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ORIGINAL ARTICLE

Risk factors associated with recurrence of surgically resected node-positive non-small cell lung cancer

Yoichi Ohtaki[1] · Kimihiro Shimizu[1] · Kyoichi Kaira[2] · Toshiteru Nagashima[1] · Kai Obayashi[1] · Seshiru Nakazawa[1] · Seiichi Kakegawa[1] · Hitoshi Igai[1] · Mitsuhiro Kamiyoshihara[1] · Masahiko Nishiyama[3] · Izumi Takeyoshi[1]

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Abstract
Purpose The aim of this study was to identify risk factors for recurrence in non-small cell lung cancer (NSCLC) patients with lymph node metastases after surgical resection.
Methods We reviewed 66 consecutive patients with surgically resected NSCLC who had pathologically proven positive lymph nodes (pN1 or pN2). All patients underwent a preoperative 2-[^{18}F]-fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) evaluation. We analyzed the recurrence-free survival (RFS) and recurrence-free proportion (RFP) according to the clinicopathological factors.
Results A total of 27 patients were pathologically N1 and 39 were N2. The 5-year overall survival rate and the RFS rate were 47.2 and 27.7 %, respectively. The cut-off values for the SUV_{max} of the tumor and the lymph node ratio (LNR) were determined to be 6.5 and 0.12, respectively, using a receiver operating characteristics curve analysis. Both univariate and multivariate analyses revealed three significant independent factors for RFS: namely, the SUV_{max} of the tumor, the LNR, and the use of adjuvant chemotherapy. Only the SUV_{max} was an independent significant predictor of the RFP.
Conclusions Both the SUV_{max} and the LNR can serve as prognostic factors for patients with pN + NSCLC. Our study suggests that the LNR could be a stronger prognostic factor than the N classification of the TNM system and the SUV_{max} may predict recurrence in node-positive NSCLC patients.

Keywords Non-small cell lung cancer · FDG-PET · Lymph node ratio (LNR) · Lymph node metastasis · SUV_{max}

Introduction

Lung cancer remains the most common cause of cancer deaths worldwide. Non-small cell lung cancer (NSCLC) accounts for approximately 85 % of all lung cancers. An analysis of data from a Japanese Lung Cancer Registry study showed the 5-year overall survival rates of patients with pathological stages IIA, IIB, and IIIA NSCLC to be 61.0, 47.4, and 32.8 %, respectively [1]. More than half of all patients with surgically resected lung cancer with pathologically lymph node metastases have relapse of the cancer, and the patient outcomes remain poor. However, some patients with lymph node metastases survive without relapse.

2-[^{18}F]-fluoro-2-deoxy-D-glucose (^{18}F-FDG) positron emission tomography (PET) has been used to predict occult nodal metastases in NSCLC patients of clinical N0 [2–4], and is widely used for lymph node staging, in combination with CT findings [5–7]. Many studies have evaluated

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✉ Kimihiro Shimizu
kmshimizu@gmail.com

[1] Department of Thoracic and Visceral Organ Surgery, Gunma University Graduate School of Medicine, Maebashi, Gunma, Japan

[2] Department of Oncology Clinical Development, Gunma University Graduate School of Medicine, Maebashi, Gunma, Japan

[3] Department of Molecular Pharmacology and Oncology, Gunma University Graduate School of Medicine, Maebashi, Gunma, Japan

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the utility of ^{18}F-FDG-PET and have shown that the maximum standardized uptake value (SUV_{max}) of a tumor is useful for predicting both recurrence and the prognosis in patients with early-stage NSCLC [8–11], as with other prognostic factors [12]. However, few data on the prognostic significance of the SUV_{max} in patients with surgically resected NSCLC and pathological lymph node metastases are available.

The lymph node ratio (LNR) is the ratio of metastatic lymph nodes to all dissected lymph nodes and is known to predict the survival of NSCLC patients undergoing radical resection. The LNR has been reported to be more valuable in this context than the N descriptor of the TNM classification [13–16].

In this study, we retrospectively investigated the risk factors of recurrence after surgical resection of NSCLC in patients with lymph node metastases. To clarify which subset of patients in particular had a survival benefit from receiving adjuvant chemotherapy, we further classified the patients according to the risk factors and analyzed the survival for each group. To this end, we used the SUV_{max} value of the main tumor via ^{18}F-FDG-PET and the LNR.

Patients and methods

Patient selection and the follow-up

Between 2006 and 2012, a total of 384 consecutive patients underwent surgical resection of primary lung cancer in our department. All patients signed Institutional Review Board-approved informed consent forms. After excluding 127 patients who did not meet our study criteria, the remaining 257 NSCLC patients, who underwent complete resection, were included (Supplementary Figure 1). Clinical nodal stages were defined according to the CT and PET-CT findings. In a CT scan, a mediastinal lymph node with a short axis diameter measuring 10 mm or more was determined to indicate clinical N2 (cN2) disease. On PET-CT, an SUV_{max} value greater than 2.5 was diagnosed as a PET-positive lymph node [17–19]. In cN2 cases, primary surgical resection featured only single-station N2. We did not routinely perform invasive techniques for mediastinal nodal staging, such as video-assisted thoracoscopic surgery, endobronchial ultrasound-guided transbronchial needle aspiration, or mediastinoscopy. Furthermore, of the 257 patients, 66 patients with positive lymph nodes pathologically proven after surgery were enrolled in this study. Adjuvant chemotherapy was administered to patients according to the postoperative performance status and age. Platinum-based chemotherapies were administered if possible. The follow-up evaluation and recurrence diagnosis were performed as previously described [20].

^{18}F-FDG PET-CT procedure

Patients fasted for at least 5 h before the ^{18}F-FDG PET examination, received intravenous injections of 200–250 MBq 18-fluoro-2-deoxy-D-glucose, and rested for approximately 1 h before imaging. Image acquisition was performed using an Advance NXi PET scanner and Discovery PET/CT scanner (GE Healthcare, Milwaukee, WI, USA). Two-dimensional emission scanning was performed from the groin to the top of the skull. The acquired data were reconstructed via iteratively ordered subset expectation maximization. To evaluate the ^{18}F-FDG accumulation, the tumor was first examined visually, and the peak SUV of the entire tumor was subsequently determined. The highest SUV value (thus, the SUV_{max}) was used in our analysis.

Histological studies

All surgical specimens were fixed in 10 % (v/v) formalin and embedded in paraffin. The tumors were cut into approximately 5 mm thick blocks, and serial 4-μm thick sections were stained with hematoxylin and eosin (HE) and reviewed by an experienced pathologist. The Elastica-Masson method was used to visualize elastic fibers. Blood and lymphatic vessels were identified via HE and Elastica-Masson staining. Vascular invasion and lymphatic permeation were histologically diagnosed by identifying cancer cells within the blood and lymphatic vessels, respectively. Pleural invasion was evaluated via Elastica-Masson staining. Histological diagnoses were made according to the revised third edition of the World Health Organization Classification of Tumours.

Lymph node dissection and the lymph node ratio (LNR)

Lymph node (LN) dissection was routinely performed on nodal stations 2R, 4R, 7 and hilar nodes of patients with right upper lobe and middle lobe carcinoma; and 2R, 4R, 7, 8, 9, and hilar nodes of those with right lower lobe carcinoma. On the left side, 4L, 5, 6, 7, and hilar nodes were dissected in those with upper lobe carcinoma; and 4L, 5, 6, 7, 8, 9, and hilar nodes were dissected in those with lower lobe carcinoma. Selective lymph node dissection was performed only in clinical T1 N0 lung cancer cases. Thus, nodes 2 and 4 were not dissected in those with lower lobe carcinoma and node 7 was not dissected in patients with upper lobe carcinoma. We treated resected lymph nodes carefully not to dissect them into pieces, and precisely calculated the LNR.

Although most patients underwent dissection of at least 10 regional LNs during surgery, to ensure the quality of the nodal status evaluation (the extent of LN dissection was as recommended in the literature) [21], others from whom

Table 1 Prognostic factors of the recurrence-free survival

Characteristics	Number of patients (total = 66)	3-year RFS rate (%)	Univariate analysis *p* value[a]	Multivariate analysis	
				Hazard ratio (95 % CI)	*p* value[b]
Age (years)					
<70	35	39.7	0.483		
≥70	31	31.4			
Sex					
Male	46	36.3	0.687		
Female	20	34.3			
Smoking history					
Never	16	43.8	0.585		
Ever	50	33.1			
PS					
0	58	38.0	0.130		
1	8	18.8			
CEA (ng/mL)					
≤5.0	43	35.6	0.762		
>5.0	23	36.6			
Laterality					
Right	39	40.0	0.473		
Left	27	31.1			
Clinical nodal staging					
cN0	41	36.4	0.829		
cN1	16	38.6			
cN2	9	44.4			
Histology					
Adenocarcinoma	46	39.2	0.376		
Non-adenocarcinoma	20	27.8			
SUV_{max} of the tumor					
≤6.5	23	70.9	<0.001†	1	0.002†
>6.5	43	19.6		3.88 (1.66–9.06)	
Pathological T status					
pT1	12	75.0	0.009†	1	0.263
pT2–4	54	25.9		2.02 (0.59–6.89)	
Pathological nodal involvement					
pN1	27	42.6	0.207		
pN2	39	31.6			
LNR					
≤0.12	30	52.0	0.005†	1	0.023†
>0.12	36	23.0		2.18 (1.12–4.24)	
Lymphatic permeation					
Ly (−)	5	60.0	0.265		
Ly (+)	61	33.9			
Vascular invasion					
V (−)	14	25.0	0.303		
V (+)	52	38.8			
Pleural invasion					
PL (−)	25	44.2	0.204		
PL (+)	41	30.4			

Table 1 continued

Characteristics	Number of patients (total = 66)	3-year RFS rate (%)	Univariate analysis *p* value[a]	Multivariate analysis	
				Hazard ratio (95 % CI)	*p* value[b]
Tumor differentiation					
Well/moderate	50	33.6	0.867		
Poorly	16	40.9			
EGFR mutation					
Mutant	18	41.6	0.604		
Wild-type	48	33.6			
KRAS mutation					
Mutant	6	22.2	0.659		
Wild-type	60	36.9			
Adjuvant chemotherapy					
Yes	33	49.8	0.021†	1	0.028†
No	33	20.2		2.05 (1.08–3.87)	

PS performance status, *CEA* preoperative serum carcinoembryonic antigen level, *LNR* lymph node ratio

† Denotes significance

[a] Log-rank test

[b] Cox's proportional hazard model

less than 10 nodes were harvested were also included in this study because all underwent dissection of all the nodal stations mentioned above. The LNR was defined as the number of involved nodes divided by the total number of nodes removed [22].

DNA extraction and mutational analysis

After surgical removal, a portion of each sample was immediately frozen and stored at −80 °C prior to DNA extraction. Genomic DNA was extracted from a 3–5 mm cube of tumor tissue using DNA Mini Kits (Qiagen, Hilden, Germany), and subsequently diluted to a concentration of 20 ng/μL. *EGFR* and *KRAS* mutations in lung cancer tissues were analyzed via PNA-enriched sequencing, as described previously [23–25].

Statistical analysis

The recurrence-free survival (RFS) was defined as the time between the date of resection and the date of the first recurrence of lung cancer or the date of death from any cause. Patients without recurrence were censored from the analysis at the time of the last negative follow-up. The length of the recurrence-free period was measured from the date of surgery to the date of the first recurrence or the last follow-up. The recurrence-free proportion (RFP) was defined as the ratio of the patients who were free from recurrence. Patients without recurrence were censored from the analysis at the time of the last negative follow-up, and patients who died without evidence of recurrence were also censored.

To determine the appropriate prognostic SUV_{max} and LNRs, patients were subdivided into two cohorts via receiver operating characteristic (ROC) curve analyses. In univariate analyses, the RFS rate and RFP were estimated by the Kaplan–Meier method, and among-group survival differences were compared using the log-rank test. Multivariate analyses were performed using Cox's proportional hazard model. The Chi square test was performed for comparison of the relationship between the SUV_{max}, the LNR, and clinicopathological features.

All reported p values were two-sided, and the significance level was set at $p < 0.05$. All analyses were performed using the SPSS version 20.0 software program (Dr. SPSS II for Windows, standard version 20.0; SPSS Inc., Chicago, IL, USA).

Results

Patient characteristics

The characteristics of all 66 patients with lymph node metastases are listed in Supplementary Table 1. The median patient age was 69 years, and 46 males were included. The histological findings were as follows: adenocarcinoma ($n = 46$), squamous cell carcinoma ($n = 18$), large cell carcinoma ($n = 1$), and large cell neuroendocrine carcinoma ($n = 1$). The SUV_{max} ranged from 1.19 to 17.30 (median 3.5). A total of 27 patients were of pathological N1 and 39 were of N2. *EGFR* mutations were detected in 18 patients (27 %) and 33 (50 %) received adjuvant chemotherapy.

Table 2 Prognostic factors of the recurrence-free proportion

Characteristics	Number of patients (total = 66)	3-year RFP (%)	Univariate analysis *p* value[a]	Multivariate analysis	
				Hazard ratio (95 % CI)	*p* value[b]
Age (years)					
<70	35	39.7	0.987		
≥70	31	39.3			
Sex					
Male	46	41.6	0.402		
Female	20	34.3			
PS					
0	58	40.6	0.530		
1	8	26.3			
Smoking history					
Never	16	43.8	0.837		
Ever	50	37.7			
CEA (ng/mL)					
≤5.0	43	40.9	0.446		
>5.0	23	36.6			
Laterality					
Right	39	41.1	0.742		
Left	27	37.3			
Clinical nodal staging					
cN0	41	38.4	0.971		
cN1	16	38.5			
cN2	9	44.4			
Histology					
Adenocarcinoma	46	43.7	0.337		
Non-adenocarcinoma	20	29.5			
SUV_{max} of the tumor					
≤6.5	23	74.1	<0.001†	1	0.001†
>6.5	43	23.0		4.48 (1.79–11.20)	
Pathological T status					
pT1	12	75.0	0.017†	1	0.427
pT2–4	54	29.6		1.65 (0.48–5.66)	
Pathological nodal involvement					
pN1	27	53.3	0.039†	1	0.750
pN2	39	31.6		1.09 (0.65–1.83)	
LNR					
≤0.12	30	62.6	<0.001†	1	0.055
>0.12	36	23.0		2.86 (0.98–8.39)	
Lymphatic permeation					
Ly (−)	5	75.0	0.126		
Ly (+)	61	37.0			
Vascular invasion					
V (−)	14	29.6	0.593		
V (+)	52	41.8			
Pleural invasion					
PL (−)	25	50.6	0.147		
PL (+)	41	32.2			

Table 2 continued

Characteristics	Number of patients (total = 66)	3-year RFP (%)	Univariate analysis *p* value[a]	Multivariate analysis	
				Hazard ratio (95 % CI)	*p* value[b]
Tumor differentiation					
Well/moderate	50	37.5	0.871		
Poorly	16	43.6			
EGFR mutation					
Mutant	18	41.6	0.872		
Wild-type	48	38.4			
KRAS mutation					
Mutant	6	44.4	0.897		
Wild-type	60	39.0			
Adjuvant chemotherapy					
Yes	33	53.2	0.047[†]	1	0.062
No	33	22.5		1.89 (0.97–3.68)	

RFP recurrence-free proportion, *PS* performance status, *CEA* preoperative serum carcinoembryonic antigen level, *LNR* lymph node ratio

[†] Denotes significance

[a] Log-rank test

[b] Cox's proportional hazard model

Supplementary Figure 2A shows the overall survival (OS) curve. The median follow-up time for surviving patients was 28.8 months. The overall 5-year survival rate after surgery was 47.2 %. The RFS curve is shown in Supplementary Figure 2B. The recurrence-free 5-year survival rate was 27.9 %.

Recurrence-free survival, recurrence-free proportion, and independent prognostic factors

Supplementary Figure 3 shows an ROC curve identifying optimal cut-off values for the LNR and the SUV_{max} in predicting lung cancer recurrence. The ROC areas under the curve were 0.683 ($p = 0.013$) for the LNR and 0.694 ($p = 0.007$) for the SUV_{max}, and the cut-off values were determined to be 0.12 for the LNR and 6.5 for the SUV_{max}.

A univariate analysis showed that the tumor SUV_{max}, pathological T status, the LNR, and administration of adjuvant chemotherapy were significant prognostic factors regarding the RFS (Table 1). A multivariate analysis revealed that a tumor SUV_{max} higher than 6.5, an LNR over 0.12, and lack of adjuvant chemotherapy were significant, independent predictors of a poorer RFS [SUV_{max} >6.5: hazard ratio (HR) 3.88, $p = 0.002$; LNR >0.12: HR 2.18, $p = 0.023$; adjuvant chemotherapy: HR 2.05, $p = 0.028$] (Table 1).

We also determined the RFP focusing exclusively on lung cancer recurrence (Table 2). A univariate analysis showed that the tumor SUV_{max}, pathological T status, pathological nodal stage, the LNR, and adjuvant chemotherapy were significant prognostic factors regarding the RFP (Table 2). A multivariate analysis revealed that a tumor SUV_{max} greater than 6.5 was a significant, independent predictor of relapse (max SUV >6.5: HR 4.48, $p = 0.001$) (Table 2). Although significance was not attained, the LNR and adjuvant chemotherapy also exerted marginally significant prognostic impacts on recurrence ($p = 0.055$ and $p = 0.062$, respectively). Regarding the OS, the tumor SUV_{max}, pathological T status, *EGFR* mutation, and *KRAS* mutation were significant prognostic factors according to the univariate analysis. However, no independent significant factor of the OS was evident upon the multivariate analysis (data not shown).

Table 3 shows the relationships between clinicopathological features and the two independent prognostic factors (the SUV_{max} and the LNR). The SUV_{max} was significantly associated both with the histology and pathological T status, and the LNR exhibited significant relationships with sex, pathological nodal involvement, and lymphatic permeation.

Recurrence-free survival by independent prognostic factors

The RFS curves stratified by the numbers of the two independent risk factors, i.e., an SUV_{max} higher than 6.5 and an LNR over 0.12, are shown in Fig. 1a. All among-group survival differences were significant. The prognosis of the no-risk-factor group was optimal (3- and 5-year RFS rates were both 91.7 %), whereas that of the two-risk-factor group was extremely poor (3- and 5-year RFS rates were 12.0 and 6.0 %, respectively). The RFP curves drawn by reference to the numbers of the same

Table 3 Relationship between the SUV_{max}, LNR, and clinicopathological features

Variables	*N*	SUV max		*p* value[a]	LNR		*p* value[a]
		≤6.5 (*N* = 23)	>6.5 (*N* = 43)		≤0.12 (*N* = 30)	>0.12 (*N* = 36)	
Age (years)							
<70	35	13	22	0.678	15	20	0.652
≥70	31	10	21		15	16	
Sex							
Male	46	15	31	0.562	25	21	0.028†
Female	20	8	12		5	15	
PS							
0	58	22	36	0.157	26	32	0.783
1	8	1	7		4	4	
Smoking history							
Never	16	7	9	0.391	6	10	0.463
Ever	50	16	34		24	26	
CEA (ng/mL)							
≤5.0	43	17	26	0.275	21	22	0.450
>5.0	23	6	17		9	14	
Laterality							
Right	39	15	24	0.459	18	21	0.891
Left	27	8	19		12	15	
Clinical nodal staging							
cN0	41	18	23	0.082	20	21	0.074
cN1	16	2	14		9	7	
cN2	9	3	6		1	8	
Histology							
Adenocarcinoma	46	21	25	0.005†	19	27	0.304
Non-adenocarcinoma	20	2	18		11	9	
SUV_{max} of the tumor							
≤6.5	23	–	–		12	11	0.423
>6.5	43	–	–		18	25	
Pathological T status							
pT1	12	8	4	0.011†	8	4	0.103
pT2–4	54	15	39		22	32	
Pathological nodal involvement							
pN1	27	8	19	0.459	24	3	<0.001†
pN2	39	15	24		6	33	
Lymphatic permeation							
Ly (−)	5	3	2	0.220	5	0	0.011†
Ly (+)	61	20	41		25	36	
Vascular invasion							
V (−)	14	4	10	0.579	9	5	0.111
V (+)	52	19	33		21	31	
Pleural invasion							
PL (−)	25	12	13	0.080	15	10	0.064
PL (+)	41	11	30		15	26	
Tumor differentiation							
Well/moderate	50	18	32	0.729	24	26	0.463
Poorly	16	5	11		6	10	

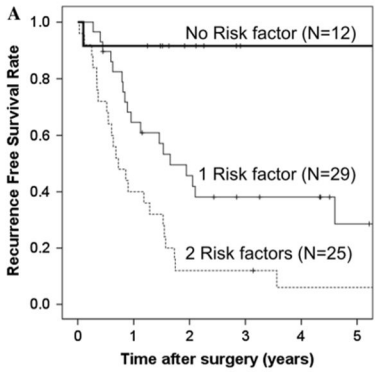
Table 3 continued

Variables	*N*	SUV max		*p* value[a]	LNR		*p* value[a]
		≤6.5 (*N* = 23)	>6.5 (*N* = 43)		≤0.12 (*N* = 30)	>0.12 (*N* = 36)	
EGFR mutation							
Mutant	18	8	10	0.316	6	12	0.226
Wild-type	48	15	33		24	24	
KRAS mutation							
Mutant	6	2	4	0.935	3	3	0.815
Wild-type	60	21	39		27	33	

PS performance status, *CEA* preoperative serum carcinoembryonic antigen level, *LNR* lymph node ratio

† Denotes significance

[a] Pearson's Chi square test



P-values in survival difference		
		P-value※
No RF vs	1 RF	0.01
	2 RFs	< 0.001
1 RFs vs	2 RFs	0.005

※ : by log-rank test. RF: risk factor

P-values in survival difference		
		P-value※
No RF vs	1 RF	0.005
	2 RFs	< 0.001
1 RFs vs	2 RFs	0.001

※ : by log-rank test. RF: risk factor

Fig. 1 Recurrence-free survival curves stratified by two independent risk factors, an SUV_{max} higher than 6.5 and an LNR higher than 0.12, are shown (**a**). The survival differences among all groups were significant. The prognosis of the no-risk-factor group was optimal (in terms of the 3- and 5-year RFS rates: both 91.7 %), whereas that of the one-risk-factor group was intermediate (3- and 5-year RFS rates: 38.1 and 28.6 %, respectively), and that of the two-risk-factor group was extremely poor (3- and 5-year RFS rates: 12.0 and 6.0 %, respectively). As the number of risk factors increased, the survival rates decreased. Recurrence-free proportion curves by the numbers of the same risk factors are shown in **b**. The survival differences were similar to those exhibited by the RFS curves, and all among-group survival differences were significant. All patients with no risk factors remained relapse-free during the follow-up

risk factors are shown in Fig. 1b. The survival differences were similar to those revealed by the RFS curves, and all among-group survival differences were significant. All patients with no risk factors remained relapse-free during the follow-up.

Figure 2 shows the RFS curves according to the administration (or not) of adjuvant chemotherapies in various groups differing in the numbers of risk factors. Although no significant survival difference was evident between the no-risk-factor group (Fig. 2a) and the one-risk-factor group

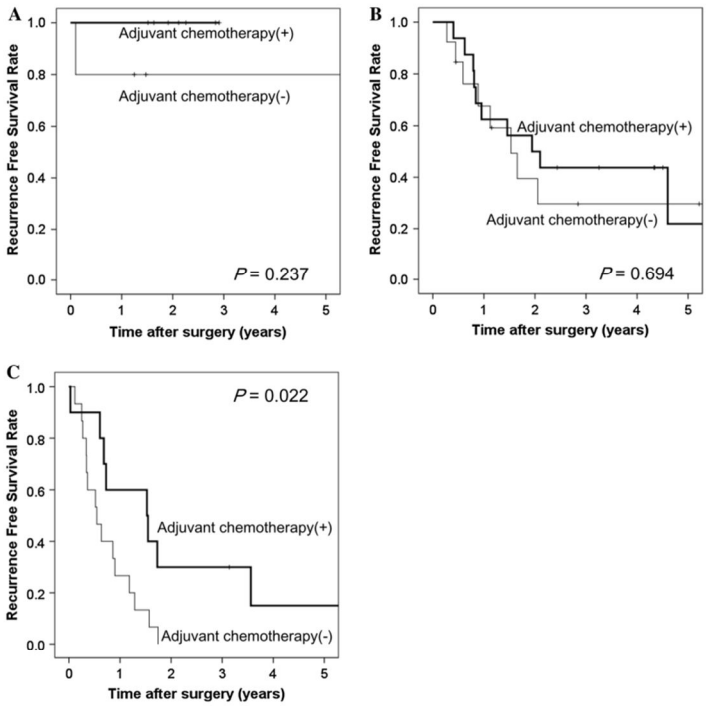


Fig. 2 Recurrence-free survival curves by treatment or not with adjuvant chemotherapies in terms of the numbers of risk factors present (**a** no risk factor, **b** one risk factor, **c** two risk factors). Although no significant survival difference was evident between the no-risk-factor group ($p = 0.237$, **a**) and the one-risk-factor group ($p = 0.694$, **b**), the prognoses of patients given adjuvant chemotherapies were better than others. In particular, in the two-risk-factor group, the survival difference was significant ($p = 0.022$, **c**)

(Fig. 2b), the prognoses of patients who received adjuvant chemotherapies were better than those who did not receive such treatment, with reference to each risk factor. In particular, in the two-risk-factor group the survival of those who received adjuvant chemotherapy was significantly better than that of those who did not receive chemotherapy (Fig. 2c).

Figure 3 shows the RFS curves by the SUV_{max} in adenocarcinoma (Fig. 3a) and non-adenocarcinoma patients (Fig. 3b), and by LNRs in adenocarcinoma (Fig. 3c) and non-adenocarcinoma patients (Fig. 3d). Regardless of the histology, patients with an SUV_{max} higher than 6.5 or LNRs over 0.12 had poorer prognoses than those without such values.

Discussion

In the present study, both the SUV_{max} of the primary tumor via ^{18}F-FDG-PET and the LNR were shown to be independent prognostic factors of the RFS in NSCLC patients with lymph node metastases (thus of the pathological N1 and N2). However, only the SUV_{max} was a good predictor of tumor recurrence in node-positive NSCLC patients.

^{18}F-FDG-PET is useful in various forms of lung cancer assessment, including the clinical diagnosis, evaluation of the pre-treatment extent of lymph node and distant metastasis, post-treatment assessment of the metabolic response, and determination of therapeutic effects after chemotherapy or radiotherapy [26, 27]. The intensity of the ^{18}F-FDG accumulation by the main tumor reflects the metabolic activity thereof. Previous studies have shown that ^{18}F-FDG-PET data and the tumor SUV_{max} are useful to predict recurrence in and the prognosis of NSCLC patients with stage IA [9], stage I [8, 28], and stage I or II [29, 30] disease, or T1 adenocarcinoma [11]. Okereke et al. showed that the SUV_{max} was predictive of the survival, particularly in patients with no mediastinal lymph node metastasis [10]. A systematic review and a meta-analysis by the

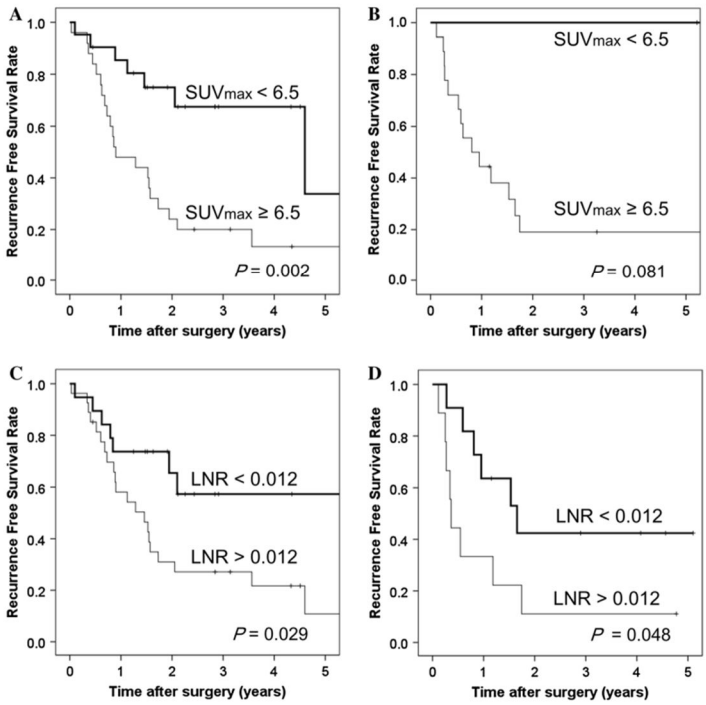


Fig. 3 Recurrence-free survival curves stratified by the cut-off values of the SUV_{max} in adenocarcinoma (**a**) and non-adenocarcinoma (**b**) patients, and the cut-off values of the LNR in adenocarcinoma (**c**) and non-adenocarcinoma patients (**d**). Regardless of tumor histology, patients with an SUV_{max} higher than 6.5 and LNRs higher than 0.12 had poorer prognoses than those who did not

European Lung Cancer Working Party showed that the SUV_{max} was a prognostic value in 13 studies on NSCLC [31]. The SUV increases when the tumor diameter becomes greater or when the cancer is at an advanced stage [10, 32]. Therefore, we examined the prognostic significance of the SUV_{max} in pathological node-positive NSCLC patients. In practical terms, the SUV_{max} was correlated with the pathological T factor, however, the SUV_{max} was also shown to be an independent prognostic factor, whereas the pathological T factor was not. Our study thus suggests that the SUV_{max} of the main tumor could be the most valuable surrogate marker of tumor aggressiveness and cancer recurrence in NSCLC patients with lymph node metastases. ^{18}F-FDG-PET findings on primary tumors have been reported to predict both the survival and local control in NSCLC patients treated with radiotherapy [33, 34] and chemoradiotherapy [35, 36]. This suggests that ^{18}F-FDG-PET is also useful for evaluating the prognoses of patients with locally advanced lung cancer, regardless of treatment modality.

The LNR has also been reported to be a good predictor of recurrence and the survival after complete resection of NSCLC [13–16, 22, 37–39]. Qiu et al. reported that the LNR was a valuable prognostic marker, particularly in patients with pathological N1 disease [14]. Some reports have shown that the LNR was a significant prognostic factor in N1 NSCLC patients [16, 22, 37], and others showed that this was also the case in both N1 and N2 patients, or in one or the other group [13, 15, 38, 39]. The cut-off LNR values differed among reports, ranging from 0.12 (12 %) to 0.35 (35 %). Therefore, the "true" cut-off value must be validated in a large cohort of N1 and N2 patients, evaluated both individually and in combination, and the significance thereof compared with that of N descriptors of the TNM classification. As the LNR is affected by the number of dissected and examined lymph nodes [39], a low cut-off value could assure the trustworthiness of lymph node dissection and could also be applied in our present study. We found that the LNR was closely associated with both the pathological nodal stage of the TNM classification and lymphatic permeation. The LNR may also be an optimal simple surrogate marker of lymphatic expansion in NSCLC patients with lymph node metastases.

In the present study, we showed that adjuvant chemotherapy was a significant favorable prognostic factor in terms

of the RFS, and, especially, such therapy was more effective in high-risk patients with node-positive NSCLC who had a high SUV_{max} and elevated LNRs. The tumor SUV_{max} has also been reported to be a good indicator of the need for adjuvant chemotherapy in patients with pathological T1b-2aN0M0 lung adenocarcinoma [40]. Wang et al. reported that the survival rate of a high-LNR group was improved by adjuvant chemotherapy, but that of a low-LNR group was not [38]. Urban et al. reported that only N2 patients with LNRs over 50 % showed survival benefits by postoperative radiotherapy. These findings support the idea that higher SUV_{max} and LNRs indicate a further need for adjuvant treatment. Although the survival benefit of adjuvant chemotherapy might be affected by selection bias, prognostic differences in the performance status (PS) and age and correlations between the SUV_{max}, LNRs and PS, age were not significant.

The SUV_{max} is known to vary by tumor histology, and the SUV_{max} of squamous cell carcinoma is higher than that of adenocarcinoma [41]. The SUV_{max} was also associated with the histological findings in the present study, and we therefore explored whether the cut-off value for all patients was the same as the values for both adenocarcinoma and non-adenocarcinoma patients. In non-adenocarcinoma patients, the small sample size ($N = 20$) indicated that only a tendency toward an influence on the survival was evident; however, in adenocarcinoma patients, a significant survival difference was evident between the high and low SUV_{max} groups.

There are some limitations associated with the present study, including the small sample size and the short follow-up duration. It may have been better to investigate the patient prognoses after stratification into the N classes N1 and N2. However, in this study, the LNR had a stronger prognostic impact than the nodal status. We were able to define a suitable LNR cut-off value for our present patient cohort. We explored the RFS and RFP in terms of the survival, because of the risk of nodal disease recurrence, however, no significant between-group survival differences were observed when it was sought to use variables, including LNR and SUV_{max}, to predict the OS.

Conclusions

In conclusion, both the SUV_{max} and the LNR serve as prognostic factors for patients with resected pathologically node-positive NSCLC. The combination of the SUV_{max} (a clinical factor) and the LNR (a pathological factor) is potentially useful to predict the prognoses of NSCLC patients with pathological nodal disease. Further validation is required to determine the appropriate cut-off values and to clarify whether the LNR or nodal status better predicts the prognosis.

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Compliance with ethical standards

Conflict of interest All authors participated in this study and agreed on the content of this paper. None of them have any financial or other relations that could lead to a conflict of interest.

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