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The Effect of Treatment Delay, Non-Adherence to Treatment Guidelines, and Never-Smoking Status on the Survival of Lung Cancer Patients

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THE EFFECT OF TREATMENT DELAY, NON-ADHERENCE TO TREATMENT GUIDELINES, AND NEVER-SMOKING STATUS ON THE SURVIVAL OF LUNG CANCER PATIENTS

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ABSTRACT

THE EFFECT OF TREATMENT DELAY, NON-ADHERENCE TO TREATMENT GUIDELINES, AND NEVER-SMOKING STATUS ON THE SURVIVAL OF LUNG CANCER PATIENTS

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Despite many significant medical advances, lung cancer continues to cause more deaths than any of the other cancers in the United States (US), and worldwide. Timeliness of care and evidence-based guidelines are among the components of quality of care that are expected to improve patient outcomes. However, evidence on the effect of timeliness of care and adoption of evidence-based guidelines on patient survival remains lacking. In addition, there has been increasing concern on the fact that smokers are not the only group that suffers from lung cancer. Never-smokers comprise at least 10% of lung cancer patients in the US, or 25% worldwide. A better understanding of outcomes among never-smoker patients is needed. Using two nationwide cancer registries, this dissertation examines the effect of extended time-to-treatment, non-adherence to treatment guidelines, and never-smoking status on the survival of lung cancer patients. The results of our study suggest the harmful effect of extending time to treatment initiation among patients diagnosed with early stage cancer and resectable lung tumor, and the survival benefit of adherence to treatment guidelines. This study also highlights the importance of ensuring never-smoker patients received molecular testing and targeted therapy since the survival benefit among never-smokers was only evident in patients diagnosed at younger than 65-years-old. Overall, the results of this dissertation could assist in improving the provision of lung cancer treatment, which would lead to improved patient outcomes.

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LIST OF ABBREVIATIONS

aHR	Adjusted hazard ratio
AJCC	American Joint Committee on Cancer
aOR	Adjusted odds ratio
CCCP	Comprehensive Community Cancer Program
CCP	Community Cancer Program
CDC	Centers for Disease Control and Prevention
CI	Confidence interval
CoC	Commission on Cancer
CPGs	Clinical Practice Guidelines
EGFR	Epidermal Growth Factor Receptor
HR	Hazard ratio
IARC	International Agency of Cancer Research
IOM	Institute of Medicine
LCINS	Lung cancer in never-smokers
NCCN	National Comprehensive Cancer Network
NCDB	National Cancer Data Base
NNK	Nicotine-derived nitrosoaminoketone
NSCLC	Non-small cell lung cancer
OR	Odds ratio
PH	Proportional hazard
SCLC	Small cell lung cancer
SEER	Surveillance Epidemiology and End Results
TNM	Tumor-Node-Metastases

US	United States
VA	Veterans Affairs
VACCR	Veterans Affairs Central Cancer Registry
VHA	Veterans Health Administration

CHAPTER I: INTRODUCTION

1. LITERATURE REVIEW

1.1 Background

1.1.1 Epidemiology of lung cancer

Lung cancer remains a significant public health problem worldwide, being the second most common cancer. Approximately 55% of lung cancer cases occur in Asia, but the incidence rate is highest in North America.[1] In the United States (US), lung cancer is the second most common cancer after prostate cancer in males and breast cancer in females (excluding non-melanoma skin cancer).[2] The Surveillance Epidemiology and End Results (SEER) program reported an age-adjusted incidence rate of lung cancer of 55.8 per 100,000 persons between 2010 and 2014.[3] The incidence rate of lung cancer per 100,000 persons is higher among males (65.7) than females (48.4) and higher among black (63.0) than white (57.3) patients. Gender variations in lung cancer incidence are largely attributed to the different patterns of tobacco smoking and cessation between men and women.[2,4]

Lung cancer has remained the leading cause of cancer deaths since the 1950s in men and since the late 1980s in women.[5] In 2018, an estimated 234,030 people will be diagnosed with lung cancer in the US, and 154,050 will likely die of the disease. Although the mortality rate from lung cancer has decreased since the 1990s, lung cancer still accounts for 1 in 4 cancer deaths. Lung cancer-related deaths exceed the total number of deaths associated with colon, prostate, and breast cancer combined.[2]

According to the National Center for Health Statistics, the overall age-adjusted mortality rate from lung cancer over the period 2010–2014 was 44.7 per 100,000 persons.[3] The mortality rate per 100,000 persons is higher among males (55.9) than females (36.3) and among individuals aged 65 years and older (268.5) than individuals younger than 65 years (12.4). The overall difference in mortality between whites and blacks is relatively modest (45.5 vs. 48.0 per 100,000). However, black men have substantially higher mortality rates than white men (68.0 vs. 55.9 per 100,000). On the contrary, black women have slightly lower mortality rates than white women (34.6 vs. 37.5 per 100,000).[3]

1.1.2 Risk Factors for Lung Cancer

Tobacco smoking is the leading cause of lung cancer, as between 85% and 90% of lung cancer incidence is attributable to smoking.[6] However, the fact that lung cancer also occurs in never-smokers emphasizes the importance of other risk factors in the etiology of lung cancer. The following section describes the association between some of the known risk factors and lung cancer incidence.

Smoking – Active tobacco smoking is the strongest behavioral risk factor associated with lung cancer. A review of published studies reported that the risk of lung cancer in smokers is 20-times higher than in lifetime never-smokers.[7,8] The risk of lung cancer in smokers, however, depends largely on the duration of smoking and the number of cigarettes smoked.[7] Cigarette smoke contains more than 60 carcinogens.[9] Polycyclic aromatic hydrocarbons, which are the most carcinogenic compounds present in tobacco smoke, induce mutations in the p53 gene that are crucial for cell cycle dysregulation and the pathogenesis of lung cancer.[9] The tobacco-specific nitrosamine, known as nicotine-derived nitrosoaminoketone (NNK), is another major group of chemical substances found in tobacco smoke.[5]

Environmental exposures – There has been a growing body of literature suggesting the importance of environmental exposures, both indoor and outdoor, on lung cancer risk. The International Agency for Research on Cancer (IARC) has evaluated biological and chemical substances with respect to the cancer risk that those substances pose. For example, radon, secondhand tobacco smoke, asbestos, indoor emissions of coal from household combustion, and outdoor pollution are categorized as Group 1, which consists of carcinogens that affect humans. Indoor emission of biomass fuel is categorized as Group 2A (probably carcinogenic to humans).[10]

Radon has been established as the second leading cause of lung cancer in the US after tobacco smoking by the Environmental Protection Agency.[11] In a meta-analysis of 22 studies, of which 19 of them were conducted in Europe and North-America, Zhang *et al*. estimated a pooled Odds Ratio of lung cancer of 1.29 (95% CI, 1.10-1.51) between the highest and lowest exposure of residential radon. The dose-response analysis showed an increased by 7% for every 100 Bq/m3 increment in residential radon exposure (95% CI, 1.04-1.10; P for trend < 0.001).[12]

Genetics and family history – The fact that only a small percentage of smokers are diagnosed with lung cancer suggests that there is variation in individuals' susceptibility to tobacco carcinogens or other environmental exposures. One possible explanation is associated with the differences in DNA repair capacity. Individuals with lower DNA repair capacity tend to have a higher risk of lung cancer resulted from DNA-damaging carcinogens.[13]

A pooled analysis of 24 case-control studies from the International Lung Cancer Consortium showed increased risk of lung cancer associated with a family history. A 1.5-fold increased risk was evident among individuals with a first-degree relative with lung cancer, compared to those without a family history, after adjusting for smoking and other potential confounders (95% CI, 1.39–1.63). A greater association between family history and lung cancer was observed among

patients with a history of lung cancer in a sibling (OR, 1.82 [95% CI, 1.62-2.05]) than lung cancer in a father (OR, 1.25 [95% CI, 1.13-1.39]) or mother (OR, 1.37 [95% CI, 1.17-1.61).[14]

Age and Gender – The risk of lung cancer has been reported to be higher among older individuals and women.[5,15] Lung cancer risk increases as age advances.[7] According to the Surveillance, Epidemiology and End Results (SEER) program, the age-adjusted incidence rate of lung cancer among individuals aged 65 years or older in 2010–2014 was 328 per 100,000 population.[3] Increasing risk of lung cancer in the older population has been associated with the cumulative effect of tobacco-induced carcinogens over a long period, as well as declining physiological function. The lung cancer incidence rate is low in people younger than 40-years-old (for instance the incidence among people 35–39-years-old is 2.7 per 100,000 population),[4] but there has been concern about its increasing incidence in this age group.[7]

The difference in lung cancer risk by gender remains inconclusive. Analysis of cancer registry data analysis found that the age-adjusted incidence rate of lung cancer is higher among men.[3] This higher rate among men than women has been associated with the difference in tobacco smoking trend over decades, which started earlier among men than women.[3] The incidence rate data from cancer registry, however, are not adjusted by smoking. Emerging evidence controlling for the effect of smoking suggests that women are more susceptible to the carcinogenic effects of tobacco smoking than men. [16] A large population-based screening program found that women were twice as likely to be diagnosed with lung cancer as men, after adjusting for the smoking level.[17]

1.1.3. Clinical Presentation of Lung Cancer

The majority of patients who are diagnosed with lung cancer present with symptoms.[18] However, most early-stage lung cancers are asymptomatic.[19] By the time symptoms occur, the cancer has

typically progressed to a more advanced stage.[19] Symptoms of lung cancer, such as shortness of breath, cough, chest pain, hoarseness, and hemoptysis, can be directly caused by the primary tumor. Some patients, however, may present symptoms that are non-specific, such as fatigue, anorexia, and weight loss.[20] The wide range of symptoms of lung cancer, especially non-specific symptoms, might not alarm patients to seek medical care and may, therefore, potentially lead to a delay in diagnosis.[19]

In general, lung cancer can be divided into two major histologic types (non-small cell lung cancer [NSCLC] and small-cell lung cancer [SCLC]). NSCLC is the most common type and constitutes between 80% and 85% of all lung cancer cases.[2] NSCLC includes various histologic types, with the most common being adenocarcinoma and squamous cell carcinoma. SCLC, which accounts for 15–20% of all lung cancer cases, is a neuroendocrine tumor with cells that are smaller in size than most other cancer cells.[20] This cancer grows faster than NSCLC and metastasizes rapidly to other parts of the body. Some lung cancer tumors contain cells that are both SCLC and a form of NSCLC or contain more than one type of NSCLC.[18] NSCLC is divided further into multiple sub-types. The common sub-types are adenocarcinoma, squamous cell carcinoma, and large cell carcinoma.[20] The histologic sub-type is an important factor in determining chemotherapy agents.[21]

Cancer stage upon diagnosis guides treatment planning and also serves as a strong prognostic factor. In general, NSCLC staging is determined during either clinical or pathologic stages. The clinical stage is defined based on physical exams, biopsies, imaging tests, and other tests, while the pathologic stage is complemented by results of surgery, if the patient underwent surgery. When both sets of information are available, the pathologic stage is typically more accurate.[18] Lung cancer is mostly staged based on the American Joint Committee on Cancer (AJCC) TNM system, which involves: 1) T: The size of the primary tumor, 2) N: The spread of the tumor

to nearby (regional) lymph nodes, and 3) M: The extent of cancer spread to other organs of the body (metastasis).[22]

NSCLC is typically classified into four different stages (stage I—IV). Stage I is when the tumor size is no more than 5 cm and has not grown into nearby tissues. The tumor also has not spread to the lymph nodes or other parts of the body. This cancer is usually referred as early-stage cancer. Stage II and III have more extensive criteria that involve a different level of the TNM.[23] A patient is diagnosed with stage IV disease (often referred as advanced or metastatic cancer) when the cancer has spread to distant lymph nodes or other organs or parts of the body, such as the liver, bones or brain. A detailed classification according to the 8th Edition Staging from the AJCC is presented in *Appendix A*.

SCLC is commonly staged by the extent of the cancer spread. *Limited*-stage SCLC describes cancer that is only on one side of the chest, and *extensive*-stage SCLC refers to cancers that have spread widely throughout one lung, to the other lung, and lymph nodes on the other side of the chest or other parts of the body.[23]

1.1.4 Diagnosis

In general, the diagnostic process would involve a combination of collecting tumor samples for pathologic examination and imaging tests. For most types of cancer, a biopsy is done to take a small sample of the tumor tissue for laboratory testing to determine whether the tumor is cancerous and classify its histological type(s). Other procedures include bronchoscopy and needle aspiration, or more invasive procedures, such as mediastinoscopy and thoracotomy. An imaging test is intended to help doctors determining the size and location of the primary tumor and metastasis. The tests include CT scans, positron emission tomography (PET) scans, and magnetic resonance imaging. Patients with lung adenocarcinoma are also recommended molecular testing

to identify gene mutations. Results of the molecular testing will determine whether or not patients require therapy targeted to specific gene mutations (targeted therapy).[18]

1.1.5 Treatment

Cancer stage at diagnosis is a major driver of treatment options. Other factors, such as comorbidities and performance status, help to determine a patient's fitness for receiving treatment. Table 1 describes the treatment modalities by cancer stage for each NSCLC and SCLC, as recommended by the National Comprehensive Cancer Network (NCCN).

Table 1. Recommended treatment of lung cancer

Stage	Recommended treatment
	NSCLC
Stage I	• Surgery • Patients with a high risk of recurrence (based on size, location, or other factors) may be recommended for adjuvant chemotherapy after surgery
Stage II	• Surgery • Patients are recommended for adjuvant chemotherapy after surgery
Stage IIIA	• Include combinations of radiation therapy, chemotherapy (chemo), and/or surgery.
Stage IIIB	• Chemotherapy combined with radiation therapy when patient's overall health is good. Otherwise, the treatment would be either radiation therapy or chemotherapy
Stage IV	• Non-curative surgery, chemotherapy, targeted therapy, immunotherapy, or radiation therapy, depending on patients' condition
	SCLC
Limited stage	• Chemotherapy combined with radiation therapy
Extensive stage	• Chemotherapy

Source: NCCN Clinical Practice Guidelines in Oncology[24,25]

Most patients with stage I and some stage II patients can potentially receive curative treatment with surgery. Adjuvant chemotherapy is given for stage I and II patients who are deemed at high risk of recurrence. Patients with stage III NSCLC are usually treated with a combination of chemotherapy and radiotherapy. In some patients with stage IIIA NSCLC, the treatment might also include surgery. Patients diagnosed with stage IV have had their cancer metastasized, and thus, cure is not usually the goal of the treatment. Most of stage IV patients

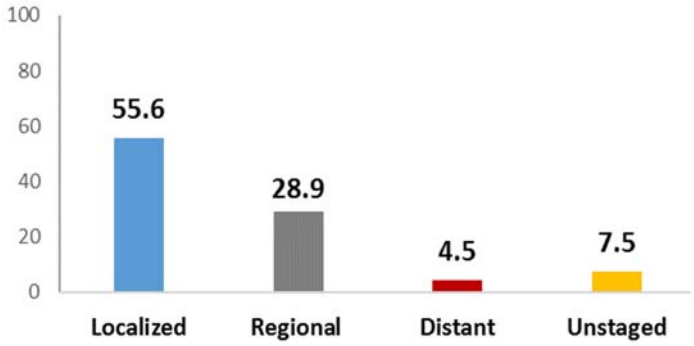
receive systemic therapy, and only if they are in good health, they may undergo surgery and radiation therapy to relieve their symptoms.[23]

Treatment decision-making for SCLC is complex. A patient with limited-stage cancer without any metastasis to the lymph nodes might be recommended for surgery, followed by chemotherapy.[26] However, such a case is rare because cancer has typically spread by the time it is detected. If the cancer is found in the lymph nodes, the patient may receive chest radiotherapy, which is often given simultaneously with chemotherapy. While this approach is more effective than giving one treatment after the other, the simultaneous application of radiation and chemotherapy increases the side effects of the treatment.[26,27] On the other hand, extensive-stage SCLC has typically metastasized widely, rendering surgery or radiation therapy ineffective. Patients with extensive-stage SCLC often receive chemotherapy to shrink cancer, treat symptoms, and extend survival. However, some patients might be unable to tolerate the side effects of standard doses of chemotherapy and are accordingly recommended to receive lower doses of chemotherapy or palliative care only.[27,28]

1.1.6 Survival of Lung Cancer Patients

Despite the advances in medical technology and improvements in the survival rates of early-stage lung cancer, the survival of all stages combined remains low.[3] Less than half of the patients (44%) survive at least one year after diagnosis, and 5-year survival rates are substantially lower (18.1%). Fifty-seven percent of patients are diagnosed at an extensive stage, for which the 5-year survival rate is less than 5%.[3] Figure 1 illustrates the 5-year survival rate by stage at diagnosis based on data from the SEER program.[3]

Figure 1. Five-year survival (percent) by stage at diagnosis, SEER 2007–2013



Based on 2013 estimates, 22.2% of women with lung cancer survived for at least 5 years, which exceeds the 15.6% 5-year survival rate among men.[3] The higher 5-year survival rate among women was consistent across all stages at diagnosis.[3] The reasons for better survival in women remains unclear. However, the fact that more women present with lung adenocarcinoma at a younger age at diagnosis might contribute to their better outcomes.[7,21] A large multi-center study of lung cancer patients with stage III and IV diseases in Germany found that women were nearly twice as likely to have Epidermal Growth Factor Receptor (EGFR) mutations than men (OR,1.85 [95% CI, 1.48–2.32]) and EGFR mutations have been reported to lead to a better prognosis.[29] Hormonal factors might be the only definite difference between women and men, with estrogen receptor α and β being among the prognostic factors in lung cancer.[30]

Racial disparity in survival has been observed between African Americans and whites.[31,32] A later stage at diagnosis and lack of access to care have been reported to be potential contributors to this disparity.[33] A study demonstrated that the racial disparity diminished when the analysis was adjusted for receipt of evidence-based treatment.[33] Ganti et al. (2014) reported that racial disparity in survival was not evident within the Veterans Affairs (VA) health system, a single-payer

system with universal health care. In this population, African Americans exhibited slightly better survival rates than whites.[34]

In the next sections, we will discuss treatment-related factors that are associated with patient survival, as well lung cancer in specific populations (never-smokers and Veterans), as the focus of this dissertation.

1.2 Treatment Delay

1.2.1 Recommended Diagnosis-to-Treatment Interval

A patient's journey through lung cancer care trajectories can extend over a long period. Delay in any interval within this continuum potentially puts patients at a higher risk of more advanced disease progression, and subsequently a poorer prognosis.[35] At the very least, a delay could increase the psychological distress of patients and their families.[36,37]

Clinical recommendations of time to initiate treatment varies between countries. In summary, however, existing guidelines outlined that diagnostic testing should be completed between 2 and 4 weeks after a patient consulted a specialist, and treatment should be initiated no more than 4 weeks after diagnosis. Table 2 summarizes the recommended time-to-treatment from several countries.[38,39] Unlike those countries, the US does not have established guidelines pertinent to recommended time-to-treatment for cancer care. In 2000, RAND Health (US) issued a proposed recommendation of treatment initiation for NSCLC other than metastatic cancer within 6 weeks of diagnosis.[40] The recommendation was formulated based on an extensive review of the literature by an expert panel.[40]

Table 2. Existing guidelines on the diagnosis-to-treatment interval

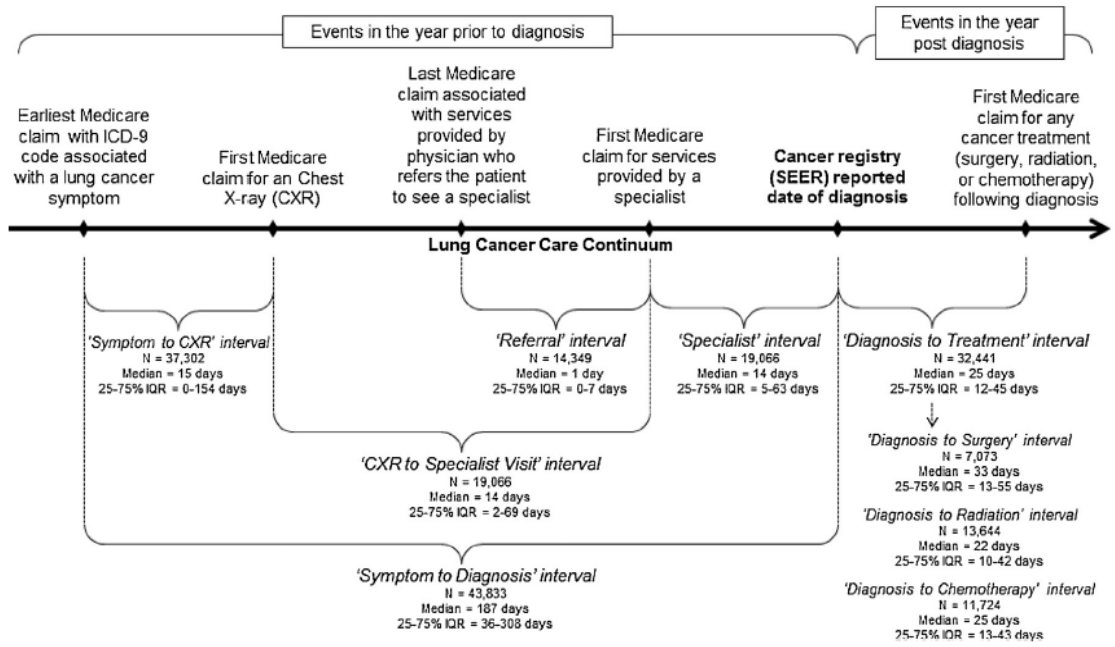
Country	Recommendation
Sweden[41]	In at least 80% of patients: • Diagnostic tests should be completed within 4 weeks from consultation with a chest physician • Treatment should be started within 2 weeks after consultation with a chest physician
The United Kingdom[38]	• Radical radiotherapy should start within 2 weeks after it is requested • The maximum time interval between the general practitioner consultation and the treatment is 62 days • A maximum wait time of 1 month from diagnosis to treatment for all cancers
Canada[42]	• A maximum of 4 weeks from the first visit to a family physician to diagnosis • Waiting time from completion of diagnostic tests to surgery should not exceed 2 weeks

1.2.2 Treatment Delay among Lung Cancer Patients

Treatment delay is not uncommon among cancer patients. Between 28.0% and 56.7% of lung cancer patients experience treatment delays.[43-45] Using data from SEER-Medicare, Nadpara *et al*. (2011) illustrated the average time necessary for a patient to go through the lung cancer care trajectories (Figure 2).[46] On average, it takes a total 212 days, or approximately 7 months, for Medicare beneficiaries with incident of lung cancer to begin treatment since a symptom is evaluated. The median interval from the time a patient sees his/her provider for symptom evaluation until lung cancer is diagnosed is 187 days. This is the longest time interval that a patient should go through since it involves multiple examinations (chest X-ray, referral by a primary physician to the specialist, and diagnostic procedures). This symptom-to-diagnosis interval time could, in fact, extend up to 308 days. The next is the diagnosis-to-treatment interval, which on average takes up to 25 days (IQR = 33 days). Patients who undergo surgery would have to wait longer (33 days), compared to those who receive radiation therapy and chemotherapy (22 and 25 days, respectively).[46] It should be noted that these data were collected among Medicare beneficiaries. Uninsured patients are likely to wait longer to begin treatment. Risk factors for

treatment delays include older age, black race, higher comorbidity score, early or localized stage of cancer, and high-volume facilities.[43,44]

Figure 2. Time to diagnosis and treatment among continuously enrolled Medicare Fee-for-service beneficiaries with an incident lung cancer diagnosis in the United States, 2003–2006



Reprinted from Nadpara et al., 2015 with permission from Elsevier.[46]

1.2.4 Impact of Treatment Delay on Patients' Survival

Despite the fact that studies pertaining to the association between treatment delay and outcome are increasing in prevalence, the results remain unclear.[39] Many studies did not demonstrate a significant negative effect of treatment delay on survival,[47,48] and others found that prolonged delay is linked with better survival.[41,49] A possible explanation for the latter findings is the fact that patients with more severe disease burden tend to experience shorter waiting times between diagnosis and treatment. Hence, disease severity might modify the effect of delay on patient outcomes. From a methodological standpoint, most previous studies were limited in size,

which precluded an analysis of the data stratified by disease severity. This limitation is even complicated by the variation in the definition of treatment delay used in existing studies (as illustrated in Table 3), making comparisons between studies challenging.[39] Table 3 describes the definitions of delay used in several previous studies.

Table 3. Definition of delay used in several past studies

Study	Location	Data source	Definition of delay
Samson, *et al*. 2015[45]	The US	NCDB and another single-site hospital-based study	Resection **8 weeks or greater** from the time of diagnosis.
Gomez, *et al*. 2015[44]	The US	SEER-Medicare and Texas Cancer Registry-Medicare	**More than 35 days** after diagnosis.
Yorio, *et al*. 2009[48]	The US	Multi-sites hospital-based study	Image-to-treatment interval. Several categorizations were used: 1. < 30; 31–60; 61–90; ≥ 91 2. 42 days (Swedish Lung Cancer Study Group) 3. 98 days (RAND Corporation)
Myrdal, *et al*. 2004[41]	Sweden	Two sites hospital-based study	Two types of delay: 1. Symptom-to-treatment delay 2. Hospital delay (the length of time from the first hospital visit to the start of treatment) Interval is analyzed as continuous and categorical variables separately (< 1 mo; 1–2 mo; 2–3 mo; and > 3 mo)
Diaconescu, *et al*. 2011[49]	Canada	Single site hospital-based study	The interval between the date of the first abnormal radiology that was suspicious for lung cancer and the dates starting treatment. The delay is analyzed as a continuous variable.
Murchie, *et al*. 2014[47]	Scotland	Scottish Cancer Registry	**More than 34 weeks** interval from presentation to treatment.

**all studies were on NSCLC, except for Murchie et al. (2014) who studied colorectal cancer*

To the best of our knowledge, there have been only three large studies that demonstrated a positive association between treatment delay and survival. An analysis of 28,732 NSCLC patients from the SEER-Medicare and Texas Cancer Registry (TCR)-Medicare databases revealed that adherence to the recommendation of the diagnosis-to-treatment interval was associated with improved survival in patients with localized disease (aHR, 0.86 [95% CI, 0.80–0.91]). On the

contrary, adherence was associated with poorer survival for patients with metastatic cancer who died within 1 year (aHR, 1.35 [95% CI, 1.28–1.42]).[44] Among 27,022 stage I NSCLC patients receiving surgical resection in the National Cancer Data Base (NCDB), each week of delay to surgery increased the hazard for mortality by 0.4% (aHR, 1.004 [95% CI, 1.002–1.007].[45]

1.3 Adherence to Treatment Guidelines

1.3.1 Clinical Practice Guidelines in Cancer Care

Clinical practice guidelines help to translate research findings into evidence-based clinical practice, guiding decision making in the complex field of cancer care.[50] The Institute of Medicine defined clinical practice guidelines as "Statements that include recommendations intended to optimize patient care that is informed by a systematic review of the evidence and an assessment of the benefits and harms of alternative care options." (IOM, 2011, p. 4)[51]

A review by von Dincklage *et al*. (2013) identified 31 lung cancer guidelines published between 2008 and 2013 by 19 organizations within and outside the US.[52] In the US, one of the largely adopted guidelines in oncology is the CPGs established by the National Comprehensive Cancer Network (NCCN). The NCCN-issued guidelines are developed and updated by more than one thousand clinicians and oncology researchers from the 27 leading cancer centers that are part of the NCCN.

1.3.2 Factors Associated with Adherence to Clinical Practice Guidelines

According to IOM's report, the translation of evidence-based recommendations into clinical cancer care remains slow and limited.[51] Non-adherence to CPGs can be affected by both provider and patient-related factors. From providers' level, the lack of comprehensive systematic review

in the development of the guidelines might result in different guidelines being developed for a particular field, causing conflicting advice and could lead to non-adoption of the CPGs. The review by Dincklage *et al*. showed that nine of the 31 published guidelines were either developed without the basis of systematic reviews or lacked information about the development method.[52] IOM also noted limitations in the monitoring and measurement process of the implementation of the clinical guidelines.[51] At patient level, age, comorbidities, and economic factors are among the independent characteristics that predict adherence to guidelines.[53,54]

1.3.3 Impact of Clinical Practice Guidelines on Patients' Outcome

In general, successful implementation of clinical practice guidelines could potentially improve healthcare quality and patient outcomes.[51,52] For instance, a study of colorectal cancer suggested that non-adherence to treatment guidelines in patients with stage III disease was associated with an 80% increase in the risk of death compared with patients whose treatment adheres to the guidelines.[53]

1.4 Lung Cancer in Never-Smokers

1.4.1 Epidemiology of Lung Cancer in Never-Smokers

Given the large share of preventable cases of lung cancer, tobacco cessation has been the central issue of lung cancer control. However, an estimated 15% of lung cancer cases in men and 53% in women, or equal to 25% of lung cancer worldwide are not attributable to active tobacco smoking.[6] In the US, at least 1 in 10 lung cancer cases occur among never-smokers.[6,55] The term never-smokers refers to individuals who have never smoked or who have smoked fewer than 100 cigarettes over their lifetime.[56,57] When non-tobacco-related lung cancer deaths are considered to be a single category, this type of cancer ranks between the 6th and 8th leading cause of cancer

deaths in the US, taking the lives of 16,000–24,000 people per year.[58,59] This fact makes lung cancer in never-smokers a significant public health burden.

Although it remains unclear whether there is an increasing trend in the incidence of lung cancer among never-smokers (LCINS), a study analyzing cohorts and registries data between 1959 and 2004 did not observe an increase in the US.[60] However, a large cohort study among male never-smokers in Sweden suggested a significant increase in incidence of LCINS from 1.5 per 100,000 persons in 1976–1980 to 5.4 per 100,000 persons in 1991–1995.[61] Findings pertinent to the epidemiology of LCINS have been inconclusive and geographically varied, but a number of studies have shown that the incidence of LCINs is higher among females, African Americans, and Asians, and that the death rate is higher among males.[57,58] In terms of age at diagnosis, two systematic reviews suggested that studies in Asian countries reported that never-smokers tend to be diagnosed at a younger age than ever-smokers while studies in Western countries found the opposite or no difference in age at diagnosis by smoking status.[13,57] Based on the clinical profile, adenocarcinoma is the most frequent histologic type among LCINS.[13,62]

Despite the importance of LCINS and the growing interest in research in this area over the last two to three decades, it is difficult to ascertain the actual incidence data because most population-based registries do not collect information on smoking status. Existing estimates in the US were derived mostly from a few cohort studies and a limited registry of a specific population.[60,63] The estimated incidence rates of LCINS are presented in Table 4. A number of studies have attempted to investigate the risk factors and outcomes of LCINS. However, most of the studies are hospital-based, with small sample size. An improved understanding of the incidence and etiology of LCINS could assist in designing lung cancer prevention and control strategies.

Table 4. Age-standardized incidence rates of lung cancer among never-smokers in the US

Source	Years of follow-up	Age-standardized incidence rates, per 100,000 person-years (95% CI)	
		Female	Male
1. Connecticut Tumor Registry (CT)	1935–1940	8.5 (95% CI not available)	N/A
2. Nurses' Health Study (NHS)	1976–2002	15.2 (9.1–24.5)	N/A
3. Health Professionals Follow-Up Study (HPFS)	1986–2002	N/A	11.2 (6.5–19)
4. California Teachers Study (CTS)	1995/1996 to 2002	20.8 (13.5–31.2)	N/A
5. Multiethnic Cohort (MEC) Study	1993/1996 to 2001	20.7 (13.5–31.1)	13.7 (9.0–21.5)
6. First National Health and Nutrition Examination Survey Epidemiologic Follow-Up Study (NHEFS)	1971/1975 to 1992	19.3 (14.2–27.5)	12.7 (10.2–18.2)
7. Cancer Prevention Study II, Nutrition Survey (CPS-II Nutrition)*	1992–2003	17.1 (11.8–22.3)	11.4 (8.3–14.6)
8. Women's Health Study (WHS)*	1993–2006	9.4 (5.7–13.1)	N/A

**Incidence rates were calculated only for European descents due to a very limited number of cases of non-European descents.*
***Age of subjects were 40–79 years, except for CT (40–69 years).*
Source: Wakelee et al., 2007[63]

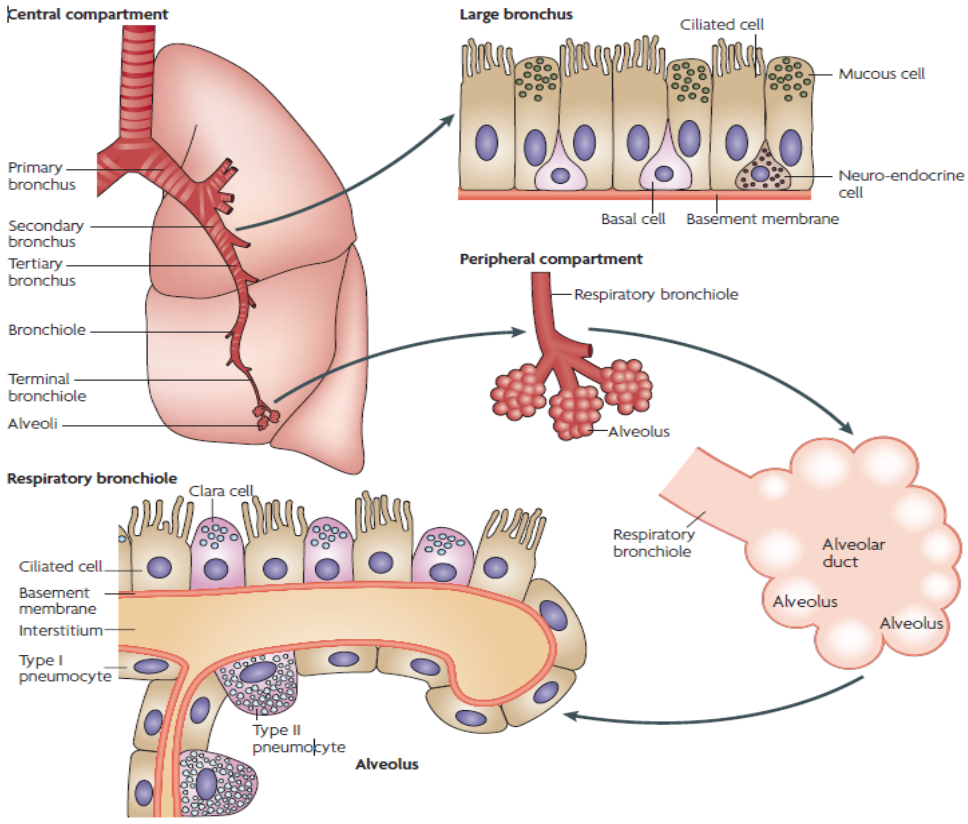
Radon and secondhand smoke are major contributors for LCINS in the US.[64] Other exposures, such as asbestos, arsenic, air pollution, diesel exhaust, and household cooking fumes, have also been shown to be associated with an increased risk for the disease in studies conducted in Asia.[65] A systematic review of studies among never-smokers reported an increased risk of LCINS by 26% (95%CI, 1.07–1.47) associated with secondhand smoking, and an increased risk by 40% (95% CI, 1.17-1.68) associated with family history of lung cancer.[57] Genetic susceptibility also plays a role in the development of LCINS.[57]

1.4.2 Pathology of Lung Cancer in Never-Smokers

Anatomically, the lung can be divided into central and peripheral compartments (Figure 3).[13] According to Sun *et al*. (2007), tobacco-induced lung cancer occurs in both central and peripheral airways. Lung cancer in never-smokers, however, typically occurs in the peripheral compartment.[13] Tumors in the peripheral compartment frequently asymptomatic, and thus,

might not be detected at early stages.[66] In addition, tumors in the peripheral airways are more likely to metastasize to regional lymph nodes and distant sites since they are located closer to the blood circulation.[66]

Figure 3. Lung anatomical compartments



Reprinted from Sun et al., 2007 with permission from Nature Publishing Group.[13]

1.4.3 Outcomes of Lung Cancer in Never-Smokers

Lung cancer in never-smokers has major clinical implications. A large proportion of never-smokers diagnosed with lung cancer harbor genetic mutations that are responsible for the initiation of lung cancer and affect sensitivity to treatment.[59] Epidermal Growth Factor Receptor (EGFR), EML4-ALK fusion, and deregulation of MET signaling are the commonly identified genetic abnormalities.[67]

EGFR mutations are more frequent among never-smokers than smokers. The clinical implication is that never-smokers tend to have a better response to treatment with EGFR small molecule inhibitors, and thus, are expected to have a higher survival rate than ever-smokers, although the results have been inconsistent.[67] The differences in the clinical features of lung cancer between never-smokers and ever-smokers suggest the need to consider LCINS as a separate entity.[62]

1.5 Lung Cancer in Veterans

In general, compared with the general population, the incidence of lung cancer is higher, and survival is poorer, among veterans, although the overall results have been inconsistent.[68-70] Among the veteran population, the higher incidence of lung cancer is associated with higher rates of smoking compared to the general population. Additionally, veterans who smoke tend to be heavy smokers.[71] And thus poorer survival has been linked with high comorbidities. Data from 1970–1982 shows that the incidence rate of lung cancer among males in the Veterans Affairs (VA) health system was 76% higher than the estimate from the SEER Cancer Registries.[69] An analysis of the Pennsylvania Cancer Registry found that 5-year survival among veterans with lung cancer was 12%, lower than among civilians (15%).[68] In contrast, another study found that survival was better among patients in the VA health system compared with non-VA patients, which could be explained by diagnoses at earlier stages among VA patients as a result of better access to care.[70]

The veteran population is unique not only due to their distinct demographic characteristics but also exposure to various risk factors other than smoking, which is likely to be at a higher level than that of the general population. The known risk factors among this population include Agent Orange, radon, asbestos, depleted uranium used in weapons and armor shielding, beryllium, fuel exhaust, and other battlefield emissions. Therefore, it is reasonable to expect that the incidence

of lung cancer in never-smokers in this population will be higher than the incidence in the general population.

To the best of our knowledge, the only available estimate for lung cancer among non-smoking US Veterans is the mortality rate from Dorn's study conducted among male veterans in 1955–1969.[72] The death rates of lung cancer in non-smoking male veterans varied between 13.4 and 19.6 per 100,000 persons in this study.[72] In comparison, the death rates for never-smoking males in the general population was 18.7 per 100,000 persons for 1959–1972 and 17.1 per 100,000 persons for 1982–2000.[58]

2. SUMMARY OF RESEARCH GAPS

The persistently high mortality of lung cancer has led to a number of studies aiming at understanding the prognostic factors of lung cancer. Nevertheless, it remains unclear how some of those factors are associated with the survival of lung cancer patients, which this dissertation tries to address.

2.1 Time-to-Treatment in Lung Cancer Patients

Delayed treatment has been hypothesized to be associated with decreased patient survival. However, findings from studies of multiple cancers show mixed results. Several studies confirmed this hypothesis,[47,73] while other studies reported contrasting results.[41,49] Evidence from studies in lung cancer patients has been limited and inconclusive. Our review of the literature identified three US studies that showed a significant increase in mortality risk associated with treatment delay in patients with NSCLC. These studies, however, have several limitations. One study was

restricted to elderly patients (aged 66 years and older) who were Medicare beneficiaries, and thus, the generalization of the findings was limited.[44] As older age is an independent, strong predictor of survival, the question remains whether the effect of treatment delay is independent of age. The other two studies investigated the effect of delay only in surgery, and thus, further investigation is needed to determine whether the negative effect of delay also presents in patients receiving other treatment modalities.[45,73] Most of the remaining studies in lung cancer reported counter-intuitive results, of which a longer time-to-treatment was associated with improved survival; a phenomenon known as the 'waiting time paradox.' The paradox poses a critical question of whether the findings truly represent the association between time-to-treatment and survival. To arrive at a more robust and inclusive conclusion to aid clinical practice and improve patients' outcomes, further research on the effect of extended time-to-treatment on patients' survival in a broader population and including various treatment modalities is vital.

2.2 Adherence to Treatment Guidelines in Lung Cancer

Providing evidence-based treatments, as represented by clinical practice guidelines, is one of the keys to improving quality of cancer care. However, the implementation of clinical guidelines can be challenging due to various factors, such as patient preference and contraindications. Especially in a highly aggressive disease like SCLC, therapeutic nihilism – the perception that treatments may not be useful – might also affect physicians' recommendation or patients' decisions about the treatment. Many studies have described treatment patterns in various cancer patients, including SCLC,[74] but fewer have examined the extent to which patients receive care that adheres to the clinical practice guidelines.[75,76] One US study demonstrated an increasing use of radiation and chemotherapy in patients diagnosed with limited stage SCLC between 1992 and 2007.[74] Another

study among patients of 65-years-old or older reported low, but increasing, use of chemotherapy in SCLC patients between 1985 and 2005.[28] Those two studies did not address the gap in the literature about the level to which existing guidelines for treatment of SCLC patients have been adopted, and its trend over time. Furthermore, since clinical guidelines are commonly developed based on randomized controlled trials, the impact of guidelines adherence in a real-world setting remains a subject for investigation. Although evidence-based treatment should, intuitively, lead to better survival, empiric data are needed to promote the adoption of clinical guidelines to improve patients' outcomes.

2.3 Lung Cancer in Never-Smokers (LCINS)

An estimated 1 in 4 lung cancer patients worldwide, or 10% in the US, do not have a history of active tobacco smoking.[6] Previous studies have indicated variation in the epidemiology of LCINS by regions (Asian vs. Western countries), which might have been affected by differences in the major risk factors.[13,57] Findings have been inconclusive, for instance, about whether the risk of developing LCINS is higher among female than male, or whether never-smokers with lung cancer are diagnosed at a younger age than their ever-smoker counterparts. The mortality rate from LCINS is relatively high, surpassing those of several other cancers, such as myeloma and brain cancers.[58] However, whether or not the survival of never-smokers with lung cancer is different from ever-smokers remains inconclusive.

The major challenge of studies in LCINS is the limited registries that provide information on smoking status. The majority of the studies in LCINS have been single-center hospital-based with a relatively small number of sample, which might limit their power to detect small effect sizes. The Veterans Affairs Health System offers an opportunity to analyze a relatively large number of

patients with information on smoking status, through their Veterans Affairs Central Cancer Registry (VACCR). The registry will also allow us to study a population that is unique from the general population. Veterans are known to have had a higher risk of lung cancer exposures other than active tobacco smoking, and they may also have other distinct characteristics that could affect their survival.

Gaps identified in the three above areas have led to the development of this dissertation. We expect the results of this dissertation to contribute to an improved understanding of the prognostic factors of lung cancer.

3. SPECIFIC AIMS

Although lung cancer mortality in the US has declined over the last two decades, lung cancer continues to affect a significant number of people, and less than 20% of patients survive for at least 5 years.[3] Ensuring early diagnosis and quality continuum of care are key to improving patient survival. This dissertation focuses on factors associated with survival of lung cancer patients. We investigated two modifiable factors within the realm of cancer treatment: timeliness of care and adherence to treatment guidelines; and never-smoking status. For the latter, the focus of our dissertation was the never-smoker veteran population.

The overall goal of this dissertation was to improve our understanding of the provision of treatment in lung cancer patients and its impact on patients' overall survival, as well as the epidemiology of lung cancer in the never-smoker patients and their survival. The dissertation is composed of three studies, which are presented in detail in Chapters II–IV. To achieve the objectives, this dissertation pursued the following specific aims:

Study 1: To examine the effect of extended time-to-treatment on the survival of non-small cell lung cancer (NSCLC) patients.

Hypothesis: Treatment started more than four weeks after diagnosis (beyond the commonly recommended guidelines) increases the risk of mortality.

Study 2: To examine the effect of non-adherence to treatment guidelines on the survival of small cell lung cancer (SCLC) patients.

Hypothesis: Non-adherence to treatment guidelines increases the risk of mortality.

Study 3: To analyze survival of never-smokers with lung cancer in the VA Health Care System.

Hypothesis: Never-smokers with lung cancer have better survival than ever-smokers.

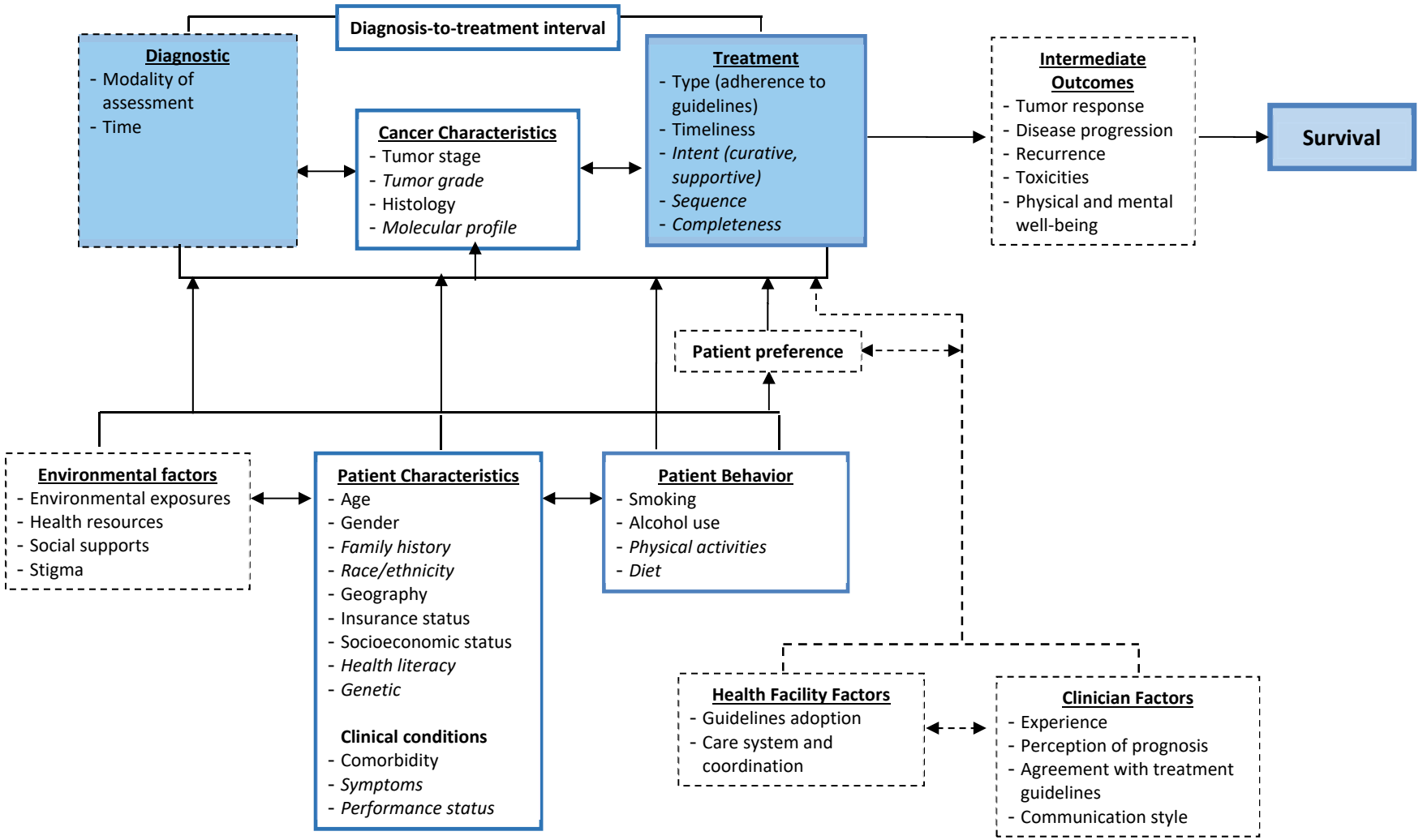
4. CONCEPTUAL FRAMEWORK

We prepared a conceptual model framework to guide this dissertation in identifying study variables, developing the research design, and interpreting study findings. The framework helped us to put into perspective the pathway in which each of the prognostic factors affects patients' survival and how some of those factors are interrelated. We adapted the conceptual model developed by Carpenter *et al*. (2012), which was originally used to measure cancer comparative effectiveness research data needs. The Carpenter's model was developed through semi-structured discussions with 76 clinicians and comparative effectiveness researchers affiliated with the Agency for Healthcare Research and Quality.[77]

Patient outcome (e.g., survival) is a result of multiple factors that play a role throughout the illness trajectory that includes diagnosis and treatment. After cancer diagnosis, most patients go through a so-called diagnosis-to-treatment interval before treatment is initiated. Patient-level,

healthcare provider-level, and environment-level factors drive the decisions about the timing of treatment initiation and the type of treatment, subsequently affecting patients' survival. Patient-level factors include patients' characteristics and clinical conditions, behavior, and cancer characteristics. We modified the Carpenter's model by adding patient preference as we consider patient preference, in interaction with provider-level factors, plays an important role in treatment decision making. We also differentiate between health facility and clinician factors to clearly illustrate factors that influence adherence to guidelines and treatment decision in each health facility and clinician level. Given that this dissertation is a retrospective secondary data analysis, we were unable to investigate some of the prognostic factors (as indicated by the dashed lines or the italic texts in Figure 4).

Figure 4. Conceptual framework of factors affecting the survival of lung cancer patients



** Modified from the proposed new model of measures for patient-centered cancer outcomes research (Carpenter et al., 2012).*

***** Predictors in dashed-line boxes and factors in italic are not studied in this dissertation; boxes with the blue line are the central of this dissertation.***

5. METHODOLOGY

To achieve the aims of the dissertation, we conducted three studies of secondary data with a retrospective cohort design. We utilized two nationwide hospital-based databases: the National Cancer Data Base and the Veterans Affairs Central Cancer Registry. Overall 5-year survival was used as the primary outcome of all three studies. We also analyzed predictors for extended time-to-treatment and non-adherence to treatment guidelines. In our first study, we used the term 'extended time-to-treatment' to represent treatment initiated more than 4 weeks after diagnosis, or what in other studies is referred as treatment delay. The multivariable analyses were done using Cox regression and logistic regression. Detailed descriptions of the methods used to address each study aim are given in Chapters II–IV.

5.1 National Cancer Data Base

The National Cancer Data Base (NCDB) is a clinical oncology database sourced from hospital registry data collected by more than 1,500 Commission on Cancer (CoC)-accredited facilities. The database is jointly sponsored by the American College of Surgeons and the American Cancer Society. The database represents approximately 70% of newly diagnosed cancer cases in the US.[78]

Hospitals accredited by the CoC are required to abstract and follow all cancer cases diagnosed and/or initially treated at the corresponding hospital. The National Cancer Data Base applies the reporting standard similar to state health departments and federal cancer registry data systems, including the SEER program and the National Program of Cancer Registries.[78] Given the fact that the database only covers cases reported by CoC-accredited facilities, the data might not be representative of all hospitals across the US.[79] Nevertheless, in addition to its wide coverage, the

NCDB offers a valuable opportunity to analyze more in-depth clinical information that is not present in most cancer registries, such as comorbidity score, time-to-treatment, and chemotherapy status.

5.2 Veterans Affairs Central Cancer Registry

By design, the Veterans Affairs Central Cancer Registry (VACCR) consists information on cancer diagnosis and treatment submitted by local cancer registry staff at each of the 132 Veterans Affairs Medical Centers (VAMCs), which diagnose and/or treat veterans with cancer.[80] The VACCR is unique, as the database offers the opportunity to study cancers in never-smokers, which is not feasible using other cancer registries due to the absence of smoking status information.

The database only consists of the veteran population who are eligible to receive VA health care benefits. The Department of Veterans Affairs estimated that there are 5.6 million beneficiaries out of 22.3 million veterans.[81] The basic eligibility criteria for military members to qualify for VA health care benefits includes, but is not limited to, the following:[82]

- Individuals who served in active military service and were separated under any condition other than dishonorable discharge.
- Current and former members of the Reserves or National Guard who were called to active duty by a federal order and completed the full period for which they were called or ordered to active duty.
- Family members of Veterans - under certain circumstances, family members of Veterans are eligible for health benefits, such as the spouse or widow(er) and the dependent children of a qualifying sponsor who died of a service-connected disability, etc.

CHAPTER II: IMPACT OF TIME-TO-TREATMENT ON OVERALL SURVIVAL OF NON-SMALL CELL LUNG CANCER PATIENTS - AN ANALYSIS OF THE NATIONAL CANCER DATABASE

Abstract

Background: The association between time-to-treatment and outcomes in lung cancer has not been conclusively established. In this study, we have evaluated the effect of time-to-treatment on the overall 5-year survival of non-small cell lung cancer (NSCLC) patients with different cancer stages at diagnosis. **Methods**: We analyzed data of adult patients newly diagnosed with NSCLC in 2003–2011 (N = 693,554) from the National Cancer Data Base (NCDB). Extended Cox regression with Counting Process was used to model the effect of time-to-treatment on survival, adjusted for demographic and clinical factors. The multivariable analyses were performed separately for the different stage at diagnosis groups. Time-to-treatment was defined as the interval between diagnosis and treatment initiation, with the categories of (i) 0 day, (ii) 1 day–4 weeks, (iii) 4.1–6.0 weeks, and (iv) > 6 weeks (the 1 day–4 weeks group was considered the reference group). **Results**: We found that, compared to treatment initiated between 1 day and 4 weeks after diagnosis, time-to-treatment 4.1–6.0 weeks was associated with a lower risk of death among patients with early-stage cancer (aHR, 0.84 [95% CI, 0.82-0.85]), with locally advanced cancer (aHR, 0.82 [95% CI, 0.80-0.83]), and with metastatic cancer (aHR, 0.75 [95% CI, 0.74-0.76]). Similarly, a lower risk of death was also associated with time-to-treatment longer than 6 weeks in patients with any cancer stage at diagnosis. However, a subset analysis among early-stage patients who received surgery only showed that extended time-to-surgery was associated a higher risk of death ($aHR_{4.1\text{-}6.0\ weeks}$, 1.06 [95% CI, 1.03–1.09]; $aHR_{>6\ weeks}$ 1.17 [95% CI, 1.14–1.20]). **Conclusion**: Our findings highlight that although time-to-treatment should not be compromised, it is imperative to ensure that

patients receive optimal pre-treatment assessments rather than rushing the treatment. Future research should focus on examining clinical characteristics to determine an optimal time-to-treatment to achieve best possible survival for NSCLC patients.

Introduction

Lung cancer is the leading cause of cancer deaths in the United States (US) and worldwide.[1] The 1- and 5-year overall survival rates of lung cancer patients (47% and 18%, respectively) are lower than those of other common cancers.[3] Therefore, much research has been conducted to improve our understanding regarding the multiple factors that affect the survival of lung cancer patients.

In general, timely care has been shown to positively affect patients' survival. Timeliness of care is defined as the system's capacity to provide care quickly after a need is recognized.[83] Delayed initiation of treatment could increase psychological distress and affect disease prognosis among cancer patients.[35,37] A large population-based study in the US reported that 36.7% of lung cancer patients experienced treatment delay (diagnosis-to-treatment interval of >35 days).[73] Age, race, stage at diagnosis, comorbidity, and type of hospital have also been associated with treatment delay.[43,44]

Despite the important effect of time-to-treatment on patients' outcomes, previous studies in lung cancer have been inconclusive. A study of non-small cell lung cancer (NSCLC) patients aged 66 years old and older showed an adverse effect of prolonged time-to-treatment on survival.[44] An adverse effect of extended time-to-treatment was also found in two other studies of early-stage NSCLC patients who had surgery.[45,73] On the other hand, several studies reported that longer time-to-treatment was associated with improved survival.[41,46,49] This association is often referred as the 'waiting time paradox' and has also been observed in other cancers, such as colorectal and

endometrial cancer.[84] A possible reason for this paradox is that patients with more severe conditions tend to receive treatment right away, but despite the immediate treatment, their severe condition still leads to poor outcomes. The inconsistent results of studies on time-to-treatment might also be related to the variation in the definition and cut-off point used as the recommendations on time-to-treatment of NSCLC also vary.[38-40] For instance, in the United States (US), a proposed recommendation of treatment initiation for NSCLC other than metastatic cancer is within 6 weeks of diagnosis, while the general recommendation in the United Kingdom is within 4 weeks after diagnosis.[38] In the Netherlands, however, the treatment is recommended to start within 35 calendar days of the patient's first visit to a pulmonologist.[85]

Since timeliness of care is modifiable, evidence pertaining to its effect on survival is of particular importance.[86] The objective of this study was to examine the effect of time-to-treatment on the overall survival of NSCLC patients. We utilized a national hospital-based dataset that provided a more representative sample of NSCLC patients in the US than the previous studies.

Methods

We analyzed the National Cancer Data Base (NCDB) for the period 2003–2011. The NCDB is a national hospital-based oncology dataset, collected from more than 1 500 Commission on Cancer accredited facilities. The database is jointly sponsored by the American College of Surgeons and the American Cancer Society and is estimated to represent nearly 70% of new cancer diagnoses in the US. [87,88] The NCDB records information about patient demographics, clinical characteristics, treatment, and outcomes. This study used de-identified data, and thus, was exempt from the Institutional Review Board review.

Study population

Patients aged 18 years and older who were diagnosed with NSCLC from 2003 to 2011 and underwent any surgery, chemotherapy or radiation at the reporting facilities as their first-course treatment were considered eligible for this study.

Outcome and predictors

The primary outcome of this study was 5-year overall survival (OS) time, defined as the time from the date of diagnosis to the date of death, or the last contact if the patient was still alive or lost to follow-up (the time was censored). The primary predictor was time-to-treatment, defined as the period between diagnosis and initiation of any first-course treatment. We categorized time-to-treatment based on the commonly recommended time-to-treatment and the proposed recommendation in the US (within the first 4 weeks and 6 weeks after diagnosis, respectively).[40] The categories of time-to-treatment are: (i) 0 day, (ii) 1 day to 4 weeks, (iii) 4.1–6.0 weeks, and (iv) > 6 weeks, with 1 day to 4 weeks as the reference group. We distinguished 0 day from the 1 day to 4 weeks on the assumption that patients who received treatment on the same day of diagnosis might harbor specific conditions different from other patients (e.g., have less severe symptoms and were thus eligible for prompt tumor removal procedure or require an emergent procedure). The covariates adjusted in the analysis were the age at diagnosis, sex, race, urban/rural status, distance to the reporting hospital, primary payer, facility type, stage at diagnosis, histology, treatment type, and Charlson-Deyo comorbidity score.[89] Detailed information about how variables in the NCDB are defined by the American College of Surgeons is provided elsewhere.[87]

Statistical analysis

Descriptive statistics were presented as proportions for the categorical variables, and medians with inter-quartile range (IQR) for the continuous variables. In the bivariate analysis, a chi-square test was used to study the association between each of the patient characteristics and time-to-treatment. The association between each predictor and OS time was examined using a Cox Proportional Hazards model.

Prior to the analysis, we examined the Proportional Hazards (PH) assumption to determine whether the hazards ratio (HR) for any pair of levels of predictors other than time-to-treatment was constant over time. Using a graphical approach and Schoenfeld's test, we identified non-proportionality of the HRs for several predictors, including time-to-treatment, suggesting that the hazard rates were not constant over time. We handled this non-proportionality of HRs differently for the time-to-treatment variable and other predictors. We considered the time-to-treatment variable as having an inherent time-dependent nature. The risk of death of the patients differed before and after receiving treatment. Prior to starting treatment, patients have a relatively similar risk to those who did not receive treatment. The risk changes after they start or completed treatment. To take into account this time-dependent risk, we applied the Counting Process method.[90] By this approach, each case was handled as two observations: one from the time of diagnosis to receiving treatment, and one from starting treatment to either death or loss to follow up. Other predictors that do not satisfy the PH assumption were handled through Stratified Cox regression.[90] We fitted the Counting Process and Stratified Cox regression in the final analyses.

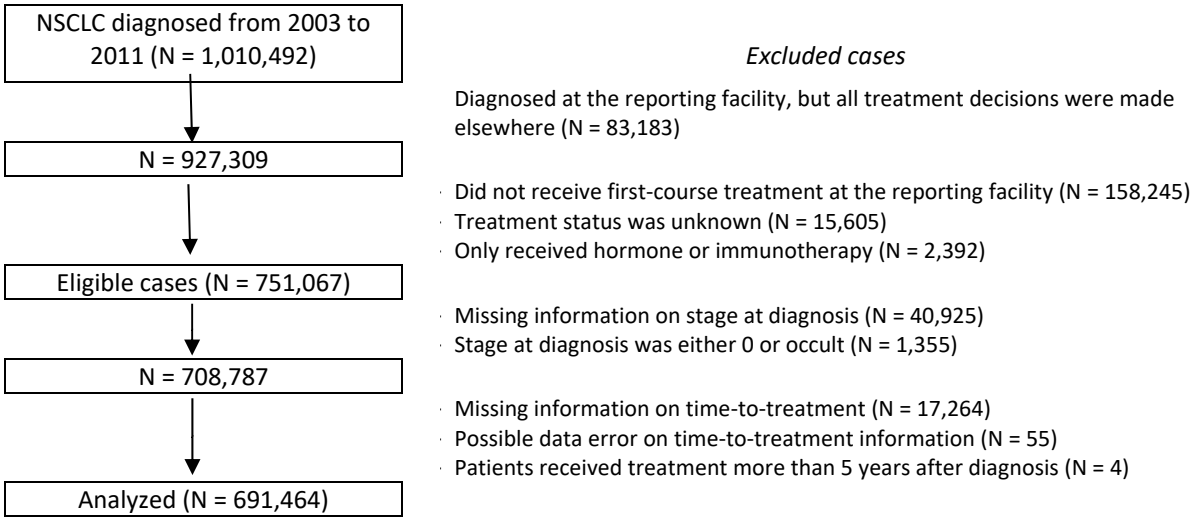
Multivariable analyses were performed separately for the different stage at diagnosis group, which were divided into early-stage (stage I and II), locally advanced (stage III), and metastatic disease (stage IV). We performed subset analyses for patients considered as having a relatively

good prognosis (early-stage patients who received surgery only). For this purpose, we excluded patients who died within the first month after diagnosis since they are likely to have more severe clinical conditions than the rest of the patients. The Kaplan-Meier estimator was used to produce survival estimates.[91] The significance level for the analysis was set at p-value < 0.05. All statistical analyses were performed using the statistical software package SAS, version 9.4 (SAS Institute Inc., Cary, NC).

Results

From 2003 to 2011, the NCDB recorded 1,010,492 patients diagnosed with NSCLC. We excluded 259,425 cases who were not eligible for our study due to, for example, not receiving treatment in the reporting facilities or having unknown treatment status. Out of 751,067 eligible cases, we excluded 59,603 (7.9%) largely due to missing information on stage at diagnosis and time-to-treatment (Figure. 5). In total, 691,464 patients were included in the analysis. There were no substantial differences between the excluded and analyzed cases, except for histology and comorbidity score. The cases included in the analysis had a higher proportion of adenocarcinoma (46.4%) and comorbidity scores of either 1 or 2 (39.3%) compared to the excluded cases (37.3% and 33.8%, respectively). The median follow-up period was 15 months (IQR = 30).

Figure 5. Selection of study population



1. Descriptive analysis of time-to-treatment and patients' characteristics

Overall, 42.6% of patients started treatment more than 4 weeks after diagnosis. The median time-to-treatment was different between patients with metastatic cancer (18 days, [IQR, 11–36]) and less advanced stages. The median for patients with early stage and locally advanced disease was 28 days (IQR, 2–51) and 27 days (IQR, 13–46), respectively.

Patients' demographic and clinical characteristics are presented in Table 5. Time-to-treatment was significantly associated with all patient demographic and clinical characteristics analyzed in this study (please see the note under Table 5). The proportion of patients receiving treatment within the first 4 weeks of diagnosis appears to be higher among those who were younger than 65 years, of high income, had private insurance, diagnosed with early-stage or had surgery. Patients with Medicare (mostly age ≥ 65 years) tended to start treatment more than 6 weeks after diagnosis. The median OS time was 54 months (IQR = 95) for early stage, 15 months (IQR = 29.2) for a locally advanced stage, and 6.4 months (IQR = 11.3) for patients with metastatic cancer.

Table 5. Patients' socio-demographic and clinical characteristics by time-to-treatment [a]

	0 days n (%)	1 day - 4 weeks n (%)	4.1-6 weeks n (%)	> 6 weeks n (%)	Total n (%)
Sex					
Male	49,251 (48.9)	164,691 (55.7)	62,251 (54.1)	94,263 (52.4)	370,456 (53.6)
Female	51,536 (51.1)	131,060 (44.3)	52,841 (45.9)	85,571 (47.6)	321,008 (46.4)
Age at Diagnosis					
<65 year	39,355 (39.1)	125,625 (42.5)	41,071 (35.7)	57,733 (32.1)	263,784 (38.2)
65-74 year	37,243 (37.0)	97,484 (33.0)	40,641 (35.3)	63,675 (35.4)	239,043 (34.6)
75+ year	24,189 (24.0)	72,642 (24.6)	33,380 (29.0)	58,426 (32.5)	188,637 (27.3)
Racial Group					
White	89,131 (88.4)	255,578 (86.4)	100,561 (87.4)	151,589 (84.3)	596,859 (86.3)
Black	8,591 (8.5)	30,661 (10.4)	11,000 (9.6)	22,354 (12.4)	72,606 (10.5)
Other	2,216 (2.2)	7,297 (2.5)	2,628 (2.3)	4,511 (2.5)	16,652 (2.4)
Unknown	849 (0.8)	2,215 (0.8)	903 (0.8)	1,380 (0.8)	5,347 (0.8)
Urban/Rural					
Metro	80,011 (79.4)	227,819 (77.0)	88,734 (77.1)	141,738 (78.8)	538,302 (77.9)
Urban	14,332 (14.2)	47,290 (16.0)	18,613 (16.2)	26,752 (14.9)	106,987 (15.5)
Rural	1,867 (1.9)	6,952 (2.4)	2,560 (2.2)	3,427 (1.9)	14,806 (2.1)
Unknown	4,577 (4.5)	13,690 (4.6)	5,185 (4.5)	7,917 (4.4)	31,369 (4.5)
Distance to Hospital					
<=10 miles	48,695 (48.3)	155,000 (52.4)	59,042 (51.3)	93,773 (52.2)	35,651 (51.6)
11-50 miles	38,043 (37.8)	105,671(35.7)	42,296 (36.8)	63,715 (35.4)	249,725 (36.1)
51-100 miles	7,268 (7.2)	16,630 (5.6)	6,591 (5.7)	10,820 (6.0)	41,309 (6.0)
>100 miles	3,947 (3.9)	9,109 (3.1)	3,817 (3.3)	6,455 (3.6)	23,328 (3.4)
Unknown	2,834 (2.8)	9,341 (3.2)	3,346 (2.9)	5,071 (2.8)	20,592 (2.9)
Primary Payer					
Not Insured	2,127 (2.1)	11,524 (3.9)	2,843 (2.5)	4,642 (2.6)	21,136 (3.1)
Private Insurance	34,327 (34.1)	96,985 (32.8)	34,205 (29.7)	45,406 (25.3)	210,923 (30.5)
Medicaid	4,318 (4.3)	17,905 (6.1)	5,717 (5.0)	10,657 (5.9)	38,597 (5.6)
Medicare	56,907 (56.5)	159,124 (53.8)	68,263 (59.3)	111,653 (62.1)	395,947 (57.3)
Other government insurance	1,025 (1.0)	3,539 (1.2)	1,464 (1.3)	2,871 (1.6)	8,899 (1.3)
Unknown	2,083 (2.1)	6,674 (2.3)	2,600 (2.3)	4,605 (2.6)	15,962 (2.3)
Facility Type					
CCP	8,828 (8.8)	34,131 (11.5)	12,951 (11.3)	18,899 (10.5)	74,809 (10.8)
CCCP	54,302 (53.9)	174,009 (58.8)	64,497 (56.0)	93,999 (52.3)	386,807 (55.9)
Academic/Research Program	37,357 (37.1)	87,141 (29.5)	37,510 (32.6)	66,760 (37.1)	228,768 (33.1)
Other	300 (0.3)	470 (0.2)	134 (0.1)	176 (0.1)	1,080 (0.2)
Stage at Diagnosis					
Stage I	58,140 (57.7)	52,336 (17.7)	34,514 (30.0)	69,743 (38.8)	214,733 (31.1)
Stage II	9,998 (9.9)	20,247 (6.9)	11,866 (10.3)	20,401 (11.3)	62,512 (9.0)
Stage III	15,580 (15.5)	73,597 (24.9)	32,801 (28.5)	47,672 (26.5)	169,650 (24.5)
Stage IV	17,069 (16.9)	149,571 (50.6)	35,911 (31.2)	42,018 (23.4)	244,569 (35.4)
Histology					
Adenocarcinoma	57,537 (57.1)	130,411 (44.1)	51,939 (45.1)	80,613 (44.8)	320,500 (46.4)
Large-cell	4,015 (4.0)	12,455 (4.2)	4,015 (3.5)	5,477 (3.1)	25,962 (3.8)
Squamous cell	22,773 (22.6)	76,202 (25.8)	34,268 (29.8)	55,784 (31.0)	189,027 (27.3)
Adenosquamous	2,259 (2.2)	4,099 (1.4)	1,872 (1.6)	2,980 (1.7)	11,210 (1.6)
NSCLC, NOS	8,794 (8.7)	63,364 (21.4)	19,875 (17.3)	29,740 (16.5)	121,773 (17.6)
Others	5,409 (5.4)	9,220 (3.1)	3,123 (2.7)	5,240 (2.9)	22,992 (3.3)

Table 5. (cont'd)

	0 days n (%)	1 day - 4 weeks n (%)	4.1-6 weeks n (%)	> 6 weeks n (%)	Total n (%)
Charlson/Deyo Comorbidity Score					
0	56,523 (56.1)	184,555 (62.4)	71,285 (61.9)	107,284 (59.7)	419,647 (60.7)
1	32,673 (32.4)	80,266 (27.1)	31,819 (27.7)	50,920 (28.3)	195,678 (28.3)
2	11,591 (11.5)	30,930 (10.5)	11,988 (10.4)	21,630 (12.0)	76,139 (11.0)
Treatment received					
Surgery only	62,359 (61.9)	45,206 (15.3)	28,223 (24.5)	52,532 (29.2)	188,320 (27.2)
Radiation only	4,556 (4.5)	64,785 (21.9)	17,861 (15.5)	36,697 (20.4)	123,899 (17.9)
Chemotherapy only	3,909 (3.9)	51,526 (17.4)	19,852 (17.3)	26,783 (14.9)	102,070 (14.8)
Chemoradiation	9,379 (9.3)	102,717 (34.7)	33,225 (28.9)	41,198 (22.9)	186,519 (27.0)
Surgery + chemo and/or radiation	19,728 (19.6)	28,389 (9.6)	15,104 (13.1)	21,502 (12.0)	84,723 (12.3)
Unknown/others	856 (0.9)	3,128 (1.1)	827 (0.7)	1,122 (0.6)	5,933 (0.9)

Abbreviations: CCP, Community Cancer Program; CCCP, Comprehensive Community Cancer Program; NSCLC, Non-Small Cell Lung Cancer; NOS, Not Otherwise Specified; IQR, Inter-quartile Range.

[a] The chi-square test for all comparisons resulted in a p-value < 0.001.

2. The effect of time-to-treatment on overall survival

The multivariable analyses showed different effects of time-to-treatment on overall survival between patients with an early and advanced stage of diseases.

2.1. Early-stage disease: The multivariable analysis (Table 6) showed a lower risk of death in patients who received treatment at the same day of diagnosis, compared to those who initiated treatment between 1 day and 4 weeks after diagnosis (adjusted HR [aHR] = 0.84 [95% CI, 0.82–0.85]). Similarly, lower risk of death was also associated with time-to-treatment longer than 4 weeks (aHR, 0.93 [95% CI, 0.91–0.95]) and longer than 6 weeks of diagnosis (aHR, 0.92 [95% CI, 0.91–0.94]) (Table 6). However, a subset analysis among patients who received surgery only, showed that surgery between 4 and 6 weeks was associated with a 6% increased risk of death (aHR, 1.06 [95% CI, 1.03–1.09]). A higher risk of death (17%) was detected among early-stage patients who received surgery more than 6 weeks after diagnosis (aHR, 1.17 [95% CI, 1.14–1.20]) (Table 7).

2.2. Locally-advanced stage: Compared to treatment initiated 1 day to 4 weeks after diagnosis, either shorter or longer time-to-treatment was associated with a lower risk of death ($aHR_{0\ day}$ 0.73 [95% CI, 0.71–0.74]; $aHR_{4.1\text{-}6.0\ weeks}$ 0.82 [95% CI, 0.80–0.83]; $aHR_{>6\ weeks}$ 0.71 [95% CI, 0.70–0.72]).

2.3. Metastatic cancer: Similar to findings in patients with locally advanced disease, we observed a lower risk of death among patients who received treatment at the same day of diagnosis or after 4 weeks ($aHR_{0\ day}$ 0.75 [95% CI, 0.73–0.76]; $aHR_{4.1\text{-}6.0\ weeks}$ 0.75 [95% CI, 0.73–0.76]; $aHR_{>6\ weeks}$ 0.58 [95% CI, 0.57–0.59]).

Table 6. Adjusted Hazard Ratios (aHR [95% CI]) for 5-year mortality associated with time-to-treatment*

Time-to-Treatment	Early stage (N = 277,245)	Locally advanced disease (N = 169,650)	Metastatic disease (N = 244,569)
0 day	0.84 (0.82–0.85)	0.73 (0.71–0.74)	0.75 (0.74–0.76)
1 day to 4 weeks	*Ref*.	*Ref*.	*Ref*.
4.1-6.0 weeks	0.93 (0.91–0.95)	0.82 (0.80–0.83)	0.75 (0.74–0.76)
>6 weeks	0.92 (0.91–0.94)	0.71 (0.70–0.72)	0.58 (0.57–0.59)

Abbreviations: CI, Confidence Interval.
*Model was adjusted for age, sex, race, urban/rural, distance to hospital, facility type, primary payer, Charlson/Deyo comorbidity score, histologic type, and treatment modalities.

Table 7. Adjusted Hazard Ratios (aHR [95% CI]) for 5-year mortality, associated with time-to-treatment in early-stage patients who received surgery only*

	aHR [95% CI]
0 day	0.91 (0.89-0.93)
1 day to 4 weeks	Ref.
4.1-6.0 weeks	1.06 (1.03-1.09)
>6 weeks	1.17 (1.14-1.20)

*Model was adjusted for age, sex, race, urban/rural, distance to hospital, facility type, primary payer, Charlson/Deyo comorbidity score, and histologic type.

Excluded patients who died within 1 month after diagnosis.

Discussion

The Institute of Medicine has established timeliness of care as one of the dimensions of healthcare quality.[92,93] However, delay in receiving treatment remains a problem in a fairly significant proportion of cancer patients.[43,44] Although the present study was not able to prove the hypothesis of adverse effects of extended time-to-treatment on the OS of overall NSCLC patients, we showed that extended time-to-treatment is an independent predictor of mortality among early-stage patients who receive surgery.

Our findings indicate a complex association between time-to-treatment and survival. Contrary to our hypothesis, time-to-treatment longer than four weeks was significantly associated with a lower risk of death among patients of all cancer stage. In early-stage patients, however, the difference in risk of death by time-to-treatment is subtle compared to patients with locally advanced or metastatic cancers. However, a subset analysis among early-stage patients who received surgery alone, who were considered as having a better prognosis than the rest of the groups, showed an association of the opposite direction. Compared to treatment initiated within 1 day to 4 weeks, a longer time-to-treatment among these patients was associated with a decreased 5-year survival. Although the increased risk was modest among those who received treatment within 1 day to 4 weeks, the risk was amplified among patients who were treated more than 6 weeks after diagnosis, providing strong evidence of the effect of time-to-treatment.

Our findings were generally inconsistent with previous study findings. One study among US veterans showed an increased risk of death associated with greater timely care (aHR, 1.6 [95% CI, 1.3-1.9]), independent of type of treatment.[94] Another study among Medicare beneficiaries reported varying results, of which an improved OS was associated with a diagnosis-to-treatment

interval of ≤ 35 days in localized disease (aHR, 0.86 [95% CI, 0.80–0.91]) and among patients with distant disease who survived ≥ 1 year (aHR, 0.86 [95% CI, 0.74–0.99]), but was associated with a decreased OS for patients who survived < 1 year.[44] Nevertheless, our findings in early-stage patients who received surgery were consistent with results reported in two previous studies. A study using NCDB data among patients with stage I NSCLC, but with a different analytical approach, found that each week of delay of surgery increased the hazard of death by 0.4% (aHR, 1.004 [95% CI, 1.002–1.007]).[45] Another study on delay in surgery among patients diagnosed at a community center suggested a similar association but was not statistically significant (aHR, 1.04 [95% CI, 1.00–1.09]).[73]

Similar to our overall analysis, counter-intuitive results that extended time-to-treatment are associated with longer survival have been reported by multiple studies in the US and other countries, not limited to lung cancer.[47,84] This phenomenon is commonly referred as the 'waiting time paradox.'[95] The premise behind the waiting time paradox is that the association between time-to-treatment and OS is likely affected by the disease severity at presentation. Patients who were treated early might have severe symptoms, and inherently have a worse prognosis compared to patients treated with longer time-to-treatment. Another possible reason for the finding is that among patients with shorter time-to-treatment, the treatment plan might involve a less comprehensive evaluation that puts patients at risk for a worse prognosis.

Our stratification analysis by disease stage failed to distinguish patients' severity level that affects both time-to-treatment and survival, suggesting a mix of patients' risk within the same stage. Among early-stage patients who received surgery, however, the patient population was likely more homogenous with respect to their clinical conditions. Therefore, the subset analysis among this population was able to show the adverse effect of extended time-to-treatment.

The adverse effect of extended time-to-treatment on OS can be explained by disease progression. A prolonged waiting period might cause some patients to become ineligible for curative-intent therapy, thus reducing their chance of cure. This premise has been shown in multiple studies of radiotherapy.[35,96] A prospective study of 29 lung cancer patients waiting for radical radiotherapy showed that 21% of potentially curable patients became incurable, and the cross-sectional tumor size increased more than three times over the waiting period.[35]

The strengths of the present study are mainly related to the wide coverage of the database and the large sample size. The sample size allowed us to perform stratification analyses, without being underpowered. Furthermore, the database enabled us to account for various potential confounders. In a study of colorectal cancer, control for more comprehensive confounders led to a different interpretation of the effect of time-to-treatment on OS.[47] Our analysis included patients with multiple primary cancers, who are commonly excluded from analyses using cancer registry data.[97] This inclusion might lead to a higher risk of death in our study cohort. However, a subset analysis of patients with single primary cancer yielded similar results (*data not shown*), as was also found in other studies.[97,98]

Our results were also subject to several limitations. The CoC-approved hospitals included in the NCDB are typically larger, located in urban locations, and provide a higher degree of oncology-related specialization, compared to non-CoC-approved hospitals.[79] Thus, the data might not represent all hospitals in the US. The influence of unmeasured confounders, particularly those that may affect the decision to either expedite or postpone treatment (e.g., tumor aggressiveness, performance status), was likely the reason for the counter-intuitive findings among locally advanced and metastatic NSCLC.

Our results did not lead us to conclude that longer time-to-treatment leads to better survival. Instead, we believe that longer time-to-treatment does not seem to have detrimental effects for patients, especially those with a more advanced disease stage. Therefore, ensuring comprehensive examination and preparation will benefit patients more, rather than rushing the treatment. However, in patients with operable cancer, it is critically important not to delay treatment. Future research should focus on identifying patients' clinical characteristics that could significantly predict the tolerable time-to-treatment to achieve better outcomes, which would be beneficial for patients and provide a solid basis for improving clinical standards. Such research would also be particularly relevant given the fact that guidelines for timing of treatment initiation of NSCLC vary.

Conclusions

This study supports the idea that allocating time for optimal pre-treatment assessments, although leading to a longer time-to-treatment interval, is likely to benefit patients' survival. However, it seems prudent for treatment to start within 4 weeks of diagnosis in patients with resectable early-stage lung cancer. This finding is relevant to the expected increased identification of early-stage patients following improvements in screening programs and recent recommendations from the US Preventive Services Task Force. Despite the multiple factors that lead to treatment delay, every attempt must be made to decrease treatment delays caused by system-based factors.

CHAPTER III: ADHERENCE TO TREATMENT GUIDELINES IN PATIENTS WITH SMALL CELL LUNG CANCER - PREDICTORS AND IMPACT ON PATIENTS' SURVIVAL

Abstract

Background: Small cell lung cancer (SCLC) is a lethal disease with just a 6.5% of 5-year survival rate. Treatment for SCLC has not changed much over the past three recent decades, but data on the level of adherence to treatment guidelines and its effect on survival are lacking. **Methods**: We conducted secondary data analyses of patients newly diagnosed with SCLC in 1998—2012 who were recorded in the National Cancer Data Base. Adherence was assessed based on the National Comprehensive Cancer Network Guidelines. Multilevel logistic regressions were used to analyze predictors of non-adherence to treatment guidelines. Cox Frailty regressions were used to examine the effect of guidelines adherence on patients' 5-year overall survival. Data were analyzed separately for limited stage (LS) and extensive stage (ES) SCLCs. **Results**: Our study found that patients who did not receive guideline-recommended treatment were more likely to be older, black, have a high comorbidity burden, and be uninsured or beneficiaries of Medicare/Medicaid. Patients diagnosed/treated in cancer centers in the South and West regions were more likely not to receive guideline-recommended treatment, compared to patients in the Northeast region. After controlling for other covariates, receiving inadequate treatment (not adhere to the guidelines) was associated with higher risk of death in patients with LS-SCLC (aHR, 1.93 [95% CI, 1.88–1.98]) and ES-SCLC (aHR, 2.02 [95% CI, 1.97–2.07]). **Conclusion**: This study provides evidence of the strong survival benefit of receiving guidelines-recommended treatment. Further research is needed to identify patient and provider-level factors that could preclude patients from receiving guidelines-recommended treatment.

Introduction

Small cell lung cancer (SCLC) is a very aggressive sub-type of lung cancer, with rapid growth and metastasis.[27] This disease represents about 13% of all lung cancer cases in the United States (US), which translates into nearly 30,000 patients diagnosed with SCLC every year.[2,99] The overall 5-year survival rate of SCLC patients is approximately 6.5%.[3] More than half of the patients are diagnosed at an extensive stage with extensive metastases, of whom less than 5% survive two years after diagnosis.[99]

Treatment for SCLC has not changed much in the last 30 years. Chemotherapy has been the cornerstone of treatment for all stages, while a combination of chemotherapy and radiotherapy is recommended for patients with a limited stage of the disease.[27] Recent data suggest that patients with limited stage SCLC might benefit from surgery.[26] In general, initial responses to treatment of SCLC are extremely high.[27] Although the majority of patients experience relapse within two years, treatment with chemotherapy and radiotherapy leads to rapid relief of symptoms and improves survival. [27,100]

Despite the known benefits of the treatments, some SCLC patients might not receive guideline-recommended treatments.[101] Most patients with SCLC have a history of heavy smoking, which leads to the development of other comorbid conditions that often preclude SCLC patients from receiving stage-appropriate treatment.[28] Considering the low survival rate and that without treatment patients have a 2.5-times greater risk of death,[101] prompt treatment decisions are essential to facilitate optimal outcomes. For many patients and their families, making a decision about treatment that has uncertain outcomes along with potential side effects is very difficult, especially when combined with the life-changing news of a cancer diagnosis with a poor prognosis. Some patients may choose not to undergo aggressive treatment of any kind, regardless of whether or not they are recommended by experts in the field following consensus guidelines.

A study among elderly patients with SCLC indicated low, but increasing, use of chemotherapy.[28] Using a National Cancer Data Base (NCDB), Gaspar *et al*. (2012) reported the treatment pattern in SCLC patients diagnosed between 1992 and 2007.[74] However, to what extent the treatment has been provided with respect to existing guidelines for SCLC treatment and predictors of guidelines non-adherence remain unclear. This information is important to help identify barriers to receiving guideline-recommended treatment to improve quality of care. To address this gap, we analyzed more recent NCDB data to analyze the trend and factors associated with adherence to SCLC clinical guidelines and examined the impact of guidelines adherence on patients' survival.

Methods

We analyzed a retrospective longitudinal data from the National Cancer Data Base (NCDB), a hospital-based oncology dataset collected from more than 1,500 Commission on Cancer accredited facilities nationwide. The database is jointly sponsored by the American College of Surgeons and the American Cancer Society. The NCDB represents nearly 70% of new cancer diagnoses in the US.[88] The data source for this study is a de-identified database, and thus, was exempt from the Institutional Review Board review.

Study population

The study population was composed of patients aged 18 years or older, newly diagnosed with primary SCLC between 1998 and 2012. Our analysis included only patients who received their first-course treatment at the reporting facility. We excluded cases with the following conditions from the analysis: without information on stage at diagnosis, incomplete information about treatment status, did not receive treatment due to either contraindication or died prior to

planned treatment. Patients diagnosed with stage I, II or III were classified as a limited stage, and patients with metastatic cancer or stage IV were classified as an extensive stage. Our data covered a follow-up period of patient's status until 2012, with a median follow-up time of 8.5 months (IQR = 13.2).

The primary outcome of interest

In this study, we utilized the National Comprehensive Cancer Network (NCCN) Guidelines to define 'adherence' and 'adequate' treatment.(National Comprehensive Cancer Network, 2016) For the limited stage of disease (LS-SCLC), treatment was considered as 'adequate' or 'adhered to the guidelines,' if the patients received either chemo-radiation or surgery plus chemotherapy; irrespective of the treatment sequence. Treatment of patients with extensive stage disease (ES-SCLC) was deemed 'adequate' or 'adhered to the guidelines,' if they received multiple chemotherapy agents. To evaluate the impact of adherence to treatment guidelines, we analyzed patients' 5-year overall survival as the outcome, which was defined as the time from the date of diagnosis to the date of death (from all causes) or the date of the last contact of record in the dataset.

We included data from the period of 1998–2012 to analyze the trend of treatment provision, but we only included cases diagnosed from 2003 onwards to analyze factors associated with non-adherence and its impact on patients' survival. This approach was taken because data on comorbidity, which is an important factor affecting treatment planning and survival, were not collected prior to 2003. For survival analysis, we did not include cases diagnosed in 2012 as these cases do not have follow-up information.

Statistical analysis

Descriptive statistics are presented as proportions for the categorical variables, and medians with inter-quartile ranges for the continuous variables. In the bivariate analysis, a chi-square test or Wilcoxon test was used, as appropriate, to examine the association between each of the predictors and adherence to treatment guidelines.

In the multivariable analysis, we applied multilevel regressions with hospital as the random effect to adjust for the clustering effect or potential dependence among patients diagnosed/treated from the same hospital. The multivariable analyses were performed separately for LS-SCLC and ES-SCLC. We included in the multivariable model factors that showed significant association with the outcome in the univariate analysis. Factors that were included in the analyses were the age at diagnosis, sex, race, urban/rural status, distance to hospital, primary payer, facility type, facility region, Charlson-Deyo comorbidity score, treatment type, and year of diagnosis.

To examine factors associated with adherence to treatment guidelines, we applied multilevel binary logistic regressions, by excluding patients who did not receive treatment at the reporting facilities. We tested for interaction terms between age and comorbidity, but the results were not statistically significant ($p = 0.624$ in LS-SCLC; $p = 0.073$ in ES-SCLC), and thus no interaction term included in the model.

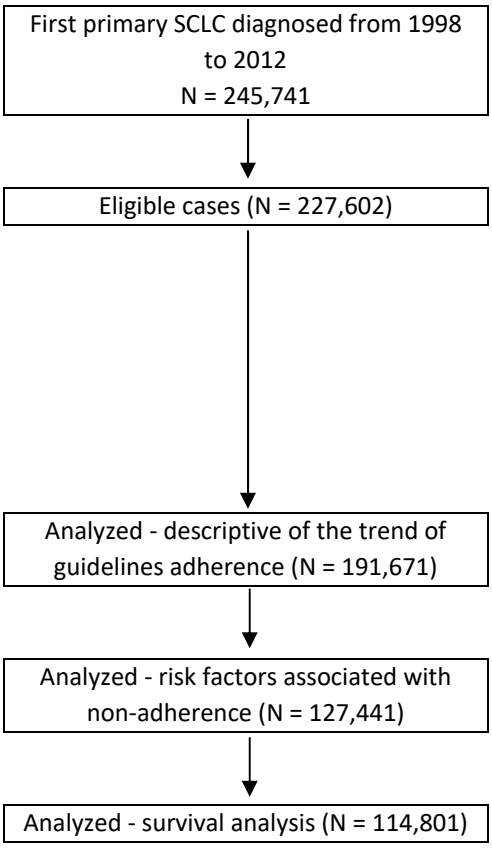
The median overall survival (OS) time was estimated using the Kaplan-Meier estimator. The primary predictor for the survival analysis was guideline adherence, adjusted for patients' demographic and clinical factors mentioned above. Prior to the analysis, we examined the Proportional Hazards (PH) assumption using a graphical approach and Schoenfeld's test to determine whether the hazards ratio (HR) for each predictor was constant over time. The graphical approach suggested no violation to the PH assumption. We applied Cox Frailty regression (a multilevel form of survival analysis) to examine the effect of guidelines adherence

on patients' survival. In the survival analysis, treatment adequacy was categorized into three categories: (a) adequate treatment, (b) inadequate treatment or (c) no treatment at all. The purpose of the categorization was to examine in more detail the effect of guidelines adherence on patients' survival. The significance level for the analyses was set a priori at p-value < 0.05. All statistical analyses were performed using the statistical software package SAS, version 9.4 (SAS Institute Inc., Cary, NC).

Results

We identified 245,741 patients diagnosed with SCLC since 1998 to 2012. Out of these cases, we excluded those who were diagnosed at the reporting facility but for whom all treatments or decisions not to treat were made elsewhere (N = 18,139). Of the 227,602 eligible cases, we excluded cases with either missing information on stage at diagnosis or occult stage (N = 20,227), cases who did not receive treatment due to contraindications or died before treatment could be initiated (N = 5,373), and cases with incomplete information on treatment in which we could not determine their adherence status (N = 10,331).

Figure 6. Selection of the study population



A total of 191,671 patients were included in the descriptive analysis of the characteristics of SCLC patients by treatment adequacy (Table 8). Our study population was predominantly white (90.1%) and resided in either metro or urban areas (92.9%), with a median age at diagnosis of 66 years (IQR = 14). Nearly 62% of the patients used Medicare, Medicaid or other government insurance. More than half of the patients were diagnosed with an extensive stage of cancer (59.9%). Nearly 43% of the patients had at least one comorbidity listed in the Charlson-Deyo Comorbidity Score.

Table 8. Characteristics of SCLC patients by treatment received

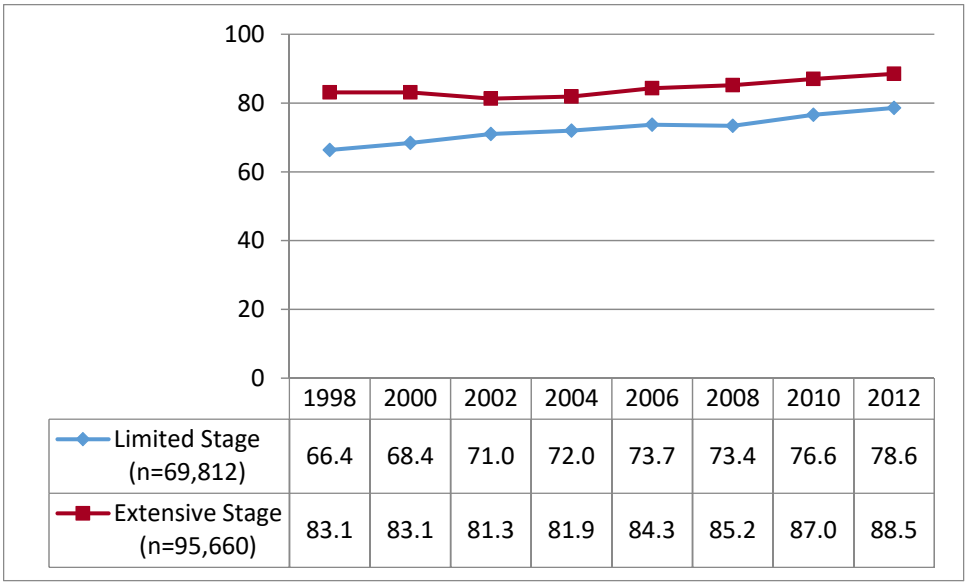
Patients' characteristics	Adequate (N = 130,849)		Inadequate (N = 34,623)		No treatment (N = 26,199)		Total (N = 191,671)	
	n	%	n	%	n	%	n	%
Sex								
Male	65,456	50.0	16,992	49.1	12,801	48.9	95,249	49.7
Female	65,393	50.0	17,631	50.9	13,398	51.1	96,422	50.3
Age group								
< 65	65,114	49.8	11,664	33.7	6,984	26.7	83,762	43.7
65–74	45,357	34.7	12,156	35.1	8,780	33.5	66,293	34.6
75+	20,378	15.6	10,803	31.2	10,435	39.8	41,616	21.7
Median, years (IQR)	65 (± 14)		69 (± 14)		72 (± 15)		66 (± 14)	
Race								
White	118,302	90.4	30,710	88.7	23,600	90.1	172,612	90.1
Black	9,717	7.4	2,987	8.6	1,936	7.4	14,640	7.6
Others	1,984	1.5	628	1.8	413	1.6	3,025	1.6
Missing	846	0.7	298	0.9	250	1.0	1,394	0.7
Urban/rural								
Metro	98,072	75.0	26,286	75.9	20,180	77.0	144,538	75.4
Urban	23,579	18.0	5,869	17.0	4,172	15.9	33,620	17.5
Rural	3,383	2.6	818	2.4	586	2.2	4,787	2.5
Missing	5,815	4.4	1,650	4.8	1,261	4.8	8,726	4.6
Insurance								
Not Insured	5,882	4.5	1,373	4.0	1,115	4.3	8,370	4.4
Private Insurance	46,410	35.5	8,479	24.5	5,095	19.5	59,984	31.3
Medicaid	9,948	7.6	2,111	6.1	1,444	5.5	13,503	7.0
Medicare	63,671	48.7	20,968	60.6	17,482	66.7	102,121	53.3
Other Government Insurance	1,702	1.3	441	1.3	221	0.8	2,364	1.2
Missing	3,236	2.5	1,251	3.6	842	3.2	5,329	2.8
Facility type								
Academic/Research Program	33,947	25.9	9,206	26.6	6,389	24.4	49,542	25.9
Comprehensive CCP	77,820	59.5	20,183	58.3	15,588	59.5	113,591	59.3
Community Cancer Program	18,870	14.4	5,192	15.0	4,191	16.0	28,253	14.7
Missing	212	0.2	42	0.1	31	0.1	285	0.2
Facility region								
Northeast	24,097	18.4	6,506	18.8	4,440	17.0	35,043	18.3
Midwest	40,524	31.0	9,175	26.5	6,725	25.7	56,424	29.4
South	51,189	39.1	14,548	42.0	11,240	42.9	76,977	40.2
West	15,039	11.5	4,394	12.7	3,794	14.5	23,227	12.1
Stage of SCLC								
Limited stage	50,439	38.6	19,373	56.0	7,068	27.0	76,880	40.1
Extensive stage	80,410	61.5	15,250	44.1	19,131	73.0	114,791	59.9
Comorbidity score**								
0/none	52,638	59.8	11,592	54.3	8,969	49.5	73,199	57.4
1	25,125	28.6	6,370	29.8	5,655	31.2	37,177	29.2
2+	10,194	11.6	3,391	15.9	3,480	19.2	17,065	13.4

**CCP: Community Cancer Program; **Excluded cases diagnosed prior to 2003*

Trend of adherence to the treatment guideline

A total of 13.6% of SCLC patients in our study population did not receive treatment in the reporting facilities. Among those who underwent treatment, 79% received treatment that adhered to the guidelines. The proportion of adherence to treatment guidelines increased significantly from 1998 to 2012. The increase, however, was more noticeable in LS-SCLC (66.4% to 78.6%; $p < 0.001$) compared to ES-SCLC patients (83.1% to 88.5%; $p<0.001$) (Figure 7). The majority of LS-SCLC patients who received inadequate treatment (non-adhere to the guidelines) were treated mainly with chemotherapy alone (75.6%). Among ES-SCLC patients with inadequate treatment, 65.1% did not receive chemotherapy (mostly received radiation alone) and about 26% received single-agent chemotherapy.

Figure 7. Trend of adherence to treatment guidelines in SCLC patients, 1998-2012*



	1998	2000	2002	2004	2006	2008	2010	2012
Limited Stage (n=69,812)	66.4	68.4	71.0	72.0	73.7	73.4	76.6	78.6
Extensive Stage (n=95,660)	83.1	83.1	81.3	81.9	84.3	85.2	87.0	88.5

**excluding patients who did not receive treatment at the reporting facilities*

Factors associated with adherence to treatment guidelines

Age, insurance, comorbidity score, facility type, facility region, and year of diagnosis were independent predictors of guidelines non-adherence in both LS-SCLC and ES-SCLC (Table 9). After adjusting for other covariates, patients aged 65–74 years had a nearly 50% higher risk to receiving inadequate treatment compared to patients diagnosed younger than 65 years old ($aOR_{LS\text{-}SCLC}$ = 1.40, 95% CI = 1.31–1.50; $aOR_{ES\text{-}SCLC}$ = 1.37, 95% CI = 1.27–1.46). The risk for receiving inadequate treatment was even higher among patients diagnosed at 75 years or older ($aOR_{LS\text{-}SCLC}$ = 3.24, 95% CI = 3.00–3.49; $aOR_{ES\text{-}SCLC}$ = 2.51, 95% CI = 2.33–2.71).

Another strong predictor of guidelines non-adherence was comorbidity. Compared to having a comorbidity score of zero, a high comorbidity burden (score of 2 or higher) were associated with nearly 1.5-times greater risk of receiving treatment that do not adhere to the guidelines in patients with LS-SCLC (aOR, 1.84 [95% CI, 1.71–1.97]) and ES-SCLC (aOR, 1.30 [95% CI, 1.22–1.40]), respectively. In both LS-SCLC and ES-SCLC, non-insured patients or those who were covered by Medicare/Medicaid were more likely to receive inadequate treatment, compared to patients with private insurance.

We identified regional differences in guidelines non-adherence. LS-SCLC patients who were diagnosed/treated in cancer centers in the South and West regions had about 22-25% higher odds to receive inadequate treatment (aOR_{South} = 1.25 [95% CI, 1.12–1.39]; aOR_{West} = 1.22 [95% CI, 1.07–1.97]), compared to the Northeast region. Among ES-SCLC patients, however, we did not find significant increased risk of guidelines non-adherence associated with South and West region. On the contrary, in both stage groups, being diagnosed/treated in facilities in the Midwest was associated with a reduced risk of guidelines non-adherence ($aOR_{LS\text{-}SCLC}$ = 0.83 [95% CI, 0.70–0.88]; $aOR_{ES\text{-}SCLC}$ = 0.73[95% CI, 0.65–0.82]), compared to the Northeast region. Our analysis also showed

that patients diagnosed in more recent years, with either ES-SCLC or LS-SCLC, were less likely to receive inadequate treatment, compared to those who were diagnosed earlier.

Table 9. Adjusted Odds Ratios (aOR [95% CI]) for receiving treatment that did not adhere to the guidelines among SCLC patients who received treatment at the reporting facilities*

	LS-SCLC (N = 44,490)		ES-SCLC (N = 64,847)	
	Crude OR (95% CI)	**Adjusted OR (95% CI)**	**Crude OR (95% CI)**	**Adjusted OR (95% CI)***
Sex		**		**
Female	1.00	–	1.00	–
Male	0.98 (0.94–1.02)	–	1.04 (0.99–1.08)	–
Age at Diagnosis, year				
<65	1.00	1.00	1.00	1.00
65–74	1.57 (1.49–1.65)	1.40 (1.31–1.50)	1.35 (1.28–1.42)	1.37 (1.27–1.46)
75+	3.64 (3.43–3.85)	3.24 (3.00–3.49)	2.52 (2.38–2.67)	2.51 (2.33–2.71)
Race		**		
White	1.00	–	1.00	1.00
Black	1.03 (0.95–1.12)	–	1.13 (1.04–1.23)	1.13 (1.04-1.23)
Other	1.08 (0.92–1.28)	–	1.13 (0.96–1.34)	1.08 (0.91-1.29)
Urban/Rural**		**		**
Metro	1.00	–	Ref.	–
Urban	1.05 (0.94–1.26)	–	0.92 (0.86–0.99)	–
Rural	1.09 (0.94–1.26)	–	1.04 (0.90–1.22)	–
Insurance				
Private Insurance	1.00	1.00	1.00	1.00
Medicaid	1.30 (1.18–1.43)	1.39 (1.27–1.52)	1.09 (0.99–1.20)	1.15 (1.05–1.26)
Medicare	2.12 (2.02–2.24)	1.35 (1.27–1.44)	1.61 (1.53–1.69)	1.09 (1.01–1.16)
Other government insurance	0.99 (0.82–1.22)	0.89 (0.74–1.08)	2.27 (1.91–2.69)	2.13 (1.79–2.54)
Not Insured	1.34 (1.19–1.52)	1.47 (1.31–1.65)	1.31 (1.17–1.46)	1.40 (1.26–1.56)
Distance to Hospital				**
<=10 miles	1.00	1.00	1.00	–
11-50 miles	0.96 (0.91-1.00)	1.01 (0.96-1.07)	0.91(0.87-0.96)	–
51-100 miles	1.33 (1.20-1.48)	1.44 (1.29-1.60)	0.92 (0.83-1.03)	–
>100 miles	1.25 (1.08-1.45)	1.41 (1.20-1.65)	0.99 (0.85-1.16)	–
Facility Type				
Academic/ Research Program	1.00	1.00	1.00	1.00
Community Cancer Program (CCP)	1.07 (0.95-1.19)	1.01 (0.90-1.13)	0.93 (0.83-1.05)	0.94 (0.83-1.06)
Comprehensive CCP	0.99 (0.90-1.09)	0.87 (0.79-0.96)	0.90 (0.81-0.99)	0.87 (0.78-0.97)

Table 9. (cont'd)

	LS-SCLC (N = 44,490)		ES-SCLC (N = 64,847)	
	Crude OR (95% CI)	**Adjusted OR (95% CI)**	**Crude OR (95% CI)**	**Adjusted OR (95% CI)***
Facility Region				
Northeast	1.00	1.00	1.00	1.00
Midwest	0.83 (0.74–0.93)	0.80 (0.71-0.89)	0.72 (0.64–0.81)	0.73 (0.65–0.82)
South	1.20 (1.08–1.32)	1.25 (1.12-1.39)	0.98 (0.87–1.09)	1.00 (0.90–1.12)
West	1.23 (1.08–1.40)	1.22 (1.07-1.40)	1.04 (0.91–1.19)	1.06 (0.93–1.22)
Charlson/Deyo Comorbidity Score				
0/none	1.00	1.00	1.00	1.00
1	1.42 (1.36–1.50)	1.38 (1.31-1.45)	1.02 (0.96–1.07)	1.00 (0.95–1.06)
2+	2.01 (1.88–2.15)	1.84 (1.71-1.97)	1.35 (1.26–1.44)	1.30 (1.22–1.40)
Year of Diagnosis				
2003–2005	1.00	1.00	1.00	1.00
2006–2008	0.89 (0.85–0.94)	0.86 (0.82-0.92)	0.81 (0.76–0.85)	0.80 (0.76–0.85)
2009+	0.78 (0.74–0.82)	0.74 (0.70-0.78)	0.66 (0.63–0.70)	0.66 (0.62–0.69)

** Cases diagnosed prior to 2003 were excluded from the analysis due to unavailability of comorbidity information, and excluding patients who did not receive treatment at the reporting facilities.*
*** The variable was not included in the final model for LS-SCLC.*

Impact of adherence to treatment guidelines on 5-year survival

Patients with either LS-SCLC or ES-SCLC who received adequate treatment had significantly better survival than those who received inadequate or no treatment at all (median survival time of 18 months vs. 8 months vs. 2 months in LS-SCLC, respectively; 8.4 months vs. 2.1 months vs. 0.9 months in ES-SCLC, respectively) (Table 10). Thirty-nine LS-SCLC patients who received adequate treatment survive at least 2-year, substantially higher than 16.8% in the group receiving inadequate treatment. About 19% of the ES-SCLC patients who received adequate treatment survived up to two years, as opposed to 6.6% in patients who received inadequate treatment (Table 11). Unadjusted survival curves by treatment adequacy are presented in *Appendix B*.

Table 10. Median survival time (95% CI) of SCLC patients

	Median survival time (95% CI), in months			
	Limited stage	p-value*	**Extensive stage**	p-value*
Adequate treatment	18.3 (18.0–18.5)	< 0.001	8.4 (8.3–8.5)	< 0.001
Inadequate treatment	8.7 (8.5–9.7)		2.1 (2.0–2.2)	
No treatment	2.2 (2.1–2.4)		0.9 (0.9–0.9)	

**Log-rank test*

Table 11. Unadjusted survival probabilities (95% CI) of SCLC patients

	Limited stage	**Extensive stage**
	2-year survival	
Adequate treatment	0.392 (0.386–0.398)	0.080 (0.078–0.083)
Inadequate treatment	0.168 (0.161–0.176)	0.034 (0.031–0.038)
No treatment	0.082 (0.073–0.090)	0.021 (0.018–0.024)
	The 5-year survival	
Adequate treatment	0.187 (0.182–0.192)	0.022 (0.021–0.024)
Inadequate treatment	0.066 (0.031–0.071)	N/A
No treatment	N/A	0.007 (0.006–0.009)

N/A: no cases survived, or the number was too small to report

After controlling for other covariates, receipt of inadequate treatment doubled the risk of death in both LS-SCLC (aHR, 1.93 [95% CI, 1.88–1.98]) and ES-SCLC (aHR, 2.02 [95% CI, 1.97–2.07]) patients. Patients who did not receive treatment at all had more than three times higher risk of death ($aHR_{LS\text{-}SCLC}$ = 3.65 [95% CI, 3.52–3.79]; $aHR_{ES\text{-}SCLC}$ = 3.22 [95% CI, 3.15–3.30]) (Table 12).

Table 12. Adjusted Hazard Ratios (aHR [95% CI]) for 5-year mortality in SCLC

	LS-SCLC (N = 41,535)	ES-SCLC (N = 64,499)
Treatment received		
Adequate	1.00	1.00
Inadequate	1.93 (1.88–1.98)	2.02 (1.97–2.07)
No treatment	3.65 (3.52–3.79)	3.22 (3.15–3.30)
Sex		
Female	1.00	1.00
Male	1.18 (1.15–1.20)	1.17 (1.15–1.19)
Age at Diagnosis, year		
< 65	1.00	1.00
65–74	1.13 (1.09–1.17)	1.10 (1.07–1.13)
75+	1.51 (1.46–1.57)	1.41 (1.37–1.45)
Race		
White	1.00	1.00
Black	0.96 (0.92–0.99)	0.93 (0.91–0.96)
Other	0.88 (0.81–0.96)	0.79 (0.74–0.84)
Urban/Rural		
Metro	1.00	1.00
Urban	1.00 (0.97–1.03)	1.01 (0.99–1.03)
Rural	1.03 (0.96–1.10)	1.04 (0.99–1.09)
Primary Payer		
Private Insurance	1.00	1.00
Medicaid	1.21 (1.16–1.27)	1.14 (1.11–1.18)
Medicare	1.16 (1.13–1.20)	1.13 (1.10–1.16)
Other government insurance	1.17 (1.02–1.22)	1.13 (1.05–1.21)
Not Insured	1.18 (1.11–1.25)	1.18 (1.14–1.23)
Facility Region*		
Northeast	1.00	1.00
Midwest	1.03 (0.99–1.07)	1.09 (1.06–1.11)
South	1.01 (0.98–1.04)	1.02 (0.99–1.04)
West	0.99 (0.95–1.04)	1.04 (1.01–1.08)
Charlson/Deyo Comorbidity Score		
0/none	1.00	1.00
1	1.17 (1.14–1.20)	1.18 (1.16–1.20)
2+	1.45 (1.40–1.50)	1.43 (1.38–1.47)
Year of Diagnosis		
2003–2005	1.00	1.00
2006–2008	0.97 (0.94–0.99)	0.98 (0.96–1.00)
2009+	0.92 (0.89–0.94)	0.97 (0.95–0.99)

Discussion

As emphasized by the Institute of Medicine (IOM), clinical practice guidelines are essential for translating evidence to guide the complexities of cancer patients' care and improve health care quality and outcomes.[51] Using a large hospital-based cancer registry, this study described the adherence to stage-specific guidelines in the treatment of SCLC patients. Our study showed that 2 out of 10 SCLC patients did not receive guideline-recommended treatment. This is in addition to the nearly 14% of patients who did not receive any treatment. To put our findings into perspective, the adherence level found in our study was substantially lower than the level reported in non-small cell lung cancer (NSCLC) patients treated at academic institutions affiliated with a National Cancer Institute-designated cancer centers, which showed more than 90% adherence, even in stage IV disease.[75] In our study population, improved guideline adherence over the last 15 years was evident in all stages of SCLC but was least pronounced in ES-SCLC.

In this study, we were unable to determine whether guideline non-adherence was largely attributed to system-based factors, patients' clinical conditions, or rather represents patients' personal choice. Palliative care might partly explain non-receipt of chemotherapy in ES-SCLC patients as nearly one-third (29.1%) of these patients were recorded as receiving palliative care. In both LS-SCLC and ES-SCLC, the risk of non-adherence was higher in older patients, uninsured or Medicare/Medicaid beneficiaries, and patients with higher comorbidity scores. These factors have also been reported as determinants of guideline non-adherence in NSCLC and other cancers.[75,76] Guideline adherence in care for LS-SCLC patients also varied by the geographic regions of the facilities, with those in the Northeast having a better adherence than those in the South and the West.

Age was a strong predictor of non-adherence in our study population, as has been reported in studies of multiple cancers.[54,76] A higher toxicity rate and side effects following treatment in older patients have been suggested as key reasons for under-utilization of standard therapy in this group.[102,103] Elderly patients also tend to have more comorbidities, which are associated with higher toxicities in treatment.[102,104] Thus, there are indications of preference in the treatment of the elderly population, as oncologists might recommend less aggressive treatment simply due to the advanced age of the patients. An online survey with 200 oncologists indicated that they are less likely to choose intensive cancer therapy for older patients, even if the patient is highly functional and has a low comorbidity score.[105] In that study, the oncologists were randomly assigned one of two surveys with vignettes that were identical except for patient age (< 65 years or > 70 years). For one of the vignettes describing a case of stage IIA breast cancer patients with ECOG score of 0 (fully active, able to carry on all pre-disease performance without restriction), 93% of the oncologists recommended intensive adjuvant treatment for a patient aged 63, but only 66% would recommend it if the patient was 75-years-old. Another study, which analyzed SEER-Medicare data, reported the underutilization of chemotherapy in older patients, independent of their performance status.[28]

More recent evidence challenges the practice of recommending less aggressive treatment to older patients solely based on age.[102] Despite having a higher rate of toxicity, studies have shown similar outcomes of standard therapy in the elderly population in comparison to younger patients.[106,107] Furthermore, a report from another study evaluating performance status in 503 lung cancer patients showed no correlation between age and poor performance status.[108] However, caution should be taken when evaluating treatment outcomes in the elderly patients, especially when comparing it with the younger patients; there is a potential selection bias because the elderly who receive standard therapy are likely in far better health condition than those who

do not. Thus, the analysis will tend to result in overestimating the benefit among the elderly. Nevertheless, the fact that a higher number of older patients received inadequate treatment, while the disease is predominantly in the elderly, calls for more efforts to be directed toward providing evidence-based care for this population, as recommended by the IOM.[50] Research to provide predictive assessments to help physicians in determining patients' fitness for intensive therapies in this population is essential.

One of the interesting findings from our study was the indication of regional differences in guideline adherence, independent of other risk factors. This finding was statistically significant only in LS-SCLC patients, which required multimodality therapies. Patients who were treated in the South and the West regions were more likely to receive inadequate treatment, compared to the Northeast region. An opposite finding was evident among patients treated in the Midwest region. Our findings might indicate potential disparities in access to quality cancer care, or represent differences in other underlying factors, or both. Population-wise, the South region comprises the largest proportion of residents with less than a high school education and the lowest quartile of income level. Additionally, variations persist in travel time between primary physician and referral cancer care, as demonstrated by Onega et al.[109] Compared to the Northeast region, the South has the longest median travel times to the nearest NCI cancer center or academic-based care, although the difference was not substantial for travel time to reach any specialized cancer care. For instance, the median travel time to the nearest NCI cancer center for a population in the South was 164 min (IQR, 70–272), compared to only 36 min (IQR, 16–75) for the population in the Northeast. Likewise, the population in the West experience longer travel times than the Northeast's population. In terms of healthcare supply; the Northeast region had the highest per capita oncologists for hospital referral regions (3.2 per 100,000 residents).[109] Although the study by Onega *et al*. showed that patients in the Midwest also had similar

disadvantages as those in South and West regions, our study showed that patients treated in the Midwest had better adherence level than patients in the Northeast. Our analysis, however, was not able to verify the reason for this finding.

Despite the importance of clinical practice guidelines, it should be noted that there are limitations in the guidelines themselves, as well as the system-based factors that are associated with the development and implementation of the guidelines.[50] A review conducted by the IOM showed great variability in the quality of existing clinical practice guidelines (CPGs) in cancer care, which stems from limited individual scientific studies and limited systematic reviews of the guidelines upon which the CPGs have been based. On average, the CPGs reviewed by IOM only met 50% of the IOM standards for practice guidelines. Further, lack of dissemination, the voluntary nature of guideline implementation, and a lack of monitoring might also contribute to the limited adoption of existing guidelines.[50]

Guideline adherence has been hypothesized to lead to improved patient survival. Our study confirmed this hypothesis in patients with SCLC, regardless of the stage of disease at diagnosis. Our study also corroborates the work of others with a relatively similar survival benefit evident in both younger and older patients, although interpretation should be made with caution due to potential selection bias. These findings highlight the importance of improving guideline adherence to increase the overall survival of SCLC patients. There is also a need to put more focus on patients' outcomes beyond survival (e.g., quality of life), especially when dealing with the least curable cancers, such as SCLC.

Our findings should be interpreted in light of several limitations. The database used in this study only included hospitals that are accredited by the Commission on Cancer (CoC) of the American College of Surgeons. These hospitals are mainly larger facilities with higher care

specialties, which might not be representative of all hospitals in the US. Thus, our findings might over-estimate the actual level and trend of guideline adherence in facilities with lower levels of cancer care specialty facilities. In addition, our analysis used less conservative criteria for adherence in LS-SCLC as we did not consider the sequence of chemo-radiation or type of chemotherapy agents. Furthermore, the effect of unmeasured confounders of treatment adherence, such as functional status, cannot be ruled out.

Conclusion

This study provides evidence of moderate guideline adherence level in the care of SCLC patients, which might have contributed to the relatively modest improvement in the survival of SCLC patients over the past three decades. Further research is needed to identify factors that contribute to low adherence, from both the provider and patient viewpoint. Every attempt should be made to ensure that patients are offered, and have access to, optimal treatment while keeping patient preferences at the forefront.

CHAPTER IV: CHARACTERISTICS AND SURVIVAL OF NEVER-SMOKERS WITH LUNG CANCER - A VETERANS' AFFAIRS CENTRAL CANCER REGISTRY ANALYSIS

Abstract

Background: An estimated 16,000 to 24,000 never-smokers died of lung cancer in the US annually. Although never-smokers could benefit from targeted therapy for genetic mutations that commonly occurred in this population, previous findings on the survival of never-smokers with lung cancer, as compared to ever-smokers, have been conflicting. **Methods**: Using data from the Veterans Affairs Central Cancer Registry (VACCR) from 2001 to 2008, we examined the characteristics and 5-year survival of never-smokers with lung cancer, as compared with ever-smokers. Cox Proportional Hazards regressions were used to examine the effect of never-smoking status on survival. **Results**: We found that the median age at diagnosis in never-smokers (73 years, IQR = 17) was older than in ever-smokers (68 years, IQR = 17, p-value < 0.001). The proportion of females among never-smokers (3.3%) was almost twice the proportion in ever-smokers (1.8%). Adenocarcinoma is the most common histology among never-smokers (34.7%), with a higher proportion than in ever-smokers (26.0%). After adjusting for sex, alcohol use, stage at diagnosis, histology, and treatment modality, an increased risk of death associated with smoking status was only significant in patients diagnosed at less than 65-years-old (aHR, 1.19 [95% CI, 1.06–1.33]), but not in the older group (aHR, 1.02 [95% CI, 0.95–1.09]). **Conclusion**: Our study demonstrated differences in the clinical and demographic characteristics between never- and ever-smokers with lung cancer. Never-smokers, in general, do not experience better survival than ever-smokers. Future research should focus on understanding the etiology and early symptoms of lung cancer in never-smokers, and establish screening and early diagnosis methods.

Introduction

An estimated 10–25% of lung cancer cases worldwide, and 10–15% in the United States (US), occur among never-smokers.[6,7] When considered as a single disease, separate from incidence in ever-smokers, lung cancer in never-smokers (LCINS) is among the top ten leading causes of US cancer deaths, accounting for an estimated 16,000 to 24,000 deaths annually.[58]

LCINS is clinically important as it presents with tumor biology and prognosis that are considered distinct from lung cancers in ever-smokers.[13] Never-smokers are more often diagnosed with adenocarcinoma and are more likely to exhibit certain gene mutations that respond well to targeted therapy.[59] Thus, never-smokers with lung cancer are likely to have better survival than ever-smokers. However, the absence of smoking history might contribute to delays in diagnosis and lead to never-smokers being diagnosed at later stages of lung cancer.[110] From a psychological viewpoint, as a commonly perceived self-inflicted disease, lung cancer creates an unjust stigma for never-smokers who are diagnosed with the disease, which has been associated with delays in seeking medical help among lung cancer patients.[111,112] These clinical and psychological implications highlight the importance of studying LCINS.

Despite the importance of LCINS, the epidemiology and outcomes of never-smokers with lung cancer in comparison to ever-smokers remain inconclusive. The gap in research on LCINS is partly related to the absence of information on smoking status in most population-based registries, making research with large sample sizes of never-smokers particularly challenging. A better understanding of LCINS is particularly relevant in a population that is at a high-risk for non-tobacco-related exposures, such as the veterans. Although the smoking prevalence is higher in Veterans compared to the general population, [71,113] Veterans are often exposed to other cancer risk factors during their services, such as Agent Orange, radon, asbestos, depleted uranium, and

other battlefield emissions. The high smoking prevalence in active military members could also pose never-smoker veterans at high risk of second-hand smoking exposure during service.

In this study, we analyzed data from the Veterans Affairs (VA) healthcare system to investigate the demographic and clinical characteristics and mortality of never-smokers with lung cancer. An improved understanding of LCINS is important not only for the development and delivery of efficient and effective preventive measures but also to increase the awareness of the clinical community and the public about the risk of lung cancer in never-smokers.

Methods

This study is a retrospective data analysis of lung cancer cases diagnosed at the Veterans Affairs Medical Centers (VAMCs) from 2001 to 2008. The cases were identified from the Veterans Affairs Central Cancer Registry (VACCR); a database consisting of information on cancer diagnosis and treatment at each of VAMC. Cancers diagnosed at VA facilities represent approximately 3% of the total cancer incidence in the US.[114] The VACCR database collects information on smoking status, which is not available in most cancer registries. From the database, we abstracted information on smoking status, age, sex, race, alcohol use, histology, and treatment modality. We categorized the self-reported smoking status into never-smokers and ever-smokers. The latter category includes both former and current smokers.

Study population

Only patients with invasive lung cancer and complete information on smoking status were included in the analysis. The definition of never-smokers in the VACCR is similar to the National Health Interview Survey, which is defined as having smoked fewer than 100 cigarettes in a

lifetime.[115] This study was approved by the Institutional Review Board (IRB) of the Veterans Health Administration.

Statistical analysis

Descriptive analyses included all lung cancer cases, while the survival analysis was limited to non-small cell lung cancer (NSCLC). Descriptive statistics of categorical variables are presented as proportions while continuous variables are presented as medians with the relevant inter-quartile range. Chi-square and t-tests were used to analyze the association between each predictor and smoking status, as applicable. In the survival analysis, the primary predictor was smoking status, and the primary outcome was 5-year survival. Survival time was defined as the time from the date of diagnosis to the date of death or the date of the last contact. Median survival time was estimated using Kaplan-Meier estimates.

We tested a two-way interaction between smoking status and age, and between smoking status and stage at diagnosis, on survival. A significant interaction was only identified with age groups: (a) less than 65 years, and (b) 65 years and beyond ($p = 0.018$). Hence, the multivariable survival analyses were performed separately for each of the age groups. The 65 years cut-off was chosen based on the commonly accepted definition for elderly. We also performed analyses by stage at diagnosis to allow for comparison with findings from previous studies. Additionally, we compared the effect of smoking status on survival in lung adenocarcinoma and other histology types to investigate the specific survival benefit of adenocarcinoma. Prior to the analyses, we assessed the Proportional Hazards (PH) assumption to determine whether the hazards ratio (HR) for each predictor was constant over time. For this purpose, the graphical approach and Schoenfeld's test were applied. We found that the violation of PH assumption was negligible, and thus, Cox Proportional Hazards regressions were used. The significance level for all analyses was

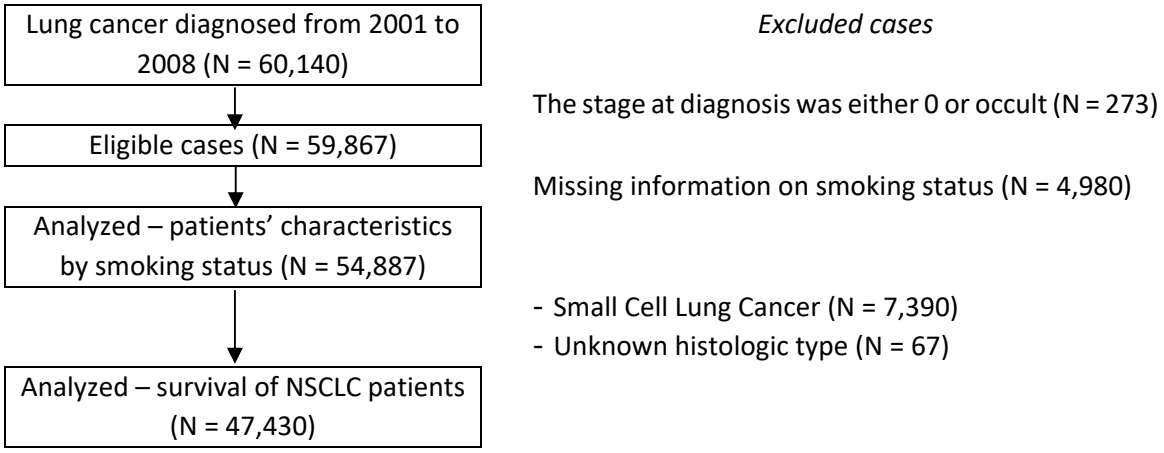
set at a p-value < 0.05. All statistical analyses were performed using the statistical software package SAS, version 9.2 (SAS Institute Inc., Cary, NC).

Results

Patients' characteristics by smoking status

There were 60,140 patients with lung cancer recorded in the VACCR from 2001 to 2008. We excluded 273 cases whose stage at diagnosis was either 0 or occult. A total of 59,867 cases were eligible for this study, of which 4,980 cases (8.3%) were excluded due to missing information on smoking status. A total of 54,887 cases were included in the analysis. The median follow-up time of the study population was 7 months (IQR = 12).

Figure 8. Selection of the study population



Never-smokers comprise 3.6% (1,970 out of 54,887 lung cancer cases) of lung cancer patients diagnosed in the VA health system. The study population was predominantly male (98.2%) and white (81.8%). The demographic and clinical characteristics of lung cancer patients were significantly different when comparing smoking status groups. Never-smokers were diagnosed

with lung cancer at an older age (median of 73 years [IQR = 17]) than ever-smokers (median of 68 years [IQR = 15]). The proportion of female never-smokers (3.3%) was almost twice the proportion in ever-smokers (1.8%). A higher proportion of adenocarcinoma was found in never-smokers (34.7%) than in ever-smokers (26.0%), and the opposite trend was detected for squamous cell carcinoma (21.4% and 29.2%, respectively). The difference in the cancer stage at diagnosis between the groups was negligible (Table 13).

Table 13. Characteristics of lung cancer patients in the VA health system by smoking status

Characteristics	**Never-smokers (N = 1,970) n (%)**	**Ever-smokers (N = 52,917) n (%)**	**Total (N = 54,887) n (%)**	**p-value**
Median age at diagnosis (IQR), years	73 (IQR = 17)	68 (IQR = 15)	69 (IQR = 15)	< 0.001
Age group				< 0.001
<40 years	5 (0.2)	26 (0.1)	31 (0.1)	
40—49 years	41 (2.1)	1,193 (2.2)	1234 (2.2)	
50—59 years	287 (14.6)	10,905 (20.6)	11,192 (20.4)	
60—69 years	456 (23.1)	16,989 (32.1)	17,445 (31.8)	
70+ years	1,181 (60.0)	23,804 (45.0)	24,985 (45.5)	
Sex				< 0.001
Male	1,902 (96.6)	51,975 (98.2)	53,877 (98.2)	
Female	66 (3.3)	936 (1.8)	1,002 (1.8)	
Not recorded	2 (0.1)	6 (0.01)	8 (0.01)	
Race				0.003
White	1,604 (81.4)	43,268 (81.8)	44,872 (81.8)	
Black	308 (15.6)	8,496 (16.1)	8,804 (16.1)	
Other	31 (1.6)	441 (0.8)	472 (0.9)	
Not recorded	27 (1.4)	712 (1.4)	739 (1.4)	
Alcohol use				< 0.001
Never	1,539 (78.1)	14,225 (26.9)	15,764 (28.7)	
Former	89 (4.5)	13,690 (25.9)	13,779 (25.1)	
Current	250 (12.7)	18,804 (35.5)	19,054 (34.7)	
Not recorded	92 (4.7)	6,198 (11.7)	6,290 (11,5)	

Table 13. (cont'd)

Characteristics	Never-smokers (N = 1,970) n (%)	Ever-smokers (N = 52,917) n (%)	Total (N = 54,887) n (%)	p-value
Histology				< 0.001
Squamous	422 (21.4)	15,439 (29.2)	15,861 (28.9)	
Adenocarcinoma	684 (34.7)	13,749 (26.0)	14,433 (26.3)	
Large cell	37 (1.9)	1,300 (2.5)	1,337 (2.4)	
Non-small cell carcinoma, NOS	343 (17.4)	9,766 (18.5)	10,109 (18.4)	
Other NSCLC	289 (14.7)	5,407 (10.2)	5,696 (10.4)	
Small cell lung cancer	191 (9.7)	7,199 (13.6)	7,390 (13.5)	
Other specified histology	3 (0.2)	19 (0.04)	22 (0.04)	
Unknown	1 (0.1)	38 (0.1)	39 (0.1)	
Stage at diagnosis				0.030
I and II	519 (26.4)	14,089 (26.6)	14,608 (26.6)	
III	448 (22.7)	14,123 (26.7)	14,571 (26.6)	
IV	814 (41.3)	22,199 (42.0)	23,013 (41.9)	
Not recorded	189 (9.6)	2,506 (4.7)	2,695 (4.9)	
Treatment				< 0.001
No surgery/radiation/ chemotherapy	731 (37.1)	15,529 (29.4)	16,260 (29.6)	
Surgery only	286 (14.5)	7,593 (14.4)	7,879 (14.4)	
Radiation only	252 (12.8)	8,229 (15,6)	8,481 (15.4)	
Chemotherapy only	297 (15.1)	8,374 (15.8)	8,671 (15.8)	
Chemo-radiation	286 (14.5)	9,943 (18.8)	10,229 (18.6)	
Surgery and chemotherapy and/or radiation	92 (4.7)	2,895 (5.5)	2,987 (5.4)	
Not recorded	26 (1.3)	354 (0.7)	380 (0.7)	

IQR: Interquartile range; NOS: Not otherwise specified

Survival of NSCLC patients by smoking status

Only 18% of the NSCLC patients survived for at least 5 years. After adjusting for sex, alcohol use, stage at diagnosis, histology, and treatment modality, an increased risk of death associated with smoking status was only statistically significant in patients diagnosed at less than 65-years-old (aHR, 1.19 [95% CI, 1.06–1.33]), but not in the older group (aHR, 1.02 [95% CI, 0.95–1.09]) (Table 14).

Table 14. Adjusted Hazard Ratios (aHR [95% CI]) for 5-year mortality by age group, NSCLC

Characteristics	Age < 65 years old (N = 18,383)	Age 65+ years old (N = 23,766)
Smoking status		
Ever-smokers vs. Never-smokers (*Ref*)	1.19 (1.06–1.33)	1.02 (0.95–1.09)
Sex		
Male vs. female (*Ref*)	1.14 (1.01–1.30)	1.08 (0.94–1.24)
Alcohol consumption		
Never	1.00	1.00
Former	1.02 (0.97–1.07)	1.06 (1.03–1.10)
Current	1.00 (0.96–1.05)	0.99 (0.96–1.03)
Stage at diagnosis		
Stage I and II	1.00	1.00
Stage III	2.03 (1.91–2.16)	1.88 (1.81–1.96)
Stage IV	3.69 (3.47–3.92)	3.13 (3.01–3.26)
Histology		
Squamous	1.00	1.00
Adenocarcinoma	0.99 (0.95–1.04)	1.00 (0.97–1.04)
Large cell	1.13 (1.02–1.25)	1.20 (1.10–1.31)
Non-small cell carcinoma, NOS	1.06 (1.01–1.11)	1.05 (1.01–1.09)
Other NSCLC	1.06 (0.99–1.13)	1.04 (0.99–1.09)
Treatment		
Surgery and chemotherapy and/or radiation	1.00	1.00
Surgery only	1.20 (1.08–1.32)	1.18 (1.08–1.29)
Radiation only	3.35 (3.07–3.65)	2.57 (2.36–2.80)
Chemotherapy only	1.66 (1.52–1.81)	1.57 (1.44–1.71)
Chemo-radiation	1.61 (1.48–1.75)	1.47 (1.35–1.60)
No surgery/ chemotherapy/ radiation	4.09 (3.76–4.45)	3.47 (3.20–3.77)

A multivariable analysis stratified by stage at diagnosis detected statistically significant association only between smoking status and survival in patients diagnosed with stage III cancer ($aHR_{stage\ I\ and\ II}$ = 1.05 [95% CI, 0.92–1.18]; $aHR_{stage\ III}$ = 1.14 [95% CI, 1.02–1.27]; $aHR_{stage\ IV}$ = 1.02 [95% CI, 0.94–1.10]) (Table 15). Stratified analyses by histology, adjusted for other predictors, showed that the survival benefit of never-smokers was statistically significant only in patients with lung adenocarcinoma (aHR, 1.21 [95% CI, 1.10–1.34]), but not in other histologies (aHR, 0.99 [95% CI, 0.92–1.06]) (Table 16).

Table 15. Adjusted Hazard Ratios (aHR [95%CI]) for 5-year mortality in never-smokers compared to ever smokers NSCLC patients, by stage at diagnosis*

	Stage I & II (N = 13,942)	Stage III (N = 12,599)	Stage IV (N = 18,510)
Ever- vs. never-smokers (*Ref*)	1.05 (0.92–1.18)	1.14 (1.02–1.27)	1.02 (0.94–1.10)

*The model was adjusted for age, sex, alcohol consumption, histology, and treatment modality

Table 16. Adjusted Hazard Ratios (aHR [95%CI]) for 5-year mortality in NSCLC patients, by histology*

	Adenocarcinoma (N = 12,334)	Non-adenocarcinoma (N = 27,364)
Ever- vs. never-smokers (*Ref*)	1.21 (1.10–1.34)	0.99 (0.92–1.06)

*The model was adjusted for age, sex, alcohol consumption, stage at diagnosis, and treatment modality

A comparison of prognostic factors between never- and ever-smoker groups (Table 17) showed that most of the predictors assessed in this study showed a relatively similar effect on the survival of each never- and ever-smokers group, except for sex and histology. In never-smokers, there was an indication of a lower risk of death in males, although it was not statistically significant. In contrast, males in the ever-smoker group had a significantly higher risk of death than their female counterparts. In the never-smoker group, patients with adenocarcinoma had about 16% lower risk of death than patients with squamous lung cancer (aHR, 0.84 [95% CI, 0.72–0.98]), but this association was not evident in ever-smoker groups (Table 17).

Table 17. Adjusted hazard ratios (aHRs [95%CI]) of 5-year mortality by smoking status, NSCLC

Characteristics	Never-smokers (N = 1,775)	Ever-smokers (N = 38,198)
Age at diagnosis		
<65 years vs. 65+ years old (*Ref*)	0.83 (0.72–0.094)	0.96 (0.94–0.98)
Sex		
Male vs. female (*Ref*)	0.87 (0.62–1.21)	1.15 (1.04–1.26)
Alcohol consumption		
Never	1.00	1.00
Former	1.01 (0.79–1.30)	1.05 (1.02–1.08)
Current	1.13 (0.96–1.34)	0.99 (0.97–1.03)
Stage at diagnosis		
Stage I and II	1.00	1.00
Stage III	1.78 (1.49–2.12)	1.94 (1.87–2.01)
Stage IV	3.34 (2.82–3.95)	3.35 (3.23–3.46)
Histology		
Squamous	1.00	1.00
Adenocarcinoma	0.84 (0.72–0.98)	1.01 (0.98–1.04)
Large cell	1.33 (0.91–1.94)	1.16 (1.08–1.24)
Non-small cell carcinoma, NOS	0.99 (0.84–1.17)	1.06 (1.03–1.09)
Other NSCLC	0.95 (0.78–1.15)	1.05 (1.01–1.09)
Treatment		
Surgery and chemotherapy and/or radiation	1.00	1.00
Surgery only	0.98 (0.69–1.40)	1.22 (1.14–1.31)
Radiation only	2.28 (1.63–3.18)	2.93 (2.76–3.12)
Chemotherapy only	1.30 (0.92–1.82)	1.65 (1.55–1.76)
Chemo-radiation	1.44 (1.03–2.01)	1.56 (1.47–1.66)
No surgery/ chemotherapy/ radiation	3.21 (2.33–4.42)	3.79 (3.57–4.02)

Discussion

Exposures to risk factors other than active tobacco smoking during military services could pose a critical concern for the risk of lung cancer among never-smoker Veterans. Although our study indicated a small proportion of LCINS in the VA health system in 2001–2008 (3.6%), this number translates to more than 1,800 lives affected by the detrimental effects of the disease. Our study reported differences in demographic and clinical profiles by smoking status and, to some extent, indicated different findings compared to studies in the general population.

Previous studies on the epidemiology of LCINS yielded inconsistent results. Several studies reported a younger age at diagnosis among never-smokers than ever-smokers,[110,116] but others found the opposite or no difference.[60,63] In our study population, never-smokers were diagnosed at an older age than ever-smokers. Our findings substantiate previous studies that reported gender variations in LCINS.[65,110] Although the number of females in our study was considerably small, the proportion of lung cancer in never-smoker females was nearly twice that of ever-smokers. Gender variation in LCINS has been linked to the role of estrogen in the pathogenesis of lung cancer.[13,62]

The histologic types of LCINS in our study population appeared to be distinct from findings in most previous studies. Although adenocarcinoma is the most common histologic type (35.7%), consistent with previous studies, the proportion was substantially lower than as reported by previous studies (50–87%).[65,116,117] We also found a relatively high share of squamous carcinoma (20.9%) and small-cell lung cancer (9.7%); two histologic types that are strongly associated with active tobacco smoking. A review of 17 published studies found 3.4-times more adenocarcinomas than squamous cell carcinomas in never-smokers.[13] Although some might argue that the high proportion of 'not otherwise specified' (NOS) category in our study might confound the findings, this proportion of NOS group was relatively similar to what has been reported elsewhere.[118] The different histological type in our study was likely due to the predominantly male patient composition, as adenocarcinoma has been reported to be higher among females.[118] Moreover, our findings resemble a study among non-smoking male construction workers with lung cancer in Sweden that found 40% of cases were adenocarcinomas, and 19% were squamous cell carcinomas.[61] Hence, our study points to the importance of gender variation in the histology of LCINS, and further, the need to investigate the effect of occupational-related exposures on tumor histology in the Veteran population.

The need to investigate occupational-related exposures is heightened by the indication that genetic susceptibility might not play a major role in the etiology of LCINS in our study population. Previous studies found genetic susceptibility in LCINS patients who had early onset of disease (less than 50-years-old). In our study population, the proportion of never-smokers diagnosed with lung cancer at younger than 50-years-old was only 2.7%, which was not statistically different from ever-smokers (2.3%). Our study did not find substantial differences in the stage at diagnosis by smoking status. Patients in the VA health system have been reported to be diagnosed at an earlier stage of cancer, compared to the general population, suggesting adequate access to preventive and chronic disease care within the Veterans Health Adminsitration (VHA).[70,119]

The limited information in our data did not allow us to investigate factors associated with the incidence of LCINS, but several risk factors have been discussed in the literature. Radon and second-hand smoking have been considered as major contributors to LCINS in the US.[7] The veterans, however, are different from the general population in regards to their exposure to cancer risk factors during service. Although smoking prevalence among active military members has declined, historically the prevalence was very high. A survey in 1980 showed that 51% of active military members smoked within 30 days preceding the survey.[71] The high smoking prevalence during service could lead to high exposure to environmental tobacco smoke. Deployed veterans were also exposed to service-related risk factors, such as depleted uranium, Agent Orange, asbestos, burn pits, and diesel exhaust. These substances have been suspected to cause adverse health outcomes, although the association with lung cancer has been limited, mixed or not proven. The Institute of Medicine (IOM) concluded that there was limited or suggestive evidence that Agent Orange used in the Vietnam War was associated with lung cancer.[120] This is of particular concern for our study since more than one-third of VHA users (36%) are veterans who were deployed during the Vietnam War era.[71] Abundant evidence has also shown the effect of

radiation on lung cancer, but IOM suggests that the military members post-World War II were more likely exposed to a low dose of radiation if they were exposed at all, which does not pose harm.[71] Given the methodological challenges in investigating the effect of service-related exposures on the occurrence of lung cancer, the influence of those exposures could not be completely ruled out.

LCINS has been found to have a better prognosis than ever-smokers in some studies, but not in others.[65,116,121] Our multivariable analysis found age- and histologic-specific effects of smoking status on the 5-year survival of NSCLC patients. The survival differences were specific to patients who were diagnosed at less than 65-years-old and among patients with lung adenocarcinoma. The absence of a significant effect of smoking status among the elderly is likely explained by the higher disease burden coupled with the lower functionality due to aging, or competing risks of death from other causes.

One of the explanations for survival differences by smoking status is that, compared to never-smokers, ever-smokers tend to have smoking-related comorbidities that might preclude them from receiving adequate treatment, leading to poor prognosis. Also, a higher portion of never-smokers with lung adenocarcinoma exhibit activating mutations in the *epidermal growth factor receptor* (EGFR) gene. The EGFR mutation itself is a prognostic factor in lung cancer since patients with this mutation demonstrate good clinical outcomes when treated with the EGFR-tyrosine kinase inhibitor (TKI). A review by Sun *et al*. reported EGFR mutations in 58% of never smokers, but only in 13% of ever-smokers.[13] However, a study among the veteran population found that the proportion of clinically actionable EGFR mutations among never-smoker veterans with lung adenocarcinoma (28.6%) appeared to be lower than in the general population, which might explain the limited survival benefit among never-smokers.[122] In addition, although EGFR

mutations have been found to be higher among females, the association between gene mutations and unique risk factors among the veterans deserves further investigation.

Findings from our study raise the question of whether LCINS in veterans differs from the general population and highlights the need for further research on the epidemiology and outcomes of LCINS among veterans. It should be noted that our data includes patients diagnosed before the professional guidelines on EGFR mutation testing were endorsed in 2011.[123] However, one study of NSCLC patients in the VAMCs in 2011–2013 indicated variability in genetic consultation services and documented a number of cases that did not comply with the clinical guidelines for targeted therapy, which could influence the quality of care. [122] Fortunately, in 2015, the Department of Veterans Affairs launched a National VA Precision Oncology Program to improve genetic diagnostic testing for personalized medicine.[124] Going forward, it is crucial to ensure that the program is implemented comprehensively to ensure the maximum benefit for veterans.

Gaps in the understanding of LCINS remain and point to opportunities for further research. Identification and validation of biomarkers for early diagnosis of LCINS could improve clinical practice. Given the absence of extensive cellular and molecular damages caused by tobacco, studies focusing on never-smokers could help shed light on the etiology of lung cancer, beyond active smoking. Also, as part of promoting research on LCINS, cancer registries need to consider incorporating smoking status information.

To our knowledge, this study is the first to discuss LCINS in the veteran population specifically. Our study has the advantage of a large number of never-smokers, unlike previous studies. Nevertheless, our findings were subject to several limitations. First, our study population might not be generalizable to all US veterans, since only about 30% of the veterans were enrolled in the

VA healthcare system.[81] The enrolled Veterans tended to have lower socio-economic status and poorer socio-economic and health conditions.[81] Another limitation was the use of self-reported smoking status, which is subject to misclassification. However, a validation study of self-reported smoking status indicated a non-significant misclassification.[115] The database that we used does not provide information on important predictors, such as secondhand smoking and occupation-related exposures, and thus, limited our ability to explain the epidemiological and clinical differences found in this study. We analyzed data for the period of 2001–2008, which might not have reflected the current situation of VA patients. However, a more recent analysis of NSCLC patients undergoing EGFR testing from 2011 to 2013 showed a relatively similar proportion of never-smokers (4%).[122]

Our study was not intended to solely link lung cancer incidence among veterans with service-related exposures. We were aware that veterans are likely to be exposed to occupational or residential risk factors in their later life after being discharged from the military.

Conclusion

Given the decline in the prevalence of smoking in the US and other Western countries, we expect an increased proportion of never-smoker patients with lung cancer. Finding ways to reduce LCINS might serve as the next key step in reducing the overall incidence of lung cancer. Future research should focus on understanding the etiology and early symptoms of LCINS, and establish a means for screening and early diagnosis. Physicians' understanding of these symptoms and risk factors will further stress the importance of including lung cancer as a possible suspect in never-smokers who present with symptoms that might lead to lung cancer. Therefore, diagnosis and interventions could be made earlier to ultimately promote better outcomes.

CHAPTER V: DISCUSSION

The past decades have witnessed major advances in medical science, including the treatment of lung cancer. Nevertheless, more than half of lung cancer patients die within 1 year of diagnosis.[3] Although multiple prognostic factors for lung cancer patients' survival have been discussed in the literature, gaps in knowledge remain for some of the factors, for which evidence has been either limited or inconclusive. This dissertation focused on the effect of extended time-to-treatment, non-adherence to treatment guidelines, and never-smoking status on the overall survival of lung cancer patients. Since time-to-treatment and adherence to treatment guidelines are modifiable, a better understanding of those factors could help improve patients' survival. Of particular interest, we also studied the effect of never-smoking status on the survival of NSCLC patients amid concerns about the distinct biology of lung cancer in never-smokers.

5.1 Summary of Findings from the Present Study and Its Relevance to the Literature

In the first study (Chapter II), we examined the effect of extended time-to-treatment on the survival of patients diagnosed with NSCLC. Despite the presumed association between treatment delay and patients' survival, previous studies have shown mixed results. Limited sample size, lack of adjustment for important confounders, and variation in the cut-off point of treatment delay are among the potential explanations for the inconsistent findings. The NCDB offers the opportunity to study a large sample of NSCLC patients and thereby address some of those challenges.

We hypothesized that an extended time-to-treatment is associated with reduced survival. Results of the multivariable analyses, however, showed that patients who waited longer than the

commonly recommended interval (i.e., more than 4 weeks after diagnosis) had a lower risk of death, compared to those who began treatment within the first 4 weeks of diagnosis. These results were consistent across different stage groups. The effect was larger in patients with metastatic cancer, while the Hazard Ratios (HRs) in patients diagnosed with early-stage cancer were close to the null value (HR = 1), suggesting the differences in risk of death in the latter group of patients might not be clinically meaningful. However, a subset analysis among early-stage patients who received surgery only revealed findings in the opposite direction. Findings among early-stage patients who received surgery only support our hypothesis that extended time-to-treatment is associated with poorer survival.

Our study corroborates findings from previous studies but contradicts with several studies.[39,95] Lower hazard ratios associated with treatment delay have also been reported in previous studies of lung and other cancers.[46,47,84] These findings could reflect the situation in which patients with a longer time-to-treatment might receive a more comprehensive evaluation, especially a detailed analysis of molecular markers within their tumors, thus leading to better survival. An alternative explanation from a methodological point-of-view is that our findings could also be affected by *confounding by severity*, a condition in which the exposure (in our case, the time-to-treatment) is driven by the disease severity.[125,126] Patients with advanced disease or poorer disease biology might receive expedited treatment due to the severity of their condition. Thus, these patients inherently have a worse prognosis compared to other patients, regardless of the time to initiate treatment. To minimize the effect of confounders, we have adjusted multiple factors and stratified our analysis by stage at diagnosis. However, severity or patients clinical conditions may largely vary within the same stage at diagnosis, and thus, the stratification by stage may not be sufficient to reduce the effect of any unmeasured confounder.

In our study population, 42.6% of NSCLC patients began treatment more than 4 weeks after diagnosis. A longer time-to-treatment could be a consequence of more extensive evaluation and coordination of care, as treatment of lung cancer often involves a multidisciplinary team and multiple assessments. A longer median time-to-treatment in patients with early-stage cancer compared to those with metastatic cancer, as demonstrated in this study, could also be associated with preoperative evaluation.[127] Lung cancer resections require thorough assessments, including cardiovascular evaluation, and assessment of lung function and exercise capacity.[128,129] The process is then followed-up with a re-evaluation to ensure patients' eligibility for resection.[128] Since the majority of lung cancer patients are either former or current smokers; they are at high risk for cardiovascular disease and other smoking-related comorbidities. Such conditions require further evaluation, which might lead to a longer time-to-treatment interval. Also, to improve their lung capacity, patients who are current smokers are also advised to quit smoking within 8 weeks before surgery.[130] Delayed treatment can also be caused by non-clinical factors, such as insurance, or merely patients' choice to begin treatment. Although multiple factors can affect time-to-treatment, it is important to ensure that patients do not experience treatment delay for any avoidable reasons.

Besides timeliness of care, another important effort to improve patient outcomes is to ensure patients receiving care that has been proven effective and incorporated into clinical practice guidelines. This premise led us to the second study (Chapter 3), in which we examined the trend and predictors of non-adherence to treatment guidelines among SCLC patients, and its impact on patients' survival. Use of the NCDB enabled our study to portray a broad picture of treatment provision as the database represents nearly 70% of cancer patients in the US and spanning for a long period. Our study found a moderate, but increasing, level of adherence to treatment guidelines for SCLC patients between 1998 and 2012. Among patients who are deemed eligible

for the treatment, 78.9% of LS-SCLC and 87.4% of ES-SCLC patients received treatment that adheres to the guidelines. Those proportions, however, are lower than adherence to treatment guidelines in NSCLC and other cancers, such as colon cancer.[75,76] The multivariable analysis showed that LS-SCLC and ES-SCLC patients of older age, higher comorbidity score, and uninsured or using Medicare/Medicaid had a significantly higher risk of receiving treatments that do not adhere to the guidelines. Our findings are consistent with previous studies.[75,76]

Our study found that facility region was an independent predictor for non-adherence. Patients who were treated in the South and the West regions were more likely to receive treatments that do not adhere to the guidelines, compared to the Northeast region. In Chapter III, we discussed how this finding might reflect potential disparities in access to quality cancer care, such as the population's socioeconomic status and travel time. On the other hand, patients who were diagnosed/treated in facilities in the Midwest region were more likely to receive guidelines-adherence, compared to those of the Northeast region. This finding is relatively unexpected given the fact that, compared to the Northeast, the oncologist per capita is lower and travel time to the referral hospitals is longer in the Midwest.[109] Although we were not able to explain this finding, it should be noted that the database used for this study may over-represent patients from the urban areas, and thus, do not provide a comprehensive picture about the Midwest area as a whole. In our study, for example, only 3.4% of patients from the Midwest lived in the rural areas.

In this study, patients who do not receive guideline-recommended treatment had twice the risk of death of those who received guideline-recommended treatment, after adjusting for other covariates. Our findings showed that the reduction in survival among patients receiving inadequate treatment was consistent in both LS-SCLC and ES-SCLC patients and in both younger (≤ 65-years-old) and the elderly (>65-years-old) patients.

Our third study (Chapter IV) examined the survival among never-smoker patients in the VA health system, who were diagnosed with lung cancer. The VACCR database is among the very limited secondary data that collect information on smoking status and allowed us to study a specific population that is presumed to have a higher level of exposure to occupational risk factors for lung cancer. With a relatively large number of never-smokers, the VACCR provides a unique opportunity to overcome a major limitation of previous studies that had a small sample size. To our knowledge, this is the first study to focus on the characteristics and survival of never-smokers diagnosed with lung cancer in the US Veteran population. A previous study by different authors examined the effect of smoking on survival in the same population, but the study was not focused on never-smokers.[131]

The proportion of LCINS in our study population was only 3.6%; however, this proportion translates to a significant number (more than 1,800 patients in 2001–2008). The demographic and clinical characteristics of never-smokers with lung cancer in our study population appears to be different from studies of LCINS in the general population. For example, although the percentage of females in the never-smoker group is higher than among ever-smokers, the percentage is relatively lower than what we would have expected. However, the fact that female patients were only 2% of our study population limited our ability to examine gender differences.

In addition to second-hand smoking and occupational-related exposures during services, another potential factor that could increase the risk of lung cancer among never-smokers is the presence of Chronic Obstructive Pulmonary Disease (COPD). COPD has been shown to drive the occurrence of lung cancer through inflammation of the lung tissue. Although COPD is closely associated with smoking, Veterans are at high risk for development of COPD due to occupational-related exposures in addition to tobacco smoking, which could increase their risk for lung cancer.[132]

Our study did not demonstrate a survival benefit among never-smokers in general. A subset analysis, however, showed a positive effect on survival among never-smokers diagnosed at ages of less than 65 years. The absence of survival benefit among older patients may be associated with the lower physical functions among this group. A better survival associated with never-smoking status was also seen among patients with adenocarcinoma, independent of age. Findings from our study differ from several previous studies that have reported lower mortality risk among never-smokers regardless of the age at diagnosis.[121,133,134] Nevertheless, our study offers an association between smoking and survival of lung cancer patients that is consistent with the biology of lung cancer. It appears that, given the fatality of lung cancer, once a patient is diagnosed with the disease, smoking status is no longer a strong prognostic factor.

5.2 Implications

The three factors investigated through this dissertation have important clinical and public health implications. Our first two studies provided evidence on the importance of two important modifiable factors related to the quality of cancer care that has been highlighted by IOM. [50,51] Findings from the third study shed light on the importance of never-smokers among the lung cancer patient population.

Time to treatment initiation appears to be crucial for early-stage patients with a resectable tumor. It is prudent to ensure that this group of patients receive surgery within the first four weeks of diagnosis. For the rest of the patient population, however, extended time-to-treatment does not appear to have an adverse effect on survival. More comprehensive assessments, although possibly resulting in extended waiting time, are likely to bring more survival benefit to the patients rather than rushing the treatment. The survival benefit will likely affect patients with

advanced cancer who exhibit particular molecular abnormalities. This patient group would likely benefit from targeted therapy. Targeted therapy, however, requires additional time to perform mutation testing, which will guide clinicians in determining the type of targeted drugs that are most likely to work for the patient. In practice, the molecular testing can take up to several weeks.

The window period between diagnosis and treatment initiation gives patients and their informal caregivers (e.g., family) time to discuss their treatment options with their clinicians, to seek second opinions, and then decide the best treatment option. However, the length of diagnosis-to-treatment interval time should not be compromised. Moreover, the diagnosis-to-treatment interval should be seen as a part of a cancer care continuum that starts with symptom evaluation. It should be kept in mind that prior to receiving treatment after diagnosis, most patients might have experienced a waiting time between symptom evaluation and diagnosis that might affect their disease progression.

Given findings from this study as well as other previous studies with a similar notion, there might be a need to revisit existing benchmarking for time-to-treatment that has been implemented in several developed countries. In countries such as the United Kingdom and Canada, facilities that do not meet the standard minimum waiting time can be penalized, or at the very least affect their performance indicator. While time-to-treatment benchmarks are important, it is crucial to ensure that the benchmarks do not hinder optimal evaluation for treatment planning.

As treatment delay can also be influenced by facility- and clinician-related factors, it is important to emphasize that facilities should have adequate resources to perform the tests needed or have access to other external facilities that could perform the assessment. Community-cancer centers should have good referral networking with hospitals with higher specializations.

Specific for the growing needs of targeted therapy, according to the most recent guidelines, facilities should have the capacity to provide mutation testing to patients within two weeks.

In regards to the adherence to treatment guidelines by the clinicians, our study supports the need to ensure all eligible patients are offered evidence-based treatments. Findings from our study, however, should not be interpreted as a 'one-size fits all' approach. The application of existing guidelines should take into account patients' characteristics, clinical conditions, and preference; aligned with personalized medicine and patient-centered care.

Efforts should be made to address barriers to the utilization of guidelines-based treatment. From clinician' side, several issues could hinder the adoption of those guidelines. Clarity, feasibility, as well as clinicians' trust of the guidelines, are among important factors that could determine whether or not clinicians implement the guidelines. As IOM has pointed out, there is great variability in the quality of existing clinical guidelines in cancer care. [50] Robust evidence is needed to convince clinician to adopt the clinical practice guidelines, especially in diseases with a large uncertainty of the risk and outcomes, such as SCLC. Healthcare providers should ensure effective clinician-patient communication to convey evidence on the benefit of guideline-recommended treatment to the patients during treatment planning.

Specifically for elderly patients, there is a need to improve the adoption of evidence-based treatment to leverage the reduction of lung cancer deaths as the elderly accounts for about two-thirds of the patient population. Higher toxicities and comorbidity burden often preclude them from receiving standard treatment.[102] Although multiple studies have reported a higher toxicity rate among elderly patients, age alone should not be the basis for treatment decision. More recent evidence suggests that the elderly population could obtain the same survival benefits from

standard therapy as their younger counterparts.[106,107] Therefore, more efforts are needed to aid physicians in determining patients' eligibility for intensive therapies.

Studies on lung cancer outcomes should not overlook the fact that smokers are not the only population that suffers from lung cancer. Abundant evidence points to the importance of occupational and environmental risk factors for lung cancer, other than tobacco smoking. The clinical setting has started to observe changes in the proportion of lung cancer patients by smoking status. A hospital-based study from three diverse institutions in the US showed that the proportion of never-smoker among lung cancer patients increased from 8.0% in the period 1990–1995 to 14.9% in 2011–2013.[135] Whether or not the changes represent an increasing incidence of LCINS, or merely resulted from a declining smoking prevalence, remains a question. Nevertheless, the importance of never-smokers in the lung cancer landscape is worth noting.

The limited survival benefit among never-smokers with lung cancer found in this study points to the need to ensure that this group of patients receive effective treatments. Previous studies have identified that a large proportion of never-smokers with lung cancer present with gene mutations, particularly EGFR mutation. Since multiple targeted therapy agents have been proven effective for some of the gene mutations and approved by the Food and Drugs, it is imperative to improve access to molecular testing, followed by targeted therapy.

As in ever-smokers, early diagnosis also an issue in never-smokers, which might reduce their chance for a better prognosis. In our study, for example, 41.3% of LCINS patients were diagnosed at an advanced stage. Early diagnosis problem in LCINS is compounded by the fact that many LCINS cases are either asymptomatic or have non-specific symptoms, and thus they are more likely to be diagnosed through incidental detection. [136,137]

Although previous studies do not show the effectiveness of lung cancer screening among people without a history of heavy smoking, we believe that there are certain groups of the never- or non-smoking population that could benefit from lung cancer screening, for example, a population who are exposed to environmental or occupational risk factors for lung cancer, other than active tobacco smoking. Therefore, it is imperative to increase public and clinical community awareness regarding the risk of lung cancer in never-smokers, especially among the high-risk population. Increased awareness can be expected to lead to patients seeking health care early, which could potentially lead to the disease being diagnosed at an earlier stage.

5.3 Future Directions

Our findings highlight the importance of thorough assessment prior to definite treatment without compromising patients' outcomes, rather than simply meeting the benchmark of providing treatment within a specified time. However, the question of 'how long can a patient safely wait for treatment?' needs to be addressed through empiric data of the critical time points that could predict unfavorable outcome for patients. This information will be useful to revisit existing guidelines pertinent to the timeliness of cancer care. Future studies also need to examine the association between time-to-treatment and outcomes other than mortality that are also meaningful to patients, such as progression-free survival, quality of life, and psychological distress. These immediate outcomes might offer a better understanding of how the health system should be delivered to maximize patients' benefits.

Methodological approaches for studies addressing treatment delay could be challenging, as it would not be ethical to conduct an experimental study by assigning patients in delayed and non-delay groups. However, given the potential problem with confounding by severity, future

prospective studies with detailed clinical information are warranted. One potential problem that may arise from prospective studies in this field is the Hawthorne effect, in which clinicians may change their behavior (in this case, toward expediting the treatment initiation) due to being observed. However, given there is no formal established guidelines on time-to-treatment in the US and the fact that multiple studies did not show an association between treatment delay and increased mortality, bias due to the Hawthorne effect may not be of a big concern. Nevertheless, future studies should be designed to minimize this bias. For example, by random sampling or by enrolling patients periodically and mask the sample selection from the clinicians.

In regards to adherence to treatment guidelines, we identified gaps in the understanding of the reasons why guideline-recommended therapy was not included in treatment planning in some patients, even after excluding cases with contraindications. Further research is needed to understand patients' reasons for refusal to identify system-based barriers, as well as factors that lead to guideline non-adherence from the provider side, such as acceptance of guidelines and lack of resources.

The gradual decline of smoking prevalence might lead to an increased proportion of never-smokers among lung cancer patients in the future. Reducing the incidence and mortality of never-smokers with lung cancer might be the next challenge in overcoming the overall burden of lung cancer. Research opportunities in this area include understanding specific risk factors for LCINS, early diagnosis for high-risk population, and identify possible missed opportunities in which eligible patients do not receive potentially effective treatment.

In general, studies among never-smoker population provide the opportunity for a better understanding of the etiology of certain diseases, not just lung cancer, without being confounded by the damaging effect of chemical substances in tobacco on the cellular system. Molecular

epidemiologic studies might offer a useful approach to overcome some of the methodological challenges in researching occupational and environmental exposures specific to the Veterans. Also, since early diagnosis is a significant challenge in lung cancer, future studies can help identify existing biomarkers or develop risk prediction models to help detect lung cancer in high-risk populations. One of the key factors for improving the survival of never-smokers with lung cancer is through ensuring access to molecular testing and targeted therapy for patients with advanced stage cancer. Future studies can focus on examining the utilization of molecular testing and targeted therapy in the VA health system.

5.4 Study limitations

Findings from our studies should be interpreted in light of several limitations. The main limitations are associated with the nature of the observational study and secondary analysis of registry data. We could not rule out the possibilities of confounding effects from unmeasured variables. In Chapter II, we have described how 'confounding by severity' might affect our results in the first study. Confounding by severity is a major problem in clinical research, especially in observational studies. In general, stratification or use of disease severity score are among the approaches that can be employed to handle confounding by severity, as demonstrated by Torring *et al*. in a study on diagnostic delay.[138] For our study, we have stratified our analyses by stage at diagnosis. We hypothesized that, to some extent, cancer stage at diagnosis represents a disease severity score since it is a composite measure of the extent of the tumor (T), the extent of spread to the lymph nodes (N), and the presence of metastasis (M). Our stratification by cancer stage, however, might not be sufficient to eliminate the effect of other confounders. It is likely that there are other clinical variables more influential to the decision of time-to-treatment for lung cancer patients

that were not included in our study (such as performance status, type of comorbidity, and symptom burden). This is the key limitation of our study, which we worked to address by performing a subset analysis in early-stage patients who received surgery alone. We considered this group as relatively homogenous with respect to their clinical conditions. That way, we were able to show the adverse effect of extended time-to-treatment on survival.

Another approach to handle confounding by severity is through the propensity score method. However, due to the absence of more detailed clinical information, we believe that applying the propensity score approach in our study would not have dramatically altered the results, and could, in fact, resulted in matched cases which do not have similar severity. Although we could not rule out potential confounders in our study, our findings generally follow the clinical logic in the association between time-to-treatment and survival.

The NCDB has limited information to explain why patients do not receive guidelines-recommended treatment. The NCDB records indicate that, in most patients who did not receive adequate treatment, the guideline-recommended treatment was not included in their treatment plan. The NCDB's guideline for data reporting lists the exclusion reasons as either: 1) treatment not usually recommended for the disease; and/or 2) patient decided to undergo other therapeutic option(s). However, we were unable to verify the actual reason for exclusion of any therapy from the treatment plan.

Our analysis of VACCR data poses limitations on the generalizability of the findings. Our study population may not be generalizable to all US veterans. Veterans who are enrolled in the VA health benefit tended to have lower socio-economic status and poorer socio-economic and health conditions.[81] Another limitation was the use of self-reported smoking status, which is subject to misclassification. However, although of a small size, a study validating smoking status among

participants in a Lung Cancer Screening Trial showed high consistency between the self-reported status and urinary cotinine test ($\kappa = 0.85$, $P < 0.001$). [139] In addition, given the percentage of current or former smokers is high among veterans, we believe misclassification of smoking status would not affect our results.

5.4 Conclusions

In summary, this dissertation has addressed some of the gaps in the current knowledge of prognostic factors among lung cancer patients. This dissertation points to the importance of alleviating system-based barriers that could contribute to unnecessary treatment delay, sub-standard care that does not adhere to the clinical practice guidelines, and missed opportunities in providing targeted therapy for never-smokers with lung cancer. These are important aspects that should be continuously addressed to improve patients' outcomes, along with other scientific innovations in the fight against lung cancer.

APPENDICES

Appendix A: Lung cancer staging

Table A1. Definitions for T, N, and M Descriptors of the 8th Edition of the Classification of Lung Cancer

	Description
T: Primary Tumor	
TX	Primary tumor cannot be assessed, or tumor proven by the presence of malignant cells in sputum or bronchial washings but not visualized by imaging or bronchoscopy
T0	No evidence of primary tumor
Tis	Carcinoma in situ: • Tis (AIS): adenocarcinoma • Tis (SCIS): squamous cell carcinoma
T1	Tumor 3 cm or less in greatest dimension, surrounded by lung or visceral pleura, without bronchoscopic evidence of invasion more proximal than the lobar bronchus (ie, not in the main bronchus); the uncommon superficial spreading tumor of any size with its invasive component limited to the bronchial wall, which may extend proximal to the main bronchus, is also classified as T1a
T1mi	Minimally invasive adenocarcinoma
T1a	Tumor 1 cm or less in greatest dimension
T1b	Tumor more than 1 cm but not more than 2 cm in greatest dimension
T1c	Tumor more than 2 cm but not more than 3 cm in greatest dimension
T2	Tumor more than 3 cm but not more than 5 cm; or tumor with any of the following features (T2 tumors with these features are classified T2a if 4 cm or less or if size cannot be determined and as T2b if greater than 4 cm but not larger than 5 cm): • Involves main bronchus regardless of distance to the carina, but without involving the carina • Invades visceral pleura • Associated with atelectasis or obstructive pneumonitis that extends to the hilar region, either involving part of the lung or the entire lung
T2a	Tumor more than 3 cm but not more than 4 cm in greatest dimension
T2b	Tumor more than 4 cm but not more than 5 cm in greatest dimension
T3	Tumor more than 5 cm but not more than 7 cm in greatest dimension or one that directly invades any of the following: parietal pleura (PL3), chest wall (including superior sulcus tumors), phrenic nerve, parietal pericardium; or associated separate tumor nodule(s) in the same lobe as the primary
T4	Tumors more than 7 cm or one that invades any of the following: diaphragm, mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, carina; separate tumor nodule(s) in a different ipsilateral lobe to that of the primary

Table A1. Definitions for T, N, and M Descriptors of the 8th Edition of the Classification of Lung Cancer (cont'd)

	Description
N: Regional Lymph Nodes	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in ipsilateral peribronchial and/or ipsilateral hilar lymph nodes and intrapulmonary nodes, including involvement by direct extension
N2	Metastasis in ipsilateral mediastinal and/or subcarinal lymph node(s)
N3	Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral, or contralateral scalene, or supraclavicular lymph node(s)
M: Distant Metastasis	
M0	No distant metastasis
M1	Distant metastasis
M1a	Separate tumor nodule(s) in a contralateral lobe; tumor with pleural nodules or malignant pleural or pericardial effusion; most pleural (pericardial) effusions with lung cancer are due to tumor; in a few patients, however, multiple microscopic examinations of pleural (pericardial) fluid are negative for tumor, and the fluid is nonbloody and is not an exudate; where these elements and clinical judgment dictate that the effusion is not related to the tumor, the effusion should be excluded as a staging descriptor
M1b	Single extrathoracic metastasis in a single organ and involvement of a single distant (nonregional) node
M1c	Multiple extrathoracic metastases in one or several organs

Abbreviations: TNM, Tumor Nodule Metastasis.
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Table A2. Stage Grouping of the 8th Edition of the TNM Classification

Stage	T	N	M
Occult carcinoma	TX	N0	M0
0	Tis	N0	M0
IA1	T1mi	N0	M0
	T1a	N0	M0
IA2	T1b	N0	M0
IA2	T1c	N0	M0
IB	T2a	N0	M0
IIA	T2b	N0	M0
IIB	T1a, b, c	N1	M0
	T2a, b	N1	M0
	T3	N0	M0
IIIA	T1a, b, c	N2	M0
	T2a, b	N2	M0
	T3	N1	M0
	T4	N0	M0
	T4	N1	M0
IIIB	T1a, b, c	N3	M0
	T2a, b	N3	M0
	T3	N2	M0
	T4	N2	M0
	T4	N3	M0
IIIC	T3	N3	M0
	T4	N3	M0
IVA	Any T	Any N	M1a
	Any T	Any N	M1b
IVB	Any T	Any N	M1c

Abbreviations: TNM, Tumor Nodule Metastasis; T1mi, minimally invasive adenocarcinoma; Tis, tumor in situ.
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Appendix B: Unadjusted survival plots by treatment adequacy in patients with SCLC

Fig B1. Unadjusted survival plot by treatment adequacy in LS-SCLC patients

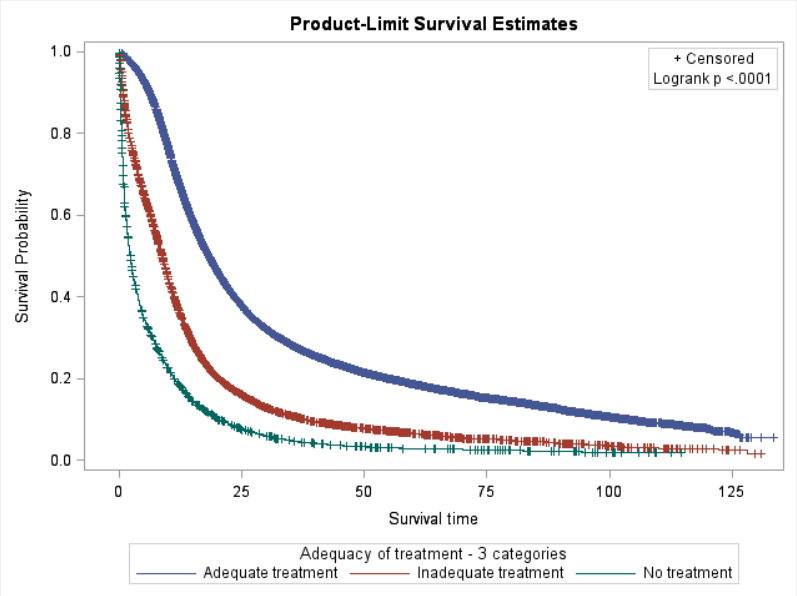
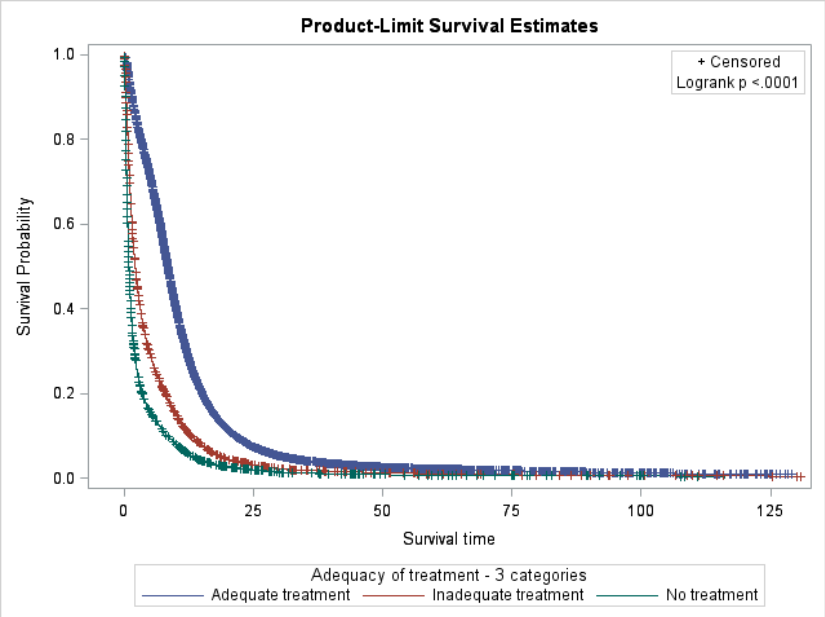


Fig B2. Unadjusted survival plot by treatment adequacy in ES-SCLC patients



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