Predictive Impact for Postoperative Recurrence of Preoperative Serum Krebs von den Lungen-6 Concentration in Pathologic Stage IA Non-Small Cell Lung Cancer

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Background. Although stage IA non-small cell lung cancer has an optimistic survival rate, up to 10% of these patients relapse after surgical procedures and die. We retrospectively analyzed clinicopathologic features of patients with stage IA non-small cell lung cancer to identify recurrence predictors and to investigate effects of preoperative serum Krebs von den Lungen-6 (PS-KL-6) concentrations.

Methods. We selected 204 consecutive patients with stage IA non-small cell lung cancer treated from December 2003 to December 2009 for this study and tested their PS-KL-6 concentrations in univariate and multivariate Cox regression analyses of recurrence-free survival (RFS).

Results. High PS-KL-6 concentration (PS-KL6^{High}) was significantly associated with sex ($p = 0.0006$), smoking status ($p = 0.0438$), histology ($p = 0.0049$), and postoperative recurrence ($p = 0.0058$). Both intratumoral blood vessel invasion ($p = 0.0345$) and PS-KL6^{High} ($p = 0.0021$) were identified as independent predictors of shorter RFS. Relative risk of patients with PS-KL6^{High} was 3.478 compared with patients with low PS-KL-6 concentration (PS-KL6^{Low}; 95% confidence interval: 1.576 to 8.013). Among patients with tumors larger than 2 cm (T1b), the PS-KL6^{High} group had significantly shorter RFS than the PS-KL6^{Low} group ($p = 0.0040$).

Conclusions. PS-KL-6 concentration is a simple and novel predictor of recurrence in patients with stage IA non-small cell lung cancer and might help to identify patients who will need more careful follow-up among T1bN0M0 series.

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L ung cancer is the leading cause of cancer death, both in Japan and worldwide. The most effective treatment for early-stage non-small cell lung cancer (NSCLC) is surgical resection. Although stage IA NSCLC has an 83.9% 5-year survival rate in Japan [1], up to 10% of patients with stage IA NSCLC relapse after surgical resection and die after undergoing complete resections.

Inflammation plays a critical role in the development and progression of various cancers by promoting cancer cell proliferation and survival, angiogenesis, and tumor metastases [2]. Inflammatory cells in the tumor microenvironment considerably affect tumor development, and markers of systemic inflammation may indicate tumor status. Krebs von den Lungen-6 (KL-6) is a murine IgG$_1$ monoclonal antibody established by immunizing a mouse with a lung adenocarcinoma cell line [3]. KL-6 is classified as a MUC1 mucin and is known to be expressed in regeneration of type II pneumocytes [4]. Serum KL-6 has been recognized as a marker for disease activity of interstitial pneumonia [5, 6] and can reportedly have a prognostic role for various cancers, including pancreas, breast, colon, and hepatocellular carcinomas, suggesting a valuable biomarker [7–11]. Some studies have also investigated KL-6 in NSCLC [12], but few studies have specifically studied stage IA disease.

Vessel invasion, including both intratumoral blood vessel invasion (BVI) and lymphatic vessel invasion (LVI) [13, 14], and tumor size [15–18] have been reported to be prognostic factors for stage IA NSCLC. Five-year survival of patients with tumors larger than 2.0 cm is lower than for patients with smaller tumors [15, 18]. Nevertheless, adjuvant chemotherapy has been shown not to substantially lengthen survival of patients with stage IA NSCLC [19, 20], although uracil-tegafur (UFT) treatment tended to improve survival among Japanese patients with 2- to 3-cm tumors in stage IA NSCLC [20]. Identifying predictors of poor prognostic factors in stage IA NSCLC can thus improve selection of candidates for multimodality therapy over the use of such factors as inflammatory variables.

Therefore, this study aimed to retrospectively analyze clinicopathologic features of patients with stage IA NSCLC to identify the predictors of postoperative

Abbreviations and Acronyms

BVI	=	blood vessel invasion
CT	=	computed tomography
LVI	=	lymphatic vessel invasion
MRI	=	magnetic resonance imaging
NSCLC	=	non-small cell lung cancer
PS-KL-6	=	preoperative serum Krebs von den Lungen-6
RFS	=	recurrence free survival
RR	=	relative risk
UFT	=	uracil-tegafur

recurrence in stage IA NSCLC and to investigate the effects of preoperative serum KL-6 (PS-KL-6) concentrations on survival.

Patients and Methods

Patients

This study was approved by the Ethics Committee of Kyushu Medical Center. From December 2003 to December 2009, 565 consecutive patients with primary lung cancer underwent a complete surgical resection at the Department of Thoracic Surgery, Kyushu Medical Center. Of these patients, we excluded patients who had had clinical evidence of infection, other inflammation, hematologic diseases or patients used drugs that might influence their hematologic data. Finally, we selected 204 of those patients with pathologic stage IA NSCLC for this study. Their clinical profiles are summarized in Table 1.

Table 1. Clinical Profiles

Variable	Value
Total assessable patients	204 (100)
Follow up, mo	50 (0–110)
Age, y	67 (39–91)
Sex	
Female	100 (49.1)
Male	104 (50.9)
Smoking status	
Never	113 (55.4)
Former	91 (44.6)
Histologic type	
Adenocarcinoma	170 (83.3)
Squamous cell carcinoma	26 (12.7)
Others	8 (4.0)
Preoperative pulmonary complications	
Emphysema	14 (6.9)
Interstitial pneumonia	6 (2.9)
Obsolete pulmonary tuberculosis	6 (2.9)
Bronchial asthma	4 (2.0)
Surgical procedure	
Lobectomy	147 (72.1)
Limited resection	57 (27.9)

Values are no. (%) or median (range).

The results were determined in follow-up examinations that occurred during a median period of 50 months (range: 0 to 110 months) after surgical resection. Postoperative follow-ups consisted of chest computed tomography (CT), abdominal CT, bone scintigraphy, and brain magnetic resonance imaging (MRI) at 6-month intervals during the first year and yearly thereafter. Chest roentgenography and blood tests that included tumor markers were checked at 3- or 4-month intervals during the first year and at 6-month intervals thereafter. The study group included 100 women and 104 men, with a mean age at their surgical resections of 67 years (range: 39 to 91 years). One hundred thirteen patients (55.4%) had never smoked, and the remaining 91 patients were former or current smokers. Their histologic types were adenocarcinoma (170 patients; 83.3%), squamous cell carcinoma (26 patients; 12.7%), and other types (8 patients; 3.9%). Thirty patients (14.7%) had preoperative pulmonary complications such as emphysema, interstitial pneumonia, obsolete pulmonary tuberculosis, and bronchial asthma. One hundred forty-seven patients (72.1%) underwent lobectomies with systemic lymphadenectomies, and 57 patients underwent limited resections, including segmentectomies or wedge resections in patients with peripheral lesions or poor pulmonary function. No patients received any adjuvant chemotherapy or radiotherapy. Postoperative recurrence occurred in 25 patients (12.3%; Table 2). Postoperative recurrence such as local and distant recurrence was defined as in a previous report [21]. The first appearance of any new lesion suspected to be recurrence of the original lung cancer was defined as postoperative recurrence and was clinically diagnosed by combinations of CT, MRI, bone scintigram, and fluorodeoxyglucose-positron emission tomography or was pathologically diagnosed if necessary. Local recurrences were defined as those occurring in the hilar or mediastinal lymph nodes, pleural cavity, bronchial stump, or staple line. Distant recurrences were defined as those occurring in the brain, lung, adrenal glands, bone, and other locations. Equivocal cases were excluded in this

Table 2. Postoperative Recurrence

Variable	No. (%)
Recurrence	
No	179 (87.7)
Yes	25 (12.3)
Recurrent pattern	
Distant	21
Brain	3
Lung	10
Liver	2
Bone	6
Skin	1
Local	4
Locoregional lymph nodes	8
Pleural dissemination	7
Bronchial stump or staple line	4