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The impact of pathological lymph node metastasis with lymphatic invasion on the survival of patients with clinically node-negative non-small cell lung cancer: A multicenter study

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ABSTRACT

Objectives: Lymphatic vessel invasion (Ly) plays a crucial role in pathological lymph node metastasis (pN), and we consider pN + Ly + disease to indicate a high affinity for the lymphatic system. This study evaluated the outcomes of patients with clinically node-negative (N0) non-small cell lung cancer (NSCLC) who presented with pN + with Ly+.

Materials and Methods: This retrospective study evaluated 1775 patients with clinically N0 stage I–III NSCLC who underwent R0 anatomical resection and systematic lymph node dissection at three institutions between January 2010 and December 2017. Patients were classified into four groups according to their pN and Ly statuses. Univariable and multivariable analyses were performed to identify factors associated with poor recurrence-free survival (RFS) and pN + Ly+.

Results: Kaplan-Meier curves revealed that the 5-year RFS rates were 90.8 % for pN–Ly– patients, 55.6 % for pN–Ly + patients, 63.4 % for pN + Ly– patients, and 41.3 % for pN + Ly + patients. Distant and lymph node recurrences were more common in the pN + Ly + group, relative to in the pN–Ly– and pN–Ly + groups (both $p < 0.001$). Multivariable analyses revealed that pN and Ly statuses were independently associated with RFS, while the solid tumor size and maximum standardized uptake value were independently associated with pN + Ly + status. The proportion of pN + Ly + disease was 17.2 % in patients with a solid-part size of $\geq$ 1.80 cm and a SUVmax of $\geq$ 3.55.

Conclusion: pN and Ly statuses were independent prognostic factors in patients with clinically N0 stage I–III NSCLC. Diseases presenting with pN + with Ly + were associated with increased rates of distant and lymph node recurrence.

1. Introduction

Lung cancer is the most common cause of cancer-related mortality worldwide [1]. However, recent advances in early detection and therapeutic modalities have failed to improve the cure rate significantly. It is likely to be related to the fact that even early-stage lung cancer can directly invade nearby tissues and lead to metastasis via the circulatory and lymphatic systems. Conventionally, clinically suspected lymph node metastasis is evaluated as having the enlarged lymph nodes on chest computed tomography (CT) and the lesions with the greater maximum standardized uptake values (SUVmax) on F18-fluorodeoxy glucose-positron emission tomography/CT (FDG-PET/CT). However, the sensitivity is far from optional [2,3]. Therefore, pathological confirmation of lymph node metastasis is additionally made by endobronchial ultrasound-guided transbronchial needle aspiration biopsies of suspected lymph nodes for further clinical diagnosis. Even though a growing number of patients are diagnosed with clinical stage I non-small cell lung cancer (NSCLC), they have an approximately 15 % risk of

Abbreviations: NSCLC, Non-small cell lung cancer; TNM, Tumor node and metastasis; ND, Node dissection; CT, Computed tomography; FDG-PET, Fluorodeoxyglucose-positron emission tomography; pN, Pathological lymph node metastasis; Ly, Lymphatic vessel invasion; OS, Overall survival; RFS, Recurrence-freesurvival.

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pathological lymph node metastasis after curative lung resection [4–6]. The lymphatic system consists of lymph nodes and lymphatic vessels. Pathological lymph node status (pN) is an important prognostic factor for patients with resected NSCLC, with 5-year survival rates of 49 % for pN1 disease, 36 % for pN2 disease, and 20 % for pN3 disease [7]. The presence of tumor cells inside the lymphatic vessels is known as lymphatic vessel invasion (Ly), which increases the risk of micro-metastasis and plays a crucial role in developing lymph node metastasis [8–11]. Furthermore, lymphatic vessels can provide a route for tumor cell dissemination even in the absence of detected Ly or lymph node metastasis [12].

Several studies have demonstrated that Ly is an independent poor prognostic factor for NSCLC, regardless of nodal involvement, although Ly is an optional descriptor scored as LX, L0, and L1 but not considered in the tumor component of the tumor, node, and metastasis (TNM) staging system [8–11,13]. Therefore, further studies are needed to clarify the prognostic relevance of Ly status. The present study aimed to evaluate whether pN and Ly statuses were associated with outcomes among patients who underwent surgical resection for clinically N0 NSCLC.

2. Materials and methods

2.1. Study population

A total of 3125 patients had undergone complete surgical resection of lung cancer at three institutions between January 2010 and December 2017. Complete surgical resection was defined based on the International Association for the Study of Lung Cancer (IASLC) Staging Committee criteria [14]. All patients had undergone preoperative CT and FDG-PET/CT for routine lung cancer staging, which was determined according to the 8th edition of the TNM classification of malignant tumors. The exclusion criteria were patients who were pathologically diagnosed with small cell lung cancer, patients with clinical stage 0 or IV disease, patients with clinical N1–3 disease, patients who underwent wedge resection, and patients who underwent ND0–1 lymph node dissection. Thus, the present study evaluated 1775 patients with clinically N0 stage I–III NSCLC who underwent R0 anatomical resection (segmentectomy or lobectomy) and systematic lymph node dissection (ND2). The CONSORT flowchart is shown in Supplement Fig. 1. The retrospective study protocol was approved by each center's institutional review board, which waived the requirement for informed consent.

2.2. Patient follow-up

Patients were examined at 6-month intervals for the first two years and at 1-year intervals thereafter. Follow-up evaluation included a physical examination, chest radiography, blood examination, and CT scan of the chest. Further evaluations, including CT scans of the abdomen, brain MRI, and bone scintigraphy, were performed when symptoms or signs of recurrence were detected. PET/CT had also been performed when appropriate. Recurrence was diagnosed by physical examination and diagnostic imaging of the lesions. The diagnosis was histologically confirmed when clinically feasible. The date of recurrence was defined as the date of histological confirmation or the date of identification based on clinic-radiological findings by a physician.

2.3. Radiographic assessment of the primary tumor

All patients had undergone preoperative CT and FDG-PET/CT. Tumor sizes were measured for the entire tumor and the solid tumor component on chest CT. Patients were instructed to fast for $\geq$ four h before intravenous injection of FDG (74–370 MBq) and rested for one h before the evaluation. The PET/CT images were acquired using a Discovery ST scanner (GE Healthcare, Little Chalfont, UK) or a Biograph scanner (Siemens Healthcare, Erlangen, Germany). Low-dose unenhanced CT images for attenuation correction and localization of PET-identified lesions were acquired from the head to the pelvic floor using a standard protocol. Immediately after the CT, PET scanning of the identical axial field of view was performed for 2–4 min per table position, based on the patient's condition and scanner performance. Variations in SUVmaxs, which radiologists judged at each institution, were minimized using an anthropomorphic body phantom (NEMA NU2−2001; Data Spectrum Corp, Hillsborough, NC, USA). A calibration factor was created by dividing the actual SUV by the mean SUV in the phantom background, and the calibrated SUVmax value was used to minimize inconsistencies between the institutions.

2.4. Pathological classification

All dissected lymph nodes were microscopically evaluated to identify any metastatic infiltration. The invasive component's size was measured using the pathological slides. Blood vessel invasion and visceral pleural invasion were evaluated using hematoxylin and eosin staining and elastica van Gieson staining. The Ly status was evaluated using hematoxylin and eosin staining and lymphatic vessel staining (D2−40) when necessary. The results for pN and Ly were used to classify patients into four groups (pN–Ly–, pN + Ly–, pN–Ly+, and pN + Ly+). Histological subtypes were determined according to the World Health Organization classification system.

2.5. Statistical analysis

Overall survival (OS) was measured from the date of surgery to the date of death because of any cause or the last day on which the patient was known to be alive. Recurrence-free survival (RFS) was measured from the date of surgery to the first date of recurrence, death because of any cause, or the last day on which the patient was known to be alive. The Kaplan-Meier method was used to create OS and RFS curves, which were compared using the log-rank test. Univariable and multivariable analyses were performed to identify factors that were associated with unfavorable OS and RFS outcomes. The univariable analyses were performed using Pearson's chi-squared test for categorical data and using Student's *t*-test or one-way analysis of variance for continuous data. A backward stepwise selection method was used to build the binominal logistic regression model. The complementary log-log plot model was used for the proportional hazards assumption, and variables with a threshold of $p <$ 0.15 were adopted for the backward stepwise model selection procedure. All tests were two-sided, and differences were considered statistically significant at p-values of $<$0.05. All analyses were performed using SPSS statistical software (version 26.0; IBM Corp., Armonk, NY, USA).

3. Result

The patients' characteristics are shown in Table 1. The median follow-up time for survivors was 31.2 months (range: 0.5–94.4 months). The histological types were adenocarcinoma for 1456 patients (82.0 %) and non-adenocarcinoma for 319 patients (18.0 %). The pathological stages were classified as stage 0–I for 1410 patients (79 %), stage II for 226 patients (13 %), and stage III for 139 patients (8%). The pN and Ly statuses were pN–Ly– for 1285 patients (72.4 %), pN + Ly– for 82 patients (4.6 %), pN–Ly + for 259 patients (14.6 %), and pN + Ly + for 149 patients (8.4 %). The Kaplan-Meier curves revealed that the 5-year OS rates were 93.3 % for pN–Ly–, 84.8 % for pN + Ly–, 82.2 % for pN–Ly+, and 68.7 % for pN + Ly+ (pN-Ly- vs. pN + Ly-, p = .004; pN-Ly- vs. pN-

Table 1
Patient characteristics.

Variables	Number of patients (%)
Age (mean ± SD)	67 ± 9
Sex	
Male	972 (55.8)
Female	803 (45.2)
Smoking status	
Smoker	1017 (57.3)
Never smoker	758 (42.7)
Surgical procedure	
Segmentectomy	247 (13.9)
Lobectomy	1526 (86.1)
Pneumonectomy	2 (0.1)
Whole-tumor size, cm (mean ± SD)	2.7 ± 1.4
Solid-part size, cm (mean ± SD)	2.2 ± 1.5
SUVmax on tumor	4.9 ± 5.3
Clinical T factor	
T1mi	89 (5.0)
T1a	213 (12.0)
T1b	621 (35.0)
T1c	443 (25.0)
T2a	221 (12.4)
T2b	85 (4.8)
T3	74 (4.2)
T4	29 (1.6)
Pathological T factor	
Tis	8 (0.4)
T1mi	15 (0.8)
T1a	562 (31.7)
T1b	440 (24.8)
T1c	24 (1.4)
T2a	542 (30.5)
T2b	57 (3.2)
T3	113 (6.4)
T4	14 (0.8)
Histology	
Adenocarcinoma	1456 (82.0)
Non-adenocarcinoma	319 (18.0)
Pathological lymph node metastasis (pN)	
pN0	1544 (87.0)
pN1	123 (6.9)
pN2	108 (6.1)
Lymphatic invasion (Ly)	
Positive (L1)	1367 (77.0)
Negative (L0)	408 (23.0)
Classification according to pN and Ly status	
pN-Ly-	1285 (72.4)
pN + Ly-	82 (4.6)
pN-Ly+	259 (14.6)
pN + Ly+	149 (8.4)

SD, standard deviation; SUVmax, the maximum standardized uptake value.

Ly+, p < .001; pN + Ly- vs. pN + Ly+, p = .040; pN-Ly + vs. pN + Ly+, p = .003; Fig. 1A). The 5-year RFS rates were 90.8 % for pN–Ly–, 55.6 % for pN + Ly–, 63.4 % for pN–Ly+, and 41.3 % for pN + Ly+ (pN-Ly- vs. pN + Ly-, p < .001; pN-Ly- vs. pN-Ly+, p < .001; pN + Ly- vs. pN + Ly+, p = .017; pN-Ly + vs. pN + Ly+, p < .001; Fig. 1B).

There was the substantial heterogeneity in the patient characteristics according to histology. Therefore, survival analysis and binomial logistic regression analysis were separately performed for patients with adenocarcinoma and non-adenocarcinoma. The 5-year OS rates among patients with adenocarcinoma were 94.7 % for pN–Ly–, 87.1 % for pN + Ly–, 87.2 % for pN–Ly+, and 73.1 % for pN + Ly+ (pN-Ly- vs. pN + Ly-, p = .043; pN-Ly- vs. pN-Ly+, p < .001; pN-Ly + vs. pN + Ly+, p = .002; Fig. 1C). The 5-year RFS rates among patients with adenocarcinoma were 92.5 % for pN–Ly–, 50.0 % for pN + Ly–, 70.4 % for pN–Ly+, and 43.2 % for pN + Ly+ (pN-Ly- vs. pN + Ly-, p < .001; pN-Ly- vs. pN-Ly+, p < .001; pN-Ly + vs. pN + Ly+, p < .001; Fig. 1D). The 5-year OS rates among patients with non-adenocarcinoma were 84.9 % for pN–Ly–, 81.7 % for pN + Ly–, 68.9 % for pN–Ly+, and 50.7 % for pN + Ly+ (pN-Ly- vs. pN-Ly+, p = .031; pN-Ly- vs. pN + Ly+, p = .001; Fig. 1E). The 5-year RFS rates among patients with non-adenocarcinoma were 80.5 % for pN–Ly–, 72.2 % for pN + Ly–, 44.7 % for pN–Ly+, and 34.2 for pN + Ly+ (pN-Ly- vs. pN-Ly+, p < .001; pN + Ly- vs. pN + Ly+, p = .026; pN-Ly + vs. pN + Ly+, p = .009; Fig. 1F).

Univariable and multivariable analyses were performed to identify factors that were associated with poor RFS among patients with clinical stage I–III NSCLC (Table 2). Older age (p = .001), larger solid-part size (p < .001), increased tumor SUVmax (p < .001), pT status (p = .001), pN status (p < .001), Ly status (p = .001), and histology (p < .001) were independently associated with poor RFS.

Given that the presence of both pN and Ly (pN + Ly+) was associated with the poorest prognosis, we aimed to identify related clinicopathological factors (Table 3). Multivariable analysis of all patients showed that older age (p = .002), male (p = .003), smoker (p = .008), larger solid-part size (p < .001), and increased tumor SUVmax (p < .001) were independently associated with the presence pN + Ly+. Among patients with adenocarcinoma, pN + Ly + was independently associated with older age (p = .006), male sex (p = .002), smoking status (p = .008), advanced clinical stage (p = .023), larger solid-part size (p < .001), and increased tumor SUVmax (p < .001; Supplement Table 1), whereas pN + Ly + was only independently associated with an increased tumor SUVmax (p = .019) in patients with non-adenocarcinoma (Supplement Table 2). As tumor SUVmax and solid-part size were the two most significant factors associated with pN + Ly + on the multivariable analysis, we performed receiver operating characteristic curve analyses to evaluate their prognostic values (Supplement Fig. 2). The area under the curve (AUC) values and the optimal cutoff values relevant to pN + Ly + among patients with adenocarcinoma were 0.620 and 1.80 cm for solid-part size and 0.721 and 3.55 for tumor SUVmax. The AUC values and the cutoff values in patients with adenocarcinoma were 0.765 and 3.12 for tumor SUVmax and 0.689 and 2.09 cm for soli-part size, whereas those with non-adenocarcinoma was 0.608 and 9.42 for tumor SUVmax (data now shown). The combination of SUVmax and solid-part size was associated with pN + Ly + more accurately than the use of the parameters of either modality alone, and pN + Ly + was observed for 17.2 % of patients with a solid-part size of ≥ 1.80 cm and a tumor SUVmax of ≥ 3.55 (Table 4). pN + Ly + was observed in 17.0 % of adenocarcinoma patients with a solid-part size of ≥ 2.09 cm and a tumor SUVmax of ≥ 3.12 (Supplement Table 3), whereas that was shown in 13.2 % of non-adenocarcinoma patients with a tumor SUVmax of ≥ 9.42 (Supplement Table 4).

Fig. 2showed the frequency of postoperative recurrences and recurrence patterns. Distant recurrence was more common in the pN + Ly + group than the pN–Ly– and pN–Ly + groups (both p < .001; Fig. 2A). Furthermore, lymph node recurrence was more frequently observed in the pN + Ly + group than the pN–Ly– and pN–Ly + groups (both p < .001; Fig. 2B). Among patients with adenocarcinoma, distant recurrence was more frequently shown in the pN + Ly + group than the pN–Ly– and pN–Ly + groups (both p < .001; Fig. 2C), and lymph node recurrence was also more common in the pN + Ly + group than the pN–Ly– and pN–Ly + groups (both p < .001; Fig. 2D). The pN + Ly + group also had the highest rates of distant recurrence (Fig. 2E) and lymph node recurrence in patients with non-adenocarcinoma (Fig. 2F).

4. Discussion

The present study revealed several important findings. First, among patients with clinically N0 NSCLC, Ly was observed in 20.8 % of adenocarcinomas and 32.6 % of non-adenocarcinomas. Second, in these cases, pN + Ly (8.0 %) was more common than pN + Ly– (3.8 %) in patients with adenocarcinoma, although only a slight difference was observed among patients with non-adenocarcinoma (10.0 % vs. 8.5 %). Third, pN and Ly were independent prognostic factors, and pN + Ly + was associated with even poorer survival and recurrence rates. Among patients with adenocarcinoma, pN + Ly + was associated

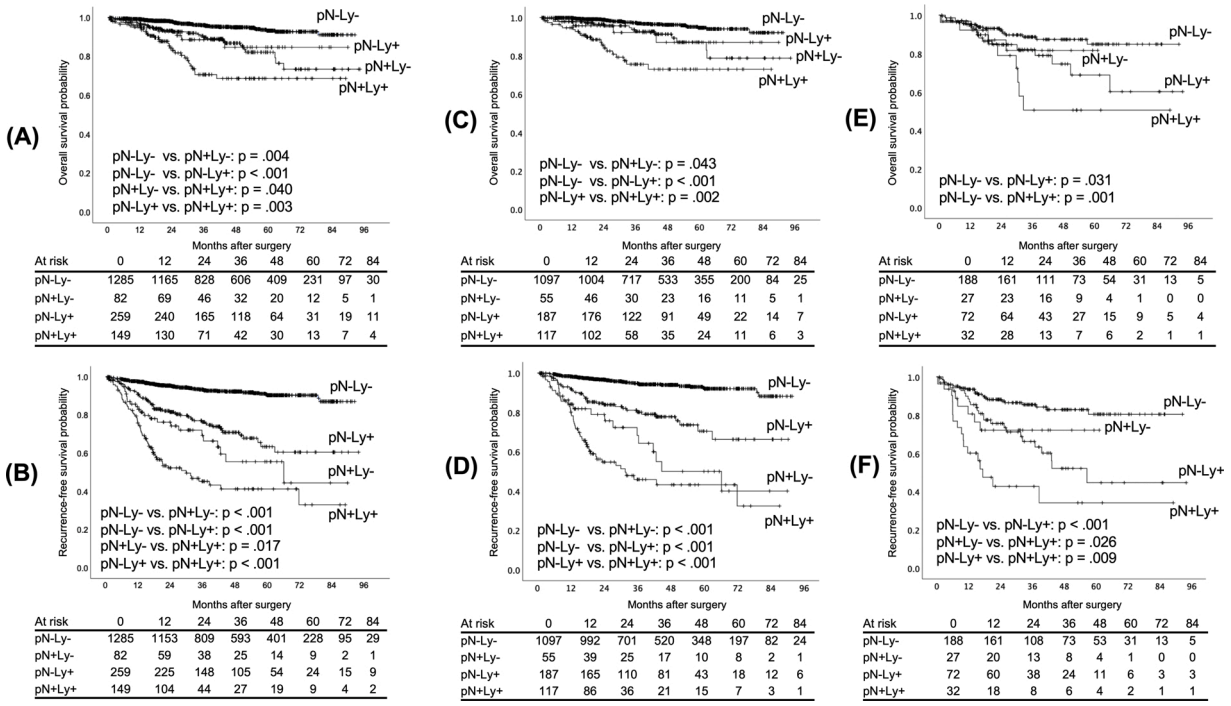

Fig. 1. Overall survival and disease-free survival among patients with clinical N0 stage I–III non-small cell lung cancer according to pathological findings regarding lymph node metastasis and lymphatic vessel invasion. (A) Overall survival and (B) disease-free survival among all patients. (C) Overall survival and (D) disease-free survival among patients with adenocarcinoma. (E) Overall survival and (F) disease-free survival among patients with non-adenocarcinoma.
pN, pathological nodal involvement; Ly, lymphatic vessel invasion.

Table 2
Univariable and multivariable analysis for RFS in patients with clinical stage I-III NSCLC.

Variables	Hazard ratio (95 % CI)	p value
Univariable analysis		
Age	1.03 (1.02–1.05)	< .001
Sex (male vs. female)	1.98 (1.51–2.60)	< .001
Smoking status (present vs. absent)	1.89 (1.43–2.49)	< .001
Procedure (lobectomy vs. segmentectomy)	2.46 (1.43–4.22)	.001
Solid-part size	1.32 (1.24−1.40)	< .001
SUVmax on tumor	1.09 (1.08−1.11)	< .001
Clinical stage (II-III vs. I)	3.52 (2.61–4.72)	< .001
pT (T2-4 vs. Tis-T1)	4.50 (3.37–6.02)	< .001
pN (positive vs. negative)	5.83 (4.51–7.52)	< .001
Ly (positive vs. negative)	4.05 (3.13–5.21)	< .001
Histology (non-adenocarcinoma vs. adenocarcinoma)	2.35 (1.79–3.09)	< .001
Multivariable analysis		
Age	1.03 (1.00–1.04)	.001
Solid-part size	1.35 (1.37–1.62)	< .001
SUVmax on tumor	1.05 (1.03–1.09)	< .001
pT	1.74 (1.25–2.42)	.001
pN	2.69 (1.94–3.72)	< .001
Ly	1.68 (1.21–2.33)	.002
Histology	2.52 (1.70–3.73)	< .001

RFS, recurrence-free survival; NSCLC, non-small cell lung cancer; CI, confidence interval; SUVmax, the maximum standardized uptake values; pT, pathological T factor; pN, pathological lymph node metastasis Ly, lymphatic invasion.

Table 3
Factors associated with lymph node metastasis and lymphatic invasion (pN + Ly+).

Variables	Odds ratio (95 % CI)	p value
Univariate analysis		
Age	1.02 (1.00–1.04)	.024
Sex (male vs. female)	1.60 (1.13–2.27)	.009
Smoking status (present vs. absent)	1.12 (0.79–1.57)	.530
Procedure (lobectomy vs. segmentectomy)	2.67 (1.34–5.32)	.005
Clinical stage (II-III vs. I)	1.72 (1.08–2.75)	.022
Solid-part size	1.21 (1.10–1.34)	<.001
SUVmax on tumor	1.09 (1.07–1.12)	<.001
Histology (non-adenocarcinoma vs. adenocarcinoma)	1.28 (0.85–1.93)	.245
Multivariate analysis		
Age	1.03 (1.01–1.04)	.002
Sex	1.97 (1.25–3.10)	.003
Smoking status	1.86 (1.18–2.94)	.008
Solid-part size	1.21 (1.10–1.34)	< .001
SUVmax on tumor	1.10 (1.07–1.13)	< .001

pN, pathological lymph node metastasis Ly, lymphatic invasion; CI, confidence interval; SUVmax, the maximum standardized uptake values.

with rates of > 40 % for overall recurrence and > 20 % for distant recurrence. Among patients with non-adenocarcinoma, pN + Ly + was associated with rates of > 50 % for overall recurrence, > 30 % for distant recurrence, and > 20 % for lymph node recurrence. Fourth, pN + Ly + was associated with solid-part size, tumor SUVmax, age, sex, and smoking status. Fifth, the combination of SUVmax and solid-part size was associated with pN + Ly + more accurately than the parameters of either modality alone. pN + Ly + was observed for 17.2 % of patients with a solid-part size of ≥ 1.80 cm and a tumor SUVmax of ≥ 3.55.

Table 4
Predictive performance of significant factors for patients with lymph node metastasis and lymphatic invasion (pN + Ly+).

Variables	No. of patients	No. of patients with pN + Ly+ (%)
Solid-part size < 1.80 cm + SUVmax < 3.55	665	13 (2.0)
Solid-part size ≥ 1.80 cm	738	93 (12.5)
SUVmax ≥ 3.55	779	113 (14.5)
Solid-part size ≥ 1.80 cm + SUVmax ≥ 3.55	407	70 (17.2)

pN, pathological lymph node metastasis Ly, lymphatic invasion; SUVmax, the maximum standardized uptake values.

Previous studies have indicated that Ly is associated with an increased risk of lymph node involvement and unfavorable outcomes in metastasis and long-term survival [8–11,13,15]. Mimae et al. have reported that 6.7 % of patients with clinical T1N0M0 adenocarcinoma had lymph node metastases and that a high Ly + rate (68 %) was observed among pN + patients [9]. They also demonstrated that Ly only independently predicted RFS among pN + patients and that pN + Ly + patients had a poorer prognosis than pN + Ly– patients [9], which agrees with our results. The lymphatic capillary vessels have a thin basement membrane and no supporting muscle that connects the collecting vessels and lymph nodes where the lymph is filtered [16,17]. Furthermore, lymphatic vessels near the primary tumor serve as an escape route for metastatic cancer cells, which can travel to the regional lymph nodes, and Ly accompanied most pN + disease. However, the pathological diagnosis fails to identify Ly in approximately 30 % of cases (in previous studies and the present study), although this does not definitively indicate that there is no Ly [9]. This finding is because slide-based pathological evaluations can be limited by the sampling methodology and the inability to visualize tissue structures in their native three-dimensional context. Nevertheless, pN + Ly + disease likely indicates substantial Ly + and pN + involvement. The possible reason that the pN + Ly + population demonstrated a poorer prognosis than other groups in the current study is involved in the molecular mechanism of the relationship between tumor lymphatic flows and metastatic capability. Tumor lymphatic vessels have complex and contradictory functions during cancer progression [16]. For example, tumor cells produce factors that promote lymphangiogenesis, such as vascular endothelial growth factor C, which can induce metastatic spread [12,17–21]. Furthermore, poor outcomes are associated with high concentrations of vascular endothelial growth factor C, increased lymphatic vascular density, and lymph node metastasis [12,19,21]. However, lymphatic vessels also provide a therapeutic target for modulating the immune response to cancer and restricting metastasis [16,22], as immune cells from the peripheral tissues can navigate to the regional lymph nodes via the lymphatic network to stimulate the immune response [17,22]. The present study revealed that pN + Ly + was associated with significantly increased nodal and distant recurrence rates relative to the other pNLy groups. Thus, pN + Ly + patients may benefit from a further refinement of their adjuvant treatment and intensive follow-up even though the administration of adjuvant therapies was not associated with RFS in patients with pN + Ly + in the current study (data not shown). Intact and functional tumor lymphatic systems may be useful for delivering anti-cancer treatment, including immune checkpoint inhibitors, and molecular targets that block lymphatic vessel-mediated metastasis might be a promising strategy for treating these tumors.

The prognostic value of Ly reportedly varies between lung adenocarcinoma and squamous cell carcinoma [23,24]. Kinoshita et al. have reported that Ly was an independent prognostic factor for adenocarcinoma but not for squamous cell carcinomas [23]. However, Masuda et al. have reported that moderate and severe Ly independently predicted an unfavorable prognosis for lung squamous cell carcinoma [24]. They demonstrated two histological patterns in lung squamous cell carcinoma according to the morphological findings of tumor infiltration to surrounding stromal tissue, and lung squamous cell carcinoma with tumor infiltration was significantly associated with venous invasion, scirrhous stromal type, and poorer postoperative survival [24]. That might be a potential reason why patients with Ly + non-adenocarcinoma had a poorer prognosis than Ly + adenocarcinoma. The present study revealed that Ly predicted a poor prognosis, regardless of histology, and that pN + Ly + was associated with a higher likelihood of postoperative metastasis among patients with non-adenocarcinoma. As there should be significant differences in the biological behaviors of these two tumor types, further studies are needed to clarify the roles of the lymphatic system in both tumor types and the potential ability to target lymphatic vessels as part of a combination treatment strategy.

The present study revealed that pN + Ly + was significantly

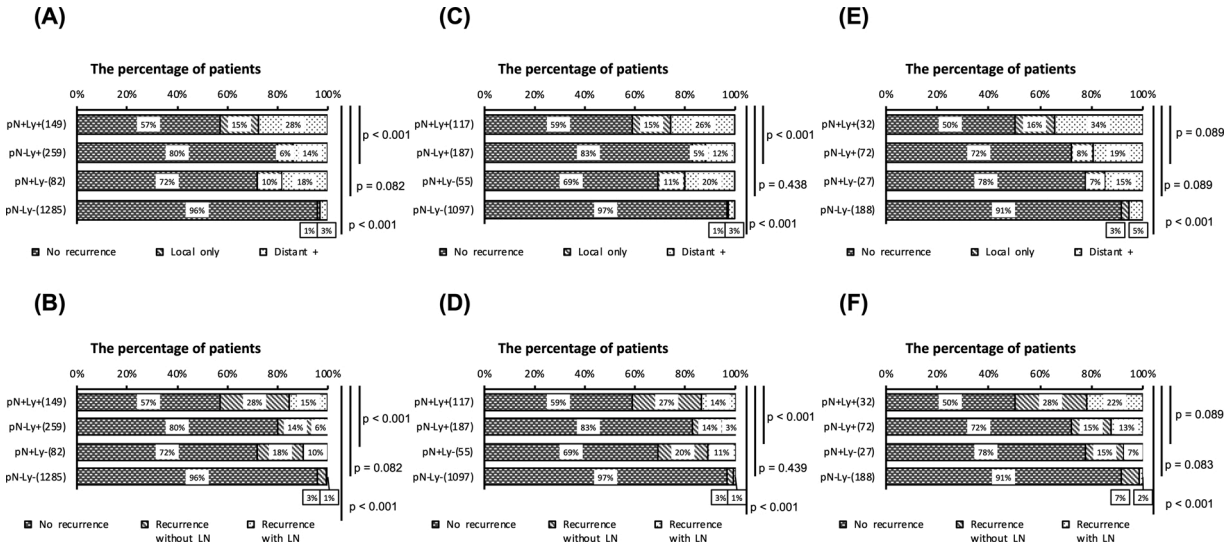

Fig. 2. Recurrence and recurrence patterns according to lymph node metastasis and lymphatic vessel invasion. (A) The proportions of patients with recurrence according to recurrence patterns and (B) the presence of lymph node metastasis. (C) The proportions of patients with recurrence of adenocarcinoma according to recurrence patterns and (D) the presence of lymph node metastasis. (E) The proportions of patients with recurrence of non-adenocarcinoma according to recurrence patterns and (F) the presence of lymph node metastasis.
LN, lymph node; pN, pathological nodal involvement; Ly, lymphatic vessel invasion.

associated with a solid-part size and tumor SUVmax in all the patients and those with adenocarcinoma patients, and with tumor SUVmax in patients with non-adenocarcinoma. To the best of our knowledge, this is the first study to identify preoperative factors that predicted pN + Ly + in clinically N0 cases of lung adenocarcinoma and non-adenocarcinoma. In this setting, the combination of PET/CT and high-resolution CT provides excellent ability to identify pathological invasive factors, including Ly, and predict prognosis among patients with early-stage NSCLC [25,26]. Therefore, further studies are needed to clarify parameters that can predict a high affinity for the lymphatic system and create prognostic subgroups of patients who might benefit from intensive adjuvant chemotherapy after systematic lymph node dissection.

This study has several limitations. First, we only retrospectively selected patients with histologically confirmed NSCLC after surgical resection. Second, the multicenter design suggests that there is a possibility of inter-center differences in the pathological diagnostic criteria. Third, the cutoff values for the tumor SUVmax were based on a calibration factor and are only likely applicable to the three participating institutions.

In conclusion, the present study revealed that pN and Ly statuses were important prognostic factors, regardless of histology, and that pN + Ly + was associated with increased rates of distant and lymph node recurrence among patients with clinically N0 NSCLC. Preoperative evaluations using high-resolution CT and PET/CT may be useful for predicting pN + Ly+, which may help guide the selection of surgical strategy and intensive adjuvant chemotherapy.

Data availability

All relevant data are included in the manuscript and the associated files.

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CRediT authorship contribution statement

Tomo Sato: Data curation, Formal analysis, Writing - original draft. **Yoshihisa Shimada:** Conceptualization, Methodology, Validation, Writing - review & editing. **Takahiro Mimae:** Supervision. **Yasuhiro Tsutani:** Supervision. **Yoshihiro Miyata:** Supervision. **Hiroyuki Ito:** Supervision. **Haruhiko Nakayama:** Supervision. **Morihito Okada:** Supervision. **Norihiko Ikeda:** Supervision.

Declaration of Competing Interest

The authors report no declarations of interest.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.lungcan.2021.05.029.

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