Exploring the Potential Different Outcomes Associated With the Different Phenotypes Under the Shared Pathologic T3N0 Designation

Terrance Peng, MPH, a Sean C. Wightman, MD, a Li Ding, MD, MPH, b Scott M. Atay, MD, a Evan T. Alicuben, MD, c Elizabeth A. David, MD, MAS, a Anthony W. Kim, MD a,*

a Division of Thoracic Surgery, Department of Surgery, Keck School of Medicine of the University of Southern California, Los Angeles, California
b Department of Preventative Medicine, Keck School of Medicine of the University of Southern California, Los Angeles, California
c Department of Cardiothoracic Surgery, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania

Received 5 May 2021; accepted 5 May 2021
Available online - 18 May 2021

ABSTRACT

Introduction: The objective of this study was to compare overall survival (OS) between patients with pT1-2N1 versus pT3N0 NSCLC and various subtypes of pT3N0 NSCLC.

Methods: The National Cancer Database was queried to identify treatment-naive patients with pathologic stage IIB primary NSCLC. Patients were included if they were diagnosed with pT3N0 or pT1-2N1 NSCLC and received definitive surgery within 4 months of diagnosis. The pT3N0 cohort was subdivided by single versus multiple concurrent T3 descriptors and single-T3 subtypes. The 5-year OS was compared using the Kaplan-Meier method, and the Cox proportional-hazards model was used to identify prognostic factors for death.

Results: A total of 16,770 patients were included (pT3N0: 7179; pT1-2N1: 9591). pT3N0 NSCLC was associated with greater 5-year OS than pT1-2N1 NSCLC (52.4% versus 47.8%, p < 0.0001). Among patients receiving adjuvant chemotherapy after surgery, multiple-T3 pT3N0 NSCLC was associated with lower 5-year OS than single-T3 pT3N0 NSCLC (49.0% versus 63.3%, p < 0.0001), and chest wall-only pT3N0 NSCLC was associated with the lowest 5-year OS across single-T3 subtypes (additional nodule: 68.3%; size: 64.5%; chest wall: 52.2%, p < 0.0001). Adjuvant chemotherapy was associated with decreased risk of death in the pT3N0 cohort (hazard ratio = 0.65, confidence interval: 0.59–0.71, p < 0.0001).

Conclusions: Patients with pT3N0 NSCLC experience greater 5-year OS after surgery compared with those with pT1-2N1 NSCLC. Multiple-T3 and chest wall-only pT3N0 NSCLC are associated with worse 5-year OS and increased risk of death relative to other T3 subtypes. Future staging systems should consider including notation distinguishing multiple T3 descriptors in pT3N0 NSCLC.

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Keywords: Lung cancer; T3; Staging; Classification

Introduction

The TNM system was introduced to facilitate standardized and unambiguous cancer classification on the basis of objective anatomical features.1,2 The American
Joint Committee on Cancer (AJCC) implemented the eighth and most recent edition of its Cancer Staging Manual in 2018, incorporating revisions to TNM classification criteria as informed by contemporary medical literature. For NSCLC, the AJCC eighth edition staging system was developed using proposals from the International Association for the Study of Lung Cancer (IASLC) and introduced substantial changes for the heterogeneous T3 subgroup. Tumors invading the diaphragm were reclassified from T3 to T4, whereas those associated with atelectasis or invading the main bronchus were reclassified from T3 to T2. In addition, tumors greater than 5 cm but less than or equal to 7 cm in greatest dimension were reclassified as T3, with size greater than 7 cm now serving as a T4 descriptor.

In 2019, a study of 683 patients with pT3N0M0 NSCLC in a Dutch national cancer registry was performed to validate revisions to the T component in the eighth edition lung cancer staging system. The authors found little evidence to support the reclassification of NSCLC tumors greater than 7 cm as T4 and noted that the various subtypes of pT3N0M0 NSCLC were associated with disparate survival outcomes. Furthermore, this study detected differences in overall survival (OS) between patients with pT3N0M0 NSCLC of different histologic types, a factor not accounted for in the eighth edition staging in fully conveying this clinically important heterogeneity.

There is potential for an infinite number of variables to be included in the staging system for NSCLC; consequently, this investigation will explore outcomes in the context of the established constraints of the current TNM rubric. The objective of this study is to compare OS between patients with stage IIB disease defined as pT3N0M0 NSCLC versus patients with stage IIB disease defined as pT1-2N1M0 NSCLC. Furthermore, this study will assess OS for pT3N0M0 NSCLC across different subtypes and those fulfilling single versus multiple T3 criteria.

Materials and Methods

Data Source

The National Cancer Database (NCDB) provides de-identified data on patient demographics, tumor characteristics, treatment modalities, and outcomes for nearly 70% of patients diagnosed with cancer in the United States each year. The NCDB collects data from approximately 1500 treatment facilities accredited by the Commission on Cancer and is jointly sponsored by the American College of Surgeons and American Cancer Society. This study was approved by the Institutional Review Board at the University of Southern California.

Patient Selection

The NCDB Participant User File (2010–2016) was queried to identify treatment-naive patients with pathologic stage IIB primary NSCLC who underwent lobectomy within four months of diagnosis. No consent was required for this study. All patients were appropriately restaged to the current eighth edition of the AJCC Cancer Staging Manual from the seventh edition criteria in the NCDB Participant User File. Patients with M1 disease; tumor size greater than 7 cm; or involvement of the carina, heart, great vessels, trachea, mainstem bronchus, esophagus, diaphragm, mediastinum, recurrent laryngeal nerves, or vertebral bodies were excluded. Patients with associated malignant pleural effusion, pleural effusion not otherwise specified, separate tumor nodules in a different ipsilateral lobe of the primary tumor, or a mainstem bronchus primary site were also excluded. Only patients with defined tumor histologic subtype and laterality were included. Patients with pT3N0 NSCLC were excluded if no data were available to specify which T3 criteria were fulfilled. The cohort selection process is illustrated in Figure 1.

Variables

Patients were divided by pathologic staging into the pT3N0 NSCLC cohort and pT1-2N1 NSCLC reference cohort. The pT3N0 cohort was further subdivided on the basis of fulfillment of single versus multiple T3 criteria. Patients with single-T3 pT3N0 NSCLC were organized into the following subgroups by T3 descriptor: the “size” subgroup (n = 3752) included NSCLC greater than 5 cm but less than or equal to 7 cm; the “chest wall” subgroup (n = 977) included NSCLC involving the parietal pleura or chest wall; the “peri-phrenic” subgroup (n = 55) included NSCLC involving the parietal pericardium or phrenic nerve; and the “additional nodule” subgroup (n = 1658) included NSCLC with separate tumor nodules in the same lobe as the primary tumor. Covariates of interest included age, sex, race, insurance, income, education, facility type, area of residence, distance to facility, Charlson-Deyo comorbidity index (CDCI), tumor laterality, primary tumor site, tumor size, histologic subtype, and receipt of adjuvant chemotherapy.

Outcomes of Interest

The primary outcome of interest was 5-year OS among patients with pT3N0 and pT1-2N1 NSCLC.
Secondary outcomes of interest included 5-year OS for patients with pT3N0 NSCLC of different subtypes and with single versus multiple T3 descriptors. Additional outcomes of interest included the rate and survival impact of adjuvant chemotherapy.

**Statistical Analysis**

Descriptive analyses were performed to report patient demographics, tumor characteristics, and adjuvant chemotherapy rates for the pT3N0 and pT1-2N1 NSCLC cohorts. The Kaplan-Meier curve and log-rank test were used to describe 5-year OS between cohorts. The Cox proportional-hazards model was used to identify independent predictors of death in the pT3N0 cohort. The proportional-hazards assumption was checked using Scaled Schoenfeld residuals. Age and tumor size were recategorized using quartiles and clinically relevant groups owing to violation of the assumption when used as continuous variables. Significance level for two-sided tests was defined as $p$ value less than 0.05. All statistical analyses were performed with Statistical Analysis System version 9.4 (SAS Institute Inc., Cary, NC).

**Results**

**Patient Characteristics and Cohort Composition**

A total of 16,770 patients met the inclusion criteria (Table 1). The mean age of the study population was 66.8 plus or minus 9.6 years. There were 7179 patients (42.8%) in the pT3N0 NSCLC cohort and 9591 patients (57.2%) in the pT1-2N1 NSCLC cohort. Groups were well-balanced with respect to sex, race, income, education, treatment facility type, location, and distance to treatment facility. Nevertheless, cohorts varied significantly by insurance type, CDCI, tumor laterality, primary tumor site, histologic subtype, and tumor size.

Among patients with pT3N0 NSCLC, 6442 met a single T3 criterion; 58.2% of single-T3 patients had size-only pT3N0 NSCLC. There were 737 multiple-T3 patients, of whom 63.9% met size and chest wall criteria simultaneously (see table in Supplementary Data 1, which lists the frequencies of all single and paired T3 descriptors). In addition, 11 patients were diagnosed with pT3N0 NSCLC simultaneously fulfilling size, chest wall, and additional nodule criteria. The composition of the pT1-2N1 cohort is also outlined in the Supplementary Materials (see table in Supplementary Data 2, which describes the pT1-2N1 and pT3N0 cohorts in greater detail).

**Comparison of pT3N0 and pT1-2N1 NSCLC**

The pT3N0 cohort experienced greater 5-year OS than the pT1-2N1 cohort (52.4% versus 47.8%, $p < 0.0001$) (Fig. 2A). In addition, 40.1% of patients with pT3N0 NSCLC and 66.2% of patients with pT1-2N1 NSCLC received adjuvant chemotherapy ($p < 0.0001$) (Table 1). Among patients who received surgery with
Table 1. Patient Demographics and Tumor Characteristics

| Variables                        | Total (N = 16,770) | pT3N0 NSCLC (n = 7179) | pT1-2N1 NSCLC (n = 9591) | p Value |
|----------------------------------|--------------------|------------------------|--------------------------|---------|
| Age (y), mean ± SD               | 66.8 ± 9.6         | 67.7 ± 9.4             | 66.1 ± 9.7               | <0.0001 |
| Sex, n (%)                       |                    |                        |                          | 0.08    |
| Female                           | 7754 (46.2)        | 3263 (45.5)            | 4491 (46.8)              |         |
| Male                             | 9016 (53.8)        | 3916 (54.6)            | 5100 (53.2)              |         |
| Race, n (%)                      |                    |                        |                          | 0.24    |
| White                            | 14,650 (87.4)      | 6294 (87.7)            | 8356 (87.1)              |         |
| Black                            | 1457 (8.7)         | 621 (8.7)              | 836 (8.7)                |         |
| Other                            | 556 (3.3)          | 219 (3.1)              | 337 (3.5)                |         |
| Missing                          | 107 (0.6)          | 45 (0.6)               | 62 (0.7)                 |         |
| Insurance, n (%)                 |                    |                        |                          | <0.0001 |
| Medicare                         | 9821 (58.6)        | 4392 (61.2)            | 5429 (56.6)              |         |
| Private/MC                       | 5184 (30.9)        | 2098 (29.2)            | 3086 (32.2)              |         |
| Medicaid                         | 1003 (6.0)         | 381 (5.3)              | 622 (6.5)                |         |
| Not insured                      | 401 (2.4)          | 159 (2.2)              | 242 (2.5)                |         |
| Other Government                 | 211 (1.3)          | 86 (1.2)               | 125 (1.3)                |         |
| Missing                          | 150 (0.9)          | 63 (0.9)               | 87 (0.9)                 |         |
| Income, n (%)                    |                    |                        |                          | 0.84    |
| ≥$33,000                         | 13,585 (81.0)      | 5819 (81.1)            | 7766 (81.0)              |         |
| <$33,000                         | 3159 (18.8)        | 1347 (18.8)            | 1812 (18.9)              |         |
| Missing                          | 26 (0.2)           | 13 (0.2)               | 13 (0.1)                 |         |
| Education, n (%)                 |                    |                        |                          | 0.17    |
| <20.9% NHS                       | 13,857 (82.6)      | 5898 (82.2)            | 7959 (83.0)              |         |
| ≥21% NHS                         | 2891 (17.2)        | 1271 (17.7)            | 1620 (16.9)              |         |
| Missing                          | 22 (0.1)           | 10 (0.1)               | 12 (0.1)                 |         |
| Facility type, n (%)             |                    |                        |                          | 0.09    |
| Comprehensive CCP                | 7303 (43.6)        | 3108 (43.3)            | 4195 (43.7)              |         |
| Academic/research                | 5799 (34.6)        | 2554 (35.6)            | 3245 (33.8)              |         |
| INCP                             | 2382 (14.2)        | 982 (13.7)             | 1400 (14.6)              |         |
| CCP                              | 1235 (7.4)         | 518 (7.2)              | 717 (7.5)                |         |
| Missing                          | 51 (0.3)           | 17 (0.2)               | 34 (0.4)                 |         |
| Location, n (%)                  |                    |                        |                          | 0.88    |
| Metropolitan                     | 13,171 (78.5)      | 5656 (78.8)            | 7515 (78.4)              |         |
| Urban                            | 2801 (16.7)        | 1189 (16.6)            | 1612 (16.8)              |         |
| Rural                            | 418 (2.5)          | 181 (2.5)              | 237 (2.5)                |         |
| Missing                          | 380 (2.3)          | 153 (2.1)              | 227 (2.4)                |         |
| Distance, n (%)                  |                    |                        |                          | 0.67    |
| >12.5 miles                      | 8684 (51.8)        | 3703 (51.6)            | 4981 (51.9)              |         |
| ≤12.5 miles                      | 8066 (48.1)        | 3466 (48.3)            | 4600 (48.0)              |         |
| Missing                          | 20 (0.1)           | 10 (0.1)               | 10 (0.1)                 |         |
| CDCI, n (%)                      |                    |                        |                          | <0.0001 |
| 0                                | 8186 (48.8)        | 3372 (47.0)            | 4814 (50.2)              |         |
| 1                                | 5750 (34.3)        | 2506 (34.9)            | 3244 (33.8)              |         |
| 2                                | 2125 (12.7)        | 974 (13.6)             | 1151 (12.0)              |         |
| ≥3                               | 709 (4.2)          | 327 (4.6)              | 382 (4.0)                |         |
| Tumor laterality, n (%)          |                    |                        |                          | <0.0001 |
| Left                             | 9590 (57.2)        | 4301 (59.9)            | 5289 (55.2)              |         |
| Right                            | 7180 (42.8)        | 2878 (40.1)            | 4302 (44.9)              |         |
| Primary site, n (%)              |                    |                        |                          | <0.0001 |
| Upper lobe                       | 9915 (59.1)        | 4464 (62.2)            | 5451 (56.8)              |         |
| Middle lobe                      | 731 (4.4)          | 266 (3.7)              | 465 (4.9)                |         |
| Lower lobe                       | 5486 (32.7)        | 2211 (30.8)            | 3275 (34.2)              |         |
| Overlapping                      | 398 (2.4)          | 149 (2.1)              | 249 (2.6)                |         |
| Lung NOS                         | 240 (1.4)          | 89 (1.2)               | 151 (1.6)                |         |
| Histologic subtype, n (%)        |                    |                        |                          | <0.0001 |
| Adenocarcinoma                   | 9665 (57.6)        | 3791 (52.8)            | 5874 (61.2)              |         |
| SCC                              | 6490 (38.7)        | 3102 (43.2)            | 3388 (35.3)              |         |
| Other                            | 615 (3.7)          | 286 (4.0)              | 329 (3.4)                |         |

(continued)
Adjuvant chemotherapy, pT3N0 NSCLC was associated with greater 5-year OS relative to pT1-2N1 NSCLC (61.6% versus 54.0%, \( p < 0.0001 \)) (Fig. 2B). Among patients who did not receive adjuvant chemotherapy after surgery, 5-year OS remained greater with pT3N0 NSCLC than pT1-2N1 NSCLC (46.2% versus 35.7%, \( p < 0.0001 \)) (Fig. 2C). Among patients with pT3N0 NSCLC who received surgery with adjuvant chemotherapy, single-T3 patients experienced significantly greater 5-year OS than multiple-T3 patients (63.3% versus 49.0%, \( p < 0.0001 \)) (Fig. 3). An analysis of single-T3 patients who received surgery with adjuvant chemotherapy revealed that the additional nodule-only subtype was associated with the greatest 5-year OS (additional nodule: 68.3%, size: 64.5%, chest wall: 52.2%; \( p < 0.0001 \)) (Fig. 4). The peri-phrenic cohort experienced a 5-year OS of 67.4% after surgery with adjuvant chemotherapy, but this group was omitted from Figure 4 owing to small sample size after 3 years. Additional survival analyses were performed between each pair of subgroups, revealing the chest wall-only cohort experienced lower 5-year OS after surgery with adjuvant chemotherapy than the additional nodule-only cohort (68.3% versus 52.2%, \( p < 0.0001 \)) (Fig. 5A) and the size-only cohort (64.5% versus 52.2%, \( p < 0.0001 \)) (Fig. 5B). Patients with size-only pT3N0 NSCLC experienced lower 5-year OS after surgery with adjuvant chemotherapy than those with the additional nodule-only subtype (68.3% versus 64.5%, \( p = 0.03 \)) (Fig. 5C).

**Table 1. Continued**

| Variables | Total (N = 16,770) | pT3N0 NSCLC (n = 7179) | pT1-2N1 NSCLC (n = 9591) | \( p \) Value |
|-----------|-------------------|-----------------------|-------------------------|-------------|
| Adjuvant chemotherapy, n (%) | | | | <0.0001 |
| No | 7538 (45.0) | 4300 (59.9) | 3238 (33.8) | |
| Yes | 9232 (55.1) | 2879 (40.1) | 6353 (66.2) | |
| Tumor size (cm), mean ±SD | | | | <0.0001 |
| 4.0 ± 1.7 | 4.7 ± 1.8 | 3.4 ± 1.5 | |

CCP, Community Cancer Program; CCI, Charlson-Deyo comorbidity index; INCP, Integrated Network Cancer Program; MC, managed care; NHS, no high school; NOS, not otherwise specified; SCC, squamous cell carcinoma.

**Figure 2.** The 5-year overall survival between pT3N0 and pT1-2N1 NSCLC cohorts. A includes all patients; B includes only patients who received adjuvant chemotherapy; and C includes only patients who did not receive adjuvant chemotherapy.
Among patients with pT3N0 NSCLC, risk of death did not significantly vary by race, insurance, income, education, location, distance to treatment facility, primary tumor site, tumor laterality, and tumor size (Table 2). Patients greater than or equal to 67 years old experienced a greater risk of death compared with patients less than 60 years old (HR = 1.83, CI: 1.17–1.91, p = 0.0002). Relative to additional nodule-only patients, chest wall-only patients and multiple-T3 patients experienced a significantly greater risk of death (chest wall: HR = 1.52, CI: 1.32–1.76, p < 0.0001; multiple-T3: HR = 1.49, CI: 1.17–1.91, p = 0.002). Receipt of adjuvant chemotherapy was associated with decreased risk of death among patients with pT3N0 NSCLC (HR = 0.65, CI: 0.59–0.71, p < 0.0001).

These findings are consistent with a recent study in the Netherlands by Blaauwgeers et al.7 Dividing their pT3N0 cohort into four subtypes (size > 7 cm, ≥2 nodules, parietal pleural invasion, and "mixed"), the authors similarly found that the greater than or equal to two nodule criterion was associated with greater 5-year OS than all other T3 descriptors. Importantly, this study also reported that patients with "mixed" pT3N0 NSCLC (i.e., two concurrent T3 descriptors) had the lowest 3- and 5-year OS. These results identified a potential gap within eighth edition stage groupings, and the authors thereby suggested that the combination of two T3 criteria should be evaluated for upgrading as a T4 descriptor in the next classification system.5–7 With the advantage of a larger sample size, this study offers evidence to support conclusions of Blaauwgeers et al.7 regarding the considerable prognostic implications of multiple-T3 pT3N0 NSCLC. Furthermore, the survival disparity observed between single-T3 versus multiple-T3 pT3N0 NSCLC arguably follows a logical pattern; if each criterion is individually sufficient to deem a T3 designation, it is
reasonable to anticipate that a combination of T3 descriptors would portend greater disease severity than an isolated T3 descriptor. Thus, the next staging system for NSCLC may benefit from incorporating a specialized notation to distinguish multiple-T3 pT3N0 NSCLC, with further investigation to determine if concurrent T3 descriptors should be considered a component of T4 disease.

This study also found that chest wall-only pT3N0 NSCLC was associated with lower 5-year OS after surgery with adjuvant chemotherapy than all other single-T3 subtypes (Fig. 4). Analyses of paired single-T3 subgroups confirmed that patients with chest wall-only pT3N0 NSCLC experienced lower 5-year OS after surgery with adjuvant chemotherapy than those with additional nodule-only pT3N0 NSCLC and those with size-only pT3N0 NSCLC (Fig. 5). Despite higher 5-year OS than the multiple-T3 subgroup, patients with chest wall-only pT3N0 had a comparatively greater increase in risk of death relative to the additional nodule-only cohort (Table 2). These findings contrast with previously published data from the IASLC, which indicated no prognostic differences between chest wall invasion and other T3 descriptors in pT3N0 NSCLC. Given that most NSCLC data in the IASLC database originate from Asia, this discrepancy may be due in part to the demographic composition of this study. In addition, this study did not investigate depth of invasion, an important prognostic factor in NSCLC with chest wall involvement. Consequently, additional research is required to determine whether chest wall involvement should be regarded as a T4 descriptor or if subclassification within the chest wall-only group is necessary to refine its prognostic value. For example, it is possible that chest wall-only pT3N0 NSCLC would be better described as T3 if tumor involvement is restricted to the pleura and T4 if exhibiting extrapleural invasion. This represents an important area of study potentially better suited for prospective analysis. Nevertheless, the results of this study indicate that the current T3 designation for chest wall invasion does not capture its prognostic severity relative to other T3 subtypes. The next staging system may benefit from further exploration of chest wall-only pT3N0 NSCLC to determine if this feature should be considered a T4 descriptor or if staging should be further refined by incorporating factors, such as depth of invasion.

Figure 5. The 5-year overall survival between pairs of single-T3 pT3N0 NSCLC subgroups. It includes only patients who received adjuvant chemotherapy. A includes the chest wall-only and additional nodule-only subgroups; B includes the chest wall-only and tumor size-only subgroups; and C includes the additional nodule-only and tumor size-only subgroups. In accordance with the data use agreement, the peri-phrenic cohort was excluded from this figure owing to small sample size (n < 10).
| Variables                      | Hazard Ratio | 95% Confidence Interval | p Value |
|-------------------------------|--------------|-------------------------|---------|
| **Age (y)**                   |              |                         |         |
| <60                           | REF          | REF                     | REF     |
| ≥60, <67                      | 0.99         | 0.86-1.15               | 0.94    |
| ≥67, <74                      | 1.24         | 1.07-1.45               | 0.005   |
| ≥74                           | 1.57         | 1.35-1.83               | <0.0001 |
| **Sex**                       |              |                         |         |
| Female                        | REF          | REF                     | REF     |
| Male                          | 1.27         | 1.17-1.38               | <0.0001 |
| **Race**                      |              |                         |         |
| White                         | REF          | REF                     | REF     |
| Black                         | 0.91         | 0.78-1.07               | 0.24    |
| Other                         | 0.84         | 0.65-1.09               | 0.19    |
| **Insurance**                 |              |                         |         |
| Medicare                      | REF          | REF                     | REF     |
| Medicaid                      | 1.18         | 0.96-1.45               | 0.11    |
| Other government              | 1.24         | 0.86-1.78               | 0.25    |
| Private/MC                    | 0.93         | 0.83-1.04               | 0.19    |
| Not insured                   | 1.11         | 0.83-1.50               | 0.48    |
| **Income**                    |              |                         |         |
| <$38,000                      | REF          | REF                     | REF     |
| ≥$38,000                      | 1.01         | 0.90-1.14               | 0.84    |
| **Education**                 |              |                         |         |
| <20.9% NHS                    | REF          | REF                     | REF     |
| ≥21% NHS                      | 0.94         | 0.84-1.06               | 0.34    |
| **Facility type**             |              |                         |         |
| Academic/research             | REF          | REF                     | REF     |
| Comprehensive CCP             | 1.14         | 1.04-1.25               | 0.005   |
| CCP                           | 1.34         | 1.14-1.57               | 0.0003  |
| INCP                          | 0.98         | 0.86-1.12               | 0.79    |
| **Location**                  |              |                         |         |
| Metropolitan                  | REF          | REF                     | REF     |
| Urban                         | 1.08         | 0.96-1.21               | 0.23    |
| Rural                         | 1.07         | 0.84-1.37               | 0.58    |
| **Distance**                  |              |                         |         |
| ≤12.5 miles                   | REF          | REF                     | REF     |
| >12.5 miles                   | 0.97         | 0.89-1.07               | 0.58    |
| **CDCI**                      |              |                         |         |
| 0                             | REF          | REF                     | REF     |
| 1                             | 1.11         | 1.01-1.21               | 0.03    |
| 2                             | 1.32         | 1.18-1.49               | <0.0001 |
| ≥3                            | 1.42         | 1.19-1.69               | 0.0001  |
| **Primary site**              |              |                         |         |
| Upper lobe                    | REF          | REF                     | REF     |
| Middle lobe                   | 0.90         | 0.71-1.13               | 0.36    |
| Lower lobe                    | 1.08         | 0.99-1.18               | 0.08    |
| Overlapping                   | 0.97         | 0.73-1.27               | 0.80    |
| Lung, NOS                     | 1.38         | 0.99-1.91               | 0.06    |
| **Tumor laterality**          |              |                         |         |
| Left                          | REF          | REF                     | REF     |
| Right                         | 0.96         | 0.89-1.05               | 0.39    |
| **Histologic subtype**        |              |                         |         |
| Adenocarcinoma                | REF          | REF                     | REF     |
| SCC                           | 1.21         | 1.11-1.31               | <0.0001 |
| Other                         | 1.39         | 1.15-1.69               | 0.0008  |

(continued)
Clinical guidelines for stage IIB NSCLC were formulated using clinical trial data and currently recommend adjuvant therapy after surgery, though no randomized studies have investigated adjuvant chemotherapy specifically for pT3N0 NSCLC. In this study, patients with pT3N0 NSCLC received adjuvant chemotherapy less frequently than those with pT1-2N1 NSCLC (Table 1). Nevertheless, 5-year OS after surgery was greater for the pT3N0 NSCLC cohort than the pT1-2N1 NSCLC cohort irrespective of adjuvant chemotherapy (Fig. 2). Within the pT3N0 NSCLC cohort, adjuvant chemotherapy was associated with a 35% reduced risk of death yet was received by only 40.1% of patients (Tables 1 and 2). Blaauwgeers et al. similarly found that only 38.7% of pT3N0 patients received postoperative chemotherapy despite a demonstrated survival benefit.

Response to adjuvant chemotherapy is nonuniform across pT3N0 NSCLC subtypes. For NSCLC tumors greater than 5 cm but less than or equal to 7 cm, adjuvant chemotherapy is associated with a 9% to 16% improvement in 5-year OS after complete resection. Adjuvant chemotherapy is also associated with improved 3-year OS for patients with additional nodule-only pT3N0 NSCLC. Nevertheless, the survival impact of adjuvant chemotherapy in pT3N0 NSCLC with chest wall involvement seems to be more complex. Previous studies have reported improved OS with adjuvant chemotherapy after complete resection for pT3N0 NSCLC involving the chest wall. In contrast, another investigation of pT3N0 NSCLC with chest wall invasion, which did not restrict the study cohort to patients receiving complete resection, found that the survival benefit of adjuvant chemotherapy varied by tumor size and surgical margin status; specifically, adjuvant chemotherapy was associated with improved survival in all patients with pT3N0 NSCLC less than or equal to 4 cm irrespective of margin status, whereas survival advantage was observed in patients with pT3N0 NSCLC greater than 4 cm only when surgical margins were negative. There is a paucity of literature investigating the role of adjuvant chemotherapy for pT3N0 NSCLC involving the parietal pericardium or phrenic nerve.

The mechanisms by which postoperative chemotherapy improves survival in pT3N0 NSCLC remain unclear, but it is hypothesized that this modality may treat a subclinical tumor burden. As revealed in this study, adjuvant chemotherapy rates are low among patients with pT3N0 NSCLC despite its survival benefit, and patients with chest wall-only or multiple-T3 subtypes face greater risk of death. Thus, increasing the use of guideline-concordant adjuvant chemotherapy is warranted for pT3N0 NSCLC overall but may be particularly critical in the context of chest wall involvement or multiple T3 descriptors, as these patients constitute an especially vulnerable population.

Limitations of this study include those inherent to retrospective designs and administrative database analyses. Manual restaging to AJCC eighth edition criteria was required for all patients; as a result, sample size was limited for certain subgroups, particularly the periphrenic cohort, after excluding patients who were missing relevant tumor data. This study therefore may not capture the full heterogeneity of the pT3N0 NSCLC patient population, as only a certain level of granularity could be supported owing to sample size limitations. In addition, the NCDB does not report on surgical complications or interventions beyond the first course of therapy, which may influence receipt of adjuvant chemotherapy.

### Table 2. Continued

| Variables                   | Hazard Ratio | 95% Confidence Interval | p Value |
|-----------------------------|--------------|-------------------------|---------|
| Tumor size (cm)             |              |                         |         |
| >0 but <1                   | REF          | REF                     | REF     |
| ≥1 but <2                   | 0.81         | 0.48-1.36               | 0.42    |
| ≥2 but <3                   | 1.06         | 0.64-1.76               | 0.83    |
| ≥3 but <4                   | 1.45         | 0.87-2.42               | 0.15    |
| ≥4 but <5                   | 1.37         | 0.81-2.29               | 0.24    |
| ≥5 but <7                   | 1.54         | 0.89-2.65               | 0.12    |
| T3 descriptor(s)            |              |                         |         |
| Additional nodule           | REF          | REF                     | REF     |
| Peri-phrenic                | 1.31         | 0.85-2.01               | 0.21    |
| Chest wall                  | 1.52         | 1.32-1.76               | <0.0001 |
| Size                        | 0.85         | 0.67-1.09               | 0.20    |
| Multiple-T3                 | 1.49         | 1.17-1.91               | 0.002   |
| Adjuvant chemotherapy       |              |                         |         |
| Did not receive             | REF          | REF                     | REF     |
| Received                    | 0.65         | 0.59-0.71               | <0.0001 |

CCP, Community Cancer Program; CDCI, Charlson-Deyo comorbidity index; INCP, Integrated Network Cancer Program; MC, managed care; NHS, no high school; NOS, not otherwise specified; REF, reference; SCC, squamous cell carcinoma.
chemistry and ultimately OS. Furthermore, the NCDB does not provide data on disease recurrence or recurrence-free survival. It is also impossible to determine which patients received inappropriate chemotherapy agents for NSCLC using the NCDB, a factor which would likely influence survival outcomes.

In conclusion, this study reveals that patients with pT3N0 NSCLC experience greater 5-year OS after surgery compared with those with pT1-2N1 NSCLC. In addition, prognosis under pT3N0 NSCLC designation varies by T3 subtype and the presence of single- versus multiple-T3 descriptors. Patients diagnosed with chest wall-only or multiple-T3 pT3N0 NSCLC experience worse 5-year OS and increased risk of death compared with other patients with single-T3 pT3N0 and pT1-2N1 NSCLC. Consequently, receipt of adjuvant chemotherapy after surgery may be especially critical for patients in these pT3N0 subgroups. The next edition of the cancer staging system may need to consider including notations to distinguish the presence of greater than or equal to 2 concurrent T3 descriptors in pT3N0 NSCLC, with further investigation required to determine if this tumor characteristic should be considered a component of T4 disease. Additional exploration of chest wall-only pT3N0 NSCLC may help elucidate whether chest wall invasion should be considered a T4 descriptor or if staging should be refined by considering factors such as depth of invasion.

CRediT Authorship Contribution

Terrance Peng: Methodology, Project Administration, Visualization, Writing—Original Draft, Writing—Review and Editing.

Sean C. Wightman, Scott M. Atay, and Elizabeth A. David: Methodology, Visualization, Writing—Review and Editing.

Li Ding: Data Curation, Formal Analysis, Funding Acquisition, Software, Writing—Review and Editing.

Evan T. Alicuben: Conceptualization, Methodology, Writing—Review and Editing.

Anthony W. Kim: Conceptualization, Methodology, Project Administration, Supervision, Writing—Original Draft, Writing—Review and Editing

Acknowledgments

Dr. Ding’s work was supported by the National Center for Advancing Translational Science of the U.S. National Institutes of Health (UL1TR001855).

Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the JTO Clinical and Research Reports at www.jtocrr.org and at https://doi.org/10.1016/j.jtocrr.2021.100186.

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