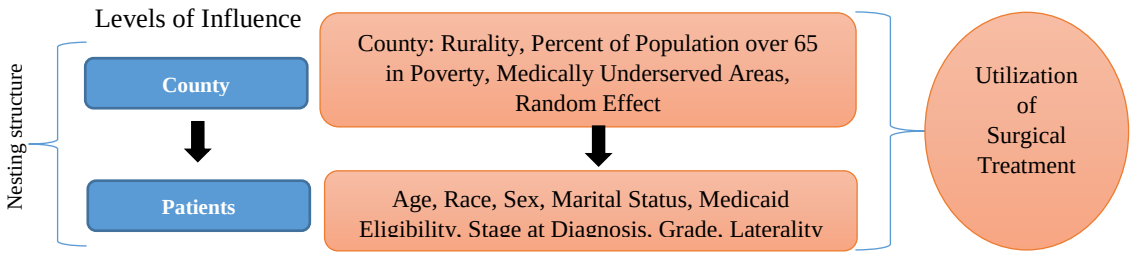
### 3.8 Paper 3 Methods

**Explore disparities in utilization of surgical lung cancer treatment across county characteristics (urban/rural, medically underserved areas, and by percent of population 65 and over in poverty) and related patient and county predictors among lung cancer patients seeking treatment**

Hypothesis 3a: County-level factors would impact surgical treatment among early stage lung cancer patients

Hypothesis 3b: Patients in rural counties, Medically Underserved Areas (MUAs), or in high poverty counties would be less likely to receive surgical treatment for early stage lung cancer

This study design incorporated multilevel logistic regression modeling techniques to account for patient fixed effects nested within counties as well as county fixed effects. Multilevel modeling was performed to identify patient and county factors influencing the utilization of surgical treatment for lung cancer. We expected a clustering of characteristics within levels of our data by county. For example, patients from the same residential area (county) tend to be more alike than patients residing different counties in terms of access to care and income. Multilevel modeling allowed us to account for these non-independent responses at each level of the model.




Conceptual multilevel model of patients nested within geographic factors associated with utilization of surgical treatment

**Figure 3.3 Conceptual Framework of Multilevel Model**

### 3.8.1 Measures

The dependent variable in our model, utilization surgical treatment center (yes/no), was defined from SEER records on patient treatment type. The first level of our multilevel logistic regression contained patient demographics and clinical characteristics from SEER data: age at diagnosis, race/ethnicity, sex, marital status, Medicaid enrollment, stage at diagnosis, grade, and laterality. We used a binary definition for rurality in this model (urban versus rural) by collapsing RUCC codes into Metro/urban versus Nonmetro/rural categories. Level-one patient factors were nested within level-two county factors including rurality, percent of the population over 65 in poverty (as a measure of socioeconomic status of the county), and Medically Underserved Area designation (MUA). MUAs are county-level assignments for counties with too few primary care providers for the population in the county.[208]

### 3.8.2 Analyses

We employed a multilevel modeling approach for this aim, specifically a basic random intercept logistic regression. This model allows the intercept to vary randomly across clusters (counties) by incorporating cluster-specific (county) random effects. First, we calculated descriptive statistics for patient-level factors across counties and test for differences by chi-square tests ($\alpha$=0.05). We then estimated the null model predicting surgery utilization from only county-level random effects. We then calculated the median odds ratio (MOR) and intraclass correlation coefficient (ICC). The MOR explains the median magnitude of the odds ratio between a randomly chosen high-risk county (rural, low SES, MUA) versus a low-risk county (urban, high SES, not MUA), providing an estimate of the amount of individual probability of surgical utilization attributed to county characteristics.[209] An MOR not equal to 1.0 indicates that the multilevel model is an appropriate statistical approach for the data being used.[209] The ICC provides a measure of the total variation in the outcome that is attributed to clustering by groups (clustering by county in our analysis). A significant ICC indicates that a multilevel modelling approach should be used for the data.[210] We then selected county-level predictors of surgical treatment for our level-two model also backward selection. After our level-two model was complete, we estimated our level-one model with patient characteristics predicting surgical utilization. Variable selection was based on coefficients with significant p-values less than or equal to 0.05 or deemed to be significant based on literature related to our research question. We assessed model fit using pseudo R-squared. After fitting our final model, we produced the estimated variance of the distribution of

random effects and odds ratios with 95% confidence intervals for predictors associated with utilizing surgical treatment among early stage lung cancer patients.

# CHAPTER 4

# RURAL DISPARITIES IN ALL-CAUSE AND LUNG CANCER-SPECIFIC SURVIVAL IN THE UNITED STATES: A SEER-MEDICARE ANALYSIS[1]

[1] Odahowski CL, Alberg A, Schootman M, Zhang J, Eberth JM. To be submitted to *Lung Cancer*

## 4.1 Abstract

Introduction

Despite declining smoking rates nationwide, lung cancer remains the leading cause of cancer-related death among both men and women in the United States. When examining stage at diagnosis, those diagnosed at distant stage have the highest risk of death with a 5-year survival of 4% compared to 54% among localized cases. For all stages combined, the five-year survival is 18%. Lung cancer survival differs by race, sex, and stage at diagnosis. Black and Native American lung cancer cases have worse survival when compared to white cases while men have worse survival than women. However, research regarding lung cancer survival differences by rurality is limited. Our objective was to investigate the relationship of rurality with all-cause survival and lung cancer-specific survival, adjusting for clinical and demographic factors.

Methods

We examined 135,627 cases of non-small cell lung cancer diagnosed between 2003-2011 from SEER-Medicare and defined rurality using Rural Urban Continuum Codes from the US Department of Agriculture. We used the Kaplan Meier estimator and Log Rank test to examine the relationship of rurality with all-cause survival and lung cancer-specific survival. We used the trend test to investigate a possible trend in survival with increasing rurality. We implemented a stratified, time-dependent Cox Proportional Hazards (PH) model to examine the relationship of rurality, stratified by race, with all-cause survival and lung cancer-specific survival controlling for patient and clinical characteristics. Based on our final models, we produced hazard ratios and 95% confidence intervals stratified by race.

Results

The log rank and trend test were significant for decreasing survival with increasing rurality for both all-cause and lung cancer-specific survival ($p<0.01$). The interaction of race and Census region was also significant in our final Cox PH model, stratified by race. In the South and West regions, small urban and rural areas had worse all-cause and lung cancer-specific survival than large urban areas, stratified by race. In the South, the all-cause hazard ratio was 1.07 (95%CI: 1.03-1.10) for small urban and 1.10 (95%CI: 1.06-1.14) for rural, compared to large urban. The South lung cancer-specific hazard ratio for small urban was 1.09 (95%CI: 1.05-1.15) and 1.10 (95%CI: 1.06-1.15) for rural in comparison to large urban. The hazard ratios were slightly higher for the West small urban (All-cause HR:1.13, 95%CI: 1.10-1.16; Lung cancer-specific HR:1.12, 95%CI: 1.08-1.15) and rural (All-cause HR:1.11, 95%CI: 1.06-1.15; Lung cancer-specific HR:1.12, 95%CI: 1.07-1.18) as compared to large urban, stratified by race. In the Midwest, all-cause and lung cancer-specific survival was worse for only rural areas compared to large urban with marginal significance, stratified by race (All-cause HR: 1.07, 95%CI: 1.01-1.12; Lung cancer-specific HR: 1.07, 95%CI: 1.01-1.14). In the Northeast, hazard ratios based on rurality were not significant for small urban (All-cause HR: 1.01, 95%CI: 0.97-1.05; Lung cancer-specific HR: 0.99, 95%CI: 0.95-1.03) or for rural (All-cause HR: 0.97, 95%CI: 0.87-1.08; Lung cancer-specific HR: 0.94, 95%CI: 0.83-1.06)

Conclusions

Rural residence was associated with lower all-cause and lung cancer-specific survival. Future research should focus on identifying factors for intervention to improve

health equity between urban and rural populations such as improvements in access to care and receipt of guideline-concordant lung cancer treatment.

Keywords: Lung cancer survival; Rurality; Cox Proportional Hazards Model; Cancer Registry

**4.2 Introduction**

Lung cancer is the leading cause of cancer-related death among both men and women in the United States with a five-year survival of only 18%.[2] However, survival improves dramatically if the cancer is detected at an early, localized stage, with an improved five-year survival rate of 54%, compared to 4% for distant stage at diagnosis.[1,2] Many factors are related to survival, including socioeconomic status and clinical characteristics such as comorbidities and histology type.[103,181,43] Racial disparities are documented for survival with black and Native American cases having lower survival compared to whites, due in part to differences in comorbidities, increased likelihood of late-stage diagnosis, and lower utilization of surgical treatment.[4,49,146,148,149,156,166] Similarly, differences by sex have shown that women fare better than men with lung cancer in terms of survival.[19,181]

Geographic variation in lung cancer survival by rurality and region needs to be further examined. Rural areas of the US have higher smoking prevalence, higher lung cancer incidence, and higher lung cancer mortality than their urban counterparts.[27,78,211] Rural cancer patients are also more likely to live in low-income areas, have a limited

supply of health care providers, and experience longer drive times to providers.[78,187,190] These factors contribute to more late-stage diagnoses and lower utilization of surgical treatment in rural patients than urban patients, both determinants of cancer survival.[185,190,211] Data from the Utah Cancer Registry showed that the 5-year survival of rural residents was 5.2% lower than for urban residents.[212] However, a similar study using Georgia Comprehensive Cancer Registry data found no significant differences in urban and rural survival after controlling for treatment.[213] Rural-urban differences in lung cancer survival may differ from across regions in the US, as many of the factors related to lung cancer survival differ by region (such as race/ethnicity, income, education, access to care, and smoking prevalence).[78,214] In the context of lung cancer, the South has the longest drive times to reach medical providers and the largest population deemed high-risk for lung cancer (defined by LDCT screening eligibility)[39,187]as well as the states with the highest lung cancer mortality-to-incidence ratios.[42] Further research is needed to examine survival disparities by rurality *and* region. Our objective was to examine differences by rurality and region in all-cause and lung cancer-specific survival time in a cohort of non-small cell lung cancer patients using SEER-Medicare linked data.

### 4.3 Methods

*Data Source*

We examined comprehensive cancer registry from the Surveillance, Epidemiology, and End Results program linked with Medicare billing data (SEER-Medicare)[199] to examine cases of non-small cell lung cancer with a first primary tumor diagnosed between 2003 and 2011. We excluded cases under age 66 to ensure at least 12

months of Medicare billing claims prior to any cancer diagnosis. We also excluded cases diagnosed post-mortem and any Medicare receipts with end stage renal disease as this condition is associated with unique clinical challenges and short life expectancy. Lung cancer clinical characteristics, survival time, and patient demographics were taken from SEER. Our main independent variable of interest, patient rurality, was defined using the patient residence at county-level at the time of diagnosis using Rural Urban Continuum Codes (RUCC). RUCC codes, developed by the US Department of Agriculture (USDA) Economic Research Service (ERS), are based on metropolitan population densities and adjacency to metro areas.[203] We collapsed the nine primary RUCC codes into the following 3 categories: 1) Large urban - Metro county of 1,000,000 population or higher, 2) Small urban - Metro county under 1,000,000 population, 3) Rural – All nonmetro counties. We used 2003 RUCC designation (based on 2000 Census data) for cases diagnosed between 2003-2009 and 2013 RUCC codes (based on 2010 Census data) to define rurality for cases diagnosed in 2010-2011. We defined regions by SEER registry locations within 4 Census regions: Midwest (Iowa, Wisconsin, and Detroit, Michigan), Northeast (New Jersey, Connecticut), South (Louisiana, Kentucky, Georgia) West (Utah, Idaho, New Mexico, Alaska Natives, all California registries, and Seattle, Washington). Cause of death from SEER records was used to define all-cause and lung cancer-specific survival and has been previously assessed for validity.[215] Our outcome variables, vital status and survival time in months, were taken also taken from SEER. We controlled for race/ethnicity (white, black, Asian, Native American, other). We did not include Hispanic ethnicity in our race/ethnicity categories as it is not self-reported in SEER, but rather assigned based on surname.[216] We also controlled for sex (male or female), Census

region (Midwest, Northeast, South, West) and stage at diagnosis (localized, regional, distant) in our model. The following covariates were tested as main exposures of interest (rurality) for model selection: year of diagnosis, patient age at diagnosis, Charlson Comorbidity Index, marital status, Medicaid enrollment at the time of diagnosis (yes or no), and treatment types (chemotherapy, radiation, surgery). Receipt of radiation and surgery were reported by SEER. We used a validated SAS macro to pull chemotherapy use from linked Medicare billing codes.[217]

*Data Analyses*

We produced descriptive statistics for our study sample demographics and performed between-group comparisons by rurality and stage at diagnosis using t-tests for continuous variables and chi-square tests for categorical variables. We used the Kaplan Meier method and the Log-Rank test to examine the unadjusted differences of all-cause and lung cancer-specific survival by levels of rurality. We used the logrank trend test to investigate a possible trend in survival with increasing rurality. We implemented multivariable survival analyses through two Cox Proportional Hazards (PH) models, one for all-cause survival and one for lung cancer-specific survival, with rurality as our primary exposure of interest. Before performing model selection, we tested the Proportional Hazard (PH) assumption for our model variables using log-log plots and Schoenfeld residual plots across time with $\alpha$=0.05. Two of our variables violated the PH assumption, race and receipt of radiation therapy. Through Likelihood Ratio testing, we determined that the best approach was to use a stratified Cox PH model, stratified by race. After examining the interaction of time with the variable for radiation therapy,

which also violated the proportional hazards assumption, we recognized a clear crossover in all-cause survival probability at 12 months post diagnosis. We implemented a time-dependent model using a heavy side function at 12 months post diagnosis for the all-cause model. In the lung cancer-specific model, the crossover of survival curves occurred earlier at month 8, and a heavy side function was implemented at 8 months post diagnosis. We determined variables necessary to include in our final model to control for confounding based on significance in our literature review and through development of a Directed Acyclic Graph (DAG). We then examined potential significant interactions between 1) rurality and sex, 2) rurality and Census region by performing additional Likelihood Ratio Tests. Once our final models were selected, we produced hazard ratios with 95% confidence intervals. We produced Kaplan Meier curves for levels of rurality in each region since the use of time-dependent Cox PH models does not allow for estimation of final adjusted survival curves.

**4.4 Results**

*Patient Characteristics*

Our final sample size included 135,627 NSCLC cases with over half (57.3%) living in large urban areas, 28% in small urban areas, and 14.8% in rural areas (Table 4.1). All patient characteristics differed significantly by level of rurality ($p<0.01$). One-third of the cases (31.2%) were 80 or more years old and the majority were white (85.0%), males (50.6%), married (50.1%), and diagnosed at a distant stage (52.7%). With respect to treatment, more than half (56.8%) received chemotherapy (defined from billing codes) while most cases did not receive surgery (76.1%) or radiation therapy (66.2%),

although recommended treatment varies depending on patient clinical factors (data not available). In the total sample 13.4% were enrolled in Medicaid, 44.7% were in the West Census region, and 30.2% had no comorbidities detected through billing data (i.e., Charlson comorbidity score=0). Missing or unknown responses were noted for race (0.2%), marital status (3.4%), and receipt of surgery (0.6%),

*Survival by Levels of Rurality*

In large urban areas, 82.2% of cases died from all-causes and 69.3% died from lung cancer during follow-up (Table 4.2). In small urban areas, 83.9% died from any cause compared to 70.8% for lung cancer, and for rural areas, 85.4% died from all-causes and 72.3% from lung cancer during follow-up. All-cause median survival was 8 months for large urban areas and 7 months for both small urban and rural areas. Lung cancer-specific median survival was 10 months for large urban areas and 9 months for both small urban and rural areas.

The Kaplan Meier and corresponding Log rank test showed significant differences for both all-cause survival and lung cancer-specific survival by levels of rurality with $p<0.01$. The logrank trend test was also significant at $p<0.01$ by decreasing levels of rurality (large urban>small urban>rural). A multiple comparison test with Bonferroni adjustment revealed significant differences in both all-cause and lung cancer-specific survival with large urban vs. small urban ($p<0.01$) and large urban vs. rural ($p<0.01$). The unadjusted survival for small urban compared to rural was not statistically different for both all-cause and lung cancer-specific survival ($p=0.05$).

*Time-Dependent Cox Proportional Hazards Model, Stratified by Race*

All covariates tested in addition to rurality (age, sex, region, marital status, Medicaid enrollment, year of diagnosis, stage at diagnosis, and treatment types) were statistically significant and retained in our final time-dependent Cox PH models, stratified by race.

*Geographic Factors*

All variables tested for inclusion in final stratified time-dependent model were statistically significant. We also found a significant interaction for region and rurality. Due to this interaction, we calculated hazard ratios for each level of rurality by Census regions (Table 4.3). In the South and West regions, small urban and rural areas had worse all-cause and lung cancer-specific survival than large urban areas, stratified by race. In the South, the all-cause hazard ratio was 1.07 (95%CI: 1.03-1.10) for small urban and 1.10 (95%CI: 1.06-1.14) for rural, compared to large urban. The South lung cancer-specific hazard ratio for small urban was 1.09 (95%CI: 1.05-1.15) and 1.10 (95%CI: 1.06-1.15) for rural in comparison to large urban. The hazard ratios were slightly higher for the West small urban (All-cause HR:1.13, 95%CI: 1.10-1.16; Lung cancer-specific HR: 1.12, 95%CI: 1.08-1.15) and rural (All-cause HR:1.11, 95%CI: 1.06-1.15; Lung cancer-specific HR:1.12, 95%CI:1.07-1.18) as compared to large urban, stratified by race. In the Midwest, all-cause and lung cancer-specific survival was worse for only rural areas compared to large urban with marginal significance, stratified by race (All-cause HR: 1.07, 95%CI: 1.01-1.12; Lung cancer-specific HR: 1.07, 95%CI: 1.01-1.14). In the

Northeast, rurality was not significantly associated with all-cause or lung cancer-specific survival with hazard ratios either very close to or less than 1.0.

*Demographic Factors*

A five-year increase in age was associated with decreased all-cause and lung cancer-specific survival, stratified by race (All-cause HR: 1.10, 95%CI: 1.10-1.11; Lung cancer-specific HR:1.08, 95%CI: 1.07-1.09). Females and Medicaid enrollees had more favorable all-cause and lung cancer-specific survival compared to males (All-cause HR: 0.83, 95%CI: 0.81-0.84; Lung cancer-specific HR: 0.84, 95%CI: 0.82-0.85) and those not on Medicaid (All-cause HR: 0.96, 95%CI: 0.94-0.99; Lung cancer-specific HR: 0.94, 95%CI: 0.92-0.96), stratified by race. Unmarried patients had a higher risk of all-cause and lung cancer-specific death than their married counterparts (All-cause HR:1.12, 95%CI:1.10-1.14; Lung cancer-specific HR: 1.12, 95%CI:1.09-1.14).

*Clinical factors*

Compared with localized stage, distant stage at diagnosis had the highest magnitude HR in our results for lung cancer-specific survival at 3.73 (95% CI: 3.62-3.83) and all-cause at 2.96 (95%CI: 2.29-3.03), stratifying by race. Regional stage was also associated with increased risk of death for both all-causes and lung cancer when compared to localized stage and stratifying by race (All-cause HR:1.65, 95%CI:1.61-1.69; Lung cancer-specific HR:1.95, 95%CI:1.89-2.00). The association of comorbidities differed for all-cause and lung cancer-specific survival. Comorbidities showed a dose-response relationship for all-cause survival stratified by race, where each one-unit

increase in the Charlson score corresponded with an increase in the all-cause hazard ratio (Table 4.3). For lung cancer-specific survival, there was a slight increase in the risk of death for patients with a Charlson score of 3 or higher compared to those with a score of 0-2 (HR: 1.18, 95%CI: 1.15-1.21). Among treatment options, those not receiving surgery had the highest hazard ratios for both all-cause and lung cancer-specific survival (All-cause HR:3.01, 95%CI: 2.93-3.09; Lung cancer-specific HR:3.28, 95%CI:3.18-3.38) compared to those who received surgery. Those who did not receive chemotherapy also had higher hazard ratios than those who did receive chemotherapy for both outcomes (All-cause HR:1.55, 95%CI:1.52-1.58; Lung cancer-specific HR:1.55, 95%CI:1.52-1.58). Receipt of radiation therapy was associated with significant differences in all-cause survival at 6 months post-diagnosis (HR:1.40, 95%CI:1.37-1.43) and marginally significant at 12 months post diagnosis (HR:1.04, 95%CI:1.01-1.07). The relationship was similar for lung cancer-specific survival at 6 months post diagnosis (HR:1.45, 95%CI:1.42-1.49). However, receipt of radiation therapy was not associated with significant differences in lung cancer-specific survival at 12 months post diagnosis (HR:0.97, 95%CI:0.95-1.00).

There was no difference in all-cause or lung cancer-specific survival for those diagnosed between 2006-2008 compared to those diagnosed in 2009-2011. However, those diagnosed between 2003-2005 had a lower hazards ratio for both outcomes (All-cause HR:0.58, 95%CI:0.56-0.59; Lung cancer-specific HR:0.56, 95%CI:0.55-0.58).

## 4.5 Discussion

Our large-scale study to assess differences in all-cause and lung cancer-specific survival found significantly worse survival for rural patients when compared to those in large urban areas. Furthermore, the association of rurality on survival differed by region, with worse survival in the South and West Census regions after adjusting for demographic and clinical factors. These results are consistent with findings from previous studies.[211,212] Atkins et al found a dose-response relationship between rurality and mortality when examining 348,002 lung cancer cases diagnosed between 2000 and 2006, where lung cancer mortality increased with increasing levels of rurality. Regional differences in access to care, screening utilization, environmental exposures, and smoking behavior contribute to observed regional differences in survival.[24,39,187]

Comorbidities appears to be a stronger factor behind observed disparities in all-cause survival. However, controlling for comorbidities did not mitigate the observed differences in survival by rurality in our results. Our data lacked a measurement of smoking status. Approximately 90% of lung cancer cases are caused by smoking.[74] Furthermore, smoking causes other chronic conditions that can make cancer treatment difficult for a patient to tolerate such as heart disease, chronic obstructive pulmonary disorder (COPD), and peripheral vascular disease. The role of smoking in rural lung cancer survival disparities should also be considered as the smoking prevalence among rural residents is higher than in urban residents[183,211,78] and the South has the highest regional smoking prevalence in the US.[39,214]

Similar to other studies, women also fared better for both all-cause and lung cancer-specific survival after adjusting for covariates in the stratified model.[19,173,180,182] Distant stage at diagnosis had a high hazard ratio (HR=3.73) compared to localized stage at diagnosis for lung cancer-specific survival. Early diagnosis should continue to be a focus of improvement in lung cancer interventions, and pursuit of equal access to LDCT screening may play a role in improving stage at diagnosis among rural populations, especially in the South with a high at-risk population based on USPSTF screening recommendations.[39] The time-dependent relationship we observed for radiation therapy (with poor survival in the first year following diagnosis) fits with the standard treatment recommendations for distant stage cases given radiation for pain management and not for curative intent. Surgery is considered the most effective treatment for NSCLC when deemed appropriate for patients.[218,219] Our findings of a high HR=3.28 for lung cancer-specific survival in those who did not receive treatment compared to those who did is likely an artifact of surgery occurring more frequently in cases with early stage at diagnosis. Over forty percent of the cases in our sample did not receive chemotherapy (43.2%), associated with 55% higher risk of all-cause and lung cancer-specific death (HR=1.55). Except for radiation therapy received in the first year, treatment of any type was associated with improved all-cause and lung cancer specific survival.

*Strengths and Limitations*

Our study had many strengths. The use of SEER-Medicare, a large population-based cohort of lung cancer patients, provides high quality data from areas covering approximately 26% of the US. The large sample size provided the statistical power to

detect small differences. The SEER component of the data provides comprehensive cancer registry data on patient clinical factors with follow-up of patients' survival. Medicare billing data also allowed us to capture existing comorbidities before diagnosis with lung cancer and chemotherapy treatment after diagnosis. Expanded research on rural health disparities is a recognized priority of the National Cancer Institute,[61] and to our knowledge, this is the first study assessing the relationship of rurality and region for both all-cause and lung cancer-specific survival.

This study is not without limitations. While SEER-Medicare is the best available data source for our research question, it is limited it in geographic coverage of the United States, particularly for rural areas. Rural underrepresentation in national data is a documented concern for rural health research and needs improvement in the future.[220–222] Rural areas in the South, particularly in Alabama, Mississippi, and Arkansas, experience particularly high state-level mortality for lung cancer.[39] Not representing these areas of documented rural disparities in our data may introduce a bias towards the null (i.e. underrepresent the magnitude of the rural survival disparity) as these states have some of the worst lung cancer mortality in the US.[223] SEER data also does not contain information on patient smoking history.[222] Approximately 90% of lung cancer cases are linked to smoking and the largest proportions of high-risk current and former smokers are in rural areas and the South.[39,55,56,78] Findings that rural lung cancer patients have worse survival could be driven by higher smoking prevalence which is directly related to higher comorbidities prevalence (e.g., COPD, heart disease) and histology that is less responsive to treatment.[224] Our definition of patients' urban or rural designation was based on the

patients' residence at the time of diagnosis. It is possible that patients move before diagnosis or following diagnosis which we were unable to measure. We also did not examine use of targeted therapy and immunotherapy given that our cohort was diagnosed between 2003-2011, before the US Food and Drug Administration (FDA) approved such drugs in 2015.[116] Our modeling approach, a time-dependent Cox PH model stratified by race, does not allow us to make direct comparisons on race, a documented disparity in lung cancer survival not captured here.

### 4.6 Conclusions

All-cause and lung cancer-specific survival were lowest among lung cancer patients in rural counties compared with urban residents. When examined by rurality and region, lung cancer cases in the South and West had the highest hazard ratios for both all-cause and lung cancer-specific survival. Comorbidities and receipt of surgery appear to be driving factors behind observed survival disparities. Future research should focus on identifying effective intervention strategies to improve health equity between urban and rural populations such as improvements in early detection, prevention and control of comorbid conditions, and receipt of guideline-concordant lung cancer treatment, especially in the South and West regions of the US.

**Table 4.1 Demographics of Non-Small Cell Lung Cancer Cases by Urban/Rural Designation, SEER-Medicare 2003-2011**

| | Large Urban | Small Urban | Rural | Total | p-value |
|---|---|---|---|---|---|
| **Total N** | 77685 | 37920 | 20022 | 135627 | |
| | | | | | |
| **Age** | | | | | <.01 |
| Mean (std) | 76.5 (6.7) | 76.2 (6.6) | 75.6 (6.5) | 76.3 (6.7) | |
| **Sex** | | | | | <.01 |
| Male | 48.9% | 51.3% | 55.8% | 50.6% | |
| Female | 51.1% | 48.7% | 44.2% | 49.4% | |
| **Race** | | | | | <.01 |
| White | 80.4% | 85.6% | 90.9% | 85.0% | |
| Black | 9.7% | 7.2% | 6.3% | 8.3% | |
| Asian or Pacific Islander | 2.6% | 2.8% | 1.4% | 6.2% | |
| Native American or Alaskan Native | 5.7% | 3.0% | 0.9% | 0.3% | |
| Other/Unknown | 1.6% | 1.4% | 0.5% | 0.2% | |
| **Census Region** | | | | | <.01 |
| Midwest | 11.8% | 9.3% | 17.2% | 11.9% | |
| Northeast | 22.2% | 17.5% | 3.4% | 18.1% | |
| South | 15.4% | 29.6% | 55.3% | 25.3% | |
| West | 50.6% | 43.6% | 24.1% | 44.7% | |
| **Marital Status** | | | | | <.01 |
| Married | 48.8% | 50.9% | 53.6% | 50.1% | |
| Not married | 47.7% | 46.0% | 43.2% | 46.6% | |
| Unknown/Missing | 3.5% | 3.2% | 3.2% | 3.4% | |
| **Medicaid Enrollment** | | | | | <.01 |
| Yes | 10.3% | 9.2% | 11.4% | | |
| No | 89.7% | 90.8% | 88.6% | | |
| **Surgery** | | | | | <.01 |
| Yes | 24.2% | 22.7% | 21.1% | 23.3% | |

| | | | | | |
|---|---|---|---|---|---|
| No | 75.5% | 76.8% | 77.0% | 76.1% | |
| Unknown/Missing | 0.3% | 0.5% | 1.8% | 0.6% | |
| **Radiation** | | | | | <.01 |
| Yes | 31.4% | 34.0% | 32.6% | 32.3% | |
| No | 67.4% | 64.8% | 64.2% | 66.2% | |
| Unknown/Missing | 1.2% | 1.2% | 3.2% | 1.5% | |
| **Chemotherapy** | | | | | <.01 |
| Yes | 52.8% | 58.9% | 68.2% | 56.8% | |
| No | 47.2% | 41.1% | 31.8% | 43.2% | |
| **Charlson Comorbidity Score** | | | | | <.01 |
| 0 | 28.7% | 31.8% | 33.1% | 30.2% | |
| 1 | 22.7% | 25.0% | 28.1% | 23.9% | |
| 2 | 12.1% | 13.0% | 14.3% | 12.7% | |
| 3 | 6.2% | 6.4% | 7.1% | 6.4% | |
| 4 | 3.3% | 3.4% | 3.6% | 3.4% | |
| 5 | 1.9% | 1.9% | 1.9% | 1.9% | |
| 6 | 1.9% | 1.6% | 1.6% | 1.8% | |
| Missing/Unknown | 23.7% | 16.9% | 10.2% | 19.8% | |
| **Year of diagnosis** | | | | | <.01 |
| 2003-2005 | 30.8% | 32.3% | 32.7% | 31.5% | |
| 2006-2008 | 34.5% | 34.1% | 34.7% | 34.4% | |
| 2009-2011 | 34.8% | 33.6% | 32.6% | 34.1% | |
| **Stage at diagnosis** | | | | | <.01 |
| Localized | 22.2% | 22.0% | 21.9% | 22.1% | |
| Regional | 24.7% | 26.1% | 25.9% | 25.2% | |
| Distant | 53.1% | 52.0% | 52.3% | 52.7% | |

**Table 4.2 Death Rates by Levels of Rurality among SEER-Medicare NSCLC Cases, 2003-2011**

| Among patients diagnosed with lung cancer: | Large Urban | Small Urban | Rural |
|---|---|---|---|
| Percentage who died from any cause | 82.2% | 83.9% | 85.4% |
| Percentage who died from lung cancer | 69.3% | 70.8% | 72.3% |

**Table 4.3 Time-Dependent Cox Proportional Hazards Results of All-Cause Survival, Stratified by Race, SEER-Medicare NSCLC Cases 2003-2011**

| | Unadjusted All-Cause | Adjusted All-Cause |
|---|---|---|
| | HR (95% CI) | HR (95% CI) |
| ***Geographic Factors*** | | |
| **Region by Rurality** | | |
| **Midwest** | | |
| Large Urban | 1.00 (Reference) | 1.00 (Reference) |
| Small Urban | 1.00 (0.96-1.05) | 1.02 (0.97-1.08) |
| Rural | 1.07 (1.03-1.12) | 1.07 (1.01-1.12) |
| **Northeast** | | |
| Large Urban | 1.00 (Reference) | 1.00 (Reference) |
| Small Urban | 0.97 (0.94-1.00) | 1.01 (0.97-1.05) |
| Rural | 0.98 (0.94-1.00) | 0.97 (0.87-1.08) |
| **South** | | |
| Large Urban | 1.00 (Reference) | 1.00 (Reference) |
| Small Urban | 1.07 (1.04-1.10) | 1.07 (1.03-1.10) |
| Rural | 1.10 (1.07-0.14) | 1.10 (1.06-1.14) |
| **West** | | |
| Large Urban | 1.00 (Reference) | 1.00 (Reference) |
| Small Urban | 1.08 (1.06-1.10) | 1.13 (1.10-1.16) |
| Rural | 1.08 (1.04-1.11) | 1.11 (1.06-1.15) |
| ***Demographic Factors*** | | |

| | | |
|---|---|---|
| **Age, 5-year increase** | 1.18 (1.18-1.19) | 1.10 (1.10-1.11) |
| **Sex** | | |
| Male | 1.00 (Reference) | 1.00 (Reference) |
| Female | 0.85 (0.84-0.86) | 0.83 (0.81-0.84) |
| **Marital Status** | | |
| Married | 1.00 (Reference) | 1.00 (Reference) |
| Not married | 1.21 (1.19-1.22) | 1.12 (1.10-1.14) |
| **Medicaid Enrollment** | | |
| Yes | 1.08 (1.06-1.10) | 0.96 (0.94-0.99) |
| No | 1.00 (Reference) | 1.00 (Reference) |
| ***Clinical Factors*** | | |
| **Stage at Diagnosis** | | |
| Localized | 1.00 (Reference) | 1.00 (Reference) |
| Regional | 1.78 (1.75-1.81) | 1.65 (1.61-1.69) |
| Distant | 47.45 (4.37-4.52) | 2.96 (2.89-3.03) |
| **Charlson Comorbidity Score** | | |
| 0 | 1.00 (Reference) | 1.00 (Reference) |
| 1 | 1.07 (1.05-1.08) | 1.14 (1.12-1.16) |
| 2 | 1.18 (1.15-1.20) | 1.25 (1.22-1.28) |
| 3 | 1.31 (1.28-1.34) | 1.35 (1.31-1.39) |
| 4 | 1.42 (1.37-1.47) | 1.43 (1.38-1.49) |
| 5 | 1.53 (1.47-1.60) | 1.61 (1.53-1.69) |
| 6 or higher | 1.69 (1.62-1.77) | 1.70 (1.61-1.78) |
| **Year of diagnosis** | | |
| 2003-2005 | 1.02 (1.00-1.04) | 0.58 (0.56-0.59) |
| 2006-2008 | 1.06 (1.05-1.08) | 1.01 (0.99-1.03) |
| 2009-2011 | 1.00 (Reference) | 1.00 (Reference) |
| **Surgery** | | |
| Yes | 1.00 (Reference) | 1.00 (Reference) |
| No | 4.647 (4.56-4.72) | 3.01 (2.93-3.09) |
| **Chemotherapy** | | |
| Yes | 1.00 (Reference) | 1.00 (Reference) |

| | | |
|---|---|---|
| No | 1.37 (1.36-1.39) | 1.55 (1.52-1.58) |
| **Radiation, less than 12 months following diagnosis** | | |
| Yes | 1.00 (Reference) | 1.00 (Reference) |
| No | 1.14 (1.12-1.16) | 1.40 (1.37-1.43) |
| **Radiation, 12 months or more following diagnosis** | | |
| Yes | 1.00 (Reference) | 1.00 (Reference) |
| No | 0.56 (0.55-0.58) | 1.04 (1.01-1.07) |

**Table 4.4 Time-Dependent Cox Proportional Hazards Results of Lung Cancer-Specific Survival, Stratified by Race, SEER-Medicare NSCLC Cases 2003-2011**

| | Unadjusted Lung Cancer-Specific | Adjusted Lung Cancer-Specific |
|---|---|---|
| | HR (95% CI) | HR (95% CI) |
| ***Geographic Factors*** | | |
| **Region by Rurality** | | |
| **Midwest** | | |
| Large Urban | 1.00 (Reference) | 1.00 (Reference) |
| Small Urban | 1.03 (0.99-1.08) | 1.03 (0.97-1.10) |
| Rural | 1.11 (1.06-1.16) | 1.07 (1.01-1.14) |
| **Northeast** | | |
| Large Urban | 1.00 (Reference) | 1.00 (Reference) |
| Small Urban | 0.95 (0.92-0.98) | 0.99 (0.95-1.03) |
| Rural | 0.96 (0.88-1.05) | 0.94 (0.83-1.06) |
| **South** | | |
| Large Urban | 1.00 (Reference) | 1.00 (Reference) |
| Small Urban | 1.08 (1.05-1.12) | 1.09 (1.05-1.15) |
| Rural | 1.10 (1.07-1.14) | 1.10 (1.06-1.15) |
| **West** | | |
| Large Urban | 1.00 (Reference) | 1.00 (Reference) |
| Small Urban | 1.08 (1.05-1.10) | 1.12 (1.08-1.15) |
| Rural | 1.09 (1.06-1.13) | 1.12 (1.07-1.18) |
| ***Demographic Factors*** | | |
| **Age, 5-year increase** | 1.15 (1.15-1.16) | 1.08 (1.07-1.09) |
| **Sex** | | |
| Male | 1.00 (Reference) | 1.00 (Reference) |
| Female | 0.86 (0.85-0.87) | 0.84 (0.82-0.85) |
| **Marital Status** | | |
| Married | 1.00 (Reference) | 1.00 (Reference) |

| | | |
|---|---|---|
| Not married | 1.18 (1.17-1.20) | 1.12 (1.09-1.14) |
| **Medicaid Enrollment** | | |
| Yes | 0.98 (0.96-1.00) | 0.94 (0.92-0.96) |
| No | 1.00 (Reference) | 1.00 (Reference) |
| ***Clinical Factors*** | | |
| **Stage at Diagnosis** | | |
| Localized | 1.00 (Reference) | 1.00 (Reference) |
| Regional | 2.15 (2.10-2.20) | 1.95 (1.89-2.00) |
| Distant | 5.80 (5.69-5.92) | 3.73 (3.62-3.83) |
| **Charlson Comorbidity Score** | | |
| 0-2 | 1.00 (Reference) | 1.00 (Reference) |
| 3 or higher | 1.18 (1.16-1.20) | 1.18 (1.15-1.21) |
| **Year of diagnosis** | | |
| 2003-2005 | 1.08 (1.07-1.10) | 0.56 (0.55-0.58) |
| 2006-2008 | 1.05 (1.03-1.06) | 1.02 (1.01-1.04) |
| 2009-2011 | 1.00 (Reference) | 1.00 (Reference) |
| **Surgery** | | |
| Yes | 1.00 (Reference) | 1.00 (Reference) |
| No | 5.58 (5.46-5.69) | 3.28 (3.18-3.38) |
| **Chemotherapy** | | |
| Yes | 1.00 (Reference) | 1.00 (Reference) |
| No | 1.37 (1.36-1.39) | 1.55 (1.52-1.58) |
| **Radiation, less than 8 months following diagnosis** | | |
| Yes | 1.00 (Reference) | 1.00 (Reference) |
| No | 1.18 (1.16-1.20) | 1.45 (1.42-1.49) |
| **Radiation, 8 months or more following diagnosis** | | |
| Yes | 1.00 (Reference) | 1.00 (Reference) |
| No | 0.55 (0.54-0.56) | 0.97 (0.95-1.00) |

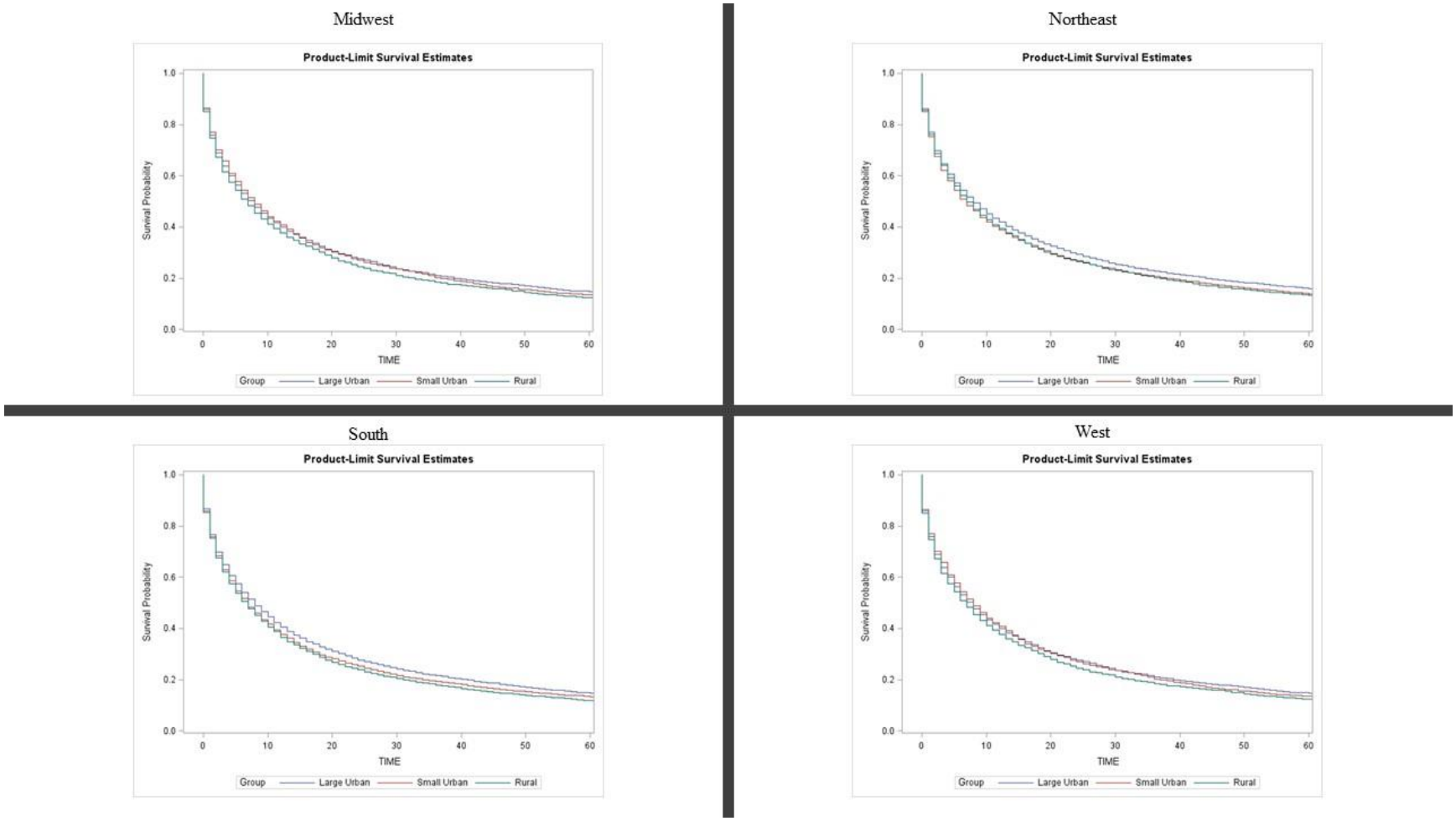



**Figure 4.1 Kaplan Meier Curves of 5-year All-Cause Survival by Rurality and Region, SEER-Medicare NSCLC Cases 2003-2011**

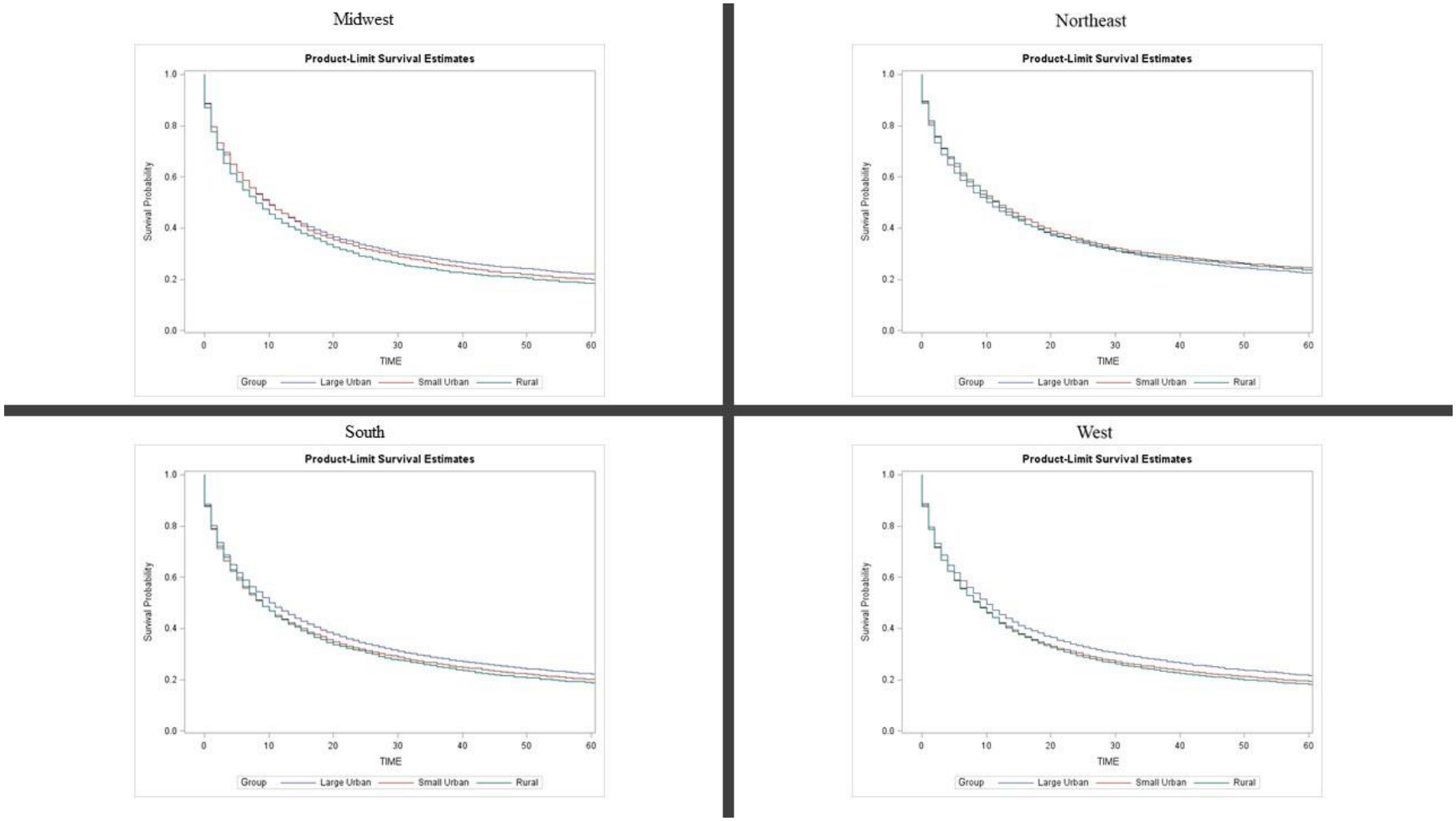



**Figure 4.2 Kaplan Meier Curves of 5-year Lung Cancer-Specific Survival by Rurality and Region, SEER-Medicare NSCLC Cases 2003-2011**

# CHAPTER 5

# TIME TO TREATMENT INITIATION AND LUNG CANCER SURVIVAL IN THE UNITED STATES: A SEER-MEDICARE ANALYSIS[2]

[2] Odahowski CL, Alberg A, Schootman M, Zhang J, Eberth JM. To be submitted to *Cancer Epidemiology*

## 5.1 Abstract

Introduction

Rural patients must travel farther for cancer care than their urban counterparts, perhaps putting them at higher risk of delayed treatment initiation. The relationship between time to treatment initiation and survival is not well characterized and there are currently no standard recommendations or quality metrics for the time between diagnosis and treatment initiation for lung cancer patients. Our aim was to examine urban/rural differences in time to treatment initiation and the relationship of time to treatment initiation (for surgery, chemotherapy and radiation separately) and lung cancer-specific survival.

Methods

We used SEER-Medicare linked data for non-small cell lung cancer (NSCLC) patients diagnosed between 2003-2011. We excluded patients under age 66 (to ensure at least 12 months of Medicare data prior to diagnosis) and those with Medicare eligibility due to end-stage renal disease. We created three treatment-specific cohorts (cancer-related surgery, chemotherapy, and radiation) using Medicare billing codes. Claims were used to identify the first treatment date and time from diagnosis to treatment initiation was examined continuously and categorized as follows: 0-4 weeks, 5-6 weeks, 7-8 weeks, 9-12 weeks, and greater than 12 weeks. We also explored a binary comparison of treatment time: 0-12 weeks versus greater than 12 weeks. We used the Kaplan Meier and logrank test to assess the unadjusted relationship of time to treatment initiation and survival for each treatment type. We then used Cox Proportional Hazards (PH) models to estimate the adjusted survival by time to treatment initiation after testing the PH

assumption for all variables included. We produced univariate and adjusted Hazards Ratios (HR) with 95% confidence intervals (CI) based on our final models by stage at diagnosis.

Results

The majority of NSCLC patients received all treatment types in 12 weeks or less. The proportion of rural residents starting treatment after 12 weeks was significantly less than the proportion starting treatment in 0-12 weeks, and the opposite was true for urban residents (surgery $p<0.01$, chemotherapy $p<0.01$, radiation $p<0.01$). Earlier treatment (within 12 weeks of diagnosis) did not results in a survival advantage in the adjusted models for chemotherapy and radiation for any stage. In the time-dependent Cox PH model for surgery, those who had surgery later than 12 weeks post diagnosis had better survival than those who had surgery in 0-12 weeks, in the first 16 months of follow up time when stratifying by radiation for all stages (HR: 0.83, 95% CI: 0.75-0.91). Beyond 16 months of follow-up, localized and regional cases who had surgery after 12 weeks had worse survival than those who had surgery in 0-12 weeks (localized HR:1.20, 95%CI:1.06-1.33; regional HR:1.18, 95%CI:1.06-1.32). The difference in survival was not significantly different for distant cases beyond 16 months of follow-up for different times to surgery initiation (distant HR:0.61, 95% CI:0.46-0.82).

Conclusions

Lung cancer treatment decisions are complex, often requiring time for diagnostic testing and consultations with many specialist physicians. Time to treatment initiation may not be an important factor for improving lung cancer survival. However, receipt of surgical treatment is most effective treatment in terms of improved survival time. Among

all of those who received treatment, a higher proportion of rural residents initiated treatment within 12 weeks of diagnosis. However, rural residents had worse survival than urban residents. Future research is needed to better understand time to treatment initiation and lung cancer survival.

## 5.2 Introduction

Treatment approaches for lung cancer vary based upon many factors including stage at diagnosis, tumor histology and location, and overall health of a patient.[105] Lung cancer treatment may include surgery, radiation, chemotherapy, or a combination thereof. Treatment approaches such as targeted therapies and immunotherapy are continuing to expand, with FDA approval starting in 2015.[116] In spite of the many treatment options available for lung cancer, in healthy adults diagnosed before metastasis, surgery is the most effective treatment approach for improved survival.[100] Staging, tumor size, tumor location(s), and patient comorbidities (i.e., medical operability) are collectively considered when determining if surgical resection is appropriate, yet surgery is often reserved for patients diagnosed in early stages.[100,218,102] In late-stages and/or people with poor health, surgery may not be an option. Hence, chemotherapy and/or radiation are considered the next best treatment approaches.[87] Depending on the stage at diagnosis, chemotherapy for lung cancer may be given prior to surgery, after surgery (adjuvant therapy), or at the same time as radiation treatment (concurrent therapy).[87,100] Similarly to chemotherapy, radiation may be given before surgery, after surgery, and in some cases alone.[87,100] Radiation prior to surgery is often an attempt to shrink tumors for easier removal. Stereotactic Body Radiation Therapy (SBRT) is high doses of radiation given in

the precise location of tumors.[115] SBRT is mostly given to patients who are not eligible for surgery and have small, well differentiated tumors. Radiation alone may also be recommended for late-stage patients as a palliative care approach.[87]

Timely treatment is one of six domains of health care quality recommended from the Institute of Medicine introduced in 2015.[122] However, as choosing the appropriate treatment approach varies from one patient to the next, the time between diagnosis and treatment initiation also varies. Additionally, optimal timing of treatment initiation and the impact of timely treatment on lung cancer on survival is not well defined in previous studies.[123–127,133,225] Recommendations from agencies such as the American Cancer Society and American Lung Association suggest starting treatment "very soon" or "within a few weeks" after a cancer diagnosis[218,226] while other organizations recommend starting treatment within 14 days (Danish Lung Cancer Registry) or 6 weeks regardless of the stage or treatment type (RAND Corporation).[126,135] The British Thoracic Society recommends surgical treatment in less than 8 weeks, radiation in less than 7 weeks, and chemotherapy in less than 4 weeks following diagnosis.[126] While some view quicker treatment initiation as superior for patient outcomes, data supporting this stance is scarce.

*Timely treatment and survival outcomes*

Timely treatment and its association with lung cancer survival is not well understood.[9–15] Publications on the topic have used a range of definitions for treatment itself (surgery, chemotherapy, or radiation) and timely treatment (e.g., median time from study sample, arbitrarily 6 weeks).[9-16] Few studies have investigated the association

between timely treatment and improved survival in lung cancer patients. A study of early-stage lung cancer patients reported an average referral time of 61.2 days following diagnosis.[127] They found that increasing weeks from diagnosis to first surgery (measured continuously) predicted worse survival.[127] However, these results were not statistically significant after adjusting for patient demographics and clinical factors. A nested case-control study of 762 lung cancer patients found shorter time intervals between diagnosis and surgical treatment to be associated with improved survival through a Kaplan-Meier analysis.[225] However, after adjusting for patient symptoms and smoking status, the results were no longer significant. Findings from a large, 12-year sample of stage I lung cancer patients from the National Cancer Database found that surgery initiation before 8 weeks post-diagnosis resulted in significantly higher survival rates.[227] A review among Medicare patients found a median time-to-treatment of 27 days.[124] In early-stage cases, treatment initiation within 35 days was associated with improved survival. There was no association between treatment time and survival for distant-stage cases.[124]

Others have reported conflicting findings, showing worse survival or no association between for timely treatment and lung cancer. In a small sample of veterans (n=129) from a single health care system, the median time to treatment was 84 days.[133] Using the median, timely treatment was defined as less than 84 days. They found that patients receiving timely treatment were more likely to die than patients receiving care after 84 days, but after stratifying by disease severity (advanced stage, non-solitary pulmonary nodules), the results were not significantly different.[133] A study of privately insured lung cancer patients in South Carolina found no association between treatment

and survival when patients received treatment within 6 weeks of diagnosis.[134] Likewise, an investigation of 482 stage I-III NSCLC patients in a single medical network in Texas from 2000-2005 found a median diagnosis to treatment time of 33 days.[128] They defined timely treatment as less than 33 days and reported no association between timely treatment and survival using Kaplan Meier survival analysis.[128] An examination of SEER-Medicare records from 2002-2007 showed a median time interval of 180 days with most patients waiting over 300 days to initiate treatment.[126] Timely treatment was defined using guidelines published by the RAND corporation and the British Thoracic Society: less than 8 weeks for surgery, 7 weeks for radiation, and 4 weeks for chemotherapy.[126,135] In their survival analysis among 16,747 patients diagnosed in 2003 or 2004, they found worse survival in patients receiving timely care as compared to those receiving care after their defined time periods.[126] The relationship between time to treatment initiation and survival in lung cancer patients remains unclear and needs further investigation.

*Disparities in Time to Treatment Initiation*

There are conflicting findings related to racial and rural disparities in the timely treatment of lung cancer. A study of the association between race and timely treatment of lung cancer among veterans found no racial differences in time to treatment, palliative care, or hospice referrals between black and white patients.[53] Conversely, a SEER-Medicare analysis of lung cancer patients from 2000-2002 reported delays in treatment were more likely among black cases than white cases.[136] Other factors associated with delays in treatment were Medicaid and Medicare dual enrollment (vs. Medicare alone),

being divorced or widowed (vs. married), and late-stage diagnosis (vs. early stage).[136] A SEER analyses using records from 2002-2007 also reported differences in time to treatment by race where non-white patients were less likely to receive timely treatment compared to white patients.[126] Rural residents with lung cancer are also less likely to receive treatment than urban residents with lung cancer.[228] Thoracic surgeons are not widely available in rural areas, potentially resulting in unequal access to high-quality surgery for rural lung cancer cases.[112,113] Rurality and region may dictate patient experiences in navigating cancer care, influencing potential differences in survival. We are interested in investigating the potential contribution of time to treatment on this rural survival disparity. Our objective was to compare the time between diagnosis and treatment initiation by rurality and region, then to examine the association of time to treatment with lung cancer-specific survival at differing thresholds of treatment initiation for surgery, chemotherapy, or radiation.

**5.3 Methods**

*Data Source*

We utilized data from the Surveillance, Epidemiology, and End Results (SEER) program linked with comprehensive Medicare fee-for-service (FFS) billing data (SEER-Medicare) for cases diagnosed with non-small cell lung cancer (NSCLC) from 2003 to 2011.[199] SEER-Medicare provides population-based cancer registry data from the SEER registry sites covering New Jersey, Connecticut, Iowa, Wisconsin, Louisiana, Kentucky, Georgia, California, Hawaii, Utah, Idaho, New Mexico, Detroit (Michigan), Seattle (Washington), and Alaska Natives. We excluded cases under age 66 to ensure at least 12

months of Medicare FFS billing data prior to diagnosis. We also excluded those with Medicare eligibility due to end-stage renal disease, patients with a missing date of diagnosis, and those who did not receive cancer-directed surgery, chemotherapy, or radiation.

*Time to Treatment Initiation*

We created three separate cohorts based on treatment type (surgery, chemotherapy, radiation). Receipt of surgery and/or radiation was reported through SEER and confirmed through Medicare billing codes with the corresponding date of services. Chemotherapy receipt and the date of services are not reported by SEER and were pulled from Medicare billing codes alone. The appendix includes the list of CPT, HCPCS, and ICD-9 billing codes used to identify cancer-directed surgery, chemotherapy, and radiation from the National Cancer Institute.[204] Diagnostic procedures, such as biopsy and surgical staging were excluded. Treatment initiation was defined by the earliest date for cancer-directed surgery, chemotherapy, and radiation following the diagnosis date. Month of diagnosis and year of diagnosis are reported by SEER. The National Cancer Institute suggests using the first day or the fifteenth day as the day of diagnosis.[229] To ensure that the diagnosis date always preceded the first treatment, the first of the month was assigned to all cases for the day of diagnosis We examined time between diagnosis and first treatment continuously and in five categories in an effort to identify the timing threshold at which survival is affected. The five categories we tested were: 0-4 weeks, 5-6 weeks, 7-8 weeks, 9-12 weeks, and greater than 12 weeks then in two categories 0-12 weeks versus greater than 12 weeks.

*Survival and Covariates*

Lung cancer-specific survival time was assessed from SEER data using vital status and survival time in months. We assessed differences in time to treatment initiation for factors in the following categories: 1) geographic factors, 2) demographic factors, and 3) clinical factors. Geographic factors included urban/rural residence, and Census region. Urban/rural status was defined by collapsing metropolitan categories and nonmetropolitan categories of Rural Urban Continuum Codes (RUCC) where metropolitan=urban and nonmetropolitan=rural.[203] We grouped registry locations into Census regions as follows:

1. Northeast: New Jersey, Connecticut
2. Midwest: Iowa, Wisconsin, Detroit, Michigan
3. South: Louisiana, Kentucky, Georgia
4. West: Seattle, California, Utah, Idaho, New Mexico, Alaska Natives, Hawaii

Demographic factors included age at diagnosis, sex, race, marital status, and Medicaid enrollment (yes/no). Clinical factors included stage at diagnosis (localized, regional, distant), Charlson comorbidity score (0-2 or 3+), year of diagnosis, and receipt of other treatment types. Charlson comorbidity score was calculated from Medicare billing codes from the 12 months prior to diagnosis using a validated SAS macro available from the National Cancer Institute.[230] We chose our reference groups as the most advantaged group in terms of survival, based on existing epidemiology data (e.g., white race, localized stage at diagnosis)

*Analyses*

For each treatment type, we produced frequencies for all variables included in the model and performed between group comparisons by time to treatment using chi-square tests with $\alpha$=0.05 by stage at diagnosis. We tested the unadjusted relationship between time to treatment and lung cancer-specific survival with Kaplan Meier curves and the logrank test. We then tested the Proportional Hazards (PH) assumption using log-log of survival probability over time for all variables included in the model. We calculated univariate Hazards Ratios (HRs) for all variables tested for inclusion and performed a backwards selection with removal levels of 0.05 coupled with likelihood ratio tests to assess model fit. Using our final models, we produced hazards ratios with 95% confidence intervals for survival of NSCLC patients by categories of time to treatment.

*Time to Surgical Treatment Model*

For surgical treatment, two variables of interest violated the PH assumption: time to surgery initiation and radiation treatment. Time to surgery initiation showed a clear crossover in survival probability at 16 months post diagnosis. To account for these violations in our model, we incorporated a variable for the interaction between time to surgery initiation and survival time at 16 months post diagnosis and stratified by radiation treatment.

When stratifying by a radiation in survival analysis, the stratified Cox PH models constructs separate partial likelihood functions for each radiation group. The multiplies the two functions are multiplied together and use values of the coefficient that maximize

the function. Therefore, the effect of radiation is absorbed into the time function and we can no longer make comparisons on this variable. Time-dependent Cox PH models allow us to account for the PH assumption of a variable, when deemed appropriate, and retain the ability to draw conclusions on that variable. Further explanations on time-dependent and stratified Cox PH models can be found elsewhere.[206,207]

*Time to Chemotherapy Treatment Model*

For our sample of patients who received chemotherapy treatment, the variable for radiation treatment also violated the PH assumption; thus, we applied a time-dependent PH model. Specifically, we created and incorporated a time dependent variable into the Cox PH model representing radiation 12 months post diagnosis or not.

*Time to Radiation Treatment Model*

Census region violated the PH assumption among our sample of patients who received radiation treatment. We chose to use a stratified Cox PH model, stratified by region. As described above, using a stratified Cox PH model accounts for the effect of region in the final model but does not allow for comparisons between regions.[206]

**5.3 Results**

*Surgery Patient Characteristics*

A final sample size of 26,365 patients were identified as receiving surgical treatment with 22,021 (83.5%) within 12 weeks of diagnosis and 4,344 (16.5%) after 12 weeks (Table 5.1). Time to surgery differed significantly by urban/rural residence

(p<0.01) where 85.7% of those receiving treatment within 12 weeks were urban residents and 14.3% were rural residents. In those receiving surgical treatment more than 12 weeks after diagnosis, the proportion was higher proportion for urban residents (87.5%) and 12.5% were rural residents. Time to surgery was significantly different by regions as well (p<0.01). The West was the only region that had a higher proportion of residents receiving surgery after 12 weeks compared to 0-12 weeks (West 0-12 weeks: 40.2%; West >12 weeks: 48.2%). Differences existed by age groups as well (p<0.01). Those over the age of 75 had higher proportions treated with surgery in 0-12 weeks compared to after 12 weeks (75+, 0-12 weeks: 46.0% 75+, >12 weeks: 43.1%). A higher proportion of non-white patients received surgery after 12 weeks compared with within 12 weeks (13.1% vs. 10.0%, p<0.01). A higher proportion of Medicaid enrollees were treated with surgery after 12 weeks (14.1%) than in 0-12 weeks (10.8%) (p<0.01), and a higher proportion of those receiving radiation received surgery after 12 weeks (21.7% vs. 8.9%, p<0.01). A higher proportion of married individuals received surgery after 12 weeks than 0-12 weeks (>12 weeks: 42.5% vs. 0-12 weeks: 37.8%, p<0.01), and a lower proportion of unmarried individuals received surgery after 12 weeks (55.0%) compared to those who received surgery within 12 weeks (59.3%, p<0.01). The majority of patients treated in 12 weeks or less were localized stage (55.8%) while the highest percent of those treated after 12 weeks were regional stage (47.8%, p<0.01). Sex was not significantly different by time to surgery (p=0.32). However, the majority of subjects that received surgery regardless of time were female (0-12 weeks: 52.7%; >12 weeks: 51.8%). Chemotherapy receipt also did not significantly differ by time to surgery (p=0.24).

*Time to Surgery and Survival*

There were no significant differences in survival for time categories less than 12 weeks (Table A.1). However, the unadjusted difference in survival with surgery initiation in 0-12 weeks versus greater than 12 weeks was significantly different in the first 16 months of follow up (logrank test, p <.0001; Kaplan Meier depicted in Figure 5.1) where those receiving surgery in less than 12 weeks had worse survival. The median survival for those who received surgical treatment was greater than our follow time (greater than 60 months), regardless of the time to initiation. Our final stratified time-dependent Cox PH model included time to surgery initiation, urban/rural residence, age, sex, Charlson comorbidity score, year of diagnosis, and stage at diagnosis, stratified by radiation. Medicaid enrollment (p=0.68), race (p=0.81), region (p=0.84) and chemotherapy (p=0.77) were dropped from the model. Surgical patient characteristics by stage at diagnosis are shown in Table 5.2.

Based on our final model, within 16 months of follow up, those who had surgery later than 12 weeks post diagnosis had better survival than those who had surgery in 0-12 weeks, when stratifying by radiation for every stage at diagnosis (localized HR:0.92, 95%CI:0.76-1.11; regional HR:0.91, 95%CI:0.80-1.03; distant HR:0.50, 95%CI:0.39-0.63) (Table 5.5). Beyond 16 months of follow-up, localized stage patients receiving surgery after 12 weeks had worse survival than localized patients receiving surgery in 0-12 weeks, stratifying by radiation (localized HR:1.20, 95%CI:1.06-1.33). The same relationship was true for regional cases where after 16 months of follow-up, patients receiving surgery after 12 weeks had worse survival than those initiation surgical treatment in 0-12 weeks, stratifying by radiation (regional HR:1.18, 95%CI:1.06-1.32).

Among distant stage cases beyond 16 months of follow-up, surgery after 12 weeks was associated with improved survival when compared to distant cases who received surgery in 0-12 weeks, stratifying by radiation (distant HR:0.61, 95%CI:0.46-0.82).

Rural residents who received surgery had worse adjusted survival than urban residents, stratified by radiation at localized stages (localized HR:1.20, 95%CI:1.09-1.33). Among regional and distant stage cases who had surgery, there was no significant difference in survival (regional HR:1.08, 95%CI:0.99-1.18; distant HR:0.96, 95%CI:0.79-1.18). Increasing comorbidities were associated with worse survival among surgery patients at every stage, though not significant among distant cases, stratifying by radiation (localized HR:1.36, 95%CI:1.23-1.51; regional HR:1.33, 95%CI:1.19-1.45; distant HR:1.19, 95%CI:0.97-1.46).

*Chemotherapy Patients Characteristics*

We identified 59,623 patients who received chemotherapy with 39,724 (66.6%) starting chemotherapy within 12 weeks following diagnosis and 19,927 (33.4%) in more than 12 weeks after diagnosis (Table 5.1). All geographic, demographic, and clinical factors differed significantly with $p<0.01$ by categories of time to treatment initiation. A higher proportion of urban residents received treatment after 12 weeks (83.5%), while a lower proportion of rural residents received treatment after 12 weeks (16.6%) ($p<0.01$). A higher proportion of males received chemotherapy within 12 weeks of diagnosis (53.5%), while a higher proportion of females received chemotherapy after 12 weeks (52.7%) ($p<0.01$). Only 15.0% percent of patients that received chemotherapy within 12 weeks

had surgery, compared to 52.2% of those that received chemotherapy after 12 weeks ($p<0.01$). Chemotherapy patient characteristics by stage at diagnosis are shown in Table 5.3.

*Time to Chemotherapy and Survival*

Our final model for time to chemotherapy initiation was a time dependent PH model stratified by radiation, with a crossover in survival probability at 4 months of follow up (Table 5.6). Region and race were not significant and dropped from the final model. Those who initiated chemotherapy later than 12 weeks post diagnosis had better survival when compared to those starting chemotherapy in 0-12 weeks at every stage at diagnosis (localized HR:0.61, 95%CI: 0.57-0.65; regional HR:0.69, 95%CI:0.65-0.72, distant HR:0.55, 95%CI:0.53-0.58). Rural residents had worse survival compared to urban residents at every stage, though not significantly different among regional cases (localized HR:1.12, 95%CI:1.04-1.20; regional HR:1.08, 95%CI:0.98-1.09, distant HR:1.09, 95%CI:1.05-1.15). Survival worsened with increasing Charlson comorbidity score at every stage of diagnosis (localized HR:1.10, 95%CI:1.02-1.19; regional HR:1.21, 95%CI:1.14-1.28; distant HR:1.13, 95%CI:1.09-1.18).

*Radiation Patients Characteristics*

A total of 34,621 patients were identified as having radiation treatment. Of all patients who received radiation, 28,538 initiated radiation within 12 weeks of diagnosis and 6,083 after 12 weeks. When comparing by time to radiation initiation, patients differed by urban/rural residence ($p<0.01$), region ($p<0.01$), age ($p<0.01$), race ($p<0.01$),

marital status (p<0.01), Medicaid enrollment (p<0.01), chemotherapy (p<0.01), surgery (p<0.01), Charlson comorbidity score (p<0.01), and stage at diagnosis (p<0.01). A higher proportion of the group starting radiation after 12 weeks also received surgery (21.3%) and/or chemotherapy (84.5%), compared to 5.6% who received radiation within 12 weeks also had surgery and 75.9% also had radiation (p<0.01). Time to radiation initiation was not different by sex (p=0.05) and year of diagnosis (p=0.97). However, more than half of those who received radiation were male (53.0% at 0-12 weeks; 51.6% at >12 weeks). Radiation patient characteristics by stage at diagnosis are shown in Table 5.4.

*Time to Radiation and Survival*

Our final model for time to first radiation treatment was Cox PH model stratified by region (Table 5.7). Urban/rural residence, race, marital status, and Charlson comorbidity score were not significant and dropped from the final model. Those starting radiation later than 12 weeks had better survival than those starting radiation within 12 weeks, stratified by region for every stage at diagnosis (localized HR:0.83, 95%CI:0.75-0.91; regional HR:0.73, 95%CI:0.69-0.77; HR:0.54, 95%CI:0.52-0.57). Increasing age was associated with increasing hazards ratios, stratified by region at all stages. Females had better survival than males (localized HR:0.79, 95%CI:0.73-0.86; regional HR:0.86, 95%CI:0.82-0.90; distant HR:0.92, 95%CI:0.89-0.95) and those on Medicaid had better survival than those not on Medicaid (localized HR:0.92, 95%CI:0.82-1.04; regional HR:0.91, 95%CI:0.84-0.98; distant HR:0.85, 95%CI:0.80-0.90), stratified by region at all stages, though not significant among localized cases.

## 5.4 Discussion

Developing treatment plans for lung cancer is a complex process, at times involving multiple physicians, tumor boards, referral times, and diagnosis procedures. Overall, we did not find an improvement in survival probability with treatment initiation within 12 weeks of diagnosis except for localized and regional surgical cases after 16 months of follow up time. For surgical treatment, the relationship between time to treatment initiation was not significant after 16 months of follow up. For chemotherapy and radiation, our results showed that those with treatment initiation after 12 weeks following diagnosis had better survival than those who received treatment by the 12-week point among all stages. We demonstrated that a higher proportion of those who had delayed chemotherapy treatment (>12 weeks) and a higher survival probability had also received surgery (52.2%) while only 15% of the early chemotherapy group (0-12 weeks) received surgery. The same trend held true for those receiving radiation after 12 weeks, where 21.3% had surgery, compared with only 5.6% of those who started radiation in 0-12 weeks.

Studies examining the time to treatment initiation of lung cancer have reported conflicting findings on the relationship with survival.[9-17] We found that those who received surgery within 12 weeks of diagnosis had worse survival in the first 16 months following diagnosis. These findings are similar to those from Gould et al where a shorter wait time was associated with worse survival.[133] However, these findings contrast with those showing shorter wait times and surgery before 8 weeks was associated with improved survival.[127,225,227] Among early-stage patients, Gomez et al showed better

survival with early treatment but among all other stages there was no association between time to surgery and survival.[124] Using SEER-Medicare data from 2000-2002, Halpern et al reported that late-stage patients were more likely to receive surgery quickly,[136] but our results showed that a higher proportion of cases treated after 12 weeks (7.5%) were distant stage, compared to 5.5% treated within 12 weeks.

Among our chemotherapy and radiation cohorts, starting chemotherapy or radiation within 12 weeks was associated with lower survival probability than those who initiated chemotherapy or radiation after 12 weeks among all stages. However, this could be attributed partially to the higher proportion of patients who started chemotherapy or radiation after 12 weeks who also had received surgery, pointing back to surgery being an effective treatment approach at improving survival for lung cancer. Also important to consider is that radiation can be given as a palliative care option for patients not eligible for surgery and/or chemotherapy due to comorbidities or advanced stage at diagnosis.[87,218] Our results are similar to those examining all treatment types together where earlier treatment was associated with worse survival or there was no significant difference in survival depending on the time to treatment initiation.[126,128,133,134] It may be informative to examine treatment types separately and sequences of treatment in future analyses to better characterize the relationship of each the time to initiation of each treatment type and survival.

Low income, black race, rural residence, and living in the South are associated with poor lung cancer survival.[4–7,28,42,187,190,228] In our results, rural residents had a higher

proportion receiving treatment within 12 weeks for all three treatment categories. However, rural residents had worse survival for surgery and chemotherapy. [4–6,10,11,13] Our surgery sample was nearly 90% white, and black patients have been shown to be more likely to decline surgery for cancer treatment than whites, even when diagnosed in early stages. Urban/rural, regional, and racial difference in lung cancer survival may be driven by disparities in access to surgical treatment as our data was restricted to only patients who received treatment.

Our study is not without limitations. While SEER provides a large, diverse data source, it is limited in the geographic coverage and underrepresents rural areas.[222] This may have underpowered our ability to detect differences between urban and rural settings, a recurring issue for using national data to study urban and rural differences.[221,222,231,232] We did not examine Medicare Part D files in our analyses. Chemotherapy only administered outpatient and billed through Part D claims were not be captured. Medicare billing codes are not intended for use in research and it is possible that some procedure codes are incorrect or missing. While we believe our list of codes was thorough, it is possible that some procedure codes were missed. SEER-Medicare is also limited to fee-for-service claims and does not include data on Medicare Advantage beneficiaries.

Our study has many strengths, including the large sample size from SEER-Medicare, a multi-site data source covering 26% of the US population.[199] Our analyses covered three treatment types (surgery, chemotherapy, radiation) providing a

comprehensive examination of treatment options available from 2003-2011, assessing the differing relationships of the treatment types and survival. Our results also provide updated data for comparison to previous publications and future work. These results may also provide meaningful insight to practicing clinicians as the time between diagnosis and treatment initiation may not be an important factor when developing treatment protocols.

We did not find evidence of a survival benefit to receiving treatment within 12 weeks of diagnosis for chemotherapy and radiation. Time to treatment initiation may not be as important as factors that influence the development of personalized treatment plans such as confirmatory testing, surgical staging, and control of patient comorbidities. We did, however, observe that the median survival of those who received surgery at any time was higher than the overall median survival for lung cancer. We also found that surgery within 12 weeks of diagnosis for localized and regional patients improved survival after 16 months of follow-up. Observed rural and racial disparities in lung cancer survival may be primarily driven by lower surgical utilization among these populations rather than differences in time to treatment initiation. Future work should focus on improving access to surgical treatment for lung cancer through expansion of the availability of surgeons to rural populations. Additional research is needed to better understand the complex relationship of time to treatment initiation and its association with lung cancer survival.

## 5.7 Tables

### Table 5.1. Demographics of SEER-Medicare NSCLC Patients by Time from Diagnosis to Treatment, 2003-2011

| Treatment Type* | Surgery N=26,365 | | Chemotherapy N=59,623 | | Radiation N=34,621 | |
|---|---|---|---|---|---|---|
| | 0-12 Weeks | >12 Weeks | 0-12 Weeks | >12 Weeks | 0-12 Weeks | >12 Weeks |
| **Total (N)** | **22,021** | **4,344** | **39,724** | **19,927** | **28,538** | **6,083** |
| **Rurality** | p<0.01 | | p<0.01 | | p<0.01 | |
| Urban | 85.7% | 87.5% | 81.9% | 83.5% | 83.0% | 84.8% |
| Rural | 14.3% | 12.5% | 18.1% | 16.6% | 17.0% | 15.2% |
| **Census Region** | p<0.01 | | p<0.01 | | p<0.01 | |
| Midwest | 11.7% | 11.1% | 13.2% | 13.1% | 15.2% | 14.9% |
| Northeast | 22.0% | 19.8% | 19.7% | 20.9% | 19.5% | 20.9% |
| South | 26.1% | 20.8% | 28.7% | 26.6% | 30.7% | 24.7% |
| West | 40.2% | 48.2% | 38.4% | 39.4% | 34.7% | 39.5% |
| ***Demographic Factors*** | | | | | | |
| **Age** | p<0.01 | | p<0.01 | | p<0.01 | |
| 66-69 | 23.7% | 25.9% | 23.5% | 23.1% | 21.5% | 24.7% |
| 70-74 | 30.4% | 31.0% | 29.6% | 28.4% | 27.3% | 28.8% |
| 75-79 | 27.0% | 26.6% | 25.4% | 25.1% | 24.9% | 25.0% |
| 80+ | 19.0% | 16.5% | 21.5% | 23.4% | 26.3% | 21.5% |
| **Sex** | p=0.32 | | p<0.01 | | p=0.05 | |
| Male | 47.3% | 48.2% | 53.5% | 47.3% | 53.0% | 51.6% |
| Female | 52.7% | 51.8% | 46.5% | 52.7% | 47.1% | 48.4% |
| **Race** | p<0.01 | | p<0.01 | | p<0.01 | |
| White | 90.0% | 86.9% | 86.9% | 85.6% | 85.0% | 82.7% |
| Non-White | 10.0% | 13.1% | 13.1% | 14.4% | 15.0% | 17.3% |
| **Marital Status** | p<0.01 | | p<0.01 | | p<0.01 | |
| Married | 37.8% | 42.5% | 40.3% | 43.6% | 54.6% | 57.0% |
| Not married | 59.3% | 55.0% | 56.9% | 53.6% | 45.4% | 43.0% |
| Unknown/Missing | 2.9% | 2.5% | 2.9% | 2.9% | | |
| **Medicaid Enrollment** | p<0.01 | | p<0.01 | | p<0.01 | |
| No | 89.2% | 85.9% | 90.6% | 88.0% | 91.0% | 89.2% |
| Yes | 10.8% | 14.1% | 9.4% | 12.0% | 9.0% | 10.8% |

| | | | | | | |
|---|---|---|---|---|---|---|
| ***Clinical Factors*** | | | | | | |
| **Radiation** | p<0.01 | | p<0.01 | | | |
| Yes | 8.9% | 21.7% | 46.3% | 30.5% | - | - |
| No | 90.0% | 76.7% | 52.0% | 68.0% | - | - |
| Unknown/Missing | 1.2% | 1.6% | 1.7% | 1.6% | - | - |
| **Chemotherapy** | p=0.24 | | | | p<0.01 | |
| Yes | 65.7% | 66.6% | - | - | 75.9% | 84.5% |
| No | 34.3% | 33.4% | - | - | 24.1% | 15.5% |
| **Surgery** | | | p<0.01 | | p<0.01 | |
| Yes | - | - | 15.0% | 52.2% | 5.6% | 21.3% |
| No | - | - | 85.0% | 47.8% | 94.4% | 78.7% |
| **Charlson Comorbidity Score** | p<0.01 | | p<0.01 | | p<0.01 | |
| 0-2 | 75.2% | 69.6% | 81.1% | 75.8% | 78.7% | 76.0% |
| 3 or higher | 11.4% | 9.5% | 12.6% | 13.2% | 13.6% | 12.7% |
| Missing/Unknown | 13.5% | 20.9% | 6.3% | 11.0% | 7.7% | 11.3% |
| **Year of diagnosis** | p=0.03 | | p<0.01 | | p=0.97 | |
| 2003-2005 | 29.9% | 30.3% | 34.8% | 37.4% | 34.7% | 34.6% |
| 2006-2008 | 34.9% | 36.5% | 36.0% | 34.7% | 33.3% | 33.5% |
| 2009-2011 | 35.2% | 33.3% | 29.1% | 27.9% | 32.0% | 32.0% |
| **Stage at diagnosis** | p<0.01 | | p<0.01 | | p<0.01 | |
| Localized | 55.8% | 44.7% | 12.0% | 41.5% | 12.2% | 20.4% |
| Regional | 38.7% | 47.8% | 28.2% | 33.0% | 28.2% | 39.3% |
| Distant | 5.5% | 7.5% | 59.8% | 25.5% | 59.6% | 40.3% |

*Treatment types are not mutually exclusive

**Table 5.2 Demographics of NSCLC Surgery Patients by Time from Diagnosis to Treatment, SEER-Medicare 2003-2011**

| Stage | Localized N=14223 | | Regional N=10607 | | Distant N=1535 | |
|---|---|---|---|---|---|---|
| **Time to Surgery** | **0-12 Weeks** | **>12 Weeks** | **0-12 Weeks** | **>12 Weeks** | **0-12 Weeks** | **>12 Weeks** |
| **Total** | **12280** | **1943** | **8532** | **2075** | **1209** | **326** |
| | **N (%)** | **N (%)** | **N (%)** | **N (%)** | **N (%)** | **N (%)** |
| ***Geographic Factors*** | | | | | | |
| **Rurality** | | | | | | |
| Urban | 10606 (86.2) | 1699 (13.8) | 7220 (79.9) | 1815 (20.1) | 1047 (78.5) | 286 (21.5) |
| Rural | 1674 (87.3) | 244 (12.7) | 1312 (83.5) | 260 (16.5) | 162 (80.2) | 40 (19.8) |
| **Census Region** | | | | | | |
| Midwest | 1451 (85.8) | 241 (14.1) | 991 (82.9) | 205 (17.1) | 142 (79.3) | 37 (20.7) |
| Northeast | 2808 (88.8) | 356 (11.3) | 1774 (79.9) | 447 (20.1) | 255 (81.2) | 59 (18.8) |
| South | 3208 (88.7) | 410 (11.3) | 2226 (84.0) | 425 (16.0) | 311 (81.8) | 69 (18.2) |
| West | 4813 (83.7) | 936 (16.3) | 3541 (78.0) | 998 (22.0) | 501 (75.7) | 161 (24.3) |
| ***Demographic Factors*** | | | | | | |
| **Age** | | | | | | |
| 66-69 | 2907 (86.7) | 445 (13.3) | 2045 (77.8) | 584 (22.2) | 256 (72.5) | 97 (27.5) |
| 70-74 | 3792 (86.6) | 588 (13.4) | 2502 (79.4) | 648 (20.6) | 395 (78.2) | 110 (21.8) |
| 75-79 | 331 (85.9) | 540 (14.1) | 2345 (81.3) | 541 (18.8) | 305 (80.3) | 75 (19.7) |
| 80+ | 2280 (86.0) | 370 (14.0) | 1640 (84.5) | 302 (15.6) | 253 (85.20 | 44 (14.8) |
| **Sex** | | | | | | |
| Male | 5515 (85.8) | 910 (14.2) | 4292 (80.8) | 1020 (19.2) | 617 (79.2) | 162 (20.8) |
| Female | 6765 (86.8) | 1033 (13.3) | 4240 (80.1) | 1055 (19.9) | 592 (78.3) | 164 (21.7) |
| **Race** | | | | | | |
| Caucasian | 11115 (86.8) | 1684 (13.2) | 7619 (81.0) | 1793 (19.1) | 1077 (78.4) | 296 (21.6) |
| Non-Caucasian | 1165 (81.8) | 259 (18.2) | 913 (76.4) | 282 (23.6) | 132 (81.5) | 30 (18.5) |
| **Marital Status** | | | | | | |
| Married | 7218 (87.3) | 1049 (12.7) | 5126 (81.7) | 1146 (18.3) | 723 (78.8) | 195 (21.2) |
| Not married | 4688 (84.7) | 849 (15.3) | 3176 (78.4) | 876 (21.6) | 458 (79.4) | 119 (20.6) |
| **Medicaid Enrollment** | | | | | | |
| Yes | 1367 (82.7) | 287 (17.4) | 906 (76.3) | 282 (23.7) | 114 (73.1) | 42 (26.9) |

| | | | | | | |
|---|---|---|---|---|---|---|
| No | 10309 (86.8) | 1570 (13.2) | 6866 (80.9) | 1623 (19.1) | 869 (77.5) | 252 (22.5) |
| ***Clinical Factors*** | | | | | | |
| **Chemotherapy** | | | | | | |
| Yes | 7734 (87.2) | 1135 (12.8) | 5908 (79.7) | 1502 (20.3) | 818 (76.2) | 256 (23.8) |
| No | 4546 (84.9) | 808 (15.1) | 2624 (82.1) | 573 (17.9) | 391 (84.8) | 70 (15.2) |
| **Radiation** | | | | | | |
| Yes | 342 (71.25) | 138 (28.8) | 1276 (65.2) | 681 (34.8) | 340 (73.1) | 125 (26.9) |
| No | 11838 (86.9) | 1782 (13.1) | 7121 (84.0) | 1357 (16.0) | 848 (81.5) | 193 (18.5) |
| **Charlson Comorbidity Score** | | | | | | |
| 0-2 | 9173 (87.6) | 1294 (12.4) | 6483 (81.3) | 1487 (18.7) | 892 (78.6) | 243 (21.4) |
| 3 or higher | 1516 (87.3) | 221 (12.7) | 841 (83.4) | 168 (16.7) | 151 (86.30 | 24 (13.7) |
| **Year of diagnosis** | | | | | | |
| 2003-2005 | 3636 (86.4) | 575 (13.7) | 2574 (80.1) | 641 (19.9) | 382 (79.4) | 99 (20.6) |
| 2006-2008 | 4359 (85.6) | 734 (14.4) | 2896 (79.8) | 733 (20.2) | 421 (78.3) | 117 (21.80 |
| 2009-2011 | 4285 (87.1) | 634 (12.9) | 3062 (81.4) | 701 (18.6) | 406 (78.7) | 110 (21.3) |

**Table 5.3 Demographics of NSCLC Chemotherapy Patients by Time from Diagnosis to Treatment, SEER-Medicare 2003-2011**

| Stage | Localized N=13015 | | Regional N=17763 | | Distant N=28845 | |
|---|---|---|---|---|---|---|
| **Time to Chemotherapy** | **0-12 Weeks** | **>12 Weeks** | **0-12 Weeks** | **>12 Weeks** | **0-12 Weeks** | **>12 Weeks** |
| **Total** | **4763** | **8252** | **11192** | **6571** | **23769** | **5076** |
| | **N (%)** | **N (%)** | **N (%)** | **N (%)** | **N (%)** | **N (%)** |
| ***Geographic Factors*** | | | | | | |
| **Rurality** | | | | | | |
| Urban | 3774 (35.5) | 6853 (64.5) | 9128 (62.4) | 5492 (37.6) | 19642 (82.2) | 4261 (17.8) |
| Rural | 989 (41.4) | 1399 (58.6) | 2064 (65.7) | 1079 (34.3) | 4127 (83.5) | 815 (16.5) |
| **Census Region** | | | | | | |
| Midwest | 603 (35.3) | 1104 (64.7) | 1379 (62.2) | 837 (37.8) | 3253 (83.1) | 663 (16.9) |
| Northeast | 817 (32.6) | 1689 (67.4) | 2329 (61.6) | 1453 (38.4) | 4666 (82.2) | 1012 (17.8) |
| South | 1582 (40.0) | 2417 (60.4) | 3509 (66.9) | 1737 (33.1) | 6316 (84.7) | 1142 (15.3) |
| West | 1761 (36.7) | 3042 (63.3) | 3975 (61.0) | 2544 (39.0) | 9534 (80.8) | 2259 (19.2) |
| ***Demographic Factors*** | | | | | | |
| **Age** | | | | | | |
| 66-69 | 875 (33.3) | 1752 (66.7) | 2698 (63.2) | 1571 (36.8) | 5753 (81.9) | 1269 (18.1) |
| 70-74 | 1305 (34.9) | 2434 (65.1) | 3453 (64.8) | 1874 (35.2) | 7005 (84.0) | 1339 (16.1) |
| 75-79 | 1299 (37.8) | 2136 (62.2) | 2884 (62.6) | 1725 (37.4) | 5918 (83.8) | 1141 (16.2) |
| 80+ | 1284 (39.6) | 1930 (60.4) | 2157 (60.6) | 1401 (39.4) | 5093 (79.3) | 1327 (20.7) |
| **Sex** | | | | | | |
| Male | 2295 (38.5) | 3668 (61.5) | 6084 (65.5) | 3202 (34.5) | 12891 (83.5) | 2545 (16.5) |
| Female | 2468 (35.0) | 4584 (65.0) | 5108 (60.3) | 3369 (39.7) | 10878 (81.1) | 2531 (18.9) |
| **Race** | | | | | | |
| Caucasian | 4259 (36.8) | 7313 (63.2) | 9851 (63.5) | 5652 (36.5) | 20417 (83.4) | 4064 (16.6) |
| Non-Caucasian | 504 (34.9) | 939 (65.1) | 1341 (59.3) | 919 (40.7) | 3352 (76.8) | 1012 (23.2) |
| **Marital Status** | | | | | | |
| Married | 2543 (36.5) | 4428 (63.5) | 6423 (64.4) | 3556 (35.6) | 13624 (83.6) | 2674 (16.4) |
| Not married | 2045 (36.3) | 3582 (63.7) | 4481 (61.2) | 2846 (38.8) | 9474 (80.9) | 2244 (19.2) |
| **Medicaid Enrollment** | | | | | | |
| Yes | 531 (35.1) | 984 (65.0) | 1070 (58.5) | 760 (41.5) | 2123 (76.8) | 643 (23.3) |

| | | | | | | |
|---|---|---|---|---|---|---|
| No | 4232 (36.8) | 7268 (63.2) | 10122 (63.5) | 5811 (36.5) | 21646 (83.0) | 4433 (17.0) |
| ***Clinical Factors*** | | | | | | |
| **Surgery** | | | | | | |
| Yes | 2096 (26.5) | 5801 (73.5) | 8014 (76.0) | 2527 (24.0) | 715 (57.8) | 523 (42.3) |
| No | 2607 (51.9) | 2418 (48.1) | 3111 (43.6) | 4021 (56.4) | 22929 (83.5) | 4522 (16.5) |
| **Radiation** | | | | | | |
| Yes | 1433 (47.7) | 1572 (52.3) | 6338 (73.90 | 2241 (26.1) | 12795 (82.4) | 2740 (17.6) |
| No | 3233 (33.0) | 6579 (67.1) | 4637 (52.5) | 4204 (47.6) | 10617 (82.5) | 2247 (17.5) |
| **Charlson Comorbidity Score** | | | | | | |
| 0-2 | 3700 (36.7) | 6388 (63.3) | 9152 (64.3) | 5081 (35.7) | 19382 (84.3) | 3610 (15.7) |
| 3 or higher | 861 (40.7) | 1254 (59.3) | 1444 (65.6) | 759 (34.5) | 2703 (81.4) | 619 (18.6) |
| **Year of diagnosis** | | | | | | |
| 2003-2005 | 1648 (33.8) | 3232 (66.2) | 4040 (62.0) | 2481 (38.1) | 8145 (82.6) | 1721 (17.4) |
| 2006-2008 | 1881 (39.1) | 2931 (60.9) | 3858 (63.7) | 2198 (36.30 | 8579 (82.8) | 1783 (17.2) |
| 2009-2011 | 1234 (37.1) | 2089 (62.9) | 3294 (63.5) | 1892 (36.5) | 7045 (81.8) | 1572 (18.2) |

**Table 5.4 Demographics of NSCLC Radiation Patients by Time from Diagnosis to Treatment, SEER-Medicare 2003-2011**

| Stage | Localized N=4725 | | Regional N=10439 | | Distant N=19457 | |
|---|---|---|---|---|---|---|
| **Time to Radiation** | **0-12 Weeks** | **>12 Weeks** | **0-12 Weeks** | **>12 Weeks** | **0-12 Weeks** | **>12 Weeks** |
| **Total** | **3483** | **1242** | **8048** | **2391** | **17007** | **2450** |
| | **N (%)** | **N (%)** | **N (%)** | **N (%)** | **N (%)** | **N (%)** |
| ***Geographic Factors*** | | | | | | |
| **Rurality** | | | | | | |
| Urban | 2847 (73.5) | 1024 (26.5) | 6644 (76.5) | 2040 (23.5) | 14191 (87.2) | 2093 (12.9) |
| Rural | 636 (74.5) | 218 (25.5) | 1404 (80.0) | 351 (20.0) | 2816 (88.8) | 357 (11.3) |
| **Census Region** | | | | | | |
| Midwest | 570 (72.9) | 212 (27.2) | 1214 (79.7) | 309 (20.3) | 2545 (86.9) | 384 (13.1) |
| Northeast | 539 (70.0) | 231 (30.0) | 1645 (75.1) | 546 (24.9) | 3366 (87.2) | 493 (12.8) |
| South | 1309 (79.3) | 342 (20.7) | 2661 (81.4) | 609 (18.6) | 4800 (89.7) | 554 (10.3) |
| West | 1065 (70.0) | 457 (30.0) | 2528 (73.2) | 927 (26.8) | 6296 (86.1) | 1019 (13.9) |
| ***Demographic Factors*** | | | | | | |
| **Age** | | | | | | |
| 66-69 | 386 (66.4) | 195 (33.6) | 1706 (72.9) | 633 (27.1) | 4051 (85.8) | 673 (14.3) |
| 70-74 | 740 (69.9) | 319 (30.1) | 2280 (76.4) | 703 (23.6) | 4782 (86.7) | 732 (13.3) |
| 75-79 | 913 (73.4) | 331 (26.6) | 2043 (76.7) | 621 (23.3) | 4135 (87.9) | 571 (12.1) |
| 80+ | 1444 (78.4) | 397 (21.6) | 2019 (82.3) | 434 (17.7) | 4039 (89.5) | 474 (10.5) |
| **Sex** | | | | | | |
| Male | 1614 (74.5) | 533 (25.5) | 4313 (77.8) | 1231 (22.2) | 9184 (87.2) | 1353 (12.8) |
| Female | 1869 (73.1) | 689 (26.9) | 3735 (76.3) | 1160 (23.7) | 7823 (87.7) | 1097 (12.3) |
| **Race** | | | | | | |
| Caucasian | 3059 (74.3) | 1057 (25.7) | 6901 (77.7) | 1978 (22.3) | 14306 (87.8) | 1995 (12.2) |
| Non-Caucasian | 424 (69.6) | 185 (30.4) | 1147 (73.5) | 413 (26.5) | 2701 (85.6) | 455 (14.4) |
| **Marital Status** | | | | | | |
| Married | 1614 (73.9) | 571 (26.1) | 4250 (75.60 | 1371 (24.4) | 9293 (86.6) | 1438 (13.4) |
| Not married | 1733 (73.5) | 626 (26.5) | 3595 (78.6) | 979 (21.4) | 7275 (88.5) | 942 (11.5) |
| **Medicaid Enrollment** | | | | | | |
| Yes | 386 (68.4) | 178 (31.6) | 810 (76.2) | 253 (23.8) | 1384 (85.9) | 228 (14.1) |

| | | | | | | |
|---|---|---|---|---|---|---|
| No | 3097 (74.4) | 1064 (25.6) | 7238 (77.2) | 2138 (22.8) | 15623 (87.6) | 2222 (12.5) |
| ***Clinical Factors*** | | | | | | |
| **Chemotherapy** | | | | | | |
| Yes | 2678 (73.8) | 949 (26.2) | 6815 (76.4) | 2105 (23.6) | 12171 (85.4) | 2083 (14.6) |
| No | 805 (73.3) | 293 (26.7) | 1233 (81.2) | 286 (18.8) | 4836 (93.0) | 367 (7.1) |
| **Surgery** | | | | | | |
| Yes | 227 (48.9) | 237 (51.1) | 977 (52.8) | 875 (47.3) | 386 (68.1) | 181 (31.9) |
| No | 3235 (76.4) | 997 (23.6) | 7043 (82.3) | 1514 (17.7) | 16575 (88.0) | 2262 (12.0) |
| **Charlson Comorbidity Score** | | | | | | |
| 0-2 | 2540 (74.0) | 891 (26.0) | 6363 (77.2) | 1884 (22.8) | 13541 (88.0) | 1847 (12.0) |
| 3 or higher | 826 (75.4) | 269 (24.6) | 1169 (82.0) | 257 (18.0) | 1892 (88.5) | 246 (11.5) |
| **Year of diagnosis** | | | | | | |
| 2003-2005 | 1040 (73.3) | 378 (26.7) | 2985 (77.9) | 845 (22.1) | 5879 (87.0) | 881 (13.0) |
| 2006-2008 | 1097 (72.7) | 412 (27.3) | 2577 (76.4) | 798 (23.6) | 5826 (87.6) | 825 (12.4) |
| 2009-2011 | 1346 (74.9) | 452 (25.1) | 2486 (76.9) | 748 (23.1) | 5303 (87.7) | 744 (12.3) |

**Table 5.5 Time-Dependent Cox PH Model of Time to Surgery and Lung Cancer-Specific Survival, Stratified by Radiation, SEER-Medicare 2003-2011**

| Surgery | Localized Stage | Regional Stage | Distant Stage |
|---|---|---|---|
| | Adjusted HR (95%CI) | Adjusted HR (95%CI) | Adjusted HR (95%CI) |
| **Time to Surgery at time <16 months** | | | |
| **0-12 weeks** | 1.00 (Reference) | 1.00 (Reference) | 1.00 (Reference) |
| **>12 weeks** | 0.92 (0.76-1.11) | 0.91 (0.80-1.03) | 0.50 (0.39-0.63)* |
| **Time to Surgery at time ≥ 16 months** | | | |
| **0-12 weeks** | 1.00 (Reference) | 1.00 (Reference) | 1.00 (Reference) |
| **>12 weeks** | 1.20 (1.06-1.33)* | 1.18 (1.06-1.32)* | 0.61 (0.46-0.82)* |
| **Rurality** | | | |
| Urban | 1.00 (Reference) | 1.00 (Reference) | 1.00 (Reference) |
| Rural | 1.20 (1.09-1.33)* | 1.08 (0.99-1.18) | 0.96 (0.79-1.18) |
| **Age** | | | |
| 66-69 | 1.00 (Reference) | 1.00 (Reference) | 1.00 (Reference) |
| 70-74 | 1.23 (1.10-1.37)* | 1.14 (1.04-1.25)* | 1.01 (0.83-1.22) |
| 75-79 | 1.43 (1.28-1.59)* | 1.30 (1.18-1.42)* | 1.01 (0.83-1.24) |
| 80+ | 1.76 (1.57-1.98)* | 1.53 (1.38-1.69)* | 1.27 (1.03-1.57)* |
| **Sex** | | | |
| Male | 1.00 (Reference) | 1.00 (Reference) | 1.00 (Reference) |
| Female | 0.67 (0.62-0.73)* | 0.77 (0.72-0.83)* | 0.72 (0.62-0.83)* |
| **Marital Status** | | | |
| Married | 1.00 (Reference) | 1.00 (Reference) | 1.00 (Reference) |
| Not married | 1.17 (1.08-1.27)* | 1.13 (1.05-1.21)* | 1.26 (1.09-1.46)* |
| **Charlson Comorbidity Score** | | | |
| 0-2 | 1.00 (Reference) | 1.00 (Reference) | 1.00 (Reference) |
| 3 or higher | 1.36 (1.23-1.51)* | 1.33 (1.19-1.45)* | 1.19 (0.97-1.46) |
| **Year of diagnosis** | | | |
| 2003-2005 | 1.29 (1.15-1.44)* | 1.25 (1.14-1.36)* | 1.27 (1.06-1.51)* |
| 2006-2008 | 1.16 (1.04-1.30)* | 1.22 (1.11-1.33)* | 1.03 (0.86-1.23) |
| 2009-2011 | 1.00 (Reference) | 1.00 (Reference) | 1.00 (Reference) |

*significant at $\alpha$=0.05

**Table 5.6 Time-Dependent Cox PH Model of Time to Chemotherapy and Lung Cancer-Specific Survival, SEER-Medicare 2003-2011**

| Chemotherapy | Localized Stage | Regional Stage | Distant Stage |
|---|---|---|---|
| | Adjusted HR (95%CI) | Adjusted HR (95%CI) | Adjusted HR (95%CI) |
| **Time to Chemotherapy** | | | |
| **0-12 weeks** | 1.00 (Reference) | 1.00 (Reference) | 1.00 (Reference) |
| **>12 weeks** | 0.61 (0.57-0.65)* | 0.69 (0.65-0.72)* | 0.55 (0.53-0.57)* |
| **Rurality** | | | |
| Urban | 1.00 (Reference) | 1.00 (Reference) | 1.00 (Reference) |
| Rural | 1.12 (1.04-1.20)* | 1.03 (0.98-1.09) | 1.09 (1.05-1.13)* |
| **Age** | | | |
| 66-69 | 1.00 (Reference) | 1.00 (Reference) | 1.00 (Reference) |
| 70-74 | 1.19 (1.08-1.30)* | 1.10 (1.04-1.17)* | 1.04 (1.00-1.08) |
| 75-79 | 1.23 (1.12-1.35)* | 1.19 (1.13-1.26)* | 1.09 (1.05-1.14)* |
| 80+ | 1.25 (1.14-1.38)* | 1.28 (1.20-1.36)* | 1.24 (1.19-1.29)* |
| **Sex** | | | |
| Male | 1.00 (Reference) | 1.00 (Reference) | 1.00 (Reference) |
| Female | 0.69 (0.65-0.74)* | 0.82 (0.78-0.85)* | 0.85 (0.82-0.87)* |
| **Marital Status** | | | |
| Married | 1.00 (Reference) | 1.00 (Reference) | 1.00 (Reference) |
| Not married | 1.10 (1.04-1.18)* | 1.08 (1.04-1.13)* | 1.12 (1.08-1.15)* |
| **Medicaid Enrollment** | | | |
| Yes | 0.87 (0.80-0.96)* | 0.85 (0.80-0.91)* | 0.82 (0.78-0.85)* |
| No | 1.00 (Reference) | 1.00 (Reference) | 1.00 (Reference) |
| **Charlson Comorbidity Score** | | | |
| 0-2 | 1.00 (Reference) | 1.00 (Reference) | 1.00 (Reference) |
| 3 or higher | 1.10 (1.02-1.19)* | 1.21 (1.14-1.28)* | 1.13 (1.09-1.18)* |
| **Radiation, time<4 months** | | | |
| Yes | 1.00 (Reference) | 1.00 (Reference) | 1.00 (Reference) |
| No | 1.92 (1.51-2.44)* | 1.81 (1.61-2.04)* | 1.20 (1.14-1.25)* |
| **Radiation, time≥4 months** | | | |
| Yes | 1.00 (Reference) | 1.00 (Reference) | 1.00 (Reference) |
| No | 1.15 (1.07-1.24)* | 1.08 (1.03-1.14)* | 0.90 (0.87-0.93)* |

| | | | |
|---|---|---|---|
| **Surgery** | | | |
| Yes | 1.00 (Reference) | 1.00 (Reference) | 1.00 (Reference) |
| No | 4.16 (3.86-4.48)* | 2.81 (2.67-2.96)* | 1.84 (1.71-1.98)* |
| **Year of diagnosis** | | | |
| 2003-2005 | 1.23 (1.13-1.34)* | 1.26 (1.19-1.33)* | 1.17 (1.13-1.21)* |
| 2006-2008 | 1.06 (0.97-1.16) | 1.13 (1.07-1.19)* | 1.09 (1.05-1.13)* |
| 2009-2011 | 1.00 (Reference) | 1.00 (Reference) | 1.00 (Reference) |

*****significant at $\alpha$=0.05

**Table 5.7 Cox PH Model of Time to Radiation and Lung Cancer-Specific Survival, Stratified by Region, SEER-Medicare 2003-2011**

| Radiation | Localized Stage | Regional Stage | Distant Stage |
|---|---|---|---|
| | Adjusted HR (95%CI) | Adjusted HR (95%CI) | Adjusted HR (95%CI) |
| **Time to Radiation** | | | |
| 0-12 weeks | 1.00 (Reference) | 1.00 (Reference) | 1.00 (Reference) |
| >12 weeks | 0.83 (0.75-0.91)* | 0.73 (0.69-0.77)* | 0.54 (0.52-0.57)* |
| **Age** | | | |
| 66-69 | 1.00 (Reference) | 1.00 (Reference) | 1.00 (Reference) |
| 70-74 | 1.15 (1.00-1.33) | 1.11 (1.04-1.19)* | 1.05 (1.01-1.10)* |
| 75-79 | 1.08 (0.94-1.24) | 1.22 (1.15-1.31)* | 1.10 (1.05-1.15)* |
| 80+ | 1.17 (1.03-1.34)* | 1.25 (1.16-1.34)* | 1.14 (1.09-1.19)* |
| **Sex** | | | |
| Male | 1.00 (Reference) | 1.00 (Reference) | 1.00 (Reference) |
| Female | 0.79 (0.73-0.86)* | 0.86 (0.82-0.90)* | 0.92 (0.89-0.95)* |
| **Medicaid Enrollment** | | | |
| Yes | 0.92 (0.82-1.04) | 0.91 (0.84-0.98)* | 0.85 (0.80-0.90)* |
| No | 1.00 (Reference) | 1.00 (Reference) | 1.00 (Reference) |
| **Chemotherapy** | | | |
| Yes | 1.00 (Reference) | 1.00 (Reference) | 1.00 (Reference) |
| No | 1.11 (1.01-1.22)* | 1.73 (1.62-1.84)* | 2.15 (2.08-2.23)* |
| **Surgery** | | | |
| Yes | 1.00 (Reference) | 1.00 (Reference) | 1.00 (Reference) |
| No | 1.46 (1.26-1.68)* | 1.77 (1.65-1.89)* | 1.61 (1.46-1.76)* |
| **Year of diagnosis** | | | |
| 2003-2005 | 1.75 (1.58-1.95)* | 1.25 (1.18-1.32)* | 1.07 (1.03-1.11)* |
| 2006-2008 | 1.40 (1.26-1.55)* | 1.11 (1.04-1.18)* | 1.05 (1.01-1.09)* |
| 2009-2011 | 1.00 (Reference) | 1.00 (Reference) | 1.00 (Reference) |

*significant at $\alpha$=0.05

## 5.8 Figures

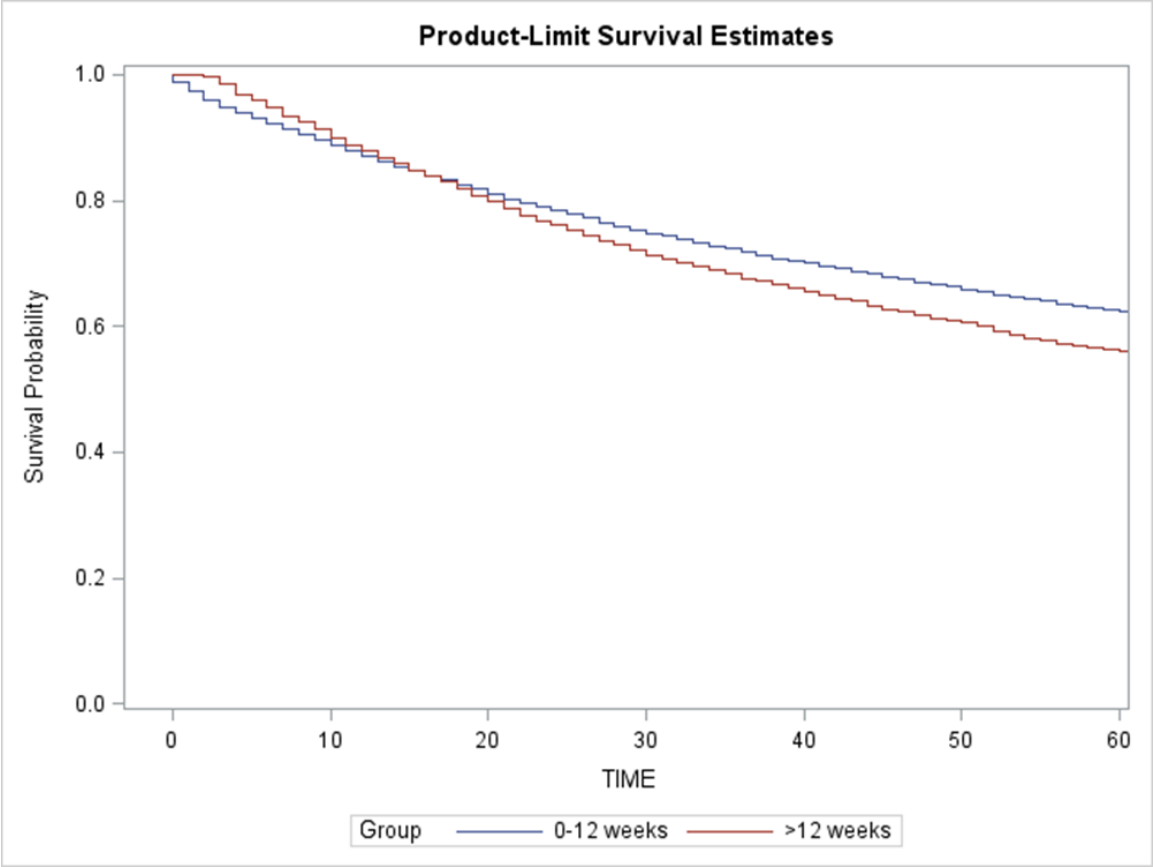



**Figure 5.1 Kaplan Meier Curve of Lung Cancer-Specific Survival by Time to Surgical Treatment Initiation, SEER-Medicare NSCLC Cases 2003-2011**

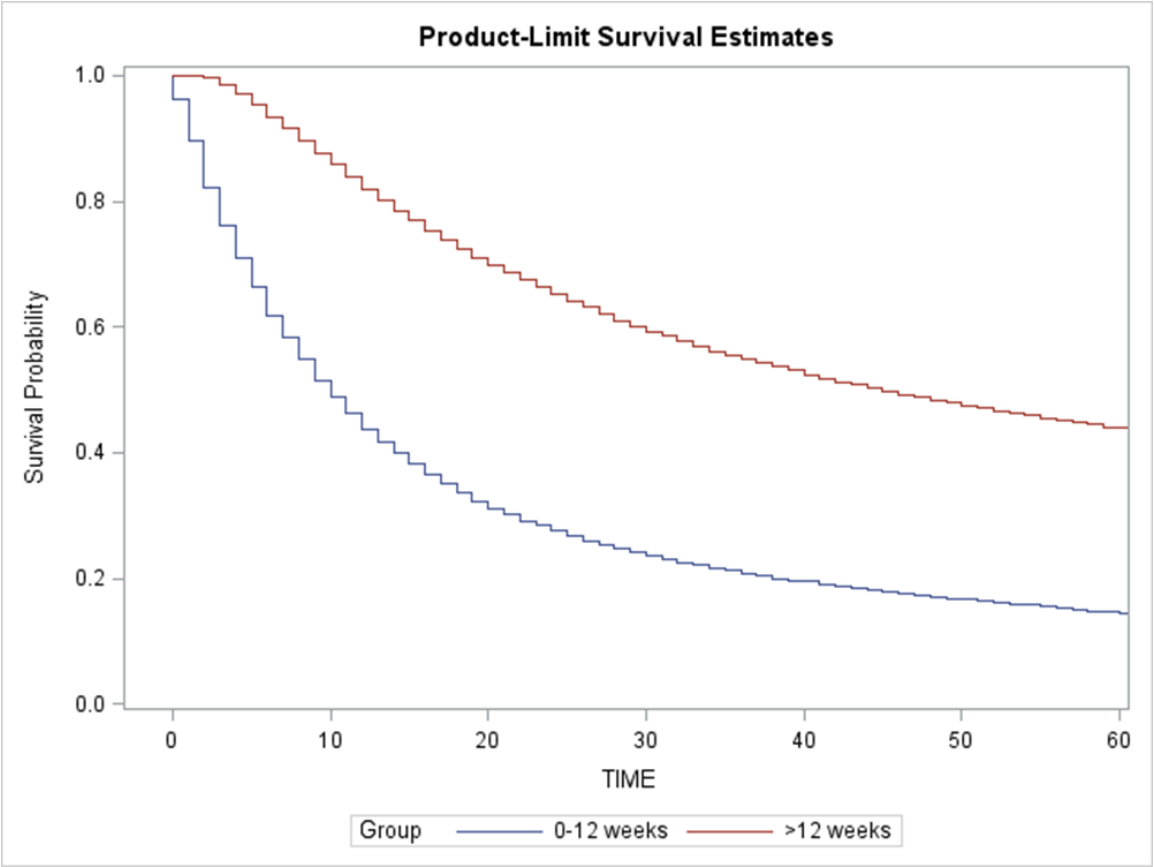



**Figure 5.2 Kaplan Meier Curve of Lung Cancer-Specific Survival by Time to Chemotherapy Treatment Initiation, SEER-Medicare NSCLC Cases 2003-2011**

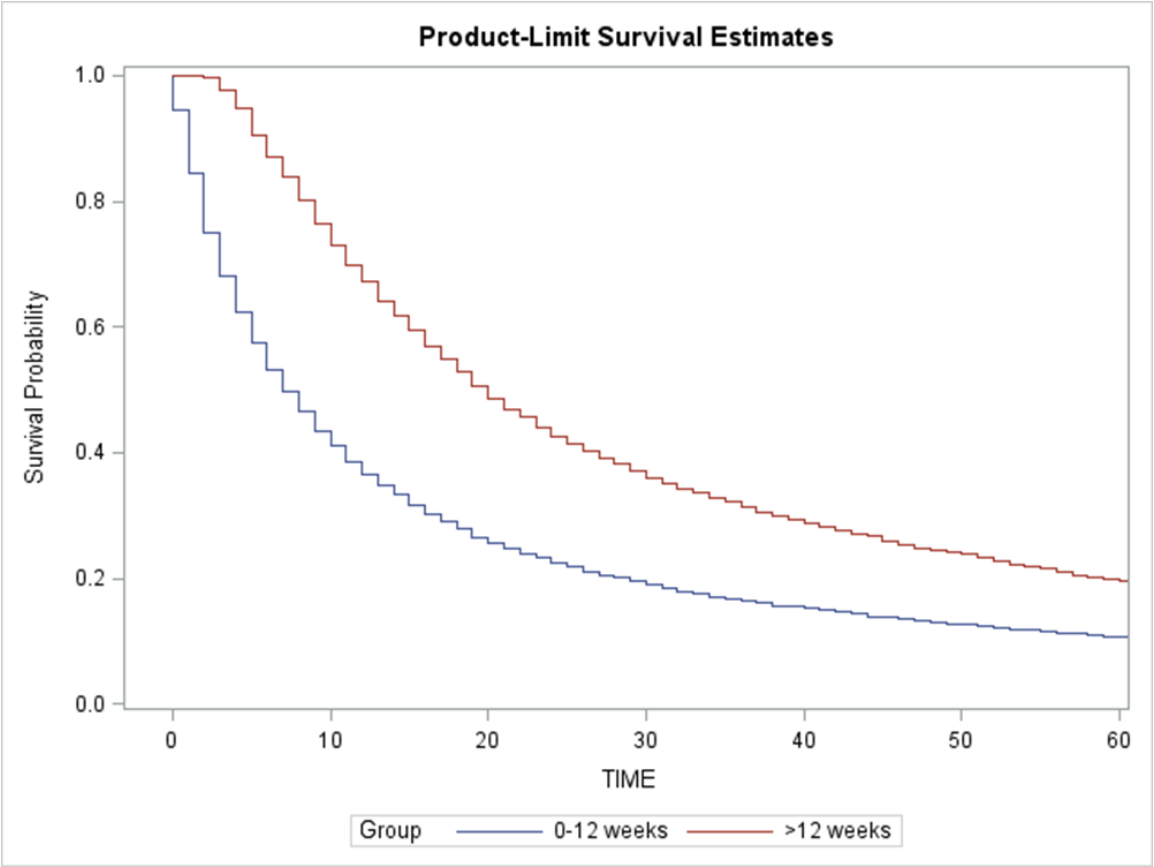



**Figure 5.3 Kaplan Meier Curve of Lung Cancer-Specific Survival by Time to Radiation Treatment Initiation, SEER-Medicare NSCLC Cases 2003-2011**

# CHAPTER 6

# PATIENT AND COUNTY LEVEL DETERMINANTS OF SURGICAL TREATMENT FOR NON-SMALL CELL LUNG CANCER: A MULTILEVEL SEER-MEDICARE ANALYSIS[3]

[3] Odahowski CL, Alberg A, Schootman M, Zhang J, Eberth JM. To be submitted to *Cancer Epidemiology, Biomarkers & Prevention*

## 6.1 Abstract

Introduction

Rural residents face a higher incidence of lung cancer, longer drive times to access care, and worse survival than urban lung cancer patients. Surgical resection is the recommended treatment approach for healthy adults diagnosed with early stages of lung cancer by the National Comprehensive Cancer Network and is considered the most effective treatment approach for improving survival among localized cases. Despite this, inequities in the utilization of surgical treatment exist for some minority groups, particularly black versus white patients. We hypothesized that observed rural survival disparities in early stage rural lung cancer patient may be due lower utilization of surgical treatment when compared to their urban counterparts, in addition to racial disparities in surgical utilization. To assess this, we examined patient- and county-level determinants of receipt of surgical treatment for non-small cell lung cancer (NSCLC), focusing on rural vs. urban disparities.

Methods

We examined patients nested within counties in a multilevel logistic regression model stratified by stage at diagnosis, predicting receipt of surgical treatment. Our sample included 63,767 localized and regional NSCLC cases diagnosed between 2003-2011 using SEER-Medicare data across the United States. Predictors examined included patient demographics, clinical characteristics and county-level factors, including urban versus rural designation, percent of the 65 and older population in poverty, and Medically Underserved Areas.

Results

Less than one-half (46.1%) of patients with early stage lung cancer received surgical treatment. Of patients diagnosed at localized stage, 56.7% received surgery compared to 42.6% of patients diagnosed at regional stage. Fewer rural residents received surgery when compared with urban residents (42.0% vs. 46.8%), and fewer black patients received surgery (32.9%) than white patients (47.1%) and those of other races (48.0%). Rural residence was not a significant predictor of surgery at the county level for local stage cases (OR=0.87, 95% CI:0.74-1.03) nor regional stage cases (OR-1.09, 95% CI:0.95-1.26). However, the odds of surgical treatment decreased per 5% increase in county-level poverty for both local and regional stages (local OR=0.83, 95% CI:0.77-0.91; regional OR=0.84, 95%CI: 0.79-0.90). Patient factors associated with lower likelihood of surgical treatment included increasing age, male sex, black race, those not married, dual Medicare/Medicaid enrollment, increasing number of comorbidities, and bilateral or midline location for both stages. In comparison to well-differentiated grade, cases with moderately differentiated grade did not have a significantly different odds of surgical treatment. All other grade categories (poorly differentiated, undifferentiated, and undetermined grade) were associated with lower odds of surgical treatment as compared to well differentiated grade.

Conclusions

While rural residence itself was not a significant predictor of surgical treatment, the association between county rurality and surgery was attenuated by area poverty, which is observed at higher rates among rural populations. Medicaid enrollment, a proxy measure of patient-level poverty, was also associated with a reduced likelihood of

receiving surgery at both stages. While the significant predictors of surgical treatment were similar for local and regional stage cases, the magnitudes of the odds ratios were stronger among local cases for increasing age, black race, and increasing comorbidities. Cancer treatment decisions are complex, and this could be an indicator that patient demographics and comorbidities play a greater role in surgical decisions among local stage cases than regional cases. Future research is needed to improve our understanding of treatment decisions among low-income and black lung cancer patients to inform the development of future interventions aimed at eliminating these disparities in lung cancer treatment.

Keywords: Non-Small Cell Lung Cancer, Healthcare Disparities, Social Determinants of Health

**6.2 Introduction**

Most rural areas in the United States have a cigarette smoking prevalence twice that of large urban areas, contributing to higher lung cancer incidence and mortality rates in rural areas.[26,78,211,233] Additionally, rural residents face higher rates of late-stage lung cancer diagnoses than urban residents.[185] The increased likelihood of late-stage diagnosis and limited treatment options for late-stage disease contributes to higher observed mortality rates for rural Americans with lung cancer [25,184,234] However, even among stage I patients diagnosed between 2000 and 2006, rural residents were less likely than their urban counterparts to receive curative surgery.[48] Combined with the sheer disease burden, rural residents also face socioeconomic disadvantages including higher poverty rates, lower education, and a higher proportion of uninsured and elderly adults than urban

residents.[48,78,183] These factors may make accessing care more difficult for rural lung cancer patients, particularly accessing specialist physicians who are sparse in rural areas.[235]

Treatment approaches for lung cancer are highly variable depending on many clinical factors such as histologic type, stage at diagnosis, and patients' health status.[100,102] In healthy adults with earlier stage cancer that has not metastasized, surgery is the most favorable treatment approach in terms of improved survival.[100] Staging, tumor characteristics, and patient comorbidities (i.e., medical operability) are collectively considered when determining if surgical resection is appropriate and is performed primarily for patients diagnosed in early stages in good health.[100,102]

Challenges in accessing care may also be impacting treatment utilization among rural cancer patients. The U.S. rural population is dispersed over 97% of the nation's land area, making travel time to cancer treatment centers a barrier many rural patients must overcome.[186,187] A geographic analysis of drive times to cancer treatment centers found that Native Americans, rural residents, and those living in the South had the longest drive times to reach any cancer treatment centers.[187] A separate study of treatment access in Nevada found that rural residents in the state were less likely to get surgery and have worse survival.[236]

Socioeconomic status (SES) also plays a role in lung cancer disparities, as lower SES is related to higher smoking rates and higher cancer incidence.[78] Among lung cancer

patients, low SES is linked to lower likelihood of surgical resection, guideline-concordant treatment, and lower survival.[6,51,195,197] Even after adjusting for comorbidities, patients with the lowest SES continue to have worse survival outcomes compared to those of higher SES.[6] For example, among lung cancer patients in Georgia, those in segregated and poor neighborhoods were less likely to receive treatment for lung cancer.[237] Differences in SES may be contributing to observed cancer disparities among rural and black populations. While some have shown that adjusting for SES eliminates rural and racial disparities,[53,195] others have demonstrated that these disparities are reduced, but not eliminated, after adjusting for SES.[146,238,239]

Patient residence (urban vs. rural), race, and SES impact receipt of cancer treatment and thus survival. Improved understanding of disparities in utilization of surgical treatment for lung cancer is a crucial step in reducing disease mortality. Our objective was to examine disparities in receipt of surgical treatment for non-small cell lung cancer by rural residence while controlling for independent patient- and county-level determinants of surgical treatment.

## 6.3 Methods

*Data*

We examined a cohort of non-small cell lung cancer (NSCLC) patients from the Surveillance, Epidemiology, and End Results (SEER) program cancer registry linked with Medicare billing data (SEER-Medicare).[200,240] Our cohort included patients diagnosed from 2003-2011, aged 66 and older to ensure a minimum of 12 months of

Medicare claims prior to lung cancer diagnosis. We excluded distant stage cases, as our interest was to assess surgical treatment with curative intent, and surgical treatment is primarily performed in early-stage cases. We also excluded patients with End Stage Renal Disease, as the prognosis and treatment recommendations for these patients greatly differ from cancer patients without ESRD. Our outcome, utilization of lung cancer-related surgical treatment (yes/no) was defined from SEER records and Medicare billing codes.[201] A full list of the billing codes used are included in the appendix, Table A.1. Patient demographics and clinical characteristics were also pulled from SEER data including age at diagnosis, race, sex, marital status, Medicaid enrollment, stage at diagnosis, tumor grade, and laterality. The Charlson comorbidity score was determined from Medicare claims from 12 months to 1 month before lung cancer diagnosis using a validated SAS macro from the National Institutes of Health.[230]

We examined geographic impacts at the county level. Patients were clustered by county of residence at the time of diagnosis as reported by SEER. We used the 2003 Rural Urban Continuum Codes (RUCC) from the U.S. Department of Agriculture to create a binary definition for rurality by collapsing county-level RUCC codes into Metro/urban versus Nonmetro/rural categories.[203] In addition to rurality, we examined county fixed effects for the percent of the population over 65 in poverty (as a measure of socioeconomic status of the county), and county Medically Underserved Area designation (MUA).[208] County MUAs are assigned by the Health Resources and Services Administration through an index score including the ratio of healthcare providers per 1,000 population.[208]

*Analyses*

We examined differences in the receipt of lung cancer-related surgical treatment by patient demographic and clinical characteristics as well as county factors using chi-square tests for categorical variables and t-tests for continuous variables. We calculated the unadjusted odds ratios (OR) with 95% confidence intervals (CI) of all patient-level covariates with surgical treatment. All tests were assessed at the significance level $\alpha$=0.05.

For the adjusted analysis, we employed a multilevel logistic regression, specifically a random intercept is applied to county level, which allows the intercept to vary randomly across counties, thus jointly estimating the county and patient effect in receipt of surgical treatment.[209] We first estimated the null model predicting surgery utilization from only county-level random effects to measure the between-county variance in receipt of surgical treatment. Using this intercept-only model we then calculated the median odds ratio (MOR) to examine the median magnitude of the odds ratio between two randomly chosen counties and the intraclass correlation coefficient (ICC). MOR expresses the amount of individual probability of surgical utilization attributed to county characteristics, where a MOR not equal to (or close to) 1.0 indicates that the multilevel model is an appropriate statistical approach for the data.[209] The ICC measures the proportion of the total variance in surgical treatment that can be attributed to the county level.[210] Next, we built our level-one model with patient characteristics predicting surgical utilization. We stratified by the patient stage at diagnosis, as treatment decision differ from one stage to another. Patient variables deemed to be significant based

on the literature related to our research question stayed in the models, and other patient characteristics were selected by backward selection based on coefficients with a p-value less than or equal to 0.05.

We tested for the need of random slopes for race, Medicaid enrollment, and Charlson comorbidity score to allow for variation of these patient factors across counties. We assessed the fit of each model by calculating the pseudo R-squared. Using the final two-level model, we produced the estimated variance of the distribution of random effects and ORs with 95% CIs for variables associated with utilizing surgical treatment among early stage lung cancer patients. We also performed a post-hoc comparison of county-level MUAs and the percent of poverty by urban and rural designations to assess the representativeness of these factors in our sample covered by SEER registries in comparison to the overall U.S.

**6.4 Results**

*Patient Characteristics and Surgical Treatment*

Our final cohort consisted of 63,767 NSCLC patients nested within 365 counties (Table 6.1). The average age was 75.9 years (std=6.4) and the majority of the sample was white (85.2%) and not enrolled in Medicaid (72.5%) (Table 6.1). Slightly more than half were female (50.7%) and married (51.6%). Over half were diagnosed at a regional stage (53.4%) and 46.6% at a localized stage. The majority of patients had right side laterality (58.2%). Undetermined tumor grade was present in 35.6% of patients and 47.8% had no comorbidities. Less than half of the total sample received surgery (46.1%).

When examining differences in surgical treatment by stage, a higher proportion of localized cases received surgery than regional cases (56.7% vs. 36.8%, Table 6.1). Among localized cases, factors associated with higher likelihood of surgery were who white race (57.8%) and not being married (64.2%, Table 6.2). Among regional cases, factors associated with a greater probability of surgery were being categorized as other races (41.2%) and married (42.0%) (Table 6.3). For both stages, factors associated with greater likelihood of surgery were urban residence, not being on Medicaid, younger age and having few comorbidities.

*County Characteristics and Surgical Treatment*

The majority of counties in which patients resided were urban (85.3%) and not designated MUAs (62.5%). The mean county-level percent poverty for the 65 and older population was 9.0%. (Table 6.1). When comparing receipt of surgical treatment, fewer local stage rural residents received surgery than urban residents (57.7% vs. 50.5%, $p<0.01$, Table 6.2). The same was true for comparing regional stage cases with 37.2% of urban cases receiving surgery and 34.7% of rural residents receiving surgery ($p=0.01$, Table 6.3). The mean county poverty for those 65 and older was similar for those who did not receive surgery than for other who did (9.2% vs. 8.8%). When examined by MUA designation, a significantly higher proportion of geographic MUA residents received surgery than those not living in MUAs (48.9% vs, 44.4%). The same was true when examined by stage at diagnosis.

*Model Selection*

The intercept-only model indicated significant variation in receipt of surgical treatment at the county level ($p<0.01$) with MOR=1.34 (Table 6.4). However, a low ICC of 0.028 indicated that only 2.8% of the variation in surgical treatment was attributed to the county level. Rurality was a borderline significant county-level fixed effect ($p=0.05$). With the addition of MUA and percent of population in poverty over 65, the fixed effect for rurality was no longer marginally significant ($p=0.77$). The fixed effect for MUA was not significant ($p=0.18$) while the percent poverty fixed effect was highly significant at $p<0.01$. We considered removing rurality and MUA from the model given the non-significant p-values (greater than 0.05) but based on significant likelihood ratio tests for the model including both rurality and including MUA, we retained both variables in the model. All patient-level demographic and clinical characteristics were significant at $p<0.01$ and kept in the model. We tested random slopes for race, comorbidities, and Medicaid enrollment, all of which were not significant and therefore not retained in the model. The final model's MOR for the random effect at the county-level was 1.38 and the ICC increased slightly to 0.033. The pseudo R-squared improved from 0.01 in the model with only county-level rurality to 0.51 in the final model for localized cases and 0.44 for regional cases.

*Multilevel Logistic Regression Results*

In our final multilevel model stratified by stage, the county-level fixed effect for the percent of poverty in the over 65 population was significant where the odds of receiving surgical treatment decreased by 17% with each 5% increase in poverty among localized stage cases (OR=0.83, 95% CI: 0.77-0.91) and by 16% for regional cases (OR=0.84, 95%CI: 0.79-0.90) (Table 6.4). At the patient-level, a 5-year increase in age also resulted in lower odds of surgical treatment for localized cases (OR=0.58, 95% CI: 0.56-0.59) and for regional cases (OR=0.74, 95%CI: 0.72-0.75). Men had lower odds of receiving surgery when compared to women at both localized and regional stages. Black patients had 43% lower odds of receiving surgery than white patients for localized stage (OR=0.60, 95% CI: 0.56-0.66) and 37% lower odds for regional cases (OR=0.63, 95%CI: 0.56-0.70). For localized cases, those of other races also had lower odds of surgical treatment than whites (OR=0.83, 95%CI: 0.73-0.95) while there was no significant difference for regional stage patients categorized as other races compared with whites (OR=1.04, 95% CI: 0.93-1.16). For both stages, non-married patients had lower odds of surgery than married patients (localized OR=0.65, 95% CI:0.61-0.69; regional OR=0.70 95% CI:0.66-0.75), and those enrolled in Medicaid had lower odds of surgery compared to those on Medicare alone (localized OR=0.83, 95% CI:0.73-0.95; regional OR=0.85, 95%CI:). An increasing number of comorbid conditions was associated with decreasing odds of surgical treatment for both localized and regional cases. In terms of laterality, when compared with right primary location the left location of tumors in localized cases had slightly lower odds of surgery (OR=0.93, 95% CI:0.88-0.99), but regional cases had higher odds of surgical treatment with left laterality vs. right (OR=1.19, 95% CI:1.13-

1.26). Bilateral or midline locations had much lower odds of surgery for both stages (localized OR=0.11, 95% CI:0.03-0.43; regional OR=0.09, 95% CI:0.04-0.17). Over one-third of the sample had undetermined tumor grade, which was associated with the lowest odds of receiving surgery compared to well-differentiated grade for both stages (localized OR=0.07, 95% CI:0.06-0.07; regional OR=0.05, 95%CI:0.05-0.06). Moderately differentiated grade was not significantly different from well differentiated for either stage. Poorly differentiated (localized OR=0.50, 95% CI:0.45-0.55; regional OR=0.54, 95%CI: 0.48-0.61) and undifferentiated (localized OR=0.54, 95% CI:0.43-0.67; regional OR=0.56, 95%CI: 0.46-0.68) grades had similarly low odds of surgery in comparison to well differentiated grade.

**6.5 Discussion**

In our examination of a large, national sample of local and regional stage NSCLC patients, only 46.1% (n=29,381) received surgical treatment, with 57.4% of those diagnosed at localized stage and 42.6% diagnosed at regional stage. In unadjusted examination of surgical utilization, a lower proportion of rural residents received surgery when compared to urban residents. When rurality was examined as a county-level fixed effect, it was a borderline significant predictor of surgical treatment utilization (p=0.05), where rural residents had decreased odds of surgical treatment. However, the relationship of rurality and surgical treatment was attenuated with the addition of fixed effects for county-level MUAs and percent poverty in the 65 and older population. The unadjusted association of patient race and surgical treatment showed that black patients had lower odds of receiving surgical treatment than white patients at both localized and regional

stages. This relationship held true for black race in the adjusted multilevel model controlling for patient demographic and clinical characteristics as well as county-level effects. While both had lower odds of surgical treatment, the magnitude of the odds ratios for black race and comorbidities were stronger among those diagnosed at localized stages when compared with regional stage.

A higher percentage of rural residents living in poverty may be driving disparities in treatment and furthermore a primary factor contributing to observed lower survival among rural patients.[233,241] When examining county-level fixed effects for surgical treatment, poverty in the 65 and older population was highly significant ($p<0.01$) with increasing poverty associated with lower odds of receiving surgical treatment. In our sample, only 14.7% the of counties were rural, compared to 19.3% of the U.S.[242] Furthermore, our data does not provide a representative sample of rural MUAs, as 54.6% of the total MUAs in the U.S. are rural and another 9.3% are partially rural.[208] In a post-hoc comparison of county-level MUAs and poverty by urban/rural designation, rural counties had a significantly higher percent of the 65 and older population living in poverty at 11.3% compared to 8.7% for urban counties ($p<0.01$). Conversely, only 6.9% of the rural counties in our sample were MUAs. In our multilevel model, MUA had a positive but non-significant association with surgical utilization (OR=1.10, 95% CI: 0.97-1.25). Like rurality, the association between MUA and surgical utilization may be driven by poverty levels, because MUA counties in our sample had a significantly lower mean percent of the population over 65 living in poverty at 8.7% compared to 9.2% in non-MUA counties ($p<0.01$). [42]

Our analysis revealed that adjusting for county-level poverty eliminated the significance of rurality and MUA. On the contrary, race remained a significant factor in our adjusted analysis, with black patients having lower odds of surgical treatment when compared to whites. Black cases of other cancer types are less likely to receive surgery as well, citing fatalism and distrust in the medical community.[243,244] Our results were similar to those previously showing that black cancer patients diagnosed at early stages are less likely to receive surgery than any other racial or ethnic group.[5,6,10–12,245] Also like other studies, [146,238,246] our results showed a reduction in racial disparities in surgical treatment after adjusting for demographics including SES via county-level poverty, though the reduction in the association was minimal when comparing black vs white cases (localized unadjusted OR=0.55 vs. localized adjusted OR=0.57; regional unadjusted OR=0.58 vs. regional adjusted OR=0.63).

While individual income is not available in SEER-Medicare data, we were able to include Medicaid enrollment as a covariate. With Medicaid enrollment functioning as a measure of individual income in our multilevel model, were able to conclude that those enrolled in Medicaid (those with low incomes) had lower odds of receiving surgical treatment than those not enrolled in Medicaid. This relationship should be reevaluated with future data to examine the potential association of Medicaid expansion under the Affordable Care Act on surgical receipt among Medicaid enrollees.

All patient-level demographic and clinical characteristics in our adjusted analysis were significantly associated with receipt of surgical treatment for local and regional

stage NSCLC. Increasing age and number of comorbidities were both associated with decreasing odds of surgical treatment. Older age and comorbidities can create challenges when deciding treatment plans for cancer patients as both are also related to worse survival among lung cancer patients.[247] Risk of surgery, recovery and quality of life following surgery must be considered when treatment recommendations are made to patients.[247] We did not assess the physician's recommendation of surgery; therefore, it is possible that older patients and those with multiple comorbidities were not considered eligible for surgical treatment.

Our results are limited by some aspects of the data source. SEER-Medicare data is restricted to Fee-for-Service beneficiaries only and does not include those enrolled in Medicare Advantage plans (approximately 25% of total Medicare beneficiaries in 2011).[248] Individual smoking history is also not available, preventing us from controlling for the potential effect of smoking on surgical treatment. Smoking has been cited as reason for delay in treatment initiation,[125] although not all current smoker patients who attempt to quit are successful. This could potentially be an additional contributor for some patients not receiving surgery. We also measured rurality at the county-level. Counties vary greatly in both population sizes and geographic area across the U.S. Using a county-level measure may have contributed to our null results. Granularity in rurality measures may be more accurate when assessed at a smaller geographic region, such as census tracts.

Our study is strengthened by the large sample size, that although limited in rural representation, still covers approximately 26% of cancer cases in the U.S. Our results provide an updated analysis the urban vs. rural comparison of lung cancer treatment since the 2017 publication of Atkins et al. based on patients diagnosed between 2000-2006.[211] We also accounted for rurality in a multilevel model as a contextual effect rather than a patient-level variable, portraying a more accurate depiction of geographic impacts on health care utilization.[249]

### 6.6 Conclusions

While rural residence itself was not a significant predictor of surgical treatment, the association of rurality was attenuated by area poverty, which is observed at higher rates among rural populations. Area deprivation, measured by the percent of the population age 65 and over living in poverty, appears to be a stronger driving factor in surgical treatment utilization than rurality itself. Medicaid enrollment, a measure of patient-level poverty, and black race were also associated with a reduced likelihood of receiving surgery. We have documented lower utilization of surgical care for local and regional lung cancer among lower socioeconomic status and black populations. The reasons for these inequities are likely complex and multifaceted. Future research is needed to understand the causes of these disparities in surgical treatment of lung cancer so strategies to eliminate them may be developed.

## 6.8 Tables

**Table 6.1 Patient and County Level Characteristics by Receipt of Surgical Treatment, NSCLC, SEER-Medicare 2003-2011**

| | Total N | No Surgery N (%) | Surgery N (%) | p-value |
|---|---|---|---|---|
| ***Level 1 Patient Demographics*** | | | | |
| **Total** | 63,767 | 34386 (53.9) | 29381 (46.1) | |
| **Age** | | | | <.01 |
| Mean (std) | 75.9 (6.4) | 77.4 (6.8) | 74.2 (5.5) | |
| **Sex** | | | | |
| Male | 31,411 | 17,141 (54.6) | 14,270 (45.4) | <.01 |
| Female | 32,356 | 17,245 (53.3) | 15,111 (46.7) | |
| **Race** | | | | |
| White | 54,313 | 28,718 (52.9) | 25,595 (47.1) | <.01 |
| Black | 4,979 | 3,341 (67.1) | 1,638 (32.9) | |
| Other | 4,475 | 2,327 (52.0) | 2,148 (48.0) | |
| **Marital Status** | | | | |
| Married | 32,870 | 15,685 (47.7) | 17,185 (52.3) | <.01 |
| Not Married | 28,850 | 17,475 (60.6) | 11,375 (39.4) | |
| Unknown/Missing | 2,047 | 1,226 (59.9) | 821 (40.1) | |
| **Medicaid Enrollment** | | | | |
| Yes | 6,456 | 4,124 (63.9) | 2,332 (36.1) | <.01 |
| No | 57,311 | 30,262 (52.8) | 27,049 (47.2) | |
| ***Level 1 Patient Clinical Characteristics*** | | | | |
| **Stage at Diagnosis** | | | | <.01 |
| Localized | 29,743 | 12,888 (43.3) | 16,855 (56.7) | |
| Regional | 34,024 | 21,498 (63.2) | 12,526 (36.8) | |
| **Comorbidities** | | | | <.01 |
| 0 | 30,465 | 14,928 (49.0) | 15,537 (51.0) | |
| 1 | 15,951 | 8,622 (54.0) | 7,329 (46.0) | |
| 2 | 3,535 | 5,022 (58.7) | 3,535 (41.3) | |
| 3 or higher | 2,980 | 5,814 (66.1) | 2,980 (33.9) | |
| **Laterality** | | | | <.01 |
| Right: origin of primary | 37,106 | 20,061 (54.1) | 17,045 (45.9) | |
| Left: origin of primary | 26,203 | 13,884 (53.0) | 12,319 (47.1) | |
| Bilateral, Midline, or Unspecified | 458 | 441 (96.3) | 17 (3.7) | |
| **Grade** | | | | <.01 |
| I, well differentiated | 5,220 | 1,328 (25.4) | 3,892 (74.6) | |
| II, moderately differentiated | 11,621 | 4,521 (28.0) | 11,621 (72.0) | |
| III, poorly differentiated | 10,175 | 8,203 (44.6) | 10,175 (55.4) | |
| IV, undifferentiated | 740 | 562 (43.2) | 740 (13.0) | |
| Undetermined | 2,953 | 19,772 (87.0) | 2,953 (13.0) | |
| ***Level 2 County Characteristics*** | | | | |

| | | | | |
|---|---|---|---|---|
| **Rurality** | | | | <.01 |
| Urban | 54,393 | 28,946 (53.2) | 25,447 (46.8) | |
| Rural | 9,374 | 5,440 (58.0) | 3,934 (42.0) | |
| **Percent Poverty in over 65 Population** | | | | <.01 |
| Mean (std) | 9.0 (3.2) | 9.2 (3.3) | 8.8 (3.0) | |
| **Medically Underserved Areas** | | | | <.01 |
| Yes | 23,927 | 12,224 (51.1) | 11,703 (48.9) | |
| No | 39,840 | 22,162 (55.6) | 17,678 (44.4) | |

**Table 6.2 Patient and County Level Characteristics by Receipt of Surgical Treatment among NSCLC Localized Stage Cases, SEER-Medicare 2003-2011**

| | Total N | Localized Stage No Surgery N (%) | Localized Stage Surgery N (%) | p-value |
|---|---|---|---|---|
| ***Level 1 Patient Demographics*** | | | | |
| **Total** | 29,743 | 12,888 (43.3) | 16,855 (56.7) | |
| **Age** | | | | <0.01 |
| Mean (std) | 76.1 (6.5) | 78.6 (6.8) | 74.3 (5.5) | |
| **Sex** | | | | 0.47 |
| Male | 13,789 | 5,944 (43.1) | 7,845 (56.9) | |
| Female | 15,954 | 6,944 (43.5) | 9,010 (56.5) | |
| **Race** | | | | <0.01 |
| White | 25,659 | 10,829 (42.2) | 14,830 (57.8) | |
| Black | 2,067 | 1,177 (56.9) | 890 (43.0) | |
| Other | 2,017 | 882 (43.7) | 1,135 (56.3) | |
| **Marital Status** | | | | <0.01 |
| Married | 13,489 | 6,899 (51.2) | 6,590 (48.9) | |
| Not Married | 15,212 | 5,443 (35.8) | 9,769 (64.2) | |
| Unknown/Missing | 1,042 | 546 (52.4) | 496 (47.6) | |
| **Medicaid Enrollment** | | | | <0.01 |
| No | 26,682 | 11,164 (41.8) | 15,518 (58.2) | |
| Yes | 3,061 | 1,724 (56.3) | 1,337 (43.7) | |
| ***Level 1 Patient Clinical Characteristics*** | | | | |
| **Comorbidities** | | | | <0.01 |
| 0 | 13,508 | 4,862 (36.0) | 8,646 (64.0) | |
| 1 | 7,577 | 3,335 (44.0) | 4,242 (56.0) | |
| 2 | 4,158 | 2,086 (49.8) | 2,099 (50.2) | |
| 3 or higher | 4,473 | 2,605 (58.2) | 1,868 (41.8) | |
| **Laterality** | | | | <0.01 |
| Right: origin of primary | 17,346 | 7,339 (42.3) | 10,007 (57.7) | |
| Left: origin of primary | 12,329 | 5,487 (44.5) | 6,842 (55.5) | |
| Bilateral, Midline, or Unspecified | 68 | 62 (91.2) | 6 (8.8) | |
| **Grade** | | | | <0.01 |
| I, well differentiated | 3,730 | 764 (20.5) | 2,966 (79.5) | |
| II, moderately differentiated | 8,338 | 1,686 (20.2) | 6,652 (79.8) | |
| III, poorly differentiated | 7,513 | 2,543 (33.9) | 4,970 (67.8) | |
| IV, undifferentiated | 534 | 172 (32.2) | 362 (67.8) | |
| Undetermined | 9628 | 7723 (80.2) | 1905 (19.8) | |
| ***Level 2 County Characteristics*** | | | | |
| **Rurality** | | | | <0.01 |
| Urban | 25,448 | 10,763 (42.3) | 14,685 (57.7) | |

| | | | | |
|---|---|---|---|---|
| Rural | 4,295 | 2,125 (49.5) | 2,170 (50.5) | |
| **Percent Poverty in over 65 Population** | | | | <0.01 |
| Mean (std) | 9.0 (3.2) | 9.3 (3.3) | 8.8 (3.0) | |
| **Medically Underserved Areas** | | | | <0.01 |
| No | 18,614 | 8379 (45.0) | 10,235 (55.0) | |
| Yes | 11,129 | 4,509 (40.5) | 6,620 (59.5) | |

**Table 6.3 Patient and County Level Characteristics by Receipt of Surgical Treatment among NSCLC Regional Stage Cases, SEER-Medicare 2003-2011**

| | Total N | Regional Stage No Surgery N (%) | Regional Stage Surgery N (%) | p-value |
|---|---|---|---|---|
| ***Level 1 Patient Demographics*** | | | | |
| **Total** | 34,024 | 21,498 (63.2) | 12,526 (36.8) | |
| **Age** | | | | <0.01 |
| Mean (std) | 75.7 (6.4) | 76.7 (6.6) | 74.1 (5.5) | |
| **Sex** | | | | 0.16 |
| Male | 17,622 | 11,197 (63.5) | 6,425 (36.5) | |
| Female | 16,402 | 10,301 (62.8) | 6,101 (37.2) | |
| **Race** | | | | <0.01 |
| White | 28,654 | 17,889 (62.4) | 10,765 (37.6) | |
| Black | 2,912 | 2,164 (74.3) | 748 (25.7) | |
| Other | 2,458 | 1,445 (58.8) | 1,013 (41.2) | |
| **Marital Status** | | | | <0.01 |
| Married | 15,361 | 10,242 (58.0) | 7,416 (42.0) | |
| Not Married | 17,658 | 10,576 (68.9) | 4,785 (31.2) | |
| Unknown/Missing | 1,005 | 680 (67.7) | 325 (32.3) | |
| **Medicaid Enrollment** | | | | <0.01 |
| No | 30,629 | 19,098 (62.4) | 11,531 (37.7) | |
| Yes | 3,395 | 2,400 (70.7) | 995 (29.3) | |
| ***Level 1 Patient Clinical Characteristics*** | | | | |
| **Comorbidities** | | | | <0.01 |
| 0 | 16,957 | 10,066 (59.4) | 6,891 (40.6) | |
| 1 | 8,374 | 5,287 (63.1) | 3,087 (36.9) | |
| 2 | 4,372 | 2,936 (67.2) | 1,436 (32.9) | |
| 3 or higher | 4,321 | 3,209 (74.3) | 1,112 (25.7) | |
| **Laterality** | | | | <0.01 |
| Right: origin of primary | 19,760 | 12,722 (64.4) | 7,0.8 (35.6) | |
| Left: origin of primary | 13,874 | 8,397 (60.5) | 5,477 (39.5) | |
| Bilateral, Midline, or Unspecified | 390 | 379 (97.2) | 11 (2.8) | |
| **Grade** | | | | <0.01 |
| I, well differentiated | 1,490 | 564 (37.9) | 926 (62.2) | |
| II, moderately differentiated | 7,804 | 2,835 (36.3) | 4,969 (63.7) | |
| III, poorly differentiated | 10,865 | 5,660 (52.1) | 5,205 (47.9) | |
| IV, undifferentiated | 768 | 390 (50.8) | 378 (49.2) | |
| Undetermined | 13,097 | 12,049 (92.0) | 1,048 (8.00) | |
| ***Level 2 County Characteristics*** | | | | |
| **Rurality** | | | | 0.01 |
| Urban | 28,945 | 18,183 (62.8) | 10,762 (37.2) | |

| | | | | |
|---|---|---|---|---|
| Rural | 5,079 | 3,315 (65.3) | 1,764 (34.7) | |
| **Percent Poverty in over 65 Population** | | | | |
| Mean (std) | 9.0 (3.2) | 9.2 (3.3) | 8.9 (3.1) | <0.01 |
| **Medically Underserved Areas** | | | | <0.01 |
| No | 21,226 | 13,783 (64.9) | 7,443 (35.1) | |
| Yes | 12,798 | 7,715 (60.3) | 5,083 (39.7) | |

**Table 6.4 Unadjusted Associations between Patient Characteristics and Surgical Treatment of NSCLC, SEER-Medicare 2003-2011**

| | Local Stage | Regional Stage |
|---|---|---|
| | **OR (95% CI)** | **OR (95% CI)** |
| ***Patient Fixed Effects*** | | |
| **Age** | | |
| 5-year increase | 0.89 (0.89-0.90) | 0.93 (0.93-0.94) |
| **Sex** | | |
| Male | 1.00 (Reference) | 1.00 (Reference) |
| Female | 0.98 (0.94-1.03) | 1.03 (0.99-1.08) |
| **Race** | | |
| White | 1.00 (Reference) | 1.00 (Reference) |
| Black | 0.55 (0.50-0.60) | 0.58 (0.53-0.63) |
| Other | 0.94 (0.86-1.03) | 1.17 (1.07-1.27) |
| **Marital Status** | | |
| Married | 1.00 (Reference) | 1.00 (Reference) |
| Not Married | 0.98 (0.94-1.03) | 1.03 (0.99-1.08) |
| **Medicaid Enrollment** | | |
| No | 1.00 (Reference) | 1.00 (Reference) |
| Yes | 0.56 (0.52-0.60) | 0.69 (0.64-0.74) |
| **Comorbidities** | | |
| 0 | 1.00 (Reference) | 1.00 (Reference) |
| 1 | 0.72 (0.68-0.76) | 0.85 (0.81-0.90) |
| 2 | 0.57 (0.53-0.61) | 0.71 (0.67-0.77) |
| 3 or more | 0.40 (0.38-0.43) | 0.51 (0.47-0.55) |
| **Laterality** | | |
| Right | 1.00 (Reference) | 1.00 (Reference) |
| Left | 0.91 (0.87-0.96) | 1.18 (1.13-1.23) |
| Bilateral, Midline, or Unspecified | 0.07 (0.03-0.16) | 0.05 (0.02-0.10) |
| **Grade** | | |
| I, well differentiated | 1.00 (Reference) | 1.00 (Reference) |
| II, moderately differentiated | 1.02 (0.92-1.12) | 1.07 (0.95-1.30) |
| III, poorly differentiated | 0.50 (0.46-0.55) | 0.56 (0.50-0.63) |
| IV, undifferentiated | 0.54 (0.45-0.66) | 0.59 (0.50-0.70) |
| Undetermined | 0.06 (0.06-0.07) | 0.05 (0.05-0.06) |

**Table 6.5 Results Summary of Multilevel Logistic Mixed Models for Surgical Treatment of NSCLC, SEER-Medicare 2003-2011**

| | **Model 1** County Random Intercept Only | **Model 2** County Random Intercept and Rurality Fixed Effect | **Model 3** County Random Intercept, Rurality and MUA Fixed Effects | **Model 4** Final Adjusted County and Patient Fixed Effects, Local Stage | **Model 4** Final Adjusted County and Patient Fixed Effects, Regional Stage |
|---|---|---|---|---|---|
| ***Pseudo $R^2$*** | | 0.00 | 0.05 | 0.51 | 0.44 |
| ***County Random Effect*** | | | | | |
| **MOR** | 1.49 | 1.34 | 1.33 | 1.38 | 1.38 |
| ***County Fixed Effects*** | | | | | |
| | | **OR (95% CI)** | **OR (95% CI)** | **OR (95% CI)** | **OR (95% CI)** |
| **Rurality** | | | | | |
| Urban | | 1.00 (Reference) | 1.00 (Reference) | 1.00 (Reference) | 1.00 (Reference) |
| Rural | | 0.95 (0.86-1.00) | 0.95 (0.87-1.02) | 0.87 (0.74-1.03) | 1.09 (0.95-1.26) |
| **Medically Underserved Areas** | | | | | |
| No | | | 1.00 (Reference) | 1.00 (Reference) | 1.00 (Reference) |
| Yes | | | 1.14 (1.02-1.26) | 1.05 (0.88-1.25) | 1.14 (1.01-1.29) |
| **Percent Poverty in over age 65** | | | | | |
| 5% increase | | | 0.85 (0.81-0.89) | 0.83 (0.77-0.91) | 0.84 (0.79-0.90) |
| ***Patient Fixed Effects*** | | | | | |
| | | | | **OR (95% CI)** | **OR (95% CI)** |
| **Age** | | | | | |
| 5-year increase | | | | 0.58 (0.56-0.59) | 0.74 (0.72-0.75) |

| | | | | | |
|---|---|---|---|---|---|
| **Sex** | | | | | |
| Male | | | | 1.00 (Reference) | 1.00 (Reference) |
| Female | | | | 0.85 (0.80-0.91) | 0.82 (0.78-0.87) |
| **Race** | | | | | |
| White | | | | 1.00 (Reference) | 1.00 (Reference) |
| Black | | | | 0.57 (0.51-0.65) | 0.63 (0.56-0.70) |
| Other | | | | 0.83 (0.73-0.95) | 1.04 (0.93-1.16) |
| **Marital Status** | | | | | |
| Married | | | | 1.00 (Reference) | 1.00 (Reference) |
| Not Married | | | | 0.65 (0.61-0.69) | 0.70 (0.66-0.75) |
| **Medicaid Enrollment** | | | | | |
| No | | | | 1.00 (Reference) | 1.00 (Reference) |
| Yes | | | | | 0.85 (0.76-0.94) |
| **Comorbidities** | | | | | |
| 0 | | | | 1.00 (Reference) | 1.00 (Reference) |
| 1 | | | | 0.75 (0.69-0.80) | 0.91 (0.85-0.97) |
| 2 | | | | 0.64 (0.58-0.70) | 0.86 (0.79-0.94) |
| 3 or more | | | | 0.46 (0.42-0.51) | 0.67 (0.61-0.73) |
| **Laterality** | | | | | |
| Right | | | | 1.00 (Reference) | 1.00 (Reference) |
| Left | | | | 0.93 (0.88-0.99) | 1.19 (1.13-1.26) |
| Bilateral, Midline, or Unspecified | | | | 0.11 (0.03-0.43) | 0.09 (0.04-0.17) |
| **Grade** | | | | | |
| I, well differentiated | | | | 1.00 (Reference) | 1.00 (Reference) |
| II, moderately differentiated | | | | 1.07 (0.96-1.19) | 1.07 (0.95-1.21) |

| | | | | | |
|---|---|---|---|---|---|
| III, poorly differentiated | | | | 0.50 (0.45-0.55) | 0.54 (0.48-0.61) |
| IV, undifferentiated | | | | 0.54 (0.43-0.67) | 0.56 (0.46-0.68) |
| Undetermined | | | | 0.07 (0.06-0.07) | 0.05 (0.05-0.06) |

# CHAPTER 7

# CONCLUSIONS

The goals for this dissertation were to investigate rural and racial disparities in lung cancer survival and treatment. The results provided updated U.S. estimates of survival by rurality and region, examined the potential association between time to treatment initiation and lung cancer survival, and identified inequities in surgical treatment for lung cancer. These results enhance the understanding of lung cancer survival disparities and identified lines of inquiry for future research.

The lung cancer landscape has evolved in many ways in recent years, with the National Lung Screening Trial results and subsequent recommendations from the USPSTF in 2013 to screen high risk patients annually. The Affordable Care Act has also changed the national healthcare environment of the country since its inception. Our results include patients diagnosed between 2003-2011, providing a useful baseline of lung cancer survival differences by rurality that can be compared to future data examining the impact of annual LDCT screening and ACA coverage.

The findings of our three papers provide additional insight into disparities in lung cancer survival. Our first paper showed that both all cause and lung cancer specific survival was lower among lung cancer patient residing in rural versus urban counties at the time of their diagnosis, particularly in the South and West regions. Comorbidities and

surgical treatment were strongly associated with the observed survival differences. These results motivated the second research topic, examining if urban vs. rural differences in time to treatment initiation could be a factor impacting the observed differences in survival. In the second paper, having lung cancer surgery within 12 weeks of being diagnosed was associated with greater survival benefit among localized and regional stage lung cancer cases compared with distant cases when examined beyond 16 months of follow-up. Conversely, in the first 16 months post-diagnosis, surgery initiation after 12 weeks was associated with better survival among all stages. Similarly, chemotherapy and radiation initiation after 12 weeks post diagnosis was associated with lower risk of death at all stages. Combinations of treatment types and differing sequences of treatments may be contributing to our results. Delays in chemotherapy may be due to surgery or procedures to confirm diagnosis, leading to a survival advantage. Further investigation accounting in a more refined fashion for patterns of care within stage of diagnosis is needed to better understand these observed differences.

The third paper, investigating racial and rural differences in the utilization of surgical treatment of lung cancer, also identified potential factors contributing to disparities in lung cancer survival. Among early stage cases, county-level poverty in the aged 65 and older population was more strongly associated than rurality with the likelihood of surgical treatment for lung cancer. Individual poverty (measured by Medicaid enrollment) and black race were also associated with a lower likelihood of surgery. Additional work is needed to better understand the complex causes of these

disparities in surgical treatment of lung cancer so strategies to eliminate them may be developed.

Overall, these findings advance understanding of the existing disparities in lung cancer treatment and survival, especially for the urban versus rural comparisons that had not previously been so thoroughly investigated. This includes the refined examination of rural vs. urban residence across regions of the United States; to our knowledge, our results are the first to also make urban vs. rural lung cancer survival comparisons by region and they revealed that the association varied by region. As expected, a greater comorbidity burden and not receiving surgical treatment were associated with worse survival. Future research that examinations the potential benefits of effective management of preexisting conditions during lung cancer treatment is warranted. For example, uncontrolled diabetes could lessen survival independently and via worsening response to lung cancer treatments. The evidence generated on time to treatment initiation and survival needs to be further refined, but in the long run this evidence could inform recommendations for timely surgical treatment in early stage cases. Consistent with prior evidence, we observed that black race continues to have a lower likelihood of surgery for lung cancer, indicating that black lung cancer patients may benefit from targeted interventions addressing patient and provider education aimed at improving utilization of surgery, when appropriate, in this population. The body of evidence presented in this document contributes an advance in understanding disparities in lung cancer survival, but this research area needs continued focus to further improve understanding of the causal factors driving disparities in lung cancer survival.

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# APPENDIX A

## CPT, HCPCS, ICD CODES FOR LUNG CANCER TREATMENT

**Table A.1 CPT, HCPCS, ICD Codes for Lung Cancer Treatment**

| Code Type | Code | Treatment Type | Description |
|---|---|---|---|
| HCPCS | C9216 | Chemotherapy | ABARELIX |
| HCPCS | J9216 | Chemotherapy | ABARELIX |
| HCPCS | J0128 | Chemotherapy | ABARELIX |
| HCPCS | S0165 | Chemotherapy | ABARELIX |
| HCPCS | J3490 | Chemotherapy | ABATACEPT |
| HCPCS | C9230 | Chemotherapy | ABATACEPT |
| HCPCS | J0129 | Chemotherapy | ABATACEPT |
| HCPCS | J9354 | Chemotherapy | ADO-TRASTUZUMAB EMTANSINE |
| HCPCS | C9131 | Chemotherapy | ADO-TRASTUZUMAB EMTANSINE |
| HCPCS | J0178 | Chemotherapy | AFLIBERCEPT |
| HCPCS | Q2046 | Chemotherapy | AFLIBERCEPT |
| HCPCS | J9400 | Chemotherapy | AFLIBERCEPT |
| HCPCS | J9015 | Chemotherapy | ALDESLEUKIN |
| HCPCS | S0087 | Chemotherapy | ALEMTUZUMAB |
| HCPCS | J9010 | Chemotherapy | ALEMTUZUMAB |
| HCPCS | J0202 | Chemotherapy | ALEMTUZUMAB |
| HCPCS | C9110 | Chemotherapy | ALEMTUZUMAB |
| HCPCS | J9215 | Chemotherapy | ALFERON |
| HCPCS | J0207 | Chemotherapy | AMIFOSTINE |

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|---|---|---|---|
| HCPCS | S0170 | Chemotherapy | ANASTROZOLE |
| HCPCS | J9017 | Chemotherapy | ARSENIC |
| HCPCS | C9012 | Chemotherapy | ARSENIC |
| HCPCS | J9019 | Chemotherapy | ASPARAGINASE |
| HCPCS | J9020 | Chemotherapy | ASPARAGINASE |
| HCPCS | J9025 | Chemotherapy | AZACITIDINE |
| HCPCS | C9416 | Chemotherapy | BCG LIVE |
| HCPCS | J9031 | Chemotherapy | BCG LIVE |
| HCPCS | Q2044 | Chemotherapy | BELIMUMAB |
| HCPCS | J0490 | Chemotherapy | BELIMUMAB |
| HCPCS | J9034 | Chemotherapy | BENDAMUSTINE |
| HCPCS | J9033 | Chemotherapy | BENDAMUSTINE |
| HCPCS | S0116 | Chemotherapy | BEVACIZUMAB |
| HCPCS | C9257 | Chemotherapy | BEVACIZUMAB |
| HCPCS | Q2024 | Chemotherapy | BEVACIZUMAB |
| HCPCS | J9035 | Chemotherapy | BEVACIZUMAB |
| HCPCS | C9214 | Chemotherapy | BEVACIZUMAB |
| HCPCS | J9040 | Chemotherapy | BLEOMYCIN |
| HCPCS | C9417 | Chemotherapy | BLEOMYCIN |
| HCPCS | S0115 | Chemotherapy | BORTEZOMIB |
| HCPCS | J9041 | Chemotherapy | BORTEZOMIB |
| HCPCS | C9207 | Chemotherapy | BORTEZOMIB |
| HCPCS | J9042 | Chemotherapy | BRENTUXIMAB |
| HCPCS | J8510 | Chemotherapy | BUSULFAN |
| HCPCS | C1178 | Chemotherapy | BUSULFAN |
| HCPCS | J0594 | Chemotherapy | BUSULFAN |
| HCPCS | J8520 | Chemotherapy | CAPECITABINE |

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|---|---|---|---|
| HCPCS | J8521 | Chemotherapy | CAPECITABINE |
| HCPCS | J9045 | Chemotherapy | CARBOPLATIN |
| HCPCS | J9047 | Chemotherapy | CARFILZOMIB |
| HCPCS | J9050 | Chemotherapy | CARMUSTINE |
| HCPCS | C9437 | Chemotherapy | CARMUSTINE |
| HCPCS | J9055 | Chemotherapy | CETUXIMAB |
| HCPCS | C9215 | Chemotherapy | CETUXIMAB |
| HCPCS | G0360 | Chemotherapy | CHEMOTHERAPY |
| HCPCS | C8954 | Chemotherapy | CHEMOTHERAPY |
| HCPCS | C8955 | Chemotherapy | CHEMOTHERAPY |
| HCPCS | G9029 | Chemotherapy | CHEMOTHERAPY |
| HCPCS | G9031 | Chemotherapy | CHEMOTHERAPY |
| HCPCS | G9030 | Chemotherapy | CHEMOTHERAPY |
| HCPCS | G9032 | Chemotherapy | CHEMOTHERAPY |
| HCPCS | G9021 | Chemotherapy | CHEMOTHERAPY |
| HCPCS | G9022 | Chemotherapy | CHEMOTHERAPY |
| HCPCS | G9023 | Chemotherapy | CHEMOTHERAPY |
| HCPCS | G9024 | Chemotherapy | CHEMOTHERAPY |
| HCPCS | G9025 | Chemotherapy | CHEMOTHERAPY |
| HCPCS | G9026 | Chemotherapy | CHEMOTHERAPY |
| HCPCS | G9027 | Chemotherapy | CHEMOTHERAPY |
| HCPCS | G9028 | Chemotherapy | CHEMOTHERAPY |
| HCPCS | G8372 | Chemotherapy | CHEMOTHERAPY |
| HCPCS | G0359 | Chemotherapy | CHEMOTHERAPY |
| HCPCS | G8373 | Chemotherapy | CHEMOTHERAPY |
| HCPCS | G8374 | Chemotherapy | CHEMOTHERAPY |
| HCPCS | G0355 | Chemotherapy | CHEMOTHERAPY |

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|---|---|---|---|
| HCPCS | C8953 | Chemotherapy | CHEMOTHERAPY |
| HCPCS | S5019 | Chemotherapy | CHEMOTHERAPY |
| HCPCS | S5020 | Chemotherapy | CHEMOTHERAPY |
| HCPCS | Q0085 | Chemotherapy | CHEMOTHERAPY |
| HCPCS | Q0084 | Chemotherapy | CHEMOTHERAPY |
| HCPCS | Q0083 | Chemotherapy | CHEMOTHERAPY |
| HCPCS | G0358 | Chemotherapy | CHEMOTHERAPY |
| HCPCS | G0362 | Chemotherapy | CHEMOTHERAPY |
| HCPCS | G0357 | Chemotherapy | CHEMOTHERAPY |
| HCPCS | S9329 | Chemotherapy | CHEMOTHERAPY |
| HCPCS | S9330 | Chemotherapy | CHEMOTHERAPY |
| HCPCS | S9331 | Chemotherapy | CHEMOTHERAPY |
| HCPCS | G0361 | Chemotherapy | CHEMOTHERAPY |
| HCPCS | J9999 | Chemotherapy | CHEMOTHERAPY |
| HCPCS | J8999 | Chemotherapy | CHEMOTHERAPY |
| HCPCS | J7150 | Chemotherapy | CHEMOTHERAPY |
| HCPCS | J3590 | Chemotherapy | CHEMOTHERAPY |
| HCPCS | S0172 | Chemotherapy | CHLORAMBUCIL |
| HCPCS | J9062 | Chemotherapy | CISPLATIN |
| HCPCS | C9418 | Chemotherapy | CISPLATIN |
| HCPCS | J9060 | Chemotherapy | CISPLATIN |
| HCPCS | 209622 | Chemotherapy | CISPLATIN |
| HCPCS | C9419 | Chemotherapy | CLADRIBINE |
| HCPCS | J9065 | Chemotherapy | CLADRIBINE |
| HCPCS | J9027 | Chemotherapy | CLOFARABINE |
| HCPCS | J9091 | Chemotherapy | CYCLOPHOSPHAMIDE |
| HCPCS | J9070 | Chemotherapy | CYCLOPHOSPHAMIDE |

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|---|---|---|---|
| HCPCS | J9092 | Chemotherapy | CYCLOPHOSPHAMIDE |
| HCPCS | J9080 | Chemotherapy | CYCLOPHOSPHAMIDE |
| HCPCS | J9090 | Chemotherapy | CYCLOPHOSPHAMIDE |
| HCPCS | C9420 | Chemotherapy | CYCLOPHOSPHAMIDE |
| HCPCS | J9096 | Chemotherapy | CYCLOPHOSPHAMIDE |
| HCPCS | J9093 | Chemotherapy | CYCLOPHOSPHAMIDE |
| HCPCS | J9097 | Chemotherapy | CYCLOPHOSPHAMIDE |
| HCPCS | J9094 | Chemotherapy | CYCLOPHOSPHAMIDE |
| HCPCS | J9095 | Chemotherapy | CYCLOPHOSPHAMIDE |
| HCPCS | C9421 | Chemotherapy | CYCLOPHOSPHAMIDE |
| HCPCS | J8530 | Chemotherapy | CYCLOPHOSPHAMIDE |
| HCPCS | C9438 | Chemotherapy | CYCLOSPORINE |
| HCPCS | J9098 | Chemotherapy | CYTARABINE |
| HCPCS | J9100 | Chemotherapy | CYTARABINE |
| HCPCS | J9110 | Chemotherapy | CYTARABINE |
| HCPCS | C9422 | Chemotherapy | CYTARABINE |
| HCPCS | C1166 | Chemotherapy | CYTARABINE |
| HCPCS | J9130 | Chemotherapy | DACARBAZINE |
| HCPCS | J9140 | Chemotherapy | DACARBAZINE |
| HCPCS | C9423 | Chemotherapy | DACARBAZINE |
| HCPCS | J9120 | Chemotherapy | DACTINOMYCIN |
| HCPCS | J9145 | Chemotherapy | DARATUMUMAB |
| HCPCS | J9151 | Chemotherapy | DAUNORUBICIN |
| HCPCS | J9150 | Chemotherapy | DAUNORUBICIN |
| HCPCS | C9424 | Chemotherapy | DAUNORUBICIN |
| HCPCS | J0894 | Chemotherapy | DECITABINE |
| HCPCS | J9155 | Chemotherapy | DEGARELIX |

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|---|---|---|---|
| HCPCS | C1084 | Chemotherapy | DENILEUKIN |
| HCPCS | J9160 | Chemotherapy | DENILEUKIN |
| HCPCS | C9272 | Chemotherapy | DENOSUMAB |
| HCPCS | J0897 | Chemotherapy | DENOSUMAB |
| HCPCS | J8540 | Chemotherapy | DEXAMETHASONE |
| HCPCS | J1094 | Chemotherapy | DEXAMETHASONE |
| HCPCS | J1100 | Chemotherapy | DEXAMETHASONE |
| HCPCS | J1190 | Chemotherapy | DEXRAZOXANE |
| HCPCS | J9165 | Chemotherapy | DIETHYLSTILBESTROL |
| HCPCS | J9170 | Chemotherapy | DOCETAXEL |
| HCPCS | J9171 | Chemotherapy | DOCETAXEL |
| HCPCS | J9000 | Chemotherapy | DOXORUBICIN |
| HCPCS | J9001 | Chemotherapy | DOXORUBICIN |
| HCPCS | C9415 | Chemotherapy | DOXORUBICIN |
| HCPCS | J9002 | Chemotherapy | DOXORUBICIN |
| HCPCS | Q2049 | Chemotherapy | DOXORUBICIN |
| HCPCS | Q2048 | Chemotherapy | DOXORUBICIN |
| HCPCS | Q2050 | Chemotherapy | DOXORUBICIN |
| HCPCS | J9180 | Chemotherapy | EPIRUBICIN |
| HCPCS | J9178 | Chemotherapy | EPIRUBICIN |
| HCPCS | C1167 | Chemotherapy | EPIRUBICIN |
| HCPCS | J9181 | Chemotherapy | ETOPOSIDE |
| HCPCS | J9182 | Chemotherapy | ETOPOSIDE |
| HCPCS | C9425 | Chemotherapy | ETOPOSIDE |
| HCPCS | C9414 | Chemotherapy | ETOPOSIDE |
| HCPCS | J8560 | Chemotherapy | ETOPOSIDE |
| HCPCS | J7527 | Chemotherapy | EVEROLIMUS |

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|---|---|---|---|
| HCPCS | J8561 | Chemotherapy | EVEROLIMUS |
| HCPCS | S0156 | Chemotherapy | EXEMESTANE |
| HCPCS | J9200 | Chemotherapy | FLOXURIDINE |
| HCPCS | C9426 | Chemotherapy | FLOXURIDINE |
| HCPCS | J9185 | Chemotherapy | FLUDARABINE |
| HCPCS | C9262 | Chemotherapy | FLUDARABINE |
| HCPCS | J8562 | Chemotherapy | FLUDARABINE |
| HCPCS | J9190 | Chemotherapy | FLUOROURACIL |
| HCPCS | S0175 | Chemotherapy | FLUTAMIDE |
| HCPCS | J9395 | Chemotherapy | FULVESTRANT |
| HCPCS | C9434 | Chemotherapy | GALLIUM |
| HCPCS | J1457 | Chemotherapy | GALLIUM |
| HCPCS | J8565 | Chemotherapy | GEFITINIB |
| HCPCS | J9201 | Chemotherapy | GEMCITABINE |
| HCPCS | C9004 | Chemotherapy | GEMTUZUMAB |
| HCPCS | J9300 | Chemotherapy | GEMTUZUMAB |
| HCPCS | J1620 | Chemotherapy | GONADORELIN |
| HCPCS | J9202 | Chemotherapy | GOSERELIN |
| HCPCS | J9226 | Chemotherapy | HISTRELIN |
| HCPCS | J9225 | Chemotherapy | HISTRELIN |
| HCPCS | J1675 | Chemotherapy | HISTRELIN |
| HCPCS | Q2020 | Chemotherapy | HISTRELIN |
| HCPCS | G0356 | Chemotherapy | HORMONE |
| HCPCS | S0176 | Chemotherapy | HYDROXYUREA |
| HCPCS | A9522 | Chemotherapy | IBRITUMOMAB |
| HCPCS | J9211 | Chemotherapy | IDARUBICIN |
| HCPCS | C9429 | Chemotherapy | IDARUBICIN |

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|---|---|---|---|
| HCPCS | C9427 | Chemotherapy | IFOSFAMIDE |
| HCPCS | J9208 | Chemotherapy | IFOSFAMIDE |
| HCPCS | S0088 | Chemotherapy | IMATINIB |
| HCPCS | S2107 | Chemotherapy | IMMUNOTHERAPY |
| HCPCS | J9213 | Chemotherapy | INTERFERON ALFA-2A |
| HCPCS | S0146 | Chemotherapy | INTERFERON ALFA-2B |
| HCPCS | J9214 | Chemotherapy | INTERFERON ALFA-2B |
| HCPCS | J9212 | Chemotherapy | INTERFERON ALFACON |
| HCPCS | J1826 | Chemotherapy | INTERFERON BETA-1A |
| HCPCS | J9228 | Chemotherapy | IPILIMUMAB |
| HCPCS | J9206 | Chemotherapy | IRINOTECAN |
| HCPCS | J9207 | Chemotherapy | IXABEPILONE |
| HCPCS | J1930 | Chemotherapy | LANREOTIDE |
| HCPCS | C9237 | Chemotherapy | LANREOTIDE |
| HCPCS | J0640 | Chemotherapy | LEUCOVORIN |
| HCPCS | J1950 | Chemotherapy | LEUPROLIDE |
| HCPCS | J9217 | Chemotherapy | LEUPROLIDE |
| HCPCS | J9219 | Chemotherapy | LEUPROLIDE |
| HCPCS | J9218 | Chemotherapy | LEUPROLIDE |
| HCPCS | S0177 | Chemotherapy | LEVAMISOLE |
| HCPCS | J0641 | Chemotherapy | LEVOLEUCOVORIN |
| HCPCS | S0178 | Chemotherapy | LOMUSTINE |
| HCPCS | J9230 | Chemotherapy | MECHLORETHAMINE |
| HCPCS | J1050 | Chemotherapy | MEDROXYPROGESTERONE |
| HCPCS | J1051 | Chemotherapy | MEDROXYPROGESTERONE |
| HCPCS | S0179 | Chemotherapy | MEGESTROL |
| HCPCS | J9245 | Chemotherapy | MELPHALAN |

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|---|---|---|---|
| HCPCS | J8600 | Chemotherapy | MELPHALAN |
| HCPCS | S0108 | Chemotherapy | MERCAPTOPURINE |
| HCPCS | J9209 | Chemotherapy | MESNA |
| HCPCS | J9250 | Chemotherapy | METHOTREXATE |
| HCPCS | J9260 | Chemotherapy | METHOTREXATE |
| HCPCS | J8610 | Chemotherapy | METHOTREXATE |
| HCPCS | J9290 | Chemotherapy | MITOMYCIN |
| HCPCS | J9291 | Chemotherapy | MITOMYCIN |
| HCPCS | J9280 | Chemotherapy | MITOMYCIN |
| HCPCS | C9432 | Chemotherapy | MITOMYCIN |
| HCPCS | J9293 | Chemotherapy | MITOXANTRONE |
| HCPCS | J0340 | Chemotherapy | NANDROLONE |
| HCPCS | J2320 | Chemotherapy | NANDROLONE |
| HCPCS | J2321 | Chemotherapy | NANDROLONE |
| HCPCS | J2322 | Chemotherapy | NANDROLONE |
| HCPCS | J2323 | Chemotherapy | NATALIZUMAB |
| HCPCS | Q4079 | Chemotherapy | NATALIZUMAB |
| HCPCS | J9261 | Chemotherapy | NELARABINE |
| HCPCS | J9299 | Chemotherapy | NIVOLUMAB |
| HCPCS | J9301 | Chemotherapy | OBINUTUZUMAB |
| HCPCS | J2352 | Chemotherapy | OCTREOTIDE |
| HCPCS | J2353 | Chemotherapy | OCTREOTIDE |
| HCPCS | J2354 | Chemotherapy | OCTREOTIDE |
| HCPCS | J9302 | Chemotherapy | OFATUMUMAB |
| HCPCS | C9297 | Chemotherapy | OMACETAXINE |
| HCPCS | J9262 | Chemotherapy | OMACETAXINE |
| HCPCS | J9263 | Chemotherapy | OXALIPLATIN |

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| HCPCS | C9205 | Chemotherapy | OXALIPLATIN |
| HCPCS | J9264 | Chemotherapy | PACLITAXEL |
| HCPCS | J9267 | Chemotherapy | PACLITAXEL |
| HCPCS | J9265 | Chemotherapy | PACLITAXEL |
| HCPCS | C9431 | Chemotherapy | PACLITAXEL |
| HCPCS | J2430 | Chemotherapy | PAMIDRONATE |
| HCPCS | C9235 | Chemotherapy | PANITUMUMAB |
| HCPCS | J9303 | Chemotherapy | PANITUMUMAB |
| HCPCS | J9266 | Chemotherapy | PEGASPARGASE |
| HCPCS | C9027 | Chemotherapy | PEMBROLIZUMAB |
| HCPCS | J9271 | Chemotherapy | PEMBROLIZUMAB |
| HCPCS | J9305 | Chemotherapy | PEMETREXED |
| HCPCS | C9213 | Chemotherapy | PEMETREXED |
| HCPCS | J9268 | Chemotherapy | PENTOSTATIN |
| HCPCS | J9306 | Chemotherapy | PERTUZUMAB |
| HCPCS | J9270 | Chemotherapy | PLICAMYCIN |
| HCPCS | J9600 | Chemotherapy | PORFIMER |
| HCPCS | J9307 | Chemotherapy | PRALATREXATE |
| HCPCS | S0182 | Chemotherapy | PROCARBAZINE |
| HCPCS | J2675 | Chemotherapy | PROGESTERONE |
| HCPCS | J9308 | Chemotherapy | RAMUCIRUMAB |
| HCPCS | 214693 | Chemotherapy | RITUXIMAB |
| HCPCS | J9310 | Chemotherapy | RITUXIMAB |
| HCPCS | J9315 | Chemotherapy | ROMIDEPSIN |
| HCPCS | C9265 | Chemotherapy | ROMIDEPSIN |
| HCPCS | A9604 | Chemotherapy | SAMARIUM |
| HCPCS | A9605 | Chemotherapy | SAMARIUM |

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| HCPCS | Q2043 | Chemotherapy | SIPULEUCEL |
| HCPCS | J9320 | Chemotherapy | STREPTOZOCIN |
| HCPCS | A9600 | Chemotherapy | STRONTIUM-89 |
| HCPCS | S0187 | Chemotherapy | TAMOXIFEN |
| HCPCS | J9328 | Chemotherapy | TEMOZOLOMIDE |
| HCPCS | C1086 | Chemotherapy | TEMOZOLOMIDE |
| HCPCS | J8700 | Chemotherapy | TEMOZOLOMIDE |
| HCPCS | J9330 | Chemotherapy | TEMSIROLIMUS |
| HCPCS | Q2017 | Chemotherapy | TENIPOSIDE |
| HCPCS | J1070 | Chemotherapy | TESTOSTERONE |
| HCPCS | J1080 | Chemotherapy | TESTOSTERONE |
| HCPCS | J1090 | Chemotherapy | TESTOSTERONE |
| HCPCS | J1060 | Chemotherapy | TESTOSTERONE |
| HCPCS | J3120 | Chemotherapy | TESTOSTERONE |
| HCPCS | J3130 | Chemotherapy | TESTOSTERONE |
| HCPCS | J0900 | Chemotherapy | TESTOSTERONE |
| HCPCS | J3150 | Chemotherapy | TESTOSTERONE |
| HCPCS | J3140 | Chemotherapy | TESTOSTERONE |
| HCPCS | J9340 | Chemotherapy | THIOTEPA |
| HCPCS | C9433 | Chemotherapy | THIOTEPA |
| HCPCS | J3262 | Chemotherapy | TOCILIZUMAB |
| HCPCS | J9351 | Chemotherapy | TOPOTECAN |
| HCPCS | J9350 | Chemotherapy | TOPOTECAN |
| HCPCS | J8705 | Chemotherapy | TOPOTECAN |
| HCPCS | C9480 | Chemotherapy | TRABECTEDIN |
| HCPCS | J9355 | Chemotherapy | TRASTUZUMAB |
| HCPCS | J3315 | Chemotherapy | TRIPTORELIN |

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| HCPCS | J9357 | Chemotherapy | VALRUBICIN |
| HCPCS | J9360 | Chemotherapy | VINBLASTINE |
| HCPCS | J9370 | Chemotherapy | VINCRISTINE |
| HCPCS | J9375 | Chemotherapy | VINCRISTINE |
| HCPCS | J9380 | Chemotherapy | VINCRISTINE |
| HCPCS | J9371 | Chemotherapy | VINCRISTINE |
| HCPCS | C9440 | Chemotherapy | VINORELBINE |
| HCPCS | J9390 | Chemotherapy | VINORELBINE |
| ICD-9 | 9928 | Chemotherapy | CHEMOTHERAPY |
| ICD-9 | 9925 | Chemotherapy | CHEMOTHERAPY |
| ICD-9 | 9929 | Chemotherapy | CHEMOTHERAPY |
| ICD-9 | 177 | Chemotherapy | CLOFARABINE |
| CPT | C9287 | Chemotherapy | BRENTUXIMAB |
| CPT | J9043 | Chemotherapy | CABAZITAXEL |
| CPT | 4180F | Chemotherapy | CHEMOTHERAPY |
| CPT | 36640 | Chemotherapy | CHEMOTHERAPY |
| CPT | 96446 | Chemotherapy | CHEMOTHERAPY |
| CPT | 96445 | Chemotherapy | CHEMOTHERAPY |
| CPT | 96440 | Chemotherapy | CHEMOTHERAPY |
| CPT | 96450 | Chemotherapy | CHEMOTHERAPY |
| CPT | 96423 | Chemotherapy | CHEMOTHERAPY |
| CPT | 96425 | Chemotherapy | CHEMOTHERAPY |
| CPT | 96422 | Chemotherapy | CHEMOTHERAPY |
| CPT | 96420 | Chemotherapy | CHEMOTHERAPY |
| CPT | 96415 | Chemotherapy | CHEMOTHERAPY |
| CPT | 96417 | Chemotherapy | CHEMOTHERAPY |
| CPT | 96416 | Chemotherapy | CHEMOTHERAPY |

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| CPT | 96413 | Chemotherapy | CHEMOTHERAPY |
| CPT | 96410 | Chemotherapy | CHEMOTHERAPY |
| CPT | 96408 | Chemotherapy | CHEMOTHERAPY |
| CPT | 96402 | Chemotherapy | CHEMOTHERAPY |
| CPT | 96401 | Chemotherapy | CHEMOTHERAPY |
| CPT | 96400 | Chemotherapy | CHEMOTHERAPY |
| CPT | 96406 | Chemotherapy | CHEMOTHERAPY |
| CPT | 96405 | Chemotherapy | CHEMOTHERAPY |
| CPT | 96411 | Chemotherapy | CHEMOTHERAPY |
| CPT | 96409 | Chemotherapy | CHEMOTHERAPY |
| CPT | 219583 | Chemotherapy | CHEMOTHERAPY |
| CPT | 96542 | Chemotherapy | CHEMOTHERAPY |
| CPT | 203682 | Chemotherapy | CHEMOTHERAPY |
| CPT | 96414 | Chemotherapy | CHEMOTHERAPY |
| CPT | 96412 | Chemotherapy | CHEMOTHERAPY |
| CPT | 242226 | Chemotherapy | CHEMOTHERAPY |
| CPT | 61517 | Chemotherapy | CHEMOTHERAPY |
| CPT | 219687 | Chemotherapy | CHEMOTHERAPY |
| CPT | 0519F | Chemotherapy | CHEMOTHERAPY |
| CPT | 96545 | Chemotherapy | CHEMOTHERAPY |
| CPT | 206820 | Chemotherapy | CHEMOTHERAPY |
| CPT | 206929 | Chemotherapy | CHEMOTHERAPY |
| CPT | 96549 | Chemotherapy | CHEMOTHERAPY |
| CPT | J9179 | Chemotherapy | ERIBULIN |
| CPT | 81350 | Chemotherapy | IRINOTECAN |
| CPT | 83520 | Chemotherapy | METHOTREXATE |
| ICD-9 | 922 | Radiation | Brachytherapy |

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| ICD-9 | 9221 | Radiation | Beam |
| ICD-9 | 9222 | Radiation | Beam |
| ICD-9 | 9223 | Radiation | Beam |
| ICD-9 | 9224 | Radiation | Beam |
| ICD-9 | 9225 | Radiation | Beam |
| ICD-9 | 9226 | Radiation | Beam |
| ICD-9 | 9227 | Radiation | Brachytherapy |
| ICD-9 | 9228 | Radiation | Isotopes |
| ICD-9 | 9229 | Radiation | General |
| ICD-9 | 923 | Radiation | Beam |
| ICD-9 | 9231 | Radiation | Beam |
| ICD-9 | 9232 | Radiation | Beam |
| ICD-9 | 9233 | Radiation | Beam |
| ICD-9 | 9239 | Radiation | Beam |
| ICD-9 | 9241 | Radiation | Beam |
| ICD-9 | 9220 | Radiation | Brachytherapy |
| ICD-9 | 9230 | Radiation | Beam |
| CPT | 0073T | Radiation | Beam |
| CPT | 0082T | Radiation | Beam |
| CPT | 0083T | Radiation | Beam |
| CPT | 0182T | Radiation | Brachytherapy |
| CPT | 0190T | Radiation | Brachytherapy |
| CPT | 0197T | Radiation | Beam |
| CPT | 19296 | Radiation | Brachytherapy |
| CPT | 19297 | Radiation | Brachytherapy |
| CPT | 19298 | Radiation | Brachytherapy |
| CPT | 20555 | Radiation | Brachytherapy |

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| CPT | 20660 | Radiation | Beam |
| CPT | 31463 | Radiation | Brachytherapy |
| CPT | 32553 | Radiation | General |
| CPT | 41019 | Radiation | Brachytherapy |
| CPT | 49411 | Radiation | General |
| CPT | 49412 | Radiation | General |
| CPT | 52250 | Radiation | Brachytherapy |
| CPT | 55859 | Radiation | Brachytherapy |
| CPT | 55860 | Radiation | Brachytherapy |
| CPT | 55875 | Radiation | Brachytherapy |
| CPT | 55876 | Radiation | General |
| CPT | 55920 | Radiation | Brachytherapy |
| CPT | 57155 | Radiation | Brachytherapy |
| CPT | 57156 | Radiation | Brachytherapy |
| CPT | 58346 | Radiation | Brachytherapy |
| CPT | 61720 | Radiation | Beam |
| CPT | 61735 | Radiation | Beam |
| CPT | 61770 | Radiation | Beam |
| CPT | 61781 | Radiation | Beam |
| CPT | 61782 | Radiation | Beam |
| CPT | 61783 | Radiation | Beam |
| CPT | 61793 | Radiation | Beam |
| CPT | 61795 | Radiation | Beam |
| CPT | 61796 | Radiation | Beam |
| CPT | 61797 | Radiation | Beam |
| CPT | 61798 | Radiation | Beam |
| CPT | 61799 | Radiation | Beam |

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| CPT | 61800 | Radiation | Beam |
| CPT | 63620 | Radiation | Beam |
| CPT | 63621 | Radiation | Beam |
| CPT | 73670 | Radiation | Beam |
| CPT | 76950 | Radiation | Beam |
| CPT | 76965 | Radiation | Brachytherapy |
| CPT | 77014 | Radiation | Beam |
| CPT | 77261 | Radiation | Beam |
| CPT | 77262 | Radiation | Beam |
| CPT | 77263 | Radiation | Beam |
| CPT | 77280 | Radiation | Beam |
| CPT | 77285 | Radiation | Beam |
| CPT | 77290 | Radiation | Beam |
| CPT | 77295 | Radiation | Beam |
| CPT | 77299 | Radiation | Beam |
| CPT | 77300 | Radiation | Beam |
| CPT | 77301 | Radiation | Beam |
| CPT | 77305 | Radiation | Beam |
| CPT | 77306 | Radiation | Beam |
| CPT | 77307 | Radiation | Beam |
| CPT | 77310 | Radiation | Beam |
| CPT | 77315 | Radiation | Beam |
| CPT | 77321 | Radiation | Beam |
| CPT | 77326 | Radiation | Brachytherapy |
| CPT | 77326 | Radiation | Brachytherapy |
| CPT | 77327 | Radiation | Brachytherapy |
| CPT | 77327 | Radiation | Brachytherapy |

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| CPT | 77328 | Radiation | Brachytherapy |
| CPT | 77328 | Radiation | Brachytherapy |
| CPT | 77331 | Radiation | General |
| CPT | 77332 | Radiation | General |
| CPT | 77333 | Radiation | General |
| CPT | 77334 | Radiation | General |
| CPT | 77336 | Radiation | General |
| CPT | 77338 | Radiation | Beam |
| CPT | 77370 | Radiation | Beam |
| CPT | 77370 | Radiation | General |
| CPT | 77371 | Radiation | Beam |
| CPT | 77372 | Radiation | Beam |
| CPT | 77373 | Radiation | Beam |
| CPT | 77380 | Radiation | Beam |
| CPT | 77381 | Radiation | Beam |
| CPT | 77385 | Radiation | Beam |
| CPT | 77386 | Radiation | Beam |
| CPT | 77387 | Radiation | Beam |
| CPT | 77399 | Radiation | General |
| CPT | 77400 | Radiation | Beam |
| CPT | 77401 | Radiation | Beam |
| CPT | 77402 | Radiation | Beam |
| CPT | 77403 | Radiation | Beam |
| CPT | 77404 | Radiation | Beam |
| CPT | 77405 | Radiation | Beam |
| CPT | 77406 | Radiation | Beam |
| CPT | 77407 | Radiation | Beam |

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| CPT | 77408 | Radiation | Beam |
| CPT | 77409 | Radiation | Beam |
| CPT | 77410 | Radiation | Beam |
| CPT | 77411 | Radiation | Beam |
| CPT | 77412 | Radiation | Beam |
| CPT | 77413 | Radiation | Beam |
| CPT | 77414 | Radiation | Beam |
| CPT | 77415 | Radiation | Beam |
| CPT | 77416 | Radiation | Beam |
| CPT | 77417 | Radiation | Beam |
| CPT | 77418 | Radiation | Beam |
| CPT | 77419 | Radiation | General |
| CPT | 77420 | Radiation | General |
| CPT | 77421 | Radiation | General |
| CPT | 77422 | Radiation | Beam |
| CPT | 77423 | Radiation | Beam |
| CPT | 77425 | Radiation | General |
| CPT | 77427 | Radiation | General |
| CPT | 77430 | Radiation | General |
| CPT | 77431 | Radiation | General |
| CPT | 77432 | Radiation | Beam |
| CPT | 77435 | Radiation | Beam |
| CPT | 77469 | Radiation | Beam |
| CPT | 77470 | Radiation | Beam |
| CPT | 77499 | Radiation | General |
| CPT | 77520 | Radiation | Beam |
| CPT | 77522 | Radiation | Beam |

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| CPT | 77523 | Radiation | Beam |
| CPT | 77525 | Radiation | Beam |
| CPT | 77750 | Radiation | Isotopes |
| CPT | 77761 | Radiation | Brachytherapy |
| CPT | 77762 | Radiation | Brachytherapy |
| CPT | 77763 | Radiation | Brachytherapy |
| CPT | 77776 | Radiation | Brachytherapy |
| CPT | 77777 | Radiation | Brachytherapy |
| CPT | 77778 | Radiation | Brachytherapy |
| CPT | 77781 | Radiation | Brachytherapy |
| CPT | 77782 | Radiation | Brachytherapy |
| CPT | 77783 | Radiation | Brachytherapy |
| CPT | 77784 | Radiation | Brachytherapy |
| CPT | 77785 | Radiation | Brachytherapy |
| CPT | 77786 | Radiation | Brachytherapy |
| CPT | 77787 | Radiation | Brachytherapy |
| CPT | 77789 | Radiation | Brachytherapy |
| CPT | 77790 | Radiation | Brachytherapy |
| CPT | 77799 | Radiation | Brachytherapy |
| CPT | 79005 | Radiation | Isotopes |
| CPT | 79030 | Radiation | Isotopes |
| CPT | 79035 | Radiation | Isotopes |
| CPT | 79100 | Radiation | Isotopes |
| CPT | 79101 | Radiation | Isotopes |
| CPT | 79200 | Radiation | Isotopes |
| CPT | 79300 | Radiation | Isotopes |
| CPT | 79400 | Radiation | Isotopes |

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| CPT | 79403 | Radiation | Isotopes |
| CPT | 79420 | Radiation | Isotopes |
| CPT | 79440 | Radiation | Isotopes |
| CPT | 79445 | Radiation | Isotopes |
| CPT | 79900 | Radiation | Isotopes |
| CPT | 79999 | Radiation | Isotopes |
| HCPCS | A9606 | Radiation | Isotopes |
| HCPCS | A9699 | Radiation | Isotopes |
| HCPCS | C1715 | Radiation | Brachytherapy |
| HCPCS | C1716 | Radiation | Brachytherapy |
| HCPCS | C1717 | Radiation | Brachytherapy |
| HCPCS | C1718 | Radiation | Brachytherapy |
| HCPCS | C1719 | Radiation | Brachytherapy |
| HCPCS | C1720 | Radiation | Brachytherapy |
| HCPCS | C1728 | Radiation | Brachytherapy |
| HCPCS | C2616 | Radiation | Brachytherapy |
| HCPCS | C2633 | Radiation | Brachytherapy |
| HCPCS | C2634 | Radiation | Brachytherapy |
| HCPCS | C2635 | Radiation | Brachytherapy |
| HCPCS | C2636 | Radiation | Brachytherapy |
| HCPCS | C2637 | Radiation | Brachytherapy |
| HCPCS | C2638 | Radiation | Brachytherapy |
| HCPCS | C2639 | Radiation | Brachytherapy |
| HCPCS | C2640 | Radiation | Brachytherapy |
| HCPCS | C2641 | Radiation | Brachytherapy |
| HCPCS | C2642 | Radiation | Brachytherapy |
| HCPCS | C2643 | Radiation | Brachytherapy |

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| HCPCS | C2698 | Radiation | Brachytherapy |
| HCPCS | C2699 | Radiation | Brachytherapy |
| HCPCS | C9726 | Radiation | Brachytherapy |
| HCPCS | C9728 | Radiation | Brachytherapy |
| HCPCS | G0173 | Radiation | Beam |
| HCPCS | G0174 | Radiation | Beam |
| HCPCS | G0242 | Radiation | Beam |
| HCPCS | G0243 | Radiation | Beam |
| HCPCS | G0251 | Radiation | Beam |
| HCPCS | G0338 | Radiation | Beam |
| HCPCS | G0339 | Radiation | Beam |
| HCPCS | G0340 | Radiation | Beam |
| HCPCS | G6003 | Radiation | Beam |
| HCPCS | G6004 | Radiation | Beam |
| HCPCS | G6005 | Radiation | Beam |
| HCPCS | G6006 | Radiation | Beam |
| HCPCS | G6007 | Radiation | Beam |
| HCPCS | G6008 | Radiation | Beam |
| HCPCS | G6009 | Radiation | Beam |
| HCPCS | G6010 | Radiation | Beam |
| HCPCS | G6011 | Radiation | Beam |
| HCPCS | G6012 | Radiation | Beam |
| HCPCS | G6013 | Radiation | Beam |
| HCPCS | G6014 | Radiation | Beam |
| HCPCS | G6015 | Radiation | Beam |
| HCPCS | G6016 | Radiation | Beam |
| HCPCS | Q3001 | Radiation | Brachytherapy |

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| HCPCS | S2270 | Radiation | Brachytherapy |
| HCPCS | S8049 | Radiation | Beam |
| HCPCS | C1325 | Radiation | Brachytherapy |
| HCPCS | C1348 | Radiation | Isotopes |
| HCPCS | C1350 | Radiation | Brachytherapy |
| HCPCS | C1700 | Radiation | Brachytherapy |
| HCPCS | C1701 | Radiation | Brachytherapy |
| HCPCS | C1702 | Radiation | Brachytherapy |
| HCPCS | C1703 | Radiation | Brachytherapy |
| HCPCS | C1704 | Radiation | Brachytherapy |
| HCPCS | C1705 | Radiation | Brachytherapy |
| HCPCS | C1706 | Radiation | Brachytherapy |
| HCPCS | C1707 | Radiation | Brachytherapy |
| HCPCS | C1708 | Radiation | Brachytherapy |
| HCPCS | C1709 | Radiation | Brachytherapy |
| HCPCS | C1710 | Radiation | Brachytherapy |
| HCPCS | C1711 | Radiation | Brachytherapy |
| HCPCS | C1712 | Radiation | Brachytherapy |
| HCPCS | C1790 | Radiation | Brachytherapy |
| HCPCS | C1791 | Radiation | Brachytherapy |
| HCPCS | C1792 | Radiation | Brachytherapy |
| HCPCS | C1793 | Radiation | Brachytherapy |
| HCPCS | C1794 | Radiation | Brachytherapy |
| HCPCS | C1795 | Radiation | Brachytherapy |
| HCPCS | C1796 | Radiation | Brachytherapy |
| HCPCS | C1797 | Radiation | Brachytherapy |
| HCPCS | C1798 | Radiation | Brachytherapy |

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| HCPCS | C1799 | Radiation | Brachytherapy |
| HCPCS | C1800 | Radiation | Brachytherapy |
| HCPCS | C1801 | Radiation | Brachytherapy |
| HCPCS | C1802 | Radiation | Brachytherapy |
| HCPCS | C1803 | Radiation | Brachytherapy |
| HCPCS | C1804 | Radiation | Brachytherapy |
| HCPCS | C1805 | Radiation | Brachytherapy |
| HCPCS | C1806 | Radiation | Brachytherapy |
| HCPCS | C2632 | Radiation | Brachytherapy |
| HCPCS | C9714 | Radiation | Brachytherapy |
| HCPCS | C9715 | Radiation | Beam |
| HCPCS | G0178 | Radiation | Beam |
| HCPCS | G0256 | Radiation | Brachytherapy |
| HCPCS | G0273 | Radiation | Isotopes |
| HCPCS | G0274 | Radiation | Isotopes |
| HCPCS | G0338 | Radiation | Beam |
| HCPCS | G0339 | Radiation | Beam |
| HCPCS | G0340 | Radiation | Beam |
| HCPCS | G0458 | Radiation | Brachytherapy |
| HCPCS | C2644 | Radiation | Brachytherapy |
| HCPCS | C2645 | Radiation | Brachytherapy |
| CPT | 3220 | Surgery | |
| CPT | 3229 | Surgery | |
| CPT | 3230 | Surgery | |
| CPT | 3239 | Surgery | |
| CPT | 3241 | Surgery | |
| CPT | 3249 | Surgery | |

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| CPT | 3250 | Surgery | |
| CPT | 3259 | Surgery | |
| CPT | 3260 | Surgery | |
| CPT | 32095 | Surgery | |
| CPT | 32096 | Surgery | |
| CPT | 32097 | Surgery | |
| CPT | 32098 | Surgery | |
| CPT | 32100 | Surgery | |
| CPT | 32124 | Surgery | |
| CPT | 32140 | Surgery | |
| CPT | 32141 | Surgery | |
| CPT | 32150 | Surgery | |
| CPT | 32402 | Surgery | |
| CPT | 32440 | Surgery | |
| CPT | 32445 | Surgery | |
| CPT | 32480 | Surgery | Lobectomy |
| CPT | 32480 | Surgery | |
| CPT | 32482 | Surgery | |
| CPT | 32484 | Surgery | Segmentectomy |
| CPT | 32486 | Surgery | |
| CPT | 32488 | Surgery | |
| CPT | 32491 | Surgery | |
| CPT | 32500 | Surgery | Wedge Resection |
| CPT | 32503 | Surgery | |
| CPT | 32504 | Surgery | |
| CPT | 32505 | Surgery | |
| CPT | 32506 | Surgery | |

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| CPT | 32507 | Surgery | |
| CPT | 32601 | Surgery | |
| CPT | 32602 | Surgery | |
| CPT | 32603 | Surgery | |
| CPT | 32605 | Surgery | |
| CPT | 32607 | Surgery | |
| CPT | 32608 | Surgery | |
| CPT | 32609 | Surgery | |
| CPT | 32610 | Surgery | |
| CPT | 32657 | Surgery | VATS Wedge Resection |
| CPT | 32657 | Surgery | |
| CPT | 32660 | Surgery | |
| CPT | 32663 | Surgery | Thoracoscopy |
| CPT | 32663 | Surgery | |
| CPT | 32663 | Surgery | |
| CPT | 32666 | Surgery | |
| CPT | 32667 | Surgery | |
| CPT | 32668 | Surgery | |
| CPT | 32669 | Surgery | |
| CPT | 32670 | Surgery | |
| CPT | 32671 | Surgery | |
| CPT | 32672 | Surgery | |
| CPT | 32673 | Surgery | |
| CPT | 32674 | Surgery | |
| CPT | 38746 | Surgery | |