

# Treating Locally Advanced Disease: An Analysis of Very Large, Hilar Lymph Node Positive Non-Small Cell Lung Cancer Using the National Cancer Data Base

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**Background.** Very large, locally advanced non-small cell lung cancers (NSCLC) remain a therapeutic challenge. This retrospective study compares the effect of treatment modalities on survival of patients with large NSCLC with hilar lymph node involvement ( $T_{3>7\text{cm}}N_1$ ).

**Methods.** The National Cancer Data Base was used to identify adult patients who were diagnosed with  $T_{3>7\text{cm}}N_1$  NSCLC from 1999 to 2005 ( $n = 642$ ). Nonsurgical treatments included chemoradiation, chemotherapy, radiation therapy, or no treatment, whereas primary surgical treatments included surgery, chemoradiation or chemotherapy prior to surgery, chemoradiation or chemotherapy after surgery, or postoperative radiotherapy. Five-year overall survival (OS) was estimated by the Kaplan-Meier method and comparisons made using log-rank tests and Cox regression models.

**Results.** A total of 642 patients were evaluated; 425 nonsurgical (66%) and 217 surgical (34%). Primary surgical therapy was associated with improved 5-year OS;

28% versus 8% and 4% for nonsurgical and no treatment, respectively ( $p < 0.001$ ). The 5-year OS were 11%, 5%, 2%, and 4% for chemoradiation, chemotherapy, radiation therapy, and no treatment, respectively ( $p < 0.001$ ). The 5-year OS were 16% for surgery only, 40% and 44% for neoadjuvant chemoradiation or chemotherapy with surgery, respectively, 40% and 38% for adjuvant chemoradiation or chemotherapy with surgery, respectively, and 18% for postoperative radiotherapy ( $p < 0.001$ ). On multivariate analysis, surgery and chemotherapy in most combinations were associated with significantly improved OS compared with chemoradiation only.

**Conclusions.** Surgery with systemic therapy delivered in a neoadjuvant or adjuvant fashion for patients with  $T_{3>7\text{cm}}N_1$  NSCLCs is associated with improvements in OS.

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Non-small cell lung cancer (NSCLC) constitutes the majority of lung cancers, with approximately one-third of patients presenting with locally advanced disease (stage III) [1]. In the 6th edition of the American Joint Committee on Cancer and the International Union Against Cancer staging system, primary tumors greater than 7 cm associated with ipsilateral hilar lymph node involvement were classified as T2N1, stage IIB lung cancers. In the 7th edition of the staging system, tumors greater than 7 cm were upstaged into the T3 primary tumor category and in combination with ipsilateral hilar lymph node involvement ( $T_{3>7\text{cm}}N_1$ ) these tumors were reclassified as stage IIIA disease [2]. This “stage shift” phenomenon has contributed to the dilemma in

understanding the optimal strategy for treating this particular subgroup of the stage IIIA lesions [3]. Multimodality therapy has become a widely employed practice for curative-intent strategy for stage IIIA disease [4, 5]. However, these treatment strategies are driven largely by studies and clinical trials focused on its major constituent, mediastinal lymph node involvement or N2 disease. The purpose of this study was to examine the efficacy of different treatment strategies on long-term survival of patients with  $T_{3>7\text{cm}}N_1$  NSCLC using a large national dataset.

## Patients and Methods

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. It is a nationwide oncology outcomes database that captures

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## Abbreviations and Acronyms

C	= chemotherapy
CCP	= community cancer program
C-S	= neoadjuvant chemotherapy + surgery
CxR	= chemoradiation
CxR-S	= neoadjuvant chemoradiation + surgery
None	= no treatment
NSCLC	= non-small cell lung cancer
NST	= nonsurgical therapy
OS	= overall survival
PST	= primary surgical therapy
RT	= radiation therapy
S	= surgery
S-C	= surgery + adjuvant chemotherapy
S-CxR	= surgery + adjuvant chemoradiation
S-PORT	= surgery + postoperative radiation therapy

detailed information of nearly 70% of all newly diagnosed cases of cancer in the United States from hospital cancer registries across the country. Therefore, the NCDB is an excellent resource to investigate patient demographics, tumor characteristics, first course of treatment, and overall 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.

This analysis was restricted to patients who were 20 years and older 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 [6]. All nonsurgical and surgical patients were selected by having a diagnosis of the following: a clinical T2 or T3 tumor measuring greater than 7 cm but 20 cm or less, clinically positive ipsilateral lymph node involvement (cN1), and no clinical signs of distant metastasis (cM0).

Patients who received surgery in the form of lobectomy or pneumonectomy with negative surgical margins were included. Treatment combination sequences were determined for each patient using NCDB data items that described the date of first course treatment from date of diagnosis. The possible treatment modalities for the nonsurgical subcohort (nonsurgical therapy [NST]) included no treatment (none), chemotherapy only (C), radiation therapy only (RT), or chemoradiation therapy (CxR). The primary surgical treatment (PST) combinations included surgery only (S), chemotherapy or chemoradiation prior to surgery (C-S or CxR-S), surgery followed by chemotherapy or chemoradiation (S-C or S-CxR), or surgery with postoperative radiation therapy (S-PORT).

Information obtained from the NCDB included patient demographics, age at diagnosis, histology and size of

primary tumor, stage, type of surgery, the addition or absence of neoadjuvant and adjuvant therapy, and survival time in months. The NCDB lacks data regarding lung cancer-specific death. Therefore, for this study overall survival (OS) was the primary study endpoint and was defined as the time from diagnosis to the date of death from any cause. Four types of treatment facilities comprised of community cancer programs (CCP), comprehensive community cancer programs (CCCP), teaching or research centers, or others were also included in all analysis. Both CCP and CCCPs have full range of services for cancer care; however CCCPs treat at least 300 cancer patients a year whereas CCCPs treat at least 650 cancer patients annually.

Comparisons of patient and tumor characteristics and provided therapy among different age groups were performed using the  $\chi^2$  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 greater than 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 (CI) 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 a  $p$  value less than 0.05.

## Results

The overall cohort was composed of 642 patients, of whom 66% underwent nonsurgical therapy (NST) and 34% underwent primary surgical therapy (PST). The median age at diagnosis was 68 years with a median follow-up time of 11 months (range, 0 to 143 months). The majority of patients were male (61%) and white (84%). By the end of the study period, 88% of the cohort had expired. Patient characteristics are shown in [Table 1](#).

Among the NST patients, 43% 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% of the PST population having undergone this type of resection ( $p = 0.002$ ). 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 over 80 years of age where 36% received no treatment followed by 23% RT only.

Surgery was associated with significant improvements in 5-year OS (PST, 28%) compared with 8% and 4% 5-year

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