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Lung: Short Report

# Multimodal Therapy for T4 N2 Non–Small Cell Lung Cancer With Additional Ipsilateral Pulmonary Nodules

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## ABSTRACT

**BACKGROUND** The optimal treatment strategy for T4 non–small cell lung cancer (NSCLC) with additional intrapulmonary nodules in a different ipsilateral lobe (T4-Add) is not well characterized across clinical N stages. This study evaluated long-term survival of patients with T4-Add N2 NSCLC who received multimodal therapy including surgical resection and chemotherapy vs concurrent chemoradiation.

**METHODS** Patients with T4-Add N2 M0 NSCLC in the National Cancer Database from 2010 to 2015 were included. Long-term survival was evaluated and compared between patients who underwent primary site surgical resection with chemotherapy and those who received concurrent chemoradiation by Kaplan-Meier analysis, Cox proportional hazards modeling, and propensity score matching on 9 common prognostic variables including comorbidities.

**RESULTS** Of the 499 patients diagnosed with T4-Add N2 M0 NSCLC who satisfied study eligibility criteria, 220 (44.1%) received primary site surgical resection with chemotherapy and 279 (55.9%) received chemoradiation. After multivariable adjusted Cox proportional hazards modeling, surgical resection with chemotherapy was associated with better long-term survival than chemoradiation. In a propensity score–matched analysis of 100 patients who received surgical resection with chemotherapy and 100 patients who received chemoradiation, patients who received surgical resection with chemotherapy had better 5-year overall survival.

**CONCLUSIONS** The results of this national analysis of patients with T4 N2 NSCLC with additional nodules in a different ipsilateral lobe suggest that multimodal therapy including surgery may confer a survival benefit compared with chemoradiation alone. These findings support further evaluation of surgical resection as part of multimodal therapy for carefully selected patients with T4-Add N2 disease.

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Various treatment regimens are offered for stage IIIB, T4 N2 non-small cell lung cancer (NSCLC) because of the heterogeneity of this disease presentation. Current National Comprehensive Cancer Network treatment guidelines consider most T4 N2 NSCLC unresectable and recommend definitive chemoradiation as primary treatment.[1] The phase 3 randomized trial ESPATUE demonstrated similar 5-year overall survival (OS) after surgical resection (44%) vs concurrent chemoradiotherapy (40%) for potentially

## IN SHORT

- T4 N2 non–small cell lung cancer presenting with additional intrapulmonary nodules in a different ipsilateral lobe (T4-Add) represents a unique subcategory of T4 N2 disease.
- Multimodal therapy that includes surgical resection and chemotherapy may confer a survival benefit over chemoradiation alone for carefully selected patients with T4-Add N2 disease.

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resectable stage IIIA-B NSCLC, including selected T4 N2 tumors.[2] This trial, however, included only T4 N2 disease presenting with invasion of surrounding structures, without specifically focusing on other T4 descriptors, including tumors >7 cm in size and tumors with additional intrapulmonary nodules in a different ipsilateral lobe (T4-Add). Treatment of T4-Add tumors, specifically, is dependent on clinical N status. Although surgical resection of both the primary tumor and additional nodules is recommended for T4-Add N0-1 disease,[1] the optimal treatment strategy for T4-Add N2 tumors is not well defined, with most patients receiving chemoradiation without surgical resection, in accordance with guidelines for all T4 N2 disease.

The objective of this study was to evaluate long-term survival of patients with T4-Add N2 NSCLC who underwent multimodal therapy including primary site surgical resection and chemotherapy compared with concurrent chemoradiation without surgical resection, in a national analysis, which has not been previously reported. We tested the hypothesis that compared with concurrent chemoradiation, primary site surgical resection and chemotherapy would be associated with improved OS for patients with T4-Add N2 tumors.

## PATIENTS AND METHODS

**DATA SOURCE.** This study was approved by the institutional review board of Massachusetts General Hospital. Data were analyzed from a deidentified Participant User File of the National Cancer Database (NCDB). The NCDB is a joint project of the American College of Surgeons Commission on Cancer and the American Cancer Society, estimated to capture 80% of newly diagnosed cases of lung cancer in the United States and Puerto Rico.[3]

**STUDY DESIGN.** Patients with T4 N2 M0 NSCLC with synchronous additional intrapulmonary nodules in a different ipsilateral lobe (T4-Add) at the time of diagnosis were identified according to the Eighth Edition *AJCC TNM Staging Manual* and *Third Edition International Classification of Diseases for Oncology* histology and topography codes. In the NCDB, intrapulmonary metastases must be documented as "tumor nodules of the same histologic type as the primary tumor" in the patient's health records.[3] Patients with other T4 tumors, including tumors >7 cm in size and tumors invading surrounding structures, were excluded. Additional exclusion criteria consisted of nonmalignant disease, history of previous unrelated malignant disease, and missing treatment or survival data. Patients diagnosed between 2010 and 2015 were included because of data availability on specific T4 staging descriptors.

Patients were stratified by definitive treatment modality: (1) chemoradiation: concurrent chemoradiation, defined as radiation ≥60 Gy within 30 days before or after chemotherapy, without surgical resection; or (2) thoracic surgery: multimodal therapy including primary site surgical resection within 6 months before or after chemotherapy (with or without radiation therapy). The primary outcome was OS measured from time of diagnosis to time of death or last follow-up.

**STATISTICAL ANALYSIS.** Baseline characteristics were compared between the chemoradiation and thoracic surgery groups by the Wilcoxon rank sum test for continuous variables and Pearson $\chi^2$ test for discrete variables. OS was compared by Kaplan-Meier analysis and multivariable adjusted Cox proportional hazards modeling, adjusting for 9 prognostic factors including age, sex, race, Charlson-Deyo comorbidity score, median census tract income, facility type, distance to facility, tumor location, and tumor histologic type. Propensity score matching was performed with a logistic regression model based on the same 9 factors determined a priori to most likely act as confounders. The most appropriately matched pairs were identified by a greedy nearest neighbor matching algorithm without replacement and caliper of 0.045 (20% standard deviation of the logit of propensity scores). Balance was assessed using standardized differences. A doubly robust estimator of OS using Cox proportional hazards modeling was calculated after propensity score weighting.[4] A case complete analysis was used to address any potential missing data.

Two additional sensitivity analyses comparing OS after thoracic surgery vs chemoradiation were performed with multivariable adjusted Cox proportional hazards models limited to: (1) patients with no comorbidities and (2) patients with primary tumors ≤3 cm in size, accounting for patients with "bulky" or extensive N2 disease. Of note, previous literature has suggested that smaller tumors are more likely to be associated with less extensive nodal disease.[5]

Model balance and diagnostics were assessed with no violation of major assumptions observed. All statistical analyses were performed with Stata Statistical Software: Release 13.0 (StataCorp LP). A 2-sided *P* value of .05 was used to define significance.

## RESULTS

**STUDY COHORT.** Of the 499 patients diagnosed with T4-Add N2 M0 NSCLC with additional intrapulmonary nodules in a different ipsilateral lobe who satisfied study inclusion criteria, 279 (55.9%) received concurrent chemoradiation without surgical resection (chemoradiation) and 220 (44.1%) underwent multimodal treatment including primary site surgical

resection and chemotherapy (thoracic surgery) (Supplemental Figure). Median follow-up for the entire cohort was 27.3 months (interquartile range, 13.1-54.6 months), and 5-year OS was 32.6% (95% CI, 28.3-36.9).

**COMPARISON OF THORACIC SURGERY VS CHEMORADIATION.** Baseline characteristics of patients who received chemoradiation or thoracic surgery are shown in Supplemental Table 1. Of the 279 patients who received chemoradiation, 145 (52.0%) received external beam radiation, 42 (15.1%) received 3-dimensional conformal therapy, 90 (32.3%) received intensity-modulated radiation therapy, and 2 (0.7%) received stereotactic body radiation. Patients who received thoracic surgery had better OS than patients who received chemoradiation both in Kaplan-Meier analysis of 5-year OS ($P < .001$; Figure A) and after multivariable adjusted Cox proportional hazards modeling (hazard ratio [HR], 0.56; 95% CI, 0.41-0.76; $P < .001$; Supplemental Table 2). A propensity score-matched analysis of these patient cohorts yielded 2 groups of 100 patients each who received thoracic surgery and chemoradiation, well balanced on baseline characteristics (Supplemental Table 3). In Kaplan-Meier analysis, thoracic surgery was associated with better 5-year OS than chemoradiation ($P = .01$; Figure B). A Cox proportional hazards analysis was performed accounting for propensity score weighting as a doubly robust estimator of OS and was consistent with the unweighted analysis (HR, 0.58; 95% CI, 0.47-0.71; $P < .001$).

**SENSITIVITY ANALYSIS. Patients With No Comorbidities.** A sensitivity analysis limited to patients with no comorbidities was performed, specifically excluding all patients with Charlson-Deyo comorbidity score >0 and patients in the chemoradiation group who did not undergo surgical resection because of contraindicating risk factors (ie, severely comorbid conditions, advanced age, or progression of the tumor before planned surgical resection). After multivariable adjusted Cox proportional hazards modeling, thoracic surgery continued to be associated with better OS than chemoradiation (HR, 0.54; 95% CI, 0.35-0.83; $P = .005$).

**Patients With Tumors ≤3 cm in Size.** To account for patients who may have had more extensive or "bulky" N2 nodal disease, an additional multivariable adjusted Cox proportional hazards model limited to patients with tumors ≤3 cm in size was performed, which more likely represent tumors with less extensive "nonbulky" nodal disease. Previous literature has demonstrated that smaller primary tumor size is associated with less extensive nodal disease.[5] In this analysis, patients who received thoracic surgery had better OS than patients who received chemoradiation (HR, 0.53; 95% CI, 0.31-0.90; $P = .019$).

## COMMENT

In this national analysis of patients with T4 N2 M0 NSCLC with additional nodules in a different ipsilateral lobe (T4-Add), patients who underwent multimodal therapy including primary site surgical resection and chemotherapy (thoracic surgery) had better OS than patients who received concurrent chemoradiation without surgical resection (chemoradiation). These results were consistent in both unadjusted and multivariable adjusted analyses, after Cox proportional hazards modeling and propensity score matching, as well as in sensitivity analyses of patients with no comorbidities and patients with primary tumors ≤3 cm in size.

One of the strengths of this study was its ability to evaluate long-term survival of patients with T4-Add N2

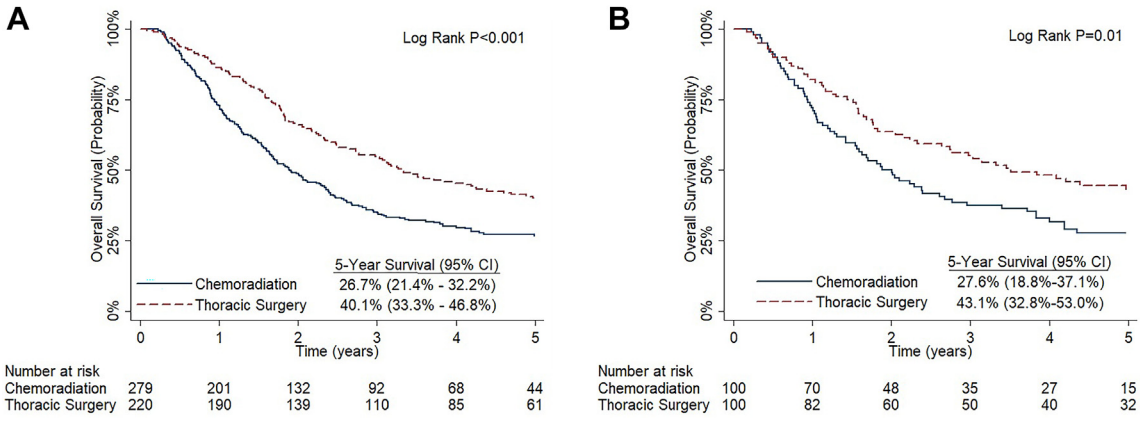


**FIGURE** Overall survival of patients with T4-Add N2 M0 non–small cell lung cancer with additional intrapulmonary nodules in a different ipsilateral lobe who underwent concurrent chemoradiation (Chemoradiation) vs multimodal therapy including primary site surgical resection and chemotherapy (Thoracic Surgery). (A) In the entire cohort. (B) After propensity score matching.

NSCLC stratified by treatment modality. The 5-year OS of all patients in this study was 32.6%. In previous studies of large-scale databases, 5-year OS of patients with T4-Add tumors was between 8% and 33%, regardless of treatment modality.[6-10] Only Nagai and coworkers,[9] using data from the Japanese Joint Committee of Lung Cancer Registry, reported 5-year OS of 10.2% specifically for patients with T4-Add N2 disease who underwent surgical resection, although this study evaluated data from 1994 without detailed information on the use of multimodal treatment regimens.

This study also addressed underlying questions about the treatment and prognosis of T4-Add N2 NSCLC, specifically whether such tumors should be treated similar to other T4 N2 disease or other T4-Add disease. Current National Comprehensive Cancer Network treatment guidelines for T4-Add N0-1 NSCLC recommend surgical resection of both the primary tumor and additional nodules but lack specific recommendations for T4-Add N2 NSCLC.[1] The few clinical trials that evaluated surgical resection for potentially resectable T4 N2 disease usually included only tumors invading surrounding structures and not tumors with additional ipsilateral intrapulmonary nodules.[2] In using the NCDB to address this question, this study included a large sample of patients with T4-Add N2 NSCLC with detailed information about their diverse treatment regimens, specifically evaluating surgical resection with chemotherapy vs chemoradiation.

This study has several limitations. First, because of its retrospective nature, there may be unobserved confounding and selection bias, despite our use of multivariable adjusted methods and propensity score matching. Second, because of limitations in the NCDB, we were unable to determine the number or specific location of additional intrapulmonary nodules or the exact treatment directed toward the additional nodules. In the NCDB, to be classified as additional intrapulmonary metastases, tumor nodules must be documented as "of the same histologic type as the primary tumor" in the patient's health records.[3] Third, data on the presence of additional intrapulmonary nodules was available only from 2010 to 2015, before the regular incorporation of immunotherapy in multimodal treatment regimens. Finally, the NCDB does not contain data on recurrence, disease-free, or disease-specific survival.

In conclusion, the results of this national analysis of patients with T4 N2 M0 NSCLC due to the presence of additional intrapulmonary nodules in a different ipsilateral lobe demonstrate that multimodality therapy that included primary site surgical resection and chemotherapy was associated with better OS than concurrent chemoradiation without surgical resection, after multivariable adjusted analysis and propensity score matching. These findings highlight the heterogeneity of stage IIIB NSCLC and support consideration of T4-Add tumors as a unique, potentially resectable subcategory of T4 N2 disease.

The Supplemental Material can be viewed in the online version of this article [https://doi.org/10.1016/j.atssr.2023.06.010] on http://www.annalsthoracicsurgery.org.

The data used in the study are derived from a deidentified National Cancer Database file. The American College of Surgeons and the Commission on Cancer have not verified and are not responsible for the analytic or statistical methodology employed or the conclusions drawn from these data by the investigator.

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## DISCLOSURES

The authors have no conflicts of interest to disclose.

## REFERENCES

1. Ettinger DS, Wood DE, Aisner DL, et al. Non–Small Cell Lung Cancer, Version 3.2022, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw*. 2022;20:497-530.

2. Eberhardt WE, Pöttgen C, Gauler TC, et al. Phase III study of surgery versus definitive concurrent chemoradiotherapy boost in patients with resectable stage IIIA(N2) and selected IIIB non–small-cell lung cancer after induction chemotherapy and concurrent chemoradiotherapy (ESPATUE). *J Clin Oncol*. 2015;33:4194-4201.

3. National Cancer Database Participant User File (PUF). 2020 Data Dictionary. American College of Surgeons; 2022. Accessed April 1, 2023. https://www.facs.org/media/brilfbgu/puf-2020-data-dictionary.pdf

4. Funk MJ, Westreich D, Wiesen C, Stürmer T, Brookhart MA, Davidian M. Doubly robust estimation of causal effects. *Am J Epidemiol*. 2011;173:761-767.

5. Verdial FC, Madtes DK, Hwang B, et al. Prediction model for nodal disease among patients with non–small cell lung cancer. *Ann Thorac Surg*. 2019;107:1600-1606.

6. Detterbeck FC, Bolejack V, Arenberg DA, et al. The IASLC Lung Cancer Staging Project: background data and proposals for the classification of lung cancer with separate tumor nodules in the forthcoming eighth edition of the TNM classification for lung cancer. *J Thorac Oncol*. 2016;11:681-692.

7. Ou SH, Zell JA. Validation study of the proposed IASLC staging revisions of the T4 and M non–small cell lung cancer descriptors using data from 23, 583 patients in the California Cancer Registry. *J Thorac Oncol*. 2008;3:216-227.

8. Watanabe S, Asamura H, Miyaoka E, et al. Results of T4 surgical cases in the Japanese Lung Cancer Registry study: should mediastinal fat tissue invasion really be included in the T4 category? *J Thorac Oncol*. 2013;8:759-765.

9. Nagai K, Sohara Y, Tsuchiya R, Goya T, Miyaoka E. Prognosis of resected non–small cell lung cancer patients with intrapulmonary metastases. *J Thorac Oncol*. 2007;2:282-286.

10. William WN Jr, Lin HY, Lee JJ, Lippman SM, Roth JA, Kim ES. Revisiting stage IIIB and IV non–small cell lung cancer: analysis of the Surveillance, Epidemiology, and End Results data. *Chest*. 2009;136:701-709.