1-1-2019

Incomplete surgical resection in Non-Small Cell Lung Cancer: A population-based cohort from the Mid-South region of the United States

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INCOMPLETE SURGICAL RESECTION IN NON-SMALL CELL LUNG CANCER: A POPULATION-BASED COHORT FROM THE MID-SOUTH REGION OF THE UNITED STATES

By

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A Dissertation

Submitted in Partial Fulfillment of the

Requirements for the Degree of

Doctor of Philosophy

Major: Epidemiology

The University of Memphis

December 2019

Dedication

This dissertation is dedicated to my family. I wish to convey a special feeling of gratitude toward my loving parents, Chun-Fa Lee and Bi-Fen Wong, who sacrificed much to afford me a world of possibilities with their unconditional love and support. I have been very blessed to have full support from my wife Hsing-Ying during my years of study. Thank you so much for your love, encouragement, understanding, and patience and for those numerous evenings and weekends without my companionship. I also want to dedicate this book to my daughter Iris. You are such a blessing to me.

Acknowledgements

A special thanks to my academic advisor Dr. Matthew Smeltzer for his guidance and encouragement during this process. Thank you so much for your insight and your precious time of help throughout the development of my dissertation. I would like to express my sincere gratitude to Dr. Raymond Osarogiagbon for allowing me to work on these three exciting research projects. I have learned a great amount of lung cancer knowledge from you.

My sincere thanks also goes to Dr. James Gurney and Dr. Kenneth Ward. I have enjoyed both your Grant Writing course and Doctoral Seminar course so much, and I would like to thank you for mentoring me on this dissertation. I wish to send appreciation to my wonderful committee member Dr. Meredith Ray on her prompt and helpful comments during the working of this dissertation. I especially appreciate your insightful discussions on the model building. Thank you all so much for your immense knowledge, kindness, and patience.

I am so grateful to the amazing thoracic research team members at Baptist Memorial Hospital-Memphis. I wish to thank Mr. Nick Faris and Ms. Carrie Fehnel for their fantastic job at helping me understand the MS-QSR database. Many thanks to Meghan Taylor. I have enjoyed the time with you in our Epidemiology doctoral program. Thank you for your warmest words and encouragements during those rough days.

Thanks to lung cancer patients and their families for their contribution to our studies, and our funding agency National Cancer Institute (R01 CA172253-01).

Thanks to many of my friends for their encouragement, support, love and their prayers during my study process and defense.

Abstract

Lee, Yu-Sheng, PhD. The University of Memphis. December 2019. Incomplete surgical resection in non-small cell lung cancer: A population-based cohort from the Mid-South region of the United State. Major Professor: Matthew P. Smeltzer, MStat, PhD

Lung cancer accounts for approximately 25% of all cancer deaths in the United States, and most long-term survivors of lung cancer undergo surgical resection. However, the effectiveness of surgical resection is impaired when tumor tissue remains at the margin of the resected specimen after the surgery, known as incomplete resection. The incidence of incomplete resection varies with patient demographic, clinical, surgeon, and institutional characteristics. The anatomic sites of margin involvement may also have impacts on long-term survival. Recommended postoperative treatment options for incomplete resection include re-resection, chemotherapy, and radiation therapy. However, some of these recommendations are not based on high-level evidence. A better understanding of the factors associated with margin positivity is needed to aid preoperative, intraoperative, and postoperative treatment decision making.

The Mid-South Quality of Surgical Resection Cohort (MS-QSR) is a population-based dataset including > 95% of surgical resections of lung cancer in the Mid-South from 2009-2019. We evaluated the MS-QSR to disentangle the positive margin's preoperative risk factors, the impact of postoperative treatments on positive margin, and survival outcomes.

Among 3,414 patients evaluated in this study, 4.9% experienced incomplete resections. Risk factors associated with incomplete resection included male sex, unknown patient's residency, advanced clinical stage (II and III), neo-adjuvant treatment, higher surgeon annual case volume, and urban location of hospital. Accurate TN (tumor and

node) staging was a protective factor. Margin positivity was independently associated with an increase in the hazard of death (aHR=1.73, 95% CI: 1.40-2.13). Compared to complete resections, the anatomic sites significantly undermined the overall survival.

We evaluated a hospital-based surgical quality metric called the risk-adjusted margin positivity (RAMP), which classified hospitals as underperformer, nonoutlier, or outperformer. In our analysis, the outperforming hospitals were more likely to attain quality criteria, had more surgeons with Cardiothoracic board certificate and predominant practice in thoracic or cardiovascular, and were more likely to be affiliated with a teaching program.

Future work should focus on better identification of patients at risk for incomplete resection, improving the implementation of current guidelines and quality care at the institutional level, and generating higher level evidence to support postoperative treatment after incomplete resection.

Table of Contents

List of Tables

List of Figures

Chapter 1

Introduction

Lung cancer is one of the most commonly occurring malignancies and is the leading cause of cancer-related death throughout most of the world and in the United States.[1,2] The American Cancer Society estimated about 230,000 people will be diagnosed with lung cancer and 143,000 lung cancer deaths will occur in 2019, representing approximately 13% of all cancer incidence and 25% of all cancer mortality in the U.S.[3]

Lung cancer can be histologically classified as non-small cell lung cancer (NSCLC), small cell lung cancer (SCLC), and lung carcinoid tumor. Among all lung cancer cases, approximately 80-85% are NSCLC, consisting of six subtypes: adenocarcinoma, squamous cell carcinoma, large cell carcinoma, neuroendocrine carcinoma, adenosquamous carcinoma, and sarcomatoid carcinoma.[4] Adenocarcinoma, previously called bronchioloalveolar carcinoma, is the most common form of NSCLC in those who have never smoked, although it can also occur in current and former smokers. Squamous cell carcinoma is known to be associated with patient's smoking history.[5] Large cell carcinoma and neuroendocrine carcinoma share some SCLC characteristics, growing and spreading fast and usually undifferentiated; however, they are typically considered as a type of NSCLC. In this study, we delineated NSCLC as patients with adenocarcinoma, squamous cell carcinoma, large cell carcinoma, neuroendocrine carcinoma, adenosquamous carcinoma, and sarcomatoid carcinoma.

The TNM (**T**umor, **N**ode, and **M**etastasis) lung cancer staging system, developed by the International Association for the Study of Lung Cancer (IASLC) International

Staging Project, is a cornerstone of communicating the extent and severity of disease, aiding physicians in determining the best treatments, providing a means of homogenizing groups of patients enrolled into clinical trials, and enabling objective outcome comparisons.[6] The T indicates the extent of the primary tumor, the N indicates the involvement of lymph nodes, and the M corresponds to the distant metastasis. Each T, N, and M component is divided into several sub-components. Various sub-components (eg. T1, N0), known as descriptors, delineate what is included within a T, N, or M component. The combination of TNM score then forms the aggregate staging groups, *Stage IA-B* (localized disease), *Stage IIA-B* (localized disease), *Stage IIIA-C* (regional disease), and *Stage IV* (distant disease). The stages of the AJCC 8th edition is detailed in Table 1.[7]

Table 1. Stage groups for the 8th Edition TNM lung cancer staging system

Stage	T	N	M
IA	T1a-c	N0	M0
IB	T2a	N0	M0
IIA	T2b	N0	M0
IIB	T1-3	N0-1	M0
IIIA	T1-4	N0-2	M0
IIIB	T1-4	N2-3	M0
IIIC	T3-4	N3	M0
IV	T1-4	N0-3	M1a-c

Treatment for lung cancer usually involves various modalities that are dependent on the stage of disease. These treatment modalities can be in sequence or concurrent. The most common treatment modalities used for non-metastatic cancer (stage I-III) are surgery, radiation therapy, and chemotherapy. Treatments can also be categorized by the timing before (neo-adjuvant) or after (adjuvant) the surgery. Neo-adjuvant treatment is performed prior to surgery to shrink the tumor making the surgery easier. Adjuvant

treatment is given post-surgery to treat any residual tumor. Both neo-adjuvant and adjuvant can be radiotherapy, chemotherapy, or combined. The National Comprehensive Cancer Network (NCCN) lung cancer treatment guidelines give the clinical practice principles for the health providers curing the disease by stages. The guidelines are summarized in Table 2.[8]

Table 2. NCCN treatment guidelines for NSCLC

Stage*	Initial Tx	Primary Tx	Margin status	Option for margins
IA		Surgery	R1/2	• Re-resection • RT
IB		Surgery	R1/2	• Re-resection ± Chemotherapy • RT ± Chemotherapy
IIA		Surgery	R1/2	• Re-resection • Chemoradiation (same time or back-to-back)
IIB (T1 or T2, N1)		Surgery	R1	• Re-resection + chemotherapy • Chemoradiation (same time or back-to-back)
			R2	• Re-resection + chemotherapy • Chemoradiation (at the same time)
IIB (T2 or T3 without invasion)		Surgery	R1	• Re-resection + chemotherapy • Chemoradiation (same time or back-to-back)
			R2	• Re-resection + chemotherapy • Chemoradiation (at the same time)
IIB (T3 with superior sulcus tumor)		Surgery + chemotherapy	R1	• Re-resection + chemotherapy • Chemoradiation (same time or back-to-back)
			R2	• Re-resection + chemotherapy • Chemoradiation (at the same time)
	Chemoradiation		R1/2	• Re-resection
IIB (T3 with other invasive tumors)		• Surgery • Chemoradiation (at the same time)	R1	• Re-resection + chemotherapy • Chemoradiation (same time or back-to-back)
			R2	• Re-resection + chemotherapy • Chemoradiation (at the same time)
	Chemoradiation		R1/2	• Re-resection

Table 2 (Continued)

Stage*	Initial Tx	Primary Tx	Margin status	Option for margins
Any other IIB		Surgery	R1	• Re-resection + chemotherapy Chemoradiation (same time or back-to-back)
			R2	• Re-resection + chemotherapy Chemoradiation (at the same time)
IIIA (N0/N1, tumor without invasion)		Surgery	R1	Chemoradiation (same time or back-to-back)
			R2	Chemoradiation (at the same time)
IIIA (N0/N1, other invasions)		Surgery	R1	• Re-resection + chemotherapy • Chemoradiation (same time or back-to-back)
			R2	• Re-resection + chemotherapy • Chemoradiation (at the same time)
	Chemoradiation/ Chemotherapy	Surgery	R1/2	• Re-resection
IIIA (N2)	Chemoradiation	Surgery	R1	• Chemoradiation (same time or back-to-back)
			R2	• Chemoradiation (at the same time)

*For the initial treatment in which depends on the clinical stage; for the postoperative treatment in which depends mainly on the pathologic stage.

In brief, for stage I to IIIA without invasion (not growing into healthy tissues), the treatment recommended by NCCN is surgical resection to remove the primary tumor. For patients with stage IIB and invasion and stage IIIA disease, the treatment can be surgery in combination with chemotherapy or chemoradiation. Per the guidelines, surgical resection is the recommended initial curative treatment modality for locoregional (clinical stage I to IIIA) NSCLC as it is associated with improved long-term survival. However, only 25-30% of NSCLC patients are eligible for this treatment. Ineligibility for surgery could be due to older age, poor lung function, or advanced stage (stage IV) at diagnosis.[9,10]

Surgical resection for NSCLC can be described by the technique and extent. Currently, the most common surgical techniques are open thoracotomy, video-assisted thoracic surgery (VATS), and robotic-assisted thoracic surgery (RATS),[11] while the surgical extent consist of pneumonectomy, lobectomy, segmentectomy, and wedge resection. Open thoracotomy is a classic procedure to remove the tumors in which surgeons access the lungs through an incision made from the front of the chest to the back passing under the armpit to the shoulder blade. The incision is made between the ribs and through the chest wall. On the other hand, VATS and RATS have much smaller incisions with 3 or 4 “key-hole”-like ports between the ribs on the side of the chest. A camera is inserted through these ports to display the lung cavity on a larger screen to the surgeon as aid during surgery.

Lobectomy removes one of the lobes of the lungs; segmentectomy removes a section of a lobe of the lung; wedge resection removes a triangle-shaped slice of tumor and a small amount of normal tissue around it; and pneumonectomy is the largest lung

resection possible (brown area in Figure 1).[8] The techniques and extents of surgery are interchangeable, meaning a patient can have RATS with any type of extent. For example, a resection eligible NSCLC patient can have lobectomy using the VATS technique or lobectomy using the RATS. On the other hand, one can have RATS technique with wedge resection or RATS technique with segmentectomy. Similar to stage, the type of surgical approach has been found to be a risk factor for positive margins and survival outcome.[12,13]

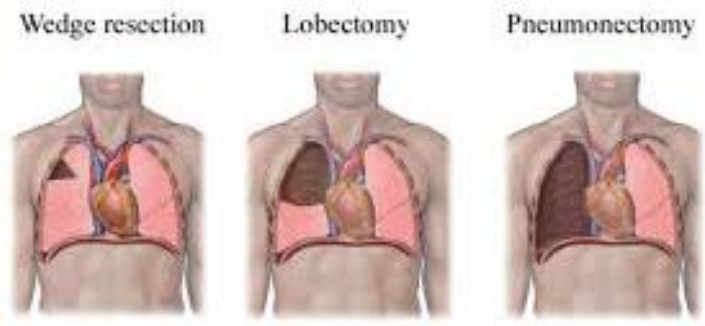

Figure 1. Extent of surgical resection
(*Source: NCCN guidelines for patients, 2018*)

The goal of surgical resection is to remove tumors from the body. This includes removing some non-cancerous tissue (surgical margin) around the edge of the tumor. Thereby, a ***negative margin***, or the absence of residual cancer cells at the edge of the resected tumor specimen,[14] achieves the goal of complete resection of the primary tumor. In contrast, a ***positive margin,*** or the presence of residual cancer cells at the edge of the resected tumor specimen,[14] does not result in complete resection of the primary tumor. The Union for International Cancer Control (UICC) R classification, an auxiliary classification within the TNM staging system, is used to denote the status of residual tumor post-resection in situations such as these with three categories: R0, R1, and R2.[15] R0 indicates no residual tumor (negative margin), R1 indicates microscopic residual

tumor along the margins, which cannot be seen by naked eye, and R2 corresponds to macroscopic residual tumor, which is visible to the naked eye.[15-17] Residual tumors can occur at different anatomic locations including at primary tumor site, at the regional lymph nodes, and/or at the distant sites.[17] An anatomic location/site of margin positivity is titled based on the location of the residual tumors. For example, a bronchial wall margin is named after its residual tumors located at the bronchial wall. The most common anatomic sites for positive margins include pulmonary artery or vein margin, peribronchial margin, chest wall margin, Mediastinum, and bronchial wall margin.[18-20] There have been on-going debates about the survival implications of different sites of margin positivity and suggest it is likely that margin positivity at different anatomic sites connote different prognostic risks.[12]

In some cases, surgeons do not realize a patient had a positive margin until the pathologic report from the microscopic review. However, positive margins are more frequently a result of surgeons being unaware of how deep the tumor had invaded peri-operatively due to the lack of thorough preoperative and intraoperative diagnosis and accurate clinical staging. The preoperative evaluations used to accurate stage lung cancer include chest radiograph, computer tomography (CT), positron emission tomography with CT (PET-CT), mediastinoscopy, endoscopic bronchial ultrasonography (EBUS), esophageal ultrasonography (EUS), and transbronchial needle aspiration (TBNA).[21] The mediastinoscopy is still considered the gold standard to investigate the mediastinal lymph nodes while bronchoscopies (EBUS, EUS, and TBNA) allow for more accurate staging of proximal hilar and all mediastinal stations.[22,23] Although the preoperative evaluations are important to the accuracy of TNM staging, a 2001 American College of Surgeons

Patient Care Evaluation revealed the use of preoperative mediastinoscopy in only 27% of patients.[24] The positive margins may be more likely with more advanced T or N category tumors; however, inaccurate clinical staging may sometimes underestimate the extent/invasion of tumor.[25] This underestimation of the tumor invasion indicates that the surgeons have not resected the tumor tissues properly which may result in an incomplete resection.

A frozen-section biopsy evaluation, which is an intraoperative distinction between benign and malignant lung tissue, is a commonly used approach to assist surgeons in determining the margin status. Studies suggest that preoperative evaluations provide more accurate staging, which is necessary to define optimal treatment and thus optimal outcomes.[23] While preoperative evaluations provide more accurate staging, intraoperative evaluations alone do not sufficiently prevent positive margins.[26] Wind and colleagues found that the improvement in accuracy has not decreased the incidence of positive margins at the bronchial wall. They hypothesized that one of the reasons was that the frozen-section evaluation was less reliable in detecting extra-mucosal residual tumors.[27] In other words, the frozen-section evaluation alone does not suffice to understand the incidence of margin positivity.

Positive margins are associated with a poor postoperative prognosis, and some previous reports suggested that patients may benefit from postoperative treatment.[6,28,29] Although some reports found that postoperative adjuvant therapies may not benefit positive margin patients, the NCCN recommends the postoperative adjuvant treatments depending on the disease stages.[29-34] According to the NCCN treatment guidelines (Table 2), postoperative treatment modalities recommended for NSCLC patients with margin

positivity include second surgical intervention (re-resection), radiotherapy, and/or chemotherapy; re-resection treatment is a preferred response to the positive margin.[8] The stage IA patients with positive margin, regardless of R1 or R2 status, are recommended to receive re-resection or the radiotherapy. Patients with stage IB disease, regardless of R1 or R2 status, are recommended to receive re-resection and/or chemotherapy or radiotherapy and/or chemotherapy. Stage IIA patients are recommended to receive re-resection and chemotherapy. R1 patients with stage IIB to IIIA disease are recommended to receive re-resection and chemotherapy or chemoradiation (same time or back-to-back). R2 patients with stage IIB to IIIA disease are recommended to receive re-resection and chemotherapy or chemoradiation (at the same time). If a patient receives preoperative chemoradiation, regardless of the R1 or R2 status, re-resection is the only recommended method.

Although the NCCN treatment guidelines play a key role in clinical settings, there is surprisingly little evidence-based data to validate the guidelines for postoperative treatment in NSCLC.[35,36] One of the few studies was conducted by Smeltzer and colleagues, among 3,461 patients with positive margin in the National Cancer Database (NCDB), and demonstrated that advanced stage patients with positive margins who followed the NCCN clinical guidelines yielded better survival outcomes, but not early stage patients.[37] This study compared treatment received by the patient, which was not always concordant with NCCN guidelines.

Inconsistent findings and limited evidence-based data are the drivers for more research to better understand the potentially reversible factors driving the risk of margin positivity. This aids preoperative and intraoperative treatment decision making and the

effects of the attainment of the NCCN treatment guidelines. Based on previous studies, we have developed a causal pathway, illustrating the associations of patient, clinical, surgeon, hospital characteristics, NCCN guidelines, with overall survival (Figure 2).

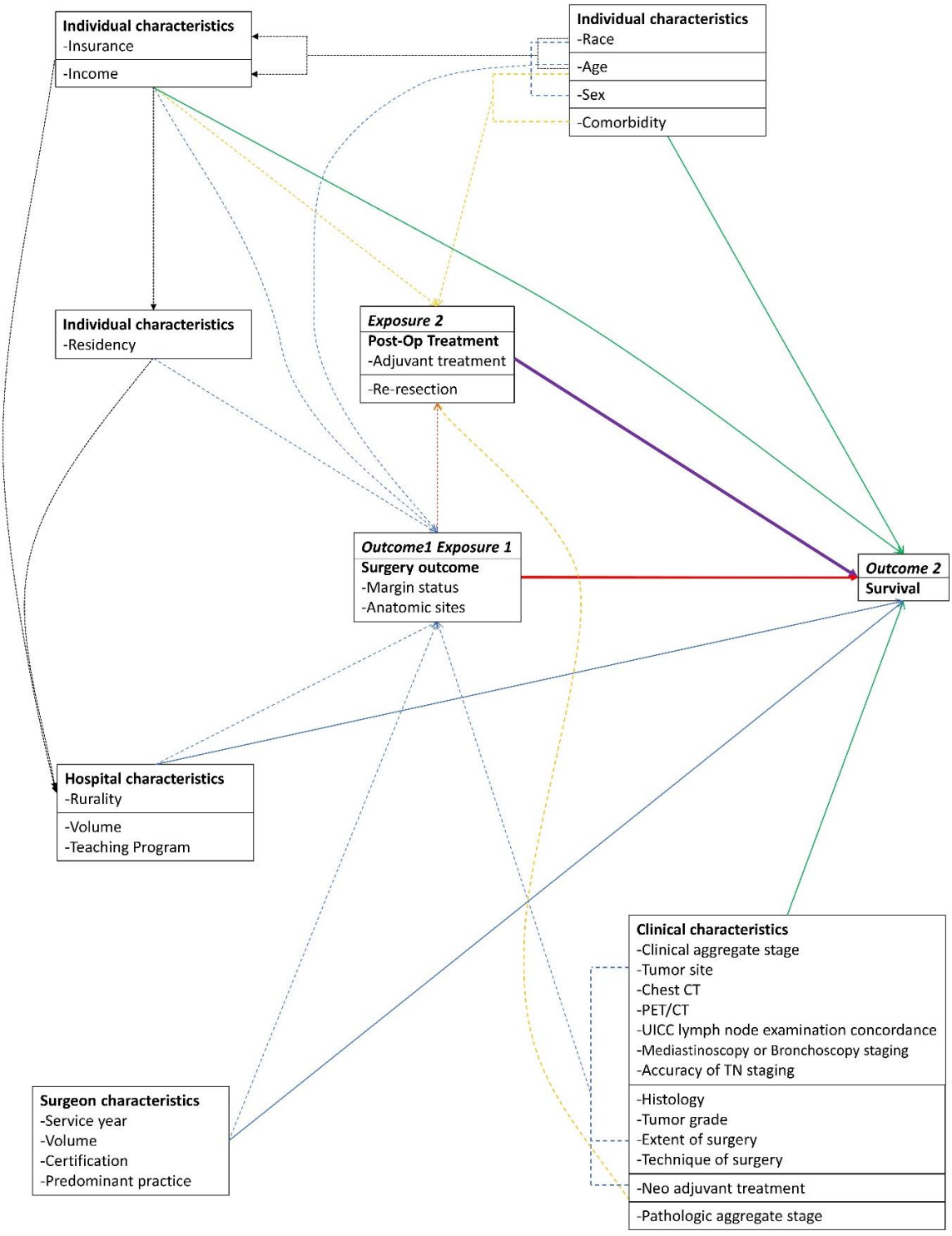

Figure 2. Causal pathway amongst the variables

Although lung cancer is a significant disease in the U.S., the public health and clinical issues of this disease vary across the states and regions. The Mid-South region (Arkansas, Mississippi, and Tennessee) is one of the most desperate regions. This region is a lung cancer hot-zone possibly due to high smoking rates, high lung cancer incidence and mortality,[2,38] and suboptimal health care quality in many areas.[39] The smoking population is more prevalent in Mid-South region comparing to other states (Figure 3).[4,38]

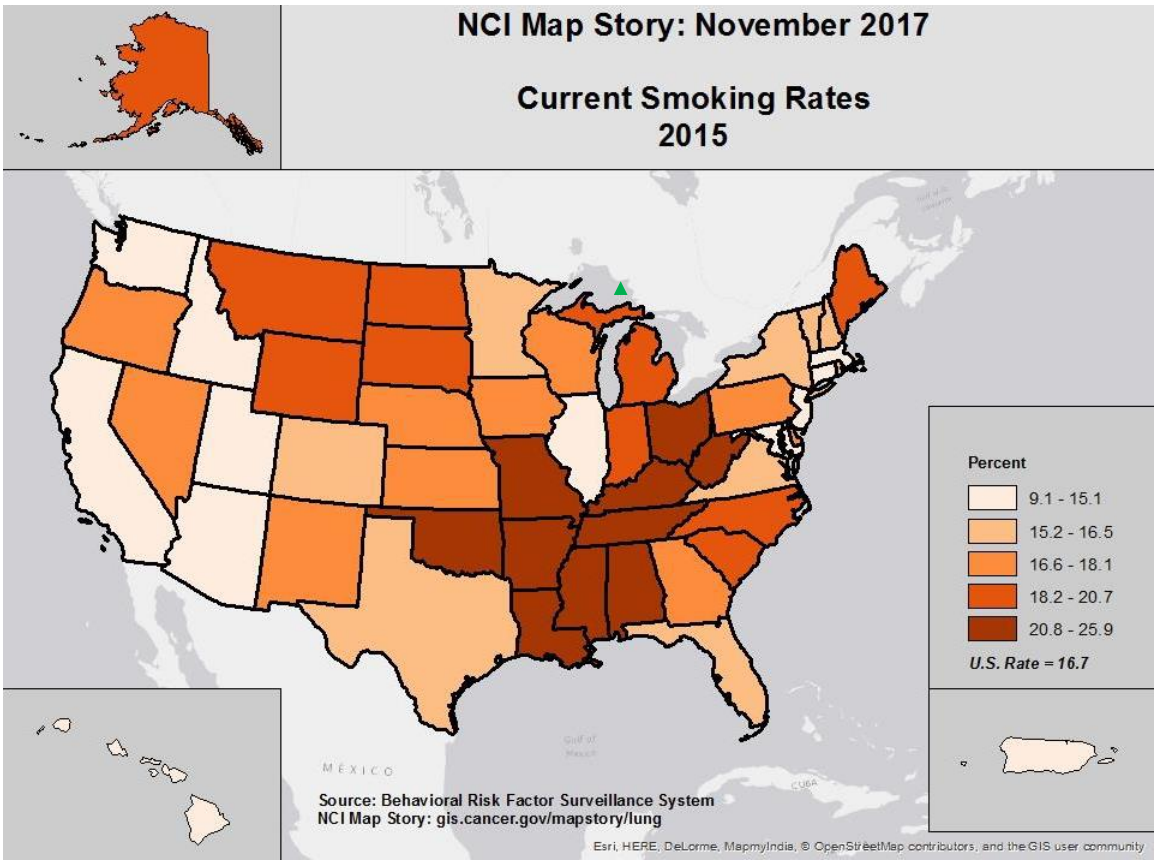

Figure 3. Map of cigarette smoking prevalence in United States in 2015 (*Source: National Cancer Institute Map Story, https://gis.cancer.gov/mapstory/lung/*)

In addition, lung cancer incidence and mortality vary widely by regions within the U.S., partially reflecting the historical and recent changes in smoking behaviors. The age-adjusted incidence of lung cancer in the Mid-South states was about 75-80 per 100,000, which is higher than the national incidence of 63.0 per 100,000 (Figure 4).[5,38,40] Lung

cancer mortality was among the highest in these states as well (Figure 5).[38] The rate of early stage NSCLC (stage I and II) curative-intent surgical resection in Tennessee from 2007 to 2011 was about 65%, similar to the national average of 66.4%. But it was significantly lower than the highest state - Utah (77.2%).[41]

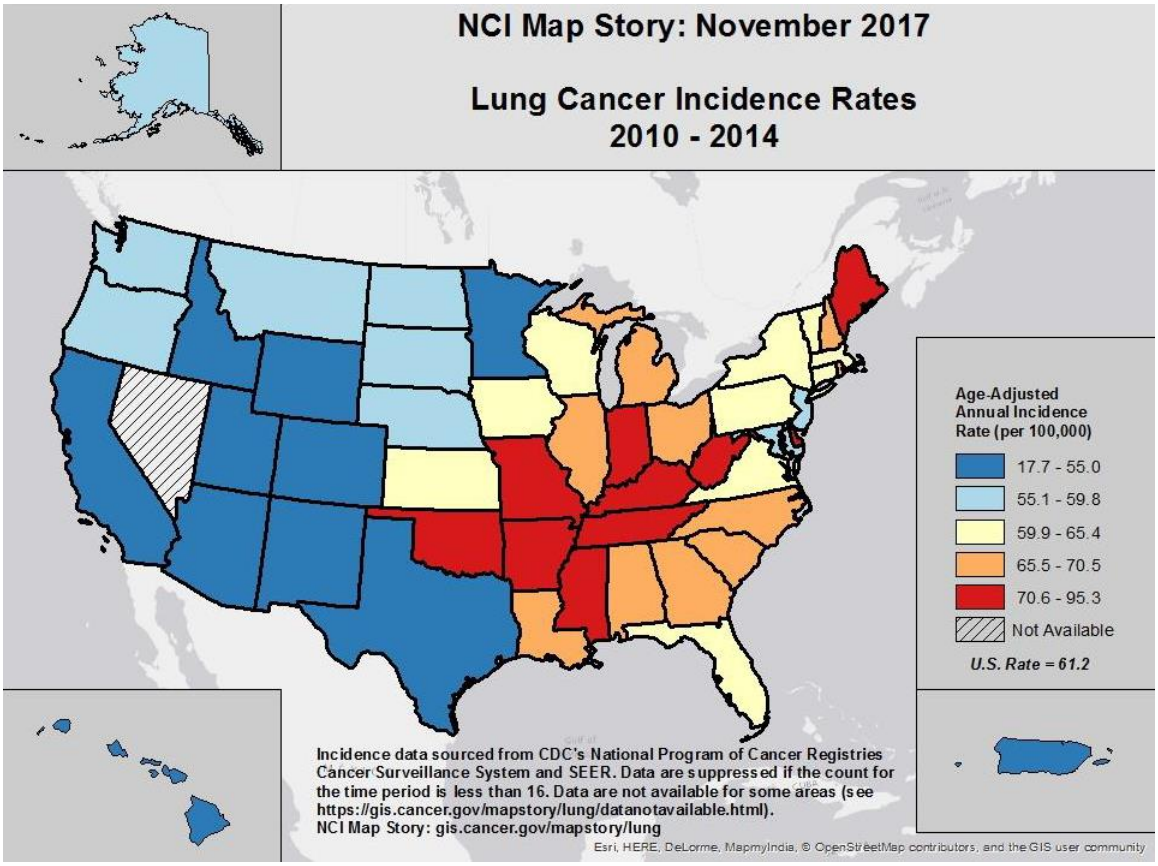

Figure 4. Map of lung cancer incidence in United States 2010-2014
(*Source: National Cancer Institute Map Story, https://gis.cancer.gov/mapstory/lung/*)

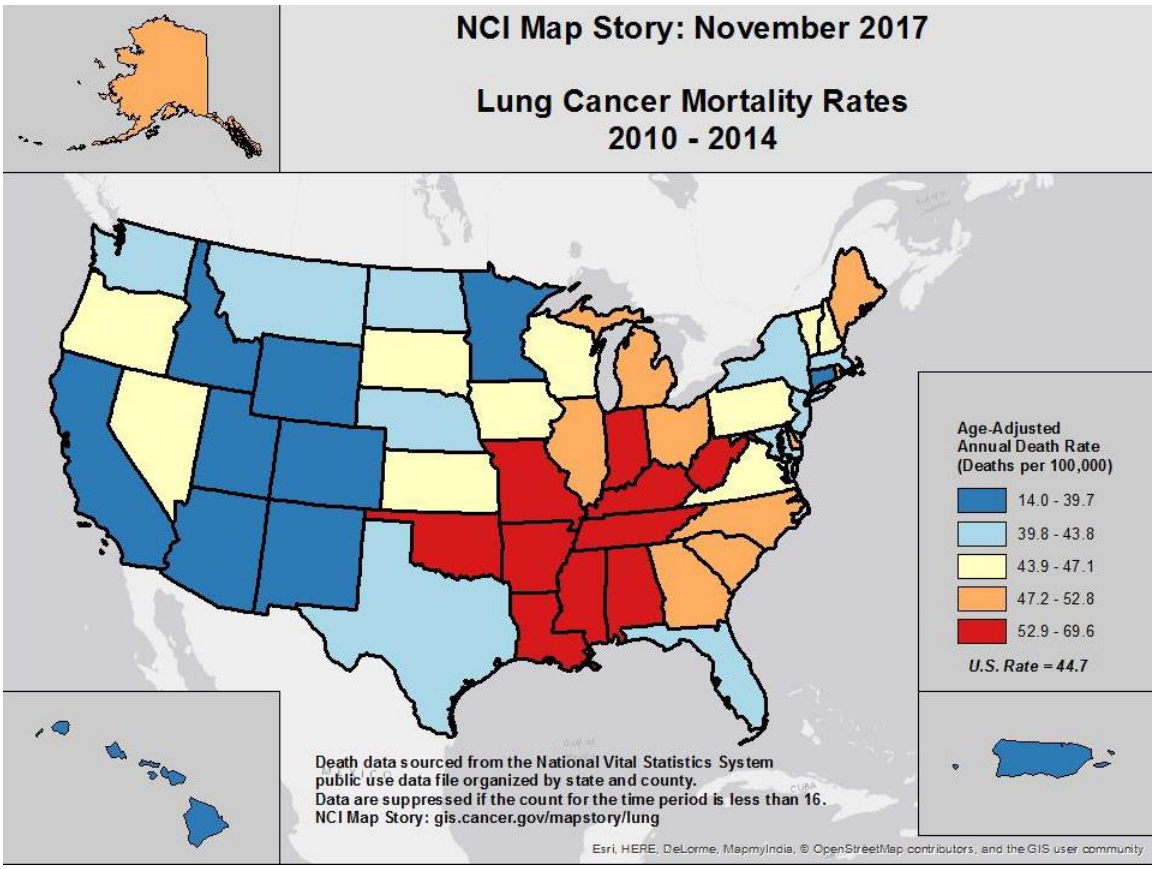

Figure 5. Map of lung cancer mortality in United States 2010-2014
(*Source: National Cancer Institute Map Story, https://gis.cancer.gov/mapstory/lung/*)

Although the curative-intent surgical resection rate in Tennessee is similar to the national level, the resection rate does not suffice to describe the value of surgery. Proper curative-intent resection requires a good quality resection (GQR),[39,42] which consists of two components: margin status and nodal examination. Many groups have attempted to define the minimally accepted standards, including the American College of Surgeons' Oncology Group (ACOSOG), the NCCN, and the OSI Pharmaceutical's RADIANT trial. All three criteria have evaluated margin status and the number of lymph node/station examined in the resections. The ACOSOG standard requires the most stringent GQR criteria and the RADIANT is the least. Osarogiagbon's study analyzed the NSCLC resections from 2004 to 2007 in the Memphis metropolitan area and found that 23% of

the NSCLC resected patients achieved the RADIANT criteria; 8.2% achieved the NCCN criteria; and only 0.9% achieved the ACOSOG criteria.[39] A second study by the same group evaluated the attainment of NCCN resection quality criteria in Mid-South region which revealed that the attainment rate increased from 2% in 2004 to 15% in 2009 to 39% in 2013. While the attainment rate was improving, it was still overall low.[28] The national margin positivity proportion was about 4.6%[12,13,16,43]; while the positive margin rate in Mid-South region was 6%;[41] the Memphis metropolitan area rate was even higher at 8.4%.[39] The rate of no mediastinal examination was about 45% in the Mid-South region which was higher than the national rate of about 40%.[44,45] Although the pattern of surgical resection for NSCLC showed trends towards higher quality in the Mid-South region, the quality gap remains.[45] Lung cancer in the Mid-South region is an important public health issue and additional work is needed to study this high-need population.

To fill knowledge gaps around margin positivity in this region, we used the Mid-South Quality of Surgical Resection (MS-QSR) Cohort to disentangle positive margin's preoperative risk factors, the impact of postoperative treatments on positive margin, and survival outcomes in the Mid-South. The MS-QSR cohort is a population-based study in 12 hospitals with 5 or more annual curative-intent lung cancer resections in four Dartmouth Hospital Referral Regions (DHRR) surrounding Memphis, Tennessee, including 95% of the lung cancer resections in the catchment area.[46] The DHRR is a geographic unit developed by the Dartmouth Atlas of Health Care to delineate regional health care markets in the U.S. The regions of DHRR are composed of zip code areas grouped together based on the referral patterns for tertiary care for Medicare beneficiaries. There are 306 regions in the U.S. and their boundaries often cross state

lines. The DHRR for Memphis, Tennessee, includes parts of eastern Arkansas, northern Mississippi, and West Tennessee. The MS-QSR cohort contains information about patient's demographic and clinical characteristics, surgeon's characteristics, and institutional characteristics from January 1, 2009. It is continuously updated in real time by trained data abstractors using source clinical data from all participating institutions, and survival updates are made through each institution's Tumor Registry at 6-month intervals.

Chapter 2

Factors Associated with Margin Positivity of Non-Small Cell Lung Cancer

Background

Previous studies have linked many risk factors to incomplete surgical resections including patient's clinical characteristics, preoperative diagnosis, extent and technique of surgery, surgeon characteristics, and hospital characteristics. Osarogiagbon's 2016 study revealed that squamous histology type, high tumor grade, advanced pathologic stage, and tumors overlapping more than a single lobe were predictors of margin positivity using the NCDB. However, this analysis was limited in scope due to the information available in the NCDB.[12] Moreover, some risk factors for positive margins were not in agreement with previous studies. For example, Osarogiagbon's study showed that positive margins were more common in patients with stage I (35.5%) and II (36.5%) NSCLC comparing to those with advanced stages (stage III).[47] On the other hand, Gress and Kaiser's study found that the rate of positive margin increases with the advance of disease stages (III and IV).[25,48] Although previous reports indicated that the preoperative diagnosis is associated with the occurrence of the margin positivity,[49] Osarogiagbon's study did not include the variables of preoperative evaluation such as PET/CT, EBUS, or EUS in their analyses. This may bias the results. In addition, studies found that the preoperative diagnosis quality was suboptimal in the Mid-South region. Faris and colleagues analyzed the surgical care quality from 2004-2013 with the MS-QSR cohort. Over the timespan, 64% of NSCLC patients had a PET-CT, and only 11% had mediastinoscopy,[45] lower than the national average of 27%.[24] Thus, re-building the model

including comprehensive variables to understand the risk factors of the positive margin is needed.

Surgeon specialty was also shown to be associated with surgical quality and long-term survival after a lung cancer resection.[50,51] Ferraris and colleagues analyzed the American College of Surgeons National Surgical Quality Improvement Project database and found that thoracic surgeons had significantly improved surgical outcomes, comparing to general surgeons.[52] Schipper et al. used the Nationwide Inpatient Sample (NIS) database analyzing the influence of surgeon specialty on the thoracic surgical outcomes. This study found that most surgical resections were performed by general surgeons (56% vs. 44%), but thoracic surgeons achieved better outcomes than general surgeons after adjusting for hospital and surgeon annual surgical volume (aHR=0.59; 95% CI: 0.41-0.85).[53] In addition, Birkmeyer's study, which used Medicare claims data from 1998 to 1999, showed that the postoperative mortality rate for lung cancer resections was higher in low-volume surgeons than high-volume surgeons.[54]

The impact of expertise at the hospital level on surgical outcomes also has been evaluated, with mixed results. Many U.S. studies have demonstrated that high surgical volume hospitals are associated with better postoperative survival outcomes.[51,55,56] An English study also suggested that NSCLC patients who received surgical resections in high-volume resection hospitals yielded better postoperative survival.[57] Furthermore, Bach's study suggested that teaching hospitals had improved survival outcomes, regardless of hospital volume.[55] Meguid's study also indicated that the surgical outcome for lung cancer resections improved at teaching hospitals using the NIS, comprising about 90% of all hospital discharges in the US. However, they revealed that the hospital

resection volume was not associated with the surgical outcomes.[58] Kozower's study used the NIS database and also found that hospital volume was not significantly associated with the mortality when volume was measured as continuous variable but was found significantly if measured as quintiles.[59] In summary, these studies did not distinctively identify the role of margin positivity in their analyses. The case volumes, surgeon specialty, and hospital's teaching status could be confounders between margin status and survival. Because overall survival is lower among the incomplete resections and the efficacy of adjuvant treatments is not well understood, it is important to understand the preoperative risk factors of margin positivity to aid in treatment decision making.

Although the impact of margin status on patient's long-term survival has been frequently reported,[12,20,26,60] little information is known about the impact of different anatomic sites on overall survival. The overall five-year survival rate for patients with R1 resections is about 14% and 0% of R2 patients survive 12 months after surgery.[20] Overall survival and treatment strategies may vary across the anatomic sites of margin positivity. Even within the same anatomic site, data on survivorship and postoperative treatments were too varied to draw meaningful conclusions on the survival impact and standard treatment modality of the margin location.[33,34,36,61-63] For example, Dilege and colleagues investigated 43 NSCLC patients who received surgical resection between January 1990 and January 1998. Of the 43 resections, 37 had complete resections and 6 had chest wall margins. The median survival time for patients with chest wall margins was 16.8 months (95% CI, 6.8-26.6 months) and the 5-year survival rate was 34%.[61] Riquet and colleagues analyzed 4,026 patients of Georges Pompidou European Hospital (Paris) and Cedar Surgery Centre (Boisguillaume) from 1984 to 2006. They reported that 216 (5.4%)

patients had positive margin. Of the 216 positive margins, 43 (19.8%) were chest wall margin. The median survival time for the patients with chest wall margin was 12 months, and the 5-year survival rate was 14%.[26] Tandberg's study investigated 74 NSCLC surgical resected patients at Duke University Medical Center from 1995 to 2014. Of these 74 patients, seven had chest wall margins. The overall 5-year survival rate of a chest wall margin was 65%.[62] Unfortunately, this study did not provide the median survival time for the chest wall margin. The hazard ratio of margin positivity was 2.43 (95% CI: 0.60-11.78), compared with those with negative margins. This study also found that radiation therapy did not improve the overall survival of patients with a chest wall margin compared to those with no adjuvant treatment. However, a study from Chiappetta's team indicated that patients with a chest wall margin and postoperative radiation therapy had better 2-year survival than patients with a chest wall margin who were untreated postoperatively.[63] To summarize, the five-year survivorship of NSCLC patients with a chest wall margin in these studies is very different from each other and the effectiveness of radiotherapy for chest wall margin is not consistent across studies.

The survival experience for patients with positive bronchial margins is different from that of patients with positive chest wall margins.[26,33,61] Riquet's study found that the 5-year survival rate of bronchial margin was 29.3%, whereas that of chest wall was 12%.[26] Lee and colleague showed that bronchial margin is a risk factor for stage I and stage II patients; the overall survival rate was 50% at year 3 and 30% at year 5. Their study also showed that postoperative treatment only improved the survival rate in stage IIIA patient with bronchial margin.[33] Nevertheless, Gebitekin's team reported a different result on bronchial margin. They found that bronchial margin does not affect survival in

patients with stage I or stage II disease and that radiation therapy did not affect the recurrence and survival of NSCLC.[34] Given the above information, this study compared survival outcomes among those with positive margins across anatomic sites. Our findings will contribute to future evidence-based guidelines and recommendations for clinical management.

Methods

Patients

As of May 10, 2019, the MS-QSR dataset had enrolled 3,640 lung cancer resected patients. Per the purpose of this study, we excluded the non-NSCLC patients and NSCLC patients with pathologic stages IV, as those were considered not eligible for surgical resection.[8,12,16,64-66] Patients with second surgical resections were excluded because they were duplicated with different study ID numbers (Figure 6). In this current study, we strictly categorized patients according to NCCN postoperative treatment criteria by stage.

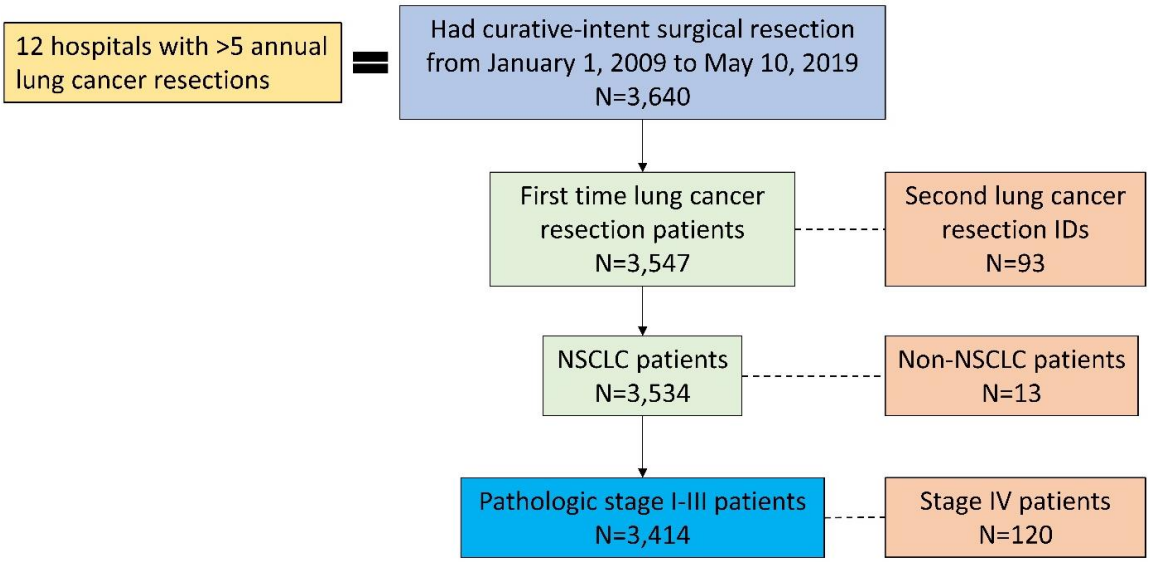

Figure 6. Consort diagram

Exposure and Outcome

We included risk factors that were significantly associated with positive margins that have been identified in previous studies.[12,14,23,48] We also included factors that were not available in previous studies but were also clinically important such as preoperative evaluations, accuracy of TN staging, technique of resection, surgeon's board certification, and surgeon's volume of lung cancer surgery in our analysis to provide a more complete picture of this issue. The accuracy of staging report was determined by comparing the independently determined pT (pathologic T) and pN categories with the officially reported pT and pN categories. Pathologic T and N categories were independently determined by trained data abstractors for each patient based on a thorough review of all details in the pathology report. These independent calculations were then audited by a second member of the research team. Accurate staging report required that each category was completed and matched the independently calculated category. Our primary outcome of interest was margin positivity, which was dichotomized as yes/no. The table below (Table 3) outlines the factors that were included in the analysis. Our secondary outcome of interest was postoperative survival. Margin positivity was the primary exposure variable as we estimated the survival outcome. The anatomic site, a secondary exposure, was defined as the location of positive surgical margins, categorized by the most prevalent sites as bronchial steam wall margin, peribronchial wall margin, chest wall margin, lung tissue margin, etc. In this analysis, the reference group was the negative margin.

Table 3. Potential risk factors included in the Logistic regression

Variables significantly associated with positive margin in previous studies	**Variables were added to this study, but not available in previous studies**
Age	Clinical stage
Race	Chest CT
Insurance status	PET/CT
Income	Mediastinoscopy
Patient residency	Mediastinoscopy or Bronchoscopy staging
Histology	UICC guideline-concordant lymph node examination
Tumor grade	Accuracy of TN staging
Tumor site	Neo-adjuvant treatment
Extent of Surgery	Technique of resection
Hospital volume	Surgeon's service year
Hospital teaching program	Surgeon's board certification
	Surgeon's volume of surgery
	Surgeon's predominant practice (general thoracic, cardiovascular, general surgery)
	Hospital rurality

Potential Confounders

According to previous studies,[16,23,31,37,50-59] potential confounders for the association between margin positivity and overall survival include age at surgery, sex, Charlson's comorbidity condition, income, insurance, histology, tumor grade, tumor site, preoperative evaluations, accuracy of TN staging, clinical stage, technique and extent of surgery, neo-adjuvant treatment, pathologic stage, adjuvant treatment, surgeon's board of certification, surgeon's predominant practice, surgeon's volume of surgery, hospital teaching status, hospital surgical volume, and rurality of hospital. To determine an unbiased estimate of the exposure and outcome, we adopted a simple 6-step directed acyclic graph (DAG) approach proposed by Shrier and Platt.[67] With this 6-step approach, we only included a subset of necessary confounders to yield an unbiased estimate of effect and the statistical efficiency of the analysis was increased due to the fewer

confounders in the model. The 6 step approach includes (1) checking that the confounders are not a descendant of exposure, (2) the confounders should be the ancestor of exposure and outcome, (3) unlink the lines emanating from exposure, (4) variables which are non-ancestor of the confounders, (5) remove all the arrowheads from the lines, and (6) the exposure is dissociated from the outcome after the above steps. Among the potential confounders, postoperative treatment was excluded from DAG because it was a descendant of margin status; Charlson's comorbidity condition and pathologic stage was excluded because it was not the ancestor of margin status; and patient's residency was also excluded since it was not an ancestor of outcome (survival). The final causal pathway is shown in Figure 7.

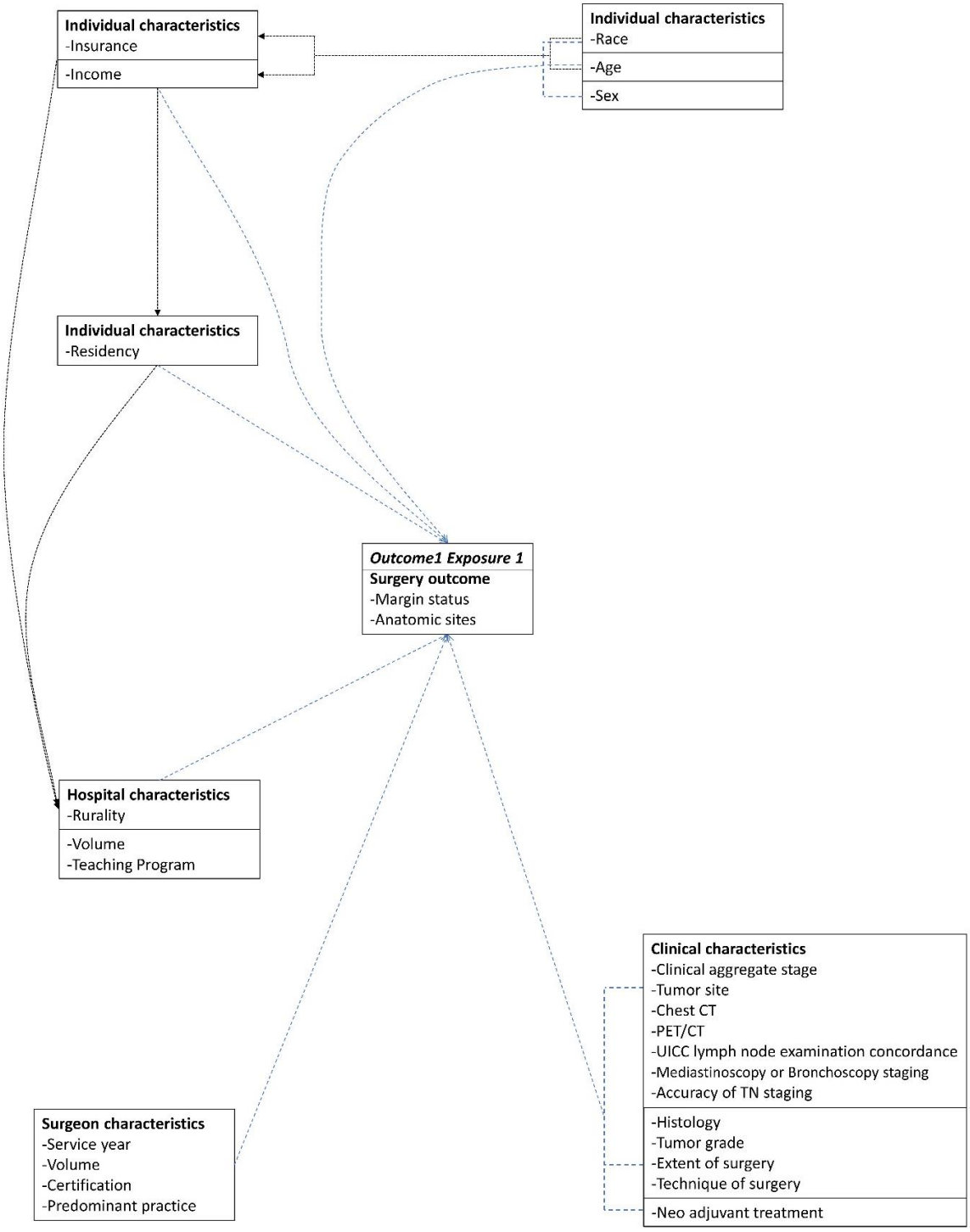

Figure 7. Causal pathway of risk factors and margin status

Statistical analysis

We summarized patient, surgeon, and facility information for the entire cohort and reported as mean and standard deviation (SD) or as frequency and percentages (%). Comparisons between complete (R0) and incomplete (R1/2) resection groups were made using the Chi-square test for categorical data and using the t-test or Wilcoxon-Mann-Whitney test for continuous data. We first estimated the associations between the potential risk factors and positive margin using univariate logistic regressions, modeling the positive margin as a function of the factors outlined above. Variables were included in the multivariable model if they met at least one of the following criteria: (1) p-value ≤0.25 in univariate model, (2) odds ratio in top 15% of all the odds ratios in univariate model, or (3) deemed clinically important.[68,69] Multivariable logistic regression models were used to evaluate associations between positive margins while adjusting for other explanatory variables. Upon arrival at the final model, collinearity via variance inflation factors (VIF) was checked and model fit statistics were also examined. We reported the p-values and model-based odds ratios or hazard ratios with 95% confidence intervals (CI).

We evaluated the crude overall survival with Kaplan-Meier estimates. Next, we assessed the adjusted hazard ratio using the Cox proportional hazard regression where survival was a function of margin status/anatomic sites with potential confounders. We checked effect modifiers (via interaction terms) prior to the investigation of the potential confounders. We picked up the variables that were deemed clinically relevant important including clinical stages, accuracy of staging, tumor site, surgeon's board certification and predominant practice, and teaching program. The significant level of effect modifiers

was set to $p<0.05$. The significant effect-modifying variables were then retained in the multivariable model as a part of main effect when we conducted the confounder examinations. With the remaining potential confounders from the 6-step DAG approach (Figure 8), we retained confounders in the multivariable model if it (1) changed the effect (HR) of the main exposure by at least 10% or (2) was deemed clinically important, regardless of statistical properties.[68,69] We started with a fully adjusted model with margin status and all the potential confounders as the explanatory variable. The involving sequences of the potential confounders were determined by the strength of the parameter estimate of each covariate. We first selected the potential confounders with the largest parameter estimate and evaluated the change in hazard ratio when adjusting and not adjusting for the confounder. If the hazard ratio associated with margin status changed greater than 10%, the variable was considered as a confounder and was retained in the multivariable model. If the change was less than 10%, we removed this variable from the model. We then checked the covariate with the second largest parameter estimate in turn and so forth. See the model selection flow chart in Figure 9. We used log-log survival curves to graphically evaluate the proportional hazard assumption. The type I error rate was controlled at the 0.05 level. All analyses were conducted by SAS 9.4 (SAS Institute Inc., Cary, NC)

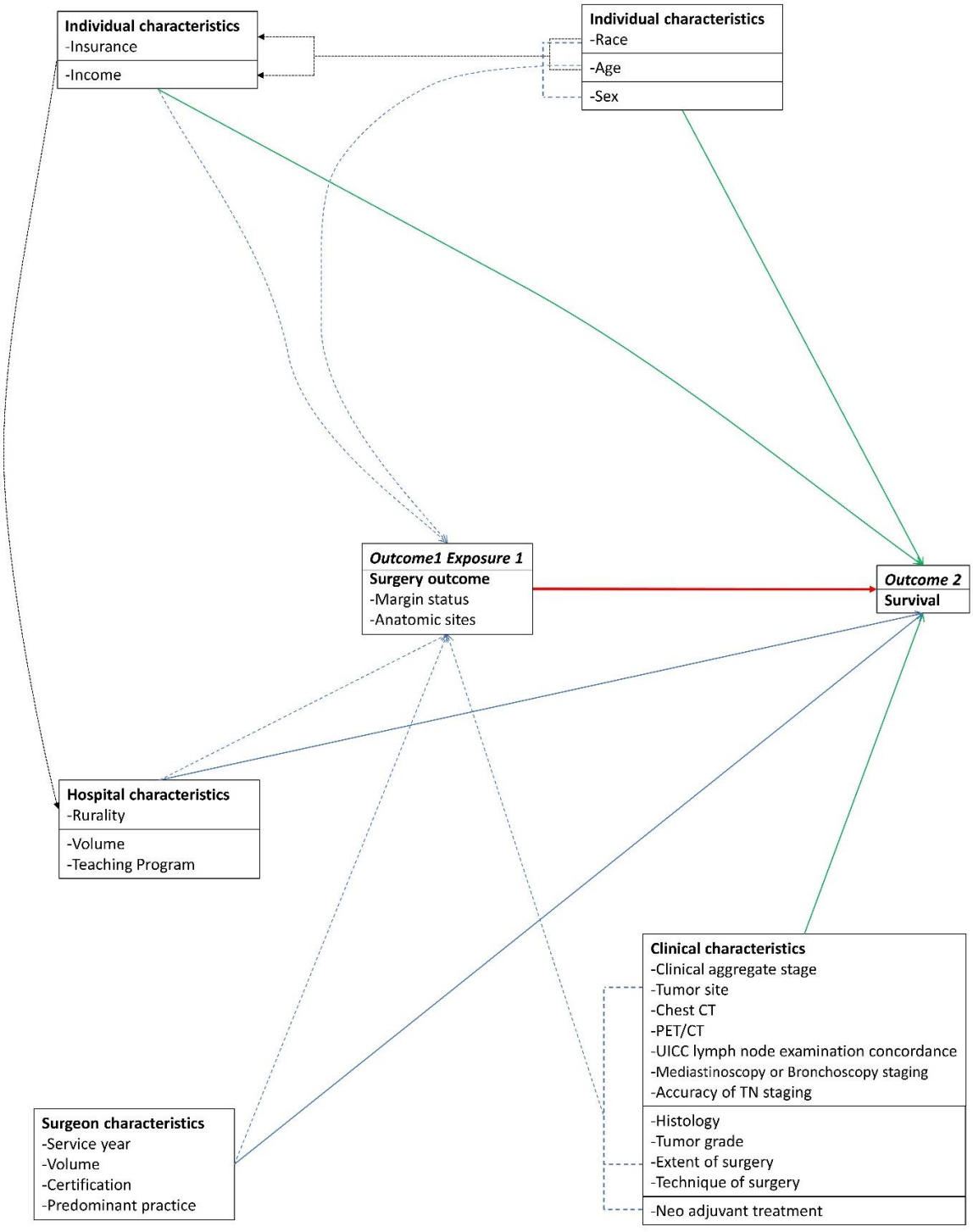

Figure 8. Causal pathway of margin status and survival

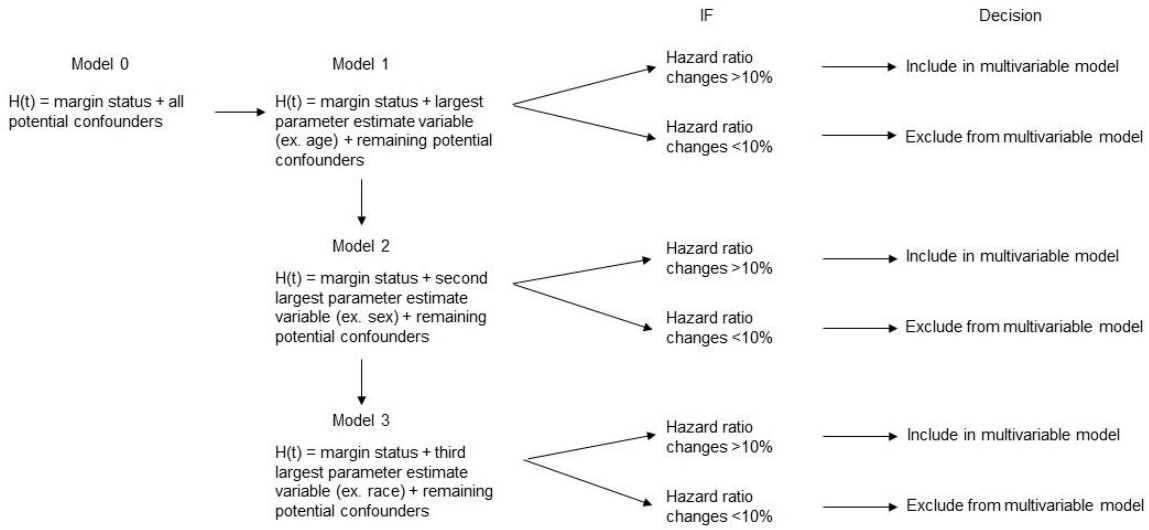

Figure 9. Variable selections for multivariable Cox proportional hazard regression

Results

The overall MS-QSR cohort consisted of 3,640 patients who had surgical resection between January 2009 and May 2019. We excluded 133 (3.7%) patients with SCLC or Stage IV disease; the 93 (2.6%) patients who had second surgery with different study IDs were also excluded from the patient list, providing an analytic cohort of 3,414 patients (Figure 6) with a median follow-up time of 3.6 years. Among these, 166 (4.9%) patients experienced incomplete resections (Table 4), of which 150 (4.4%) were R1 disease and 16 (0.5%) were R2. Patients with a positive margin were more frequently male (69% vs. 54%, $p<0.001$), had an overlapping primary tumor site (13% vs. 5%, $p<0.001$), had advanced clinical stage (II and III vs. I) (53% vs. 29%, $p<0.001$) and advanced pathologic staging (72% vs. 37%, $p<0.001$), were more likely to receive neo-adjuvant treatment (12% vs. 4%, $p<0.001$) and adjuvant treatment (34% vs. 17%, $p<0.001$), were more likely to receive open technique (72% vs. 59%, $p<0.05$) and pneumonectomy (13% vs. 5%, $p<0.001$), were more likely to have inaccurate TN staging

(10% vs. 5%, $p<0.05$), and were more likely to undergo the surgical resections in urban location of hospitals (90% vs. 82%, $p<0.05$) (Table 4).

The 166 positive margin patients had various anatomic locations, of which 44 (26.5%) were at mainstem bronchial wall; 37 (22.3%) were at peribronchial wall; 30 (18.1%) were at chest wall; 27 (16.3%) were at lung tissue; and 28 (16.8%) were at other margin locations including great vessel and mediastinum.

Moreover, patients' demographic and clinical characteristics varied by the anatomic site of the margin (Table 4). The mainstem bronchial wall margin appeared more in patients whose primary tumor was in the lower lobe (25%, $p<0.05$) and UICC guideline concordant (57%, $p<0.05$) comparing to those with other anatomic sites.

Peribronchial wall margin happened more to patients with private insurance plan (62%, $p<0.05$) and primary tumor at middle lobe (19%, $p<0.05$) and overlapping lobe (24%, $p<0.05$).

Chest wall margin existed more in patients with Medicare insurance plan (60%, $p<0.05$), squamous cell carcinoma (60%, $p<0.05$), primary tumor at upper lobe (83%, $p<0.05$), advanced clinical stage (II and III) (63%, $p<0.001$), Bilob/lobectomy (83%, $p<0.001$), and surgeons with general certifications (70%, $p<0.05$).

Lung tissue margins took place more in patients who had no insurance plan (15%, $p<0.05$), with adenocarcinoma (67%, $p<0.05$), and received wedge resection (26%, $p<0.001$) comparing to those with other anatomic sites.

Patients with other positive margins at great vessel and mediastinum were less likely to follow the UICC guidelines (75%, $p<0.05$) for the NSCLC treatment than their counterpart (Table 4).

Table 4. Demographic, clinical, surgeon, and hospital characteristics

	Margin status						
	Negative	**Positive**					
	Total negative (N=3,248)	Total positive (N=166)	Anatomic sites				
			Mainstem Bronchial margin (N=44)	Peribronchial margin (N=37)	Chest wall margin (N=30)	Lung tissue margin (N=27)	Other margins (N=28)
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Patient characteristics							
Age, mean (SD)	67.2 (9.2)	67.0 (10.5)	67.3 (12.0)	66.1 (10.3)	68.1 (12.2)	67.5 (8.7)	66.0 (8.2)
Sex							
Male	1742 (54)	115 (69)**	30 (68)	24 (65)	22 (73)	21 (78)	18 (64)
Female	1506 (46)	51 (29)	14 (32)	13 (35)	8 (27)	6 (22)	10 (36)
Race/Ethnicity							
Caucasians	2528 (78)	128 (78)	38 (86)	31 (84)	23 (77)	19 (70)	18 (64)
Hispanic	16 (0.5)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)	1 (4)
African American	670 (21)	34 (20)	5 (11)	5 (14)	7 (23)	8 (30)	9 (32)
Other	35 (1)	2 (1)	1 (2)	1 (3)	0 (0)	0 (0)	0 (0)
Charlson's comorbidity							
0	638 (21)	37 (22)	7 (16)	12 (32)	6 (20)	3 (11)	9 (32)
1	925 (29)	53 (32)	11 (25)	12 (32)	10 (33)	10 (37)	10 (36)
2+	1640 (50)	76 (46)	26 (59)	13 (35)	14 (47)	14 (52)	9 (32)

Table 4. (Continued)

	Margin status						
	Negative	**Positive**					
	Total negative (N=3,248)	Total positive (N=166)	Anatomic sites				
			Mainstem Bronchial margin (N=44)	Peribronchial margin (N=37)	Chest wall margin (N=30)	Lung tissue margin (N=27)	Other margins (N=28)
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Income (Household median)							
< 30,000	678 (21)	45 (27)	7 (16)	8 (22)	6 (20)	14 (52)	10 (36)
30,000-34,999	644 (20)	32 (19)	10 (23)	8 (22)	8 (27)	1 (4)	5 (18)
35,000-45,999	931 (29)	40 (24)	15 (34)	8 (22)	6 (20)	5 (19)	6 (21)
> 46,000	995 (30)	49 (30)	12 (27)	13 (34)	10 (33)	7 (26)	7 (25)
Insurance							
Medicare	1409 (43)	64 (39)	18 (41)	10 (27)	18 (60)	9 (33)	9 (32)*
Medicaid	476 (15)	20 (12)	5 (11)	3 (8)	7 (23)	2 (7)	3 (11)
Private	1254 (39)	74 (45)	19 (43)	23 (62)	5 (17)	12 (44)	15 (54)
Uninsured	109 (3)	8 (5)	2 (5)	1 (3)	0 (0)	4 (15)	1 (4)
Residency							
Rural	1664 (51)	78 (47)**	23 (52)	19 (51)	16 (53)	8 (30)	12 (43)*
Urban	1384 (43)	65 (39)	19 (43)	16 (43)	12 (40)	8 (30)	10 (36)
Unknown	200 (6)	23 (14)	2 (5)	2 (5)	2 (7)	11 (40)	6 (21)

Table 4. (Continued)

	Margin status						
	Negative	**Positive**					
	Total negative (N=3,248)	Total positive (N=166)	Anatomic sites				
			Mainstem Bronchial margin (N=44)	Peribronchial margin (N=37)	Chest wall margin (N=30)	Lung tissue margin (N=27)	Other margins (N=28)
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Histology							
Squamous	1098 (34)	70 (42)*	21 (48)	16 (43)	18 (60)	5 (19)	10 (36)*
Large cell	110 (3)	7 (4)	2 (5)	0 (0)	0 (0)	3 (11)	2 (7)
Adenocarcinoma	1759 (54)	73 (44)	14 (32)	17 (46)	11 (37)	18 (67)	13 (46)
NOS	278 (9)	15 (9)	7 (16)	4 (11)	1 (3)	1 (4)	2 (7)
Other	3 (0.1)	1 (0.6)	0 (0)	0 (0)	0 (0)	0 (0)	1 (4)
Tumor grade							
Well/Moderate differentiated	1763 (54)	81 (49)	23 (52)	20 (54)	14 (47)	11 (41)	13 (46)
Poorly/ undifferentiated	1051 (32)	66 (40)	19 (43)	9 (24)	14 (47)	13 (48)	11 (39)
Unknown	434 (13)	19 (11)	2 (5)	8 (22)	2 (6)	3 (11)	4 (14)
Primary tumor site							
Upper lobe	1871 (58)	97 (58)**	21 (48)	13 (35)	25 (83)	20 (74)	18 (64)*
Middle lobe	190 (6)	14 (8)	3 (7)	7 (19)	0 (0)	2 (7)	2 (7)
Lower lobe	1035 (32)	34 (21)	11 (25)	8 (22)	4 (13)	5 (19)	6 (22)
Overlapping	152 (5)	21 (13)	9 (20)	9 (24)	1 (4)	0 (0)	2 (7)

Table 4. (Continued)

	Margin status						
	Negative	**Positive**					
	Total negative (N=3,248)	Total positive (N=166)	Anatomic sites				
			Mainstem Bronchial margin (N=44)	Peribronchial margin (N=37)	Chest wall margin (N=30)	Lung tissue margin (N=27)	Other margins (N=28)
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Chest CT							
No	219 (7)	8 (5)	1 (2)	3 (8)	2 (7)	1 (4)	1 (4)
Yes	3028 (93)	157 (95)	43 (98)	34 (92)	28 (93)	26 (96)	26 (96)
PET/CT scan							
No	541 (17)	22 (13)	6 (14)	6 (16)	2 (7)	3 (11)	5 (18)
Yes	2707 (83)	144 (87)	38 (86)	31 (84)	28 (93)	24 (89)	23 (82)
Mediastinoscopy or Bronchoscopy staging							
No	2645 (81)	131 (79)	32 (73)	29 (78)	23 (77)	26 (96)	21 (75)
Yes	603 (19)	35 (21)	12 (27)	8 (22)	7 (23)	1 (4)	7 (25)
Accuracy of TN staging							
No	163 (5)	17 (10)*	1 (2)	3 (8)	5 (17)	2 (7)	6 (21)
Yes	3085 (95)	149 (90)	43 (98)	34 (92)	25 (83)	25 (93)	22 (79)
Clinical stage							
Stage 0	127 (4)	7 (4)**	0 (0)	6 (16)	0 (0)	0 (0)	1 (4)**
Stage I	2117 (65)	70 (42)	17 (39)	15 (41)	11 (37)	14 (52)	13 (46)
Stage II	552 (17)	43 (26)	10 (22)	10 (27)	15 (50)	6 (22)	2 (7)
Stage III	404 (12)	44 (27)	16 (36)	6 (16)	4 (13)	7 (26)	11 (39)
Stage IV	48 (2)	2 (1)	1 (2)	0 (0)	0 (0)	0 (0)	1 (4)

Table 4. (Continued)

	Margin status						
	Negative	**Positive**					
	Total negative (N=3,248)	Total positive (N=166)	Anatomic sites				
			Mainstem Bronchial margin (N=44)	Peribronchial margin (N=37)	Chest wall margin (N=30)	Lung tissue margin (N=27)	Other margins (N=28)
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Neo-adjuvant treatment							
No	3128 (96)	147 (88)**	42 (95)	32 (86)	25 (83)	26 (96)	22 (79)
Yes	120 (4)	19 (12)	2 (5)	5 (14)	5 (17)	1 (4)	6 (21)
Extent of surgery							
Pneumonectomy	167 (5)	22 (13)**	10 (23)	9 (24)	1 (3)	0 (0)	2 (7)**
Bilob/lobectomy	2677 (82)	123 (74)	34 (77)	27 (73)	25 (83)	19 (70)	18 (64)
Segmentectomy/ Wedge resection	136 (4)	4 (2)	0 (0)	1 (3)	1 (3)	1 (4)	1 (4)
Wedge resection	268 (8)	17 (10)	0 (0)	0 (0)	3 (10)	7 (26)	7 (25)
Technique of surgery							
Open	1933 (59)	119 (72)*	34 (77)	27 (73)	22 (73)	18 (67)	18 (64)
RATS	837 (26)	25 (15)	8 (18)	7 (19)	3 (10)	1 (4)	6 (21)
VATS	479 (15)	22 (13)	2 (5)	3 (8)	5 (17)	8 (30)	4 (14)
UICC guideline-concordant lymph node examination							
No	1763 (54)	95 (57)	19 (43)	19 (51)	16 (53)	20 (74)	21 (75)*
Yes	1485 (46)	71 (43)	25 (57)	18 (49)	14 (47)	7 (26)	7 (25)

Table 4. (Continued)

	Margin status						
	Negative	**Positive**					
	Total negative (N=3,248)	Total positive (N=166)	Anatomic sites				
			Mainstem Bronchial margin (N=44)	Peribronchial margin (N=37)	Chest wall margin (N=30)	Lung tissue margin (N=27)	Other margins (N=28)
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Pathologic stage							
Stage I	2047 (63)	46 (28)**	12 (27)	13 (35)	0 (0)	9 (33)	12 (43)**
Stage II	707 (22)	52 (31)	14 (32)	5 (14)	19 (63)	9 (33)	5 (18)
Stage III	494 (15)	68 (41)	18 (41)	19 (51)	11 (37)	9 (33)	11 (39)
Adjuvant treatment							
No	2688 (83)	110 (66)**	30 (68)	26 (70)	21 (70)	15 (56)	18 (64)
Yes	560 (17)	56 (34)	14 (32)	11 (30)	9 (30)	12 (44)	10 (36)
Surgeon Characteristics							
Board of Certification							
Cardiothoracic	1151 (35)	57 (34)	9 (80)	13 (35)	9 (30)	16 (59)	10 (36)*
General only	2097 (65)	109 (66)	35 (20)	24 (65)	21 (70)	11 (41)	18 (64)
Predominant practice (thoracic or cardiovascular)							
No	1986 (61)	103 (62)	25 (57)	24 (65)	18 (60)	17 (63)	19 (68)
Yes	1262 (39)	63 (38)	19 (43)	13 (35)	12 (40)	10 (37)	9 (32)

Table 4. (Continued)

	Margin status						
	Negative	**Positive**					
	Total negative (N=3,248)	Total positive (N=166)	Anatomic sites				
			Mainstem Bronchial margin (N=44)	Peribronchial margin (N=37)	Chest wall margin (N=30)	Lung tissue margin (N=27)	Other margins (N=28)
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Years of service, mean (SD)	30.9 (10.0)	30.6 (10.8)	31.3 (10.7)	33.1 (9.2)	31.0 (10.5)	26.7 (12.0)	29.3 (11.7)
Annual surgical volumes in lung cancer, mean (SD)	29.9 (28.0)	31.0 (29.7)	34.7 (29.7)	32.0 (30.9)	35.2 (31.4)	22.1 (26.5)	28.0 (28.9)
Hospital Characteristics							
Teaching Program							
No	1336 (41)	66 (40)	22 (50)	15 (41)	12 (40)	7 (26)	10 (36)
Yes	1912 (59)	100 (60)	22 (50)	22 (59)	18 (60)	20 (74)	18 (64)
Location of hospital							
Urban	2681 (82)	150 (90)*	40 (91)	33 (89)	25 (83)	27 (100)	25 (89)
Rural	567 (18)	16 (10)	4 (9)	4 (11)	5 (17)	0 (0)	3 (11)
Annual surgical volumes in lung cancer, mean (SD)	61.4 (45.8)	56.6 (46.1)	51.0 (43.9)	59.1 (49.5)	69.8 (49.3)	49.0 (41.4)	55.3 (45.4)

*p<0.05; **p<0.001

The univariate logistic regression models showed that male gender (OR=1.95; 95% CI: 1.39-2.73), unknown residency (OR=2.45; 95% CI: 1.51-4.00), squamous histology (OR=1.54; 95% CI: 1.10-2.15), overlapping primary tumor sites (OR=2.67; 95% CI: 1.62-4.39), clinical stage II (OR=2.36; 95% CI: 1.59-3.48) and III (OR= 3.29; 95% CI:2.23-4.87), neo-adjuvant treatment (OR=3.37; 95% CI: 2.02-5.62), pneumonectomy (OR=2.87; 95% CI: 1.77-4.63), and urban hospitals (OR=1.98; 95% CI: 1.18-3.35) were significantly associated with margin positivity. In contrast, the lower lobe primary site (OR=0.63; 95% CI: 0.43-0.94) and accurate TN staging (OR=0.46; 95% CI: 0.27-0.78) were protective factors for positive margins (Table 5).

The multivariable logistic regression in Table 5 indicated that preoperative risk factors of margin positivity included male sex (OR=1.53; 95% CI: 1.07-2.20), unknown residency vs. rural (OR=2.31; 95% CI: 1.08-4.93), clinical stage II (OR=1.92; 95% CI: 1.27-2.92) and III vs. stage I (OR=2.48; 95% CI: 1.62-3.79), neo-adjuvant treatment (OR=2.81; 95% CI: 1.60-4.96), higher surgeon annual case volume (OR=1.02; 95% CI: 1.01-1.03), and urban location of hospital vs rural (OR=1.93; 95% CI: 1.04-3.55). Accurate TN staging (OR=0.53; 95% CI: 0.30-0.94) was a protective factor for margin positivity. The model fit statistics indicated that the multivariable logistic regression model had a good to strong fit (C Statistic= 0.74). In this sample, 90% of positive margin patients had their lung cancer treatment at an urban hospital (Table 4). As shown in Table 5, we found that surgeons with higher case volumes were more likely to end up with positive margin in surgical resections. When we drilled down, we also found that the higher the annual case volume the surgeons had, the shorter the length of surgery, after

adjusting for histology, primary site, tumor grade, clinical stage, and extent and technique of surgery ($p<0.0001$).

Table 5. Univariate and multivariable logistic regression of risk factors for margin positivity

	Univariate Odds Ratio (95% CI)	p-value	Multivariable Odds Ratio (95% CI)	p-value
Age	1.00 (0.98-1.01)	0.7630	1.01 (0.99-1.03)	0.5745
Sex				
Female	1		1	
Male	1.95 (1.39-2.73)	0.0001	1.53 (1.07-2.20)	0.0216
Race/Ethnicity				
Caucasians	1		-	-
Hispanic	1.23 (0.16-9.30)	0.8448	-	-
African American	0.99 (0.68-1.46)	0.9760	-	-
Other	1.12 (0.27-4.71)	0.8776	-	-
Income (Household median)				
< 30,000	1		1	
30,000-34,999	0.75 (0.47-1.19)	0.2233	1.02 (0.57-1.82)	0.9449
35,000-45,999	0.65 (0.42-1.00)	0.0513	0.95 (0.55-1.65)	0.8635
> 46,000	0.74 (0.49-1.13)	0.1600	1.10 (0.60-2.00)	0.7664
Insurance				
Commercial	1		1	
Medicare	0.77 (0.55-1.09)	0.1349	0.84 (0.57-1.25)	0.3922
Medicaid	0.71 (0.43-1.18)	0.1875	0.84 (0.49-1.43)	0.5151
Uninsured	1.24 (0.58-2.65)	0.5714	1.07 (0.47-2.41)	0.8804
Residency				
Rural	1		1	
Urban	1.00 (0.72-1.40)	0.9911	1.17 (0.72-1.89)	0.5198
Unknown	2.45 (1.51-4.00)	0.0003	2.31 (1.08-4.93)	0.0303
Histology				
Adenocarcinoma	1		1	
Squamous	1.54 (1.10-2.15)	0.0124	1.21 (0.84-1.73)	0.3034
Large cell	1.53 (0.69-3.41)	0.2944	1.30 (0.56-3.01)	0.5464
NOS	1.30 (0.74-2.30)	0.3667	1.35 (0.74-2.49)	0.3295
Other	8.03 (0.83-78.2)	0.0727	2.77 (0.23-33.0)	0.4215
Tumor grade				
Well/Moderate differentiated	1		1	
Poorly/undifferentiated	1.37 (0.98-1.91)	0.0664	1.12 (0.79-1.60)	0.5289
Unknown	0.95 (0.57-1.59)	0.8531	0.75 (0.43-1.31)	0.3150

Table 5. (Continued)

	Univariate Odds Ratio (95% CI)	p-value	Multivariable Odds Ratio (95% CI)	p-value
Primary tumor site				
Upper lobe	1		1	
Middle lobe	1.42 (0.80-2.54)	0.2347	1.70 (0.93-3.12)	0.0843
Lower lobe	0.63 (0.43-0.94)	0.0246	0.68 (0.45-1.03)	0.0674
Overlapping	2.67 (1.62-4.39)	0.0001	1.73 (0.25-12.3)	0.5820
Chest CT				
No	1		-	-
Yes	1.42 (0.69-2.93)	0.3428	-	-
PET/CT scan				
No	1		1	
Yes	1.31 (0.83-2.07)	0.2508	1.27 (0.78-2.06)	0.3334
Mediastinoscopy or Bronchoscopy lymph node biopsies				
No	1		1	
Yes	1.17 (0.80-1.72)	0.4171	0.93 (0.61-1.42)	0.7440
Accuracy of TN staging				
No	1		1	
Yes	0.46 (0.27-0.78)	0.0041	0.53 (0.30-0.94)	0.0285
Clinical stage				
Stage I	1		1	
Stage 0	1.67 (0.75-3.70)	0.2091	1.60 (0.70-3.64)	0.2664
Stage II	2.36 (1.59-3.48)	<.0001	1.92 (1.27-2.92)	0.0022
Stage III	3.29 (2.23-4.87)	<.0001	2.48 (1.62-3.79)	<.0001
Stage IV	1.26 (0.30-5.29)	0.7521	0.84 (0.19-3.71)	0.8148
Neo-adjuvant treatment (chemotherapy or radiotherapy)				
No	1		1	
Yes	3.37 (2.02-5.62)	<.0001	2.81 (1.60-4.96)	0.0003
Extent of surgery				
Bilob/lobectomy	1		1	
Pneumonectomy	2.87 (1.77-4.63)	<.0001	0.90 (0.13-6.07)	0.9149
Segmentectomy/ Wedge resection	0.64 (0.23-1.76)	0.3869	0.95 (0.34-2.66)	0.9163
Wedge resection	1.38 (0.82-2.33)	0.2264	1.20 (0.67-2.14)	0.5455
Technique of surgery				
VATS	1		1	
Open	1.33 (0.84-2.12)	0.2277	1.05 (0.63-1.74)	0.8508
RATS	0.65 (0.36-1.16)	0.1428	0.57 (0.30-1.08)	0.0861

Table 5. (Continued)

	Univariate Odds Ratio (95% CI)	p-value	Multivariable Odds Ratio (95% CI)	p-value
UICC guideline-concordant lymph node examination				
No	1		-	-
Yes	0.89 (0.65-1.22)	0.4570	-	-
Board of Certification				
Cardiothoracic	1		-	-
General only	0.95 (0.69-1.32)	0.7726	-	-
Predominant practice (thoracic or cardiovascular)				
No	1		1	
Yes	0.96 (0.70-1.33)	0.8166	0.58 (0.33-1.00)	0.0510
Years of service	1.00 (0.98-1.01)	0.6975	-	-
Annual surgical volumes in lung cancer (Surgeon)	1.00 (0.99-1.01)	0.6113	1.02 (1.01-1.03)	0.0006
Teaching Program				
No	1		-	-
Yes	1.06 (0.77-1.46)	0.7256	-	-
Location of hospital				
Rural	1		1	1
Urban	1.98 (1.18-3.35)	0.0104	1.93 (1.04-3.55)	0.0361
Annual surgical volumes in lung cancer (Hospital)	1.00 (0.99-1.00)	0.1916	1.00 (0.99-1.00)	0.1298

Figure 10 shows overall survival by margin status. The crude five-year survival rates for patients with complete and incomplete surgical resections were 56.5% and 34.8%, respectively ($p<0.0001$). The median survival time of complete surgical resection was 6.4 years, whereas that of positive margin was 2.3 years. The chest wall margin had the worst survival outcome with five-year survival rate of 24.1% (Figure 11). The five-year survival rates of mainstem bronchial margin, peribronchial margin, and lung tissue margin were 33.9%, 34.7%, and 26.8%, respectively. The other margin location (Great vessels and Mediastinum) had the least impact on the survival rate than the above anatomic sites with five-year survival rate at 57.8%.

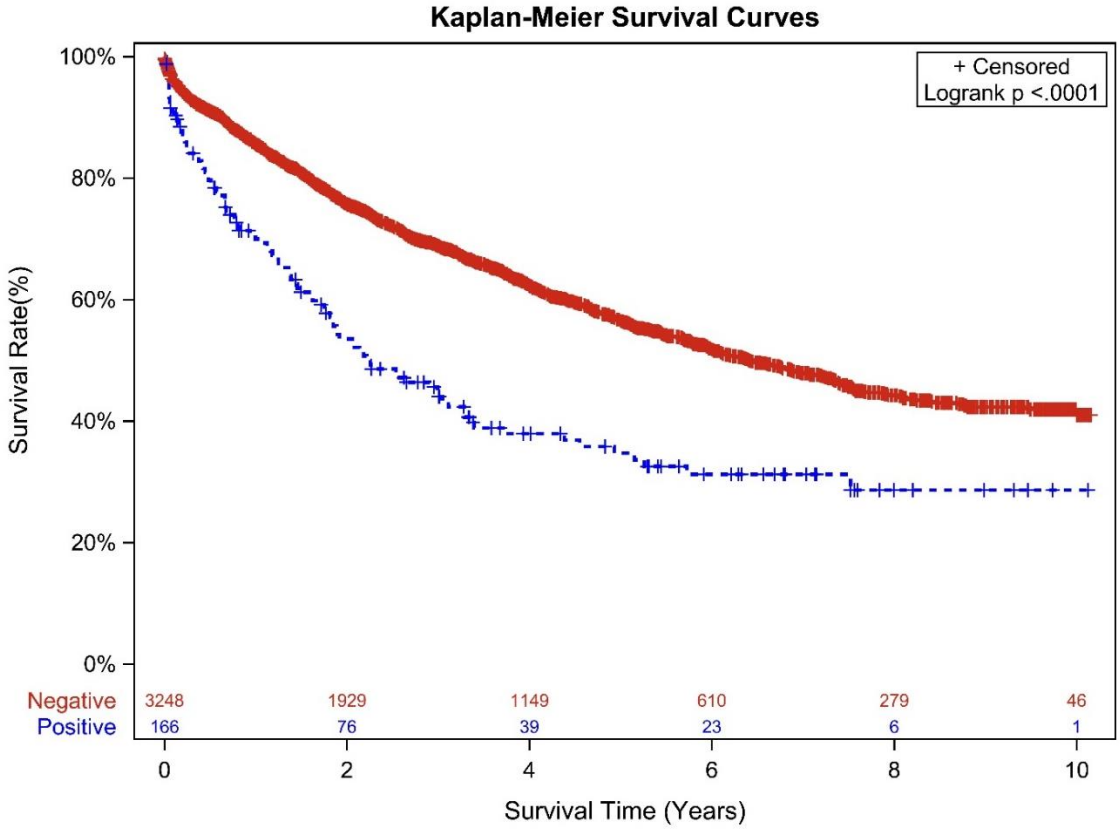

Figure 10. Kaplan-Meier survival curves by margin status

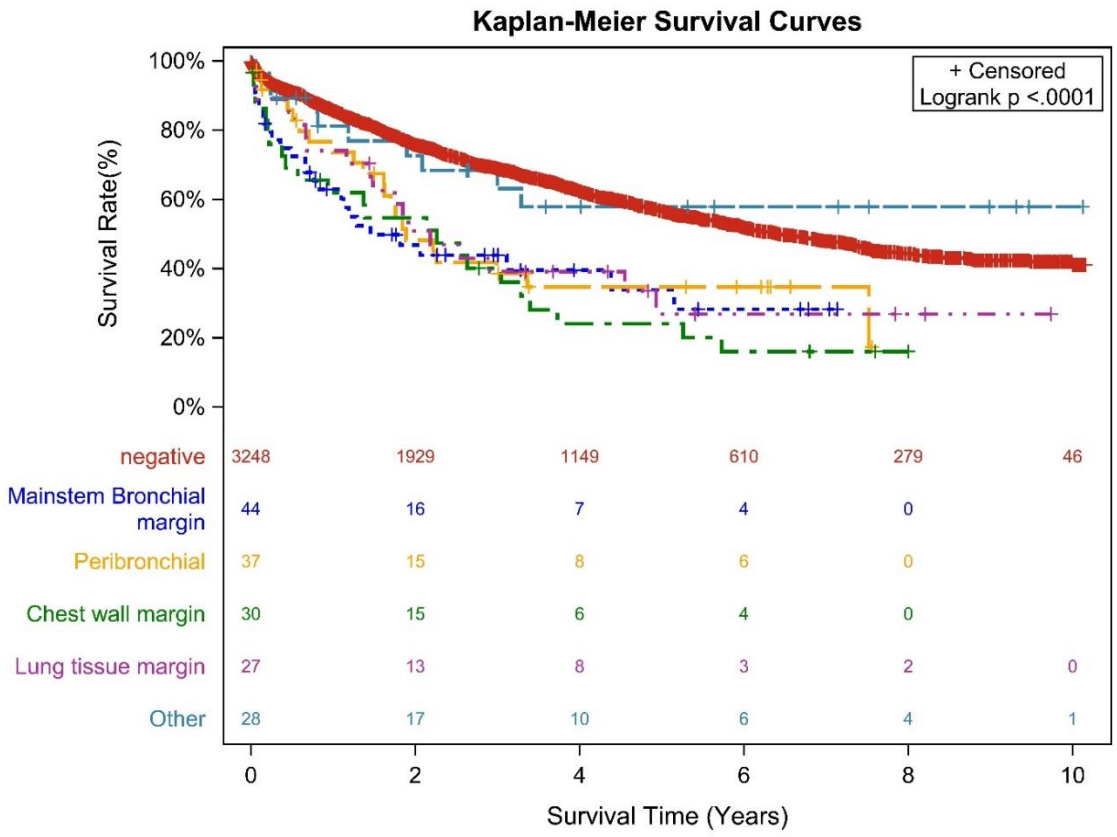

Figure 11. Kaplan-Meier survival curves by anatomic sites

Effect modifiers were not found in the Cox proportional hazard regressions estimating the relationship between margin status/anatomic sites and survival. After adjusting for potential confounders, margin positivity was independently associated with the overall survival (aHR=1.73, 95% CI: 1.40-2.13) (Table 6). We also found that the anatomic sites had different survival impacts compared to the negative margin. The mainstem bronchial wall margin (aHR=2.22, 95% CI: 1.50-3.29), peribronchial wall margin (aHR=1.76, 95% CI: 1.14-2.73); chest wall margin (aHR=1.95, 95% CI: 1.28-2.97), and lung tissue margin (aHR=1.82, 95% CI: 1.13-2.92) significantly undermined overall survival after adjusting for the confounders (Table 6). The log-log survival curves were parallel suggesting that the proportional hazard assumption was reasonable.

Table 6. Cox proportional hazard ratio regression of margin status and anatomic sites

	HR (95% CI) Main exposure: Margin status	p-value	HR (95% CI) Main exposure: Anatomic sites	p-value
Margin Status				
Negative	1		-	-
Positive	1.73 (1.40-2.13)	<.0001	-	-
Anatomic site				
Negative	-	-	1	
Mainstem Bronchial wall	-	-	2.22 (1.50-3.29)	<.0001
Peribronchial wall	-	-	1.76 (1.14-2.73)	0.0116
Chest Wall	-	-	1.95 (1.28-2.97)	0.0020
Lung Tissue	-	-	1.82 (1.13-2.92)	0.0139
Other	-	-	0.72 (0.38-1.36)	0.3157
Age	1.02 (1.02-1.03)	<.0001	1.02 (1.02-1.03)	<.0001
Sex				
Female	1		1	
Male	1.49 (1.33-1.66)	<.0001	1.50 (1.34-1.68)	<.0001
Insurance				
Commercial	-	-	1	
Medicare	1.39 (1.22-1.59)	<.0001	1.39 (1.21-1.59)	<.0001
Medicaid	1.70 (1.44-2.00)	<.0001	1.69 (1.43-1.99)	<.0001
Uninsured	1.24 (0.90-1.70)	0.1868	1.14 (0.83-1.56)	0.4362
Tumor grade				
Well/Moderate differentiated	1		1	
Poorly/undifferentiated	1.27 (1.13-1.42)	<.0001	1.26 (1.12-1.42)	0.0001
Unknown	1.02 (0.85-1.21)	0.8549	1.01 (0.85-1.20)	0.9075
Primary tumor site				
Upper lobe	1		1	
Middle lobe	1.05 (0.84-1.33)	0.6613	1.06 (0.84-1.33)	0.6411
Lower lobe	1.02 (0.91-1.15)	0.7272	1.01 (0.89-1.14)	0.8847
Overlapping	1.61 (1.29-2.00)	<.0001	1.36 (1.08-1.71)	0.0090
Mediastinoscopy or Bronchoscopy staging				
No	1		1	
Yes	1.02 (0.88-1.18)	0.8095	0.94 (0.81-1.09)	0.4277
Accuracy of TN staging				
No	1		1	
Yes	1.00 (0.79-1.27)	0.9892	1.02 (0.80-1.29)	0.8858

Table 6. (Continued)

	HR (95% CI) Main exposure: Margin status	p-value	HR (95% CI) Main exposure: Anatomic sites	p-value
Clinical stage				
Stage 0	-	-	1	
Stage I	-	-	1.40 (1.08-1.82)	0.0101
Stage II	-	-	1.41 (1.22-1.62)	<.0001
Stage III	-	-	1.61 (1.38-1.87)	<.0001
Stage IV	-	-	1.24 (0.84-1.83)	0.2742
Neo-adjuvant treatment (chemotherapy or radiotherapy)				
No	1		1	
Yes	1.46 (1.13-1.87)	0.0034	1.49 (1.16-1.91)	0.0021
Technique of surgery				
VATS	1		1	
Open	1.07 (0.91-1.26)	0.4307	1.00 (0.85-1.18)	0.9851
RATS	0.74 (0.60-0.90)	0.0029	0.79 (0.64-0.97)	0.0235
UICC guideline-concordant lymph node examination				
No	1		-	-
Yes	0.86 (0.77-0.96)	0.0089	-	-
Board of Certification				
Cardiothoracic	1		1	
General only	0.88 (0.78-1.00)	0.0578	0.88 (0.77-1.00)	0.0526
Predominant practice (thoracic or cardiovascular)				
No	1		1	
Yes	0.85 (0.72-0.99)	0.0391	0.90 (0.75-1.09)	0.3033
Annual surgical volumes in lung cancer (Surgeon)	-	-	1.00 (1.00-1.00)	0.0333
Teaching Program				
No	1		1	
Yes	1.22 (1.05-1.41)	0.0095	1.21 (1.04-1.40)	0.0128
Location of hospital				
Rural	1		1	1
Urban	1.05 (0.88-1.25)	0.6265	1.01 (0.85-1.21)	0.8741

Discussion

We evaluated factors associated with incomplete surgical resection and the survival implications of incomplete surgical resection of lung cancer in a population-based regional cohort. We identified several potential risk factors for margin positivity, including sex, patient's residency, clinical stage, neo-adjuvant treatment, surgeon annual case volume, and rurality of hospital. As in previous reports, we found worse survival outcomes in patients with incomplete resections compared to those with complete resections. Finally, we evaluated the survival implications of the site of the positive margin for patients with incomplete surgical resection.

The reported rate of margin positivity in the existing literature ranged from 1.2% to 17%.[70,71] An evaluation of the NCDB showed the national positive margin rate was 6%.[28] Our dataset, which represents a heterogeneous group of hospitals covering more than 95% of the Mid-South lung cancer surgical population, suggested an annual margin positive rate under 5%.

In the same study of the NCDB, Osarogiagbon and colleagues found that sex was not a significant risk factor for positive margins.[28] They also found that incomplete resection increased with the advanced tumor stages. Unlike the previous study, our project found that sex is significantly associated with margin status. Previous reports have also reported that positive margins may be more likely with more advanced T or N category tumors.[25] Kaiser's study found that positive margins were less frequent in early stage diseases, as 82% of the patients in their study had stage III disease.[48] Our finding was consistent with Osarogiagbon's study. We revealed that the risk for incomplete resection advances with tumor stage and positive margins are not sparse in stage I and II

NSCLC patients. Also different from previous reports,[28] Osarogiagbon's study found that sublobectomy was associated with the positive margin. However, we did not find an association between the extent of surgery and margin positivity.

Consistent with previous reports, we have demonstrated that neo-adjuvant therapy is a strong adverse factor for positive margins. Osarogiagbon's study found that neo-adjuvant treatment was associated with lower survival for the patients with incomplete surgical resection, in the NCDB cohort of the US population.[28] This finding was different from the recommendation of NCCN initial treatment guidelines for patients with invasive IIB and IIIA disease.[29] The guidelines suggested that neo-adjuvant treatment is needed prior to or concurrently with the surgery for the patients with invasive IIB and IIA disease. Further investigations may be needed to assess the associations between neo adjuvant treatment and the positive margin by stage.

We found a strong association between margin positivity and nonclinical characteristics, including sex, residency, annual case volume, and location of hospital. This finding is very different from the previous studies. These studies suggested that lack of preoperative and intraoperative evaluations was a risk factor of the positive margin.[21,24,25,45,46,49,72,73] However, as we included patient demographic, surgeon, and hospital characteristics in this analysis, these nonclinical characteristics diluted the effect of the clinical variables.

We found that the anatomic site of the positive margin was associated with overall survival. This finding agrees with a previous report.[26] However, the survival outcomes at anatomic sites in previous study were different than our findings. Our project shows that the mainstem bronchial wall margin has worse survival compared to other

anatomic sites. A study by Riquet et. al indicated that chest wall margins had the worst survival rate. They analyzed 4,026 patients of Georges Pompidou European Hospital (Paris) and Cedar Surgery Centre (Boisguillaume) from 1984 to 2006. The 5-year survival rate of chest wall margin was 12%, while the 5-year survival rate of bronchial wall margin was 29.3%.[26] Nevertheless, this previous report did not adjust for other covariates. Our finding is still noteworthy, since this is the first study to describe this in the U.S. population.

One strength of our project is the inclusion of more clinical variables and surgeon and facility factors in the analysis. This is the first study finding that the accuracy of TN staging was a protective factor for positive margins. We found a counter-intuitional association between the surgeon's annual case volume and margin positivity. Higher annual case volume surgeons had higher rates of positive margins. High annual case volume surgeons are usually more proficient providers.[53] We can only speculate on the reason. Perhaps high-volume surgeons in this region were too busy to prepare well before the surgery or it could be that the high-volume surgeons operate on more difficult cases. We found that margin involvement had a negative impact on survival, which has been well established in previous studies.

Our study is limited by the retrospective nature of the analysis and some missing details about institutional practice such as intraoperative use of pathologic examination of frozen sections. Data abstracted from Electronic Medical Records could be subject to some misclassification from coding errors, although a random selection of cases and suspicious data points are routinely audited. There could be selection bias based on which patients received surgery and which did not.

Incomplete surgical resection is a multi-dimensional problem. It is not possible to identify one single risk factor or dimension that explains the incidence of the margin positivity. Tacit acknowledgement of the negative impact of incomplete surgical resection of NSCLC has stimulated development of algorithms for the care of such patients. This project has already included the most comprehensive dimensions to understand the margin positivity and will contribute to future evidence-based guidelines and recommendations for clinical management.

Chapter 3

Risk-Adjusted Margin Positivity (RAMP) rate as a surgical quality metric

Background

Many groups have attempted to define the minimally accepted standards for surgical quality in non-small cell lung cancer, but the optimal method to define and measure surgical quality remains elusive.[39,42] Russell and colleagues were the first team to utilize the risk-adjusted model to predict surgery quality (margin status) in rectal cancer.[74] The idea of this method is to develop a tool that can be used by individual facilities to assess surgical care quality based on their unique mix of patient and clinical characteristics. The model classifies the performance of a facility as underperformer, nonoutlier, and outperformer. Lin et al. applied this risk-adjusted margin positivity model (RAMP) to NSCLC.[13] They developed a new model specifically for NSCLC using the NCDB. Their study found that the outperformers had five-year all-cause hazard ratio of 0.88 ($p<0.0001$) compared with the nonoutliers, and 0.80 ($p<0.0001$) compared with the underperformers.[13] In this study, we derived the risk of margin positivity for each MS-QSR hospital from the previously developed RAMP model by Lin et al.[13] We then classified the surgery care performance of each hospital in the Mid-South region. We developed a new RAMP model with the MS-QSR dataset to compare the two RAMP models. We also compared the agreement of the hospital performance and the NCCN and ACOSOG criteria to determine whether hospital performance derived from RAMP model was consistent with the previous developed criteria.

In the previous chapter, we discussed the influences of surgeon specialty, surgeon resection volume, hospital teaching program, and hospital resection volume on overall

survival. Thoracic compared to general surgeons, surgeons with higher volumes, teaching hospitals compared to non-teaching, and higher volume hospitals had better surgical outcomes.[50-59] Little's study found that higher hospital surgical volume was associated with several indices of better surgical care quality, including more rigorous preoperative evaluation, lower rate of margin positivity, and lower 90 day postoperative mortality)[24] which is consistent with previous studies.[28,46,72] However, these studies have been criticized for failing to account for the pragmatic issues of the hierarchical natures of patient, surgeon, and hospital levels.[13,59,75] With the MS-QSR dataset, we included these variables, not included in the previous RAMP model, in the Cox model to test the association of hospital performance and survival outcome. The results of this study will provide important information for the hospitals in the Mid-South region, identifying how well they are doing compared to national reference data. This could motivate additional work to improve surgical outcomes for NSCLC.

Methods

Patients

Because the RAMP model was developed based on NCCN pathologic stage groups from stage IA to IIIA, we only included these patients in this analysis. The NCCN pathologic stage groups were (1) stage IA (T1abc, N0); (2) stage IB (T2a, N0) and stage IIA (T2b, N0); (3) stage IIB (T1abc-T2ab, N1; T3, N0); and (4) stage IIIA (T1abc-2ab, N2; T3, N1).[29]

Observed/Expected Ratio and hospital performance

The performance of each hospital was evaluated by calculating an observed/expected (O/E) ratio in which the numerator was the observed number of the

positive margins of a hospital and the denominator was the expected number of patients with positive margin within the same hospital. Larger ratios indicated worse performance and smaller ratios indicated better performance. Lin's RAMP model estimated the expected number of positive margin resections in each hospital after accounting for patient's demographic and tumor related characteristics including age at surgery, sex, race, diagnosis year, insurance, income, comorbidity, histology, tumor grade, tumor size, location of hospital, census region, primary site, pathologic T and N category, and extent of surgery. Income information was derived from 2010 U.S. census data and categorized based on national quartiles by zip code level. Median income was then divided into four groups, <$30,000, $30,000-$34,999, $35,000-$45,999, and $46,000 above.

To obtain the expected number of margin positivity for each hospital, we first need to estimate each individual's probability of getting the incomplete surgical resection. We plugged each patient's information in the pre-built multivariable logistic regression model (RAMP model), which was read as:

$$\begin{aligned}\text{Logit P(X)} = \alpha &+ \beta_1 \times \text{Age} + \beta_2 \times \text{Sex} + \beta_3 \times \text{Race} + \beta_4 \times \text{Diagnosis Year} \\ &+ \beta_5 \times \text{Insurance} + \beta_6 \times \text{Income} + \beta_7 \times \text{Census region} \\ &+ \beta_8 \times \text{Cormobidity} + \beta_9 \times \text{Histology} + \beta_{10} \times \text{Grade} \\ &+ \beta_{11} \times \text{Tumor size} + \beta_{12} \times \text{Ruralilty} + \beta_{13} \times \text{Primary site} \\ &+ \beta_{14} \times \text{Pathologic T\_category} + \beta_{15} \times \text{Pathologic N\_category} \\ &+ \beta_{16} \times \text{Extent of resection}\end{aligned}$$

After estimating each patient's probability, we then grouped patient probabilities by hospital to obtain the expected value of incomplete resection for each hospital.

Each hospital was classified as underperformer, nonoutlier, or outperformer based on the calculated observed to expected ratio (O/E). If an institute's O/E ratio is greater than 1 and the p value was <.05, we recognized it as an underperforming institution (the

number of observed positive margin cases is higher than the number of expected cases). If an institute's O/E ratio was less than 1 and the p value was <.05, we recognized it as outperforming institution (the number of observed positive margin cases is lower than the number of expected cases). If an institute's p value of O/E ratio was >.05, we recognized it as nonoutlier institution. To test if the O/E ratio was significantly different from the null, we utilized the binomial function used in Russell's research to determine the p-value. The binomial function is: $P(X = k) = \binom{n}{k} p^k (1-p)^{n-k}$, where k denotes the actual number of events observed within the hospital, denotes the hospital surgical volume, and p denotes the model-derived expected probability of the event.[74]

We compared RAMP-based hospital performing category with the surgical quality criteria from NCCN and ACOSOG. The concordance of NCCN criteria postoperatively meant that a patient had to receive lobectomy or greater extent of resection, hilar node sampling, and mediastinal nodal sampling intraoperatively. In addition, the margin status was negative postoperatively. The concordance of ACOSOG criteria meant that a patient had to receive segmentectomy or greater extent of resection, hilar node sampling, and mediastinal nodal sampling. Moreover, the margin status of the resection was negative. Those criteria are detailed in Table 7.[29,76]

Table 7. Good Quality Resection Criteria

Group	**Resection margin**	**Anatomic extent of resection**	**Hilar Node sampling**	**Mediastinal Nodal sampling**
NCCN	Negative	Lobectomy or greater	Required	Minimum of 3 stations sampled
ACOSOG	Negative	Segmentectomy or greater	Required (Station 10 mandated)	Right sided tumor: 2, 4, and 7 Left sided tumor: 5, 6, and 7

Statistical analysis

The associations between surgeon and hospital characteristics and surgical quality criteria (NCCN/ACOSOG) and hospital performance were made using the Chi-square test or Analysis of Variance (ANOVA) for categorical data and using t test or Wilcoxon-Mann-Whitney test for continuous data. A Cox proportional hazards model was used to estimate the association between hospital performance and survival, and hazard ratios were reported with 95% confidence intervals. This Cox model did not include the individual covariates in the RAMP model in order to avoid over-adjusting since the covariates had been controlled previously in the model. We checked effect modifiers (via interaction terms) prior to the investigation of the potential confounders. We added to the model the variables that were deemed clinically relevant including NCCN stage group, surgeon's board certification and predominant practice, hospital annual case volume, rurality of hospital, and teaching program. The significance level of effect modifiers was set to $p<0.05$. The significant effect-modifying variables were then retained in the multivariable model as a part of main effect when we conducted the confounder examinations. We retained the confounder in the multivariable model if it (1) changed the effect (HR) of the main exposure by at least 10% or (2) was deemed clinically important, regardless of statistical properties.[68,69] We started with a fully adjusted model with margin status and all potential confounders as explanatory variables. The involving sequences for potential confounders were determined by the strength of the parameter estimate of each covariate. We selected potential confounders with the largest parameter estimate to compare to the change of hazard ratio. If the hazard ratio associated with margin status changed greater than 10%, the variable was considered as a confounder and

was retained in the multivariable model. If the change was less than 10%, we removed this variable from the model. We then checked the covariate with the second largest parameter estimate in turn and so forth. See the model selection flow chart in Figure 12. We used log-log survival curves to graphically evaluate the proportional hazards assumption.

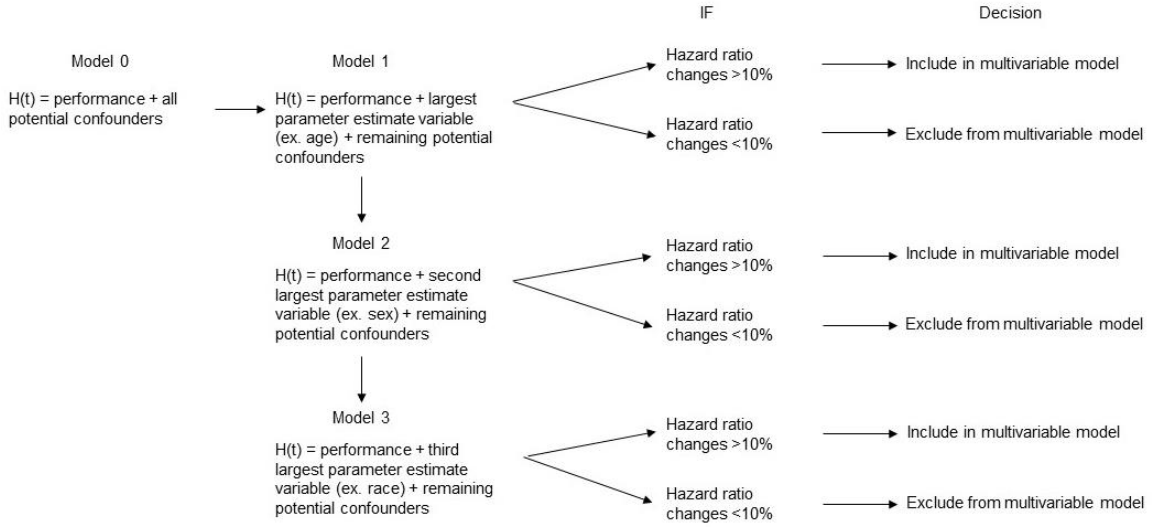

Figure 12. Variable selections for multivariable Cox proportional hazard regression

Results

A total of 840 patients underwent surgery from 2009 to 2011 in the MS-QSR cohort. Of these, 393 (47%) patients had their surgical resections in 9 nonoutlier hospitals and 447 (53%) had their surgical resections in 3 outperforming hospitals (Table 9). The distribution of O/E ratio and binomial p value is shown in Table 8. Patients with household median income less than 30,000 dollars (33%, $p<0.0001$), with commercial insurance (41%, $p=0.0009$), with unknown residency (16%, $p<0.0001$), and with squamous cell carcinoma (36%, $p=0.0132$) were more likely to be treated at the nonoutlier hospitals. On the other hand, patients with household median income greater than 46,000 dollars (32%, $p<0.0001$), with older (65 years old or older) Medicare

insurance (43%, p=0.0009), with rural residency (55%, p<0.0001), and with adenocarcinoma (57%, p=0.0132) were more likely to be treated in the nonoutlier hospitals.

Table 8. Distribution of O/E ratio and binomial p value (Year 2009-2011)

Hospital	O/E Ratio	p-value
1	0.64875	0.0154
2	0.63349	0.1550
3	0.00000	0.2177
4	0.00000	0.3208
5	0.47471	0.1274
6	0.50646	0.0886
7	0.00000	0.0071
8	0.46968	0.2519
9	1.03785	0.1674
10	0.32454	0.0108
11	0.71716	0.1901
12	0.58686	0.0948

Table 9. Patient characteristics by hospital surgical care performance (Year 2009-2011)

	Total N=840	Nonoutlier N=393 (47%)	Outperformer N=447 (53%)	p-value
	N (%)	N (%)	N (%)	
NCCN Stage groups				0.4725
IA	321 (38)	147 (37)	174 (39)	
IB, IIA	233 (28)	102 (26)	131 (29)	
IIB	187 (22)	93 (24)	94 (21)	
IIIA	99 (12)	51 (13)	48 (11)	
Age				0.4033
18-49	35 (4)	13 (3)	22 (5)	
50-64	294 (35)	146 (37)	148 (33)	
65-74	331 (39)	148 (38)	183 (41)	
75-90	180 (21)	86 (22)	94 (21)	
Sex				0.1315
Male	462 (55)	227 (58)	235 (53)	
Female	378 (45)	166 (42)	212 (47)	
Race/Ethnicity				0.0923
Caucasians	645 (77)	312 (79)	333 (75)	
Hispanic	1 (0.1)	1 (0.3)	0 (0)	
African American	186 (22)	75 (19)	111 (25)	
Other	8 (1)	5 (1)	3 (1)	
Income (Household median)				<.0001
< 30,000	205 (24)	129 (33)	76 (17)	
30,000-34,999	172 (21)	67 (17)	105 (23)	
35,000-45,999	225 (27)	101 (26)	124 (28)	
> 46,000	238 (28)	96 (24)	142 (32)	
Insurance				0.0009
Uninsured	30 (4)	21 (5)	9 (2)	
Medicaid	110 (13)	41 (10)	69 (15)	
Younger Medicare (< 65 years old)	49 (6)	29 (7)	20 (4)	
Older Medicare (65 years old +)	335 (40)	141 (36)	194 (43)	
Commercial	316 (38)	161 (41)	155 (35)	
Diagnosis Year				0.6315
2009	283 (34)	127 (32)	156 (35)	
2010	281 (34)	131 (33)	150 (34)	
2011	276 (33)	135 (35)	141 (31)	
Charlson's comorbidity				0.6622
0	176 (21)	78 (20)	98 (22)	
1	267 (32)	130 (33)	137 (31)	
2+	397 (47)	185 (47)	212 (47)	

Table 9. (Continued)

	Total N=840	Nonoutlier N=393 (47%)	Outperformer N=447 (53%)	p-value
	N (%)	N (%)	N (%)	
Residency				<.0001
Rural	425 (51)	181 (46)	244 (55)	
Urban	352 (42)	150 (38)	202 (45)	
Unknown	61 (7)	62 (16)	1 (0.2)	
Histology				0.0132
Squamous	296 (35)	143 (36)	153 (34)	
Large cell	31 (4)	23 (6)	8 (2)	
Adenocarcinoma	457 (54)	204 (52)	253 (57)	
NOS	55 (7)	22 (6)	33 (7)	
Other	1 (0.1)	1 (0.3)	0 (0)	
Tumor grade				0.4835
Well/Moderate differentiated	457 (54)	206 (52)	251 (56)	
Poorly/undifferentiated	267 (32)	128 (33)	139 (31)	
Unknown	116 (14)	59 (15)	57 (13)	
Primary tumor site				0.7429
Upper lobe	518 (62)	243 (62)	275 (62)	
Middle lobe	39 (5)	20 (5)	19 (4)	
Lower lobe	239 (29)	107 (27)	132 (30)	
Overlapping	44 (5)	23 (6)	21 (5)	
Tumor size				0.0938
≤3 cm	530 (63)	241 (61)	289 (65)	
3-5 cm	227 (27)	104 (26)	123 (28)	
>5 cm	81 (10)	46 (12)	35 (8)	
Unknown	2 (0.2)	2 (0.5)	0 (0)	
Pathologic T category				0.1163
T1	369 (44)	172 (44)	197 (44)	
T2	337 (40)	148 (38)	189 (42)	
T3	134 (16)	73 (19)	61 (14)	
Pathologic N category				0.3553
N0	656 (78)	307 (78)	349 (78)	
N1	117 (14)	50 (13)	67 (15)	
N2	67 (8)	36 (9)	31 (7)	
Extent of surgery				0.2467
Pneumonectomy	72 (9)	38 (10)	34 (8)	
Bilob/lobectomy	721 (86)	329 (84)	392 (88)	
Segmentectomy/Wedge resection	47 (6)	26 (7)	21 (5)	

With these 840 patients, we found that hospitals in outperformer category, comparing to hospitals in nonoutlier category, had more surgeons with Cardiothoracic board certification (78% vs. 69%, p=0.0045), more surgeons with predominant practice in thoracic or cardiovascular compared to general (37% vs. 19%, p<0.0001), were more likely to be affiliated with a teaching program (74% vs. 41%, p<0.0001), and to be located in a rural area (26% vs. 8%, p<0.0001). Surgeons in outperformer category had higher annual surgical case volumes in lung cancer (28.0 vs. 15.8, p<0.0001) comparing to those in the nonoutlier category. The outperformer category also had higher surgical volumes in lung cancer compared with nonoutlier category (92.0 vs. 21.6%, p<0.0001). We did not find an association between surgical care quality (NCCN and ACOSOG) and hospital performing category with these 840 patients (Table 10).

Table 10. Association of surgical care quality and hospital characteristics and hospital performance (Year 2009-11)

	Total N (%)	Nonoutlier N (%)	Outperformer N (%)	p-value
Surgical care quality				
NCCN criteria attainment				0.9256
No	625 (74)	293 (75)	332 (74)	
Yes	215 (26)	100 (25)	115 (26)	
ACOSOG criteria attainment				0.0545
No	802 (95)	381 (97)	421 (94)	
Yes	38 (5)	12 (3)	26 (6)	
Surgeon Characteristics				
Board of Certification				0.0045
General only	220 (26)	121 (31)	99 (22)	
Cardiothoracic	620 (74)	272 (69)	348 (78)	
Predominant practice (thoracic or cardiovascular)				<.0001
No	600 (71)	318 (81)	282 (63)	
Yes	240 (29)	75 (19)	165 (37)	
Annual surgical volumes in lung cancer (Surgeon), Mean (SD)	22.3 (23.6)	15.8 (17.9)	28.0 (26.4)	<.0001
Hospital Characteristics				
Teaching Program				<.0001
No	349 (42)	233 (59)	116 (26)	
Yes	491 (58)	160 (41)	331 (74)	
Location of hospital				<.0001
Urban	694 (83)	363 (92)	331 (74)	
Rural	146 (17)	30 (8)	116 (26)	
Annual surgical volumes in lung cancer (Hospital), Mean (SD)	59.1 (46.2)	21.6 (9.5)	92.0 (40.1)	<.0001

Figure 13 shows the overall survival by hospital performance. The crude five-year survival rates for nonoutlier hospitals and outperforming hospitals were 47.1% and 47.7%, respectively (p=0.8125). The median survival time of nonoutlier hospitals was 5.5 years, and that of outperforming hospitals was 5.7 years.

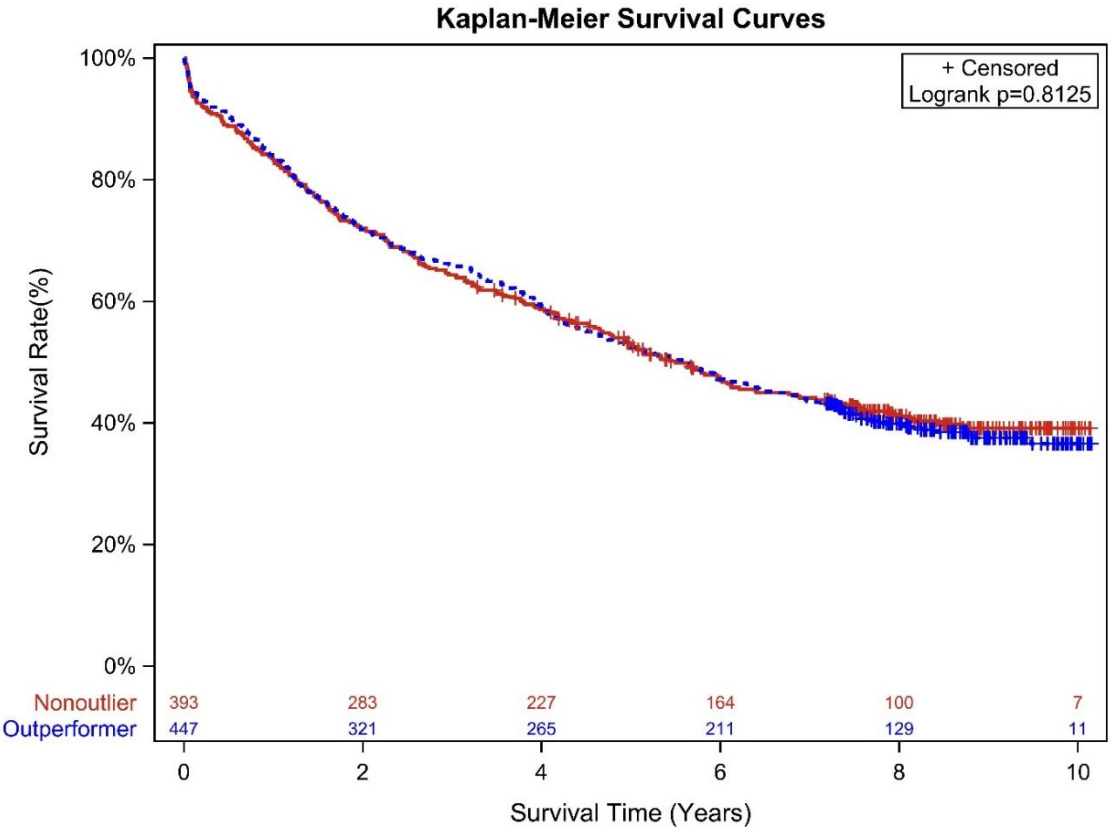

Figure 13. Kaplan-Meier survival curves by hospital performance (Year 2009-2011)

After adjusting for potential confounders, hospital performance was independently associated with overall survival. Patients who received their treatments in the nonoutlier hospitals had 1.53 times the hazard of death comparing with those received treatments in outperforming hospitals from year 2009 through 2011 (aHR=1.53, 95% CI: 1.05-2.22) (Table 11). The adjusted confounders included NCCN stage groups, adjuvant treatment, surgeon's board of certification, surgeon's predominant practice, surgeon's

year of service, surgeon's annual surgical case volume, teaching program, rurality of hospital, and hospital's annual surgical case volume.

Table 11. Cox proportional hazard regression for hospital performance (Year 2009-2011)

	HR (95% CI)	p-value
Hospital performance		
Outperformer	1	
Nonoutlier	1.53 (1.05-2.22)	0.0267
NCCN Stage groups		
IA	1	
IB, IIA	1.31 (1.04-1.64)	0.0220
IIB	1.52 (1.20-1.92)	0.0006
IIIA	1.94 (1.45-2.89)	<.0001
Adjuvant treatment		
No	1	
Yes	1.81 (1.45-2.59)	<.0001
Board of Certification		
Cardiothoracic	1	
General only	0.94 (0.75-1.18)	0.6025
Predominant practice (thoracic or cardiovascular)		
No	1	
Yes	0.95 (0.71-1.28)	0.7435
Years of service	1.01 (0.99-1.02)	0.3334
Annual surgical volumes in lung cancer (Surgeon)	0.99 (0.99-1.00)	0.1790
Teaching Program		
No	1	
Yes	1.46 (1.10-1.96)	0.0102
Location of hospital		
Urban	1	
Rural	0.72 (0.49-1.06)	0.0942
Annual surgical volumes in lung cancer (Hospital)	1.01 (1.00-1.01)	0.0237

Next, we used the whole MS-QSR cohort to develop a new RAMP model. Table 12 shows the logistic regression for predicting margin status. The distribution of O/E ratio and binomial p value are shown in Table 13. Among the whole MS-QSR cohort, in which patients underwent surgery from 2009 to 2019, a total of 2923 patients with NCCN pathologic stage IA-IIIA were included in the analysis. There were 574 (20%) patients who had their surgical resections in 6 nonoutlier hospitals and 2365 (80%) who had their surgical resections in 6 outperforming hospitals (Table 14). Patients who were treated at the outperforming hospitals were older ($p=0.0072$), had more older Medicare insurance plan (45%, $p<0.0001$), were diagnosed with lung cancer later than 2014 (54%, $p<0.0001$), lived in a rural area (50%, $p<0.0001$), had poorly/undifferentiated tumor grade (33%, $p=0.0002$), and had more advanced pathologic T category (53%, $p=0.0038$) compared to those who were treated at the nonoutlier hospitals.

Table 12. RAMP model in predicting margin status (Year 2009-2019)

	Adjusted Odds Ratio (95% CI)	p-value
Age		
18-49	1	
50-64	0.81 (0.30-2.20)	0.9093
65-74	0.59 (0.20-1.74)	0.5394
75-90	0.64 (0.20-2.02)	0.6331
Sex		
Male	1	
Female	0.61 (0.39-0.95)	0.0373
Race/Ethnicity		
Caucasians	1	
Hispanic	1.00 (0.00-1.00)	0.9873
African American	0.51 (0.27-0.95)	0.0311
Other	1.33 (0.28-6.32)	0.7239
Income (Household median)		
> 46,000	1	
< 30,000	0.81 (0.38-1.76)	0.6425
30,000-34,999	1.02 (0.49-2.11)	0.8986
35,000-45,999	0.65 (0.34-1.25)	0.1851
Insurance		
Commercial	1	
Uninsured	1.48 (0.58-3.76)	0.4063
Medicaid	1.08 (0.56-2.07)	0.9392
Younger Medicare (< 65 years old)	0.62 (0.20-1.92)	0.4007
Older Medicare (65 years old +)	1.04 (0.57-1.91)	0.9136
Diagnosis Year		
2009	1	
2010	0.51 (0.21-1.23)	0.1528
2011	0.98 (0.45-2.14)	0.9283
2012	1.03 (0.47-2.22)	0.9341
2013	0.46 (0.19-1.14)	0.0884
2014	0.56 (0.23-1.38)	0.1984
2015	0.76 (0.33-1.77)	0.5058
2016	0.57 (0.24-1.38)	0.2088
2017	0.29 (0.10-0.84)	0.0242
2018	0.46 (0.17-1.24)	0.1203
2019	0.77 (0.20-2.89)	0.6846
Charlson's comorbidity		
0	1	
1	0.94 (0.54-1.65)	0.8388
2+	0.86 (0.50-1.46)	0.5156

Table 12. (Continued)

	Adjusted Odds Ratio (95% CI)	p-value
Residency		
Urban	1	
Rural	1.14 (0.64-2.04)	0.0333
Unknown	2.55 (1.04-6.28)	0.1139
Histology		
Adenocarcinoma	1	
Squamous	1.38 (0.87-2.19)	0.9939
Large cell	0.80 (0.23-2.86)	0.4129
NOS	2.17 (1.07-4.41)	0.1886
Other	1.00 (0.00-1.00)	0.1745
Tumor grade		
Well/Moderate differentiated	1	
Poorly/undifferentiated	1.03 (0.66-1.61)	0.9202
Unknown	0.59 (0.29-1.23)	0.1661
Primary tumor site		
Upper lobe	1	
Middle lobe	1.83 (0.87-3.83)	0.0903
Lower lobe	0.64 (0.37-1.08)	0.8117
Overlapping	1.31 (0.14-12.3)	0.6289
Tumor size		
≤3 cm	1	
3-5 cm	1.19 (0.68-2.10)	0.5594
>5 cm	0.24 (0.11-0.57)	0.0011
Unknown	5.38 (0.4-71.75)	0.5971
Pathologic T category		
T1	1	
T2	1.17 (0.63-2.17)	<.0001
T3	7.55 (3.85-14.8)	<.0001
Pathologic N category		
N0	1	
N1	2.86 (1.74-4.70)	0.0001
N2	3.62 (1.88-6.97)	0.9868
Extent of surgery		
Bilob/lobectomy	1	
Pneumonectomy	1.01 (0.44-2.31)	0.7918
Segmentectomy/Wedge resection	1.31 (0.15-11.3)	0.8031

Table 13. Distribution of O/E ratio and binomial p value (Year 2009-2019)

Hospital	O/E Ratio	p-value
1	0.59387	<.0001
2	0.59348	0.0280
3	0.48387	0.1338
4	0.00000	0.0606
5	0.70811	0.1073
6	0.78874	0.0858
7	0.20882	0.0002
8	0.43698	0.1049
9	0.53283	0.0093
10	0.43467	0.0005
11	1.25656	0.1619
12	0.59141	0.0099

Table 14. Patient characteristics by hospital surgical care performance (Year 2009-2019)

	Total N=2923	Nonoutlier N=574 (20%)	Outperformer N=2365 (80%)	p-value
	N (%)	N (%)	N (%)	
NCCN Stage groups				0.1065
IA	1218 (42)	263 (44)	955 (41)	
IB, IIA	841 (29)	149 (25)	692 (30)	
IIB	590 (20)	129 (22)	461 (20)	
IIIA	274 (9)	51 (9)	223 (9)	
Age				0.0072
18-49	112 (4)	24 (4)	88 (4)	
50-64	899 (31)	190 (32)	709 (30)	
65-74	1264 (43)	222 (38)	1042 (45)	
75-90	648 (22)	156 (26)	492 (21)	
Sex				0.1475
Male	1544 (53)	279 (50)	1247 (54)	
Female	1379 (47)	295 (50)	1084 (46)	
Race/Ethnicity				0.0657
Caucasians	2285 (78)	486 (82)	1799 (77)	
Hispanic	16 (0.6)	3 (0.5)	13 (0.6)	
African American	589 (20)	96 (16)	493 (21)	
Other	33 (1)	7 (1)	26 (1)	
Income (Household median)				0.0330
< 30,000	591 (20)	98 (17)	493 (21)	
30,000-34,999	578 (20)	112 (19)	466 (20)	
35,000-45,999	833 (28)	173 (29)	660 (28)	
> 46,000	921 (32)	209 (35)	712 (31)	
Insurance				<.0001
Uninsured	93 (3)	15 (3)	78 (3)	
Medicaid	439 (15)	59 (10)	380 (16)	
Younger Medicare (< 65 years old)	121 (4)	10 (2)	111 (5)	
Older Medicare (65 years old +)	1266 (43)	220 (37)	1046 (45)	
Commercial	1004 (34)	288 (49)	716 (31)	

Table 14. (Continued)

	Total N=2923	Nonoutlier N=574 (20%)	Outperformer N=2365 (80%)	p-value
	N (%)	N (%)	N (%)	
Diagnosis Year				<.0001
2009	283 (10)	63 (11)	220 (9)	
2010	281 (10)	73 (12)	208 (9)	
2011	276 (9)	82 (14)	194 (8)	
2012	269 (9)	73 (12)	196 (8)	
2013	294 (10)	75 (13)	219 (9)	
2014	273 (9)	49 (8)	224 (10)	
2015	276 (9)	34 (6)	242 (10)	
2016	295 (10)	34 (6)	261 (11)	
2017	309 (11)	46 (8)	263 (11)	
2018	293 (10)	50 (8)	243 (10)	
2019	74 (3)	13 (2)	61 (3)	
Charlson's comorbidity				0.1081
0	630 (22)	118 (20)	512 (22)	
1	833 (28)	189 (32)	644 (28)	
2+	1460 (50)	285 (48)	1175 (50)	
Residency				<.0001
Rural	1527 (52)	350 (59)	1177 (50)	
Urban	1236 (43)	239 (40)	997 (43)	
Unknown	160 (5)	3 (1)	157 (7)	
Histology				0.5823
Squamous	988 (34)	203 (34)	785 (34)	
Large cell	87 (3)	23 (4)	64 (3)	
Adenocarcinoma	1599 (55)	318 (54)	1281 (55)	
NOS	247 (9)	48 (8)	199 (9)	
Other	2 (0.1)	0 (0)	2 (0.1)	
Tumor grade				0.0002
Well/Moderate differentiated	1615 (55)	321 (54)	1294 (55)	
Poorly/undifferentiated	926 (32)	165 (28)	761 (33)	
Unknown	382 (13)	106 (18)	276 (12)	
Primary tumor site				0.5397
Upper lobe	1700 (58)	341 (58)	1359 (58)	
Middle lobe	170 (6)	34 (6)	136 (6)	
Lower lobe	927 (32)	185 (31)	742 (32)	
Overlapping	126 (4)	32 (5)	94 (4)	

Table 14. (Continued)

	Total N=2923	Nonoutlier N=574 (20%)	Outperformer N=2365 (80%)	p-value
	N (%)	N (%)	N (%)	
Tumor size				0.0641
≤3 cm	1945 (67)	381 (64)	1564 (67)	
3-5 cm	742 (25)	148 (25)	595 (26)	
>5 cm	229 (8)	62 (11)	167 (7)	
Unknown	6 (0.2)	1 (0.2)	5 (0.2)	
Pathologic T category				0.0038
T1	1410 (48)	394 (51)	1106 (47)	
T2	1108 (38)	191 (32)	917 (39)	
T3	405 (14)	97 (16)	308 (13)	
Pathologic N category				0.1773
N0	2376 (81)	495 (84)	1881 (81)	
N1	361 (12)	60 (10)	301 (13)	
N2	186 (7)	37 (6)	149 (6)	
Extent of surgery				0.1516
Pneumonectomy	246 (8)	44 (7)	202 (9)	
Bilob/lobectomy	2539 (87)	512 (87)	2027 (87)	
Segmentectomy/Wedge resection	138 (5)	36 (6)	102 (4)	

The hospitals in outperformer category were more likely to attain the NCCN (48% vs. 35%, p<0.0001) or ACOSOC criteria (24% vs. 14%, p<0.0001) than those in nonoutlier category. We also found that hospitals in outperformer category, compared to hospitals in nonoutlier category, had more surgeons with Cardiothoracic board certification (67% vs. 56%, p<0.0001) and with predominant practice in thoracic or cardiovascular (45% vs. 22%, p<0.0001), and were more likely to have a teaching program (62% vs. 49%, p<0.0001). Surgeons in outperforming hospitals had higher surgical volumes in lung cancer (33.3 vs. 22.5, p<0.0001) comparing to the nonoutlier ones. The outperforming hospitals also had higher surgical volumes in lung cancer compared with nonoutlier hospitals (74.4 vs. 16.3%, p<0.0001) (Table 15).

Table 15. Association of surgical care quality and surgeon/hospital characteristics and hospital performance (Year 2009-2019)

	Total N (%)	Nonoutlier N (%)	Outperformer N (%)	p-value
Surgical care quality				
NCCN criteria attainment				<.0001
No	1603 (55)	382 (65)	1221 (52)	
Yes	1320 (45)	210 (35)	1110 (48)	
ACOSOG criteria attainment				<.0001
No	2285 (78)	508 (86)	1777 (76)	
Yes	638 (22)	84 (14)	554 (24)	
Surgeon Characteristics				
Board of Certification				<.0001
General only	1035 (35)	261 (44)	774 (33)	
Cardiothoracic	1888 (65)	331 (56)	1557 (67)	
Predominant practice (thoracic or cardiovascular)				<.0001
No	1743 (60)	459 (78)	1284 (55)	
Yes	1180 (40)	133 (22)	1047 (45)	
Annual surgical volumes in lung cancer (Surgeon), Mean (SD)	31.1 (28.6)	22.5 (27.8)	33.3 (28.3)	<.0001
Hospital Characteristics				
Teaching Program				<.0001
No	1189 (41)	301 (51)	888 (38)	
Yes	1734 (59)	291 (49)	1443 (62)	
Location of hospital				0.7425
Urban	2413 (83)	486 (82)	1927 (83)	
Rural	510 (17)	106 (18)	404 (17)	
Annual surgical volumes in lung cancer (Hospital), Mean (SD)	62.6 (46.0)	16.3 (7.3)	74.4 (44.2)	<.0001

Figure 14 shows overall survival by hospital performance. The crude five-year survival rates for nonoutlier hospitals and outperforming hospitals were 63.5% and 56.9%, respectively (p=0.0049). The median survival time of nonoutlier hospitals was not reached, and that of outperforming hospitals was 6.5 years. After adjusting for potential confounders, hospital performance was independently associated with overall survival. Patients who received treatment in nonoutlier hospitals had 0.79 times the hazard of death compared to those who received treatment in outperforming hospitals (aHR=0.79, 95% CI: 0.66-0.96) (Table 16).

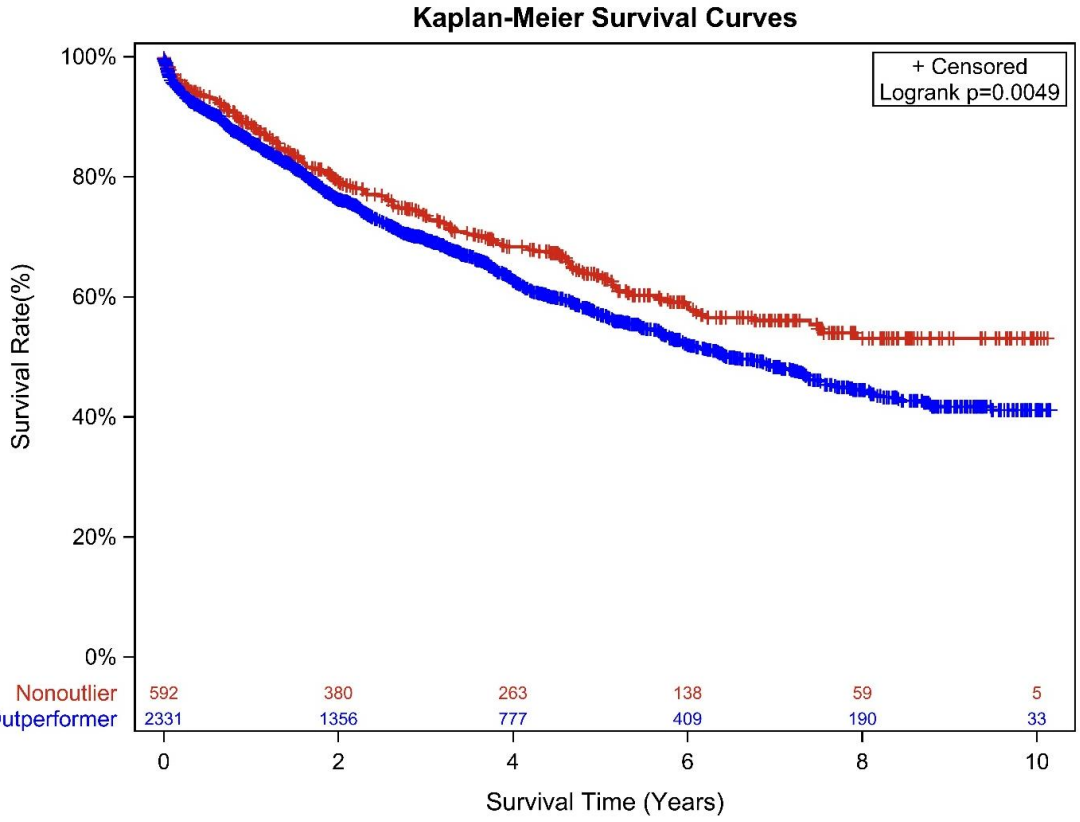

Figure 14. Kaplan-Meier survival curves by hospital performance (Year 2009-2019)

Table 16. Cox proportional hazard regression for hospital performance (Year 2009-2019)

	HR (95% CI)	p-value
Hospital performance		
Outperformer	1	
Nonoutlier	0.79 (0.66-0.96)	0.0140
NCCN Stage groups		
IA	1	
IB, IIA	1.44 (1.23-1.68)	<.0001
IIB	2.00 (1.69-2.36)	<.0001
IIIA	2.53 (2.04-3.12)	<.0001
Adjuvant treatment		
No	1	
Yes	0.93 (0.78-1.10)	0.0712
Board of Certification		
Cardiothoracic	1	
General only	0.88 (0.77-1.01)	0.1901
Predominant practice (thoracic or cardiovascular)		
No	1	
Yes	0.86 (0.69-1.08)	0.1901
Years of service	1.00 (0.99-1.01)	0.6338
Annual surgical volumes in lung cancer (Surgeon)	0.99 (0.99-1.00)	0.0721
Teaching Program		
No	1	
Yes	1.14 (0.94-1.37)	0.1829
Location of hospital		
Urban	1	
Rural	1.02 (0.84-1.25)	0.8092
Annual surgical volumes in lung cancer (Hospital)	1.00 (0.99-1.00)	0.6378

Discussion

This project applied the RAMP model to assess the association between hospital performance and overall survival. The RAMP model is a facility based-surgical quality metric.[77] This RAMP-based institutional category was strongly associated with the surgical care quality, surgeon characteristics, and hospital characteristics. The outperforming hospitals were more likely to attain the NCCN or ACOSOC criteria. Outperforming hospitals had more surgeons with Cardiothoracic board certification, more surgeons with predominant practice in thoracic or cardiovascular surgery, and more frequently had a teaching program. To our knowledge, this is the first study to show the association between NCCN or ACOSOG criteria and RAMP-based hospital performance.

We found there were 3 (25%) outperforming hospitals and 9 (75%) nonoutlier hospitals from 2009 to 2011 in the Mid-South region. When we used the whole cohort to develop the new RAMP model, we observed there were 6 (50%) outperforming hospitals and 6 (50%) nonoutlier hospitals. This was unlike Lin's study in 2017. Lin and colleagues developed a RAMP model for NSCLC margin positivity with the NCDB. They found that 79.6% of the hospitals were nonoutlier, 7.5% of the hospitals were outperformers, and 12.9% of the hospitals were underperformers. Their study also found that patients treated at outperformers had better survival than those treated at nonoutliers or underperformers.[13] Our findings differed from those of Lin et. al because we found no survival difference between outperformers and nonoutliers from 2009 to 2011.

Surgeons in outperforming hospitals had higher surgical volumes in lung cancer compared to the nonoutlier hospitals. The outperforming hospitals also had higher surgical volumes in lung cancer compared with nonoutlier hospitals. Outperforming

hospitals having higher surgical volumes is consistent with previous reports, suggesting that practice makes for better outcomes.[13] A similar observation generally applied to surgeon annual case volume.[53] In the first project, we found that higher surgeon annual case volume resulted in more margin positivity. We speculate this discrepancy was because the RAMP model was constructed with the nomogram, a multivariable logistic regression, internally validated for model discrimination and calibration by bootstrapping with 200 resamples.[74] That said, the RAMP model may provide a more accurate estimation for predicting margin positivity. However, many previous studies have suggested that the utility of volume-based structural measures for corrective intervention is limited, and the validity of the volume-outcome relationship has been questioned.[59,75] The other reason is that we cannot directly test the provider's proficiency. That suggests a need to further understand the specific institutional and provider practices that distinguish outperforming from nonoutlier facilities and surgeons.

We used the MS-QSR database to develop a new RAMP model in the prediction of margin positivity. We found that outperforming hospitals resulted in worse survival compared with the nonoutliers. This finding was different from previous studies. This result may not be generalizable to the U.S. population since the model per se was built based on only 12 hospitals, compared to the NCDB with 809 facilities. We also found that most of the patients (80%) received their cancer treatments in the outperforming hospitals from 2009 to 2019. This was very different from the findings in the study with NCDB, where only 19.5% of the patients received treatment in outperforming hospitals.[13]

Although this RAMP model was built with a national database (NCDB), this model had some limitations when it is applied. One of the components of the RAMP

model is the year of diagnosis. In Lin's model, the range of the diagnosis years were from 2004 to 2011. However, the MS-QSR cohort was started from 2009 to present. Therefore, we were not able to apply the RAMP model to the full MS-QSR cohort. A new RAMP model with a proper surrogate variable for evaluating the year of diagnosis would improve the utility of this tool. In addition, the RAMP model was developed with the nomogram, but the nomogram was not independently validated.

The metric of measuring surgical quality must be clinically relevant, rigorously validated, readily available, and standardized before they can serve as meaningful quality metrics. Although the RAMP model is not perfect and needs some improvements, the results of this project will provide important information for the hospitals in the Mid-South region, identifying how well they are doing compared to national reference data. This could motivate additional work to improve surgical outcomes in NSCLC in the future.

Chapter 4

The effect of the attainment of NCCN postoperative treatment guidelines on survival in positive margin NSCLC patients

Background

Although previous studies have shown that chemotherapy and radiotherapy may improve survival after NSCLC curative-intent resection, these studies had diverse survival outcomes associated with postoperative adjuvant treatment.[16,18,37,63] The benefit of these postoperative treatment also varied by stage and margin status.[31,78,79] This is why, in many common clinical scenarios, healthcare providers have limited evidence-based guidance from clinical data for decision-making on postoperative management.[35] The NCCN stage-based treatment guidelines are expert consensus-driven criteria for postoperative care of patients with a positive margin.[8,35,43,80] As a result, many experts view NCCN guidelines as the "standard of care" in postoperative treatment for NSCLC.[35-37,80,81]

According to NCCN treatment guidelines, postoperative treatment modalities for NSCLC margin positivity can be a second surgical intervention (re-resection), radiotherapy, and/or chemotherapy; and the re-resection treatment is a preferred response to the positive margin;[8] however, barriers and controversies exist for the implementation. For example, most patients refuse to have a second surgery[81] and surgeons are usually reluctant to do so.[12] The adjuvant therapies are alternative options to the re-resection.[12] Nevertheless, the role of postoperative adjuvant treatments remain controversial because of conflicting, often low-level, evidence on the efficacy of stage-specific recommendations for chemotherapy, radiation, or both.[10,16,18,19,27,43,74,82] Hancock's study

found that both chemotherapy and radiation were associated with improved survival in patients with microscopically positive margin (R1), irrespective of the stage.[16] Rieber's study found that a greater than 54GY radiation therapy was effective for local control and improved overall survival.[18] In addition, another study that analyzed the SEER database revealed that radiotherapy improved survival outcome for patients with N2 disease.[31] In contrast, Gulack and colleague did not find a significant difference on the overall survival of margin positivity between stage I and II patients with and without postoperative radiation treatment after lobectomy resections (HR=1.10, 95% CI: 0.90-1.35; p=0.353).[32] Several studies even found that postoperative radiotherapy was harmful and increased the risk for mortality in NSCLC patients with pathologic N0 and N1.[30,31]

Although the NCCN guidelines play an important role in clinical settings, there are surprisingly little evidence-based data to validate the guidelines for postoperative treatment in NSCLC.[35,36] Previous national data demonstrated that advanced stage patients with positive margins who followed the NCCN clinical guidelines lived longer, but not early stage patients.[37] Smeltzer and colleagues' study found that guideline recommended treatments did not always result in better overall survival for margin positive patients. For example, stage IA patients with positive margin are not suggested to receive any postoperative adjuvant, although radiotherapy is recommended by NCCN guidelines.[37] With the NCDB database in Smeltzer's study, stage IB and IIA positive margin patients were not suggested for radiotherapy, but instead, chemotherapy alone. Although the NCCN guidelines recommended radiotherapy and/or chemotherapy for patient with a positive margin, those analyses were limited in scope due to the information available in the NCDB.[12] Thus, in this study we aimed to assess the survival

impact of NCCN concordant guidelines for postoperative treatment on the NSCLC patient with positive margin. We also compared the survival impact of postoperative adjuvant treatment, regardless of the stage with the NCCN guidelines.

Methods

Patients

After a lung cancer resection, some MS-QSR patients returned to their communities and received postoperative treatment in local clinics or hospitals rather than the institutions where they had surgery. Information about postoperative treatment in the MS-QSR database may not be accurately recorded for these patients. Therefore, we excluded these 1,602 patients from the analysis. There were 1,528 patients left in current analytic cohort.

Exposure and Outcome

We evaluated whether treatment concordant with NCCN guidelines is associated with overall survival. The main exposure was NCCN guidelines attainment, dichotomized as NCCN guidelines attainment (Yes) versus no NCCN guidelines attainment (No). Per the goal of this study, the second main exposure, adjuvant treatment, was categorized as none, chemotherapy or radiotherapy, and both. The reference group for both exposures was patients with a negative margin. Overall survival served as the outcome.

Potential Confounders

According to previous studies, potential confounders for the association between postoperative treatment and overall survival might include age at surgery, sex, Charlson's comorbidity conditions, income, insurance, histology, tumor site, tumor grade, extent of

surgery, neo-adjuvant treatment, margin status, pathologic stage, surgeon's predominant practice, surgeon's volume of surgery, hospital teaching status, and hospital surgical volume. [16,31,37,50-59] We used the 6-step DAG approach[67] to include the necessary confounders to yield an unbiased estimate of effect and the statistical efficiency of the analysis is increased due to the fewer confounders in the model. Per the approach, histology, tumor site, tumor grade, preoperative evaluations, accuracy of TN staging, clinical stage, extent of surgery, and surgeon and hospital characteristics were excluded from the DAG because they were not the ancestors of the postoperative treatment. Moreover, these variables were the ancestors of margin status. Because margin status is upstream on the causal pathway from postoperative treatment to survival, it was excluded from the DAG. The final causal pathway is shown in Figure 15.

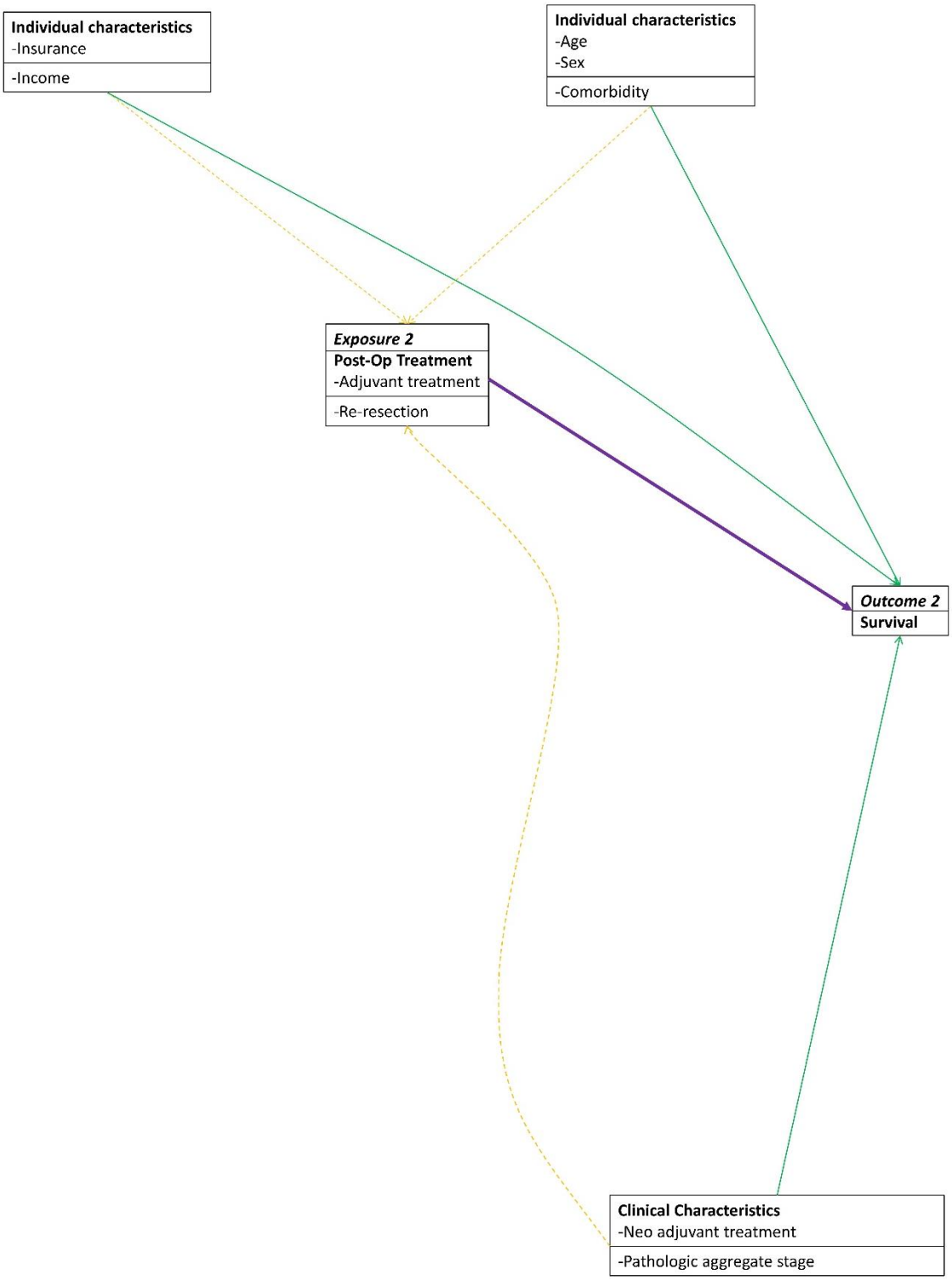

Figure 15. Causal pathway of postoperative treatment and survival

Statistical analysis

We summarized demographic and clinical information for the analytic cohort and reported as mean and standard deviation (SD) or as frequency and percentages (%). Comparisons between complete and incomplete resection groups were made using the Chi-square test for categorical data and using the t-test or Wilcoxon-Mann-Whitney test for continuous data.

We evaluated the crude overall survival curves with Kaplan-Meier estimates. Next, we assessed the adjusted hazard ratio using the Cox proportional hazard regression where survival is a function of NCCN guidelines attainment with potential confounders. With the remaining potential confounders from the 6-step DAG approach, we retained confounders in the multivariable model if it (1) changed the effect (HR) of the main exposure by at least 10% or (2) was deemed clinically important, regardless of statistical properties.[68,69] We started with a fully adjusted model with margin status and all potential confounders as the explanatory variables. The involving sequences of the potential confounders were determined by the strength of the parameter estimate of each covariate. We first selected the potential confounders with the largest parameter estimate and evaluated the change in hazard ratio when adjusting and not adjusting for the confounder. If the hazard ratio associated with margin status changed greater than 10%, the variable was considered as a confounder and was retained in the multivariable model. If the change was less than 10%, we removed this variable from the model. We then checked the covariate with the second largest parameter estimate in turn and so forth. See the model selection flow chart in Figure 16. We used log-log survival curves to graphically evaluate the proportional hazard assumption.

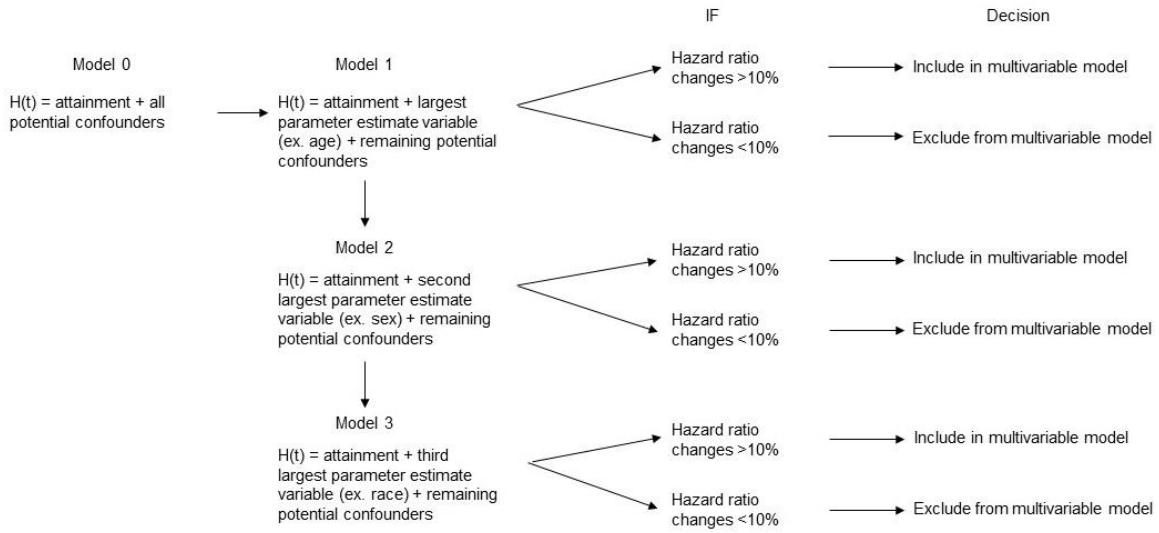

Figure 16. Variable selections for multivariable Cox proportional hazard regression

Results

Of the 1528 curative-intent NSCLC patients (Table 17), 58 (3.8%) patients were positive margin, of which 9 (15.5%) attained, and 49 (84.5%) did not attain NCCN treatment guideline. Patients with NCCN treatment guideline attainment were younger (60.1 years, p=0.0240), received neo-adjuvant treatment (22%, p=0.0334), and were more likely to have advanced (II and III vs. I) pathologic stage (89%, p<0.0001). Females (67%, p=0.0386), no comorbidity (25%, p=0.0535), and pathologic stage I (44%) patients were less likely to attain the NCCN guidelines. Regardless of the stages, no margin positive patient received a second resection (Table 18). A majority (72%) of positive margin patients did not receive any postoperative adjuvant treatment such as chemotherapy, radiotherapy, or both. There were 5 (9%) patients who received chemotherapy; 3 (5%) received radiotherapy; and 8 (14%) received both treatments.

Table 17. Demographic and clinical characteristics by NCCN treatment guidelines attainment

	Non NCCN attainment N=49	NCCN attainment N=9	Negative Margin N=1470	p-value
Age, mean (SD)	67.1 (10.2)	60.1 (14.2)	68.0 (8.7)	0.0240
Sex				0.0386
Female	33 (67)	4 (44)	723 (49)	
Male	16 (33)	5 (56)	747 (51)	
Charlson's comorbidity				0.0535
0	12 (25)	2 (22)	271 (18)	
1	11 (22)	6 (67)	421 (29)	
2+	26 (53)	1 (11)	778 (53)	
Income (Household median)				0.1439
< 30,000	5 (10)	2 (22)	213 (15)	
30,000-34,999	13 (27)	3 (33)	267 (18)	
35,000-45,999	7 (14)	3 (33)	389 (26)	
> 46,000	24 (49)	1 (11)	601 (41)	
Insurance				0.6524
Commercial	19 (39)	4 (44)	672 (46)	
Medicare	7 (14)	3 (33)	241 (16)	
Medicaid	22 (45)	2 (22)	530 (36)	
Uninsured	1 (2)	0 (0)	27 (2)	
Neo-adjuvant treatment (chemotherapy or radiotherapy)				0.0334
No	44 (90)	7 (78)	1396 (95)	
Yes	5 (10)	2 (22)	74 (5)	
Pathologic stage				<.0001
Stage I	20 (41)	1 (11)	1000 (68)	
Stage II	17 (35)	6 (67)	342 (23)	
Stage III	12 (24)	2 (22)	128 (9)	

Table 18. Distribution of postoperative treatment by NCCN pathologic stage

		None	Any adjuvant treatment				NCCN attainment
Pathologic stage	**N**		Re-resection	Chemotherapy	Radiation	Both	
IA	10 (17%)	8 (80%)	0 (0%)	1 (10%)	1 (10%)	0 (0%)	1 (10%)
IB	11 (19%)	11 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
IIA	2 (3%)	2 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
IIB (T1 or T2, N1)	9 (16%)	5 (56%)	0 (0%)	1 (11%)	0 (0%)	3 (33%)	3 (33%)
IIB (T2 or T3 without invasion)	1 (2%)	1 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
IIB (T3 with other invasive tumors)	11 (19%)	7 (64%)	0 (0%)	0 (0%)	1 (9%)	3 (27%)	3 (27%)
IIIA (N0/N1, other invasions)	8 (14%)	6 (75%)	0 (0%)	1 (13%)	1 (13%)	0 (0%)	0 (0%)
IIIA (N2)	6 (10%)	2 (33%)	0 (0%)	2 (33%)	0 (0%)	2 (33%)	2 (33%)
Total	**58**	**42 (72%)**	**0 (0%)**	**5 (9%)**	**3 (5%)**	**8 (14%)**	**9 (16%)**

The Kaplan-Meier survival curves (Figure 17) showed that patients who attained NCCN treatment guidelines had better survival than those with non-attainment in the first four years after the resection. The three-year survival rates of NCCN attainment and non NCCN attainment were 46.9% and 45.2%, respectively. The p-value of the adjusted multiple comparison for the logrank test was 0.0411. Figure 18 demonstrated the survival curves by adjuvant treatments. The three-year survival rates of chemotherapy or radiotherapy, both, and none were 66.7%, 46.9%, and 41.7%. On the other hand, the three-year survival rate of negative margin was 72.4%.

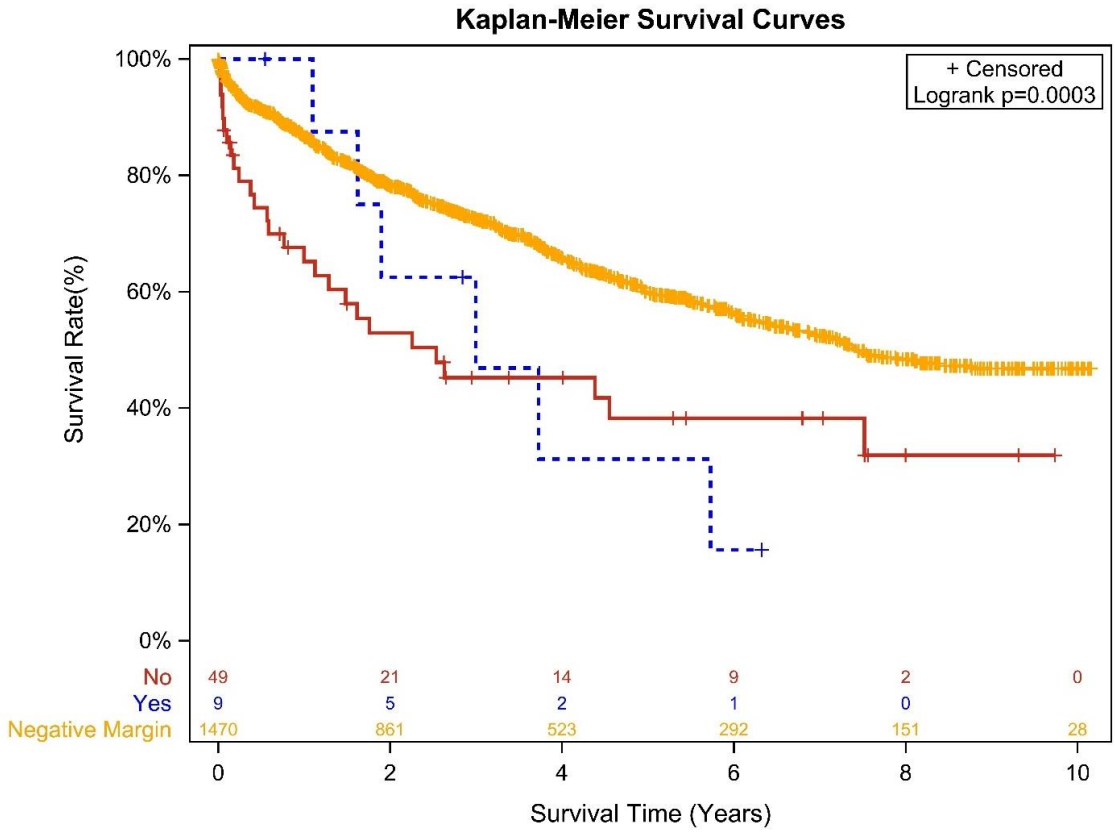

Figure 17. Kaplan-Meier survival curves by NCCN treatment guidelines attainment

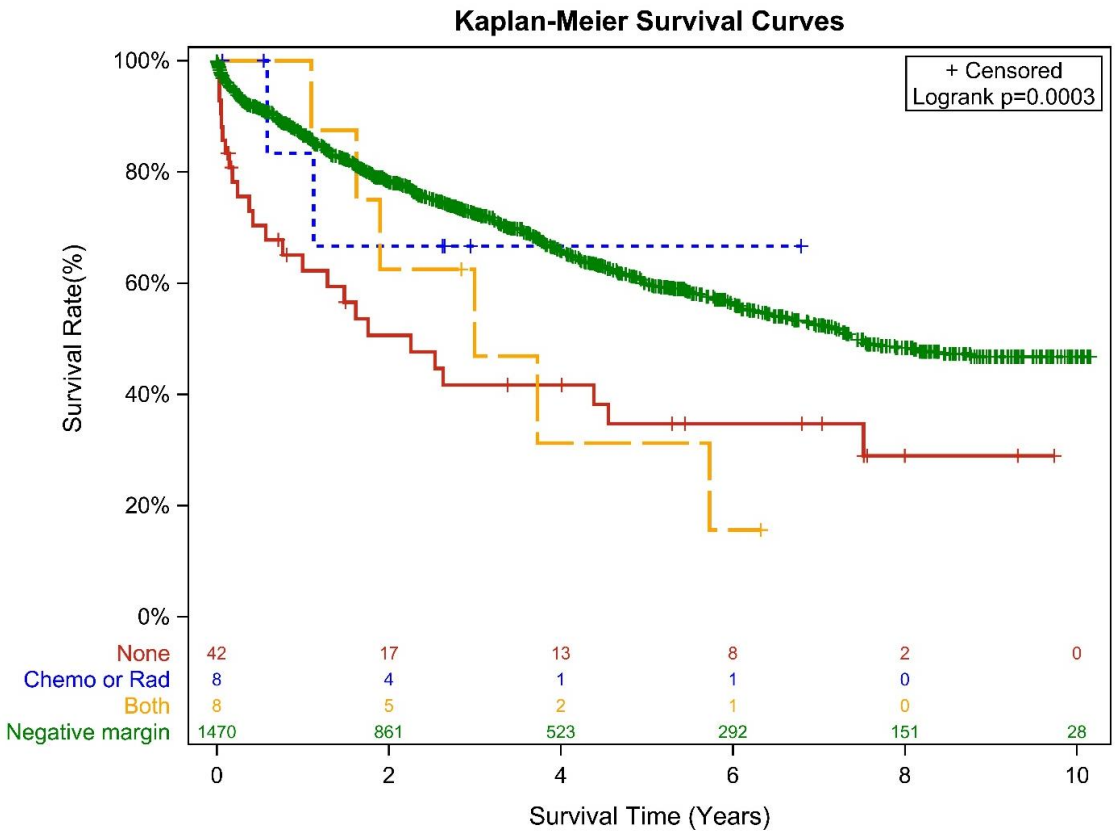

Figure 18. Kaplan-Meier survival curves by adjuvant treatments

Effect modification was not found in the Cox proportional hazards regressions. After adjusting for potential confounders, NCCN treatment guideline attainment was independently associated with overall survival. Patients who did not attain the guidelines had over 2-fold increased hazard of death (aHR=2.04, 95% CI: 1.37-3.02) compared with negative margins. The hazard of death in patients with guideline attainment is not significantly different from those with negative margin (aHR=1.55, 95% CI: 0.68-3.53) (Table 19).

Adjuvant treatment was also found to be independently associated with overall survival, regardless of the pathologic stage. Patients who received none of the postoperative treatments had 2.29 times the hazard of death (aHR=2.29, 95% CI: 1.53-3.44) compared with negative margins. The hazard of death in patients who received the

postoperative treatment (chemotherapy, radiotherapy, or both) was not significantly different from those with negative margin (Table 20).

Table 19. Cox proportional hazard ratio regression of NCCN treatment guidelines attainment

	HR (95% CI)	p-value
NCCN guidelines attainment		
Negative Margin	1	
Yes	1.55 (0.68-3.53)	0.3013
No	2.04 (1.37-3.02)	0.0004
Age	1.02 (1.00-1.03)	0.0094
Sex		
Female	1	
Male	1.37 (1.15-1.63)	0.0004
Charlson's comorbidity		
0	1	
1	2.35 (1.69-3.25)	<.0001
2+	2.51 (1.84-3.43)	<.0001
Insurance		
Commercial	1	
Medicare	1.48 (1.20-1.83)	0.0003
Medicaid	1.72 (1.34-2.21)	<.0001
Uninsured	1.00 (0.49-2.06)	0.9925
Pathologic stage		
Stage I	1	
Stage II	1.72 (1.42-2.09)	<.0001
Stage III	2.40 (1.85-3.10)	<.0001

Table 20. Cox proportional hazard ratio regression of adjuvant treatment

	HR (95% CI)	p-value
Adjuvant treatment		
Negative Margin	1	
Chemotherapy or Radiotherapy	0.52 (0.13-2.11)	0.3584
Both	1.71 (0.75-3.89)	0.2027
None	2.29 (1.53-3.44)	<.0001
Age	1.02 (1.01-1.03)	<.0001
Sex		
Female	1	
Male	1.36 (1.14-1.62)	0.0005
Charlson's comorbidity		
0	1	
1	2.66 (1.91-3.69)	<.0001
2+	2.80 (2.05-3.83)	<.0001
Neo-adjuvant treatment (chemotherapy or radiotherapy)		
No	1	
Yes	2.28 (1.65-3.17)	<.0001
Pathologic stage		
Stage I	1	
Stage II	1.74 (1.44-2.12)	<.0001
Stage III	2.33 (1.80-3.01)	<.0001

Discussion

This project evaluated the impact of NCCN guideline concordant treatment after incomplete surgical resection of lung cancer on overall survival. We found that the attainment rate is low in this analytic sub-population. Approximate 85% of patients with positive margins were not treated according to NCCN guidelines postoperatively. Our study is the first to observe this phenomenon. In a previous study evaluating postoperative treatment for NSCLC in the NCDB, Smeltzer and colleagues found that only chemotherapy was beneficial for the stage IB patients.[37] However, the NCCN guidelines recommended radiotherapy and/or chemotherapy. This suggests that more studies are needed to investigate the pragmatic reasons why the NCCN guidelines are not frequently attained.

More than 70% of the positive margin patients did not receive any postoperative treatment, including chemotherapy, radiotherapy, or both. This finding is higher than the national proportions of 45-60%.[37] Regardless of the NCCN guidelines, we found that the proportion of patients who received postoperative adjuvant therapies was also lower than the national proportion. Dr. Smeltzer analyzed the 82,440 NSCLC patients with the NCDB.[37] They found 3461 patients who were R1/R2, and 59% of R1/R2 patients received adjuvant therapies. Inconsistent with this previous report, our study observed only 28% of the positive margin patients received the adjuvant therapies.

In our study, patients who did not meet NCCN guidelines had worse survival than those with negative margins. We did not find statistically significant survival differences between patients with guideline attainment and negative margins.

Consistent with previous reports, postoperative adjuvant therapies appear beneficial to the positive margin patients. Hancock and colleagues analyzed NSCLC patients 19 years or older diagnosed as their first and only primary invasive cancer between 2003 and 2006 with the NCDB. They found that chemotherapy or chemoradiation provide superior results for stage I-III patients with positive margins.[16] However, our finding was in conflict with Smeltzer's study even though they also evaluated NSCLC patients from 2004 to 2011 with NCDB. Their study showed that adjuvant therapies were not beneficial to patients with stage IA and radiotherapy was not recommended for the stage IB and IIA patients.

Although re-resection is preferred by the NCCN guidelines, we observed no patient who received re-resection as postoperative treatment in this study. This is an interesting phenomenon. Further investigation is needed to understand why the health providers do not follow the guideline in the clinical setting.

The findings in our study may not be generalizable to the broader US population since we only included patients from one health care system. There can be selection bias when we only include patients from single health care system. A more representative population would be useful to validate this result in future studies. Additionally, we were not able to obtain the date when the patients received their postoperative treatments in our dataset. The postoperative treatments are preferably commenced within 60 days after the surgery. Sub-optimal application of postoperative treatments might influence our findings. This study is limited by the retrospective nature of the analysis. An RCT could definitively determine the best adjuvant therapy for incompletely resected NSCLC.

To our knowledge, this project provides the first evaluation of the NCCN guidelines for postoperative therapy to date in the Mid-South population. Although this is only for the sub-population of the Mid-South region, this is the beginning not the end. In patients with incomplete surgical resection, the available evidence is far less, and the existing evidences are lower level. Although RCTs can definitively determine the best adjuvant therapy for incomplete surgical resection in NSCLC, such a trial will be challenging to execute because of the low incidence of the margin positivity. The National Cancer Institute's Community Oncology Research Program could potentially be harnessed to support such a trial. The possibility of patient harm in the existing evidence void should stimulate the need to resolve this question.

Chapter 5

Summary

Surgical resection is the therapeutic option that provides the greatest survival benefit for patients with NSCLC. The goal of surgical resection is to contain the tumor entirely within the resection specimen, with gross and microscopically uninvolved margins. However, sometimes this goal is not met, resulting in an incomplete surgical resection. Factors associated with incomplete resections included demographic factors, institutional factors, and clinical characteristics. Patients with incomplete surgical resection have lower long-term survival rates. Postoperative treatment options after incomplete resection may improve overall survival, but the implementation of these treatments is sub-optimal.

In our first project, we identified that male sex, unknown patient's residency, advanced clinical stage (II and III), neo-adjuvant treatment, higher surgeon annual case volume, and urban location of hospital were the preoperative risk factors for the margin positivity. This is the first study to find that accurate TN staging was a protective factor for positive margins. We also found that margin involvement had a negative impact on survival, which was expected.[12,20,26,60]

Our study also found that the anatomic site of a positive margin has an impact on overall survival. This finding agrees with previous reports.[26,33,61,62] However, the survival outcomes at anatomic sites in previous study were different from our results. This project shows that the mainstem bronchial wall margin has the worst survival outcome than other anatomic sites; however, previous study indicated that chest wall margin had the worst survival rate.[26]

The second project used a RAMP model to assess the association between hospital performance in margin positivity and survival outcomes. The hospital performance was evaluated based on the probability of margin positivity for each patient after adjusting for patient level factors. The RAMP-based institutional category was strongly associated with surgical care quality, surgeon characteristics, and hospital characteristics. The outperforming hospitals were more likely to attain the NCCN or ACOSOC criteria, had more surgeons with Cardiothoracic board certificate and predominant practice in thoracic or cardiovascular, and were more likely to be affiliated with a teaching program. We found that the RAMP model provides a useful method for evaluating institutional quality.[74]

In the third project, we evaluated the impact of postoperative NCCN guideline attainment on long-term survival. We found that the attainment rate was low in this analytic sub-population. More than 70% of the positive margin patients did not receive any postoperative treatment, including chemotherapy, radiotherapy, or both; this is higher than the national average.[37] Regardless of whether NCCN guidelines were attained, patients were less likely to receive postoperative therapies than the national average.[37] Patients who did not attain NCCN guidelines had worse survival than those with negative margins. We did not find a statistically significant survival different between patients with guideline attainment and negative margins. Consistent with previous reports, postoperative adjuvant therapies are beneficial to positive margin patients.

Optimal care for patients with lung cancer has many factors. While surgical resection remains the best option when available, there are still deficits in quality. The goal of all curative intent resection in oncology is to achieve a disease-free tissue

specimen under the microscopy, thereby to make sure that no residual disease has been left behind. However, we found this was not attained in approximately 5% of resections in the Mid-South region of the US between 2009 and 2019. The adverse survival impact of resection with margin positivity has been confirmed for many different types of cancer.[12,14] Although postoperative adjuvant therapy is considered an alternative option for treating residual tumors, it does not improve survival. The need for additional treatment is real, but complex. The rate of the attainment of postoperative treatment criteria is very low among patients with positive margins in our cohort.

A better understanding of the potentially reversible factors driving the risk of margin positivity is needed to aid preoperative and intraoperative treatment decision making. We also need a more thorough understanding of why postoperative treatment recommendations are not followed, and additional high-level evidence to support these recommendations.

The rate of incomplete surgical resection is one standard marker of the quality of lung cancer care.[83] However, lymph node sampling at the time of surgery also has demonstrable significance.[6,49] The IASLC has proposed an updated definition of a complete resection for lung cancer that requires both positive margins and adequate lymph node sampling.[84] Integrating the lymph node sampling with the surgical margin status at surgery is a logical next step for this work.

In this dissertation, we have investigated important elements of optimal intra- and post-operative treatment for patients undergoing surgical resection for NSCLC. We found results that are consistent with the current literature, as well as several novel findings. Future work should focus on better identification of patients at risk for incomplete

resection, improving the implementation of current guidelines and quality care at the institutional level, and generating higher level evidence to support postoperative treatment after incomplete resection.

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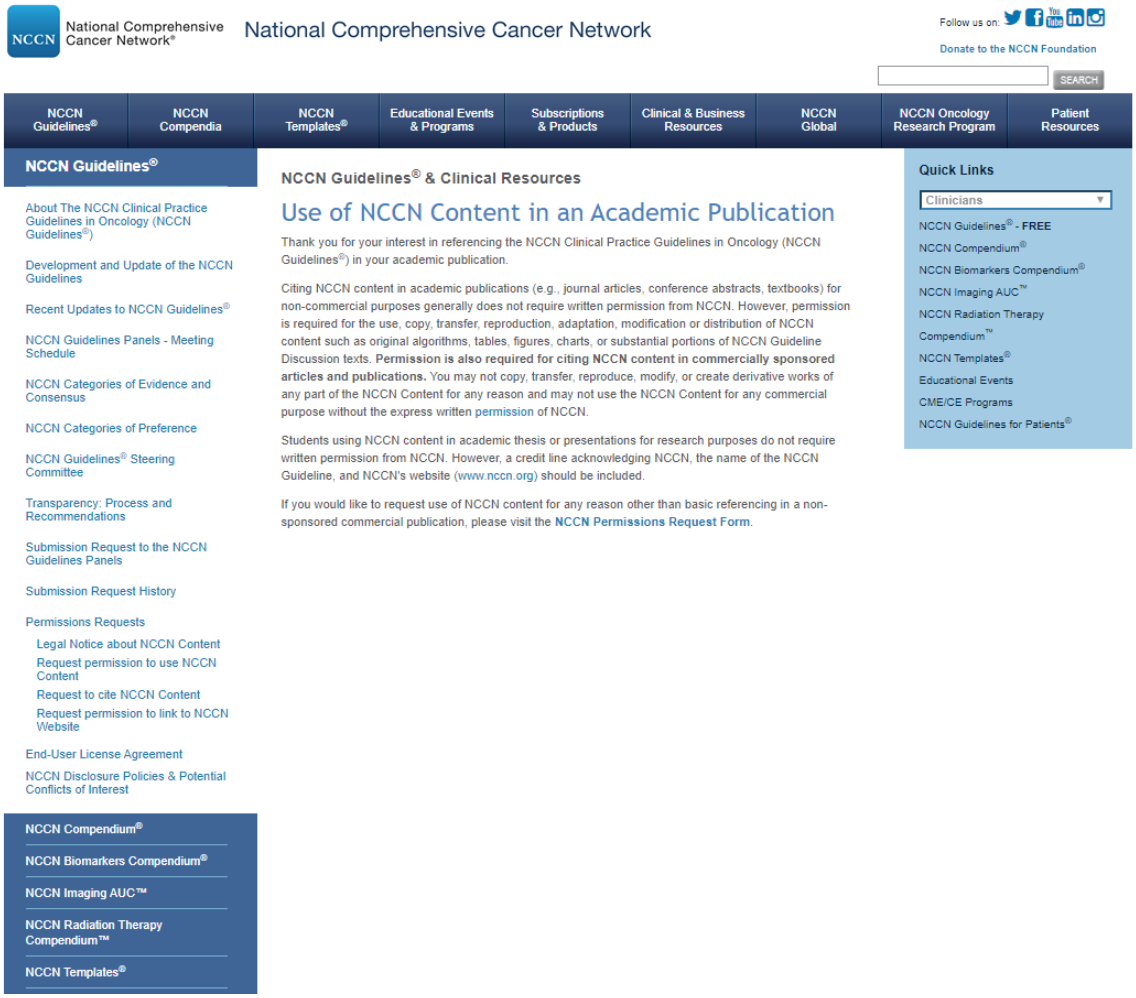

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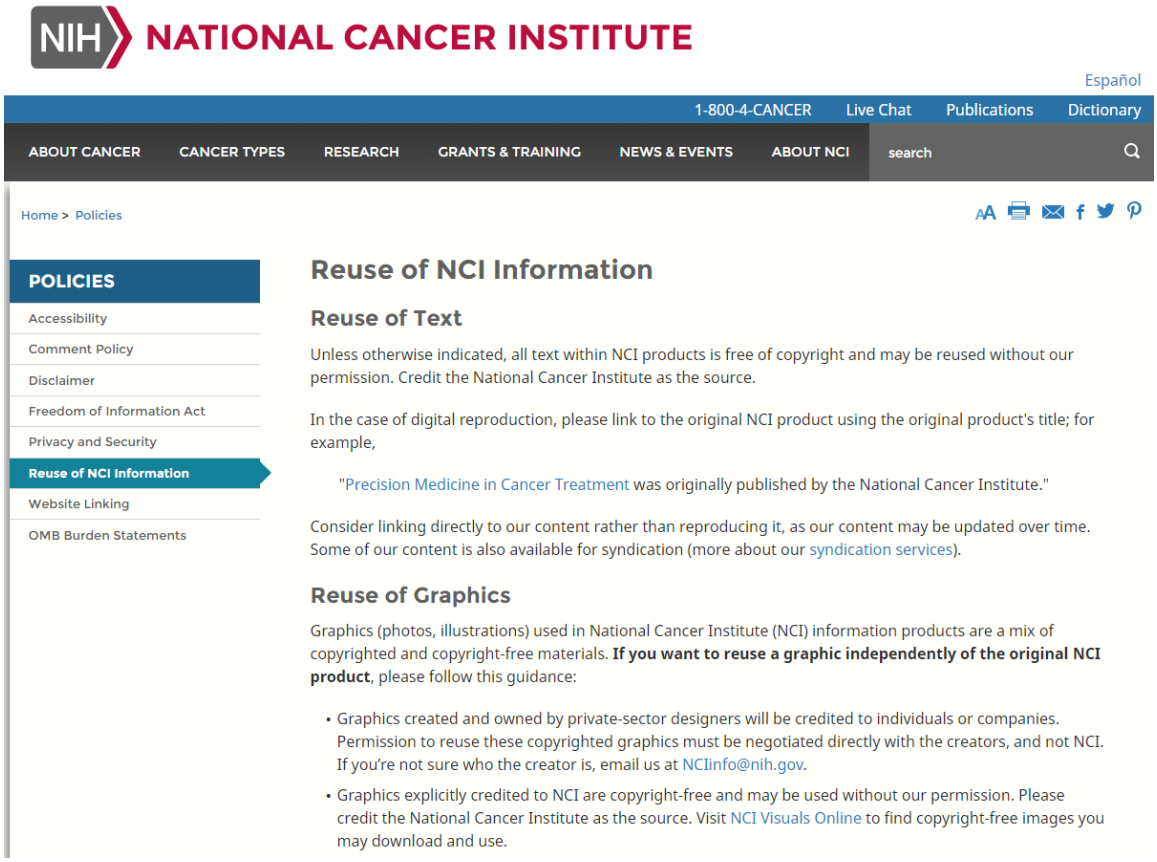
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IRB Approval

From: irb@memphis.edu <irb@memphis.edu>
Sent: Monday, October 28, 2019 10:03 AM
To: Ashley Yacoubian (mezekiel) <A.Yacoubian@memphis.edu>; Matthew Paul Smeltzer (msmltzer) <msmltzer@memphis.edu>
Subject: 2519 - Renewal: Approval - Renewal

Institutional Review Board
Division of Research and Innovation
Office of Research Compliance
University of Memphis
315 Admin Bldg
Memphis, TN 38152-3370

PI: Matthew Smeltzer
Co-Investigator:
Advisor and/or Co-PI:
Department: Epidemiology
Study Title: (Facilitated Baptist) Dissemination and implementation of a corrective intervention to improve mediastinal lymph node examination in resected lung cancer.
IRB ID: 2519
Submission Type: Renewal
Level of Review: Expedited

IRB Meeting Date:
Decision: Rely on External IRB
Approval Date: October 25, 2019
Expiration Date: October 25, 2020

Research Notes:
Findings:

The IRB has reviewed the renewal request. The University of Memphis Institutional Review Board, FWA00006815, has reviewed your submission in accordance with all applicable statuses and regulations as well as ethical principles.

Approval of this project is given with the following obligations:

1. If this IRB approval has an expiration date, an approved renewal must be in effect to continue the project prior to that date. If approval is not obtained, the human subjects consent form(s) and recruiting material(s) are no longer valid and any research activities involving human subjects must stop.
2. When the project is finished a completion form must be completed and sent to the board.
3. No change may be made in the approved protocol without prior board approval, whether the approved protocol was reviewed at the Exempt, Expedited or Full Board level.
4. Exempt approval are considered to have no expiration date and no further review is necessary unless the protocol needs modification.
5. Human subjects training is required every 2 years and is to be kept current at citiprogram.org.

Thank you,
James P. Whelan, Ph.D.
Institutional Review Board Chair
The University of Memphis.
Note: Review outcomes will be communicated to the email address on file. This email should be considered an official communication from the UM IRB.