Original Article

Risk factors of chest wall invasion in non-small cell lung cancer

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Background: The risk factors for the development of chest wall invasion (CWI) in non-small cell lung cancer (NSCLC) patients are unclear. If the risk factors for the development of CWI can be clarified, surgical treatment might be able to be performed before CWI development, thus improving the prognosis.

Methods: In the present study, we enrolled patients who received surgery for NSCLC between January 2008 and December 2019 with available data on the maximum standardized uptake value (SUV_{max}) on positron emission tomography (PET) with lesions adjacent to the visceral pleura. Furthermore, the preoperative white blood cell (WBC) count, the preoperative neutrophil-to-lymphocyte ratio (NLR), platelet (Plt) count, levels of lactate dehydrogenase (LDH) and C-reactive protein (CRP) were analyzed as predictive factors of CWI.

Results: The relationships between CWI and clinicopathological variables were analyzed, and there were significant differences between patients with and without CWI in the age (P=0.02), maximum tumor diameter on computed tomography (CT) (P<0.01), diameter of tumors adjacent to the visceral pleura (P_{max}) (P<0.01), SUV_{max} (P<0.01), maximum tumor diameter on a pathological examination (P<0.01), WBC count (P=0.03), Plt count (P=0.04), and levels of LDH (P<0.01) and CRP (P=0.01). Logistic regression analyses of the risk factors related to CWI showed that the age (P=0.02), P_{max} (P=0.02), SUV_{max} (P=0.01), and LDH (P<0.01) were significant risk factors.

Conclusions: The age, P_{max}, SUV_{max}, and LDH levels might be associated with CWI.

Keywords: Chest wall invasion (CWI); non-small cell lung cancer (NSCLC); risk factor

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Introduction

Lung cancer with chest wall invasion (CWI) is reported to account for 3% to 8% of all resected non-small cell lung cancer (NSCLC) cases (1-4). The first surgical treatment for lung cancer with CWI was described in 1947 (5), and since then, resection for NSCLC with CWI has been considered an option for multidisciplinary therapy to improve the prognosis (3,4,6-9).

CWI is categorized as T3 stage in the tumor, nodal and metastatic (TNM) staging system, 8th edition, of the American Joint Committee on Cancer (AJCC)/Union for International Cancer Control (UICC) for NSCLC, and the 5-year survival rate of NSCLC patients with T3N0M0 is reported to be 52% (10). Furthermore, the depth of CWI has been reported to potentially worsen the prognosis (3,8,11), performing resection before CWI occurs is ideal. Although CWI can be diagnosed by imaging tools, such as computed tomography (CT), magnetic resonance image (MRI), and ultrasound (12-15), the risk factors for the

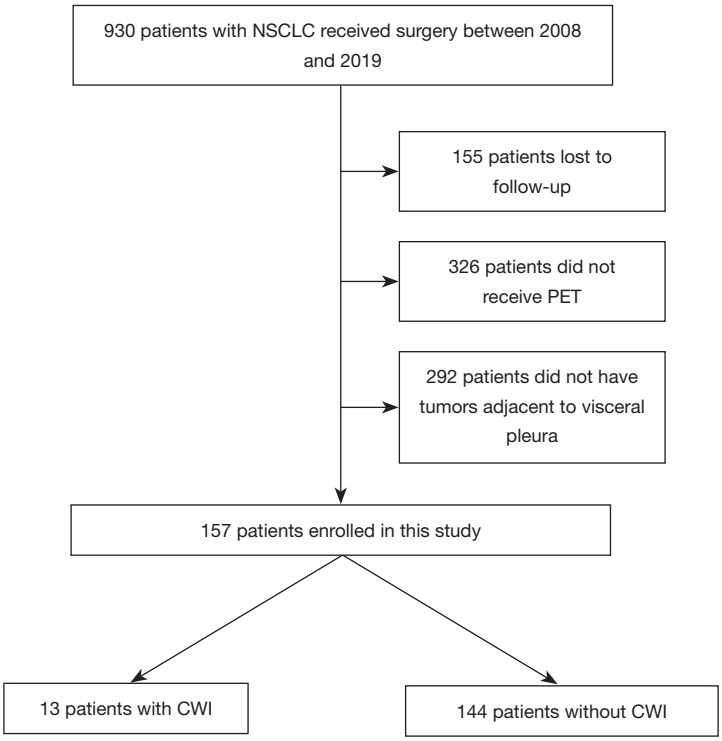

Figure 1 Flowchart for patient enrollment. NSCLC, non-small cell lung cancer; CWI, chest wall invasion; PET, positron emission tomography.

development of CWI in NSCLC patients are unclear. If these risk factors could be clarified, surgical treatment might be able to be performed before CWI development, thus improving the prognosis.

In the present study, we retrospectively analyzed the relationship between clinicopathological factors and CWI in NSCLC patients and examined whether or not it was possible to assess the risk of CWI.

We present the following article in accordance with the STROBE reporting checklist (available at http://dx.doi.org/10.21037/jtd-20-1722).

Methods

Patients

Nine hundred and thirty NSCLC patients who underwent surgery at Kanazawa Medical University between January 2008 and December 2019 were identified. Among these, 155 patients were lost to follow-up, 326 did not undergo positron emission tomography (PET), and 292 did not have a lesion adjacent to the visceral pleura. Therefore, 157 patients were enrolled in the present retrospective study (*Figure 1*). The lifetime cigarette consumption was assessed using the Brinkman index, which is calculated as the number of cigarettes smoked per day multiplied by the number of years for which the subject has smoked.

Tumor diameter

The maximum tumor diameter and diameter of tumors adjacent to the visceral pleura were measured on chest CT. The maximum tumor diameter on CT was defined as the CT_{max}, and the diameter of tumors adjacent to the visceral pleura was defined as the P_{max}. The maximum tumor diameter on a pathological examination was defined as the $Patho_{max}$.

Maximum standardized uptake value (SUV_{max})

^{18}F-fluoro-2-deoxy-glucose (^{18}F-FDG)-PET was performed with a dedicated PET camera (SIEMENS Biograph Sensation 16; SIEMENS, Erlangen Germany) before surgery. All patients fasted for 6 h before undergoing scanning. The dose of ^{18}F-FDG administered was 3.7 MBq/kg of the patient's body weight. After a 60-min uptake period, an emission scan was acquired for 3 min per bed position, and a whole-body scan was performed according to the

height of each patient. After image reconstruction, a two-dimensional (2D) round region of interest (ROI) was drawn on a slice after visual detection of the highest count on the fused CT image. For lesions with negative or faintly positive PET findings, the ROI was drawn on the fusion image obtained with the corresponding CT image. From those ROIs, the SUV_{max} was calculated.

Blood chemistry test

The preoperative white blood cell (WBC) count, platelet (Plt) count, and levels of lactate dehydrogenase (LDH) and C-reactive protein (CRP) were analyzed as predictive factors of CWI. Furthermore, the preoperative neutrophil-to-lymphocyte ratio (NLR) was analyzed as well.

Clinical and pathological diagnoses

Clinical and pathological TNM staging was performed in all patients based on the 8th edition of the AJCC/UICC classification.

Statistical analyses

Pearson's chi-square test for independence was used to compare frequencies of clinicopathologic variables. The cut-off values for the clinicopathological factors related to CWI were calculated according to a receiver operating characteristics (ROC) curve analysis. The predictive factors related to CWI were analyzed by a logistic regression analysis. All statistical analyses were two-sided, and statistical significance was defined as a P value of less than 0.05. The statistical analyses were conducted using the JMP software program (Version 13.2; SAS Institute Inc., Cary, NC, USA).

Ethical statement

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The institutional review boards of Kanazawa Medical University approved the protocol (the approval number: I392), and written informed consent was obtained from all patients.

Results

Patients' characteristics

The relationship between CWI and the clinicopathologic characteristics of these 157 patients is shown in *Table 1*. The median age of patients with CWI was significantly younger than that of the patients without CWI (65 *vs.* 68 years, P=0.04). The median values of CT_{max} (63 *vs.* 40 mm, P<0.01), P_{max} (75 *vs.* 29 mm, P<0.01), and $Path_{omax}$ (65 *vs.* 42 mm, P<0.01) of patients with CWI were significantly larger than those of patients without CWI. The median SUV_{max} of patients with CWI was significantly higher than that of patients without CWI (18.8 *vs.* 9.4, P<0.01). The median levels of LDH (238 *vs.* 193 U/L, P<0.01) and CRP (0.6 *vs.* 0.19 mg/dL, P=0.01) of patients with CWI were higher than those of patients without CWI.

Relationship between CWI and clinicopathological variables divided by an ROC curve analysis

The cut-off value for the clinicopathological variables related to pleural dissemination was calculated by an ROC curve analysis, and the relationships between CWI and the clinicopathological variables of NSCLC patients are shown in *Table 2*. There were significant differences in the age (P=0.02), CT_{max} (P<0.01), P_{max} (P<0.01), SUV_{max} (P<0.01), $Patho_{max}$ (P<0.01), WBC count (P=0.03), Plt count (P=0.04), levels of LDH (P<0.01) and CRP (P=0.01) between CWI group and non-CWI group.

Logistic regression analyses

The results of logistic regression analyses of the risk factors related to CWI are summarized in *Table 3*. The age (P=0.02), P_{max} (P=0.02), SUV_{max} (P=0.01), and LDH level (P<0.01) were identified as significant risk factors related to CWI.

Discussion

Surgical treatment for NSCLC patients with CWI has not been considered as contraindication from the last two-decades, and the prognostic improvement has been reported (1-4,6-9). Several prognostic factors for NSCLC patients with CWI were reported. The completeness of resection and involvement of lymph nodes were mainly considered prognostic factors, whereas the depth of CWI or tumor size were reported as prognostic factors in some studies (3,4,6-9). Although the prognostic factors of NSCLC patients with CWI were not analyzed in the present study, the tumor size was indicated to be a risk factor of CWI. If a large tumor invades the chest wall at an early point, surgery should be performed as soon as possible before invasion to the

Table 1 Patient characteristics

Characteristics	Chest wall invasion		P value
	Present (n=13)	Absent (n=144)	
Gender (male/female)	12/1	110/34	0.19
Age (median, range)	65 [45–82]	68 [38–89]	0.04*
Smoking index (median, range)	900 [360–2,150]	822 [0–3,660]	0.40
CEA (median, range)	6.4 [2.1–48.2]	5.2 [0.7–403.3]	0.26
CT_{max} (median, range)	63 [27–151]	40 [13–150]	<0.01*
P_{max} (median, range)	75 [19–131]	29 [3–244]	<0.01*
SUV_{max} (median, range)	18.8 [8.39–28.46]	9.4 [0.89–37.9]	<0.01*
Histology (Ad/Sq/others)	7/4/2	73/53/18	0.89
$Patho_{max}$ (median, range)	65 [22–150]	42 [10–240]	<0.01*
G (1/2/3/4)	0/5/7/1	35/61/38/10	0.09
cStage (IA/IB/IIA/IIB/IIIA)	1/1/2/4/5	33/28/22/27/34	0.79
Ly (0/1)	7/6	48/96	0.13
V (0/1)	1/12	35/108	0.36
WBC (median, range)	7,250 [3,350–10,360]	6,380 [2,980–12,150]	0.06
Plt (median, range)	30.1 [16–63.4]	24.8 [12–54.8]	0.08
NLR (median, range)	2.94 [0.88–12.48]	2.39 [0.53–9.23]	0.06
LDH (median, range)	238 [177–285]	193 [133–448]	<0.01*
CRP (median, range)	0.6 [0.09–15.79]	0.19 [0.03–45]	0.01*

*, statistical significance. CEA, carcinoembryonic antigen; CT_{max}, maximum tumor diameter on computed tomography; P_{max}, tumor diameter adjacent to visceral pleura; SUV_{max}, maximum standardized uptake value; c, clinical; Ad, adenocarcinoma; Sq, squamous cell carcinoma; $Patho_{max}$, tumor diameter on pathological exam; G, grade of differentiation; c, clinical; Ly, lymphatic invasion; V, vascular invasion; WBC, white blood cell; Plt, platelet; NLR, neutrophil-to-lymphocyte ratio; LDH, lactate dehydrogenase; CRP, C-reactive protein.

chest wall. Furthermore, the completeness of resection for NSCLC patients with CWI might be maintained before deep CWI occurs.

Because CWI (T3) with ipsilateral mediastinal lymph node metastasis (N2) is categorized as IIIB stage in the TNM staging system (8^{th} edition) (10), the presence of CWI might determine the surgical indication in some cases. Therefore, it is important to clarify the risk factors of CWI for NSCLC patients. In the present study, several risk factors for CWI were revealed. First, young patients with NSCLC tended to develop CWI more frequently than older patients in our study. Although the median age of NSCLC patients with CWI was mainly reported to be 60–64 years in previous studies (3,7,8,12,15-19), there was no significant difference in the age between the visceral pleural invasion group and the no-pleural invasion group in one study (13). Because whether or not age is a risk factor for CWI in NSCLC patients was not mentioned in previous reports (3,7,8,12,15-19), age as a risk factor for CWI in NSCLC patients should be verified in the future.

Second, the diameter of tumors adjacent to the visceral pleura was a risk factor for CWI in NSCLC patients in the present study. Because some CT findings were considered to be signs of CWI [e.g., tumor size >3 cm between the mass and the pleura; obtuse angle between the tumor and chest wall; pleural thickening (20-23)], the diameter of tumors adjacent to the visceral pleura might be a predictive risk factor for CWI.

Third, SUV_{max} was a risk factor for CWI in NSCLC patients in the present study. Although the SUV_{max} was not mentioned to be a risk factor of CWI in previous reports, it was reported to be associated with tumor aggressiveness

Table 2 Relationship between chest wall invasion and clinicopathological variables of non-small cell lung cancer patients divided by a receiver operating characteristics curve analysis

Variables	Chest wall invasion		P value
	Present (n=13)	Absent (n=144)	
Gender (male/female)	12/1	110/34	0.19
Age (<67/≥67)	9/4	54/90	0.02*
Smoking index (<400/≥400)	1/12	39/105	0.12
CEA (<14.5/≥14.5)	8/5	113/31	0.16
CT_{max} (<51/≥51)	4/9	103/41	<0.01*
P_{max} (<46/≥46)	3/10	104/40	<0.01*
SUV_{max} (<13.5/≥13.5)	3/10	103/41	<0.01*
Histology (Ad/Sq/others)	7/4/2	73/53/18	0.89
$Patho_{max}$ (<51/≥51)	3/10	94/50	<0.01*
G (1-2/3-4)	5/8	91/48	0.09
Ly (0/1)	7/6	48/96	0.13
V (0/1)	1/12	35/108	0.36
WBC (<7,500/≥7,500)	6/7	106/38	0.03*
Plt (<26.9/≥26.9)	4/9	85/59	0.04*
NLR (<2.43/≥2.43)	3/10	74/70	0.05
LDH (<204/≥204)	3/10	90/54	<0.01*
CRP (<0.32/≥0.32)	4/9	95/49	0.01*

*, statistical significance. CEA, carcinoembryonic antigen; CT_{max}, maximum tumor diameter on computed tomography; P_{max}, tumor diameter adjacent to visceral pleura; SUV_{max}, maximum standardized uptake value; c, clinical; Ad, adenocarcinoma; Sq, squamous cell carcinoma; $Patho_{max}$, tumor diameter on pathological exam; G, grade of differentiation; Ly, lymphatic invasion; V, vascular invasion; WBC, white blood cell; Plt, platelet; NLR, neutrophil-to-lymphocyte ratio; LDH, lactate dehydrogenase; CRP, C-reactive protein.

Table 3 Logistic regression analysis

Variables	OR	95% CI	P value
Age (<67/≥67)	6.15	1.30–28.94	0.02*
P_{max} (≥46/<46)	5.71	1.19–27.23	0.02*
SUV_{max} (≥13.5/<13.5)	7.57	1.40–40.78	0.01*
WBC (≥7,500/<7,500)	0.80	0.15–4.25	0.80
Plt (≥26.9/<26.9)	3.54	0.66–18.93	0.13
LDH (≥204/<204)	10.54	1.90–58.23	<0.01*
CRP (≥0.32/<0.32)	0.81	0.13–5.02	0.83

*, statistical significance. OR, odds ratio; CI, confidence interval; P_{max}, tumor diameter adjacent to visceral pleura; SUV_{max}, maximum standardized uptake value; WBC, white blood cell; Plt, platelet; LDH, lactate dehydrogenase; CRP, C-reactive protein.

(24-26). Furthermore, because the expression of Ki-67 and vascular endothelial growth factor in primary tumors was reported to be associated with SUV_{max} in NSCLC, this factor was suggested to have a close relationship with cancer proliferation, invasion, progression, and metastasis (27). Taken together, these findings suggest that SUV_{max} may be a risk factor for CWI in NSCLC patients.

Fourth, the LDH level was a risk factor for CWI in NSCLC patients in the present study. A high LDH level has been suggested to be associated with a poor prognosis in lung cancer (28-30). Furthermore, it was suggested that LDH-A, which is a cancer-specific isoform of LDH, promotes invasion in gastric cancer (31). Because a high LDH level might be associated with tumor aggressiveness, the LDH level might be a risk factor for CWI in NSCLC patients. In NSCLC patients with these risk factors, surgery should be performed as soon as possible, before CWI can occur.

Limitations

Of note, this study is associated with several limitations, including the small sample size, retrospective nature, and single-institution setting.

In conclusions, four risk factors were suggested to be related to CWI due to NSCLC: the age, diameter of tumors adjacent to the visceral pleura, SUV_{max}, and LDH level. Surgery should therefore be performed as soon as possible when these risk factors are present, before CWI can occur.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at http://dx.doi.org/10.21037/jtd-20-1722

Data Sharing Statement: Available at http://dx.doi.org/10.21037/jtd-20-1722

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/jtd-20-1722). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The institutional review boards of Kanazawa Medical University approved the protocol (the approval number: I392), and written informed consent was obtained from all patients.

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