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Comparison of recurrence risk between patients with clinically node-positive and -negative stage I non-small cell lung cancer following surgery: A propensity score matching analysis

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Abstract

Background: Identifying patients with stage I non-small cell lung cancer (NSCLC) at increased risk of tumor recurrence following surgery remains a major challenge. The current study aimed to compare disease-free survival (DFS) rates after surgery between patients with clinically node-positive (cN+) and -negative (cN0) stage I NSCLC.

Methods: Patients with pathological stage I resected NSCLC were identified from the lung cancer database of Changhua Christian Hospital in Taiwan. Patients with clinical N status 1 or 2 and pathological N status 0 were identified as the cN+/pN0 cohort, whereas others were identified as the cN0/pN0 cohort. Propensity score matching (PSM) was used to balance the baseline characteristics between both cohorts. Kaplan–Meier method and Cox proportional hazards model were used to evaluate DFS.

Results: From January 2010 to July 2019, 754 eligible patients were enrolled into the study, among whom 41 (5.4%) were cN+/pN0. The median follow-up time was 43.4 months. Before PSM, the 5-year DFS rate was 79.0% and 90.3% in cN+/pN0 and cN0/pN0 cohorts (log-rank test, $p = 0.009$), respectively. After a 1:4 PSM, multivariate analysis showed that the cN+/pN0 cohort still had a poorer DFS compared to the cN0/pN0 cohort in (hazard ratio, 3.17; $p = 0.040$).

Conclusion: Among patients with stage I resected NSCLC, cN+ patients had a worse DFS compared to cN0 patients. Surgeons should therefore consider more aggressive

Kuo-Yang Huang and Hung-Jen Chen are contributed equally as the first author.

adjuvant therapy or frequent follow-up in patients with surgically resected stage I NSCLC with cN+ status.

KEYWORDS
lymph node metastasis, non-small cell lung cancer, recurrence, staging, surgery

INTRODUCTION

Lung cancer is the leading cause of cancer-related mortality among both men and women worldwide.[1] Most lung cancers are non-small cell lung cancers (NSCLC). Surgical resection plays a vital role in the treatment of patients with early-stage NSCLC.[2] Although lobectomy has been generally accepted as an optimal procedure for early stage NSCLC, limited resection may be an option for patients who cannot tolerate a complete lobectomy due to severely compromised lung function, advanced age, or other extensive comorbidities. In general, patients with stage I NSCLC still experience a 33.9%–37.8% risk of recurrence after resection.[3] Although the TNM staging system of lung cancer has been widely used as a guide to predict the prognosis,[4] stage I NSCLC is considered as a heterogeneous group. For this reason, valuable parameters are needed to predict postoperative recurrence to determine treatment strategies, such as sublobar resection and additional perioperative systemic therapy.

The involvement of mediastinal lymph nodes is a critical prognostic factor in the planning of the treatment modality. The disparity in clinical and pathological N status may have a different influence on the risk of recurrence. Some studies have reported no significant difference in overall survival between patients who had upstaged pathological N2 disease (unsuspected N2) and those who had clinically and pathologically the same N2 disease after lobectomy for early-stage NSCLC.[5,6] In contrast, some studies demonstrated that false-positivity of mediastinal lymph nodes was independently associated with worse survival while including patients with stage I to III NSCLC.[7–10]

However, confounders that include the stage of the disease and adjuvant therapy for completely resected stage II and III NSCLC may still influence the survival analysis. The current study, therefore, aimed to compare the disease-free survival (DFS) after surgery between patients with cN+ and cN0 stage I NSCLC using a propensity matching cohort to minimize all confounders.

METHODS

Study participants

This study reviewed the prospectively maintained lung cancer database of Changhua Christian Hospital (Changhua, Taiwan) to identify consecutive patients who had undergone surgery for NSCLC between January 2010 and July 2019. The primary study group comprised patients with pathological stage I disease (clinical T1-2, N0-2, M0 according to the eighth edition of the American Joint Committee on Cancer classification) (Figure 1).[4,11] Preoperative lung cancer staging was performed according to international recommendations. All patients were initially staged using CT and PET/CT. cN1 was defined as the presence of ipsilateral peripheral, hilar, or intrapulmonary lymph nodes >10 mm in the short axis on CT or lymph node uptake exceeding that of the surrounding mediastinal tissue on PET/CT. Ipsilateral mediastinal metastatic adenopathy, including the upper, aortopulmonary, lower mediastinum, and subcarinal nodes, was considered cN2.[12] A multidisciplinary tumor board was convened to discuss the diagnosis, clinical status of N nodes, staging, and primary treatment every other week. The discussants included radiologists, medical and radiation oncologists, pathologists, nuclear medicine physician, pulmonary physicians, and thoracic surgeons with experience in endobronchial ultrasound. Our retrospective study protocol had been approved and the need for informed consent was waived by the Institutional

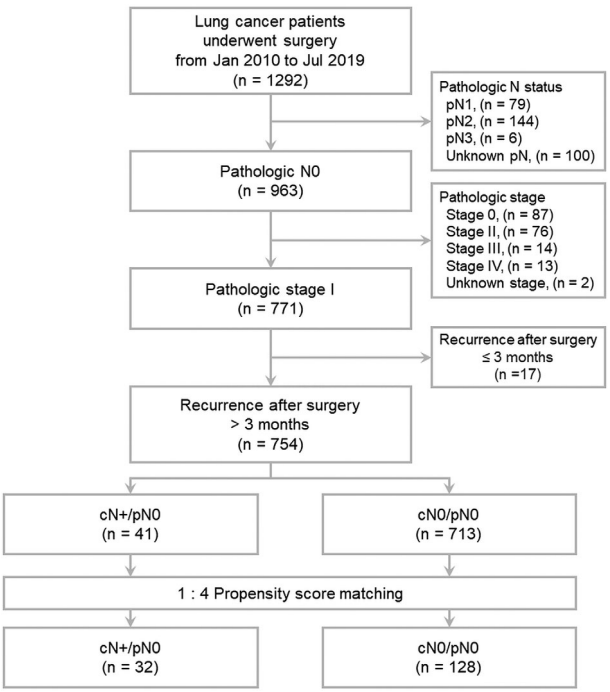

FIGURE 1 Flowchart of subject enrollment.

TABLE 1 Baseline characteristics of patients before and after matching

Variable	Before matching			After matching		
	cN0/pN0 ($n = 713$)	cN+/pN0 ($n = 41$)	*p*-value	cN0/pN0 ($n = 128$)	cN+/pN0 ($n = 32$)	*p*-value
Age, years (IQR)	64.0 (55.0–73.0)	67.0 (61.0–73.0)	0.124	66.0 (59.0–73.0)	66.5 (61.0–73.0)	0.896
Gender (%)			0.009			1.000
Male	304 (42.6)	26 (63.4)		68 (53.1)	17 (53.1)	
Female	409 (57.4)	15 (36.6)		60 (46.9)	15 (46.9)	
Histology (%)			<0.001			0.313
Adenocarcinoma	597 (83.7)	24 (58.5)		106 (82.8)	24 (75.0)	
Others	116 (16.3)	17 (41.5)		22 (17.2)	8 (25.0)	
pT status (%)			0.001			0.136
1a	160 (22.4)	2 (4.9)		15 (11.7)	2 (6.2)	
1b	192 (26.9)	4 (9.8)		34 (26.6)	4 (12.5)	
1c	133 (18.7)	10 (24.4)		22 (17.2)	10 (31.2)	
2	228 (32.0)	25 (61.0)		57 (44.5)	16 (50.0)	
cN status (%)			<0.001			<0.001
0	713 (100.0)	0		128 (100.0)	0	
1	0	24 (58.5)		0	21 (65.6)	
2	0	17 (41.5)		0	11 (34.4)	
Surgical procedure (%)			0.007			0.864
Lobectomy	386 (54.1)	31 (75.6)		90 (70.3)	22 (68.8)	
Others	327 (45.9)	10 (24.4)		38 (29.7)	10 (31.3)	
Adjuvant treatment (%)			0.261			0.510
No	544 (76.3)	27 (65.9)		95 (74.2)	21 (65.6)	
Adjuvant chemotherapy	162 (22.7)	13 (31.7)		32 (25.0)	11 (34.4)	
Others[a]	7 (1.0)	1 (2.4)		1 (0.8)	0 (0)	

Abbreviation: IQR, interquartile range.

[a]Including adjuvant radiotherapy and adjuvant chemoradiotherapy.

Review Board of Changhua Christian Hospital (approval no. 200503). All methods have been performed in accordance with the Declaration of Helsinki.

Patients with unknown pathological N status or stage and missing recurrence or survival data were excluded from the analysis. Patients who developed recurrence within 90 days after surgery were excluded considering that this suggested the presence of disseminated or circulating tumor cells at the time of surgery and underestimation of the actual tumor stage.[13] Data extracted for this study included age, sex, clinical and pathological TNM stage, histology, surgical procedure, neoadjuvant or adjuvant treatment. Surgical resection included lobectomy, wedge resection, segmentectomy, or pneumonectomy. Adjuvant treatment was defined as receiving multiagent therapy within 16 weeks of surgical resection and/or adjuvant radiation at a total radiation dose ≥45 Gray targeted to the lung or mediastinum within 16 weeks of surgical resection. The primary outcome measured was DFS, measured from the time of surgery to first recurrence, death, or last follow-up visit.

Propensity score matching

Propensity score matching (PSM) was herein used to reduce potential selection bias and imbalanced distributions of confounding factors.[14] Propensity scores were generated via logistic regression based on patient- and diseased-related variables determined to most likely be confounders. These variables included age, gender, histology, pathological T status, surgical procedure, and neoadjuvant or adjuvant treatment. PSM was performed using a 1:4 nearest neighbor matching with a caliper of 0.02 to accept a matched pair. The cN+/pN0 cohort refers to patients with a clinical N status of 1 or 2 and pathological N status of 0, whereas the cN0/pN0 cohort refers to those whose clinical and pathological N status was 0.

Statistical analysis

Continuous variables were expressed as medians and interquartile ranges (25th and 75th percentiles), whereas

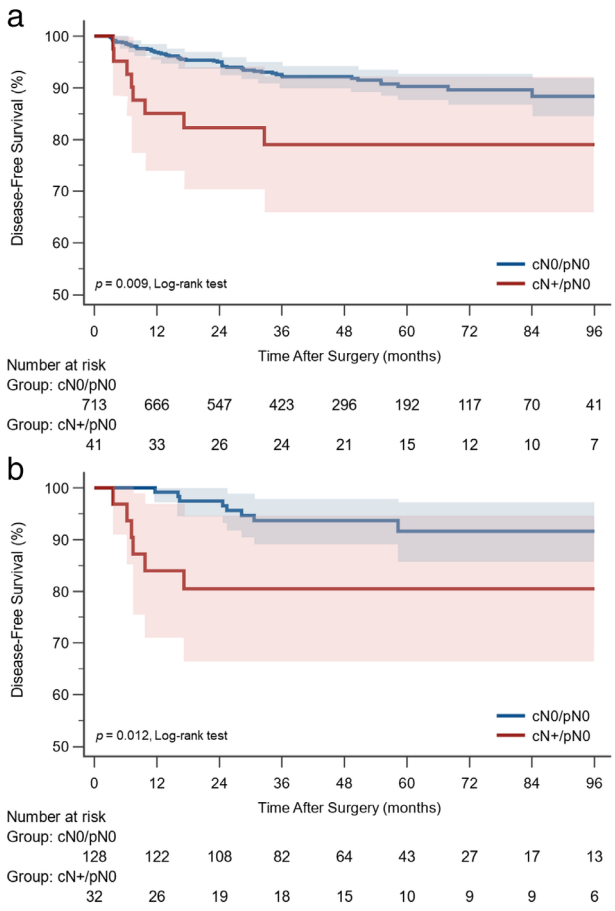

FIGURE 2 The disease-free survival between clinically node-positive (cN+/pN0) and clinically node-negative (cN0/pN0) patients with stage I resected NSCLC (a) before and (b) after propensity score matching.

categorical variables were expressed as percentages. The chi-squared and Mann–Whitney U tests were used to detect differences in categorical and continuous variables. Kaplan–Meier curves and log-rank tests were used to assess the primary outcome of DFSl. Cox proportional hazards models were used to compare DFS between the cN+/pN0 and cN0/pN0 cohorts after adjusting for age, gender, histology, pathological T status, surgical procedure, and neoadjuvant/adjuvant treatment. p-values ≤ 0.05 (two-sided) were considered statistically significant. Incidence rates (per 1000 person-years of follow-up) of postoperative recurrence in all variables were calculated for both the cN+/pN0 and cN0/pN0 cohorts. All statistical analyses were performed using MedCalc version 20 (MedCalc).

RESULTS

A total of 754 patients satisfied the inclusion criteria for this study, among whom 41 (5.4%) had cN+/pN0 status. In the cN+/pN0 group, the clinical N status was diagnosed based on CT, PET/CT, and CT and PET/CT in eight (19.5%), eight (19.5%), and 25 (61.0%) patients, respectively. Demographic, clinical, and treatment characteristics are summarized in Table 1. Before PSM, the cN+/pN0 cohort had more males, more patients with pT2 status, fewer patients with adenocarcinoma, and more patients who underwent lobectomy compared to the cN0/pN0 cohort. After 1:4 matching, which resulted in 32 patients with cN+/pN0 and 128 patients with cN0/pN0, all covariates were balanced between both cohorts except for clinical N status. Seven patients in the cN0/pN0 group underwent other treatments before and after surgery before PSM, including four who received adjuvant radiotherapy (RT), and three who received adjuvant chemoradiotherapy (CRT), whereas only one patient in the cN+/pN0 group underwent adjuvant RT before PSM. Furthermore, after PSM, only one patient underwent adjuvant CRT in the cN0/pN0 group, and none underwent other adjuvant treatment in the cN+/pN0 group.

Kaplan–Meier survival curves comparing DFS between cN+/pN0 and cN0/pN0 patients before and after PSM are plotted in Figure 2. The median follow-up time was 43.4 months (95% confidence interval [CI]: 40.9–45.6 months). The survival curves showed that before PSM, the cN+/pN0 and cN0/pN0 cohorts had a 5-year DFS rate of 79.0 and 90.3%, respectively. cN+/pN0 patients were at more risk for recurrence after surgery compared to cN0/pN0 patients ($p = 0.009$) (Figure 2a). After PSM, the cN+/pN0 and cN0/pN0 cohorts had a 5-year DFS rate of 80.5 and 91.6%, respectively. Moreover, a significant difference in DFS was observed between the cN+/pN0 and cN0/pN0 cohorts after matching ($p = 0.012$) (Figure 2b).

Cox proportional hazards model analysis for DFS before and after PSM are presented in Table 2. Univariate analysis before PSM showed that positive clinical N status (hazard ratio [HR], 2.59; 95% CI: 1.23–5.44; $p = 0.012$), non-adenocarcinoma histology (HR, 2.55; 95% CI: 1.51–4.29; $p < 0.001$), more pT2 status (HR, 5.94; 95% CI: 2.12–16.67; $p = 0.001$) and adjuvant treatment (HR, 2.72; 95% CI: 1.67–4.45; $p < 0.001$) were associated with a significantly higher risk of recurrence after surgery. However, multivariate analysis before PSM showed that positive of clinical N status was not associated with higher risk of recurrence after surgery (HR, 1.64; 95% CI: 0.76–3.55; $p = 0.208$). Following PSM, positive clinical N status was the only factor independently associated with higher risk of postoperative recurrence in the univariate (HR, 3.58; 95% CI: 1.24–10.34; $p = 0.018$) and multivariate (HR, 3.17; 95% CI: 1.05–9.56; $p = 0.040$) models.

Incidence rates of postoperative recurrence between cN+/pN0 and cN0/pN0 patients are demonstrated in Figure 3. The cN+/pN0 cohort had increased recurrence rates compared to the cN0/pN0 cohort regardless of sex, histology, pT status, surgery procedure, and presence or absence of adjuvant treatment. Furthermore, the non-adenocarcinoma (77.8 per 1000 person-years; 95% CI: 9.4–281.1) and nonlobectomy (73.0 per 1000 person-years; 95% CI: 8.9–263.9) subgroups of the cN+/pN0 cohort had the highest incidence rates of recurrence.

TABLE 2 Univariate and multivariate analyses of disease–free survival for different variables before and after matching

	Before matching				After matching			
	Univariate		Multivariate		Univariate		Multivariate	
Variable	Hazard ratio (95% CI)	*p*-value	Hazard ratio (95% CI)	*p*-value	Hazard ratio (95% CI)	*p*-value	Hazard ratio (95% CI)	*p*-value
Clinical N status								
cN0/pN0	1 (Reference)				1 (Reference)			
cN+/pN0	2.59 (1.23–5.44)	0.012	1.64 (0.76–3.55)	0.208	3.58 (1.24–10.34)	0.018	3.17 (1.05–9.56)	0.040
Age	1.02 (0.99–1.04)	0.147	1.00 (0.98–1.02)	0.978	1.02 (0.96–1.08)	0.517	1.01 (0.95–1.07)	0.739
Gender								
Male	1 (Reference)				1 (Reference)			
Female	0.75 (0.46–1.22)	0.241	1.07 (0.63–1.83)	0.799	0.79 (0.27–2.28)	0.661	0.86 (0.25–2.91)	0.804
Histology								
Adenocarcinoma	1 (Reference)				1 (Reference)			
Others	2.55 (1.51–4.29)	<0.001	2.00 (1.12–3.57)	0.019	2.09 (0.67–6.69)	0.212	2.15 (0.49–9.39)	0.309
pT status								
1a	1 (Reference)				1 (Reference)			
1b	2.30 (0.73–7.21)	0.155	2.40 (0.75–7.72)	0.142	0.45 (0.03–3.11)	0.571	0.37 (0.02–6.33)	0.495
1c	3.13 (1.00–9.82)	0.051	3.00 (0.90–10.05)	0.075	1.57 (0.16–15.12)	0.695	0.97 (0.09–10.45)	0.978
2	5.94 (2.12–16.67)	0.001	4.21 (1.30–13.58)	0.016	2.17 (0.28–17.17)	0.462	1.28 (0.13–12.50)	0.831
Surgical procedure								
Lobectomy	1 (Reference)				1 (Reference)			
Others	0.79 (0.47–1.31)	0.357	1.33 (0.76–2.31)	0.318	0.96 (0.30–3.08)	0.950	0.70 (0.17–2.97)	0.630
Adjuvant treatment[a]								
No	1 (Reference)				1 (Reference)			
Yes	2.72 (1.67–4.45)	<0.001	1.73 (0.97–3.11)	0.065	1.97 (0.68–5.68)	0.210	1.23 (0.35–4.29)	0.743

Abbreviations: CI, confidence interval.

[a]Including adjuvant chemotherapy, adjuvant radiotherapy and adjuvant chemoradiotherapy.

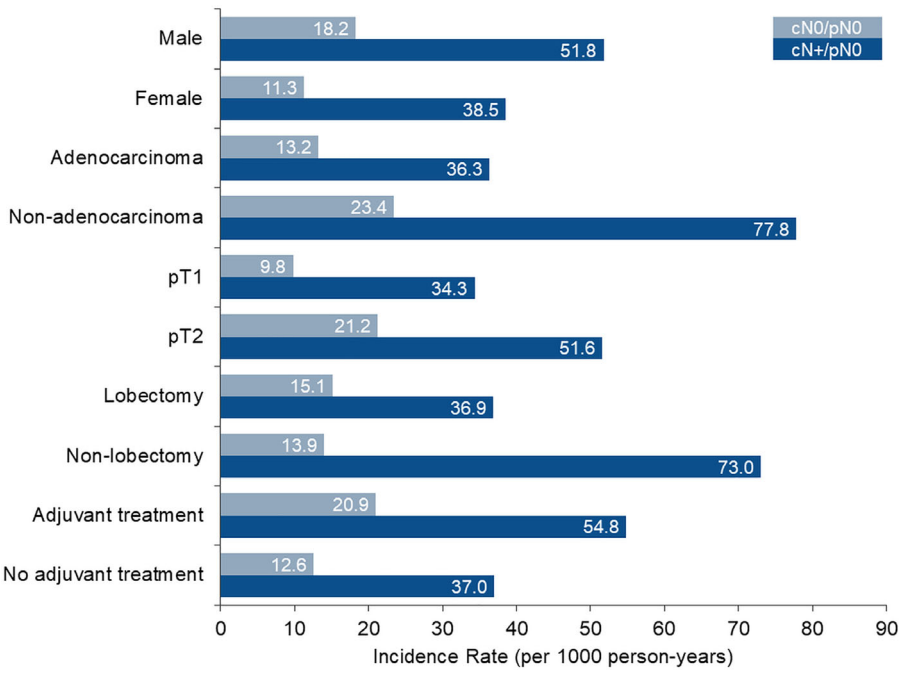

FIGURE 3 Incidence rates of postoperative recurrence between clinically node-positive (cN+/pN0) and clinically node-negative (cN0/pN0) patients with stage I resected NSCLC

DISCUSSION

To the best of our knowledge, this has been the first PSM study addressing the recurrence risk after surgery in patients with pathological stage I NSCLC according to clinical N stages. The results of our study demonstrated that positive clinical N stage was an independent prognostic factor for DFS in patients with pathological stage I NSCLC. Accordingly, the positive cN stage cohort had higher recurrence rates compared to the negative cohort in all subgroups, especially in the non-adenocarcinoma and nonlobectomy subgroups.

Multivariant analysis before PSM showed that non-adenocarcinoma histology and adjuvant treatment were associated with a significantly greater risk of recurrence after surgery. After PSM, however, the risk of recurrence was not significant. Given that the multivariant Cox regression model before and after PSM showed an HR of 2.00 (95% CI: 1.12–3.61) and 2.15 (0.48–9.39) for nonadenocarcinoma histology (Table 2), respectively, the decrease in the number of patients after PSM may have no effect of on the significance of our results, particularly in terms of risk of recurrence. Notably, neoadjuvant therapy in the cN+/pN0 cohort before and after matching had no influence on clinical and pathological N status.

The involvement of mediastinal lymph nodes has been considered a critical prognostic factor in NSCLC treatment. Evidence has suggested the superiority of PET/CT in the mediastinal staging of NSCLC.[15] Feng et al. reported that the false-positive rate of PET/CT in lung cancer staging was 6.5%.[16] Nonadenocarcinoma histology and age >65 years were independent factors associated with false-positive hilar and mediastinal lymph nodes in NSCLC staging with PET/CT.[8] However, Iskender et al. demonstrated that false-positivity of the mediastinal lymph nodes was independently associated with worse survival (HR = 0.63; $p = 0.02$).[7] Notably, the current study focused on stage I NSCLC and used the PSM method to minimize all confounding effects. Accordingly, our results showed that the cN+/pN0 group had significantly worse DFS compared to the cN0/pN0 group (HR, 3.17; $p = 0.040$) (Table 2).

Lymph nodes play an essential role in the control of tumor progression. In response to the antigenicity of tumor cells, regional lymph nodes may be able to destroy invading tumor cells entirely or at least temporarily stop their dissemination.[17] In theory, the cN+/pN0 patients should have had early-stage metastasis, which may not be detected with routine immunohistochemistry (IHC) examination. Occult lymph node metastasis has previously been reported in resected NSCLC at frequencies ranging from 22.4% to 44.9%.[18–20] Rusch et al. reviewed 1047 patients with stage I to III resected NSCLC and investigated the relationship between occult lymph node metastasis and survival.[18] A statistically significant survival difference was observed when comparing stage IB patients with positive and negative lymph node occult metastasis (HR, 1.82; $p = 0.01$). However, no such difference was observed among patients with IA tumors. Several detection methods for occult metastasis have been used, including advanced IHC and reverse transcription-polymerase chain reaction analysis for epithelial markers in NSCLC. One meta-analysis research enrolling 15 studies revealed that among patients with NSCLC, those who had with occult metastasis had inferior prognosis in terms of DFS and overall survival compared to those without occult metastasis regardless of the detection methods, study types (retrospectively and prospectively), and mean numbers of lymph node dissection.[21] However, these methods have limited use in clinical practice due to their high price.

Another theory suggests that the inflammatory microenvironment consisting of immune cells and their secretory cytokines contribute to tumor angiogenesis, metastasis, and proliferation,[22] resulting in increased cellular activity and glucose metabolism of mediastinal lymph nodes in PET scans. Correspondingly, our study demonstrated that among patients with stage I NSCLC, those with cN+ had a poorer prognosis compared to those with cN0 on both univariate ($p = 0.018$) and multivariate ($p = 0.040$) analyses after PSM (Table 2). The cN+/pN0 cohort had increased recurrence rates compared to than the cN0/pN0 cohort in all subgroups, especially in non-adenocarcinoma (77.8 per 1000 person-years) and non-lobectomy (73.0 per 1000 person-years) subgroup among cN+/pN0 patients (Figure 3).

Our study has some limitations that need to be addressed. First, this was a single-center retrospective analysis, potentially introducing selection biases and limiting the generalizability of data. Second, given the small number of patients in the cN+/pN0 group, only binary statistical analysis would be performed to determine statistical significance. Third, further advanced IHC stains of resected lymph nodes were not performed to examine the possibility of occult metastasis, which was not detected during the routine histopathological study.

In conclusion, the current study indicated that among patients with stage I resected NSCLC, those with cN+ had a worse DFS compared to those with clinically node-negative disease, with all subgroups showing higher recurrence rates. Surgeons or oncologists should therefore consider more aggressive adjuvant therapy or frequent follow-up in plainest with surgically resected node-negative stage I NSCLC with cN+ status, especially in the nonadenocarcinoma and non-lobectomy subgroups.

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CONFLICT OF INTEREST

The authors report that there are no conflict of interest.

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