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B-Type Natriuretic Peptide as a Predictor of Postoperative Cardiopulmonary Complications in Elderly Patients Undergoing Pulmonary Resection for Lung Cancer

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Background. The objective of the present study was to evaluate the utility of B-type natriuretic peptide for prediction of postoperative cardiopulmonary complications in elderly patients undergoing pulmonary resection for lung cancer.

Methods. A prospective observational study was performed involving 80 consecutive patients aged 75 years or older who underwent a scheduled pulmonary resection for lung cancer in two specialized thoracic centers between January 2008 and June 2010. Baseline clinical details were obtained, and spirometry and examination of serum B-type natriuretic peptide levels were performed before surgery. The primary endpoint was the incidence of postoperative cardiopulmonary complications.

Results. Postoperative cardiopulmonary complications were identified in 34 (43%) patients; these patients had significantly higher preoperative B-type natriuretic peptide levels than those without cardiopulmonary complications (84.0 ± 93.7 pg/mL vs 22.0 ± 18.2 pg/mL; $p < 0.0001$). The area under the receiver operating characteristic curve for B-type natriuretic peptide to predict postoperative cardiopulmonary complications after pulmonary resection for lung cancer was 0.85 (95% confidence interval 0.76 to 0.94; $p < 0.0001$). A B-type natriuretic peptide value of 30 pg/mL had a sensitivity of 79% and a specificity of 83% for predicting postoperative cardiopulmonary complications after pulmonary resection for lung cancer. The incidences of both cardiovascular and respiratory complications were significantly higher in patients with preoperative B-type natriuretic peptide levels of 30 pg/mL or more.

Conclusions. Preoperative B-type natriuretic peptide level could be a useful predictor of postoperative cardiopulmonary complications in elderly patients after pulmonary resection for lung cancer.

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Lung cancer is generally a disease of older adults, and age has been shown to be an important risk factor for morbidity and mortality after pulmonary resection [1, 2]. Because of these increased risks, elderly patients are offered curative surgery for lung cancer less often than younger patients [3, 4]. However, it is not appropriate that elderly patients be considered as unable to undergo curative surgery solely because of their advanced age. Because conventional methods of assessing operative risk provide only a limited ability to predict postoperative complications in elderly patients, it is important to identify more specific and more sensitive markers.

B-type natriuretic peptide (BNP) is a useful prognostic predictor in patients with left ventricular (LV) dysfunction independent of hemodynamic parameters, such as LV ejection fraction [5]. Excluding cardiac diseases, an increased BNP level was associated with some pulmonary diseases [6–9]. Therefore, it is plausible to expect that preoperative BNP levels could be useful for predicting postoperative cardiopulmonary complications.

We previously reported that patients in all age groups with mildly elevated preoperative BNP levels have an increased risk of developing postoperative atrial fibrillation after pulmonary resection for lung cancer [10]. In this study, elderly patients (≥ 75 years) were enrolled, and they are known to have an increased risk for postoperative complications after pulmonary resection [11]. The purpose of the present study was to evaluate the utility of serum BNP levels for predicting postoperative cardiopulmonary complications in elderly patients undergoing pulmonary resection for lung cancer.

Patients and Methods

Study Design and Population

Of 470 patients who underwent an elective pulmonary resection procedure for lung cancer at our institute from January 2008 to June 2010, this prospective observational

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study included 96 consecutive elderly patients aged 75 years or older. Complete preoperative and follow-up data were obtained for all of these patients. This study was performed at Osaka University Graduate School of Medicine and National Toneyama Hospital. The study protocol was approved by the Institutional Review Boards of both institutions, and all patients provided their written informed consent before participation. Exclusion criteria for the present analysis were cardiac rhythm other than sinus, previous atrial fibrillation, antiarrhythmic drug use, thyroid dysfunction, renal failure requiring hemodialysis, repeated pulmonary resection, and recent (<1 month) angina pectoris, myocardial infarction, or pneumonia. As a result, 16 patients were excluded. Thus, 80 patients were finally chosen.

Surgical Procedure

All patients underwent anterolateral thoracotomy or video-assisted thoracic surgery (VATS). In VATS, 3 access ports were inserted through 1 to 2 cm skin incisions in the side of the chest. One of these skin incisions was extended by 4 to 5 cm, and the resected lung lobe was removed in a plastic bag without using a rib retractor. Patients in whom VATS was replaced intraoperatively with open thoracotomy were classified as open thoracotomy patients. All patients received preoperative epidural anesthesia for pain management, which usually remained in place for 2 to 4 days or until the chest drainage tubes were removed, after which they were switched to oral analgesia. Other postoperative management methods included early ambulation and low-flow nasal oxygen supplementation, as necessary.

Preoperative Examinations

Preoperative evaluations included a detailed history and physical examination, blood gas analysis, 12-lead electrocardiogram, spirometry, and determination of serum BNP levels. None of the patients had symptomatic coronary artery disease or congestive heart failure. Physical examinations and electrocardiographic findings at rest were unremarkable in the study population. The serum BNP concentrations were determined using a chemiluminescence enzyme immunoassay (MI02 Shionogi BNP; Shionogi Pharmaceutical, Osaka, Japan). The minimum concentration of BNP detectable with this system is 4 pg/mL.

Postoperative Complications

All patients were followed up prospectively after surgery, and complications occurring during the same hospitalization as the index procedure were recorded. Cardiopulmonary complications were defined to include respiratory complications, such as pneumonia (fever > 38°C, purulent sputum, abnormal findings on chest X-ray), acute respiratory distress syndrome (partial pressure of oxygen in arterial blood-fraction of inspired oxygen less than 200 mm Hg), respiratory insufficiency requiring tracheostomy, respiratory failure requiring mechanical ventilation, atelectasis with bronchoscopic therapy, home oxygen treatment, and cardiovascular complications, including arrhythmias (atrial fibrillation, paroxysmal supraventricular tachycardia, ventricular tachycardia), angina pectoris, myocardial infarction, congestive heart failure, and thromboembolic events. As prolonged air leak and bronchopleural fistulas are considered surgical factors, they were excluded. Finally, operative mortality was defined as death within 30 days after surgery.

Statistical Analysis

Data are expressed as means ± SD or as proportions. All data were analyzed using SPSS version 11.0 (SPSS Inc, Chicago, IL). Comparisons among all parameters were analyzed by one-way analysis of variance. Comparisons between the 2 groups were made using the Mann-Whitney test, with the χ^2 test for categoric variables. Logistic regression analyses were used to explore the risk factors for complications. Receiver operating characteristic curves were constructed to determine optimal sensitivity and specificity. Probability values of less than 0.05 were considered significant.

Results

The patients' mean age was 78.4 years. Postoperative cardiopulmonary complications were identified in 34 (43%) of the 80 cases and are listed in Table 1. Overall, the most common complications were arrhythmias, especially atrial fibrillation, while pneumonia was the most common respiratory complications. The clinical and surgical characteristics of patients with and without postoperative cardiopulmonary complications are summarized in Table 2. Operative mortality was 1.3% (n = 1).

Postoperative cardiopulmonary complications were associated with male sex, smoking, and hypertension. There were no significant differences between patients with and without cardiopulmonary complications with respect to type of procedure, VATS procedure, combined resection, operating time, intraoperative blood loss, mediastinal lymph node dissection, or pathologic stage. In a comparison of the results of pulmonary function parameters between the 2 groups, patients with cardiopulmo-

Table 1. Postoperative Cardiopulmonary Complications

Variables	Number (%)
All complications	34 (43)
Cardiovascular complications	28 (35)
Atrial fibrillation	18 (23)
Paroxysmal supraventricular tachycardia	6 (8)
Ventricular tachycardia	1 (1)
Acute myocardial infarction	2 (3)
Acute arterial occlusion of the lower extremity	1 (1)
Respiratory complications	12 (15)
Pneumonia	6 (8)
Home oxygen therapy	4 (5)
Acute respiratory distress syndrome	2 (3)
Acute exacerbation of interstitial pneumonia	1 (1)

Table 2. Patient Characteristics

Variables	Without Cardiopulmonary Complications (n = 46)	With Cardiopulmonary Complications (n = 34)	*p* Value
Age (years)	77.9 ± 2.9	78.7 ± 3.1	0.63
Male	24 (52)	27 (79)	0.003[a]
Smoking history	21 (46)	26 (76)	0.005[a]
Hypertension	21 (46)	27 (79)	0.004[a]
Hypercholesterolemia	10 (22)	10 (29)	0.44
Diabetes mellitus	4 (9)	3 (9)	0.64
Ischemic heart disease	3 (7)	7 (21)	0.06
Type of procedure:			
Segmentectomy or wedge resection	8 (17)	7 (21)	0.54
Lobectomy or bilobectomy	38 (83)	27 (79)	0.54
VATS procedure	32 (70)	15 (44)	0.12
Combined resection	1 (2)	2 (6)	0.39
Operating time (minutes)	233 ± 69	236 ± 76	0.88
Blood loss (mL)	144 ± 148	214 ± 337	0.24
Mediastinal lymph node dissection	26 (57)	14 (41)	0.12
Lung cancer staging			
IA, IB	38 (83)	25 (74)	0.33
IIA, IIB	4 (9)	3 (9)	0.98
IIIA, IIIB, IV	4 (9)	6 (18)	0.24

[a] Significant ($p < 0.05$).

Values are shown as numbers (%) or means ± SD, unless otherwise indicated.

VATS = video-assisted thoracoscopic surgery.

nary complications had significantly impaired percent-predicted forced expiratory volume in 1 second (FEV_1, % predicted) ($p = 0.02$) and forced expiratory volume in 1 second/forced vital capacity (FEV_1/FVC) ($p = 0.03$) compared with those without cardiopulmonary complications (Table 3).

Table 3. Preoperative Pulmonary Function Variables

Variables	Without Cardiopulmonary Complications (n = 46)	With Cardiopulmonary Complications (n = 34)	*p* Value
VC, % predicted	101 ± 11	96 ± 14	0.12
FEV_1, % predicted	91.8 ± 16	79.6 ± 16	0.006[a]
FEV_1/FVC, %	76.4 ± 7.5	71.2 ± 13	0.03[a]
D_{LCO}, % predicted	97.6 ± 15	93.4 ± 29	0.12
RV/TLC	42.5 ± 5.1	45.0 ± 7.8	0.18
pH	7.41 ± 0.02	7.41 ± 0.01	0.69
Pa_{O_2}, Torr	86.3 ± 14	87.3 ± 12	0.79
Pa_{CO_2}, Torr	40.3 ± 2.5	40.2 ± 4.2	0.87

[a] Significant ($p < 0.05$).

Values are the means ± SD, unless otherwise indicated.

D_{LCO} = carbon monoxide diffusing capacity; FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity; Pa_{CO_2} = carbon dioxide blood partial pressure; Pa_{O_2} = arterial oxygen blood partial pressure; RV/TLC = ratio of residual volume to total lung capacity; Torr = non-SI unit of pressure; VC = vital capacity.

Figure 1 shows the preoperative BNP levels in patients with and without postoperative cardiopulmonary complications. Patients with cardiopulmonary complications had significantly higher BNP levels than those without cardiopulmonary complications (84.0 ± 93.7 pg/mL vs 22.0 ± 18.2 pg/mL; $p < 0.0001$). The preoperative serum

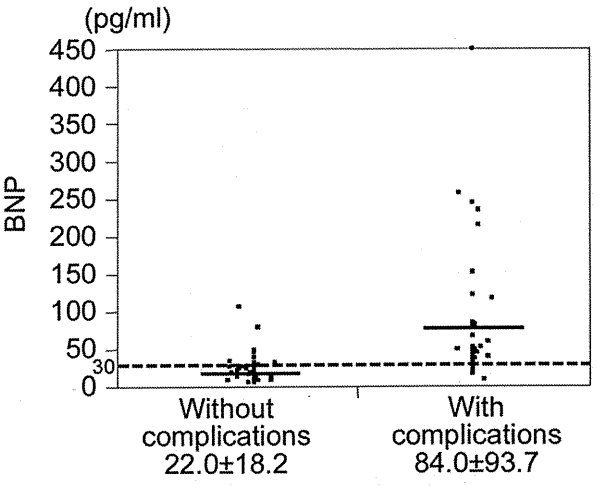

Fig 1. Preoperative B-type natriuretic peptide (BNP) levels in patients with and without postoperative cardiopulmonary complications. Patients with cardiopulmonary complications have significantly higher preoperative BNP levels than those without complications ($p < 0.0001$).

Table 4. Univariate and Multivariate Analyses of Factors for Predicting Postoperative Cardiopulmonary Complications

	Univariate Analysis		Multivariate Analysis	
Variables	Relative Risk (95% CI)	*p* Value	Relative Risk (95% CI)	*p* Value
Male	1.916 (0.762–4.821)	0.16	1.642 (0.384–6.914)	0.82
Smoking	3.869 (1.449–10.33)	0.007[a]	2.780 (0.792–20.11)	0.21
Hypertension	3.536 (1.284–9.735)	0.015[a]	3.622 (0.885–22.01)	0.11
FEV_1, % predicted	0.952 (0.918–0.988)	0.011[a]	0.962 (0.911–1.017)	0.10
BNP	1.056 (1.023–1.089)	0.0006[a]	1.080 (1.022–1.139)	0.005[a]

[a] Significant ($p < 0.05$).

BNP = B-type natriuretic peptide; CI = confidence interval; FEV_1 = forced expiratory volume in 1 second.

BNP level of the patient who died postoperatively of acute myocardial infarction was 143 pg/mL.

On univariate and multivariate analyses (Table 4), an elevated BNP level was the most significant predictor of postoperative cardiopulmonary complications in elderly patients undergoing pulmonary resection for lung cancer. The area under the receiver operating characteristic curve for preoperative BNP levels to predict postoperative cardiopulmonary complications after pulmonary resection for lung cancer was 0.85 (95% confidence interval 0.76 to 0.94; $p < 0.0001$), and the BNP level of 30 pg/mL had a sensitivity of 79%, specificity of 83%, positive predictive value of 82%, and negative predictive value of 85% for predicting postoperative cardiopulmonary complications. Finally, the patients were classified into 2 groups based on the preoperative BNP level; less than 30 pg/mL and 30 pg/mL or greater. As shown in Table 5, the incidences of both cardiovascular and respiratory complications were significantly higher in patients with preoperative BNP levels of 30 pg/mL or more.

Comment

The present results indicate that elderly patients with elevated preoperative BNP levels are at increased risk for postoperative cardiopulmonary complications after pulmonary resection for lung cancer. The preoperative BNP level was also found to be an independent predictor of postoperative cardiopulmonary complications.

The risk of surgery is usually higher in elderly patients with concomitant, age-related respiratory or cardiac disease. However, surgery still represents the main curative treatment modality for non-small cell lung cancer, and the performance of curative surgery in the elderly still represents a clinical challenge frequently faced by thoracic surgeons. Therefore, more appropriate preoperative evaluations are necessary for elderly patients undergoing pulmonary resection for lung cancer.

The BNP level has been shown to be accurate enough for diagnosing, monitoring, and predicting prognosis in patients with congestive heart failure [12], while more recently it was reported that an increased BNP level may predict postoperative cardiovascular events in patients undergoing emergency noncardiac surgery [13]. We also previously reported that lung cancer patients with mildly elevated preoperative BNP levels had an increased risk of developing postoperative atrial fibrillation [10]. Relatively younger patients were enrolled in our previous study (mean age 66.1 years). However, in this analysis of elderly patients, the incidences of not only cardiovascular

Table 5. Postoperative Cardiopulmonary Complications by Preoperative Serum BNP Level

Variables	BNP < 30 pg/mL (n = 48)	BNP ≥ 30 pg/mL (n = 32)	*p* Value
All complications	7 (15)	27 (84)	<0.0001[a]
Cardiovascular complications	7 (15)	21 (66)	<0.0001[a]
Atrial fibrillation	5	13	
Paroxysmal supraventricular tachycardia	1	5	
Ventricular tachycardia	1	0	
Acute myocardial infarction	0	2	
Acute arterial occlusion of the lower extremity	0	1	
Respiratory complications	1 (2)	11 (34)	<0.0001[a]
Pneumonia	0	6	
Home oxygen therapy	1	3	
Acute respiratory distress syndrome	0	2	
Acute exacerbation of interstitial pneumonia	0	1	

[a] Significant ($p < 0.05$).

BNP = B-type natriuretic peptide.

but also respiratory complications were significantly higher in patients with elevated preoperative BNP levels. Recently it was reported that an increased BNP level was associated with primary pulmonary hypertension [6, 7], chronic thromboembolic pulmonary hypertension [8], and chronic pulmonary disease, especially when associated with cor pulmonale [9]. The common pathway to BNP elevation in these pulmonary diseases seems to be right ventricular (RV) overload. In addition, some recent studies found that patients with RV pressure or volume overload had a leftward shift of the ventricular septum toward the center of the LV cavity [14], resulting in geometric distortion of the left ventricle. Leftward ventricular septal shift in patients with RV overload leads to an LV filling abnormality; that is, LV diastolic dysfunction. Left ventricular diastolic dysfunction has been reported to be a risk factor for arrhythmias [15], pulmonary edema [16], and mild elevation of BNP levels [17, 18]. Thus, it appears that pulmonary disease and cardiac dysfunction are closely related. Moreover, it has been reported that patients with postoperative arrhythmias frequently developed respiratory complications at the same time [19]. In this study, 6 patients developed both cardiovascular and respiratory complications.

To the best of our knowledge, this is the first study to evaluate BNP levels as a possible predictor for postoperative cardiopulmonary complications in elderly patients undergoing pulmonary resection for lung cancer. Serum BNP levels should be measured in elderly patients before surgery and effective prophylactic strategies should be considered for elderly patients with elevated preoperative BNP levels.

This study was a two-institution clinical study, which restricted our ability to generalize the results. In addition, the number of patients in the study cohort was relatively small; thus, additional investigations are necessary to define the ability of BNP to predict postoperative cardiopulmonary complications in elderly patients undergoing pulmonary resection for lung cancer. Finally, since echocardiographic examinations were not performed, there are no data regarding the presence of RV overload or LV diastolic dysfunction.

The results of the present study demonstrate that the preoperative serum BNP level could be a useful predictor of postoperative cardiopulmonary complications in elderly patients undergoing pulmonary resection for lung cancer. This finding allows stratification of patients at high risk for postoperative cardiopulmonary complications for planning an effective prophylactic strategy.

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Low Dihydropyrimidine Dehydrogenase Correlates with Prolonged Survival in Patients with Lung Adenocarcinoma Treated with 5-Fluorouracil

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Abstract. *Background: The enzyme dihydropyrimidine dehydrogenase (DPD) is involved in the metabolism of 5-fluorouracil (5-FU). The aim of this study was to clarify the correlation between the expression of DPD and the efficacy of 5-FU therapy in patients with lung adenocarcinoma (AD). Patients and Methods: We examined surgically resected specimens from 90 stage I to IIIA patients with lung ADs to determine the level of intra-tumoral DPD mRNA. Results: Administration of 5-FU improved the prognosis of patients with low DPD-expressing tumors, whereas it did not do so for patients with high DPD expressing tumors. Patients with low DPD-expressing tumors administered with 5-FU had a significantly better prognosis than those who underwent surgery alone. A Cox proportional hazards regression model revealed that administration of 5-FU was an independent variable to predict prognosis in patients with low DPD-expressing tumors. Conclusion: Quantification of DPD mRNA levels is useful for determining the subgroup of lung AD patients who would benefit most from 5-FU after surgery.*

5-Fluorouracil (5-FU) and its derivatives are widely used for treatment of various types of cancer (1). A recent study showed that postoperative oral administration of tegafur-uracil (UFT) improves survival in patients following resection of stage I lung adenocarcinoma (AD) and its administration has become standard therapy after curative resection in early non-small cell lung cancer (NSCLC) cases (2, 3). Furthermore, a novel oral form of fluorouracil S-1 was shown to have promising effects against advanced NSCLC (4). These findings indicate that 5-FU is effective for NSCLC patients and highlight the importance of detection of biomarkers for prediction of its efficacy for treating NSCLC.

Thymidylate synthase (TYMS), the target enzyme for 5-FU, catalyzes an important process for DNA biosynthesis (5, 6) and we previously reported that the prognosis of NSCLC patients is related significantly to the intratumoral *TYMS* mRNA level (7). Dihydropyrimidine dehydrogenase (DPD) is one of the key enzymes involved in the catabolism of 5-FU and its expression was found useful in predicting the efficacy of 5-FU after surgery for NSCLC based on disease-free interval during short follow-up periods (8-10). In the present study, we examined the efficacy of 5-FU in association with DPD expression in regards to prognosis, including overall survival, in patients with lung ADs over a longer follow-up period.

Patients and Methods

Ninety specimens from lung AD patients determined to be p-stage I to IIIA were obtained during surgical procedures at Osaka University Hospital, Kinki Chuo Chest Medical Center, Toneyama Hospital, and Osaka Prefectural Medical Center for Respiratory and Allergic Disease between January 1999 and March 2003. Quantification of *TYMS* and *DPD* mRNA levels in AD tissues was performed as described previously (7, 10). The obtained copy numbers of *TYMS* and *DPD* were standardized with glyceralde-hydo-3-phosphate dehydrogenase (*GAPDH*) mRNA quantity, used as an endogenous control, with the following equation: 'Result'=Log (*TYMS* or *DPD* RNA copy number in tumor)/(*GAPDH* RNA copy number in tumor)×(6.1×10^9; *GAPDH* RNA copy number in 1 μg of total RNA extracted from the peripheral blood of 30 healthy volunteers).

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Key Words: Lung adenocarcinoma, 5-fluorouracil, dihydropyrimidine dehydrogenase, thymidylate synthase, chemosensitivity.

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Table I. *Patient background data.*

Variable	Treatment		*p*-Value
	Surgery alone (control) n=60	5-FU n=30	
Age (years)	63±9.3	62±9.4	0.445
Gender			
Male	35 (58%)	20 (67%)	0.426
Female	25 (42%)	10 (33%)	
Pathologic stage			
I	38 (63%)	20 (67%)	
II	9 (15%)	6 (20%)	0.882
IIIA	13 (22%)	4 (13%)	

5-FU, 5-fluorouracil. *p*-Value, chi-square test or Mann-Whitney *U*-test.

Table II. *Thymidylate synthase (TYMS) and Dihydropyrimidine dehydrogenase (DPD) mRNA levels, and clinicopathologic factors.*

Factor	n	Log TYMS mRNA	*p*-Value	Log DPD mRNA	*p*-Value
Tumor status			0.029		0.054
pT1	49	6.90±0.29		6.89±0.48	
pT2	36	7.03±0.33		6.63±0.54	
pT3	5	7.42±0.54		6.99±0.27	
Nodal status			0.600		0.546
pN0	61	6.96±0.34		6.80±0.57	
pN1	12	7.00±0.36		6.75±0.41	
pN2	17	7.04±0.35		6.80±0.33	

p-Value, chi-square test or Mann-Whitney *U*-test.

Informed consent was obtained from all patients. Those administered UFT following surgery comprised the 5-FU group (n=30), while those who underwent surgery only, comprised the control group (n=60). UFT administration was started within 2 months after surgery and continued for more than 12 months. The dose of UFT was 300-400 mg/day and the mean duration of treatment was 21.5±7.3 months (mean±SD; range 12-26 months). The clinical backgrounds of the patients are summarized in Table I. There was no difference in clinical factors between the groups. The median follow-up period was 78±23 months (range 17-115 months) after surgery.

Chi-square, Mann-Whitney *U*, and Kruskal-Wallis tests were used to compare the results, while survival rates were estimated by the method of Kaplan and Meier and compared using log-rank test, using Statview version 5.0 for Windows (Abacus Concepts, Berkeley, CA, USA). A *p*-value of <0.05 was considered to be statistically significant.

Results

Quantification of *TYMS* and *DPD* mRNA levels in NSCLC tissues was successfully performed for all specimens. Intratumoral *TYMS* and *DPD* mRNA levels ranged from 6.28 to 8.04 (mean±SD; 6.98±0.34) and 5.36 to 8.28 (6.79±0.59), respectively. The results for *TYMS* and *DPD* mRNA levels are summarized in Table II. *TYMS* mRNA levels were associated with tumor status, while *DPD* mRNA levels were not associated with tumor or nodal status.

Thirty-five (39%) of the 90 patients developed distant metastasis after surgery. In regards to tumor stage, 12 (21%) out of 58 patients in stage I, 8 (53%) out of 15 patients in stage II, and 15 (88%) out of 17 patients in stage IIIA suffered from recurrent disease. Categorized by group, 27 (45%) out of 60 patients and 8 (27%) out of 30 in the control and 5-FU groups, respectively, had recurrence. There was no significant difference in overall survival rate between the groups (Figure 1A). Similar to a previous report (7), *TYMS* mRNA levels were significantly correlated to overall survival when dichotomized at the mean *TYMS* mRNA level (Figure 1B).

Next, we evaluated the correlation between *DPD* expression and efficacy of 5-FU. *DPD* mRNA levels were significantly correlated to overall survival in the 5-FU group, but not in the control group when dichotomized at the mean *DPD* mRNA level (Figure 2). In the 5-FU-group, the 5-year survival rate was 92% for the low DPD-expressing subgroup and 68% for the high DPD-expressing subgroup. Patients with low DPD-expressing tumors, who were administered 5-FU had a significantly better prognosis than those who underwent surgery alone (Figure 3A); the 5-year survival rates were 92% for the 5-FU group and 53% for the control group. These findings suggest that the intratumoral *DPD* mRNA level may be a possible predictor for efficacy of 5-FU administration after surgery for NSCLC. On the other hand, patients with high DPD-expressing tumors administered 5-FU had a tendency for a worse prognosis as compared to those who underwent surgery alone (Figure 3B).

We analyzed 5 variables, namely tumor status, nodal metastasis, *TYMS* mRNA expression, *DPD* mRNA expression, and 5-FU administration, using a Cox proportional hazards regression model to determine their effects on overall survival in NSCLC patients (Table IIIA). Multivariate analysis revealed that p-N2 and *TYMS* mRNA expression were independent variables for predicting overall survival (Table IIIB). Furthermore, in patients with low DPD-expressing tumors, multivariate analysis showed that *TYMS* mRNA expression and administration of 5-FU, were each independent variables predicting prognosis (Table IIIC).

Discussion

We performed quantitative assays of intratumoral *TYMS* and *DPD* mRNA levels to assess their association with clinicopathological factors, as well as the feasibility of applying them to predict the efficacy of 5-FU therapy in

patients with NSCLC over a long term. TYMS activity is necessary for cell proliferation because it catalyses an essential step in DNA synthesis, while its overexpression is reported to be associated with tumor proliferation, as well as poor prognosis, in a variety of cancer types (11, 12). As shown in Table IIIB, multivariate analysis revealed that a high level of *TYMS* mRNA was independently correlated to overall survival with a high hazard ratio, indicating that this marker can precisely perform prognosis for patients with lung AD. Determination of gene expression by RT-PCR is a useful technique for small-sized specimens, thus quantification of *TYMS* mRNA levels is clinically sensitive and useful for determining the prognosis of AD patients (7).

As DPD is a rate-limiting enzyme in the catabolism of 5-FU, its high expression in tumors is reported to result in a low sensitivity to 5-FU therapy (13). In the present study, we evaluated the efficacy of 5-FU administration as adjuvant chemotherapy, in relation to intratumoral *DPD* mRNA levels in lung AD patients. Our results revealed that *DPD* expression was significantly inversely correlated to the overall survival of patients administered 5-FU following surgery, indicating that patients with low levels of *DPD* expression in cancer tissue are sensitive to 5-FU. Furthermore, for patients with low DPD-expressing tumors, those administered 5-FU had a significantly better prognosis than those who underwent surgery alone. These findings suggest that the intratumoral *DPD* mRNA level is a possible predictor for the efficacy of 5-FU administration after surgery in lung AD patients. Interestingly, in patients with high DPD-expressing tumors, those administered 5-FU had a tendency for worse prognosis than those who underwent surgery alone (Figure 3B), suggesting that 5-FU may not have benefits for patients with high DPD-expressing tumors. Multivariate analysis showed that administration of 5-FU was an independent variable predicting prognosis of patients with low DPD-expressing lung ADs. Based on these results, determination of *DPD* mRNA levels in lung AD tumors may provide important information for clinicians to decide whether or not to proceed with 5-FU-based chemotherapy for their patients.

Based on our findings for biomarkers associated with 5-FU therapy, it is considered important to evaluate the expressions of TYMS and DPD before establishing a protocol for made-to-order chemotherapy for NSCLC patients (14). In addition, investigation of the effects of more aggressive adjuvant therapy for patients with NSCLC who have elevated *TYMS* or *DPD* mRNA levels is also necessary. Takizawa *et al.* reported that *in vitro* sensitivity to platinum-derived drugs, such as cisplatin and carboplatin, was associated with the expression of *TYMS* and *DPD* in NSCLC specimens (15). They hypothesized that these may be novel markers of DNA repair capacity and may also be linked with chemosensitivity to drugs other than 5-FU. Furthermore, it is important to clarify the roles of TYMS and DPD in regards to chemosensitivity toward various chemotherapy regimens, as their inhibition is now receiving attention for new cancer treatment drugs development. Recently, S-1, a combination of tegafur, gimeracil, and oteracil potassium (Taiho Pharmaceutical), was developed for clinical use (4). Gimeracil is a stronger inhibitor of DPD than uracil when used with UFT. However, Takeda *et al.* reported that a high level of DPD expression predicted resistance to S-1-based chemotherapy in patients with advanced NSCLC (16). Therefore, additional investigations of the effects of new

Table III.

A. Univariate analysis of overall survival in all patients.

Factors	Hazard ratio	95% CI	*p*-Value
Tumor status			
pT3 *vs.* pT1	3.71	1.05-13.2	0.042
pT2 *vs.* pT1	1.91	0.93-3.90	0.079
Nodal status			
pN2 *vs.* pN0	3.33	1.54-7.21	0.002
pN1 *vs.* pN0	1.73	0.67-4.45	0.259
TYMS mRNA			
High *vs.* low	4.17	1.81-9.03	0.001
DPD mRNA			
High *vs.* low	1.09	0.55-2.520	0.804
Administration			
5-FU *vs.* none	1.46	0.68-3.15	0.337

B. Multivariate analysis of overall survival in all patients.

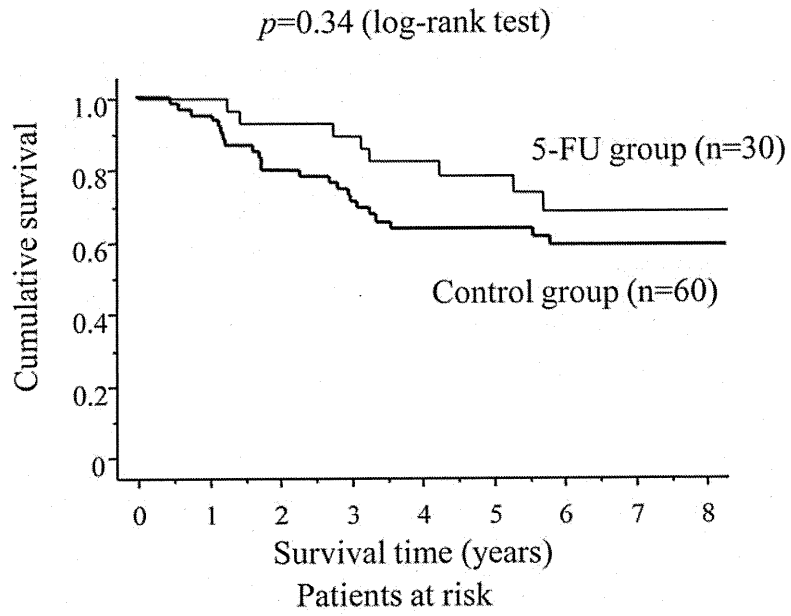
Factor	Hazard ratio	95% CI	*p*-Value
Tumor status			
pT3 *vs.* pT1	2.51	0.69-9.12	0.161
pT2 *vs.* pT1	1.27	0.59-2.75	0.546
Nodal status			
pN2 *vs.* pN0	2.56	1.16-5.66	0.020
pN1 *vs.* pN0	1.41	0.51-3.87	0.511
TYMS mRNA			
High *vs.* low	3.42	1.46-8.02	0.005

C. Multivariate analysis of overall survival in patients with low DPD-expressing tumors.

Factor	Hazard ratio	95% CI	*p*-Value
Nodal status			
pN2 *vs.* pN0	1.42	0.42-4.76	0.570
pN1 *vs.* pN0	0.85	0.22-3.27	0.816
TYMS mRNA			
High *vs.* low	5.31	1.17-24.0	0.030
Administration			
5-FU *vs.* none	7.60	1.02-56.7	0.050

CI, Confidence interval. TYMS, Thymidylate synthase. DPD, Dihydropyrimidine dehydrogenase. 5-FU, 5-fluorouracil.

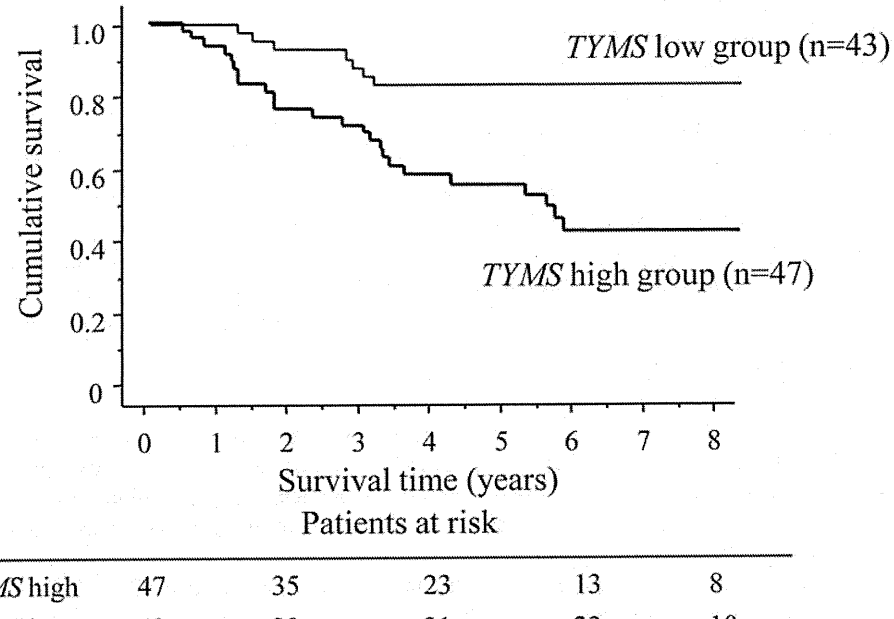
A



Patients at risk

Control	60	47	32	24	12
5-FU	30	27	22	12	6

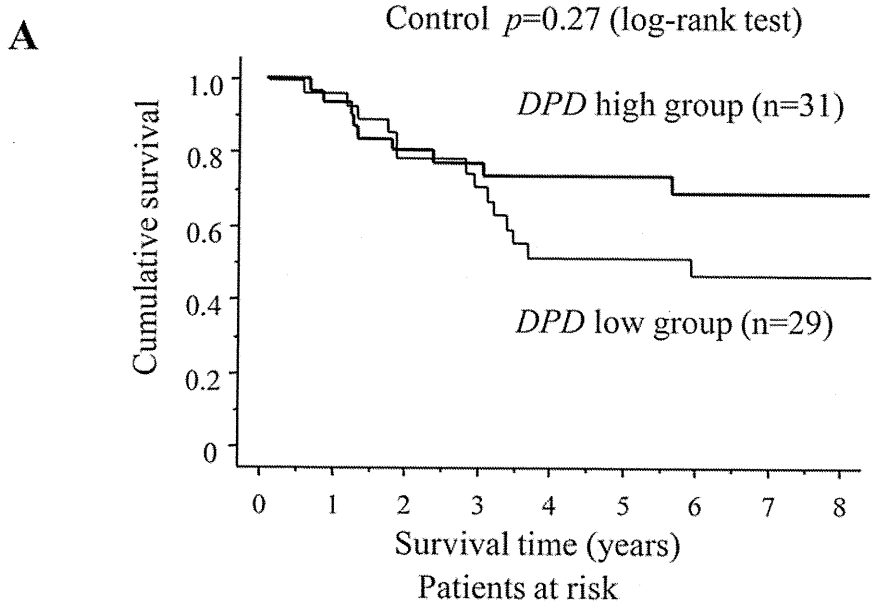
B



Patients at risk

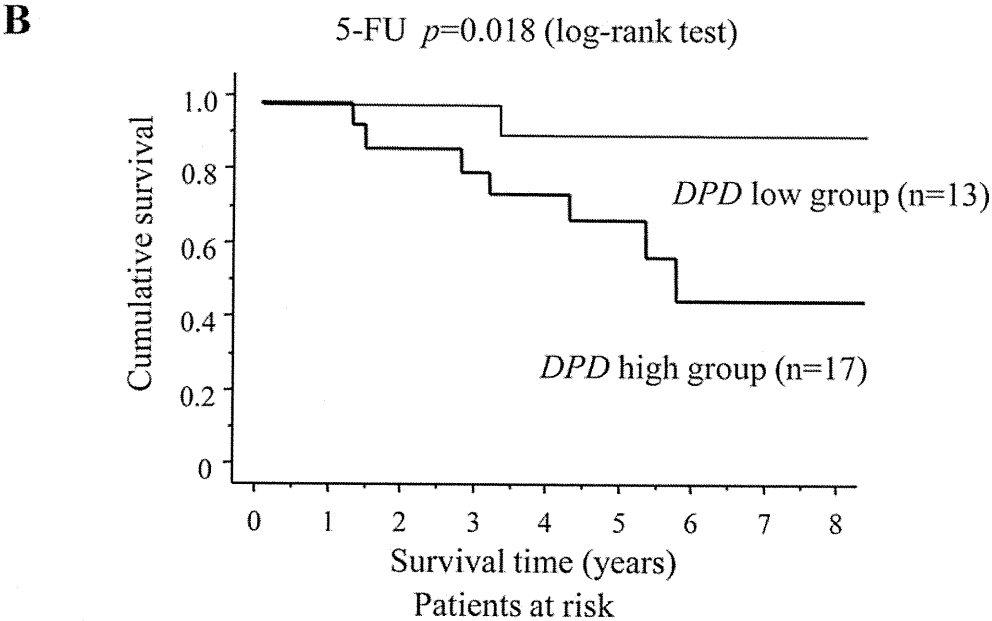
TYMS high	47	35	23	13	8
TYMS low	43	39	31	23	10

Figure 1. *A: Overall survival curves for patients administered and those not administered 5-fluorouracil (5-FU) after surgery. B: Overall survival curves for patients with high and low thymidylate synthase (TYMS) mRNA levels in resected cancer tissues when dichotomized at the mean TYMS mRNA level.*



Patients at risk

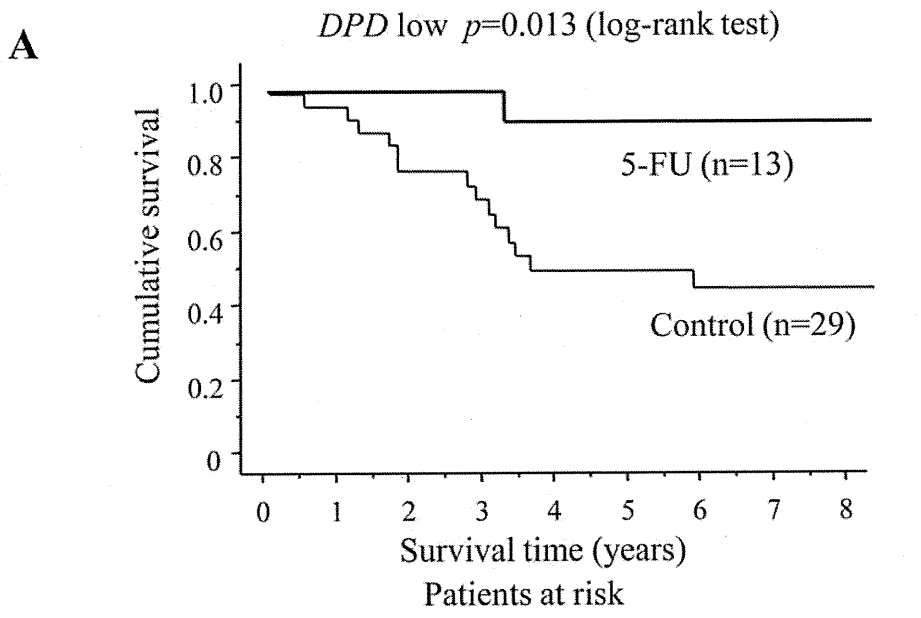
DPD high	31	25	19	14	7
DPD low	29	22	13	10	5



Patients at risk

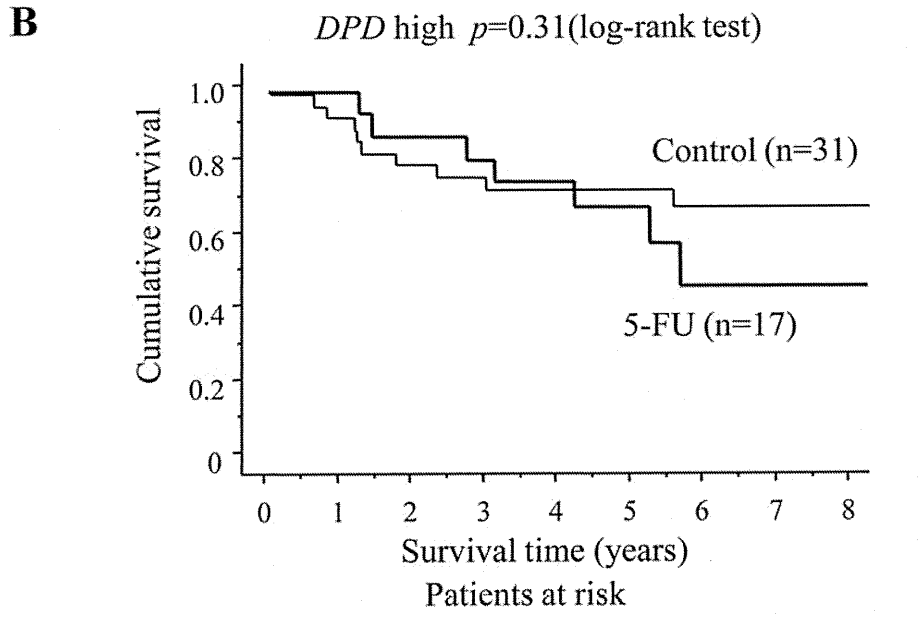
DPD high	17	14	11	3	2
DPD low	13	13	11	9	4

Figure 2. *A: Overall survival curves for patients with low and high dihydropyrimidine dehydrogenase (DPD)-expressing tumors who did not receive 5-fluorouracil (5-FU) when dichotomized at the mean DPD mRNA level. B: Overall survival curves for patients with low and high DPD-expressing tumors who received 5-FU.*



Patients at risk

Control	29	22	13	10	5
5-FU	13	13	11	9	4



Patients at risk

Control	31	25	19	14	7
5-FU	17	14	11	3	2

Figure 3. *A: Overall survival curves for patients with dihydropyrimidine dehydrogenase (DPD)-expressing tumors: comparison between those who underwent surgery alone and those who received 5-fluorouracil (5-FU) when dichotomized at the mean TYMS mRNA level. B: Overall survival curves for patients with high DPD-expressing tumors: comparison between those who underwent surgery alone and those who received 5-FU.*

regimens with other anticancer drugs and molecular targeting therapies for NSCLC patients with high DPD-expressing tumors are necessary.

In conclusion, using real-time RT-PCR, assessment of *TYMS* and *DPD* expressions in tumors from patients with NSCLC can provide precise prognostic information and predict the efficacy of 5-FU therapy after resection.

Conflicts of Interest Statement

The Authors have no conflicts of interest to declare.

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Significance of microscopic invasion into hilar peribronchovascular soft tissue in resection specimens of primary non-small cell lung cancer

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ABSTRACT

Introduction: The significance and handling of microscopic invasion of non-small cell lung cancer (NSCLC) into hilar peribronchovascular soft tissue (SHEATH+) have not been defined in the TNM classification by AJCC/UICC; nevertheless, SHEATH+ may be equivalent to spread into the mediastinum. Also, assessment of the margin of peribronchial resection is challenging because of the technical difficulty of inking, and intraoperative and postoperative artifacts.
Methods: Records of 592 consecutive Asian patients with primary NSCLC (excluding adenocarcinoma in situ) who had, without any preoperative therapy, undergone lobectomy, sleeve lobectomy and pneumonectomy were examined. SHEATH+, simply defined as invasion of hilar peribronchovascular soft tissue, without categorizing any invasive patterns, and its significance were statistically analyzed.
Results: Forty-four SHEATH+ cases demonstrated significantly advanced TNM stages, and were statistically associated with central occurrence, pN1-3, and vascular invasion, as assessed by logistic regression analysis. No statistically significant differences were observed between TNM stage-adjusted frequency of recurrence and recurrence-free intervals. Kaplan–Meier's estimates of the rate of overall and recurrence-free survival after surgery showed no statistically significant differences between SHEATH+ and SHEATH–. Cox's multivariate analysis suggested SHEATH was not a statistically independent prognostic factor under the TNM classification by AJCC/UICC (7th edition).
Conclusions: SHEATH+ in NSCLC was simply associated with central occurrence and advanced TNM stages. To the best of our knowledge, this is the first report on the significance of SHEATH+ in NSCLC.

1. Introduction

Anatomically, the main bronchus, the pulmonary artery and the pulmonary vein pass through the hilum of the lung that is occupied by soft tissue and covered with the mesopneumonium, where the visceral pleura reflects to continue as the parietal pleura (Fig. 1). Peribronchovascular soft tissue (SHEATH) is composed mainly of fat, neurofibers, lymphatics, vascula, and entrapped lymph nodes. Although the range of the mediastinum has not been microscopically defined, SHEATH enters the mediastinum without encountering any barrier; therefore, invasion of microscopic carcinoma into this space (SHEATH+) may theoretically be equivalent to spread to the mediastinum. In the course of conventional operations such as lobectomies, sleeve lobectomies and pneumonectomies, thoracic surgeons tend to regard such invasion of macroscopic carcinoma as true spread to the mediastinum. Pathologists, on the other hand, sometimes encounter SHEATH+ in such resected formalin-fixed specimens, and have great difficulty in assessing the possibility that some mediastinal soft tissues are included in SHEATH, and in discriminating true microscopic mediastinal soft tissue invasion into SHEATH+, because there is no histological difference between hilar peribronchovascular and mediastinal soft tissues.

The TNM classification by AJCC/UICC (7th edition) and the staging of primary lung cancers proposed by the International Association for the Study of Lung Cancer (IASLC) have been used since January 2010. The Staging Manual in Thoracic Oncology published by IASLC refers to hilar fat invasion detected at pathological exami-

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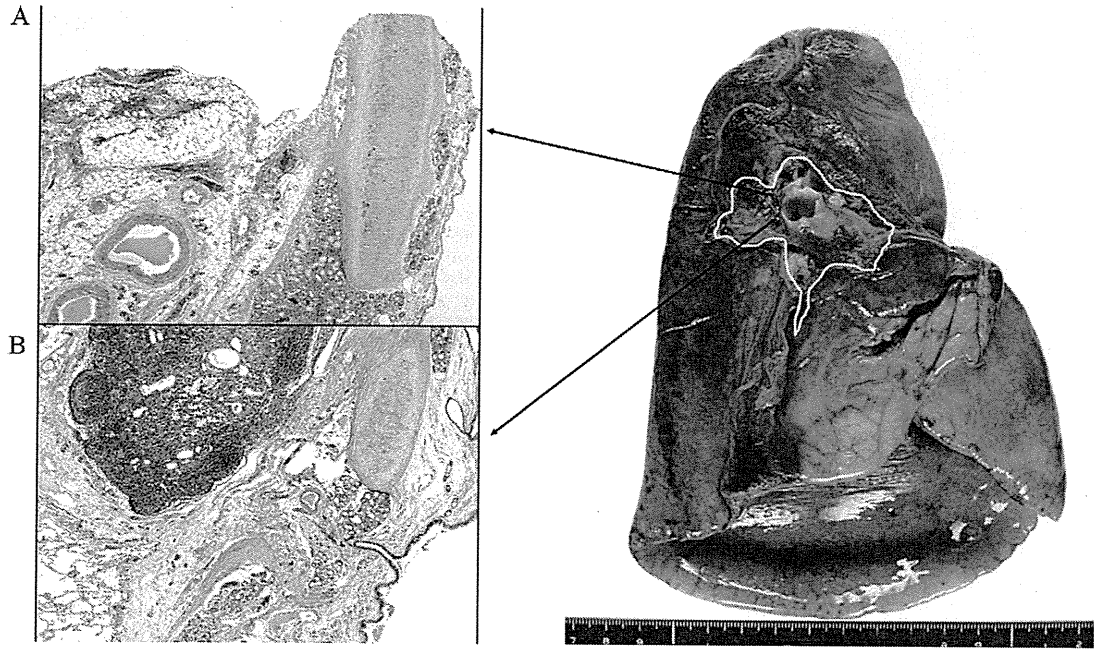

Fig. 1. Lobectomy specimen. Note the white line along the resection margin of the mesopneumonium and the close vicinity of the mediastinal side. The hilar peribronchovascular space around the bronchial resection margin is composed of fat, vascula, lymphatics (A), fibrous tissue, and lymph nodes (B).

nation of resected specimens and recommends a dialogue between the surgeon and the pathologist because of the lack of data for giving advice [1]. Invasion into hilar fat is not an event that upgrades the T factor: pT4.

Here, we retrospectively studied the characteristics and significance of SHEATH+/−, despite the possibility of its containing some mediastinal soft tissues, with the use of resected specimens of primary non-small cell lung cancer (NSCLC) from patients given no preoperative therapy.

2. Materials and methods

The subjects (592 consecutive Asian patients) had undergone lobectomy, sleeve lobectomy, and pneumonectomy for primary NSCLC without any preoperative therapy, between January 2002 and December 2005 at Kobe University Hospital and Hyogo Cancer Center in Japan. Excluded were subjects with localized bronchioloalveolar carcinoma (adenocarcinoma in situ), salivary gland type lung tumors, carcinoids and small-cell carcinoma as well as its combined types. Informed consent was obtained from all the subjects.

All resected specimens were inflated through the respective bronchi by gravity drainage with 10% neutral buffered formalin until maximally expanded, and then immediately fixed for one to three days. A routine histopathologic workup with paraffin embedding was carried out. Sections (3 microns thick) stained with hematoxylin and eosin and elastica van Gieson were examined under a light microscope. The cancers were staged according to the 7th edition of the AJCC/UICC TNM classification [2,3], and graded according to the World Health Organization classification of lung tumors published in 2004 [4]. Also, the PL category was used to describe the pathological extent of pleural invasion [1].

SHEATH+ was theoretically categorized into three patterns: direct invasion, lymphatic or vascular invasion, and extranodal invasion (Figs. 2–5). Since many cases demonstrated combinations of these patterns, subcategorization was not used in the study. SHEATH+ was simply and practically defined, without assessing the resection margins of SHEATH, as microscopic NSCLC invasion into the hilar peribronchovascular soft tissue under the following criteria: (1) at the proximal (mediastinal) side, across the line along the lung surface, around the hilum, (2) outside the outer rim of the bronchial cartilage and (3) inside the mesopneumonium.

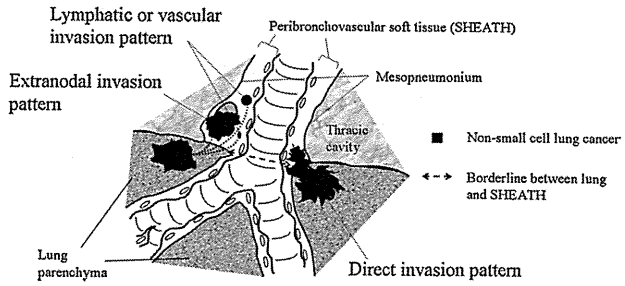

Fig. 2. Schema of pulmonary hilar structure and patterns of microscopic carcinoma invasion into peribronchovascular soft tissue.

The bronchial resection margin (BRM) was considered the bronchial wall from the bronchial mucosa to the outer rim of the cartilage.

The age of patients at the time of surgery is designated as "Age".

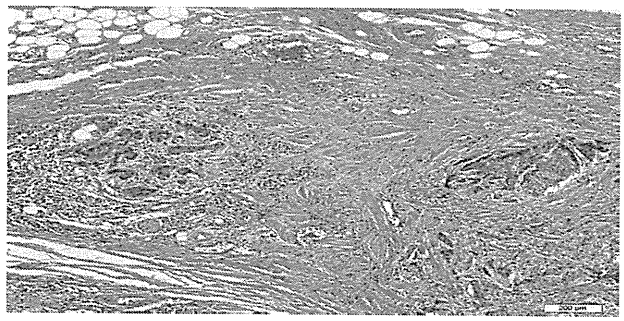

Fig. 3. Direct invasion into hilar peribronchovascular soft tissue attributed to local outgrowth of cancer. Most cases demonstrate desmoplasia and/or inflammatory cells.

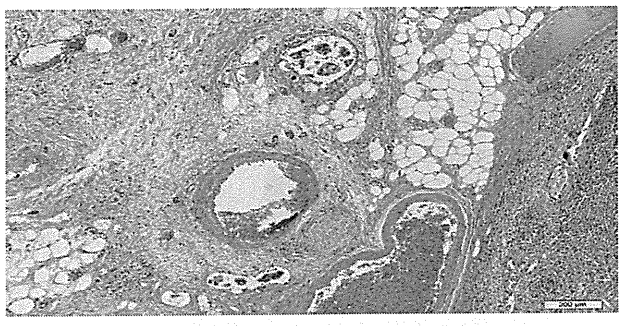

Fig. 4. Lymphatic invasion into hilar peribronchovascular soft tissue.

The area of the proximal spread of lung cancer was defined as follows: "Central", involving subsegmental and more proximal bronchi; "Intermediate", involving more distal bronchi with the cartilage than "Central"; "Peripheral", the bronchioles and alveoli.

The interval to recurrence was calculated from the date of surgery to the date of the identification of recurrence.

Statistical analyses were carried out using the SPSS statistical software package: SPSS® base 11.0J, SPSS® advanced models™ 11.0J, and SPSS® regression models™ 9.0J (SPSS Japan Inc., Tokyo, Japan). The difference of distribution in a 2×2 contingency table was analyzed by Fisher's exact test. The difference of median and distribution between the two independent groups was analyzed by the Mann-Whitney U test (two-sided), and the difference of mean and distribution among no fewer than three independent groups was analyzed by the Kruskal–Wallis test. The binary logistic regression analysis against SHEATH+/− was carried out by the direct entry method. Survival was estimated by the product limit method of Kaplan and Meier, and differences in survival were determined by the log-rank test. A multivariate survival analysis was conducted by the direct entry method of Cox's proportional hazards regression model. In the two survival analyses, zero time was the date of surgical resection, and censoring was death or discontinuation of follow-up. $P < 0.05$ was considered statistically significant [5].

3. Results

Among the 592 patients, squamous cell carcinoma (SQCC) ($P < 0.01$) and advanced TNM stages ($P = 0.01$) were significantly more prevalent in men than in women. SQCC occurred at significantly more proximal sites than did non-SQCC ($P < 0.01$), and was associated with significantly more major operations such as sleeve lobectomy, bilobectomy, and pneumonectomy ($P < 0.01$); there was, however, no statistically significant difference in TNM stages ($P = 0.10$) between SQCC and non-SQCC.

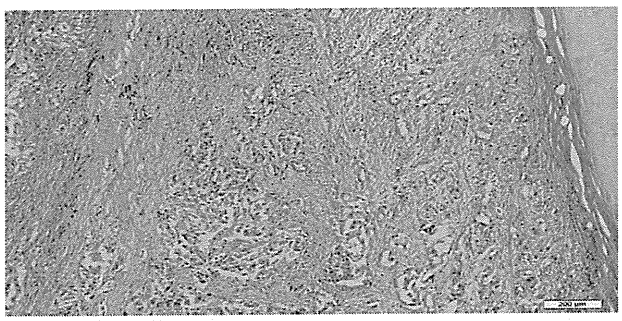

Fig. 5. Extranodal invasion into hilar peribronchovascular soft tissue between lymph node and bronchial cartilage. Black dots on the left side show a trace of lymph node anthracosis. Most cases demonstrate desmoplasia and/or inflammatory cells.

Table 1
Clinicopathological differences by SHEATH.

Clinicopathological data	SHEATH−	SHEATH+	*P*
Total	548	44	
Gender			
Men	382	36	
Women	166	8	0.12
Age [median ± 2SD years old]	67 ± 19	67 ± 14	0.84
Histopathologic type			
Squamous cell carcinoma	159	19	
Invasive adenocarcinoma	328	18	
Adenosquamous carcinoma	18	1	
Large cell carcinoma	10	0	
Large cell neuroendocrine carcinoma	10	3	
Combined large cell neuroendocrine carcinoma	5	0	
Sarcomatoid carcinoma	18	3	0.26
Large diameter [median ± 2SD mm]	38 ± 38	47 ± 52	<0.01
Stage			
0	0	0	
IA	130	2	
IB	156	1	
IIA	99	8	
IIB	72	4	
IIIA	74	20	
IIIB	3	5	
IV	14	4	<0.01
Lung and main lobe			
Right			
Upper lobe	191	10	
Middle lobe	30	3	
Lower lobe	140	9	
Left			
Upper lobe	115	11	
Lower lobe	72	11	0.02
Treatment			
Lobectomy	501	19	
Sleeve lobectomy	37	21	
Bilobectomy	2	1	
Unilateral pneumonectomy	8	3	<0.01
Area of extension of lung cancer			
Peripheral	283	8	
Intermediate	197	17	
Central	48	17	
Not available	20	2	<0.01
Pleural invasion			
PL0	351	27	
PL1	88	5	
PL2	47	5	
PL3	62	7	0.53
Lymphatic invasion			
Positive	265	41	
Negative	283	3	
Not available	0	0	<0.01
Vascular invasion			
Positive	271	40	
Negative	272	4	
Not available	5	0	<0.01
Adjuvant therapy			
Yes	131	11	
No	397	32	
Not available	20	1	0.86
Recurrence			
Yes	194	29	
No	348	15	
Not available	6	0	<0.01

SD: standard deviation.

Only 1 of the 44 cases of SHEATH+, stage IIIA and 42-month survival, demonstrated positive BRM caused by mucosal lymphatic invasion; the remaining cases were negative. SHEATH+ had significantly more advanced TNM stages (Table 1). Binary logistic regression analysis of SHEATH (Table 2) revealed that central occurrence, pN1-3 and vascular invasion were statistically significant factors in SHEATH+, regardless of the type of carcinoma: SQCC or otherwise. Overall, SHEATH+ tended to involve more recurrences, but there was no statistically significant difference in terms of TNM

Table 2
Binary logistic regression analysis against SHEATH.

Factors	Unfavorable	Favorable	Risk Ratio	95% CI	P
Lung	Left	Right	1.94	0.91–4.10	0.08
Lobe	L	U and M	1.13	0.53–2.43	0.75
Area of extension of lung cancer	Central	Non-central	4.16	1.64–10.55	<0.01
Histopathologic type	SQCC	non-SQCC	1.46	0.60–3.55	0.40
Pathologic T category	pT3-4	pT1-2	1.31	0.57–3.04	0.52
Pathologic N category	pN1-3	pN0	9.24	3.00–28.41	<0.01
Pathologic M category	pM1	pM0	2.99	0.63–14.23	0.17
Lymphatic invasion	Positive	Negative	3.69	0.98–13.88	0.05
Vascular invasion	Positive	Negative	5.61	1.82–17.28	<0.01

CI: confidence interval, U: upper lobe, M: middle lobe, L: lower lobe, SQCC: squamous cell carcinoma.

Table 3
Relation between SHEATH, recurrence, and stage-adjusted survival rate.

	Stages I–II			Stages III–IV		
	SHEATH–	SHEATH+	P	SHEATH–	SHEATH+	P
Recurrence	134/456	7/15	0.16	60/86	22/29	0.64
Recurrence-free interval [median ± 2SD months]	20 ± 31	20 ± 33	0.95	12 ± 24	8 ± 15	0.08
5-Year overall survival [%(available data)]	70 (457)	64 (15)	0.23	32 (91)	20 (29)	0.21
Without adjuvant therapy	71 (341)	71 (7)	0.50	30 (56)	22 (25)	0.48
With adjuvant therapy	69 (99)	67 (7)	0.77	37 (32)	25 (4)	0.20
5-Year recurrence-free survival [%(available data)]	87 (322)	86 (8)	0.97	74 (26)	51 (7)	0.13
Without adjuvant therapy	85 (248)	100 (4)	0.40	66 (14)	63 (6)	0.82
With adjuvant therapy	96 (61)	67 (4)	0.05	80 (11)	0 (1)	<0.01

SD: standard deviation.

stage-adjusted frequency or of recurrence-free interval, which held particularly for the higher stages (Table 3). By SHEATH, no statistically significant difference was observed in the distribution of the total number of recurrence sites; remarkably, however, there was no recurrence at BRM in SHEATH+ (Table 4).

The overall and recurrence-free survival rates distributed by TNM stage and SHEATH showed that cases with more advanced TNM stages had poorer prognosis, with no statistically significant difference between SHEATH+ and SHEATH– (Table 3 and Fig. 6). Moreover, the survival rates might not have been influenced by adjuvant therapy. According to Cox's multivariate analysis, age, gender, lobe, category and lymphatic invasion were statistically significant prognostic factors. On the other hand, SHEATH, whether positive or negative, was not a statistically independent prognostic factor (Risk ratio 1.10) (Table 5).

Table 4
Total number of recurrence sites distributed by SHEATH.

Recurrence sites	SHEATH–	SHEATH+	P
Bronchial resection margin	15	0	
Lymph node	87	15	
Ipsilateral lung	47	7	
Contralateral lung	34	8	
Pleural dissemination	31	6	
Chest wall	3	0	
Brain	34	4	
Bone	27	5	
Liver	11	5	0.82
Adrenal gland	11	3	
Skin	3	1	
Kidney	3	1	
Pericardium	2	0	
Meninges	2	0	
Peritoneum	1	1	
Spinal cord	1	0	
Skeletal muscle	1	0	
Epidural space	1	0	

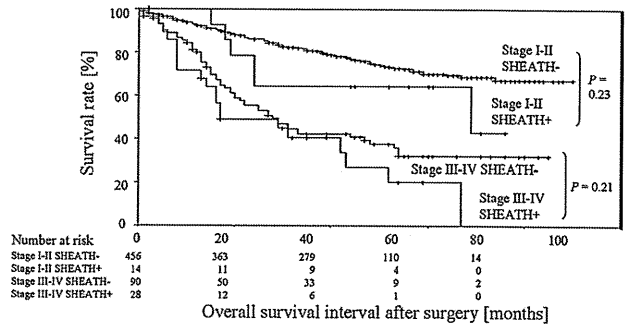

Fig. 6. Stage-adjusted overall survival distribution by SHEATH. There is no statistically significant difference by log-rank test in terms of SHEATH.

4. Discussion

In 2005 the staging committee of IASLC proposed the definition of complete resection in lung cancer surgery. To be defined as complete, lung resection required all of the following: (a) free resection margins proved microscopically should be bronchial, venous and atrial stumps, peribronchial soft tissue, and any peripheral margin near the tumor or additionally resected tissue, (b) systematic nodal dissection in its wider form or, if not carried out, lobe-specific systematic nodal dissection, (c) there should be no extracapsular extension of the tumor in nodes removed separately or those at the margin of the main lung specimen and (d) the highest mediastinal node removed must be negative [6].

According to the residual tumor (R) classification of TNM by AJCC/UICC, R1 (microscopic residual tumor) generally means resection lines and planes containing the tumor assessed by histopathological examination of resection specimens, namely incomplete resection [2,3,7]. Nonetheless, still vague is whether the presence of NSCLC in peribronchial soft tissues or within a lymph node located at the resection margin should be staged as R1, and

Table 5
Cox's multivariate analysis of prognostic factors by the direct entry method in NSCLC.

Factors	Unfavorable	Favorable	Risk Ratio	95% CI	*P*
Age	≥75 y.o.	<75 y.o.	1.64	1.13–2.37	0.01
Gender	Men	Women	1.76	1.17–2.65	0.01
Lung	Right	Left	1.01	0.74–1.39	0.93
Main lobe	L	U and M	1.72	1.26–2.34	<0.01
Area of extension of lung cancer	Central	Non-central	1.30	0.82–2.07	0.26
Histopathologic type	Non-iAD	iAD	1.32	0.94–1.84	0.11
Pathologic T category	pT3-4	pT1-2	2.33	1.69–3.24	<0.01
Pathologic N category	pN1-3	pN0	2.35	1.63–3.39	<0.01
Pathologic M category	pM1	pM0	2.23	1.06–4.68	0.03
SHEATH	Positive	Negative	1.10	0.66–1.84	0.71
Lymphatic invasion	Positive	Negative	1.50	1.01–2.24	0.05
Vascular invasion	Positive	Negative	1.38	0.97–1.97	0.07
Adjuvant therapy	Yes	No	0.92	0.65–3.39	0.65

CI: confidence interval, y.o.: years old, U: upper lobe, M: middle lobe, L: lower lobe, iAD: invasive adenocarcinoma.

whether the presence of NSCLC in the bronchial submucosa in cases with negative epithelial margins should be classified as R0 or R1 [8]. Moreover, two different tumor locations are speculated for R1: (1) at the resection margin and (2) at a distance of 1 mm or less from the resection margin [9,10].

In follow-up data on patients with R1 in NSCLC, patterns of R1 and survival analyses along the patterns are of great interest, but the results are not easily comparable because of imprecise study designs involving gender, histopathology, control arm, adjuvant therapy, and terminology (Tables 6 and 7) [11–24]. Nevertheless,

Table 6
Summary of R1 patterns at the bronchial resection margin from references.

Literature	Resected	R1 at the bronchial resection margin				
	NSCLC	*n*	%		Breakdown	%
Shields [11]	2371 (Men only)	67	2.8	31	Submucosal	1.3
				24	Peribronchial	1.0
Soorae et al. [12]	434	64	14.7	34	Direct extension	7.8
				14	Lymphatic permeation	3.2
				10	Carcinoma in situ	2.3
				6	Parabronchial	1.4
Kaiser et al. [13]	2890	45 (extramucosal only)	1.6	36	Peribronchial	1.2
				9	Submucosal lymphatics	0.3
Liewald et al. [14]	805	21	2.6	10	Peribronchial	1.2
				8	Mucosal	1.0
				3	Submucosal lymphatics	0.4
Massard et al. [15]	NA	40 (stages I–III)	NA	20	Carcinoma in situ	NA
				15	Peribronchial	NA
				5	Mucosal	NA
Hofmann et al. [16]	596	26	4.4	15	Peribronchial	2.5
				6	Submucosal	1.0
				5	Extrabronchial	0.8
Law et al. [17]	NA	64	NA	29	Mucosal	NA
				18	Peribronchial	NA
				9	Carcinoma in situ	NA
				8	Lymphatic permeation	NA
Snijder et al. [18]	834 (stage I)	23	2.8	12	Carcinoma in situ	1.4
				8	Mucosal	1.0
				3	Peribronchial	0.4
Passlick et al. [19]	1162	54	4.6	22	Lymphangiosis carcinomatosa	1.9
				32	Others, not-detailed	2.8
Gebitekin et al. [20]	735	40	5.4	35	Peribronchial	4.8
				5	Submucosal lymphatics	0.7
Ghiribelli et al. [21]	1384	47	3.4	30	Extramucosal	2.2
				17	Mucosal	1.2
Lequaglie et al. [22]	4530	56	1.2	56	Mucosal	1.2
Dienemann et al. [23]	2464 (with SCLC)	81 (NSCLC only)	NA	30	Peribronchial	NA
				25	Submucosal	NA
				22	Mucosal	NA
				4	Carcinoma in situ	NA
Riquet et al. [24]	4026	105	2.6	60	Peribronchial	1.5
				45	Bronchial	1.1

NSCLC: non-small cell lung cancer, SCLC: small cell lung cancer, NA: not available.

Table 7
Summary of survival and characteristics of patients with R1 at the bronchial resection margin from references.

Literature	Survival and characteristics in patients with R1 at the bronchial resection margin
Shields [11]	One of the 21 patients with peribronchial R1 and two of 26 patients with submucosal R1 survived for five years or longer.
Soorae et al. [12]	Fifteen, all men with squamous cell carcinoma (ave. 2.9 cm), of 64 patients with R1 lived for 5 years or more. In submucosal and peribronchial lymphatic R1, 78.6% died within 1 year and the remainder within 3 years. Seven of 10 patients with carcinoma in situ lived for 5 years or more; positive hilar nodes in four patients.
Kaiser et al. [13]	Thirty-three of forty-five patients with extramucosal R1 had stage IIIa disease. Recurrent disease developed in 34 of 45 patients with extramucosal R1. Recurrence was local in 60% and 23% of N0 and N2 groups. There was no difference in survival between patients with local and distant initial site of recurrence.
Liewald et al. [14]	Eighteen of twenty-one patients received postoperative radiation therapy with a total dose of 50 Gy. Extramucosal R1 had poorer prognosis (median survival 10.3 months) than mucosal R1 (25 months).
Massard et al. [15]	All patients except the three most recent underwent adjuvant radiation therapy. Five-year survival with R1 of carcinoma in situ excluding unrelated deaths was 55.0 ± 16.6% (N0 71.1 ± 18.0%). Five-year survival with peribronchial R1, excluding unrelated deaths, was 23.3 ± 11.8%. Prognosis of peribronchial R1 was similar to that of N2 disease, and in situ carcinoma did not influence survival per se.
Hofmann et al. [16]	Twenty patients with R1 stage IIIA. Seventeen of twenty-one patients with bronchial (submucosal and peribronchial) R1 had N2 disease. Median survival of patients with extrabronchial and bronchial R1 was 39 and 6 months, respectively.
Law et al. [17]	Five-year survivors of carcinoma in situ and invasive carcinoma of bronchial mucosa were 6 and 9, respectively. None with peribronchial malignancy survived three years. Seven of eight cases with lymphatic permeation died within two years.
Snijder et al. [18]	Five-year survival of patients with invasive R1 and carcinoma in situ was 27.3% and 58%, respectively. Five-year survival of patients with carcinoma in situ was equivalent to the R0 group (54%). Patients with R1 had more recurrences (carcinoma in situ 75%, invasive tumor 63.6%) than those with R0 (48.5%).
Passlick et al. [19]	Median survival of patients with R1 of lymphangiosis carcinomatosa and of others was 13.3 and 20.1 months, respectively. Multivariate Cox's analysis revealed R1 of lymphangiosis carcinomatosa as an independent prognostic parameter.
Gebitekin et al. [20]	Five-year survival of patients with R0 and R1 was 32% and 21.6%, respectively; the difference was not significant. Five-year survival of patients with R0 and R1 at stage IIIa disease was 17% and 0%, respectively ($P < 0.001$)
Ghiribelli et al. [21]	Survival was not correlated with the type of R1, the N0 vs. N+, or the squamous vs. adenocarcinoma.
Lequaglie et al. [22]	Patients with stages I and II (6.5%) and with stage IIIa (17%) received postoperative chemotherapy. Patients with stages I and II (58%) and with stage IIIa (41%) underwent postoperative radiation therapy. There was no real difference in the rate of survival between patients with and without residual disease (66.1% vs. 64.5% at stage I; 63.5% vs. 62.5% at stage II; 16.8% vs. 21% at stage IIIa, respectively).
Dienemann et al. [23]	Forty-three patients received postoperative radiation therapy. Median survival of patients with R0, mucosal, submucosal, and peribronchial R1 was 37, 17, 16 and 12 months, respectively. (One of the 26 patients with submucosal R1 and 6 of 36 with peribronchial R1 were non-NSCLC patients.)
Riquet et al. [24]	Five-year survival rate for R1 (216 of 4026 NSCLC patients (5.4%)) was 20.1% (vs. R0 46%), not modified by the T, N, adjuvant therapy. (R1: bronchus and peribronchus (48.4%), chest wall (19.8%), great vessels and atrium (13.8%), lymph nodes (11.5%), others (6.5%)) (Neoadjuvant therapy performed, R0 10.8%, R1 24.1%) Five-year survival rate for bronchial and peribronchial R1 was 26.3%; lymph nodes R1, 10.7%; other R1, 15.6%. Local recurrence was observed in 33 of 173 patients with R1 (R0 4.4%), and 15 of 79 patients with bronchial and peribronchial R1. Multivariate analysis confirmed R1 to be an independent factor of poor prognosis, after N, age, T, type of resection, and histology.

NSCLC: non-small cell lung cancer.

the R1 resection margin with non-mucosal spread, particularly peribronchial and lymphatic invasion, may be an adverse prognostic factor compared with R1 of carcinoma in situ. There is a 74% chance (131 of 177 cases) of mediastinal lymph node metastasis (i.e., N2 disease) when the peribronchial tumor is located at the resection margin [13–16,23–25]. The prognosis of R1 patients with peribronchial invasion is similar to that of those with stage III disease because of frequent recurrence in the form of distant metastasis. For patients with stages I–II tumors who could easily tolerate re-operation, further resection may be an acceptable treatment option that could improve survival [26]. The different patterns of tumor spread at BRM may be biologically relevant, and further studies are needed on the basis of standardized morphological terminology such as Thunnissen and den Bakker's proposal and comparable definitions of bronchial and extrabronchial histology [25].

As to whether an extended resection of the so-called peribronchial tumor growth is warranted if it can be diagnosed from frozen sections of the BRM, there is no satisfactory information on the subject. Frozen-section evaluation of BRM may, however, be helpful and important particularly in central NSCLC and sleeve lobectomy, especially that incomplete resection should be avoided to preclude unfavorable prognosis. Nonetheless, a study of 268 lung cancers subjected to lobectomy and pneumonectomy after BRM frozen section analysis has shown 243 (90.6%) true negatives, 16 (6.0%) true positives (11 mucosal, 3 submucosal, 1 lymphatic, 1 peribronchial), 4 (1.5%) false positives, and 5 (1.9%) false negatives [27]. This may be due to not only the difficulty of the interpretation of histology, but also the quality of the representative frozen-section sample. Peribronchial fat tissue may present difficulty when slicing BRM tissue with a cryostat-microtome. The poor quality of frozen sections, compared with permanent formalin-fixed sections, is not favored by pathologists. Thoracic surgeons and pathologists should be aware of the relevance of intraoperative BRM examination for the purpose of increasing the reliability of frozen-section analysis. The association of SHEATH+ with lymphatic/vascular invasion and lymph node metastasis may suggest, together with the site of recurrence (not preferential at BRM) (Table 4), that finding SHEATH+ at frozen section should not lead to additional surgery to aim for R0 in contrast to the possible consequences of posi-

tive BRM at frozen section. A study of the microscopic proximal invasive patterns of 70 resected NSCLCs has revealed that SQCC extends more proximally (mainly bronchial extension) than adenocarcinoma (mainly peribronchial extension), whereas the latter extends more distantly and the farthest: the extension from the edge of the visible tumor being 3.0 cm for adenocarcinoma and 2.0 cm for SQCC. A 1.5 cm long bronchial resection from the macroscopic tumor has provided clear margins in 93% of NSCLC cases [28], with differences among some studies in terms of the farthest extension [12,27,29,30]. Consequently, it may be reasonable to suggest that frozen section analysis should be restricted to those cases in which preoperative evaluation has shown that the distance from the tumor to the assumed BRM is 20 mm or less [28,31].

SHEATH, whether positive (R1) or negative (R0), should essentially be diagnosed as strictly as possible with prognosis in mind. Assessment of the true margin of SHEATH does, however, present considerable difficulty because simultaneous cutting and inking is challenging for thoracic surgeons, and intraoperative artifacts may interfere while exposing the bronchial wall through the mesopneumonium: heat degeneration, tissue defect, and shrinkage induced by an electric knife; elastic retraction and shrinkage may also occur during the fixation of resected specimens [17]. Since margin assessment always involves risk, particularly of false-positives, and since SHEATH frozen section analysis may be inappropriate for intraoperative consultation, a simple definition of SHEATH+ would be of practical use.

Although this is the first study where SHEATH+ is systemically evaluated, statistically it may have no potential clinical significance of SHEATH. SHEATH+ has not been identified as an independent prognostic factor under the 7th edition of AJCC/UICC TNM classification; in NSCLC it is simply associated with central occurrence and more advanced TNM stages. Moreover, our results suggest that the 7th edition of AJCC/UICC TNM classification is suitable for NSCLC regardless of SHEATH+/−, although the detailed invasive patterns of SHEATH+ were not taken into consideration. Further studies are needed; nevertheless, pathologists need not hesitate in assessing SHEATH+ in conventionally resected specimens: lobectomies, sleeve lobectomies, and pneumonectomies.

Conflict of interest statement

The authors have no conflict of interest to declare.

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