January 2014

# Treating Very Large Non-Small Cell Lung Cancers: A Survival Analysis Using National Cancer Databases

Amy Moreno

# Treating Very Large Non-Small Cell Lung Cancers:

# A Survival Analysis using National Cancer Databases

A Thesis Submitted to the
Yale University School of Medicine
in Partial Fulfillment of the Requirements for the
Degree of Doctor of Medicine

by

Amy Catherine Moreno

2014

**ABSTRACT**

TREATING VERY LARGE NON-SMALL CELL LUNG CANCERS: A SURVIVAL ANALYSIS USING NATIONAL CANCER DATABASES.

Amy C. Moreno, Daniel Morgensztern, Daniel J. Boffa, Roy H. Decker, James B. Yu, Frank C. Detterbeck, Zuoheng Wang, Michal G. Rose, and Anthony W. Kim. Department of Thoracic Surgery, Yale University School of Medicine, New Haven, CT.

Very large primary non-small cell lung cancers (NSCLC), defined as those >7 cm, remain a therapeutic challenge due to known survival disadvantage compared to smaller tumors and lack of specific studies in this population. This study compares the effect of various treatment modalities on survival of patients with large NSCLC with none or positive hilar lymph node involvement ($T3_{>7cm}N0$ and $T3_{>7cm}N1$, respectively).

The Surveillance, Epidemiology, and End Results (SEER) database was used to identify patients undergoing a lobectomy or pneumonectomy for $T3_{>7cm}N0$ NSCLC from 1999 to 2008. Patients were categorized into groups based on type of surgery performed and whether neoadjuvant radiation therapy (NRT) was used. The National Cancer Data Base (NCDB) was used to identify adult patients who were diagnosed with $T3_{>7cm}N1$ NSCLC from 1999-2005. Nonsurgical treatments included chemoradiation, chemotherapy, radiation therapy, or no treatment whereas primary surgical treatments included surgery only, chemoradiation or chemotherapy prior to surgery (CxR-S or C-S, respectively), chemoradiation or chemotherapy after surgery (S-CxR or S-C, respectively), or postoperative radiation therapy (S-PORT). Five-year overall (OS) and

lung cancer specific survival (LCSS) were estimated by the Kaplan-Meier method and comparisons made using log-rank tests and Cox regression models.

A total of 1,301 surgical patients with $T3_{>7cm}N0$ NSCLC were evaluated using the SEER database, including 1,232 undergoing primary surgical therapy (PST) and 69 receiving NRT. NRT was not associated with improvements in 5-year OS (48% vs. 41%, *P*=.06) or LCSS (59% vs. 52%, *P*=.12) compared to PST. Lobectomies were associated with better 5-year OS (43% vs. 33%; *P*=.006) and LCSS (54% vs. 43%, *P*=.005) compared to pneumonectomies. On multivariate analysis, NRT did not produce any significant advantage in OS (*P*=.24) and LCSS (*P*=.21). Using the NCDB, a total of 642 patients with $T3_{>7cm}N1$ NSCLC were evaluated: 425 nonsurgical and 217 primary surgical treatments. Primary surgical treatments were associated with an improved 5-year OS of 28% compared to 8% and 4% for primary nonsurgical treatments and no treatments, respectively (*P*<.001). Specific nonsurgical treatment 5-year OS were 11%, 5%, 2%, 4% for chemoradiation, chemotherapy, radiation therapy, and no treatment, respectively (*P*<.001). Primary surgical treatment 5-year OS were 16%, 44%, 40%, 40%, 38%, and 18% for surgery only, CxR-S, C-S, S-CxR, S-C, and S-PORT, respectively (*P*<.001). On multivariate analysis, surgery and chemotherapy in most combinations were associated with significantly improved OS compared to chemoradiation only (C-S hazard ratio (HR), 0.4 [95% confidence interval, 0.18-0.88], *P*=.02; CxR-S HR, 0.41 [0.19-0.9], *P*=.03; S-C HR, 0.4 [0.19-0.85], *P*=.02).

Our results demonstrate that neoadjuvant radiation therapy, which most likely was a combination of chemotherapy and radiation, was not associated with improvements in OS or LCSS compared to primary surgical therapy for patients with $T3_{>7cm}N0$ NSCLC.

When feasible, lobectomy appears more beneficial than pneumonectomy in terms of long-term survival. For patients with $T3_{>7cm}N1$ NSCLC, surgery with systemic therapy delivered in a neoadjuvant or adjuvant fashion is associated with improvements in long-term overall survival. Finally, when surgical resection is not feasible, definitive chemoradiation therapy should be considered as an equal alternative to surgical resection alone.

**ACKNOWLEDGEMENTS**

The author would like to thank Dr. Anthony Kim for his guidance, mentorship, and support throughout the development of this project and my medical school experience in general. My appreciation also goes out to everyone who collaborated with me on the publications listed below, the Yale Office of Student Research for funding my endeavors, members of the Yale Department of Radiation Oncology with whom I have continued similar research projects with, my family for all of their support, and finally to God for giving me the passion towards making a lasting impact in the field of medicine.

**Disclosure**

Portions of the following thesis were taken from previously published work authored by Amy Moreno. All co-authors have agreed for this material to be used for the following publication. The previous publications being referred to include:

Moreno AC, Morgensztern D, Yu JB, et al. Impact of preoperative radiation on survival of patients with T3N0 >7-cm non-small cell lung cancers treated with anatomic resection using the Surveillance, Epidemiology, and End Results database. *The Journal of Surgical Research.* Apr 3 2013.

Moreno AC, Morgensztern D, Boffa DJ, Decker RH, Yu JB, Detterbeck FC, Wang Z, Rose MG, Kim AW. Treating locally advanced disease: An analysis of very large, hilar lymph node positive non-small cell lung cancer using the National Cancer Data Base. *Annals of Thoracic Surgery.* Article in Press 2014.

**TABLE OF CONTENTS**

## INTRODUCTION

With approximately 288,190 newly diagnosed cases estimated in 2013, lung cancer is a dangerously prevalent disease in the United States. It is the second most common cancer in both men and women, accounting for roughly 14% of all new cancers. As the most common cause of cancer deaths, lung cancer takes the lives of almost one-third of all cancer patients annually, a toll that surpasses colon, breast, and prostate cancer deaths combined[1]. While the chances of a man or woman to develop lung cancer in his or her lifetime nowadays is about 1 in 13 or 1 in 16, respectively, it is interesting to note that lung cancer was once considered a very rare disease prior to the 20$^{th}$ century. By 1900, only about 140 cases had been published in medical literature. Shortly thereafter, findings of primary lung tumors in autopsied bodies began to rise dramatically. In 1912, Isaac Adler, author of the world's first monograph on lung cancer, was one of the first to infer a possible association between tobacco abuse (and alcohol) with the simultaneous "decided increase" in incidence of malignant neoplasms of the lung[2]. A global lung cancer epidemic was later recognized in the 1940s and 1950s as growing evidence of the epidemiology, cellular pathology, and chemical analytics pointed back to cigarettes as the primary cause[3]. However, with the expansion of cigarette manufacturing and effective propagandizing to the public, this evidence was argued for years while a worldwide addictive habit quickly solidified.

Tobacco smoking is now undisputedly the leading risk factor for lung cancer. According to the 2012 International Agency for Research on Cancer (IARC) risk assessment, lung cancer kills about 1.59 million people per year globally with 80-95% of cases entirely preventable[4,5]. Other risk factors include radon, a naturally occurring

radioactive gas that results from the breakdown of uranium in soil and rocks, asbestos exposure, and a history of radiation therapy to the lungs or chest for other cancers such as Hodgkin's lymphoma[5]. Lung cancer is primarily a disease of the elderly with two out of three people diagnosed being over the age of 65. This finding has been thought to correlate with an increased likelihood of tobacco smoke exposure with increasing age. For unknown reasons, black men are about 20% more likely to develop lung cancer than white men[1]. Major public awareness campaigns, banning of cigarette smoking in public areas, and a steadfast mission to detect and aggressively treat lung cancer as early as possible have all created a small appearing yet significant impact towards thwarting the rising trend of lung cancer. Over the past decade, rates for new lung and bronchus cancers have been falling on average 1.3% each year and mortality trends are similarly decreasing by about 2.3% per year for men and 0.7% per year among women[6,7].

When analyzing lung cancers histologically, they can be broadly divided into two main types: small cell and non-small cell lung cancer (NSCLC). NSCLC constitutes the majority of lung cancers and includes histologic subtypes such as adenocarcinoma, large cell carcinoma, and squamous cell carcinoma. Roughly one-quarter of patients with NSCLC are diagnosed at an early stage (stage I or II), and treatment typically includes surgery with or without chemotherapy in order to achieve curative rates of 60-80% and 40-50% for stages I and II disease, respectively[8-10]. On the other extreme of the spectrum, treatment goals for stage IV disease usually involve palliative measures to deal with metastatic disease. For the remaining 35% to 45% of patients diagnosed with stage III NSCLC, curative-intent treatment is a controversial topic. The differences in treatment

within stage III owes to the inclusion of a heterogeneous group of lesions that constitute this stage.

According to the 7th edition of the American Joint Committee on Cancer (AJCC) and the International Union Against Cancer (UICC) staging system, stage III lung cancer can be divided into two broad subcategories, stage IIIA and stage IIIB disease[11]. Each stage can be further analyzed by the TNM classification method that incorporates information regarding tumor dimensions (T), lymph node invasion (N), and whether metastatic disease is present (M). Stage IIIA mirrors the heterogeneity of all of stage III disease as it is also constituted by a heterogeneous mix of lesion sets [Table 1]. With respect to tumor size and/or extension, T3 lesions encompass lesions that invade the chest wall, are central in nature, or are associated with additional tumors in the same lobe. Tumors that are greater than 7 cm also fall into the T3 primary tumor category.

Tumor size has long since been recognized as a valuable prognostic factor in NSCLC. Adopted worldwide in 1974, the TNM classification is revised nearly every 10 years. Prior to the 7th edition of the AJCC staging system, the 6th edition defined only one tumor size cut off of 3 cm to separate T1 from T2 lesions. This threshold value for tumor size was selected after several studies demonstrated a significant difference in survival between patients with ≤3 cm (T1) and >3 cm (T2) lesions[12-15]. Since then more studies indicating survival differences at other larger tumor sizes led to the further division of T2 lesions to T2a (>3 cm but ≤5 cm) and T2b (> 5 cm but ≤7 cm) lesions and the upstaging of tumors >7 cm to a T3 status[11,16,17]. These major revisions that focused mainly on the T descriptor carry a significant impact on diagnostic staging and subsequent treatment selection. More specifically, very large tumors >7 cm with no lymph node involvement

were upstaged from stage IB to stage IIB ($T3_{>7\ cm}N0$) disease while tumors >7 cm with positive ipsilateral hilar lymph node involvement were upstaged from stage IIB to stage IIIA ($T3_{>7\ cm}N1$) disease.

Many clinicians, in particular surgeons, would agree that T3N0 tumors benefit from surgical resection as the initial mode of therapy. Current National Comprehensive Cancer Network (NCCN) and American College of Chest Physicians (ACCP) guidelines recommend lung-sparing anatomic resections (lobectomy) over pneumonectomies if anatomically appropriate and margin-negative resections can be achieved[10,18]. The use of definitive, neoadjuvant, or adjuvant chemotherapy with or without radiation therapy for this subset of patients with early stage disease is arguable due to the absence of metastatic spread to local lymph nodes and reasonably high curative rates with surgery alone. However, data from the CALGB study which demonstrated that a statistically significant survival advantage exists for patients with early stage NSCLC tumors ≥4 cm who are treated with adjuvant paclitaxel/carboplatin would then suggest that given the large nature of these tumors, there is a benefit of adding adjuvant therapy[19]. Moreover, there may be a potential impact of neoadjuvant therapy on "downstaging" or reducing tumor burden prior to surgical resection for patients with very large tumors that are categorized as early stage disease. In clinical practice, the optimal strategy for this group remains undefined.

Similarly, the optimal treatment strategy for $T3_{>7\ cm}N1$ NSCLC is controversial. Part of the confusion results from a lack of studies analyzing patterns of care and associated survival outcomes for this particular group of patients. As noted earlier, Stage IIIA disease represents a heterogeneous set of locally advanced lung cancers that

occasionally include surgical resection as part of a multimodality treatment algorithm[9,18,20]. Most studies analyzing the role of neoadjuvant or adjuvant therapy for the very large T3 lesion subset of T3 lesions are frequently buried among general data analyzing neoadjuvant or adjuvant therapy for stage II or III disease[21-23]. With the recent upstaging of $T3_{>7\ cm}N1$ NSCLC to a Stage IIIA designation it is difficult to assess the effects of treatment on survival for this subset of patients when most studies on Stage IIIA disease are primarily focused on treating mediastinal or N2 nodal disease. Looking at this heavily studied population, patients with N2 nodal disease who comprise the majority of Stage IIIA NSCLC cases are approached with a wide variation in treatment strategies that are heavily influenced by physician interpretation of the actual extent of the disease and the patient's ability to withstand treatment[24-26]. Overall, there is a general consensus that patients with Stage III NSCLC would benefit from a multimodality therapeutic approach whenever feasible[20,27]. However, it is arguable that results from studies evaluating the effect of various treatments for N2 nodal disease can be directly applied to patients with $T3_{>7\ cm}N1$ NSCLC lesions.

In general, there are not very many studies that specifically address variations in the treatment of $T3_{>7\ cm}N0$ and $T3_{>7\ cm}N1$ lesions. It is clear that very large tumors that are greater than 7 cm with no or minimal hilar lymph node involvement present a unique set of problems for clinicians. Large lesions typically will not respond completely to the effects of definitive chemotherapy and radiation therapy. Similarly, as aforementioned, the benefit of these very large tumors in the context of neoadjuvant therapy remains questionable. The challenge associated with resecting these large tumors is that the extent of the operation required to remove these lesions is substantial and often times followed

by adjuvant therapy in clinical practice. To our knowledge, there has been no study assessing current treatment patterns and their effect on long-term survival for patients with very large NSCLCs with no or minimal lymph node involvement.

## STATEMENT OF PURPOSE AND SPECIFIC HYPOTHESIS

The purpose of this study was to examine the efficacy of different treatment strategies on long-term survival of patients with very large NSCLC tumors clinically staged as $T3_{>7cm}N0$ or $T3_{>7\ cm}N1$ using large national datasets. Our primary hypothesis is that there is a practice pattern that exists which may be associated with an improved outcome for very large tumors with none or minimal lymph node burden. Our secondary hypothesis is that within this group, whether there is a difference or not, there are specific characteristics associated with certain patients with very large tumors that result in more favorable outcomes.

## SPECIFIC AIMS

1. To identify current patterns of treatment for very large NSCLCs that are clinically staged as $T3_{>7cm}N0$ or $T3_{>7cm}N1$
2. To determine the practice pattern associated with the best clinical outcomes including the longest survival
3. To identify factors that are associated with improved clinical outcomes compared to other patients with stage $T3_{>7cm}N0$ or $T3_{>7cm}N1$ NSCLC undergoing alternative modalities of treatment

## METHODS

NOTE: All data analysis described below was performed by the primary author.

*Data Sources*

This study utilized two national cancer databases. The Surveillance, Epidemiology, and End Results database provided clinical, demographic, and treatment data for patients diagnosed with very large (>7 cm) NSCLC tumors with no lymph node involvement ($T3_{>7cm}N0$ disease). The National Cancer Database provided clinical, demographic, treatment and overall survival data for patients diagnosed with very large (>7 cm) NSCLC tumors with positive ipsilateral hilar lymph node involvement ($T3_{>7cm}N1$ disease).

### *The Surveillance Epidemiology End Results (SEER) Public-Use Dataset*

The Surveillance, Epidemiology, and End Results (SEER) database, a national cancer surveillance program, has collected clinicopathologic data on all incident cancer cases since 1973 and now includes 18 regional population-based cancer registries that cover approximately 28% of the United States population. Sponsored by the National Cancer Institute, the database is highly representative of national demographics and contains information on primary tumor site, tumor histology and morphology, stage at diagnosis, first course of treatment, follow up, and cause of death[28].

*Patient Selection*

We restricted the analysis to patients who were of age 20 years and older and were diagnosed with NSCLC from 1999 to 2008. As the current seventh edition AJCC

lung cancer staging definition for Stage IIB tumors is broad and complex, we selectively specified for a clinical TNM staging diagnosis of a tumor size >7 cm with no clinical lymph node involvement (cN0) or metastasis (cM0) in our inclusion criteria. All eligible patients had histologically confirmed NSCLC. The histology of the tumors coded in the SEER database according to the third edition of the *International Classification of Disease for Oncology* (ICD-O-3) was used to classify tumors into the following five categories: large cell carcinomas (ICD-O-3 codes 8012 and 8013); squamous cell carcinomas (ICD-O-3 codes 8050-8052 and 8070-8078); adenocarcinomas (ICD-O-3 codes 8140, 8141, 8143, 8147, 8250-8255, 8260, 8310, 8430, 8480, 8481, 8490, and 8571-8575); adenosquamous carcinomas (ICD-O-3 codes 8560 and 8570); and other NSCLC tumors (ICD-O-3 codes 8010, 8020, 8046)[29]. All patients with distant metastasis or tumor sizes less than 7 cm were excluded. The SEER program Coding and Staging Manual was consulted to select patients who received definitive surgical therapy in the form of a lobectomy (surgical codes 30-45) or pneumonectomy (surgical codes 55-70)[30]. These patients were then categorized into groups depending on type of surgery performed and whether neoadjuvant radiation therapy (NRT) was provided prior to surgery. The final sample size included 1,301 patients.

***The National Cancer Database (NCDB)***

The National Cancer Data Base (NCDB) is a joint project of the Commission on Cancer of the American College of Surgeons and the American Cancer Society. Begun in 1989, it is a nationwide oncology outcomes database that captures detailed information of nearly 70% of all newly diagnosed cases of cancer in the United States and currently

contains over 29 million records from hospital cancer registries across the country[31]. Therefore, the NCDB is an excellent resource to investigate patient and tumor characteristics, radiation, chemotherapy, complications, and long-term survival. The data used in this study are derived from a deidentified NCDB file. The American College of Surgeons and the Commission on Cancer have not verified and are neither responsible for the analytic or statistical methodology employed, nor the conclusions drawn from these data by the investigator. All information regarding patient and tumor characteristics, initial treatment, and outcomes were selected for the cohort using the "βPUF (Participant User File) Data Dictionary Item" descriptions found at the National Cancer Database website[32].

*Patient Selection*

The analysis was restricted to patients who were age 20 years and older and diagnosed with NSCLC as their only cancer diagnosis from 1999 to 2005. The *International Classification of Disease for Oncology* (ICD-O-3) codes used in the NCDB to identify the NSCLC cohort has been previously described above in the "*The Surveillance Epidemiology End Results (SEER) Public-Use Dataset"* section and the following subcohorts were created: large cell carcinomas, squamous cell carcinomas, adenocarcinomas, adenosquamous carcinomas, and other NSCLC tumors. All patients had a documented tumor size >7 cm but ≤20 cm, clinically positive ipsilateral lymph node involvement (cN1) and no distant metastasis (cM0). There is a group of patients in the NCDB with tumor sizes labeled as 7 cm which could potentially include a subset of patients with larger tumors that were estimated downward, but for the purposes of this

portion of the study which focused on proper $T3_{>7cm}N1$ NSCLC identification they were excluded. Patients who received surgical therapy in the form of lobectomy or pneumonectomy with negative surgical margins were included. Similar surgical codes as recorded in the SEER $T3_{>7cm}N0$ NSCLC analysis above were used.

Treatment combination sequences were determined for each patient using NCDB data items that described the date of treatment (either surgical, chemotherapy/systemic, or radiation therapy) in relation to date of diagnosis. The possible treatment modalities for the nonsurgical sub-cohort (NST) included no treatment (None); chemotherapy only (C); radiation therapy only (RT); or chemoradiation therapy (CxR). The primary surgical treatment (PST) combinations included the following: surgery only (S); chemotherapy prior to surgery (C-S); chemoradiation prior to surgery (CxR-S); surgery followed by chemotherapy (S-C); surgery followed by chemoradiation (S-CxR); or surgery and postoperative radiation therapy (S-PORT).

Preoperative or neoadjuvant radiation therapy is often a proxy for preoperative chemoradiation and is seldom provided without chemotherapy prior to surgery. However, we found minimal patients with records indicating neoadjuvant radiation therapy without chemotherapy prior to surgery. As this treatment modality represented a disproportionate minority, it was excluded from the analysis. Any patient with distant metastasis or records indicating therapy was for palliative measures was excluded. Patients undergoing surgical resections with positive margins were also excluded for several reasons including small sample size (less than 10% of the surgical population) and the likelihood that this select group of patients received adjuvant therapy due to the positive surgical

margins which could therefore skew the results in evaluating the impact of adjuvant therapy after complete surgical resection. The final sample size included 642 patients.

### *Variables*

Patient information obtained from the SEER database included gender, age, race/ethnicity, age at diagnosis, histology and size of primary tumor, stage along with degree lymph node involvement, type of surgery, the performance of neoadjuvant radiation therapy (NRT), survival time, and cause of death. Patient information obtained from the NCDB included gender, age, race/ethnicity, age at diagnosis, histology and size of primary tumor, stage along with degree lymph node involvement, type of surgery, the addition or absence of neoadjuvant and adjuvant therapy, and survival time in months.

For both databases, patients who had a lobectomy include a simple lobectomy, sleeve lobectomy, bilobectomy, and extended lobectomy while those with a pneumonectomy consist of both a simple and extended pneumonectomy. The location of each tumor was identified for each patient and categorized into one of the following groups: right upper lobe (RUL), right middle lobe (RML), right lower lobe (RLL), left upper lobe (LUL), or left lower lobe (LLL) lesions.

Overall survival (OS) was the primary study endpoint and was defined as the time from diagnosis to the date of death from any cause. Lung cancer-specific survival (LCSS), defined as the time of diagnosis to the date of death from lung cancer, was also evaluated in our SEER database analysis. The NCDB, however, lacks data regarding lung cancer specific death and therefore LCSS was not evaluated for this portion of the study.

Pertaining to the NCDB only, four types of treatment facilities comprised of community cancer programs (CCP), comprehensive community cancer programs (Comprehensive CCP), teaching/research centers, or others were also included in all analysis. Both CCP and Comprehensive CCPs have full range of services for cancer care; however CCPs treat at least 300 cancer patients a year whereas Comprehensive CCPs treat at least 650 cancer patients annually. Variables that were considered but could not be included in the study due to limitations of available data in the NCDB included performance status, specific details regarding staging procedures (i.e. CT/PET imaging, lymph node staging procedure), medications, and comorbidities (a comorbid condition scale in the form of Charlson/Deyo scores is available in the NCDB but only from 2003 onward and thus was not included in our multivariate analysis).

### *Statistical Analysis*

*$T3_{>7cm}N0$ NSCLC, SEER Analysis*

The overall survival (OS) and lung cancer-specific survival (LCSS) functions stratified by type of surgery in the presence or absence of NRT were calculated using the Kaplan-Meier method. Patients who were still alive at the end of the study were treated as censored observations in the survival analysis. The log-rank test was used to evaluate whether there were differences in the OS and LCSS among the treatment groups. Comparisons on patient and tumor characteristics and provided therapy amongst different age groups were performed using the Chi-squared test. The multivariable Cox regression model was used to assess the effect of NRT followed by surgery as an independent predictor of OS and LCSS. Hazard ratios (HR) and corresponding 95% confidence

intervals were constructed in models adjusted for patient and tumor characteristics. Data analysis was performed using SAS for Windows, version 9.2 (SAS Institute; Cary, NC).

*$T3_{>7cm}N1$ NSCLC, NCDB Analysis*

Comparisons on patient and tumor characteristics and provided therapy amongst different age groups were performed using the Chi-squared test. The OS functions stratified by type of surgery in the presence or absence of neoadjuvant and adjuvant therapy were calculated using the Kaplan-Meier method. Patients who were still alive at the end of the study were treated as censored observations in the survival analysis. The log-rank test was used to evaluate whether there were differences in the OS among the treatment groups. The multivariable Cox regression model with backward elimination of covariates with a $P$ value >0.1 was used to assess whether various patient and tumor characteristics (age, sex, race, histology, location of tumor, tumor size, facility type) along with chosen therapy were significant independent predictors of OS. Hazard ratios (HR) and corresponding 95% confidence intervals were constructed in models adjusted for patient and tumor characteristics and therapeutic approaches. Data analysis was performed using SAS for Windows, version 9.2 (SAS Institute; Cary, NC). Statistical significance was defined as $P$ <.05.

## RESULTS

### *$T3_{>7\ cm}N0$ NSCLC, SEER Analysis*

*Patient and tumor characteristics*

The cohort was composed of 1,301 patients of whom 69 patients (5%) received NRT followed by surgery as compared to 1,232 patients (95%) who had primary surgical therapy (PST) (Table 1). The median follow-up time for the entire cohort was 25 months (mean, 35 months; range, 0-131 months). The median age of the total population was 68 years (mean, 67 years; range, 31- 94 years). Forty-nine patients (71%) in the NRT group were male and 800 patients (65%) who had PST were male. No male over 80 years of age received NRT in comparison to 92 males (7%) above the age of 80 who received PST. Most patients were Caucasian in both treatment groups (88% NRT; 86% PST). By the end of the study period, 60% of the cohort (779 patients) had expired due to either lung cancer-related mortality (568 patients; 44%) or other causes of death.

Adenocarcinoma was the predominant histology comprising 46% of the entire cohort (593 patients) followed by squamous cell carcinoma which comprised 38% (500 patients) of the entire cohort. In the NRT group, squamous cell carcinoma (42%; 29 patients) was more prevalent than adenocarcinoma (29%; 20 patients). Tumor size did not significantly vary among the different age populations ($P$=.16) in the entire cohort and between the two treatment groups. Overall, patients with tumor sizes 8-8.9 cm had the highest incidence of definitive treatment with either NRT followed by surgery (21 patients, 30%) or PST (391 patients, 32%) as compared to those with larger tumors. Tumors 7.1-7.9 cm were the second most prevalent size group in the overall cohort (288 patients; 22%). Although distribution of tumor size was nearly equal among the different

age and treatment groups, tumor lobe location varied significantly ($P$<.0001). For the entire cohort, right-sided tumors were more common than left-sided (56% vs. 44%) with RUL and RLL lesions accounting for 52% of all tumors. Nearly 85% of patients treated with NRT had upper lobe lesions (RUL, 46%; LUL, 38%).

*Therapeutic approach*

For the entire cohort, lobectomy was the most commonly employed surgical approach with 85% of the population (1,110 patients) having undergone this type of resection. The remaining 15% (191 patients) underwent pneumonectomy. The incidence of lobectomies performed increased with advancing age while pneumonectomy incidence decreased with increased age ($P$=<.0001). As noted earlier, PST was performed on the majority of patients whereas only 5% (69 patients) received NRT followed by surgery. Paralleling the overall cohort, patients in the NRT group underwent lobectomy (53 patients, 77%) more than pneumonectomy. Upon analysis of therapy provided in relation to age, the incidence of NRT decreased with advanced age while the incidence of PST increased to a peak of 35% for patients between the ages of 70-79 years ($P$<.0001). The majority of patients treated with NRT were among the youngest age groups (20-69 years, 83%) whereas PST was performed mainly on a higher age population (60-79 years; 66%) (Table 1).

The occurrence of NRT and PST was also analyzed in relation to tumor size. Patients with smaller tumor sizes in the overall cohort had a higher incidence of being treated with either NRT followed by surgery or PST than patients with increased tumor size. Similarly, smaller tumors were more likely to have been treated with a lobectomy or

pneumonectomy as compared to larger tumors, although the proportion of lobectomies over pneumonectomies was greatest for tumors between 8-8.9 cm (Fig. 1).

*Univariate survival analysis*

The addition of NRT was not associated with improvements in the 5-year OS (48% vs. 41%, *P*= .06) or LCSS (59% vs. 52%, *P*=0.12) compared to PST (Fig. 2). By type of surgery performed, lobectomies were associated with significantly improved 5-year OS (43% vs. 33%; *P*=.006) and LCSS (54% vs. 43%, *P*=.005) in comparison to pneumonectomies for the entire cohort (Fig. 3). When patients were further divided by type of surgery performed in the presence or absence of NRT, NRT did not significantly improve the 5-year OS (NRT, 51% vs. PST, 43%; *P*=.08) or LCSS (NRT, 60% vs. PST, 54%; *p*=.19) in patients who had a lobectomy. Similarly, patients who had a pneumonectomy did not benefit by the addition of NRT prior to surgery when considering 5-year OS (NRT, 36% vs. PST, 32%; *P*=.33) and LCSS (NRT, 56% vs. PST, 42%; *P*=.24). Irrespective of survival time, however, the survival curves for PST, in general, were consistently worse than for NRT followed by either a lobectomy or pneumonectomy.

*Multivariate analysis*

After adjusting for patient and tumor characteristics, NRT was not associated with significantly improved OS (*P*=.24) and LCSS (*P*=.21) for the entire cohort. Multivariate regression analysis identified gender, age, tumor size, and type of surgery performed as significant factors affecting OS, whereas only age, tumor size, and type of surgery were

found to significantly impact LCSS. Tumors ≥10 cm were associated with worse OS (hazard ratio [HR] 1.39; *P*=.007) and LCSS (HR 1.54; *P*=.002) when compared to tumors 7.1-7.9 cm. Pneumonectomies were associated with significantly worse OS (HR, 1.32; *P*=.007) and LCSS (HR, 1.38; *P*=.005) when compared to lobectomies (Table 2).

In a secondary analysis on the 69 patients who underwent NRT prior to surgery, gender statistically affected survival with females having better OS (HR 0.27 [95% confidence interval, 0.1-0.7], *P*=.007) and LCSS (HR 0.13 [0.03-0.51], *P*=.003) as compared to males. Adenosquamous tumors had a significantly increased overall (HR 6.18 [1.26-30.2], *P*=.02) and lung-cancer specific (HR 11.69 [2.13-64.19], *P*=.005) mortality risk than other histological types. The use of NRT prior to a lobectomy did not produce a significant advantage in OS (*P*=.86) or LCSS (*P*=.7) in comparison to NRT followed by a pneumonectomy (Table 3).

### *$T3_{>7\ cm}N1$ NSCLC, NCDB Analysis*

*Patient and tumor characteristics*

The overall cohort was composed of 642 patients of whom 425 patients (66%) underwent nonsurgical therapy (NST) and 217 patients (34%) underwent primary surgical therapy (PST). The median age of the entire cohort was 68 years (range, 29-90 years) with a median follow up time of 11 months (range, 0-143 months). The majority of patients were male (390 patients, 61%) and Caucasian (539 patients, 84%) and between the ages 60-79 years (415 patients, 65%). By the end of the study period, 88% of the cohort (565 patients) had expired. Patient characteristics are shown in Table 4.

*Therapeutic approach*

Among the 425 NST patients, 43% (184 patients) were treated with CxR, 16% RT, 15% Chemo, and 26% None. For the PST patients, 49% had S, 11% C-S, 14% CxR-S, 16% S-C, 5% S-CxR, and 5% S-PORT. Lobectomy was the most commonly employed surgical approach with 60% (131 patients) of the PST population having undergone this type of resection (*P*=.002). The remaining 40% of the PST group underwent pneumonectomy. For the entire cohort, definitive CxR was the most prevalent treatment among all age groups except patients ≥80 years of age where 36% (28 patients) received no treatment followed by 23% (18 patients) RT only. About half of the patients in the overall cohort were treated in a comprehensive cancer center program (51%, 330 patients). A similar proportion was noted in the NST and PST groups separately.

*Pathologic lymph node involvement*

For PST patients, pathologic lymph node involvement (pN) was evaluated. Among 56 patients who underwent neoadjuvant therapy prior to surgical resection (C-S, CxR-S), 45% had an indeterminate pN reported (pNX), 27% had pN0, 25% had pN1 and 3% had pN2. Patients who underwent surgical resection in the absence or presence of adjuvant therapy (S, S-C, S-CxR, S-PORT; n= 161) had 14% pN0, 72% pN1, 8% pN2, and 6% pNX (*P*<.001).

*Univariate survival analysis*

Surgery was associated with significant improvements in 5-year OS (PST, 28%) compared to 8% and 4% 5-year OS for NST and None, respectively (*P*<.001) (Fig. 4).

Lobectomy was associated with a significantly better 5-year OS compared to pneumonectomy among PST patients (L, 31%; P, 23%; *P*=.03). Smaller tumor sizes were associated with improved OS compared to tumors ≥10 cm for the PST cohort (*P*= .006) whereas tumor size variation did not affect OS for NST patients (*P*=.2).

The long-term survival of surgical and nonsurgical patients was further analyzed by dividing patients by specific type of therapy provided. For NST patients there was a significant stepwise improvement in 5-year OS with the addition of systemic therapy over localized radiation therapy (None, 4%; RT, 2%; Chemo, 5%; CxR, 11%; *P*<.001). Surgical patients who only received localized therapy had worse 5-year OS in comparison to any multimodality treatment combination which included chemotherapy (S, 16%; S-PORT, 18%; C-S, 40%; CxR-S, 44%; S-C, 38%; S-CxR, 40%; *P*<.001) (Fig. 5).

*Multivariate analysis*

After adjusting for patient and tumor characteristics, multivariate regression analysis on the entire cohort identified age and type of surgery performed as significant factors affecting OS (Table 5). Pneumonectomy was associated with a 49% increased likelihood of death compared to lobectomy (hazard ratio [HR] 1.49 [95% confidence interval, 1.08-2.05], *P*=.01). Type of therapy was also found to be an independent predictor of OS. Using definitive CxR as a reference, chemotherapy had a nonsignificant increase in HR whereas all other nonsurgical therapeutic approaches had a significantly increased likelihood of death: Chemo HR 1.25 [0.93-1.68], *P*=.13; RT HR 1.5 [1.12-2.01], *P*=.007; None HR 2.87 [2.23-3.69]; *P*<.001. Local therapy in the form of surgery

only was not associated with a significant difference in survival compared to definitive CxR (S HR 0.8 [0.41-1.54], *P*=.5) whereas nearly all surgery with chemotherapy combinations were associated with statistically improved OS in comparison to CxR only (C-S HR 0.4 [0.18-0.88], *P*=.02; CxR-S HR 0.41 [0.19-0.9], *P*=.03; S-C HR 0.4 [0.19-0.85], *P*=.02) with the exception of S-CxR which demonstrated a trend towards survival improvement (HR 0.5 [0.19-1.34], *P*=.17).

A separate multivariate analysis on the NST groups paralleled the results of the overall cohort. Monotherapy was associated with an increased likelihood of death compared to chemoradiation (Chemo HR 1.2 [0.92-1.66], *P*=.16; RT HR 1.5 [1.14-2.05], *P*=.005). A comparison between the nonsurgical therapies demonstrated no significant differences in HR between chemotherapy and RT but all three forms of NST were associated with significantly improved survival compared to no treatment. In a separate analysis of PST patients, tumors ≥10 cm were associated with worse OS (HR 1.89 [1.2-3]; *P*=.007) when compared to tumors 7.1-7.9 cm (Table 6). As seen on analysis of the overall cohort, all multimodality therapies incorporating chemotherapy in a neoadjuvant or adjuvant fashion among PST patients were associated with significantly reduced likelihood of death compared to surgical resection only with the exception of S-CxR which had a nonsignificant reduction in HR of 0.6 [0.26-1.35], *P*=.22. Finally, pneumonectomies were associated with a significantly worse OS (HR 1.43 [1.02-1.99]; *P*=.04) when compared to lobectomies among the PST group.

## DISCUSSION

### *$T3_{>7\ cm}N0$ NSCLC, SEER Study*

Surgery in the form of a lobectomy or pneumonectomy depending on the extent of disease is still considered the gold standard, primary treatment for stage II NSCLC disease. Adjuvant chemotherapy is sometimes recommended in certain high-risk cases in order to reduce the risk of distance metastases which is the primary cause of death in patients with NSCLC who die within 5 years of a complete surgical resection[8,33] However, the use of neoadjuvant therapy remains controversial for the management of early stage NSCLC. This study is reflective of current practice patterns for this subset of patients with Stage IIB NSCLC in that 95% of the cohort underwent surgery in the absence of neoadjuvant therapy.

For early stage disease, complete surgical resection offers reasonably high rates of cure. Definitive radiation therapy is only recommended for patients with early stage lung cancer who are medically inoperable or refuse surgery due to potential adverse effects from treatment-related toxicities and limited survival benefit[33]. In the SEER database, neoadjuvant radiation therapy (NRT) was assumed to be a proxy for preoperative chemoradiation due to the fact that preoperative radiation therapy alone has been eschewed as the standard of care practice for at least two decades. Presumably, all patients in this study had surgery of the primary tumor as part of a curative intent paradigm. As stage II lung cancer has lower survival rates than stage I disease after surgical resection, in part, due to higher distant recurrences the administration of preoperative chemotherapy in addition to NRT would seem reasonable in order to

minimize systemic dissemination. This same rationale has been the justification for trimodality therapy among patients with more advanced stages of resectable lung cancer.

This study did not demonstrate a significant survival benefit associated with NRT prior to surgery in patients with $T3_{>7\ cm}N0$ NSCLC tumors. The absence of a survival difference mirrors the mixed survival results associated with neoadjuvant chemoradiation followed by surgical resection for locally advanced NSCLC[21,34-37]. However, the 5-year OS and LCSS rates achieved with NRT were non-significantly improved after trimodality treatment in comparison to PST. Possible reasons for the absence of survival benefit in our analysis might be inadequate power in the NRT group, the potential use of NRT on larger tumors that underwent shrinkage prior to surgical resection, and variations in radiation administered lending to the need to further investigate this finding on a larger scale.

The role of neoadjuvant or induction therapy has long since been studied in patients with resectable, early stage NSCLC. Neoadjuvant chemotherapy was shown to be feasible and safe by the Bimodality Lung Oncology Team (BLOT) trial in 2003[38] and to produce significantly lower risks in distant cancer recurrence in early stage NSCLC[23]. In two consecutive Intergroupe Francophone de Cancerologie Theracique or IFCT phase-III trials, patients with stage IB or II NSCLC were given platinum-based neoadjuvant chemotherapy followed by surgery and pathologic complete response (pCR), defined by the absence of viable cancer cells in the resected surgical specimen, was evaluated. Among the 492 patients analyzed, 41 (8.3%) achieved pCR and upon multivariate analysis, pCR after preoperative chemotherapy was found to be a strong and favorable prognostic factor of OS (Relative Risk [RR]= 0.34; 95% CI = 0.18–0.64) and disease-free

survival (RR = 0.29; 95% CI = 0.16–0.56). Patients with Stage IB/II NSCLC in this study who achieved pCR had a significantly improved 5-year OS of 80% compared with 55.5% in the non-pCR group[39].

Some clinicians have advocated the addition of preoperative radiation therapy to systemic therapy in order to improve control of localized disease to lead to more of a complete response than neoadjuvant chemotherapy alone. In a smaller study by Lococo et al., 31 patients with T3/T4 node-negative NSCLC were given induction chemoradiotherapy prior to surgery and survival patterns evaluated and compared to 40 T3/4N0 patients who directly underwent surgery. Reasonably safe and low toxicity rates were recorded and complete pathologic response was obtained in 22% of the neoadjuvant therapy group. Pathologic downstaging after neoadjuvant therapy, whether complete or partial, was found to be the only independent factor associated with a better outcome after surgery. Surprisingly, no significant differences were found when 5-year OS in the neoadjuvant group (44%) and the surgery only group (37%) were compared[40]. These results are similar to this study in that patients who received neoadjuvant therapy exhibited a trend towards improved, though non-significant, survival rates compared to patients who underwent surgical resection only (48% vs. 41%, respectively).

As with any form of surgical treatment, complete surgical resection is essential in offering the best chance for cure. In Lococo et al.'s study, patients who underwent an incomplete resection of their tumor had a rate of dying that was greater than 5 times when compared to patients with negative surgical margins[40]. Our study evaluated long-term survival of patients treated with surgery who obtained negative margins in order to exclude patients that were likely to receive adjuvant therapy for treatment of residual

disease. Given the very large nature of $T3_{>7\ cm}N0$ NSCLC tumors, complete surgical resection becomes increasingly challenging so the use of neoadjuvant therapy in order to potentially reduce tumor burden or to allow for a more conservative surgery such as a lobectomy is appealing. However, our results demonstrated no significant difference in long-term survival compared to surgery alone.

Apart from achieving complete surgical resection, the type of surgery performed may heavily affect survival patterns. No reports regarding randomized trials comparing lobectomies to pneumonectomies for patients with NSCLC can be found in the literature although several retrospective studies have shown improved 5-year OS rates of about 37-48% with a lobectomy compared to 29-36% with a pneumonectomy[41,42]. With current ACCP guidelines recommending a lobectomy over a pneumonectomy whenever complete pathologic resection can be obtained[8,33], our study demonstrates that this recommendation is commonly applied in clinical practice as 85% of the entire cohort had undergone this type of surgical resection. Moreover, lobectomies in our study were associated with a similar and significantly improved 5-year OS estimate of 43% compared to 33% with pneumonectomies.

Interestingly, two factors that have been shown to influence the effectiveness of a surgery are how the surgery was performed and who performed it. Video-assisted thoracoscopic surgery or VATS is a relatively recently developed surgical approach that allows surgeons to view the inside of the chest cavity and remove the lung through small incisions. Contrary to the traditional open thoracotomy which requires a longer incision through one or more major muscles of the chest wall and the spreading of ribs to reach the lung, a VATS lobectomy has been associated with shorter hospital stays, fewer

complication rates and equivalent survival rates when compared to open lobectomy especially when used to resect early stage NSCLC[43-53]. Furthermore, several studies have shown lower complication rates and better long-term survival after anatomic pulmonary resections performed by thoracic and cardiac surgeons instead of general surgeons[54-57]. As the tumor sizes in our study were very large it is likely that many of the patients who underwent a lobectomy had it performed via thoracotomy although information regarding method of surgical procedure or surgeon subspecialty is unavailable in the SEER database and thus was not accounted for in our analysis.

Tumor size has been recognized as a significant prognostic factor of survival outcomes, particularly in patients with early stage NSCLC[15,58,59]. Similarly, Morgensztern and colleagues recently demonstrated that tumor size is an independent predictor of overall and lung-cancer specific survival in patients with locally advanced disease. Patients with stage IIIA tumors >7 cm had a 14% increased risk of death from any cause and an 18% increased risk of lung cancer death in comparison to stage IIIA tumors 5.1-7 cm in diameter. Moreover, the influence of tumor size on survival was reflected in the improved OS and LCSS of patients with stage IIIB with small tumors than Stage IIIA with larger tumors[60]. In our study, increasing tumor size was also associated with a higher risk in both overall and lung-cancer specific mortality upon multivariate analysis of the surgical subcohort. Tumors >10 cm in specific had significantly worse outcomes when compared to any smaller tumor size category. This finding suggests a potential size cutoff at 10 cm from which maximum therapeutic benefit on survival can be expected. The decision for surgical resection of tumors >10 cm should be approached with caution as we believe that the observed worse outcomes in these patients may be in part the result of

a greater incidence of perioperative complications and postoperative residual disease. For patients treated with neoadjuvant radiation therapy prior to surgery, tumor size was not a significant predictor of OS (*P*=.18) and LCSS (*P*=.2).

This study has several limitations that are generally inherent in any retrospective study of large databases. Information regarding the administration of chemotherapy, either as neoadjuvant or adjuvant therapy, is unavailable in the SEER database therefore we could not comment on the influence of neoadjuvant chemotherapy alone or neoadjuvant chemotherapy when used concurrently with radiotherapy therapy on long-term survival of patients with $T3_{>7\ cm}N0$ NSCLC. It was also not possible to discern if some of the patients underwent their neoadjuvant radiation therapy as part of a treatment paradigm for a superior sulcus tumor. It is both possible and likely that some superior sulcus tumors were included in this study, but presumably this number was reflective of the proportion of superior sulcus tumors resected in the overall thoracic surgery population which is less than 5%[61,62]. Arguably, the most significant limitation of this study is the lack of knowledge regarding the use of adjuvant chemotherapy. In the study period, the authors recognize that data emerged showing a benefit of adjuvant chemotherapy for resected tumors >4 cm[19]. In the SEER database there is no ability to discern which patients with tumors >7 cm received adjuvant chemotherapy and therefore, the primary surgery cohort invariably included this subset of patients. Additionally, no information regarding radiotherapy technique including total dose, fraction size, and beam energy was available and was therefore not accounted for in our analysis. Variations in chemotherapy and radiotherapy regimens are likely in our study population and may have influenced the lack of significant NRT benefit on survival over anatomic

pulmonary resection alone. However, this study did adjust for all available patient and tumor characteristics.

In conclusion, the administration of neoadjuvant radiation therapy that most likely represented chemoradiation therapy prior to surgery was not associated with improvements in overall or lung-cancer specific survival as compared to primary surgical therapy. Therefore, despite the large tumor size there is no significant associated benefit from the use of neoadjuvant therapy for NSCLC tumors >7 cm with no lymph node involvement. Respectable survival can be achieved after pulmonary anatomic resection in this patient population. In terms of surgical approach, a lobectomy over pneumonectomy appears to have a more favorable associated survival irrespective of tumor size, age, gender, and histology. Tumors <10 cm in size, particularly tumors 7.1-7.9 cm, are associated with the best long-term survival after surgery.

### *$T3_{>7\ cm}N1$ NSCLC, NCDB Study*

After assessing survival outcomes associated with neoadjuvant therapy followed by surgery for very large, node-negative NSCLC tumors, we sought to evaluate the effect of neoadjuvant therapy and other various forms of multimodality therapy on long-term survival of similarly sized tumors with positive lymph node involvement as studies are lacking in this subpopulation of recently upstaged Stage IIIA disease. This study demonstrates that patients who underwent multimodality therapy incorporating chemotherapy in a neoadjuvant or adjuvant fashion had a significantly reduced likelihood of death compared to those who underwent localized therapy or definitive chemoradiation therapy.

Improved survival of patients with locoregionally advanced NSCLC after induction therapy has been demonstrated by several studies and is thought to reflect early control of local and distant micrometastasis. In a randomized clinical trial involving 60 patients with Stage IIIA NSCLC, Rosell and colleagues observed that preoperative chemotherapy with mitomycin, ifosfamide, and cisplatin followed by surgery resulted in a significantly increased median survival of 26 months compared to 8 months in patients treated with surgery alone[63]. In another trial performed at M.D. Anderson Cancer Center, 60 patients with clinical Stage IIIA NSCLC were randomly assigned between 1987 and 1993 to receive neoadjuvant chemotherapy with cyclophosphamide, etoposide, and cisplatin followed by surgery or surgery alone. This trial demonstrated a median survival and 3-year survival rate of 64 months and 60%, respectively, for patients who underwent neoadjuvant chemotherapy compared to 11 months and 15%, respectively, for patients in the surgery only treatment group[64]. Both of these trials show evidence of improved survival rates with neoadjuvant chemotherapy. Several critiques exist for these trials in that they were small, involved a heterogeneous set of Stage IIIA lesions, and included adjuvant therapy in the form of radiotherapy or more systemic therapy. Furthermore, other trials have failed to demonstrate any significant survival benefit with induction chemotherapy for locally advanced NSCLC[23]. Neoadjuvant chemoradiation therapy studies have also shown that it is both safe and feasible to administer to patients with stage III NSCLC although there are mixed results in terms of its exact survival benefit[21,23,36,37,65-69] . Potential disadvantages to this trimodality therapy approach include delayed control of the primary tumor with surgery and an increase in surgical morbidity and mortality after induction therapy. However, the findings of this study clearly

demonstrates an improvement in survival associated with neoadjuvant chemotherapy with or without radiation therapy followed by surgery for patients with $T3_{>7cm}N1$ NSCLC lesions in comparison to surgery alone.

For patients treated with surgery followed by adjuvant chemotherapy in our study there was a significantly improved 5-year OS estimate of 38% compared to 16-18% for local surgical therapy (surgery alone or S-PORT). While a few trials and meta-analyses have demonstrated that adjuvant cisplatin-based chemotherapy can significantly improve long-term survival in select groups of Stage II and IIIA NSCLC patients[70], many other trials have failed to show an advantage in disease-free survival or overall survival with postoperative chemotherapy[71-74]. Problems such as inconsistent or mixed staging, lack of effective chemotherapeutic agents prior to the 1990s, and incomplete administration of planned doses have been prevalent issues within these studies. Interestingly, this study shows that the timing of chemotherapy administration with respect to surgery does not appear to affect survival. Neoadjuvant chemotherapy with or without radiotherapy produced similar survival rates compared to adjuvant chemotherapy in the PST cohort which were significant compared to surgery only and definitive chemoradiation.

Among the PST subcohorts that received systemic therapy, adjuvant chemoradiation therapy was an exception in that it had an associated survival benefit that was not significant (HR 0.5 [0.19-1.34], $P$=.17) compared to the others. Several randomized controlled trials primarily involving patients with positive N2 nodal disease such as the North American Intergroup trial E3590 have not shown any improvement in disease-free and overall survival when radiation therapy is added to adjuvant chemotherapy[66,75,76]. However, no sub-analysis on the effects of treatment on survival of

patients with $T3_{>7cm}N1$ NSCLC lesions if present has been performed. The small sample size of patients who underwent adjuvant chemoradiation therapy may have influenced the lack of significance for the 40% reduction in likelihood of death associated with S-CxR over surgical resection only and warrants for further investigation of this finding on a larger scale. Overall, these results suggest that the continuous debate of which form of multimodality therapy is superior for managing locally advanced disease is irrelevant when pertaining to $T3_{>7cm}N1$ lesions.

Various patient and tumor characteristics can render a patient a poor surgical candidate. Multiple comorbidities, poor pulmonary function, and significant spread of disease are all factors that are known to lead to a worse prognosis, a realization that has encouraged the discovery of the most optimal treatment strategy in medically inoperable patients with locally advanced disease. Many earlier trials that evaluated the effectiveness of sequential or concurrent chemotherapy with radiotherapy in comparison to radiotherapy alone for unresectable Stage III NSCLC demonstrated improved though non-significant survival times[77-80]. However, the average cohort size was small with about 150 patients and there was much variability regarding chemotherapeutic agents used and the administration of radiotherapy between these trials. Improvements in platinum chemotherapy and radiotherapy techniques later on likely influenced the change in observing a significant survival advantage associated with this bimodality treatment[81,82]. In the Cancer and Leukemia Group B (GALGB) 8433 trial in particular, patients with Stage III NSCLC who were treated with sequential chemotherapy followed by radiation therapy were estimated to have a 2.8 fold higher 5-year OS estimate than patients who received radiotherapy alone[83]. In our study, definitive chemoradiation

therapy was the most prevalent nonsurgical treatment strategy with similarly significant improvements in long-term survival in comparison to radiation therapy or chemotherapy alone (5-year OS: 11%, 2%, 5%, respectively).

As discussed in our $T3_{>7cm}N0$ NSCLC SEER analysis study**,** tumor size has been recognized as a significant prognostic factor of survival outcomes, particularly for early stage disease. In this study, tumor size was not found to be an independent predictor of overall survival upon multivariate analysis of the entire cohort. However, tumor size became a significant factor when analyzing the PST cohort only. Similar to $T3_{>7cm}N0$ NSCLC tumors ≥10 cm that were surgically resected, patients in the PST cohort exhibited significantly worse outcomes in survival with a hazard ratio of 1.9 (CI, 1.2-3) when compared to tumors 7.1-7.9 cm. These results suggest a potential hazard associated with surgical resection in the absence or presence of neoadjuvant or adjuvant therapy when treating very large tumors. Therefore the decision for surgical resection of tumors ≥10 cm should be approached with caution as surgery appears to provide a significant survival advantage only when part of a multimodality therapy involving systemic therapy.

Although the NCDB contains a wealth of clinicopathologic and treatment data, this study has several limitations in addition to the ones that are generally inherent to any retrospective study of large databases. A major limitation was that knowledge of the performance status of the patients in each group was not available. Therefore, patients with better performance statuses may have been eligible and undergone more interventional treatments (such as surgery with chemotherapy) associated with improved survival which may have influenced the findings of this study. The majority of the

patients in this study did not undergo surgery, and so while this scenario certainly is plausible, it would seem unlikely that this explanation was the sole rationale for the selection of the treatment modalities. Similarly, excluding the patients with positive margins may have resulted in a group of surgery patients who would have been more biased toward experiencing more favorable outcomes.

Information regarding chemotherapy, radiation therapy, or surgical therapy administered is variable with many therapy descriptions being grouped into broad categories defined by the NCDB. In the NCDB there is no ability to discern which patients among those who received neoadjuvant chemotherapy prior to surgery (C-S, CxR-S) also received adjuvant systemic therapy and therefore, these groups invariably included this subset of patients. Pathologic "surprise" mediastinal lymph node involvement (N2), although only comprising 11% of the PST cohort, may have influenced the selected use of adjuvant chemotherapy or chemoradiation following surgical resection in some of these patients who generally have poorer outcomes due to greater lymph node spread of their disease. While this consideration has the potential to lower the effects of adjuvant systemic therapy on survival, it reinforces the observed significant survival advantage associated with adjuvant chemotherapy following surgical resection. Similar to the broad definitions of therapy, information regarding specific details of staging such as CT/PET scans and brain MRI imaging or type of lymph node staging procedure is unavailable in the NCDB. Additionally, our primary endpoint was overall survival as information on lung-cancer specific survival is lacking in the NCDB. However, this study did adjust for all available patient and tumor characteristics. Lastly and cumulatively, since the NCDB is a cancer registry it is difficult to isolate a possible

pathophysiologic mechanism for the observed differences in survival. Indubitably, these most likely are multifactorial in origin.

Lymph node downstaging has been associated with improved survival and has been used to gauge the efficacy of chemoradiation therapy[22,84,85]. Determining whether downstaging has occurred depends upon the knowledge of lymph node involvement prior to the initiation of chemoradiation therapy coupled with pathologic information following resection. For patients who received induction chemotherapy or chemoradiation in this study, it is not possible to determine which patients were truly downstaged with systemic therapy prior to surgical resection. Moreover, there is the possibility that a reduction in tumor size and lymph node sterilization after neoadjuvant chemotherapy or chemoradiation allowed for a more conservative resection such as a lobectomy over a pneumonectomy in this group resulting in a selection bias. A more surprising finding from the available pathologic lymph node data available is the fact that there is a considerable percentage of patients that had no known pathologic lymph node status (Nx) identified. It is unclear if this observation is secondary to either the true underperformance of lymph nodes sampling at the time of resection or an artifact of data collection.

This study is one of the largest known national database studies focused on evaluating the effects of widely practiced treatment algorithms on long-term survival of patients with $T3_{>7cm}N1$ NSCLC. Although approximately two-thirds of the patients were treated nonsurgically, pulmonary resections with chemotherapy, either with neoadjuvant or adjuvant therapy, were associated with the best 5-year overall survival. Systemic therapy in a multimodality setting appears to be crucial in maximizing long-term survival

regardless of timing of administration to surgical resection. Finally, when surgical resection is not feasible, definitive chemoradiation therapy should be considered as an equal alternative to surgical resection alone when treating Stage IIIA-N1 NSCLC disease.

In general, very large tumors that are greater than 7 cm with no or minimal hilar lymph node involvement present a unique set of problems for clinicians. Even though complete resection of these tumors may appear daunting, both studies revealed that the majority of surgical patients were able to achieve complete resection via a lobectomy which is a more conservative surgical approach that was associated with significant improvements in long-term survival compared to a pneumonectomy. However, caution should be taken when dealing with tumors ≥10 cm in size regardless of lymph node involvement. While trimodality therapy in the form of neoadjuvant or adjuvant therapy with surgery was associated with the best survival outcomes in patients with very large tumors with positive hilar lymph node involvement, the same does not appear to be true for cases of node-negative disease. Neoadjuvant therapy followed by surgery for treatment of $T3_{>7\ cm}N0$ NSCLC was associated with a modest trend toward improved survival when compared to surgery alone although these results were shown to be non-significant. Taken into context of the overall staging system, $T3_{>7\ cm}N0$ NSCLC tumors tend to behave like other subsets of early stage NSCLC lesions in that multimodality therapy with surgery following neoadjuvant therapy does not appear to offer a greater survival advantage. The spread of disease to local hilar lymph nodes in $T3_{>7\ cm}N1$ NSCLC makes the optimal treatment strategy less straight-forward. However, it appears that several approaches to multimodality therapy are beneficial in this subset of patients as long as systemic therapy is involved.

## TABLES AND FIGURES

### *$T3_{>7\ cm}N0$ NSCLC, SEER Study*

TABLE 1- Characteristics of Patients from the Overall Cohort and Each Age Group

| **Characteristics** | **Overall Cohort (n= 1301)** | **20-59 yr (n= 293)** | **60-69 yr (n= 413)** | **70-79 yr (n= 441)** | **80+ yrs (n= 154)** | ***P* Value** |
|---|---|---|---|---|---|---|
| **Therapy Sequence** | | | | | | |
| PST | 1232 (95) | 261 (89) | 388 (94) | 430 (98) | 153 (99) | <.0001 |
| NRT | 69 (5) | 32 (11) | 25 (6) | 11 (2) | 1 (1) | |
| **Men, n (%)** | **849 (65)** | **180 (61)** | **279 (68)** | **298 (68)** | **92 (60)** | .11 |
| *NRT*\| *PST* | 49\|800 | 20\|160 | 19\|260 | 10\|288 | 0\|92 | |
| **Race** | | | | | | |
| White | **1119 (86)** | **227 (77)** | **360 (87)** | **394 (89)** | **138 (89)** | <.0001 |
| *NRT*\| *PST* | 61\|1058 | 27\|200 | 23\|337 | 13\|384 | 1\|137 | |
| Black | **115 (9)** | **45 (15)** | **36 (9)** | **26 (6)** | **8 (5)** | |
| *NRT*\| *PST* | 4\|111 | 2\|43 | 1\|35 | 1\|25 | 0\|8 | |
| Other | **67 (5)** | **21 (7)** | **17 (4)** | **21 (5)** | **8 (5)** | |
| *NRT*\| *PST* | 4\|63 | 3\|18 | 1\|16 | 0\|21 | 0\|1 | |
| **Histology** | | | | | | |
| SCC | **500 (38)** | **83 (28)** | **166 (40)** | **191 (43)** | **60 (39)** | <.0001 |
| *NRT*\| *PST* | 29\|471 | 13\|70 | 11\|155 | 5\|186 | 0\|60 | |
| Adenocarcinoma | **593 (46)** | **140 (48)** | **172 (42)** | **204 (46)** | **77 (50)** | |
| *NRT PST* | 20\|573 | 8\|132 | 7\|165 | 4\|200 | 1\|76 | |
| Large Cell | **88 (7)** | **25 (8)** | **34 (8)** | **19 (4)** | **10 (7)** | |
| *NRT*\| *PST* | 6\|82 | 4\|21 | 2\|32 | 0\|19 | 0\|10 | |
| Adenosquamous | **34 (3)** | **8 (3)** | **11 (3)** | **13 (3)** | **2 (1)** | |
| *NRT*\| *PST* | 2\|32 | 0\|8 | 1\|10 | 1\|12 | 0\|2 | |
| Other | **86 (7)** | **37 (13)** | **30 (7)** | **14 (3)** | **5 (3)** | |
| *NRT*\| *PST* | 12\|74 | 7\|30 | 4\|26 | 1\|13 | 0\|5 | |

| | | | | | | |
|---|---|---|---|---|---|---|
| **Laterality** | | | | | | |
| Right | **735 (56)** | **180 (61)** | **220 (53)** | **247 (56)** | **88 (57)** | .19 |
| *NRT*\| *PST* | 37\|698 | 18\|162 | 12\|208 | 6\|241 | 1\|87 | |
| Left | **566 (44)** | **113 (39)** | **193 (47)** | **194 (44)** | **66 (43)** | |
| *NRT*\| *PST* | 32\|534 | 14\|99 | 13\|180 | 5\|189 | 0\|66 | |
| **Lobe** | | | | | | |
| RUL | **341 (26)** | **107 (36)** | **105 (25)** | **92 (21)** | **37 (24)** | <.0001 |
| *NRT*\| *PST* | 32\|309 | 17\|90 | 11\|94 | 4\|88 | 0\|37 | |
| RML | **58 (4)** | **19 (6)** | **19 (5)** | **13 (3)** | **7 (4)** | |
| *NRT*\| *PST* | 0\|58 | 0\|19 | 0\|19 | 0\|13 | 0\|7 | |
| RLL | **336 (26)** | **54 (18)** | **96 (23)** | **142 (32)** | **44 (29)** | |
| *NRT*\| *PST* | 5\|331 | 1\|53 | 1\|95 | 2\|140 | 1\|43 | |
| LUL | **276 (21)** | **61 (21)** | **112 (27)** | **80 (18)** | **23 (15)** | |
| *NRT*\| *PST* | 26\|250 | 12\|49 | 10\|102 | 4\|76 | 0\|23 | |
| LLL | **290 (23)** | **52 (18)** | **81 (20)** | **114 (26)** | **43 (28)** | |
| *NRT*\| *PST* | 6\|284 | 2\|50 | 3\|78 | 1\|113 | 0\|43 | |
| **Tumor size, cm** | | | | | | |
| 7.1-7.9 | **288 (22)** | **68 (23)** | **85 (21)** | **99 (23)** | **36 (23)** | .16 |
| *NRT*\| *PST* | 17\|271 | 9\|59 | 7\|78 | 1\|98 | 0\|36 | |
| 8-8.9 | **412 (32)** | **87 (30)** | **129 (31)** | **143 (32)** | **53 (34)** | |
| *NRT*\| *PST* | 21\|391 | 7\|80 | 9\|120 | 5\|138 | 0\|53 | |
| 9-9.9 | **213 (16)** | **51 (17)** | **68 (16)** | **74 (17)** | **20 (13)** | |
| *NRT*\| *PST* | 9\|204 | 4\|47 | 3\|65 | 2\|72 | 0\|20 | |
| 10-11.9 | **195 (15)** | **36 (12)** | **78 (19)** | **66 (15)** | **15 (10)** | |
| *NRT*\| *PST* | 16\|179 | 8\|28 | 5\|73 | 3\|63 | 0\|15 | |
| ≥12 | **193 (15)** | **51 (18)** | **53 (13)** | **59 (13)** | **30 (20)** | |
| *NRT*\| *PST* | 6\|187 | 4\|47 | 1\|52 | 0\|59 | 1\|29 | |

**(Table continues…)**

| | | | | | | |
|---|---|---|---|---|---|---|
| **Type of Surgery** | | | | | | |
| Lobectomy | **1110 (85)** | **230 (78)** | **346 (84)** | **388 (88)** | **146 (95)** | <.0001 |
| *NRT\| PST* | 53\|1057 | 26\|204 | 18\|328 | 8\|380 | 1\|145 | |
| Pneumonectomy | **191 (15)** | **63 (22)** | **67 (16)** | **53 (12)** | **8 (5)** | |
| *NRT\| PST* | 16\|175 | 6\|57 | 7\|60 | 3\|50 | 0\|8 | |

Abbreviations: PST= primary surgical therapy; NRT= neoadjuvant radiation therapy. *P* Value based on $x^2$ test.

TABLE 2- Multivariate analysis on overall and lung cancer-related mortality for overall cohort

| | **Overall Mortality** | | **Lung Cancer-Specific Mortality** | |
|---|---|---|---|---|
| **RISK FACTOR** | **HR (95% CI)** | ***P* Value** | **HR (95% CI)** | ***P* value** |
| **Sex** | | | | |
| Male | Reference | | Reference | |
| Female | 0.82 (0.7-0.96) | .01 | NA | .35 |
| **Age at diagnosis** | | | | |
| 20-59 yr | Reference | | Reference | |
| 60-69 yr | 1.47 (1.19-1.83) | .0005 | 1.36 (1.07-1.73) | .0127 |
| 70-79 yr | 1.84 (1.49-2.26) | <.0001 | 1.57 (1.23-1.99) | .0002 |
| 80+ yr | 2.33 (1.8-3.01) | <.0001 | 1.9 (1.41-2.57) | <.0001 |
| **Tumor size, cm** | | | | |
| 7.1-7.9 | Reference | | Reference | |
| 8-8.9 | 1.15 (0.94-1.41) | .17 | 1.16 (0.91-1.47) | .23 |
| 9-9.9 | 1.13 (0.89-1.43) | .33 | 1.13 (0.85-1.51) | .39 |
| 10-11.9 | 1.39 (1.09-1.76) | .007 | 1.54 (1.17-2.03) | .002 |
| ≥12 | 1.34 (1.05-1.7) | .019 | 1.49 (1.13-1.97) | .005 |
| **Type of Surgery** | | | | |
| Lobectomy | Reference | | Reference | |
| Pneumonectomy | 1.32 (1.08-1.6) | .007 | 1.38 (1.1-1.73) | .005 |

TABLE 3- Multivariate analysis on overall and lung cancer-related mortality for NRT sub-cohort

| | **Overall Mortality** | | **Lung Cancer-Specific Mortality** | |
|---|---|---|---|---|
| **RISK FACTOR** | **HR (95% CI)** | ***P* Value** | **HR (95% CI)** | ***P* value** |
| **Sex** | | | | |
| Male | Reference | | Reference | |
| Female | 0.27 (0.1-0.7) | .007 | 0.13 (0.03-0.51) | .003 |
| **Histology** | | | | |
| SCC | Reference | | Reference | |
| Adenosquamous | 6.18 (1.26-30.2) | .03 | 11.69 (2.13-64.19) | .005 |
| Adenocarcinoma | 0.45 (0.18-1.13) | .09 | 0.43 (0.14-1.31) | .14 |
| Large Cell | 1.13 (0.37-3.48) | .84 | 1.5 (0.46-4.88) | .5 |
| Other | 1.41 (0.53-3.73) | .49 | 1.61 (0.49-5.31) | .43 |
| **Age at diagnosis** | | .11 | | .91 |
| **Tumor size** | | .18 | | .2 |
| **Type of Surgery** | | .86 | | .7 |

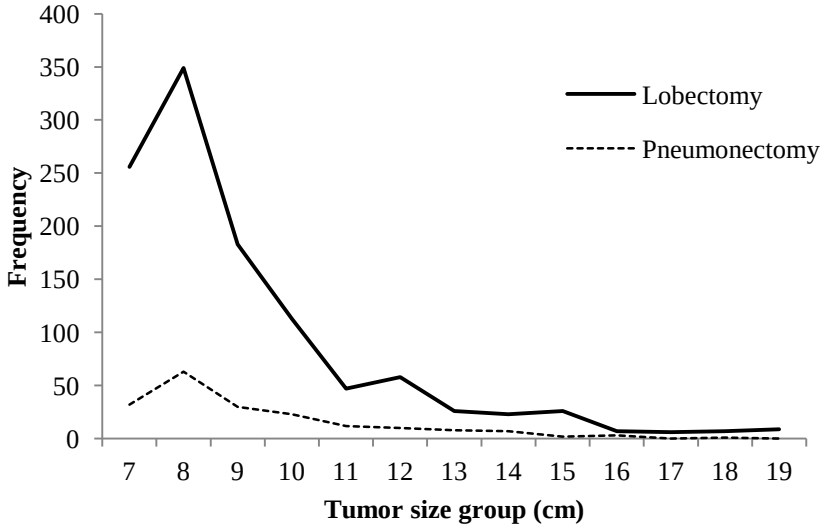


Fig. 1. Frequency of type of surgery performed by tumor size. Tumor size group 7 cm begins at 7.1 cm.

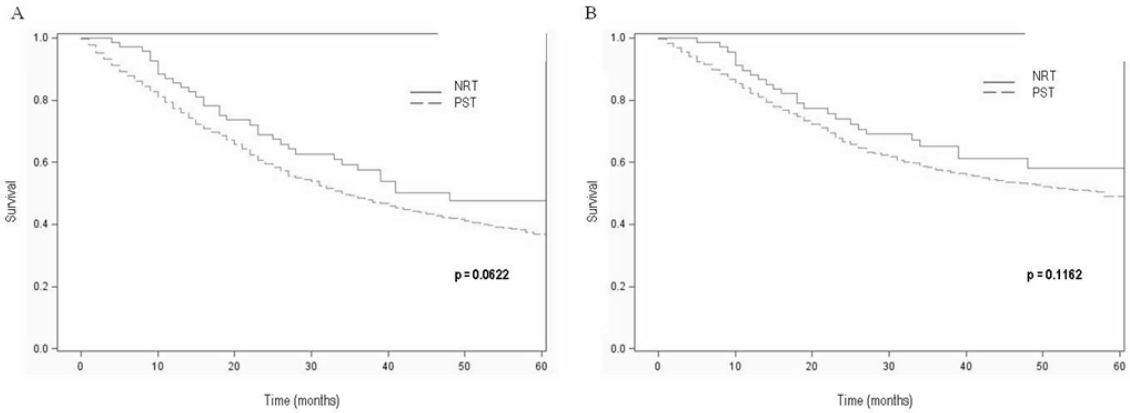


Fig. 2. A) OS and B) LCSS estimates for overall cohort stratified by type of therapy sequence.

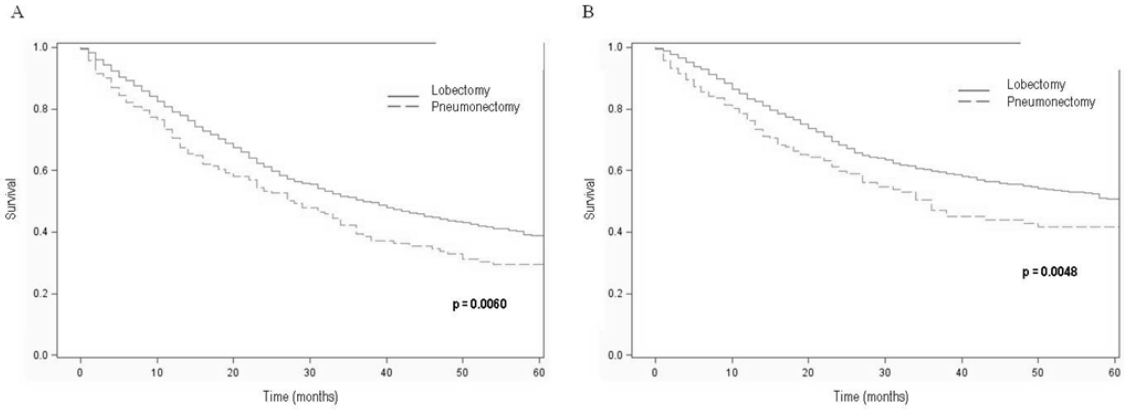


Fig. 3. A) OS and B) LCSS estimates for overall cohort stratified by type of surgery performed.

## *$T3_{>7\ cm}N1$ NSCLC, NCDB Study*

TABLE 4- Patient and tumor characteristics for the overall cohort by age group

| **Characteristics** | **Overall Cohort (n=642)** | **20-59 yr (n=150)** | **60-69 yr (n=209)** | **70-79 yr (n=206)** | **80+ yr (n=77)** | ***P* value** |
|---|---|---|---|---|---|---|
| **Gender** | | | | | | |
| Male, n (%) | 390 (61) | 92 (61) | 133 (64) | 128 (62) | 37 (48) | .11 |
| Female | 252 (39) | 58 (39) | 76 (36) | 78 (38) | 40 (52) | |
| **Race** | | | | | | |
| Black | 89 (14) | 35 (23) | 25 (12) | 19 (9) | 10 (13) | .01 |
| Other | 14 (2) | *** | *** | *** | *** | |
| White | 539 (84) | 112 (75) | 178 (85) | 183 (89) | 66 (86) | |
| **Histology** | | | | | | |
| Adenocarcinoma | 139 (22) | 39 (26) | 41 (20) | 46 (22) | 13 (17) | .26 |
| Other | 224 (35) | 59 (39) | 70 (33) | 66 (32) | 29 (38) | |
| Squamous cell | 279 (43) | 52 (35) | 98 (47) | 94 (46) | 35 (45) | |
| **Tumor Location** | | | | | | |
| LLL | 101 (16) | 17 (11) | 36 (17) | 36 (17) | 12 (16) | .21 |
| LUL | 183 (29) | 46 (31) | 58 (28) | 58 (28) | 21 (27) | |
| RLL | 110 (17) | 16 (11) | 37 (18) | 44 (21) | 13 (17) | |
| RML | 22 (3) | *** | *** | *** | *** | |
| RUL | 226 (35) | 67 (45) | 70 (33) | 60 (29) | 29 (38) | |
| **Tumor Size** | | | | | | |
| 7.1-7.9 cm | 136 (21) | 37 (25) | 38 (18) | 47 (23) | 14 (18) | .78 |
| 8-8.9 cm | 238 (37) | 57 (38) | 79 (38) | 70 (34) | 32 (42) | |
| 9-9.9 cm | 121 (19) | 25 (17) | 45 (22) | 39 (19) | 12 (15) | |
| ≥10 cm | 147 (23) | 31 (20) | 47 (22) | 50 (24) | 19 (25) | |
| **(Table continues…)** | | | | | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| **Surgical Approach** | | | | | | |
| Lobectomy | 131 (21) | 48 (32) | 37 (18) | 39 (19) | *** | <.001 |
| Pneumonectomy | 86 (13) | 24 (16) | 39 (19) | 21 (10) | *** | |
| Nonsurgical | 316 (49) | 62 (41) | 118 (56) | 96 (47) | 40 (52) | |
| None | 109 (17) | 16 (11) | 15 (7) | 50 (24) | 28 (36) | |
| **Therapy** | | | | | | |
| CxR | 184 (29) | 39 (26) | 80 (38) | 54 (26) | 11 (14) | <.001 |
| Chemo | 65 (10) | 15 (10) | 22 (11) | 17 (8) | 11 (14) | |
| RT | 67 (10) | *** | 16 (8) | 25 (12) | 18 (23) | |
| None | 109 (17) | 16 (11) | 15 (7) | 50 (24) | 28 (36) | |
| CxR-S | 31 (5) | 15 (10) | 11 (5) | *** | *** | |
| C-S | 25 (4) | *** | 11 (5) | *** | *** | |
| S | 106 (17) | 25 (17) | 38 (18) | 36 (17) | *** | |
| S-CxR | 10 (2) | *** | *** | *** | *** | |
| S-C | 34 (5) | 14 (9) | 12 (6) | *** | *** | |
| S-PORT | 11 (2) | *** | *** | *** | *** | |
| **Facility** | | | | | | |
| CCP | 120 (19) | 20 (13) | 48 (23) | 35 (17) | 17 (22) | .003 |
| Comprehensive CCP | 330 (51) | 71 (47) | 103 (49) | 118 (57) | 38 (49) | |
| Teaching or research | 177 (8) | 58 (39) | 56 (27) | 44 (21) | 19 (25) | |
| Other | 15 (2) | *** | *** | *** | *** | |

CCP, community cancer program; C-S, neoadjuvant chemotherapy + surgery; CxR-S, neoadjuvant chemoradiation + surgery; CxR, chemoradiation; RT, radiation therapy; S, surgery; S-C, surgery + adjuvant chemotherapy; S-CxR, surgery + adjuvant chemoradiation; S-PORT, surgery + postoperative radiation therapy.

TABLE 5- Multivariate analysis predicting overall survival among the overall cohort

| **Risk Factor** | **HR** | **95% CI L** | **95% CI U** | ***P* value** |
|---|---|---|---|---|
| **Age** | | | | |
| 20-59 yr | 1.00 | | | |
| 60-69 yr | 1.18 | 0.93 | 1.5 | .17 |
| 70-79 yr | 2.1 | 1.65 | 2.67 | <.001 |
| 80+ yr | 2.01 | 1.48 | 2.74 | <.001 |
| **Type of Surgery** | | | | |
| Lobectomy | 1.00 | | | |
| Pneumonectomy | 1.49 | 1.08 | 2.05 | .01 |
| **Therapy** | | | | |
| CxR | 1.00 | | | |
| Chemo | 1.25 | 0.93 | 1.68 | .13 |
| RT | 1.5 | 1.12 | 2.01 | .007 |
| None | 2.87 | 2.23 | 3.69 | <.001 |
| CxR- S | 0.41 | 0.19 | 0.9 | .03 |
| C-S | 0.4 | 0.18 | 0.88 | .02 |
| S | 0.8 | 0.41 | 1.54 | .5 |
| S-CxR | 0.5 | 0.19 | 1.34 | .17 |
| S-C | 0.4 | 0.19 | 0.85 | .02 |
| S-PORT | *** | *** | *** | *** |

HR, Hazard ratio; 95% CI L, lower limit; 95 CI U, upper limit; CCP, community cancer program; C-S, neoadjuvant chemotherapy + surgery; CxR-S, neoadjuvant chemoradiation + surgery; CxR, chemoradiation; RT, radiation therapy; S, surgery; S-C, surgery + adjuvant chemotherapy; S-CxR, surgery + adjuvant chemoradiation; S-PORT, surgery + postoperative radiation therapy.

***, Value unavailable due to small sample size.

TABLE 6- Multivariate analysis predicting overall survival among the PST cohort

| **Risk factor** | **HR** | **95% CI L** | **95% CI U** | ***P* value** |
|---|---|---|---|---|
| **Age** | | | | |
| 20-59 yr | 1.00 | | | |
| 60-69 yr | 1.18 | 0.79 | 1.77 | .42 |
| 70-79 yr | 2.48 | 1.63 | 3.77 | <.001 |
| 80+ yr | 2.9 | 1.33 | 6.36 | .008 |
| **Tumor Size** | | | | |
| 7.1-7.9 cm | 1.00 | | | |
| 8-8.9 cm | 1.09 | 0.71 | 1.67 | .68 |
| 9-9.9 cm | 1.36 | 0.8 | 2.29 | .25 |
| ≥10 cm | 1.89 | 1.2 | 3 | .007 |
| **Type of Surgery** | | | | |
| Lobectomy | 1.00 | | | |
| Pneumonectomy | 1.43 | 1.02 | 1.99 | .04 |
| **Therapy** | | | | |
| S | 1.00 | | | |
| CxR- S | 0.5 | 0.3 | 0.85 | .01 |
| C-S | 0.54 | 0.32 | 0.93 | .02 |
| S-C | 0.49 | 0.31 | 0.78 | .003 |
| S-CxR | 0.6 | 0.26 | 1.35 | .22 |
| S-PORT | 1.29 | 0.66 | 2.53 | .46 |

HR, Hazard ratio; 95% CI L, lower limit; 95 CI U, upper limit; CCP, community cancer program; C-S, neoadjuvant chemotherapy + surgery; CxR-S, neoadjuvant chemoradiation + surgery; CxR, chemoradiation; RT, radiation therapy; S, surgery; S-C, surgery + adjuvant chemotherapy; S-CxR, surgery + adjuvant chemoradiation; S-PORT, surgery + postoperative radiation therapy.

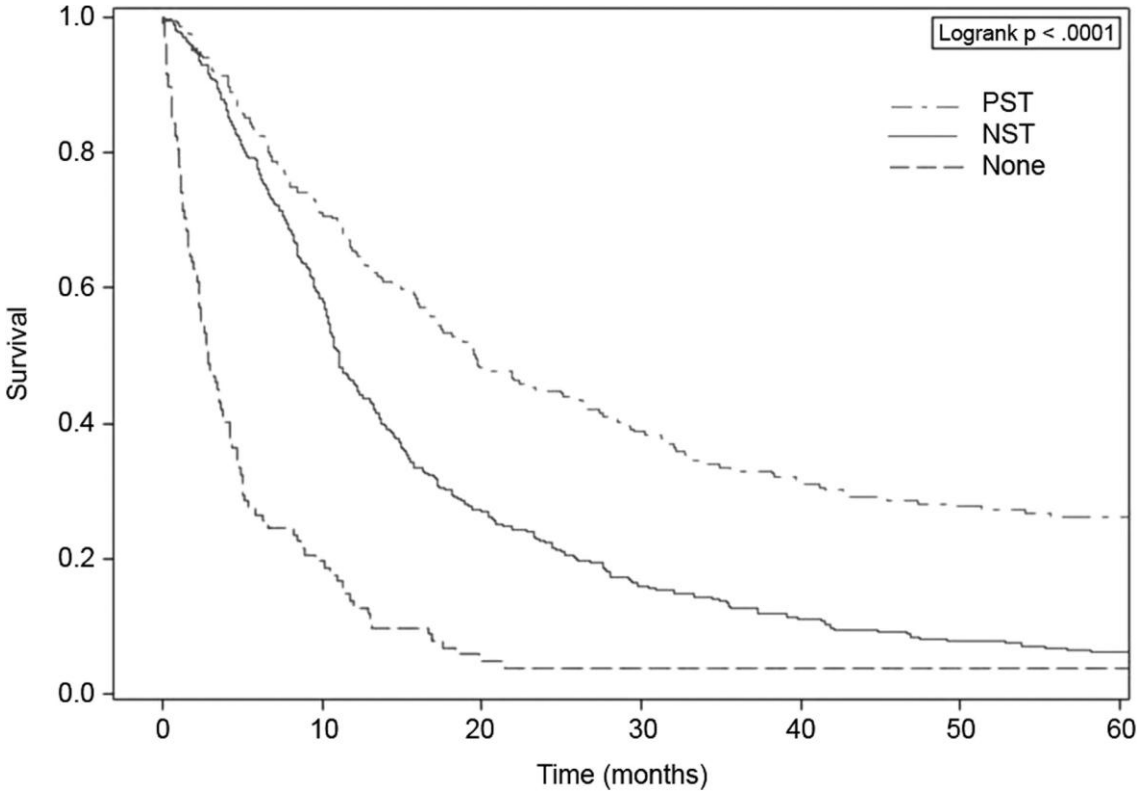


Fig. 4. Overall survival estimates for overall cohort stratified by primary therapy. PST, primary surgical therapy; NST, nonsurgical therapy.

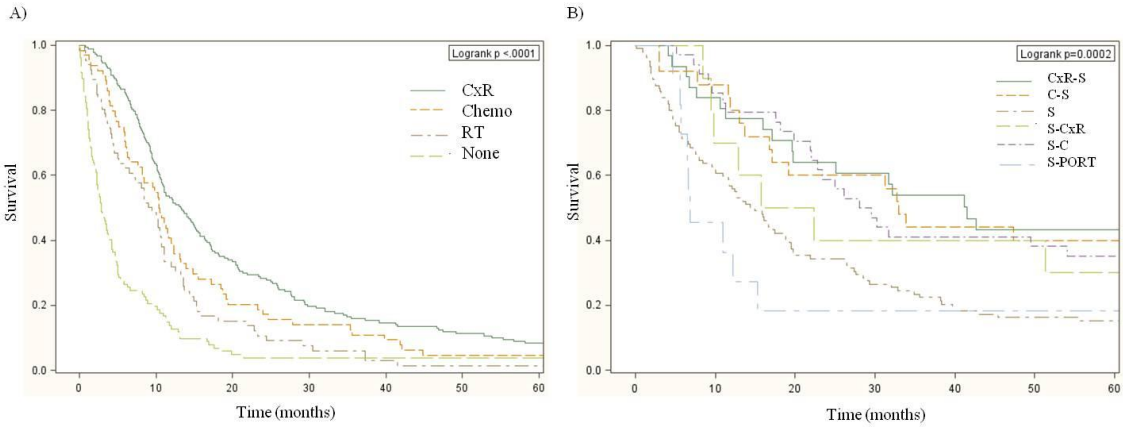


Fig. 5. Overall survival estimates for A) NST and B) PST cohorts stratified by therapy. C-S, neoadjuvant chemotherapy + surgery; CxR-S, neoadjuvant chemoradiation + surgery; CxR, chemoradiation; RT, radiation therapy; S, surgery; S-C, surgery + adjuvant chemotherapy; S-CxR, surgery + adjuvant chemoradiation; S-PORT, surgery + postoperative radiation therapy.

**REFERENCES**


**1.** What are the key statistics about lung cancer? http://www.cancer.org/cancer/lungcancer-non-smallcell/detailedguide/non-small-cell-lung-cancer-key-statistics. Accessed December, 2013.

**2.** Adler I. *Primary Malignant Growths of the Lungs and Bronchi*. New York: Longmans, Green, and Co.; 1912.

**3.** Proctor RN. The history of the discovery of the cigarette-lung cancer link: evidentiary traditions, corporate denial, global toll. *Tob Control.* Mar 2012;21(2):87-91.

**4.** (IARC) IAfRoC. GLOBOCAN 2012: Estimated Cancer Incidence, Mortality, and Prevalence Worldwide in 2012. 2013; http://globocan.iarc.fr/Pages/fact_sheets_cancer.aspx.

**5.** What are the risk factors for non-small cell lung cancer? http://www.cancer.org/cancer/lungcancer-non-smallcell/detailedguide/non-small-cell-lung-cancer-risk-factors. Accessed December, 2013.

**6.** Lung Cancer Trends. 2012; http://www.cdc.gov/cancer/lung/statistics/trends.htm.

**7.** SEER State Fact Sheets: Lung and Bronchus Cancer. http://seer.cancer.gov/statfacts/html/lungb.html.

**8.** Scott WJ, Howington J, Movsas B. Treatment of stage II non-small cell lung cancer. *Chest.* Jan 2003;123(1 Suppl):188S-201S.

**9.** Gadgeel SM, Ramalingam SS, Kalemkerian GP. Treatment of lung cancer. *Radiol Clin North Am.* Sep 2012;50(5):961-974.

**10.** Howington JA, Blum MG, Chang AC, Balekian AA, Murthy SC. Treatment of stage I and II non-small cell lung cancer: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest.* May 2013;143(5 Suppl):e278S-313S.

**11.** AJCC 7th Edition Lung Cancer Staging. http://cancerstaging.org/references-tools/quickreferences/Documents/LungMedium.pdf.

**12.** Mountain CF. The international system for staging lung cancer. *Semin Surg Oncol.* Mar 2000;18(2):106-115.

**13.** Mountain CF, Carr DT, Anderson WA. A system for the clinical staging of lung cancer. *Am J Roentgenol Radium Ther Nucl Med.* Jan 1974;120(1):130-138.

**14.** Patz EF, Jr., Rossi S, Harpole DH, Jr., Herndon JE, Goodman PC. Correlation of tumor size and survival in patients with stage IA non-small cell lung cancer. *Chest.* Jun 2000;117(6):1568-1571.

**15.** Mountain CF. Revisions in the International System for Staging Lung Cancer. *Chest.* Jun 1997;111(6):1710-1717.

**16.** Cangir AK, Kutlay H, Akal M, Gungor A, Ozdemir N, Akay H. Prognostic value of tumor size in non-small cell lung cancer larger than five centimeters in diameter. *Lung Cancer.* Dec 2004;46(3):325-331.

**17.** Goldstraw P, Crowley J, Chansky K, et al. The IASLC Lung Cancer Staging Project: proposals for the revision of the TNM stage groupings in the forthcoming (seventh) edition of the TNM Classification of malignant tumours. *J Thorac Oncol.* Aug 2007;2(8):706-714.

**18.** NCCN Clinical Practice Guidelines in Oncology: Non-Small Cell Lung Cancer. 2013; http://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf. Accessed August, 2013.

**19.** Strauss GM, Herndon JE, 2nd, Maddaus MA, et al. Adjuvant paclitaxel plus carboplatin compared with observation in stage IB non-small-cell lung cancer: CALGB 9633 with the Cancer and Leukemia Group B, Radiation Therapy Oncology Group, and North Central Cancer Treatment Group Study Groups. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* Nov 1 2008;26(31):5043-5051.

**20.** Ramnath N, Dilling TJ, Harris LJ, et al. Treatment of stage III non-small cell lung cancer: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest.* May 2013;143(5 Suppl):e314S-340S.

**21.** Albain KS, Rusch VW, Crowley JJ, et al. Concurrent cisplatin/etoposide plus chest radiotherapy followed by surgery for stages IIIA (N2) and IIIB non-small-cell lung cancer: mature results of Southwest Oncology Group phase II study 8805. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* Aug 1995;13(8):1880-1892.

**22.** Bueno R, Richards WG, Swanson SJ, et al. Nodal stage after induction therapy for stage IIIA lung cancer determines patient survival. *Ann Thorac Surg.* Dec 2000;70(6):1826-1831.

**23.** Depierre A, Milleron B, Moro-Sibilot D, et al. Preoperative chemotherapy followed by surgery compared with primary surgery in resectable stage I (except

T1N0), II, and IIIa non-small-cell lung cancer. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. Jan 1 2002;20(1):247-253.

**24.** Martins RG, D'Amico TA, Loo BW, Jr., et al. The management of patients with stage IIIA non-small cell lung cancer with N2 mediastinal node involvement. *J Natl Compr Canc Netw*. May 2012;10(5):599-613.

**25.** Tanner NT, Gomez M, Rainwater C, et al. Physician preferences for management of patients with stage IIIA NSCLC: impact of bulk of nodal disease on therapy selection. *J Thorac Oncol*. Feb 2012;7(2):365-369.

**26.** Veeramachaneni NK, Feins RH, Stephenson BJ, Edwards LJ, Fernandez FG. Management of stage IIIA non-small cell lung cancer by thoracic surgeons in North America. *Ann Thorac Surg*. Sep 2012;94(3):922-926; discussion 926-928.

**27.** Biswas T, Sharma N, Machtay M. Controversies in the management of stage III non-small-cell lung cancer. *Expert Rev Anticancer Ther*. Jan 8 2014.

**28.** SEER: Surveillance, Epidemiology and End Results Program. http://seer.cancer.gov/about/overview.html.

**29.** ICD-O-3 SEER Site/Histology Validation List. http://seer.cancer.gov/icd-o-3/sitetype.icdo3.d20121205.pdf.

**30.** SEER Program Coding and Staging Manual 2012. http://seer.cancer.gov/archive/manuals/2012/AppendixC/lung/surgery_codes.pdf.

**31.** Natinoal Cancer Data Base. http://www.facs.org/cancer/ncdb/.

**32.** The NCDB: BetaPUF Data Dictionary Items. http://ncdbpufbeta.facs.org/?q=node/259. Accessed August, 2013.

**33.** Scott WJ, Howington J, Feigenberg S, Movsas B, Pisters K, American College of Chest P. Treatment of non-small cell lung cancer stage I and stage II: ACCP evidence-based clinical practice guidelines (2nd edition). *Chest.* Sep 2007;132(3 Suppl):234S-242S.

**34.** Kim AW, Liptay MJ, Bonomi P, et al. Neoadjuvant chemoradiation for clinically advanced non-small cell lung cancer: an analysis of 233 patients. *Ann Thorac Surg.* Jul 2011;92(1):233-241; discussion 241-233.

**35.** Koshy M, Goloubeva O, Suntharalingam M. Impact of neoadjuvant radiation on survival in stage III non-small-cell lung cancer. *International journal of radiation oncology, biology, physics.* Apr 1 2011;79(5):1388-1394.

**36.** Edelman MJ, Suntharalingam M, Burrows W, et al. Phase I/II trial of hyperfractionated radiation and chemotherapy followed by surgery in stage III lung cancer. *Ann Thorac Surg.* Sep 2008;86(3):903-910.

**37.** Albain KS, Swann RS, Rusch VW, et al. Radiotherapy plus chemotherapy with or without surgical resection for stage III non-small-cell lung cancer: a phase III randomised controlled trial. *Lancet.* Aug 1 2009;374(9687):379-386.

**38.** KM P, RJ G, DJ G. Bimodality lung oncology team (BLOT) trial of induction paclitaxel/carboplatin in early stage non-small cell lung cancer: long-term follow-up of a phase II trial. *Proc Am Soc Clin Oncol.* 2003;22(633).

**39.** Mouillet G, Monnet E, Milleron B, et al. Pathologic complete response to preoperative chemotherapy predicts cure in early-stage non-small-cell lung cancer: combined analysis of two IFCT randomized trials. *J Thorac Oncol.* May 2012;7(5):841-849.

**40.** Lococo F, Cesario A, Margaritora S, et al. Induction therapy followed by surgery for T3-T4/N0 non-small cell lung cancer: long-term results. *Ann Thorac Surg.* May 2012;93(5):1633-1640.

**41.** Suen HC, Meyers BF, Guthrie T, et al. Favorable results after sleeve lobectomy or bronchoplasty for bronchial malignancies. *Ann Thorac Surg.* Jun 1999;67(6):1557-1562.

**42.** Okada M, Yamagishi H, Satake S, et al. Survival related to lymph node involvement in lung cancer after sleeve lobectomy compared with pneumonectomy. *The Journal of thoracic and cardiovascular surgery.* Apr 2000;119(4 Pt 1):814-819.

**43.** Scott WJ, Allen MS, Darling G, et al. Video-assisted thoracic surgery versus open lobectomy for lung cancer: a secondary analysis of data from the American College of Surgeons Oncology Group Z0030 randomized clinical trial. *The Journal of thoracic and cardiovascular surgery.* Apr 2010;139(4):976-981; discussion 981-973.

**44.** Whitson BA, Groth SS, Duval SJ, Swanson SJ, Maddaus MA. Surgery for early-stage non-small cell lung cancer: a systematic review of the video-assisted thoracoscopic surgery versus thoracotomy approaches to lobectomy. *Ann Thorac Surg.* Dec 2008;86(6):2008-2016; discussion 2016-2008.

**45.** Scott WJ, Matteotti RS, Egleston BL, Oseni S, Flaherty JF. A comparison of perioperative outcomes of video-assisted thoracic surgical (VATS) lobectomy with open thoracotomy and lobectomy: results of an analysis using propensity score based weighting. *Ann Surg Innov Res.* 2010;4(1):1.

**46.** Park HS, Detterbeck FC, Boffa DJ, Kim AW. Impact of hospital volume of thoracoscopic lobectomy on primary lung cancer outcomes. *Ann Thorac Surg.* Feb 2012;93(2):372-379.

**47.** Cheng D, Downey RJ, Kernstine K, et al. Video-assisted thoracic surgery in lung cancer resection: a meta-analysis and systematic review of controlled trials. *Innovations (Phila).* Nov 2007;2(6):261-292.

**48.** Detterbeck F. Thoracoscopic versus open lobectomy debate: the pro argument. *Thorac Surg Sci.* 2009;6:Doc04.

**49.** Yan TD, Black D, Bannon PG, McCaughan BC. Systematic review and meta-analysis of randomized and nonrandomized trials on safety and efficacy of video-assisted thoracic surgery lobectomy for early-stage non-small-cell lung cancer. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* May 20 2009;27(15):2553-2562.

**50.** Farjah F, Wood DE, Mulligan MS, et al. Safety and efficacy of video-assisted versus conventional lung resection for lung cancer. *The Journal of thoracic and cardiovascular surgery.* Jun 2009;137(6):1415-1421.

**51.** Paul S, Altorki NK, Sheng S, et al. Thoracoscopic lobectomy is associated with lower morbidity than open lobectomy: a propensity-matched analysis from the STS database. *The Journal of thoracic and cardiovascular surgery.* Feb 2010;139(2):366-378.

**52.** Whitson BA, Andrade RS, Boettcher A, et al. Video-assisted thoracoscopic surgery is more favorable than thoracotomy for resection of clinical stage I non-small cell lung cancer. *Ann Thorac Surg.* Jun 2007;83(6):1965-1970.

**53.** Flores RM, Park BJ, Dycoco J, et al. Lobectomy by video-assisted thoracic surgery (VATS) versus thoracotomy for lung cancer. *The Journal of thoracic and cardiovascular surgery.* Jul 2009;138(1):11-18.

**54.** Farjah F, Flum DR, Varghese TK, Jr., Symons RG, Wood DE. Surgeon specialty and long-term survival after pulmonary resection for lung cancer. *Ann Thorac Surg.* Apr 2009;87(4):995-1004; discussion 1005-1006.

**55.** Schipper PH, Diggs BS, Ungerleider RM, Welke KF. The influence of surgeon specialty on outcomes in general thoracic surgery: a national sample 1996 to 2005. *Ann Thorac Surg.* Nov 2009;88(5):1566-1572; discussion 1572-1563.

**56.** Ellis MC, Diggs BS, Vetto JT, Schipper PH. Intraoperative oncologic staging and outcomes for lung cancer resection vary by surgeon specialty. *Ann Thorac Surg.* Dec 2011;92(6):1958-1963; discussion 1963-1954.

**57.** von Meyenfeldt EM, Gooiker GA, van Gijn W, et al. The relationship between volume or surgeon specialty and outcome in the surgical treatment of lung cancer: a systematic review and meta-analysis. *J Thorac Oncol.* Jul 2012;7(7):1170-1178.

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

**59.** Wisnivesky JP, Yankelevitz D, Henschke CI. The effect of tumor size on curability of stage I non-small cell lung cancers. *Chest.* Sep 2004;126(3):761-765.

**60.** Morgensztern D, Waqar S, Subramanian J, Gao F, Trinkaus K, Govindan R. Prognostic significance of tumor size in patients with stage III non-small-cell lung cancer: a surveillance, epidemiology, and end results (SEER) survey from 1998 to 2003. *J Thorac Oncol.* Oct 2012;7(10):1479-1484.

**61.** Archie VC, Thomas CR, Jr. Superior sulcus tumors: a mini-review. *The oncologist.* 2004;9(5):550-555.

**62.** Parissis H, Young V. Treatment of pancoast tumors from the surgeons prospective: re-appraisal of the anterior-manubrial sternal approach. *Journal of cardiothoracic surgery.* 2010;5:102.

**63.** Rosell R, Gomez-Codina J, Camps C, et al. A randomized trial comparing preoperative chemotherapy plus surgery with surgery alone in patients with non-small-cell lung cancer. *The New England journal of medicine.* Jan 20 1994;330(3):153-158.

**64.** Roth JA, Fossella F, Komaki R, et al. A randomized trial comparing perioperative chemotherapy and surgery with surgery alone in resectable stage IIIA non-small-cell lung cancer. *Journal of the National Cancer Institute.* May 4 1994;86(9):673-680.

**65.** Machtay M, Lee JH, Stevenson JP, et al. Two commonly used neoadjuvant chemoradiotherapy regimens for locally advanced stage III non-small cell lung carcinoma: long-term results and associations with pathologic response. *The Journal of thoracic and cardiovascular surgery.* Jan 2004;127(1):108-113.

**66.** Keller SM, Adak S, Wagner H, et al. A randomized trial of postoperative adjuvant therapy in patients with completely resected stage II or IIIA non-small-cell lung

cancer. Eastern Cooperative Oncology Group. *The New England journal of medicine.* Oct 26 2000;343(17):1217-1222.

**67.** Friedel G, Budach W, Dippon J, al. E. Phase II trial of a trimodality regimen for stage III non-small-cell lung cancer using chemotherapy as induction treatment with concurrent hyperfractionated chemoradiation with carboplatin and paclitaxel followed by subsequent resection: a single-center study. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2010(28):942-948.

**68.** Thomas M, Rube C, Hoffknecht P, et al. Effect of preoperative chemoradiation in addition to preoperative chemotherapy: a randomised trial in stage III non-small-cell lung cancer. *Lancet Oncol.* Jul 2008;9(7):636-648.

**69.** Clamon GH, Parekh KR. Mortality related to neoadjuvant therapy and surgery for stage III non-small-cell lung cancer. *Clinical lung cancer.* Jul 2008;9(4):213-216.

**70.** Heon S, Johnson BE. Adjuvant chemotherapy for surgically resected non-small cell lung cancer. *The Journal of thoracic and cardiovascular surgery.* Sep 2012;144(3):S39-42.

**71.** Chemotherapy in non-small cell lung cancer: a meta-analysis using updated data on individual patients from 52 randomised clinical trials. Non-small Cell Lung Cancer Collaborative Group. *BMJ.* Oct 7 1995;311(7010):899-909.

**72.** Niiranen A, Niitamo-Korhonen S, Kouri M, Assendelft A, Mattson K, Pyrhonen S. Adjuvant chemotherapy after radical surgery for non-small-cell lung cancer: a randomized study. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* Dec 1992;10(12):1927-1932.

**73.** Ohta M, Tsuchiya R, Shimoyama M, et al. Adjuvant chemotherapy for completely resected stage III non-small-cell lung cancer. Results of a randomized prospective study. The Japan Clinical Oncology Group. *The Journal of thoracic and cardiovascular surgery.* Oct 1993;106(4):703-708.

**74.** Wada H, Hitomi S, Teramatsu T. Adjuvant chemotherapy after complete resection in non-small-cell lung cancer. West Japan Study Group for Lung Cancer Surgery. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* Apr 1996;14(4):1048-1054.

**75.** Pisters KM, Kris MG, Gralla RJ, et al. Randomized trial comparing postoperative chemotherapy with vindesine and cisplatin plus thoracic irradiation with irradiation alone in stage III (N2) non-small cell lung cancer. *Journal of surgical oncology.* Aug 1994;56(4):236-241.

**76.** Dautzenberg B, Chastang C, Arriagada R, et al. Adjuvant radiotherapy versus combined sequential chemotherapy followed by radiotherapy in the treatment of resected nonsmall cell lung carcinoma. A randomized trial of 267 patients. GETCB (Groupe d'Etude et de Traitement des Cancers Bronchiques). *Cancer.* Sep 1 1995;76(5):779-786.

**77.** Soresi E, Clerici M, Grilli R, et al. A randomized clinical trial comparing radiation therapy v radiation therapy plus cis-dichlorodiammine platinum (II) in the treatment of locally advanced non-small cell lung cancer. *Seminars in oncology.* Dec 1988;15(6 Suppl 7):20-25.

**78.** Mattson K, Holsti LR, Holsti P, et al. Inoperable non-small cell lung cancer: radiation with or without chemotherapy. *European journal of cancer & clinical oncology.* Mar 1988;24(3):477-482.

**79.** Morton RF, Jett JR, McGinnis WL, et al. Thoracic radiation therapy alone compared with combined chemoradiotherapy for locally unresectable non-small cell lung cancer. A randomized, phase III trial. *Annals of internal medicine.* Nov 1 1991;115(9):681-686.

**80.** Trovo MG, Minatel E, Franchin G, et al. Radiotherapy versus radiotherapy enhanced by cisplatin in stage III non-small cell lung cancer. *International journal of radiation oncology, biology, physics.* 1992;24(1):11-15.

**81.** Le Chevalier T, Arriagada R, Quoix E, et al. Radiotherapy alone versus combined chemotherapy and radiotherapy in unresectable non-small cell lung carcinoma. *Lung Cancer.* Mar 1994;10 Suppl 1:S239-244.

**82.** Sause WT, Scott C, Taylor S, et al. Radiation Therapy Oncology Group (RTOG) 88-08 and Eastern Cooperative Oncology Group (ECOG) 4588: preliminary results of a phase III trial in regionally advanced, unresectable non-small-cell lung cancer. *Journal of the National Cancer Institute.* Feb 1 1995;87(3):198-205.

**83.** Dillman RO, Herndon J, Seagren SL, Eaton WL, Jr., Green MR. Improved survival in stage III non-small-cell lung cancer: seven-year follow-up of cancer and leukemia group B (CALGB) 8433 trial. *Journal of the National Cancer Institute.* Sep 4 1996;88(17):1210-1215.

**84.** Suntharalingam M, Paulus R, Edelman MJ, et al. Radiation therapy oncology group protocol 02-29: a phase II trial of neoadjuvant therapy with concurrent

chemotherapy and full-dose radiation therapy followed by surgical resection and consolidative therapy for locally advanced non-small cell carcinoma of the lung. *International journal of radiation oncology, biology, physics.* Oct 1 2012;84(2):456-463.

**85.** Trodella L, Granone P, Valente S, et al. Neoadjuvant concurrent radiochemotherapy in locally advanced (IIIA-IIIB) non-small-cell lung cancer: long-term results according to downstaging. *Annals of oncology : official journal of the European Society for Medical Oncology / ESMO.* Mar 2004;15(3):389-398.