The Independent Prognostic Effect of Lymph Node Dissection on Patients With Stage IA NSCLC With Different T Stages

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Background: Currently, the extent of lymph node evaluation necessary for patients with early-stage non-small-cell lung cancer (NSCLC) remains controversial according to the latest ESMO and NCCN guidelines. In this study, we aimed to evaluate the survival effect of different numbers of lymph nodes examined (LNE) and regions of lymph nodes removed (LNR) in patients with stage IA NSCLC.

Method: All patients with stage IA NSCLC undergoing lobectomy or bilobectomy were selected from the surveillance, epidemiology, and end results (SEER) database. The number of LNE and LNR were stratified into 4 groups (0, 1–2, 3–8, and ≥ 9 lymph nodes) and 3 groups (0, 1–3, and ≥ 4 regions) respectively. Additionally, the survival curves of overall survival (OS) and cancer-specific survival (CSS) were plotted and compared with the Kaplan-Meier method and log-rank test. Independent prognostic clinicopathological factors were evaluated via Cox proportional hazard regression and subgroup analysis.

Results: Totally, 12,490 patients with stage IA NSCLC were enrolled in our study. Patients with ≥ 9 LNE and ≥ 4 LNR in both the T1b and T1c stages consistently demonstrated the significantly best OS and CSS outcomes. In the multivariate analysis, patients with ≥ 9 LNE consistently had a significantly better CSS [hazards ratio (HR) (95% CI):0.539 (0.438–0.663)], and those with ≥ 4 LNR consistently had a significantly better OS [HR (95% CI):0.678 (0.476–0.966)]. Furthermore, ≥ 9 LNE and ≥ 4 LNR were associated with better survival in most subgroups.

Conclusion: This study demonstrated that ≥ 9 LNE and ≥ 4 LNR are highly recommended for stage IA2 and stage IA3 patients but optional for stage IA1 patients.

Keywords: non-small cell lung cancer (NSCLC), lymph node dissection, prognosis, X-tile software, surveillance, epidemiology and end results (SEER) database
INTRODUCTION

Lung cancer is currently one of the most common and deadliest cancers in the world (1). Non-small-cell lung cancer (NSCLC) is the most common subtype and accounts for almost 85% of all lung cancer cases (2). Currently, the AJCC eighth edition TNM stage has been the basis for the choice of NSCLC treatment. According to the ESMO and NCCN guidelines for NSCLC, lobectomy is still the standard treatment for stage I NSCLC. However, for the management of lymph nodes during surgery, the choice between systematic lymphadenectomy (LA) and lymph node sampling (LS) remains unclear (3, 4). The International Association for the Study of Lung Cancer (IASLC) defined systematic nodal dissection, which had excision of ≥6 lymph nodes and ≥3 nodal stations, including the subcarinal station (5).

In a prospective study during the 1990s, the difference in survival benefit between LA and LS was not observed in NSCLC patients with pN0 (6). Additionally, the same conclusion was supported by the results of the American College of Surgery Oncology Group (ACOSOG) Z0030 Trial (7). However, another previous study during the 2000s oppositely confirmed that LA was associated with better survival than LS in stage I NSCLC patients (8). The ESTS guidelines in 2006 also recommended LA in NSCLC patients (9). Beyond that, the positive influence of more lymph nodes sampled on survival in stage I NSCLC patients was confirmed (10, 11). Therefore, the prognostic effects of the number of lymph nodes examined (LNE) and scope of regional lymph nodes removed (LNR) in patients with stage IA NSCLC are still unclear and need to be solved.

In this study, we performed a retrospective population-based analysis of the surveillance, epidemiology, and end results (SEER) cancer database and aimed to assess the prognostic effect of LNE and LNR in patients with stage IA NSCLC who underwent anatomic pulmonary resection. Moreover, we used the AJCC eighth edition TNM stage as the basis for staging NSCLC in our study, which has not been used in previous studies.

METHODS

Patient Selection

The SEER database is funded by the Nation Cancer Institute and covers approximately 28% of the United States population (12). Therefore, it is a comprehensive and representative source of demographic, clinicopathological, and survival information from many kinds of cancer patients. According to the guidelines of the SEER database, permission to use the data was obtained (reference number 14,683-Nov2019). For the further analysis of the T stage, we needed to divide the T stage into three groups (T1a, T1b, and T1c) according to the eighth edition (AJCC) American Joint Committee on Cancer TNM stage. For the SEER database, the latest T stage classification can only be inferred from the variable “CS TUMOR SIZE (2004–2015),” which is only available for patients diagnosed between 2004 and 2015. Therefore, all patients with stage IA NSCLC diagnosed between 2004 and 2015 were selected from the SEER database.

The specific inclusion criteria were as follows: (1) patients diagnosed with only one primary lung cancer (ICD-O-3 primary site codes: C340-343 and C348-349); (2) patients diagnosed with NSCLC (ICD-O-3 histology code: large cell carcinoma 8012–8014; adenocarcinoma 8140–8147, 8250–8255, 8310, 8333, 8470, 8480, 8481, 8490, 8550, and 8551; squamous cell carcinoma 8052, 8070–8078, and 8083; and adenosquamous cell carcinoma 8560); (3) T stage classified into four groups (0, 1–2, 3–8, and ≥9); (4) patients treated with lobectomy and lymph node sampling (LS); and (5) patients with positive histological or immunohistochemical diagnosis.

The exclusion criteria were as follows: (1) patients diagnosed with autopsy; (2) patients without complete demographic and clinicopathological information; (3) patients without a record of chemotherapy and radiotherapy; (4) patients without complete survival states and time; (5) patients without the scope of lymph nodes removed and the number of lymph nodes examined; (6) patients with a follow-up time of <1 month.

Statistical Analysis

In our study, we used the National Cancer Institute’s SEER*Stat software [version 8.3.6; SEER 18 Regs Custom Data (with additional treatment fields), November 2018 Sub (1975–2016 varying) database]. Age, gender, race, histology, grade, T stage (AJCC eighth edition), number of LNE, the scope of regional LNR, chemotherapy, and radiotherapy were included as possible confounding factors. Additionally, overall survival (OS) and cancer-specific survival (CSS) were used as prognostic indicators. Before the statistical analyses, stratified cut-off points of the number of lymph nodes examined were determined by using X-tile software (version 3.6.1) (13). Consequently, the number of lymph nodes examined was classified into four groups (0, 1–2, 3–8, and ≥9). Additionally, the LNR has been classified into 3 groups (0, 1–3, and ≥4 regions) which was set up by the SEER database. All related demographic and clinicopathological characteristics were presented as numbers and percentages. Associations between T stage groups and demographic and clinicopathological characteristics were analyzed by Pearson’s chi-square test, which was similarly used to identify the correlation between LNE and LNR. Survival curves were generated by the Kaplan-Meier method and compared by log-rank tests. Furthermore, Cox proportional hazards ratio regression models were performed to assess the influence of all variables on OS and CSS by using forward stepwise methods for both univariate and multivariate analysis.

A two-tailed p-value < 0.05 was considered statistically significant. All statistical analysis was conducted using SPSS (version 26.0; IBM Corporation, Armonk, NY, USA) and R (version 3.6.3; R Development Core Team, http://www.r-project.org).
TABLE 1 | Clinicopathological characteristics of NSCLC patients in the SEER database.

| Variable                        | Total (n = 12,490) | T1a (n = 1,074, 8.6%) | T1b (n = 6,353, 50.9 %) | T1c (n = 5,063, 40.5%) | P value |
|---------------------------------|--------------------|-----------------------|-------------------------|------------------------|---------|
| Age                             |                    |                       |                         |                        |         |
| <70                             | 7,281 (58.3%)      | 705 (65.6%)           | 3,867 (60.9%)           | 2,709 (53.5%)          | P < 0.001 |
| ≥70                             | 5,209 (41.7%)      | 369 (34.4%)           | 2,486 (39.1%)           | 2,354 (46.5%)          |         |
| Gender                          |                    |                       |                         |                        |         |
| Male                            | 5,276 (42.2%)      | 384 (35.8%)           | 2,614 (41.1%)           | 2,278 (45.0%)          | P < 0.001 |
| Female                          | 7,214 (57.8%)      | 690 (64.2%)           | 3,739 (58.9%)           | 2,785 (55.0%)          |         |
| Race                            |                    |                       |                         |                        |         |
| White                           | 10,490 (84.0%)     | 929 (86.5%)           | 5,350 (84.2%)           | 4,211 (83.2%)          | P = 0.048 |
| Black                           | 1,031 (8.3%)       | 83 (7.7%)             | 510 (8.0%)              | 438 (8.7%)             |         |
| Other                           | 969 (7.8%)         | 62 (5.8%)             | 493 (7.8%)              | 414 (8.2%)             |         |
| Histology                       |                    |                       |                         |                        |         |
| ADC                             | 9,046 (72.4%)      | 821 (76.4%)           | 4,767 (75.0%)           | 3,458 (68.3%)          | P < 0.001 |
| SCC                             | 2,925 (23.4%)      | 224 (20.9%)           | 1,347 (21.2%)           | 1,354 (26.7%)          |         |
| LCC                             | 265 (2.1%)         | 20 (1.9%)             | 114 (1.8%)              | 131 (2.6%)             |         |
| ASC                             | 254 (2.0%)         | 9 (0.8%)              | 125 (2.0%)              | 120 (2.4%)             |         |
| Grade                           |                    |                       |                         |                        |         |
| Well differentiated             | 2,925 (23.4%)      | 388 (36.1%)           | 1,534 (24.1%)           | 1,003 (19.8%)          | P < 0.001 |
| Modestly differentiated         | 6,104 (48.9%)      | 461 (42.9%)           | 3,176 (50.0%)           | 2,467 (48.7%)          |         |
| Poorly differentiated           | 3,316 (26.5%)      | 219 (20.4%)           | 1,582 (24.9%)           | 1,515 (29.9%)          |         |
| Undifferentiated                | 145 (1.2%)         | 6 (0.6%)              | 125 (2.0%)              | 120 (2.4%)             |         |
| The number of lymph nodes examined |                |                       |                         |                        |         |
| 0                               | 376 (3.0%)         | 38 (3.5%)             | 190 (3.0%)              | 148 (2.9%)             | P = 0.357 |
| 1–2                            | 1,223 (9.8%)       | 107 (10.0%)           | 647 (10.2%)             | 469 (9.3%)             |         |
| 3–8                            | 5,628 (45.1%)      | 477 (44.4%)           | 2,892 (45.5%)           | 2,259 (44.6%)          |         |
| ≥9                             | 5,263 (42.1%)      | 452 (42.1%)           | 2,624 (41.3%)           | 2,187 (43.2%)          |         |
| The scope of regional lymph nodes removed |             |                       |                         |                        | P = 0.376 |
| 0 region                       | 349 (2.8%)         | 36 (3.4%)             | 183 (2.9%)              | 130 (2.6%)             |         |
| 1–3 regions                    | 2,194 (17.6%)      | 203 (18.9%)           | 1,115 (17.6%)           | 876 (17.3%)            |         |
| ≥4 regions                     | 9,947 (79.6%)      | 835 (77.7%)           | 5,055 (79.6%)           | 4,057 (80.1%)          |         |
| Chemotherapy                    |                    |                       |                         |                        | P < 0.001 |
| No                             | 12,055 (96.5%)     | 1,046 (97.4%)         | 6,177 (97.2%)           | 4,832 (95.4%)          |         |
| Yes                            | 435 (3.5%)         | 28 (2.6%)             | 176 (2.8%)              | 231 (4.6%)             |         |
| Radiotherapy                    |                    |                       |                         |                        | P = 0.001 |
| No                             | 12,270 (98.2)      | 1,059 (98.6%)         | 6,285 (98.6%)           | 4,946 (97.7%)          |         |
| Yes                            | 220 (1.8%)         | 15 (1.4%)             | 88 (1.4%)               | 117 (2.3%)             |         |

ADC, Adenocarcinoma; SCC, Squamous cell carcinoma; LCC, Large Cell Carcinoma; ASC, Adenosquamous carcinoma.

RESULTS

Demographic and Clinicopathological Characteristics of the Patients

A total of 12,490 patients with stage IA NSCLC were enrolled in our study, among which 1,074 (8.6%), 6,353 (50.9%), and 5,063 (40.5%) patients were diagnosed with T1a, T1b, and T1c disease, respectively. Detailed information about demographic and clinicopathological characteristics is shown in Table 1 (stratified by T stage). The chi-square test confirmed that patients with different T stages had significant differences in age (P < 0.001), gender (P < 0.001), race (P = 0.048), histology (P < 0.001), grade (P < 0.001), chemotherapy (P < 0.001), and radiotherapy (P = 0.001). However, there was no significant difference in either the number of LNE (P = 0.357) or the scope of regional LNR (P = 0.376). Furthermore, there was a significant correlation between the number of LNE and the scope of regional LNR, with P < 0.001 and Pearson’s R = 0.698 (Table 2).

Survival Analysis

The median OS for patients with stage IA NSCLC who underwent lobectomy or bilobectomy according to the number of LNE was 77 months for 0 LNE, 107 months for 1–2 LNE, 122 months for 3–8 LNE, and 139 months for ≥9 LNE. Moreover, the difference in OS was significant (P < 0.001). Although the median CSS in
TABLE 2 | The correlation between the number of lymph nodes examined and the scope of regional lymph nodes removed.

| Variable                              | Total (n = 12,490) | The scope of regional lymph nodes removed | P value |
|---------------------------------------|--------------------|------------------------------------------|---------|
|                                       | (n = 349, 2.8%)    | (n = 2,194, 17.6%)                        |         |
| ≥4 regions                            | 5,263 (42.1%)      | 14 (0.6%)                                | 9 (2.6%) | 30 (1.4%) | 5,224 (52.5%) | 0.001 |
| 1–2 regions                           | 1,223 (9.8%)       | 8 (2.3%)                                 | 1,185 (44.0%) | 30 (0.3%) |
| 0 region                              | 376 (3.0%)         | 965 (44.0%)                              | 4,641 (46.7%) |

In early-stage NSCLC patients, there is still controversy regarding the management of lymph nodes. In the randomized ACOSOG Z0030 trial, there was no significant survival difference...
| Variable                              | Overall survival | Cancer specific survival |
|---------------------------------------|------------------|-------------------------|
|                                       | Univariate       | Multivariate            | Univariate       | Multivariate      |
|                                       | Hazard ratio (95%CI) | P value | Hazard ratio (95%CI) | P value | Hazard ratio (95%CI) | P value | Hazard ratio (95%CI) | P value |
| **Age**                               |                  |                      |                |                |                        |          |                        |          |
| < 70                                  | Reference        |                      | 1.907 (1.790–2.031) | < 0.001 | Reference            |          | 1.479 (1.373–1.633) | < 0.001 |
| ≥ 70                                  | Reference        |                      | 1.883 (1.766–2.007) | < 0.001 | Reference            |          | 1.524 (1.396–1.665) | < 0.001 |
| **Gender**                            |                  |                      |                |                |                        |          |                        |          |
| Male                                  | Reference        |                      | 0.650 (0.610–0.692) | < 0.001 | Reference            |          | 0.716 (0.657–0.781) | < 0.001 |
| Female                                | Reference        |                      | 0.702 (0.659–0.748) | < 0.001 | Reference            |          | 0.777 (0.712–0.849) | < 0.001 |
| **Race**                              |                  |                      |                |                |                        |          |                        |          |
| White                                 | Reference        |                      | 1.008 (0.988–1.131) | = 0.898 | Reference            |          | 1.166 (1.004–1.354) | < 0.001 |
| Black                                 | Reference        |                      | 1.060 (0.944–1.191) | < 0.001 | Reference            |          | 1.165 (1.002–1.354) | P = 0.047 |
| Other                                 | Reference        |                      | 0.635 (0.547–0.738) | < 0.001 | Reference            |          | 0.699 (0.573–0.852) | < 0.001 |
| **Histology**                         |                  |                      |                |                |                        |          |                        |          |
| ADC                                   | Reference        |                      | 1.724 (1.609–1.846) | < 0.001 | Reference            |          | 1.387 (1.256–1.531) | < 0.001 |
| SCC                                   | Reference        |                      | 1.278 (1.189–1.375) | < 0.001 | Reference            |          | 1.017 (0.917–1.128) | P = 0.748 |
| LCC                                   | Reference        |                      | 1.562 (1.281–1.905) | < 0.001 | Reference            |          | 1.468 (1.134–1.899) | P = 0.004 |
| ASC                                   | Reference        |                      | 1.203 (0.981–1.474) | = 0.076 | Reference            |          | 1.021 (0.766–1.360) | P = 0.888 |
| **Grade**                             |                  |                      |                |                |                        |          |                        |          |
| Well differentiated                   | Reference        |                      | 1.856 (1.687–2.042) | < 0.001 | Reference            |          | 2.127 (1.850–2.446) | < 0.001 |
| Moderately differentiated             | Reference        |                      | 1.931 (1.736–2.148) | < 0.001 | Reference            |          | 2.930 (2.537–3.385) | < 0.001 |
| Poorly differentiated                 | Reference        |                      | 2.390 (2.184–3.103) | < 0.001 | Reference            |          | 3.144 (2.225–4.443) | < 0.001 |
| Undifferentiated                      | Reference        |                      | 1.496 (1.108–2.019) | < 0.001 | Reference            |          | 1.930 (1.296–2.576) | P = 0.001 |
| **T stage**                           |                  |                      |                |                |                        |          |                        |          |
| 1a                                    | Reference        |                      | 1.221 (1.071–1.393) | = 0.003 | Reference            |          | 1.319 (1.089–1.596) | P = 0.005 |
| 1b                                    | Reference        |                      | 1.174 (1.029–1.339) | = 0.017 | Reference            |          | 1.254 (1.036–1.518) | P = 0.020 |
| 1c                                    | Reference        |                      | 1.416 (1.241–1.616) | < 0.001 | Reference            |          | 1.638 (1.354–1.983) | < 0.001 |
| **The number of lymph nodes examined**|                  |                      |                |                |                        |          |                        |          |
| 0                                     | Reference        |                      | 0.724 (0.610–0.858) | < 0.001 | Reference            |          | 0.681 (0.5420.856)  | < 0.001 |
| 1–2                                   | Reference        |                      | 0.999 (0.700–1.425) | < 0.001 | Reference            |          | 0.734 (0.583–0.923) | P = 0.008 |
| 3–8                                   | Reference        |                      | 0.910 (0.646–1.281) | < 0.001 | Reference            |          | 0.627 (0.511–0.769) | < 0.001 |
| ≥ 9                                   | Reference        |                      | 0.829 (0.587–1.172) | < 0.001 | Reference            |          | 0.539 (0.438–0.663) | P < 0.001 |
| **The scope of lymph nodes removed**  |                  |                      |                |                |                        |          |                        |          |
| 0 region                              | Reference        |                      | 0.681 (0.577–0.803) | < 0.001 | Reference            |          | 0.648 (0.519–0.808) | < 0.001 |
| 1–3 regions                           | Reference        |                      | 0.743 (0.520–1.062) | P = 0.103 | Reference            |          | 1.392 (1.152–1.682) | P = 0.001 |
| ≥ 4 regions                           | Reference        |                      | 0.678 (0.476–0.966) | < 0.001 | Reference            |          | 1.392 (1.152–1.682) | P = 0.001 |
| **Chemotherapy**                      |                  |                      |                |                |                        |          |                        |          |
| No                                    | Reference        |                      | 1.385 (1.201–1.598) | < 0.001 | Reference            |          | 2.108 (1.787–2.487) | < 0.001 |
| Yes                                   | Reference        |                      | 2.511 (2.113–2.985) | < 0.001 | Reference            |          | 3.023 (2.428–3.763) | < 0.001 |
| **Radiotherapy**                      |                  |                      |                |                |                        |          |                        |          |
| No                                    | Reference        |                      | 2.764 (2.329–3.280) | < 0.001 | Reference            |          | 4.232 (3.491–5.129) | < 0.001 |
| Yes                                   | Reference        |                      | 2.511 (2.113–2.985) | < 0.001 | Reference            |          | 3.023 (2.428–3.763) | < 0.001 |

ADC, Adenocarcinoma; SCC, Squamous cell carcinoma; LCC, Large Cell Carcinoma; ASC, Adenosquamous carcinoma.
FIGURE 1 | Kaplan-Meier survival curves of the number of lymph nodes examined in IA non-small cell lung cancer (NSCLC) patients who underwent lobectomy or bilobectomy. Overall survival comparison among 0, 1–2, 3–8, and ≥9 lymph nodes examined in stage IA (A) NSCLC patients including T1a (C), T1b (E), and T1c (G). Cancer-specific survival comparison among 0, 1–2, 3–8, and ≥9 lymph nodes examined in stage IA (B) NSCLC patients including T1a (D), T1b (F), and T1c (H).
FIGURE 2 | Kaplan-Meier survival curves of the scope of regional lymph nodes removed in IA non-small cell lung cancer (NSCLC) patients who underwent lobectomy or bilobectomy. Overall survival comparison among 0, 1–3, and ≥4 regions of lymph nodes removed in stage IA (A) NSCLC patients including T1a (C), T1b (E), and T1c (G). Cancer-specific survival comparison among 0, 1–3, and ≥4 regions of lymph nodes removed in stage IA (B) NSCLC patients including T1a (D), T1b (F), and T1c (H).
TABLE 4 | Multivariate analysis of overall survival and cancer-specific survival without the number of lymph nodes examined.

| Variable                      | Overall survival | Cancer specific survival |
|-------------------------------|------------------|-------------------------|
|                               | Hazard ratio (95%CI) | P value | Hazard ratio (95%CI) | P value |
| Age                           |                  |           |                      |         |
| <70                           | Reference        |           | Reference            |         |
| ≥70                           | 1.884 (1.767–2.008) | p < 0.001 | 1.526 (1.397–1.667) | p < 0.001 |
| Gender                        |                  |           |                      |         |
| Male                          | Reference        |           | Reference            |         |
| Female                        | 0.701 (0.658–0.747) | p < 0.001 | 0.775 (0.710–0.848) | p < 0.001 |
| Race                          |                  |           |                      |         |
| White                         | Reference        |           | Reference            |         |
| Black                         | 1.069 (0.952–1.200) | P = 0.261 | 1.178 (1.014–1.369) | P = 0.033 |
| Other                         | 0.636 (0.548–0.739) | p < 0.001 | 0.701 (0.575–0.856) | p < 0.001 |
| Histology                     |                  |           |                      |         |
| ADC                           | Reference        |           | Reference            |         |
| SCC                           | 1.277 (1.187–1.373) | p < 0.001 | 1.017 (0.917–1.128) | P = 0.753 |
| LCC                           | 1.574 (1.291–1.919) | p < 0.001 | 1.507 (1.164–1.949) | p = 0.002 |
| ASC                           | 1.195 (0.975–1.465) | P = 0.086 | 1.003 (0.753–1.336) | P = 0.984 |
| Grade                         |                  |           |                      |         |
| Well differentiated           | Reference        |           | Reference            |         |
| Moderately differentiated     | 1.636 (1.484–1.805) | < 0.001  | 1.986 (1.722–2.289) | p < 0.001 |
| Poorly differentiated         | 1.931 (1.736–2.148) | < 0.001  | 2.521 (2.165–2.934) | p < 0.001 |
| Undifferentiated              | 1.487 (1.102–2.006) | P = 0.010 | 1.880 (1.262–2.801) | P = 0.002 |
| T stage                       |                  |           |                      |         |
| 1a                            | Reference        |           | Reference            |         |
| 1b                            | 1.177 (1.031–1.342) | P = 0.016 | 1.261 (1.041–1.526) | P = 0.018 |
| 1c                            | 1.414 (1.293–1.614) | p < 0.001 | 1.642 (1.357–1.987) | p < 0.001 |
| The scope of lymph nodes removed |                        |           |                      |         |
| 0 region                      | Reference        |           | Reference            |         |
| 1–3 regions                   | 0.717 (0.607–0.847) | p < 0.001 | 0.677 (0.542–0.848) | P = 0.001 |
| ≥4 regions                    | 0.594 (0.508–0.695) | p < 0.001 | 0.552 (0.448–0.680) | p < 0.001 |
| Chemotherapy                  |                  |           |                      |         |
| No                            | Reference        |           | Reference            |         |
| Yes                           | 1.394 (1.154–1.684) | P = 0.001 |                     |         |
| Radiotherapy                  |                  |           |                      |         |
| No                            | Reference        |           | Reference            |         |
| Yes                           | 2.525 (2.125–3.001) | p < 0.001 | 3.060 (2.458–3.809) | p < 0.001 |

ADC, Adenocarcinoma; SCC, Squamous cell carcinoma; LCC, Large Cell Carcinoma; ASC, Adenosquamous carcinoma.

between systematic lymph node dissection and sampling in early-stage NSCLC patients (7). However, Wu et al. demonstrated in another randomized trial that the 5-year survival rate of mediastinal lymph node dissection was significantly better than that of mediastinal lymph node sampling (82.16% vs. 57.49%) in stage I NSCLC patients (15). In a retrospective study including 24,273 stage I NSCLC patients, Varlotto et al. consistently demonstrated that lymphadenectomy compared with no lymphadenectomy and more LNE were associated with significantly better OS and CSS (16). In addition, David et al. performed a retrospective study including 15,195 NSCLC patients and demonstrated a higher number of lymph nodes sampled with better OS and CSS in stage I patients (17). However, previous studies did not further study the difference among the extent of lymph node dissection in patients with stage IA NSCLC.

There are some important results from this study that is worthy of attention. First, most patients had more than 4 LNR (> 75%) and more than 3 LNE (> 85%) assessed, regardless of T stage (Table 1). This reflects the close attention given to the management of lymph nodes in early-stage NSCLC by thoracic surgeons. Second, more than 40% of patients had either 3–8 or ≥9 LNE, which indicated that the number of LNE remains controversial in early-stage NSCLC. At present, the ESMO and NCCN guidelines do not recommend a minimum number of LNE and LNR for patients with stage IA NSCLC (3, 4). According to previous studies, the positive prognostic effects of more extensive dissection have been demonstrated in...
TABLE 5 | Multivariate analysis of overall survival and cancer-specific survival without the scope of lymph nodes removed.

| Variable                  | Overall survival | Cancer specific survival |
|--------------------------|------------------|-------------------------|
|                          | Hazard ratio (95%CI) | P value | Hazard ratio (95%CI) | P value |
| Age                      |                  |           |                    |         |
| <70                      | Reference        |           | Reference          |         |
| ≥70                      | 1.881 (1.764–2.006) | p < 0.001 | 1.524 (1.396–1.665) | p < 0.001 |
| Gender                   |                  |           |                    |         |
| Male                     | Reference        |           | Reference          |         |
| Female                   | 0.702 (0.659–0.749) | p < 0.001 | 0.777 (0.712–0.849) | p < 0.001 |
| Race                     |                  |           |                    |         |
| White                    | Reference        |           | Reference          |         |
| Black                    | 1.059 (0.943–1.190) | P = 0.331 | 1.165 (1.002–1.354) | P = 0.047 |
| Other                    | 0.634 (0.546–0.737) | p < 0.001 | 0.699 (0.573–0.852) | p < 0.001 |
| Histology                |                  |           |                    |         |
| ADC                      | Reference        |           | Reference          |         |
| SCC                      | 1.277 (1.187–1.374) | p < 0.001 | 1.017 (0.917–1.128) | P = 0.746 |
| LCC                      | 1.540 (1.264–1.878) | p < 0.001 | 1.468 (1.134–1.899) | P = 0.004 |
| ASC                      | 1.211 (0.988–1.485) | P = 0.065 | 1.021 (0.766–1.360) | P = 0.888 |
| Grade                    |                  |           |                    |         |
| Well differentiated      | Reference        |           | Reference          |         |
| Moderately differentiated | 1.637 (1.485–1.806) | < 0.001 | 1.986 (1.723–2.290) | p < 0.001 |
| Poorly differentiated    | 1.933 (1.737–2.150) | < 0.001 | 2.526 (2.170–2.941) | p < 0.001 |
| Undifferentiated         | 1.519 (1.126–2.050) | P = 0.006 | 1.930 (1.296–2.876) | P = 0.001 |
| T stage                  |                  |           |                    |         |
| 1a                       | Reference        |           | Reference          |         |
| 1b                       | 1.171 (1.026–1.336) | P = 0.019 | 1.254 (1.036–1.518) | P = 0.020 |
| 1c                       | 1.412 (1.237–1.612) | p < 0.001 | 1.638 (1.354–1.983) | p < 0.001 |
| The number of lymph nodes examined |            |           |                    |         |
| 0                        | Reference        |           | Reference          |         |
| 1–2                      | 0.782 (0.659–0.928) | P = 0.005 | 0.734 (0.583–0.923) | P = 0.008 |
| 3–8                      | 0.662 (0.567–0.772) | p < 0.001 | 0.627 (0.511–0.769) | p < 0.001 |
| ≥4                       | 0.593 (0.508–0.693) | p < 0.001 | 0.539 (0.438–0.663) | p < 0.001 |
| Chemotherapy             |                  |           |                    |         |
| No                       | Reference        |           | Reference          |         |
| Yes                      | 1.392 (1.152–1.682) | P = 0.001 |                    |         |
| Radiotherapy             |                  |           |                    |         |
| No                       | Reference        |           | Reference          |         |
| Yes                      | 2.495 (2.099–2.965) | p < 0.001 | 3.023 (2.428–3.763) | p < 0.001 |

ADC, Adenocarcinoma; SCC, Squamous cell carcinoma; LCC, Large Cell Carcinoma; ASC, Adenosquamous carcinoma.

early-stage colon cancer (18), breast cancer (19), and gastric cancer (20). Additionally, Rucker et al. consistently demonstrated that the assessment of more lymph nodes was associated with better survival in pT1–2N0M0 small cell lung cancer (21). In our study, the lowest HR of OS and CSS existed in both ≥9 LNE and ≥4 LNR via univariate Cox proportional hazards regression analysis. However, ≥9 LNE only had a significant independent effect on CSS, and ≥4 LNR only had a significant independent effect on OS via multiple analyses (Table 2). The correlation between LNE and LNR can explain the outcome of multiple analyses, which demonstrated that the effect of LNE on OS may be caused by the LNR and that the effect of LNR on CSS may be caused by LNE (Tables 3–5). However, a significant effect of different LNE and LNR assessments on survival was not observed among stage IA1 NSCLC patients (Figures 1, 2). Thus, extensive lymph node dissection should be recommended for stage IA2 and IA3 NSCLC patients and is optimal for stage IA1 NSCLC patients. Third, chemotherapy and radiotherapy proved to be associated with significantly worse survival in patients with stage IA NSCLC by the Cox proportional hazards regression model, which was also demonstrated by a previous study (22). However, because of the small number of patients with stage IA NSCLC receiving chemotherapy and radiotherapy, the negative effect of
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FIGURE 3 | Survival (A) and cancer-specific survival (B) comparison among 0, 1–2, 3–8, and ≥9 lymph nodes examined in different clinicopathological subgroups analysis. Blue, yellow and purple boxes represent the hazard ratios (HRs) of 1–2, 3–8 and ≥9 lymph nodes examined respectively. The lines represent the 95% CI of HR.

Chemotherapy and radiotherapy still needs to be confirmed by randomized controlled trials.

There are some advantages to our study. First, we restaged the patients diagnosed between 2004 and 2015 according to the eighth edition TNM staging, which is recommended in the present guidelines (23). Second, all selected patients with stage IA NSCLC were treated with anatomic pulmonary resection, which is the standard therapy for this group of patients. Thus, the bias associated with different surgical procedures was eliminated. Third, we analyzed the effects of the number of LNE and the scope of LNR on patients with stage IA NSCLC with different T stages, which has not been simultaneously studied in previous studies. Fourth, we included many prognostic factors in the Cox proportional hazards regression model, including age, gender, race, histology, grade, T stage, chemotherapy, and radiotherapy. Ost et al.
previously demonstrated that demographic and pathological characteristics were associated with prognostic effects (24). Thus, radiotherapy and chemotherapy were included to further explore the effect of adjuvant therapy on patients with stage IA NSCLC. Fifth, the data of 12,490 patients with stage IA NSCLC were collected from the SEER database rather than from a single institute in order to yield more credible results to guide clinical practice.

However, there are also several limitations to our study. First, as this was a retrospective study, the methods of lymph node dissection were not available, and the chemotherapy and radiotherapy regimens were also unknown. Thus, the results from our study still need to be confirmed in randomized controlled trials. Second, Koike et al. demonstrated that age and tumor size were significant predictors of mediastinal lymph node metastasis in clinical patients with stage IA NSCLC.
NSCLC (25). However, the number of LNE in different nodal stations was not identified in our study, which indicated that there probably existed inadequate mediastinal lymph node dissection in patients with stage IA NSCLC. Additionally, the number of LNE in intrapulmonary and mediastinal lymph node stations could respectively have a prognostic effect on patients with stage IA NSCLC, which needs to be further explored.

CONCLUSION

This study contributes knowledge with the goal of resolving the existing controversy about extensive lymph nodes dissected in patients with stage IA NSCLC treated with standard curative anatomic pulmonary resection. Especially in the T1b and T1c subgroups, postoperative patients with more extensive lymph nodes dissected had significantly better OS and CSS.

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DATA AVAILABILITY STATEMENT

Publicly available datasets were analyzed in this study. This data can be found at: https://seer.cancer.gov/about/overview.html and the reference number was 14,683-Nov2019.

AUTHOR CONTRIBUTIONS

LZ, DZ, and RZ: conception and design. YL, YW, and LZ: administrative support. DZ, RZ, XZ, XY, and KX: provision of study materials or patients. DZ, RZ, GW, ZH, and LY: collection and assembly of data. DZ, RZ, WW, and GG: data analysis and interpretation. All authors wrote the manuscript and approved the final version of the manuscript.

ACKNOWLEDGMENTS

The authors sincerely thank all the staff of the SEER program for their important work and diligent effort.
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