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Prognostic Implications of Postoperative Infectious Complications in Non-Small Cell Lung Cancer

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Background: Few studies have evaluated the long-term impact of postoperative infectious complications in patients with non-small cell lung cancer (NSCLC). We aimed to determine the impact of infectious complications on long-term outcomes after surgical resection for NSCLC. **Methods:** We performed a retrospective study of 1,380 eligible patients who underwent pulmonary resection for NSCLC from 2003 to 2012. Complications were divided into infectious complications and non-infectious complications. Kaplan-Meier survival analysis was used to compare unadjusted 5-year cancer-specific survival (CSS) rates and recurrence-free survival (RFS) rates. Cox regression was used to determine the impact of infectious complications on 5-year CSS and RFS. **Results:** The rate of total complications and infectious complications was 24.3% and 4.3%, respectively. In the node-negative subgroup, the 5-year CSS and RFS rates were 75.9% and 57.1% in patients who had infectious complications, compared to 87.9% and 78.4% in patients who had no complications. Infectious complications were a negative prognostic factor for 5-year RFS (hazard ratio, 1.92; 95% confidence interval, 1.00–3.69; p=0.049). In the node-positive subgroup, the 5-year CSS rate and RFS were 44.6% and 48.4% in patients who had infectious complications, compared to 70.5% and 48.4% for patients who had no complications. **Conclusion:** Postoperative infectious complications had a negative impact on CSS and RFS in node-negative NSCLC. Our findings may help improve risk assessment for tumor recurrence after pulmonary resection for node-negative NSCLC.

Key words: 1. Non-small-cell lung carcinoma
2. Complication
3. Prognosis

Introduction

Lung cancer is the most common cause of cancer-related death, and the overall 5-year survival rate for lung cancer is only 16% [1,2]. Recently, video-assisted thoracic surgery (VATS) has been widely performed to treat early-stage non-small cell lung cancer (NSCLC), leading to a decreased incidence of postoperative complications [3]. Nevertheless, due to the increasing age of patients who are candidates for surgery, the incidence of complications is still high, with complications observed in 31% of VATS resections for lung cancer [4].

These complications are not only relevant for as-

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sessing the short-term outcome of surgery, but are also prognostic factors that may influence postoperative survival. To date, some studies have shown a relationship between postoperative complications and the eventual prognosis of renal cell carcinoma [5], breast cancer [6], esophageal cancer [7], stomach cancer [8,9], and colon cancer [10-12].

The pathophysiology of how postoperative complications can influence long-term survival is not well understood; however, complications could lead to systemic inflammation, which might facilitate the recurrence of cancer [13]. The first study investigating postoperative complications and NSCLC outcomes showed that the presence of complications was related to poor long-term survival [14], and that infectious complications showed a strong negative relationship with long-term survival [15]. However, there were no studies in which this correlation between infectious complications and prognosis was evaluated according to stage and recurrence rate.

Therefore, the goal of this study was to evaluate the effect of postoperative complications on postoperative recurrence and overall survival depending on the presence of nodal metastasis in NSCLC.

Methods

1) Patients

A total of 1,621 patients who underwent pulmonary resection for NSCLC from June 2003 to December 2012 were included in this study. The following patients were excluded: (1) 115 patients who underwent a second operation for recurrence or metachronous cancer, (2) 30 patients who died within 90 days after the operation, (3) 13 patients who were diagnosed with small cell lung cancer after surgery, and (4) 83 patients who underwent incomplete resection. After exclusion, clinicopathologic data such as age, sex, diabetes mellitus (DM), chronic obstructive pulmonary disease (COPD), Charlson score, albumin level, histology, the extent of resection, whether VATS was used, lymph node metastasis, pathologic staging (according to the American Joint Committee on Cancer seventh edition), and the presence of complications were collected retrospectively from 1,380 patients, based on a prospective lung cancer database. This study was approved by the Institutional Review Board of Seoul National University Bundang Hospital (B-1503-292-107) and the requirement to obtain informed consent from patients was waived due to the retrospective design of the study.

2) Complications

Postoperative complications were defined according to the criteria outlined in the Society for Thoracic Surgeons database, and were considered to be complications that occurred within the same hospitalization or during the first 4 weeks after the operation [16]. Postoperative complications were categorized into infectious and non-infectious complications, with infectious complications consisting of pneumonia, acute respiratory distress syndrome (ARDS), empyema, bronchopleural fistula (BPF), wound infection, and sepsis. Non-infectious complications were defined as pulmonary complications (prolonged air leakage for longer than 7 days, atelectasis requiring bronchoscopy), cardiovascular complications (arrhythmia, myocardial infarction, deep vein thrombosis, pulmonary embolism), neurologic complications (delirium, transient ischemic attack, stroke, vocal cord palsy), ileus requiring a nasogastric tube, chylothorax, and renal dysfunction.

3) End point

The primary end point was recurrence-free survival (RFS) from the date of the operation to the date of confirmed recurrence. Recurrences included both local recurrences and distant metastasis, while metachronous primary lung cancer and primary cancer in other organs were excluded. The secondary end point was cancer-specific survival (CSS) from the date of the operation to the date of cancer-related death. Cancer-related death included death from the progression of cancer and treatment-related death; however, deaths from trauma or cardiovascular events and other cancer-related causes of death were not included.

4) Statistical analysis

Univariate analysis using the Kaplan-Meier log-rank test was used to compare the CSS and RFS according to each variable. Multivariate analysis using the Cox proportional hazards model included prognostic factors that were found to be statistically significant in univariate analysis. All p-values <0.05 were consid-

Table 1. Characteristics of patients with and without complications

Characteristic	Complications (−) (n=1,045)	Complications (+) (n=335)	p-value
Age (yr)			<0.001
<60	357 (34.2)	77 (23.0)	
≥60	688 (65.8)	258 (77.0)	
Sex			<0.001
Female	414 (39.6)	72 (21.5)	
Male	631 (60.4)	263 (78.5)	
Diabetes mellitus			0.832
None	888 (85.0)	286 (85.4)	
Yes	157 (15.0)	49 (14.6)	
Chronic obstructive pulmonary disease			0.006
None	952 (91.1)	289 (86.3)	
Yes	93 (8.9)	46 (13.7)	
Albumin (g/dL)	4.19	4.08	0.001
Histology			<0.001
Adenocarcinoma	739 (70.7)	182 (54.3)	
Squamous cell carcinoma	221 (21.1)	124 (37.0)	
Others	85 (8.1)	29 (8.7)	
Charlson score			0.007
<2	865 (82.8)	255 (76.1)	
≥2	180 (17.2)	80 (23.9)	
Type of surgery			0.915
Sublobar	165 (15.8)	56 (16.7)	
Simple lobectomy	631 (60.4)	200 (59.7)	
Complex lobectomy	195 (18.7)	60 (17.9)	
Pneumonectomy	53 (5.1)	19 (5.7)	
Video-assisted thoracic surgery			<0.001
Yes	640 (61.2)	127 (37.9)	
No	405 (38.8)	208 (62.1)	
T stage			0.002
T1	517 (49.5)	127 (37.9)	
T2	443 (42.4)	175 (52.2)	
T3	59 (5.6)	23 (6.9)	
T4	26 (2.5)	10 (3.0)	
N stage			0.003
N0	767 (73.4)	220 (65.7)	
N1	156 (14.9)	59 (17.6)	
N2	119 (11.4)	52 (15.5)	
N3	3 (0.3)	4 (1.2)	

Values are presented as number (%) or mean.

ered to indicate statistical significance, and statistical analysis was performed using IBM SPSS ver. 22.0 (IBM Corp., Armonk, NY, USA).

Results

1) All patients

Postoperative complications developed in 335 patients (24.3%). Table 1 compares the characteristics of patients with complications and patients without complications. All factors except the extent of resection and incidence of DM were found to be different in the 2 groups. Patients with complications had more COPD and lower preoperative albumin levels than those without complications. Postoperative complications developed more frequently in patients with

Table 2. Characteristics of patients with infectious complications and those with non-infectious complications

Characteristic	Non-infectious complications (n=276)	Infectious complications (n=59)	p-value
Age (yr)			0.058
<60	69 (25.0)	8 (13.6)	
≥60	207 (75.0)	51 (86.4)	
Sex			0.102
Female	64 (23.2)	8 (13.6)	
Male	212 (76.8)	51 (86.4)	
Diabetes mellitus			0.476
None	235 (85.1)	48 (81.4)	
Yes	41 (14.9)	11 (18.6)	
Chronic obstructive pulmonary disease			0.003
None	250 (90.6)	47 (79.7)	
Yes	26 (9.4)	12 (20.3)	
Albumin (g/dL)	4.17	4.00	<0.001
Histology			0.275
Adenocarcinoma	156 (56.5)	26 (44.1)	
Squamous cell carcinoma	95 (34.4)	29 (49.2)	
Other	25 (9.1)	4 (6.8)	
Charlson score			0.328
<2	213 (77.2)	42 (71.2)	
≥2	63 (22.8)	17 (28.8)	
Type of surgery			0.145
Sublobar	46 (16.7)	10 (16.9)	
Simple lobectomy	170 (61.6)	30 (50.8)	
Complex lobectomy	42 (17.0)	13 (22.0)	
Pneumonectomy	13 (4.7)	6 (10.2)	
Video-assisted thoracic surgery			0.197
Yes	109 (39.5)	18 (30.5)	
No	167 (60.5)	41 (69.5)	
T stage			0.334
T1	106 (38.4)	21 (35.6)	
T2	144 (52.2)	31 (52.5)	
T3	20 (7.2)	3 (5.1)	
T4	6 (2.2)	4 (6.8)	
N stage			0.044
N0	189 (68.5)	31 (52.5)	
N1	44 (15.9)	15 (25.4)	
N2	40 (14.5)	12 (20.3)	
N3	3 (1.1)	1 (1.7)	

Values are presented as number (%) or mean.

metastatic lymph nodes than in those without metastatic lymph nodes. Infectious complications developed in 59 (17.6%) of the 335 patients with complications. The most common infectious complication was pneumonia, which occurred in 44 patients, followed by empyema in 8 patients, ARDS in 7 patients, BPF in 7 patients, and wound infections in 7 patients. Most instances of ARDS and BPF occurred in combination with other infectious complications. The most minor infectious complication, wound infection, did not occur in combination with other infectious complications, except in 1 case. BPF was confirmed by bronchoscopy, and 3 of the 7 patients with BPF were managed by surgical repair. Patients with infectious complications were more likely to have lymph node metastasis than patients with non-infectious compli-

Table 3. Univariate analysis of CSS and RFS in all patients

Characteristic	5-year CSS	p-value	5-year RFS	p-value
Age (yr)				
<60	87.5		71.3	
≥60	76.2	0.001	66.8	0.257
Sex				
Female	84.5		70.5	
Male	77.2	<0.001	67.1	0.113
Histology				
Adenocarcinoma	82.7		70.0	
Squamous cell carcinoma	78.4	0.029	69.8	0.423
Other	61.5	0.006	49.4	<0.001
Charlson score				
<2	81.6		69.5	
≥2	72.1	0.003	63.3	0.065
Type of surgery				
Sublobar	78.8		69.5	
Simple lobectomy	80.3	0.235	68.7	0.765
Complex lobectomy	80.9	0.431	66.0	0.582
Pneumonectomy	73.4	0.286	69.1	0.859
Video-assisted thoracic surgery				
Yes	89.1		76.1	
No	70.5	<0.001	58.9	<0.001
T stage				
T1	85.1		79.5	
T2	77.9	<0.001	59.7	<0.001
T3	62.8	0.012	39.6	0.001
T4	62.3	0.856	43.4	0.693
N stage				
N0	86.6		77.2	
N1	69.2	<0.001	55.5	<0.001
N2	58.7	0.071	34.4	<0.001
N3	-	0.001	-	<0.001
Complications				
No	83.2		70.3	
Yes	69.6	<0.001	61.9	0.016
Type of complication				
Non-infectious	71.5		63.5	
Infectious	60.1	0.022	54.1	0.090

Values are presented as %.
CSS, cancer-specific survival; RFS, recurrence-free survival.

cations (Table 2).

2) Follow-up

The median follow-up duration among the 1,380 patients was 50.4 months (range, 3.0 to 135.1 months). A total of 25 patients were lost to follow-up, and 296 patients (21%) died, including 252 cases of cancer-related death and 44 cases of death due to other causes. Among the 252 instances of cancer-related death, 194 were due to cancer progression and 58 were treatment-related. Recurrence occurred in 395 patients (29%), with locoregional recurrence in 171 patients and distant metastasis in 224 patients. The 5-year CSS and RFS rates were 79.8% and 68.3%, respectively.

Among the 1,045 patients without postoperative

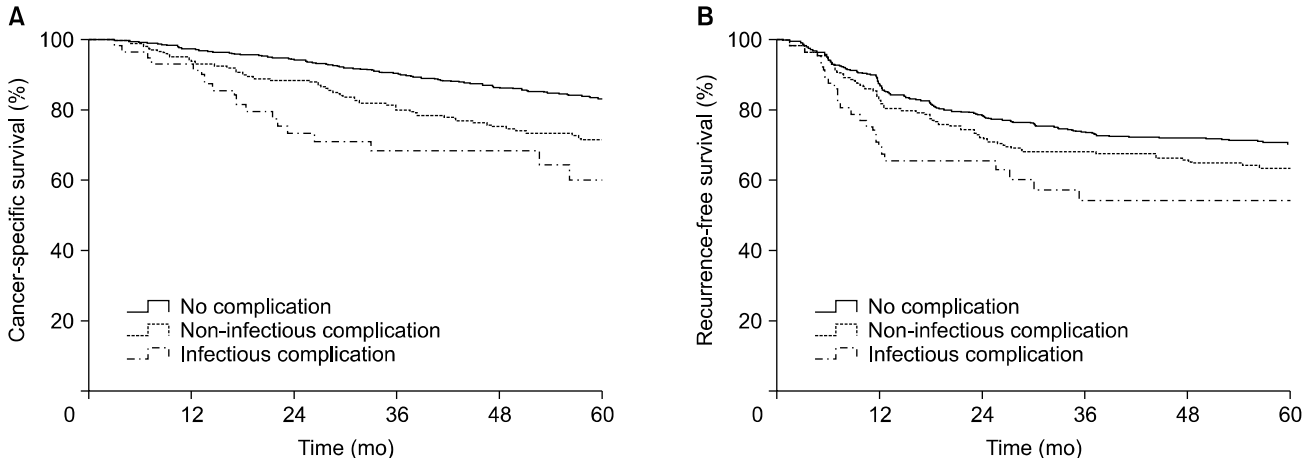

Fig. 1. Kaplan-Meier analysis of cancer-specific survival (A) and recurrence-free survival (B) according to the presence and type of complications in all patients.

Table 4. Multivariate analysis of CSS and RFS in all patients

Characteristic	5-year CSS	p-value	5-year RFS	p-value
Age (yr)				
<60	1.00			
≥60	1.70 (1.24–2.31)	0.001		
Sex				
Female	1.00			
Male	1.31 (0.96–1.80)	0.086		
Charlson score				
<2	1.00			
≥2	1.33 (0.99–1.79)	0.058		
T stage				
T1	1.00		1.00	
T2	1.07 (0.79–1.44)	0.633	1.58 (1.24–2.00)	<0.001
T3	1.99 (1.27–3.14)	0.003	2.77 (1.92–4.00)	<0.001
T4	1.44 (0.76–2.70)	0.256	1.95 (1.17–3.27)	<0.001
N-stage				
N0	1.00	<0.001	1.00	
N1	2.86 (2.06–3.96)	<0.001	2.06 (1.57–2.68)	<0.001
N2	3.41 (2.47–4.71)	<0.001	3.10 (2.40–4.00)	<0.001
N3	17.87 (7.69–41.51)	<0.001	8.43 (3.43–20.75)	<0.001
Histology				
Adenocarcinoma	1.00		1.00	
Squamous cell carcinoma	0.77 (0.55–1.07)	0.121	0.75 (0.58–0.97)	0.029
Other	1.77 (1.22–2.56)	0.003	1.66 (1.23–2.24)	0.001
Complications				
No	1.00		1.00	
Non-infectious	1.48 (1.11–1.97)	0.007	1.13 (0.89–1.44)	0.308
Infectious	1.99 (1.24–3.22)	0.004	1.54 (1.00–2.38)	0.048

Values are presented as hazard ratio (95% confidence interval).
CSS, cancer-specific survival; RFS, recurrence-free survival.

Table 5. Univariate analysis of CSS and RFS in N(−) patients

Characteristic	5-year CSS	p-value	5-year RFS	p-value
Age (yr)				
<60	94.4		84.9	
≥60	83.1	<0.001	73.7	0.002
Sex				
Female	90.3		77.9	
Male	84.2	<0.001	76.7	0.203
Histology				
Adenocarcinoma	90.1		80.3	
Squamous cell carcinoma	80.9	<0.001	72.7	0.005
Other	70.7	0.195	58.4	0.026
Charlson score				
<2	88.5		78.8	
≥2	78.4	0.002	70.1	0.032
Video-assisted thoracic surgery				
Yes	92.9		81.9	
No	77.6	<0.001	68.4	<0.001
T stage				
T1	91.8		87.2	
T2	83.8	<0.001	68.8	<0.001
T3	58.8	0.001	42.3	0.002
T4	77.8	0.205	44.9	0.972
Complications				
No	88.0		78.4	
Yes	82.0	0.020	72.8	0.104
Type of complication				
Non-infectious	82.9		74.6	
Infectious	74.2	0.109	59.2	0.101

Values are presented as %.
CSS, cancer-specific survival; RFS, recurrence-free survival.

complications, 160 (15%) died and 284 (27%) experienced recurrence. In contrast, among the 335 patients with postoperative complications, 92 (28%) died and 111 (33%) experienced recurrence. This was a significant difference. Even more strikingly, of the 59 patients with infectious complications, 21 (36%) died and 23 (39%) experienced recurrence.

In the univariate analysis, an age of 60 years old or more, being male, non-adenocarcinoma histology, a Charlson score of 2 or more, undergoing VATS, a higher T stage, a higher N stage, and the presence of complications were negative prognostic factors for 5-year CSS, and non-adenocarcinoma histology, undergoing VATS, a higher T stage, a higher N stage, and the presence of complications were negative prognostic factors for 5-year RFS (Table 3). The 5-year CSS rate was lower to a statistically significant extent in patients with complications than in those without complications (69.6% versus 83.2%, $p<0.001$). The 5-year RFS rate was also lower in patients with complications than in those without complications (61.9% versus 70.3%, p=0.016).

The 5-year CSS rate of patients with infectious complications was statistically significantly lower than the CSS rate of patients without infectious complications (60.1% versus 83.2%, $p<0.001$) and that of patients with non-infectious complications (60.1% versus 71.5%, p=0.022) (Fig. 1A). In contrast, the 5-year RFS rate of patients with infectious complications was significantly lower than that of patients without complications (54.1% versus 70.3%, p=0.004), but a statistically significant difference was not found in comparison to patients with non-infectious complications (54.1% versus 63.5%, p=0.090) (Fig. 1B).

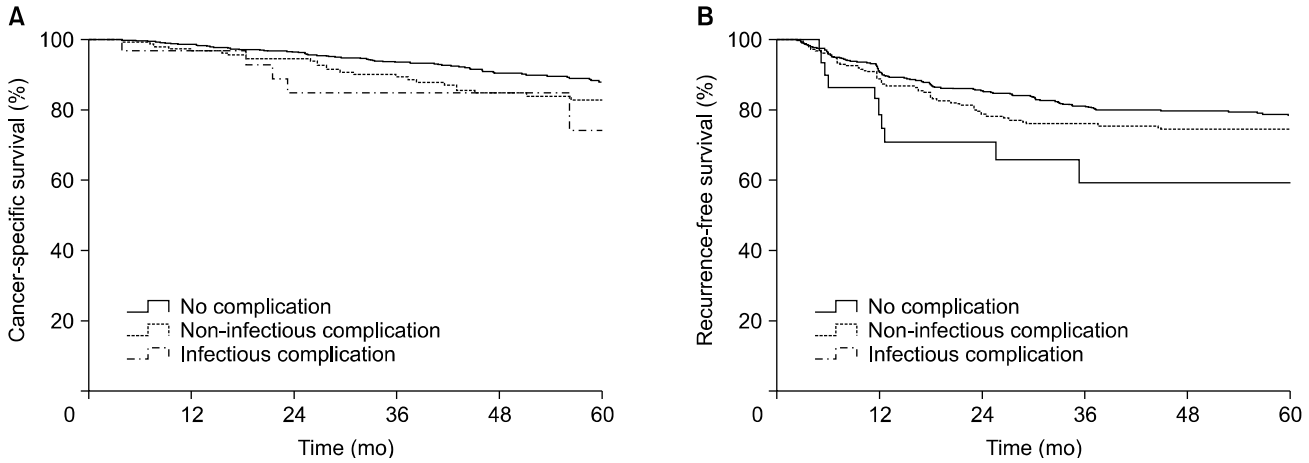

Fig. 2. Kaplan-Meier analysis of cancer-specific survival (A) and recurrence-free survival (B) according to the presence and type of complications in N(−) patients.

Table 6. Multivariate analysis of CSS and RFS in N(−) patients

Characteristic	5-year CSS	p-value	5-year RFS	p-value
Age (yr)				
<60	1.00		1.00	
≥60	2.77 (1.59–4.85)	<0.001	1.53 (1.08–2.17)	0.016
Sex				
Female	1.00			
Male	1.30 (0.81–2.08)	0.265		
Charlson score				
<2	1.00		1.00	
≥2	1.32 (0.87–2.01)	0.189	1.24 (0.89–1.73)	0.192
Histology				
Adenocarcinoma	1.00		1.00	
Squamous cell carcinoma	1.38 (0.86–2.20)	0.171	1.01 (0.71–1.42)	0.940
Other	2.25 (1.29–3.91)	0.004	1.80 (1.18–2.74)	0.006
T-stage				
T1	1.00		1.00	
T2	1.62 (1.05–2.48)	0.26	2.51 (1.82–3.47)	<0.001
T3	3.9 (2.14–7.08)	<0.001	4.84 (2.99–7.84)	<0.001
T4	1.89 (0.44–8.08)	0.387	5.76 (2.58–12.86)	<0.001
Complications				
None	1.00		1.00	
Non-infectious	1.26 (0.82–1.94)	0.289	1.03 (0.73–1.44)	0.867
Infectious	2.23 (1.01–4.92)	0.046	1.92 (1.00–3.67)	0.049

Values are presented as hazard ratio (95% confidence interval).
CSS, cancer-specific survival; RFS, recurrence-free survival.

In the multivariate analysis, an age of 60 years or older, non-adenocarcinoma and non-squamous cell carcinoma histology results, a higher N stage, and the presence of complications were independent negative prognostic factors for CSS (Table 4). Infectious and non-infectious complications were also independent negative prognostic factors for CSS (hazard ratio [HR], 1.48; 95% confidence interval [CI], 1.11–1.97 and HR, 1.99; 95% CI, 1.24–3.22, respectively). Non-adenocarcinoma and non-squamous cell carcinoma

Table 7. Univariate analysis of CSS and RFS in N(+) patients

Characteristic	5-year CSS	p-value	5-year RFS	p-value
Age (yr)				
<60	72.5		41.5	
≥60	59.0	0.150	48.4	0.264
Sex				
Female	64.2		43.6	
Male	63.1	0.712	47.3	0.222
Histology				
Adenocarcinoma	57.8		33.1	
Squamous cell carcinoma	75.0	0.002	65.9	<0.001
Other	45.2	0.002	32.9	<0.001
Charlson score				
<2	65.0		45.8	
≥2	58.3	0.178	47.2	0.878
T-stage				
T1	51.0		36.7	
T2	68.8	0.020	51.3	0.019
T3	69.7	0.789	36.0	0.126
T4	52.5	0.495	41.7	0.469
Complications				
No	70.8		48.4	
Yes	46.6	0.001	39.6	0.343
Type of complication				
Non-infectious	47.3		35.7	
Infectious	44.6	0.466	48.4	0.771

Values are presented as %.
CSS, cancer-specific survival; RFS, recurrence-free survival.

histology results, a higher T stage, a higher N stage, and infectious complications were independent negative prognostic factors for RFS; however, non-infectious complications were not an independent negative prognostic factor for RFS (Table 4).

3) Node-negative patients

In the univariate analysis of node-negative patients (Table 5), the 5-year CSS rate of patients with infectious complications was lower than that of patients without complications (74.2% versus 88.0%, p=0.006); however, no significant difference was observed compared to patients with non-infectious complications (74.2% versus 82.9%, p=0.109) (Fig. 2). The same findings were observed for the 5-year RFS rate, in which a significant difference was found when patients with infectious complications were compared to those without any complications (59.2% versus 78.4%, p=0.012), but no significant difference was found compared to patients with non-infectious complications (59.2% versus 74.6%, p=0.101) (Fig. 2). In the multivariate analysis, infectious complications were found to be an independent negative prognostic factor negatively affecting both CSS and RFS (HR, 2.23; 95% CI, 1.01–4.92; p=0.046 and HR, 1.92, 95% CI, 1.00–3.67; p=0.049, respectively) (Table 6).

4) Node-positive patients

The univariate analysis of prognostic factors in node-positive patients is presented in Table 7. The 5-year CSS rate was lower in patients with infectious complications than in patients without complications (44.6% versus 70.8%, p=0.005), but was not significantly lower in patients with non-infectious complications (44.6% versus 47.6%, p=0.446) (Fig. 3). The 5-year RFS rate was not significantly different among node-positive patients with infectious complications, no complications, and non-infectious complications (48.4% versus 48.4% versus 35.7%, p=0.614) (Fig. 3).

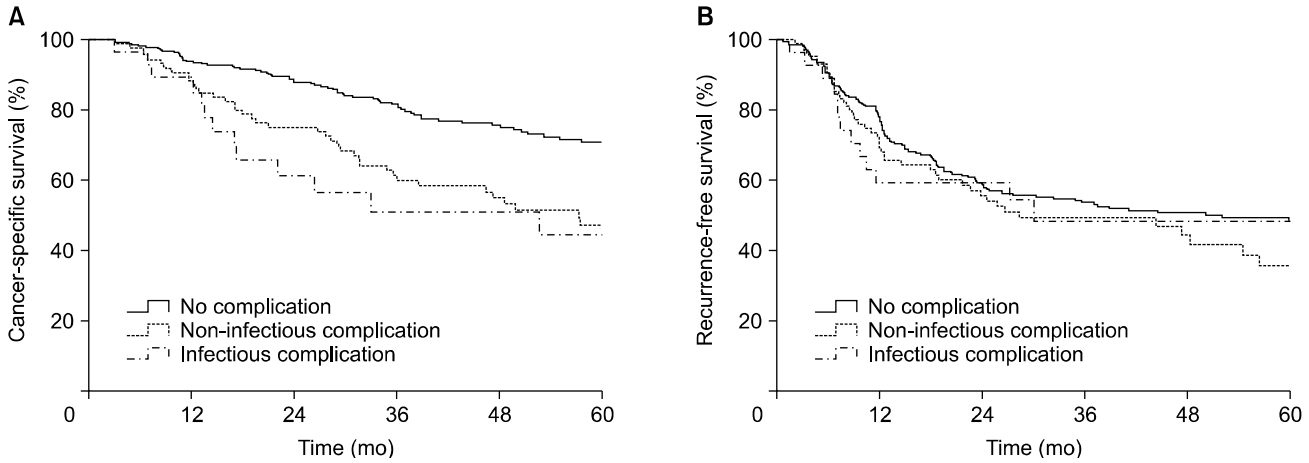

Fig. 3. Kaplan-Meier analysis of cancer-specific survival and recurrence-free survival according to the presence and type of complications in N(+) patients.

Discussion

This study evaluated the relationship between infectious complications and postoperative recurrence and survival in NSCLC patients. In node-negative NSCLC patients, infectious complications were an independent negative prognostic factor for cancer-specific death and recurrence after curative surgery. The influence of infectious complications on tumor recurrence is not well understood. Rueth et al. [14] demonstrated that pulmonary complications were a negative prognostic factor affecting 5-year cancer-specific mortality in stage I NSCLC. Andalib et al. [15] reported that patients with major infectious complications, such as pneumonia, empyema, or mediastinitis, had the lowest overall survival among all patients included in their study. However, some studies have found that postoperative complications were not associated with long-term outcomes in cancer patients [17-19]. Moreover, some studies have even found that infectious complications were a positive prognostic factor for long-term outcomes. Jeys et al. [20] demonstrated that overall survival was higher in osteosarcoma patients with deep wound infection after surgery. Ruckdeschel et al. [21] also found a higher survival rate in lung cancer patients with postoperative empyema.

There are several possible mechanisms explaining how complications after surgical resection are related to the long-term prognosis. First, the immune response to infection may influence whether recurrence occurs. The fact that cell-mediated immunity and humoral immunity are involved in the regression and progression of tumors is well established [22]. McGuirk and Mills [23] demonstrated that regulatory T cells induced by an infection suppress Th1 immunity, thereby preventing the development of infection-induced immunopathology, which enhances the activity of cancer cells [24]. Second, the presence of an increased amount of cytokines derived from the response to infection may induce the proliferation of tumor cells. Salvans et al. [25] found that serum from colorectal cancer patients with anastomotic leaks increased tumor cell proliferation in vitro. Alonso et al. [26] demonstrated that increased serum levels of interleukin-6 and vascular endothelial growth factor resulting from intraperitoneal infection were associated with tumor recurrence after cancer surgery. Third, it is possible that confounding factors are involved, which may be associated not only with infectious complications, but also with postoperative recurrence. In this study, patient characteristics such as age, sex, Charlson score, histology, whether VATS was performed, and the T stage were found to be different between patients with complications and those without complications, even though it is unclear whether these factors actually have an effect on the postoperative prognosis. However, differences were also observed in patient characteristics in other studies that assessed postoperative infectious complications in other cancers [8,9,12]. Since the data were evaluated using multivariate Cox proportional hazard

regression models to overcome the confounding effect, the presence of these differences in the baseline characteristics may not pose a major problem. Finally, adjuvant therapy may be delayed or not be applied in patients with infectious complications. Artinyan et al. [12] found that chemotherapy was performed less frequently in patients with stage III colon cancer who experienced complications, and they could not clearly determine the effect of delayed adjuvant therapy on tumor recurrence. However, although the time sequence of adjuvant therapy was not evaluated in this study, infectious complications showed a significant relationship with recurrence and survival in node-negative patients in whom adjuvant chemotherapy was not scheduled.

In order to control for the effect of nodal status on tumor recurrence, subgroup analysis according to nodal status was performed. In node-negative patients, patients with infectious complications had lower 5-year CSS and RFS rates than those without complications. However, in node-positive patients, the 5-year RFS rate was not significantly different among patients with infectious complications, no complications, and non-infectious complications. Although long-term outcomes according to the presence of pulmonary complications were also analyzed, no statistically significant difference regarding long-term outcomes was found compared to patients with non-pulmonary complications, although the 5-year CSS and RFS rates of both groups were significantly lower than those observed in patients without complications.

The first limitation of this study is that the severity and duration of infections were not investigated. All infectious complications, ranging from simple wound infections to severe chronic empyema, were categorized as a single variable. However, the incidence of infectious complications was low, and in particular, few cases of minor infectious complications were observed. Therefore, the authors could not classify cases of infectious complications based on severity. The second limitation is that no consensus exists regarding the definition of infectious complications. For example, pneumonia, empyema, and ARDS could be categorized as pulmonary complications or as infectious complications. Rueth et al. [14] demonstrated that pulmonary complications, in which pneumonia, empyema, and ARDS were included, were a predictor of 5-year CSS rates. The third limitation is that that the incidence of complications was 24.4%, which is lower than that of 2 previous studies by about 50% [14,15]. Although the previous 2 studies that have directly addressed this question collected data from a local database based on diagnosis codes in the ninth revision of the International Classification of Diseases, the present study collected data from a single center based on voluntary reporting. The incidence of complications is known to be higher in centers without a specialized thoracic surgeon [27]. Reports regarding the incidence of complications in specialized centers have found a complication rate of approximately 32% in thoracotomy and 3%–13.3% in VATS [28]. In this study, the incidence of complications was 34% in thoracotomy and 16.5% in VATS, similar to previously reported results.

In conclusion, infectious complications were a negative prognostic factor for tumor recurrence in NSCLC patients without node involvement. In order to prevent infectious complications, meticulous surgical procedures should be implemented, along with perioperative care that includes antibiotics. After infectious complications occur, follow-up examinations should reflect an elevated level of caution relating to tumor recurrence. Our results may contribute to further studies assessing whether adjuvant therapy is necessary in early-stage NSCLC patients with severe infectious complications.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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