The Prognostic Impact of Lymph Node Dissection on Primary Tumor Resection for Stage IV Non–Small Cell Lung Cancer: A Population-Based Study

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Objective: Selected patients with stage IV non–small cell lung cancer (NSCLC) who underwent primary tumor resection have witnessed a survival benefit. Whether additional lymph node dissection (LND) would result in a better effect remain unknown. We investigated the prognostic impact of LND on patients with stage IV NSCLC who received primary tumor resection (PTR).

Methods: Patients with stage IV NSCLC who underwent PTR were identified from the Surveillance, Epidemiology, and End Results database from 2004 to 2016. Propensity-score matching was performed to minimize the confounding effect, and lung cancer-specific survival (CSS) and overall survival (OS) were compared after matching. Multivariable Cox regression was used to identify prognostic factors and to adjust for covariates in subgroup analysis. The effect of the number of lymph nodes examined on the CSS was evaluated by repeating the Cox analysis in a binary method.

Results: A total of 4,114 patients with stage IV NSCLC who receive surgery met our criteria, of which 2,622 (63.73%) underwent LND and 628 patients were identified 1:1 in LND and non-LND groups after matching. Compared with the non-LND group, the LND group had a longer CSS (median: 23 vs. 16 months, p < 0.001) and OS (median: 21 vs. 15 months, p < 0.001). Multivariable regression showed that LND was independently associated with favorable CSS [hazard ratio (HR) = 0.78, 95% confidence interval (CI) 0.69–0.89, P < 0.001] and OS (HR = 0.79, 95% CI 0.70–0.89, P < 0.001). Subgroup analysis suggested that LND is an independent favorable predictor to survival in the surgical patients who were older age (>60 years old), female, T3-4, N0, and M1a stage and those who underwent sublobar resection. In addition, a statistically significant CSS
survival gain from LND.

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to 55% of which were diagnosed as stage IV due to occult onset
(2). The National Comprehensive Cancer Network (NCCN)
guidelines recommend surgical intervention in select cases of
stage IV NSCLC with single brain or adrenal metastases but a
primary tumor is otherwise T1–2, N0–1 or T3, N0 (3).

Accumulating literatures suggesting that primary tumor
resection (PTR) could improve survival for patients with stage
IV NSCLC (4–7), particularly those with ipsilateral pleural
dissemination (8–15), synchronous bone metastasis (16, 17),
and extrathoracic oligometastatic (7, 18–20).

Systematic lymph node dissection (LND) or sampling during
lung resection was also recommended by the NCCN guidelines
for stages I–II and resectable stage IIIA NSCLC (3). From an
oncological point of view, it can decrease locoregional recurrence
and facilitate more accurate pathological staging for guiding
subsequent therapy, which is associated with a survival beneﬁt
(21, 22). It is assumed that LND may bring better survival in
patients with stage IV NSCLC who received surgery. However,
little clinical evidence supports this assumption. To explore this
issue, we performed a population-based study using the SEER
data, to investigate the prognostic effect of LND in patients with
stage IV NSCLC who received PTR, and tried to identify the
surgical patients’ characteristics that were associated with
survival gain from LND.

INTRODUCTION

Lung cancer is the leading cause of cancer-related death
worldwide (1). About 85% of lung cancer pathological type
was classiﬁed as non–small cell lung cancer (NSCLC), and up
to 55% of which were diagnosed as stage IV due to occult onset
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Statistical Analysis

The patients were divided into LND and non-LND groups
according to with or without LND during surgery (a binary
variable). The LND indicates that at least one regional lymph
node (LN) was examined without distinguishing between
systemic mediastinal or lobe-speciﬁc LND, whereas the non-LND
means no node examined. Propensity-score matching (PSM) was
used to balance baseline covariates. A logistic regression model
was built to calculate the propensity scores of the following covariates:
age, gender, histology, differentiation, tumor position, TNM stage,
metastatic site resection, and chemoradiotherapy. The caliper was
set at 0.01. The LND group was matched with the non-LND group
by 1:1 using the nearest propensity score without replacement.
Covariates were considered comparable when standardized mean
differences (SMDs) were below 0.10.

Cancer-speciﬁc survival (CSS) was deﬁned as the date of
diagnosis to the date of cancer-speciﬁc death, and overall survival
(OS) was the time from diagnosis to death from any cause; both
were estimated by the Kaplan–Meier method and compared with
the log-rank test between two groups. Multivariable Cox
proportional hazard regression model was constructed to
identify factors associated with CSS and OS and was applied
to adjust covariates in the subgroup analysis for exploring
whether LND would associate with survival beneﬁt in the

Cases of lung cancer (C34.0–34.9) diagnosed from 2004 to 2016
were extracted from the SEER database (SEER-Stat 8.3.6)
according to the site code classiﬁcations. This range was
selected because the American Joint Committee on Cancer
(AJCC) Tumor-Node-Metastasis (TNM) stage and
Collaborative Stage (CS) information was available since 2004,
and patients diagnosed after 2016 were excluded to ensure an
adequate follow-up time. Adult patients were included by
following criteria: 1) pathologically conﬁrmed NSCLC (the
major histologic subtypes of adenocarcinoma and squamous
cell carcinoma); 2) diagnosed as stage IV (the TNM stage was
reclassiﬁed to the AJCC eighth edition based on the accessible
information); and 3) diagnosed as the ﬁrst primary malignancy
in lifetime; 4) with one primary site and received the primary
tumor resection. Patients were excluded if: 1) information on
primary tumor position, TNM stage, surgical status, regional
nodes examined, survival month, or treatment modality was
unavailable; 2) the patients had T0 local disease.

Abbreviations: SEER, Surveillance, Epidemiology, and End Results; NSCLC, non–small cell lung cancer; PTR, primary tumor resection; LND, lymph node dissection; LNs, lymph nodes; CSS, cancer-speciﬁc survival; OS, overall survival; SLR, sublobar resection; PSM, propensity-score matching; IQR, interquartile range.
particular population. Multivariable regression included all variables with $p < 0.15$ in the univariable analysis.

The impact of the number of LNs examined was evaluated in a binary way by repeating the Cox proportional hazards regression model for variable adjustment as follows. Survival was incrementally compared between any patient with 0 to a certain number of LNs examined and those with greater than that specific number. The base reference was the whole cohort of non-LND. This accumulative method was explained (24). Hypothesis testing was conducted in two-sided with R software (version 3.6.1, https://cran.r-project.org/). A $p$-value of 0.05 was used to define significance and was presented without adjustment for multiplicity.

RESULTS

Baseline Characteristics
A design flow chart was shown (Supplementary Figure 1). Of all 4,114 eligible patients who underwent PTR, 2,622 (63.73%) were LND group. The distribution of LNs examined was shown [median: 7; interquartile range (IQR), 3 to 13] (Figure 1). In addition, 1,492 (36.27%) were non-LND groups. Distinctive differences in age, histology, differentiation, tumor position, TNM stage, surgical types, chemoradiotherapy, and metastasis site resection were noted between the two groups. In particular, LND was associated with a lower T/N descriptor, which indicated that the baseline characteristics of the two groups were not comparable. After the 1:1 PSM, 1,256 patients with stage IV NSCLC underwent with or without LND in surgery were enrolled in the survival analysis. Baseline characteristics showed balance (Table 1).

Impact of Lymph Node Dissection on Survival
In the matched cohort of stage IV NSCLC surgical patients, the LND group had significantly longer CSS and OS. The median CSS time of 23 months (IQR, 7–38) for the LND group versus 16 months (IQR, 5–31) for the non-LN resection group [HR = 0.78, 95% confidence interval (CI) 0.69–0.89, $P < 0.001$] (Figure 2A). The median OS was 21 months (IQR, 7–37) and 15 months (IQR, 5–31) in LND and non-LND groups, respectively (HR = 0.79, 95% CI 0.70–0.89, $P < 0.001$) (Figure 2B).

Lymph Node Dissection as an Independent Prognostic Factor
In the multivariable Cox analysis of the matched cohorts, LND was independently associated with improved CSS (HR = 0.78, 95% CI 0.69–0.90, $P < 0.001$) and OS (HR = 0.78, 95% CI 0.69–0.88, $P < 0.001$) in stage IV NSCLC surgical patients. Age, gender, TNM stage,
differentiation, surgery types, chemoradiotherapy, and metastatic sites resection were also independent prognostic factors (Table 2). We further explored whether LND was associated with survival benefits in specific subgroups of the surgical population. As a whole, both CSS (Figure 3A) and OS (Figure 3B) showed similar results in corresponding subgroups. The potential favorable features for the surgical patients who received LND included: old (>60 years old), females, T3-4, N0, M1a, and sublobar resection (SLR).

**Prognosis of Each Additional Lymph Node Examination**

Cox proportional hazards regression model was performed to determine the adjusted mortality benefit of examining every additional LN. A statistically significant CSS benefit was associated with each additional LN examined through 25 LNs, which suggests that higher volume of examined LNs in stage IV NSCLC surgical patients might improve survival (Figure 4).

**TABLE 1** | Baseline characteristics for patients with Stage IV NSCLC before and after PSM.

|                      | Before PSM | SMD | After PSM | SMD |
|----------------------|------------|-----|-----------|-----|
|                      | Non-LN dissection (n = 1,492) | LN dissection (n = 2,622) | Non-LN dissection (n = 628) | LN dissection (n = 628) |
| **Age**              |            |     |           |     |
| ≤60                  | 470 (31.5) | 908 (34.7) | 0.376 | 194 (30.9) | 215 (34.2) | <0.001 |
| 60–75                | 738 (49.5) | 1,333 (50.8) |            | 312 (49.7) | 312 (49.7) |     |
| >75                  | 284 (19.0) | 380 (14.5) |            | 122 (19.4) | 101 (16.1) |     |
| **Gender**           |            |     |           |     |
| Male                 | 746 (50.0) | 1,297 (49.5) | 0.742 | 325 (51.8) | 305 (48.6) | 0.032 |
| Female               | 746 (50.0) | 1,325 (50.5) |            | 303 (48.2) | 323 (51.4) |     |
| **Histology**        |            |     |           |     |
| Squamous carcinoma   | 182 (12.2) | 456 (17.4) | 0.053 | 91 (14.5) | 79 (12.6) | <0.001 |
| Adenocarcinoma       | 1,096 (73.5) | 1,695 (64.6) |            | 444 (70.7) | 428 (68.2) |     |
| Other                | 214 (14.3) | 471 (18.0) |            | 90 (14.8) | 121 (19.3) |     |
| **Differentiation**  |            |     |           |     |
| Well                 | 168 (11.3) | 203 (7.7) | <0.001 | 68 (10.8) | 69 (11.0) | <0.001 |
| Moderately           | 425 (28.5) | 834 (31.8) |            | 170 (27.1) | 149 (23.7) |     |
| Poorly               | 464 (31.3) | 1,183 (45.1) |            | 227 (36.1) | 252 (40.1) |     |
| Undifferentated      | 46 (3.1) | 104 (4.0) |            | 25 (4.0) | 27 (4.3) |     |
| Unknown              | 389 (26.1) | 296 (11.4) |            | 138 (22.0) | 131 (20.9) |     |
| **Position**         |            |     |           |     |
| Peribronchial        | 12 (0.8) | 27 (1.0) | 0.030 | 6 (1.0) | 7 (1.1) | 0.010 |
| Intralobar           | 1,217 (81.6) | 2,342 (89.3) |            | 521 (83.0) | 539 (85.8) |     |
| Both                 | 28 (1.9) | 85 (3.2) |            | 12 (1.9) | 12 (1.8) |     |
| Unknown              | 235 (15.8) | 168 (6.4) |            | 89 (14.2) | 70 (11.1) |     |
| **AJCC T status**    |            |     |           |     |
| T1                   | 237 (15.9) | 468 (17.8) | 0.183 | 117 (18.6) | 149 (23.7) | 0.051 |
| T2                   | 290 (19.4) | 1,069 (40.8) |            | 161 (25.6) | 129 (20.5) |     |
| T3                   | 281 (18.8) | 446 (17.0) |            | 108 (17.2) | 114 (18.2) |     |
| T4                   | 684 (45.8) | 639 (24.4) |            | 242 (38.5) | 236 (37.6) |     |
| **AJCC N status**    |            |     |           |     |
| N0                   | 822 (55.1) | 1,264 (48.2) | 0.297 | 342 (54.5) | 329 (52.4) | <0.001 |
| N1                   | 109 (7.3) | 519 (19.8) |            | 64 (10.2) | 68 (10.5) |     |
| N2                   | 431 (28.9) | 770 (29.4) |            | 183 (29.1) | 202 (32.2) |     |
| N3                   | 130 (8.7) | 69 (2.8) |            | 39 (6.2) | 31 (4.9) |     |
| **AJCC M status**    |            |     |           |     |
| M1a                  | 420 (28.2) | 485 (18.5) | 0.376 | 161 (25.6) | 144 (22.9) | <0.001 |
| M1b                  | 348 (23.3) | 679 (25.9) |            | 139 (22.1) | 131 (20.9) |     |
| M1                   | 724 (48.5) | 1,458 (55.6) |            | 328 (52.2) | 353 (56.2) |     |
| **Primary surgery**  |            |     |           |     |
| Sublobar resection   | 1,243 (83.3) | 523 (19.9) | 0.355 | 430 (68.5) | 416 (66.2) | 0.060 |
| Lobectomy            | 231 (15.5) | 1,814 (69.2) |            | 180 (28.7) | 191 (30.4) |     |
| Pneumonectomy        | 18 (1.2) | 285 (10.9) |            | 18 (2.9) | 21 (3.3) |     |
| **Radiation**        |            |     |           |     |
| No                   | 1,039 (69.6) | 1,569 (59.8) | 0.221 | 418 (66.6) | 399 (63.5) | <0.001 |
| Yes                  | 453 (30.4) | 1,053 (40.2) |            | 210 (33.4) | 229 (36.5) |     |
| **Chemotherapy**     |            |     |           |     |
| No/Unknown           | 500 (39.5) | 1,150 (43.9) | 0.110 | 268 (42.7) | 279 (44.4) | 0.010 |
| Yes                  | 902 (60.5) | 1,472 (56.1) |            | 360 (57.3) | 349 (55.6) |     |
| **Surgery to metastasis site** |            |     |           |     |
| No                   | 1,085 (72.7) | 1,576 (52.8) | 0.174 | 379 (60.4) | 371 (59.1) | <0.001 |
| Yes                  | 407 (27.3) | 1,406 (47.2) |            | 249 (39.6) | 257 (40.9) |     |

PSM, propensity score matching; NSCLC, non–small cell lung cancer; LN, lymph node; AJCC, American Joint Committee on Cancer.
DISCUSSION

It is now virtually universally accepted that there are subsets of patients with stage IV NSCLC who benefit from curative intent therapy, with surgery being done very selectively (5, 25). Studies suggested that PTR was associated with improved survival in patients with NSCLC with pleural carcinomatosis or extrathoracic metastatic, particularly for those with single-organ metastasis (7, 11, 14, 17, 19, 20). Further studies identified the specific group with <60 years old, female, adenocarcinoma, well differentiation, tumor site in lobe, T1-2, N0, and M1a that were potentially associated with more favorable survival (7, 26).

Systematic LND and sampling remains the standard part in surgical treatment to early and middle stage NSCLC, for that it could reduce local recurrence and guide subsequent therapy by determining the pathological stage, which could result in improved survival (27–29). For some reasons, few reports are concerned with the oncological benefit of LND in patients with advanced NSCLC with surgery. In clinical practice, the conduct of LND will be hindered by intraoperative adverse conditions such as LN adhesion, tissue edema, and complex anatomy for avoiding unexpected bleeding. Another more important reason is common sense holds that LND should not be a routine procedure in metastatic solid tumor patients.

The Lymph Nodes Dissection Effect

Whether LND would bring better outcomes in patients with advanced NSCLC who receive surgical treatment remains unknown. In this study, the clinical significance of LND in patients with stage IV NSCLC who underwent PTR was investigated using data from the SEER database. The results show that LND was an independent prognostic factor associated with improved survival, especially in the surgical patients who were older age (>60 years old), female, T3-4, N0, and M1a and those treated with SLR. In addition, a CCS benefit was associated with an increasing number of LNs examined through 25 LNs.

The possible reasons for LND that may have a survival benefit in stage IV NSCLC are as follows: 1.) LND eliminates tumor cells in draining LN regions as they could tip the balance against anti-tumor immune response and facilitate the spread of metastatic tumor cells (30); 2.) pathological LN metastasis with lymphatic invasion does present in clinically node-negative (N0), which is associated with increased rates of distant and LNs recurrence (31), and lymphadenectomy could stop latent self-seeding of primary tumor cells through lymphatic stations by clearing potential positive LNs; 3.) salvage surgery after targeted therapy could contribute to prolonged OS by reducing the local tumor burden (32), and LND may play a similar role in lymphatic nodes involved.

Lymph Nodes Dissection and Surgery

The LND was performed on the basis of surgery; therefore, the relation between LND and surgery is worth discussing. The previous studies showed that surgery was associated with more survival benefits in patients with stage IV NSCLC with lower T stage as T1-2 (26) compared with those with higher T, and lobectomy might have better survival versus SLR (33). This present study suggests LND might benefit stage IV NSCLC patients who underwent surgery with higher T stage like T3-4 and those who received SLR, as compared with the non-LND. We speculate that LND is complementary to surgery in survival, because the more advanced T stage (the larger tumor size) and the less excision (like SLR) would lead to the greater probability of occult lymphatic metastasis, which is associated with worse survival due to regional recurrence. Thus, the LND may bring survival benefit by the possible mechanism mentioned above. We suggest that when limited resection was applied to the larger primary tumors in patients with stage IV NSCLC for palliative or curative intent, the significance of LND should be more emphasized. This assumption is consistent with the finding in early-stage NSCLC. Studies revealed that greater extent of the LND should be done to larger primary tumor size during surgery in clinical stage I NSCLC regarding survival (24) and indicated that SLR with a more...
extensive lymphadenectomy was associated with equivalent survival with lobectomy in stage I tumors < 2 cm (34).

**The Volume of Lymph Nodes Examined**

Whether higher numbers of examined LNs in patients with stage IV NSCLC would improve survival is also worth discussing. A minimum of 10 examined LNs for dissection or sampling for T (1-3)N(0)M(0) NSCLC patients was recommended for better prognosis (35). The previous study found that a greater number of LNs examined are associated with more accurate node staging and better long-term survival in resected early-stage NSCLC and recommended the 16 LNs as the cutoff point for evaluating the quality of LN examination (36). In this study, we found similar

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**TABLE 2 | Multivariable analysis for lung cancer–specific survival in patients with NSCLC with surgery.**

| Characteristic      | Cancer-Specific Survival | Overall Survival |
|---------------------|--------------------------|------------------|
|                     | HR (95% CI)              | P Value          | HR (95% CI)              | P Value          |
| Age                 |                          |                  |                            |                  |
| <60                 | 1.00 (reference)         |                  | 1.00 (reference)         |                  |
| 60-75               | 1.22 (1.05–1.43)         | 0.012            | 1.23 (1.06–1.43)         | 0.007            |
| >75                 | 1.89 (1.55–2.31)         | <0.001           | 1.81 (1.49–2.20)         | <0.001           |
| Gender              |                          |                  |                            |                  |
| Male                | 1.00 (reference)         |                  | 1.00 (reference)         |                  |
| Female              | 0.69 (0.60–0.79)         | <0.001           | 0.70 (0.62–0.80)         | <0.001           |
| Histology           |                          |                  |                            |                  |
| Squamous carcinoma  | /                        |                  | 1.00 (reference)         |                  |
| Adenocarcinoma      | /                        |                  | 0.75 (0.62–0.90)         | 0.002            |
| Other               | /                        |                  | 0.97 (0.77–1.20)         | 0.754            |
| Differentiation     |                          |                  |                            |                  |
| Well                | 1.00 (reference)         |                  | 1.00 (reference)         |                  |
| Moderately          | 1.52 (1.16–2.00)         | 0.002            |                            |                  |
| Poorly              | 1.61 (1.24–2.09)         | <0.001           |                            |                  |
| Undifferentiated    | 1.73 (1.17–2.56)         | 0.006            |                            |                  |
| Unknown             | 1.55 (1.17–2.05)         | 0.002            |                            |                  |
| Position            |                          |                  |                            |                  |
| Peribronchial       | 1.00 (reference)         |                  | 1.00 (reference)         |                  |
| Intralobar          | 1.31 (0.67–2.56)         | 0.437            | 1.43 (0.76–2.71)         | 0.27             |
| Both                | 2.54 (1.13–5.71)         | 0.024            | 2.68 (1.24–5.80)         | 0.012            |
| Unknown             | 1.33 (0.66–2.67)         | 0.419            | 1.44 (0.75–2.79)         | 0.278            |
| AJCC T status       |                          |                  |                            |                  |
| T1                  | 1.00 (reference)         |                  | 1.00 (reference)         |                  |
| T2                  | 1.16 (0.95–1.43)         | 0.154            | 1.09 (0.90–1.32)         | 0.368            |
| T3                  | 1.26 (1.00–1.60)         | 0.054            | 1.29 (1.04–1.61)         | 0.022            |
| T4                  | 1.34 (1.10–1.62)         | 0.003            | 1.35 (1.13–1.61)         | 0.001            |
| AJCC N status       |                          |                  |                            |                  |
| N0                  | 1.00 (reference)         |                  | 1.00 (reference)         |                  |
| N1                  | 1.60 (1.25–1.95)         | <0.001           | 1.48 (1.19–1.83)         | <0.001           |
| N2                  | 1.51 (1.30–1.78)         | <0.001           | 1.53 (1.32–1.78)         | <0.001           |
| N3                  | 1.72 (1.28–2.29)         | <0.001           | 1.78 (1.34–2.36)         | <0.001           |
| AJCC M status       |                          |                  |                            |                  |
| M1a                 | 1.00 (reference)         |                  | 1.00 (reference)         |                  |
| M1b                 | 1.34 (1.07–1.68)         | 0.01             | 1.42 (1.15–1.78)         | 0.001            |
| M1                  | 1.31 (1.09–1.59)         | 0.005            | 1.35 (1.12–1.62)         | 0.001            |
| Primary surgery     |                          |                  |                            |                  |
| Sublobectomy        | 1.00 (reference)         |                  | 1.00 (reference)         |                  |
| Lobectomy           | 0.70 (0.60–0.82)         | <0.001           | 0.69 (0.60–0.80)         | <0.001           |
| Pneumonectomy       | 0.49 (0.33–0.74)         | 0.001            | 0.44 (0.29–0.64)         | <0.001           |
| Lymph node dissection|                         |                  |                            |                  |
| No                  | 1.00 (reference)         |                  | 1.00 (reference)         |                  |
| Yes                 | 0.78 (0.69–0.90)         | <0.001           | 0.78 (0.69–0.88)         | <0.001           |
| Radiation           |                          |                  |                            |                  |
| No                  | 1.00 (reference)         |                  | 1.00 (reference)         |                  |
| Yes                 | 1.44 (1.24–1.67)         | <0.001           | 1.50 (1.30–1.73)         | <0.001           |
| Chemotherapy        |                          |                  |                            |                  |
| No                  | /                        |                  | 1.00 (reference)         |                  |
| Yes                 | /                        |                  | 0.74 (0.64–0.84)         | <0.001           |
| Surgery to metastasis site |             |                  |                            |                  |
| No                  | 1.00 (reference)         |                  | 1.00 (reference)         |                  |
| Yes                 | 0.77 (0.69–0.94)         | <0.001           | 0.76 (0.70–0.85)         | <0.001           |

*PSM, propensity score matching; NSCLC, non–small cell lung cancer; LN, lymph node; AJCC, American Joint Committee on Cancer.*
results in stage IV NSCLC and suggested that the increasing number of LNs examined in a range of 1 to 25 nodes was associated with survival benefits. These findings show the efficacy of LNs numbers management not only in the early-stage NSCLC but also in the advanced NSCLC.

**Limitations**

Although this study supports the clinical efficacy of LND in stage IV NSCLC surgery patients, the results should be interpreted with caution for several limitations. 1.) It is not clear what criteria were used for selecting patients with stage IV NSCLC for surgery with or...
CONCLUSION

This study shows that LND with a certain range of lymph nodes number examined is associated with improved survival of patients with stage IV NSCLC who receive primary tumor resection, particularly in those who were older (>60 years old), female, T3-4, N0, and M1a stage and those underwent SLR, as compared with non-LND. We suggest that when surgery was indicated in patients with stage IV NSCLC, the significance of LND should be emphasized. The results may have implications for guidelines on lymph nodes management in selective advanced NSCLC for surgery.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

YDZ and ZC contributed to the study design. YCZ and YDZ contributed to data analysis and interpretation. YCZ, YDZ, KD, XC, and BX contributed to data collection. All authors contributed to the drafting of the article and to its revisions. All authors contributed to the article and approved the submitted version.

ACKNOWLEDGMENTS

We thank all the staffs who work with the Surveillance, Epidemiology, and End Results program in the National Cancer Institute. We thank Dr. Liang for guidance of study design and data analysis.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2022.853257/full#supplementary-material

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