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Postoperative Complication after Non-Small Cell Lung Cancer Resection is a Prognostic Factor

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Abstract

Background: The relationship between the postoperative complication and prognosis in Non-Small Cell Lung Cancer (NSCLC) patients who have undergone surgery has not been elucidated.

Methods: Clinical data were analyzed for 549 patients with NSCLC. We divided the patients into preceding period (2009-2013) and late period (2014-2018). Comorbidity was evaluated by the Charlson comorbidity index. The postoperative complication was categorized into five grades according to the Clavien-Dindo classification.

Results: Preceding period included 191 patients and late period 358. There were significant differences in differentiation (p<0.01), Ly (p<0.01), pStage (p<0.01), operative procedure (p<0.01) and Clavien-Dindo grade (p<0.01). Because the patient characteristics were significantly different, we adjusted the patient background using propensity score matching. The RFS (p=0.55) and OS (p=0.40) of the propensity score matched patients classified by preceding period and late period were not significant prognostic differences. The RFS of the patients with Clavien-Dindo grade II-IIIb tended to be worse (p=0.06), and the OS was significantly lower than that of 0-I (0.02). Although the Clavien-Dindo grade (HR, 2.61; p=0.01) was identified as significant prognostic factors in the univariate analysis for propensity score matched patients, the Clavien-Dindograde was not significant prognostic factor in the multivariate analysis (HR, 1.60; p=0.25).

Conclusion: The severity of postoperative complication classified by the Clavien-Dindo grade might have a prognostic impact on the long-term outcomes in patients who have undergone surgery for NSCLC.

Keywords: Postoperative complication; Clavien-Dindo; Comorbidity; Non-small cell lung cancer; Surgery; Prognosis

Introduction

Although lung cancer is the leading cause of cancer-related mortality worldwide, some reports from high-volume centers showed improved short- and long-term surgical outcomes after pulmonary resection [1-4]. Furthermore, it was demonstrated improvements of survival for Non-Small Cell Lung Cancer (NSCLC) patients over time [5]. However, it is unclear whether these improvements of survival for NSCLC patients depend on improved therapy and medical care or improved screening work.

Several studies have shown a poor prognosis due to postoperative complications after surgery for gastrointestinal cancers [6-10]. Furthermore, it was reported that systemic inflammation as a postoperative complication may carry a risk of inducing cancer recurrence [11,12]. However, other studies have reported that the postoperative complication did not influence the prognosis, so the actual situation is controversial [13,14].

The Clavien-Dindo classification, established in 1992, is a simple and feasible grading system for all types of postoperative complications [15]. In 2004, the Clavien-Dindo classification was modified to allow for the grading of life-threatening complications and long-term disability caused by a complication [16]. This revised version defines five grades of severity (Grade I, II, IIIa, IIIb, IVa, IVb, and V), and the suffix "d" (for "disability") is used to denote any postoperative impairment. This modified Clavien-Dindo classification has been used widely in clinical practice. However, the relationship between the postoperative complication and prognosis in NSCLC patients who have undergone surgery has not been elucidated.

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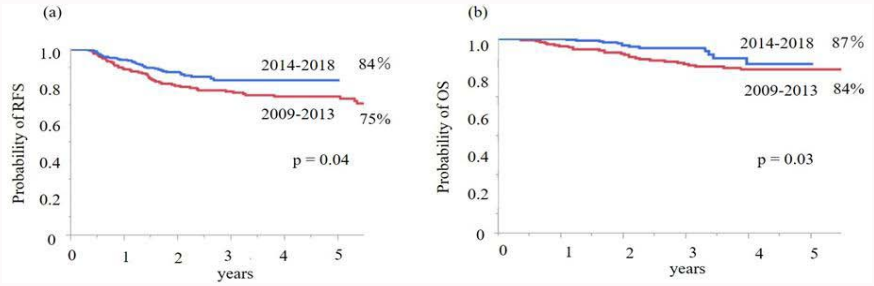

Figure 1: (a) The relapse-free survival is significantly higher in late period than in preceding period. (b) The overall survival is significantly higher in late period than in preceding period.

Table 1: Patient characteristics.

Generations	2009-2013 (n=191)	2014-2018 (n=358)	P value
Gender (male/female)	109/82	227/131	0.14
Age, median, range (y.o.)	69 (33-83)	70 (34-89)	0.17
Charlson comorbidity index (0/1/2/3/4/5/6)	111/49/29/2/0/0/0	179/98/63/13/3/1/1	0.25
Smoking index, median, range	400 (0-3000)	600 (0-3600)	0.08
CEA, median, range (ng/ml)	3.7 (0.6-148.2)	3.6 (0.5-142.6)	0.51
Differentiation (G1/2/3/4)	92/73/23/1	112/159/58/13	<0.01
Ly (0/1)	106/85	242/116	<0.01
V (0/1)	108/83	190/168	0.43
Histology (Ad/Sq/Others)	148/39/4	267/69/22	0.1
pStage (IA/IB/IIA/IIB/IIIA)	91/50/18/14/18	229/55/26/28/20	<0.01
Operative procedure (Part/Seg/Lob/Bilob/Pneum)	27/2/151/5/6	89/30/229/3/7	<0.01
Clavien-Dindo grade (0/I/II/IIIa/IIIb)	160/2/15/13/1	242/22/35/55/4	<0.01

CEA: Carcinoembryonic Antigen; Ly: Lymphatic Invasion; V: Vascular Invasion; Ad: Adenocarcinoma; Sq: Squamous Cell Carcinoma; pStage: Pathological Stage; Part: Partial Resection; Seg: Segmentectomy; Lob: Lobectomy; Bilob: Bi-lobectomy; Pneum: Pneumonectomy

In the present study, we evaluated the trends of clinical characteristics over time and the prognostic impact of postoperative complication classified by the Clavien-Dindo system after surgery for NCSLC patients.

Materials and Methods

Patients

Eight hundred and five NSCLC patients who underwent complete resection with the Video-Assisted Thoracic Surgery (VATS) technique in Kanazawa Medical University between January 2009 and December 2018 were identified. Among these, 549 patients with NSCLC had available data. These patients were therefore enrolled in the present retrospective study; we divided the patients into preceding period (2009-2013) and late period (2014-2018).

Regarding the data collected, the clinical factors were the gender, age, smoking history, comorbidity, Carcino Embryonic Antigen (CEA). The smoking history was assessed using the Brinkman index, which is calculated as the numbers of cigarettes smoked per day multiplied by the number of years for which the subject has smoked. The comorbidity was evaluated by the Charlson comorbidity index [17]. Pathological factors were the histological type, differentiation, Lymphatic Invasion (Ly), Vascular Invasion (V), Pathological stage (pStage). Perioperative factors were the operative procedure, postoperative complication. The postoperative complication was categorized into five grades according to the Clavien-Dindo classification.

Statistical analyses

The cumulative survival rates were calculated by the Kaplan-Meier methods, and survival curves were compared using the log-rank test. Univariate and multivariate analyses using the Cox proportional hazard model were conducted to obtain the risk factors for the Relapse-Free Survival (RFS) and the Overall Survival (OS). 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).

The present study was conducted in accordance with the amended Declaration of Helsinki. The Institutional Review Boards of Kanazawa Medical University approved the protocol (approval number: I392), and written informed consent was obtained from all of the patients.

Results and Discussion

Patients characteristics

The clinic pathologic characteristics of the 549 included patients are listed in Table 1. Preceding period (2009 to 2013) included 191 patients and late period (2014 to 2018) 358. There were significant differences in differentiation (p<0.01), Ly (p<0.01), pStage (p<0.01), operative procedure (p<0.01) and Clavien-Dindo grade (p<0.01). Because patient's characteristics were significantly different, we adjusted the patient background using propensity score matching (Table 2).

Survival analyses

The RFS and OS of the all patients classified by preceding

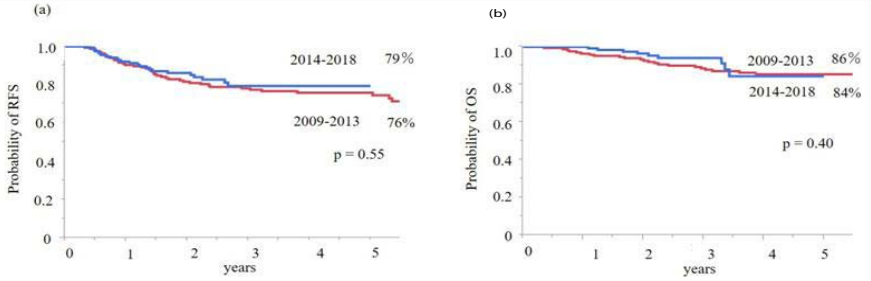

Figure 2: (a) The relapse-free survival of propensity score matched patients is not significantly different by preceding and late period. (b) The overall survival of propensity score matched patients is not significantly different by preceding and late period.

Table 2: Propensity score match.

Generations	2009-2013 (n=169)	2014-2018 (n=169)	P value
Gender (male/female)	93/73	102/67	0.51
Age, median, range (y.o.)	69 (33-83)	69 (41-86)	0.83
Charlson comorbidity index (0/1/2/3)	102/41/24/2	91/51/27/0	0.27
Smoking index, median, range	400 (0-3000)	540 (0-3600)	0.42
CEA, median, range (ng/ml)	3.6 (0.6-148.2)	3.7 (0.5-128.5)	0.72
Differentiation (G1/2/3/4)	74/73/22/0	69/69/26/5	0.13
Ly (0/1)	102/67	104/65	0.82
V (0/1)	94/75	98/71	0.66
Histology (Ad/non-Ad)	131/38	124/45	0.37
pStage (IA/IB/IIA/IIB/IIIA)	83/44/17/11/14	101/27/12/15/14	0.12
Operative procedure (Part/Seg/Lob/Bilob/Pneum)	27/2/132/3/5	21/9/133/2/4	0.23
Clavien-Dindo grade (0-I/II- IIIb)	149/29	140/29	1

CEA: Carcinoembryonic Antigen; Ly: Lymphatic Invasion; V: Vascular Invasion; Ad: Adenocarcinoma; pStage: Pathological Stage; Part: Partial Resection; Seg: Segmentectomy; Lob: Lobectomy; Bilob: Bi-lobectomy; Pneum: Pneumonectomy

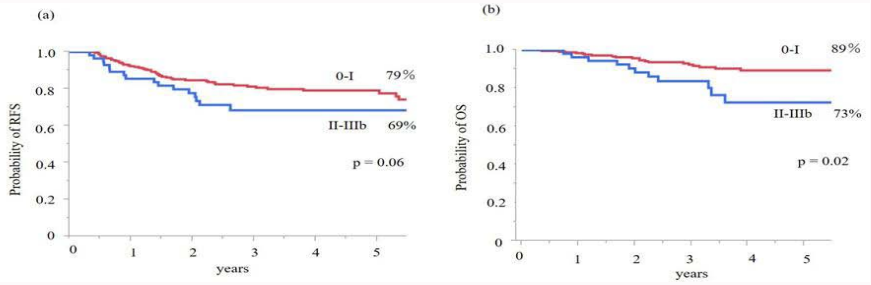

Figure 3: (a) The relapse-free survival tends to be higher in patients with postoperative complications classified as Clavien-Dindo grade O or I than in grade II to IIIb. (b) The overall survival is significantly higher in patients with postoperative complications classified as Clavien-Dindo grade O or I than in grade II to IIIb.

period and late period are shown in Figure 1. There were significant prognostic differences in the RFS (p<0.04) and the OS (p=0.03). The RFS and OS of the propensity score matched patients classified by preceding period and late period is shown in Figure 2. There were not significant prognostic differences in RFS (p=0.55) and OS (p=0.40). The RFS and OS of propensity score matched patients classified by Clavien-Dindo grade is shown in Figure 3. The RFS of the patients with Clavien-Dindo grade II-IIIb tended to be worse (p=0.06). The OS of the patients with Clavien-Dindo grade II-IIIb was significantly lower than that of 0-I (0.02).

Univariate and multivariate analyses

The univariate and multivariate analyses of the factors affecting the RFS for propensity score matched patients are summarized in Table 3. The gender (Hazard Ratio [HR], 3.55; 95% Confidence Interval [CI], 2.00-6.79; p<0.01), smoking status (HR, 2.97; 95% CI, 1.72-5.48; p<0.01), CEA (HR, 2.02; 95% CI, 1.25-3.27; p<0.01), differentiation (HR, 3.36; 95% CI, 1.93-6.20; p<0.01), Ly (HR, 3.69; 95% CI, 2.23-6.32; p<0.01), V (HR, 3.58; 95% CI, 2.15-6.17; p<0.01), histologic type (HR, 2.16; 95% CI, 1.30-3.51; p<0.01), and pStage (HR, 4.36; 95% CI, 2.71-7.06; p<0.01) were identified as significant prognostic factors in the univariate analysis. The multivariate analysis showed that Gender (HR, 2.86; 95% CI, 1.13-7.39; p=0.02) and the pStage (HR, 2.49; 95% CI, 1.43-4.36, p<0.01) were significant prognostic factor for the RFS.

The univariate and multivariate analyses of the factors affecting the OS for propensity score matched patients are summarized in Table 4. The gender (HR, 23.69; 95% CI, 5.08-421.85; p<0.01), smoking status (HR, 11.29; 95% CI, 3.40-69.86; p<0.01), CEA (HR, 4.66; 95% CI, 2.21-10.68; p<0.01), differentiation (HR, 4.47; 95% CI,

Table 3: Cox proportional hazard analyses for factors affecting relapse free survival.

Univariate analysis				Multivariate analysis			
Variables		HR (95%CI)	p-value	Variables		HR (95%CI)	p-value
Gender	Female	1	<0.01	Gender	Female	1	0.02
	Male	3.55 (2.00-6.79)			Male	2.86 (1.13-7.39)	
Age	< 70y	1	0.07				
	≥ 70y	1.53 (0.95-2.50)					
CCI	0-2	1	0.61				
	3	1.75 (0.09-8.00)					
Smoking status	Never	1	<0.01	Smoking status	Never	1	0.54
	Former/ Current	2.97 (1.72-5.48)			Former/Current	0.74 (0.30-1.95)	
CEA	≤ 5 ng/ml	1	<0.01	CEA	≤ 5 ng/ml	1	0.2
	> 5 ng/ml	2.02 (1.25-3.27)			> 5 ng/ml	1.37 (0.83-2.25)	
Differentiation	G1	1	<0.01	Differentiation	G1	1	0.28
	G2-4	3.36 (1.93-6.20)			G2-4	1.43 (0.75-2.89)	
Ly	Absent	1	<0.01	Ly	Absent	1	0.2
	Present	3.69 (2.23-6.32)			Present	1.57 (0.78-3.24)	
V	Absent	1	<0.01	V	Absent	1	0.46
	Present	3.58 (2.15-6.17)			Present	1.30 (0.64-2.70)	
Histology	Ad	1	<0.01	Histology	Ad	1	0.72
	Non-Ad	2.16(1.30-3.51)			Non-Ad	1.10 (0.63-1.91)	
pStage	I	1	<0.01	pStage	I	1	<0.01
	II-IIIA	4.36 (2.71-7.06)			II-IIIA	2.49 (1.43-4.36)	
Procedure	Part/Seg	1	0.98				
	Lob	0.99 (0.54-2.00)					
Clavien-Dindo grade	0-I	1	0.61				
	II-IIIb	1.65 (0.09-8.00)					

CCI: Charlson Comorbidity Index; CEA: Carcinoembryonic Antigen; Ly: Lymphatic Invasion; V: Vascular Invasion; Ad: Adenocarcinoma; pStage: Pathological Stage; Part: Partial Resection; Seg: Segmentectomy; Lob: Lobectomy or more

1.86-13.23; p<0.01), Ly (HR, 2.83; 95% CI, 1.36-6.28; p<0.01), V (HR, 5.61; 95% CI, 2.46-15.12; p<0.01), histologic type (HR, 2.55; 95% CI, 1.22-5.18; p=0.01), pStage (HR, 9.75; 95% CI, 4.54-23.29; p<0.01), operative procedure (HR, 5.32; 95% CI, 1.14-94.84; p=0.039, and Clavien-Dindo grade (HR, 2.61; 95% CI, 1.21-5.37; p=0.01) were identified as significant prognostic factors in the univariate analysis. The multivariate analysis showed that gender (HR, 10.64; 95% CI, 1.38-233.09; p=0.02), CEA (HR, 2.67; 95% CI, 1.25-6.20, p=0.01), and the pStage (HR, 5.48; 95% CI, 2.21-15.27, p<0.01) were a significant prognostic factor for the OS.

Discussion

Although the survival of NSCLC patients received surgery seemed to be improved over time, it was considered that the improvement of prognosis was affected by the change of patient characteristics in the present study. Because the proportion of early-stage NSCLC patients has been increasing by progress of screening work, the RFS and OS of NSCLC patients received surgery were significantly improved over time. However, the RFS and OS of propensity score matched NSCLC patients dividing into preceding period and late period were not significantly different in the present study. In other word, the progress of surgical techniques and Perioperative managements were not improved the survival of NSCLC patients received surgery over the last decade in the present study. Although previous study suggested that the improved survival of NSCLC were deem attributable to improved therapy and medical care rather than improved screening work, the differences of patient characteristics were not adjusted, it was not unclear that therapy and medical care improved the survival rather than screening work [5].

We demonstrated that postoperative complications classified as Clavien-Dindo ≥ II tend to be worse prognosis in patients who have undergone surgery for NSCLC. The Clavien-Dindo classification has been used to evaluate the severity of postoperative complications in several fields of surgery, and the utility was reported in several reports [18-20]. A previous study reported that major infectious complications, such as pneumonia, empyema, and mediastinitis, influenced a poor prognosis in patients who had undergone lung cancer surgery [11]. Furthermore, postoperative complication was associated with the patient prognosis in gastrointestinal cancers [6-22]. In these reports, it was suggested that an inflammatory reaction might promote tumor proliferation, avoidance of apoptosis, progression of metastasis, and resistance to drug therapy. Although inflammatory complications, such as pneumonia and urinary tract infection, developed in only 14 patients (4%) in the present study, the RFS and OS in patients with postoperative complications classified as Clavien-Dindo ≥ II tended to be lower than in those without such complications. Postoperative complications classified as Clavien-Dindo ≥ II require additional treatment, which can cause

Table 4: Cox proportional hazard analyses for factors affecting overall survival.

Univariate analysis				Multivariate analysis			
Variables		**HR (95%CI)**	**p-value**	**Variables**		**HR (95%CI)**	**p-value**
Gender	Female	1	<0.01	Gender	Female	1	0.02
	Male	23.69 (5.08-421.85)			Male	10.64 (1.38-233.09)	
Age	< 70y	1	0.88				
	≥ 70y	0.94 (0.45-1.92)					
CCI	0-2	1	N.A.				
	3-4	N.A.					
Smoking status	Never	1	<0.01	Smoking status	Never	1	0.99
	Former/Current	11.29 (3.40-69.86)			Former/Current	1.00 (0.19-8.48)	
CEA	≤ 5 ng/ml	1	<0.01	CEA	≤ 5 ng/ml	1	0.01
	> 5 ng/ml	4.66 (2.21-10.68)			> 5 ng/ml	2.67 (1.25-6.20)	
Differentiation	G1	1	<0.01	Differentiation	G1	1	0.47
	G2-4	4.47 (1.86-13.23)			G2-4	1.52 (0.50-5.52)	
Ly	Absent	1	<0.01	Ly	Absent	1	0.22
	Present	2.83 (1.36-6.28)			Present	0.53 (0.20-1.48)	
V	Absent	1	<0.01	V	Absent	1	0.29
	Present	5.61 (2.46-15.12)			Present	1.91 (0.58-6.83)	
Histology	Ad	1	0.01	Histology	Ad	1	0.87
	Non-Ad	2.55 (1.22-5.18)			Non-Ad	1.06 (0.49-2.27)	
pStage	I	1	<0.01	pStage	I	1	<0.01
	II-IIIA	9.75 (4.54-23.29)			II-IIIA	5.48 (2.21-15.27)	
Procedure	Part/Seg	1	0.03	Procedure	Part/Seg	1	0.33
	Lob	5.32 (1.14-94.84)			Lob	2.51 (0.44-47.54)	
Clavien-Dindo grade	0-I	1	0.01	Clavien-Dindo grade	0-I	1	0.25
	II-IIIb	2.61 (1.21-5.37)			II-IIIb	1.60 (0.70-3.45)	

CCI: Charlson Comorbidity Index; N.A: Not Available; CEA: Carcinoembryonic Antigen; Ly: Lymphatic Invasion; V: Vascular Invasion; Ad: Adenocarcinoma; pStage: Pathological Stage; Part: Partial Resection; Seg: Segmentectomy; Lob: Lobectomy or more

inflammatory reactions. Although the severity of postoperative complication was reported to have a detrimental impact on the long-term outcomes, particularly cancer-specific outcomes, in patients undergoing surgery for colorectal cancer, the relationship between the severity of the postoperative complication and the prognosis in patients who have undergone surgery for NSCLC has not yet been revealed. Based on the present findings, the severity of postoperative complication classified by Clavien-Dindo grade might have some prognostic influence on the long-term outcomes in patients who have undergone surgery for NSCLC.

Previous studies reported that the presence of comorbidities was associated with a worse survival in lung cancer patients than their absence [23-28]. Although the Charlson comorbidity index has often been used to evaluate the severity of comorbidity, with a good utility reported, the severity boundary is not clear [23,25,26]. We found no significant prognostic difference between the patients with a Charlson comorbidity index ≤ 2 and those with an index >2 in the present study. Because the Charlson comorbidity index was not developed specifically for patients with NSCLC, it might not have adequately affected the prognosis in the present study. In the future, a new comorbidity index should be developed that emphasizes the different effects of certain comorbidities.

Several limitations associated with the present study warrant mention. First, the study is retrospective, and there is a possibility of unobserved cofounding and selection bias. Second, the present study was performed at a single institution, and the number of patients was small.

Conclusion

Because the progress of surgical techniques and perioperative managements were not improved the survival of NSCLC patients received surgery over the last decade, it was not unclear that therapy and medical care improved the survival rather than screening work. Our findings suggested that the severity of postoperative complications classified by Clavien-Dindo grade might have a prognostic impact on the long-term outcomes in patients who have undergone surgery for NSCLC. In addition, a new comorbidity index should be developed with emphasize on the different effects of some specific comorbidities.

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Availability of Data and Materials

The data sets supporting the conclusions of the present study are included in this published article.

Author's Contribution

N. M. performed the research, collected and analyzed the data and wrote the paper. S. I., A. F., A.S., and K. U. contributed to sample collection. H. U. contributed to supervision of this study and revision of the manuscript.

Ethics Approval and Consent to Participate

The Institutional Review Boards of Kanazawa Medical University approved the protocol of this study, and written informed consent was obtained from all patients.

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