

Risk factors for pulmonary infection after diagnostic bronchoscopy in patients with lung cancer

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ABSTRACT

Pulmonary infection is a relatively rare but serious complication of flexible bronchoscopy. The aim of this study was to identify the risk factors for pulmonary infectious complications after diagnostic bronchoscopy in patients with lung cancer. We retrospectively analyzed the medical records of 636 patients who underwent bronchoscopic biopsy for lung cancer diagnosis between April 2011 and March 2016. We compared patients' characteristics, chest computed tomography and bronchoscopic findings, undertaken procedures, and final diagnoses between patients who developed the complication and those who did not. Pulmonary infection after the diagnostic bronchoscopy occurred in 19 patients (3.0%) and included pneumonia in 16 patients and lung abscess in 3. Patients with larger lesions, presence of endobronchial lesions, histology of small cell lung cancer, and advanced disease stage tended to develop pulmonary infectious complications more often. Our multivariate analysis revealed that a larger lesion size and the presence of endobronchial lesions were independently associated with post-bronchoscopy pulmonary infection. Although we found no mortality associated with the infections, two patients were left with significant performance status deterioration after the pulmonary infection and received no anticancer treatment. In conclusion, endobronchial lesions and a larger lesion size are independent risk factors for the incidence of infections following bronchoscopic biopsy in patients with lung cancer.

Keywords: bronchoscopy, pneumonia, lung abscess, lung cancer

Abbreviations:

FB: Flexible bronchoscopy

PS: performance status

CT: computed tomography

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INTRODUCTION

Flexible bronchoscopy (FB) is an essential procedure employed for diagnosis and staging

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of lung cancer.¹⁻³ Although FB is generally a safe procedure,^{4,5} the development of infectious complications such as pneumonia, lung abscess, and empyema following the procedure have been reported at a rate of 0.2–5.2%.⁶⁻⁹ The development of an infection may delay anticancer treatment due to the prolonged antibiotic course for the infection, or it may result in anticancer treatment change because of a worsening performance status (PS). Thus, in the present study, we sought to identify the risk factors for infectious complications after FB in patients with lung cancer.

MATERIALS AND METHODS

Patients

We retrospectively reviewed the medical and database records of 656 consecutive patients who underwent bronchoscopic forceps biopsy or needle aspiration for the diagnosis or nodal staging of lung cancer at the Nagoya University Hospital between April 2011 and March 2016. We excluded patients who had been treated with antibiotics for infection at the time of the procedure ($n = 12$) and those with missing data on bronchoscopy ($n = 8$) from the study. As a result, we analyzed data from a total of 636 patients for this study. A variety of flexible bronchoscopes (BF-P260, BF-1T260, BF-6C260, BF-Q290, and BF-UC260FW; Olympus; Tokyo, Japan) were used in the study. Although specific informed consents were not required for this retrospective study, informed consents for each bronchoscopy were obtained before the respective procedures. The institutional review board approved the study (approval number: 2017–0438).

Oxygen saturation was continuously monitored by pulse oximetry, and nasal oxygen was administered to maintain the oxygen saturation at a level $>90\%$ during the procedure. Lidocaine (2%) was topically applied to the upper airways before sedation. For sedation during bronchoscopy, the patients received intravenous administration of midazolam. All FB procedures were performed via the transoral approach. Each bronchoscopist decided on which procedures to use from a list including conventional transbronchial biopsy, transbronchial biopsy using endobronchial ultrasonography with a guide sheath, endobronchial biopsy, endobronchial ultrasound-guided transbronchial needle aspiration, bronchial brushing, bronchoalveolar lavage, and conventional transbronchial needle aspiration. Biopsies were repeatedly obtained until an adequate number of specimens had been collected for pathological examination. Prophylactic antibiotics were administered according to the attending physicians' decision. All procedures were performed in an in-patient setting and a chest radiograph was examined the next morning for a decision on discharge.

Data collection

Data about the patients' characteristics, laboratory investigations, chest computed tomography (CT) and pulmonary function test findings within 3 months of the FB, the procedures performed, midazolam doses, procedure duration, bronchoscopic findings, incidence and detail of pulmonary infectious complications, the diagnostic yield, and the initial treatment were collected and compared between the patients with and without infectious complications. The definition of bleeding was use of adrenaline or cold saline to stop bleeding.¹⁰ We defined patients with pulmonary infectious complications as those who developed new or progressive pulmonary infiltrate or cavity formation and ≥ 2 of the following: documented temperature $>37.4^\circ\text{C}$; increased cough; sputum production; pleuritic chest pain; leukocytosis (white blood cell [WBC] count >10000 cells/ μL) at >24 h but <2 weeks after the bronchoscopy.⁷ The patients received chemotherapy, radiation, chemoradiotherapy, surgery, or no treatment, and in some cases, we were not able to find the type of treatment provided to them for anticancer therapy. We defined positive endobronchial

lesions as visible lesions of the bronchial tree from the trachea to the subsegmental bronchi, which presented as an exophytic mass, a submucosal lesion, or an extrinsic compression.^{11,12} The physicians who reviewed the CT scan images and bronchoscopic findings were blinded to the occurrence of complications at the time of review.

Statistical analysis

We used Mann–Whitney *U*-tests (or *t*-tests if the data were normally distributed) and Pearson's chi-square (or Fisher's exact tests if the expected numbers in table were low) for the statistical analyses of continuous and categorical variables, respectively, to compare the data between patients with and without infectious complications. A Receiver Operating Characteristic curve analysis was performed to decide the cutoff value of the lesion size. We examined the risk factors for pulmonary infectious development after FB using multivariate logistic analysis. $P < 0.05$ was considered as statistically significant, and all tests were two sided. We performed all analyses using the SPSS software program (version 24; IBM, Armonk, USA) and JMP Pro (version 14.2; SAS Institute Inc., Cary, NC, USA).

RESULTS

During the study period, 19 patients developed pulmonary infectious complications (pneumonia in 16 patients and lung abscess in 3 patients) for a rate of 3.0% after FB for lung cancer diagnosis. The patients' characteristics are presented in Table 1. We found no significant differences in the age, gender proportion, or body mass index between the individuals in the two groups. Although not statistically significant, the PS was worse in patients who developed complications ($p = 0.086$). The Charlson Comorbidity Index and the results of the pulmonary function tests were similar in both the groups. We found no patients with diabetes mellitus in the complication group. Two patients in the complication group and four in the non-complication group who had rheumatoid arthritis had used immunosuppressive agents at the time of the procedure, but no other patients had used immunosuppressive or anticancer agents. The histology of small cell carcinoma was more common, whereas that of adenocarcinoma was less common in the complication group than in the no-complication group ($p = 0.007$). Patients with infectious complications had a more advanced stage of the malignant disease than those without them.

The characteristics of the lesion specimens and the procedures used to obtain them are shown in Table 2. We found no significant differences between the two groups regarding the location of the biopsied lesions. The mean lesion size was significantly larger in patients who developed infectious complications than in those who did not (58 mm versus 30 mm, respectively; $p < 0.001$). The prevalence of endobronchial lesions was significantly higher in the complication group than in the non-complication group (79% versus 25%, respectively; $p < 0.001$). Endobronchial biopsy was performed more often in the complication group. The rate of patients who required the use of adrenaline or cold saline to stop bleeding was significantly higher in the complication group (42% versus 18%, respectively; $p = 0.016$). The median procedure time (from insertion of bronchoscope to removal) was shorter in the complication group than in the control group (19 min versus 33 min respectively; $p < 0.001$). The number of patients who received antibiotic prophylaxis did not significantly differ between the groups (10% in the complication group versus 4% in the no-complication group; $p = 0.213$). Among patients with endobronchial lesions, there were no significant differences in the number of patients who received antibiotic prophylaxis between the infection and non-infection groups (20% versus 13.8%, respectively; $p = 0.364$). A multivariate analysis revealed that the lesion size [odds ratio, 12.47; 95% confidence interval, 1.55–100.43;

Table 1 Characteristics of patients with or without pulmonary infectious complications

		With complications (n = 19)*	Without complications (n = 617)*	P-value
Age, median (range)		65 (47–82)	71 (40–88)	.071 [†]
Gender, M/F		15/4	423/194	.335 [‡]
Body mass index [§]		21.5 ± 3.5	22.1 ± 3.3	.411 [‡]
Smoking history	Current smoker	10	194	.063
	Ex-smoker	8	267	
	Never used	1	155	
Performance status	0–1	16	584	.086
	≥ 2	3	33	
CCI	0–3	18	555	.422
	≥4	1	62	
Comorbidities, n (%)	COPD	3 (15)	131 (21)	.407
	Interstitial lung disease	2 (10)	56 (9)	.531
Pulmonary function test	%FEV ₁	84.5 ± 22.9 (n = 13)	95.6 ± 24.5 (n = 508)	.107 [¶]
	FEV ₁ /FVC	66.1 ± 10.9 (n = 13)	69.5 ± 11.1 (n = 508)	.277 [¶]
	%VC	96.9 ± 18.2 (n = 13)	102.8 ± 18.9 (n = 508)	.274 [¶]
Histology	Adenocarcinoma	5	360	.007
	Squamous cell carcinoma	7	148	
	SCLC	5	48	
	Others**	2	61	
Stage	I	0	223	<.001
	II	3	79	
	IIIA	1	103	
	IIIB	2	25	
	IV	13	168	
	Unknown	0	19	
Initial Treatment	Surgery	3	305	.001
	Chemoradiotherapy	1	27	
	Radiation alone	1	66	
	Chemotherapy alone	8	141	
	No treatment	6	42	

Abbreviations: n: number, PS: performance status, CCI: Charlson Comorbidity Index, SCLC: small cell lung cancer.

* Expressed as median (range), mean ± SD or n. †From Mann–Whitney *U*-test. ‡From Pearson χ^2 test. §Calculated as weight in kilograms divided by height in meters squared. ||From Fisher's exact test. ¶From *t*-test. **Others = NSCLC (non-small cell lung cancer)-NOS (not otherwise specified), large cell carcinoma, large cell neuroendocrine carcinoma, adenosquamous carcinoma and cartinoid.

Table 2 Characteristics of specimen lesions and results of bronchoscopy

		With complications (n = 19)*	Without complications (n = 617)*	P-value
Sites	Upper lobe	7	229	.925 [†]
	Middle lobe/Lingular segment	1	33	
	Lower lobe	7	174	
	Trachea/Main bronchus	0	7	
	Lymph nodes	1	72	
	Multiple lesions	3	102	
Size, mm, median (range)		58 (35–111)	30 (7–170)	<.001 [‡]
Endobronchial lesion, n (%)		15 (79)	153 (25)	<.001 [§]
Procedures	TBB	6	371	<.001 [†]
	EBB	8	63	
	EBUS-TBNA	1	77	
	EBUS-TBNA+TBB	0	72	
	EBUS-TBNA+EBB	3	22	
	Others	1	12	
Midazolam dose (mg)		4.84 ± 2.07	4.92 ± 1.97	.86 [¶]
Bleeding, ^{**} n (%)		8 (42.1)	114 (18.4)	.0168 [§]
Procedure duration, min, median (range)		19 (16-41)	33 (8-100)	<.001 [‡]
Antibiotic prophylaxis, n (%)		2 (10)	27 (4)	.213 [‡]
Diagnosis	Success	18	496	.093 [†]
	Failure	1	121	

Abbreviations: n: number, TBB: transbronchial biopsy, EBB: endobronchial biopsy, EBUS-TBNA: endobronchial ultrasound-guided transbronchial needle aspiration.

*Expressed as mean ± SD or n. [†]From Fisher's exact test. [‡]From Mann-Whitney U-test. [§]From Pearson χ^2 test. ^{||}Others = Bronchoalveolar lavage (BAL) or conventional TBNA. [¶]From t-test. ^{**}Number of patients who required the use of adrenaline or cold saline to stop bleeding.

p=0.017] and the endobronchial lesion positivity (odds ratio, 3.97; 95% confidence interval, 1.08–14.61; p=0.03) were significantly associated with pulmonary infection after bronchoscopic biopsy (Table 3).

In 168 patients with endobronchial lesions, 15 patients (8.9%) developed pulmonary infection. We found no significant differences in types of endobronchial lesion or the histology between the groups.

There was no statistically significant difference in the rate of patients who underwent endobronchial biopsy. We found no significant differences in the number of patients who required the use of adrenaline or cold saline to stop bleeding (Table 4).

The median durations from bronchoscopy to the onset of pulmonary infection and to the initiation of antibiotic treatment were 8 and 11 days, respectively (ranging from 2 to 14 days and from 4 to 27 days, respectively). We did not identify the pathogenic organisms from the sputa at the time of diagnosis of pulmonary infection. No patients had positive blood cultures. No death occurred as a result of the complications, and all 19 patients recovered with the given treatment.

Table 3 Logistic regression analysis of factors affecting pulmonary infectious complications

Variables		Univariate OR (95%CI)	P-value	Multivariate OR (95%CI)	P-value
Histology	SCLC	4.23 (1.32–11.59)	.001	1.87 (0.59–5.83)	.281
	Others*	1 (ref)		1 (ref)	
Stage	IV	5.79 (2.24–16.7)	<.001	1.69 (0.57–5.00)	.342
	Others†	1 (ref)		1 (ref)	
Size (mm)	> 35	27.33 (5.58–493.04)	.001	12.47 (1.55–100.43)	.017
	≤ 35	1 (ref)		1 (ref)	
Bleeding‡	Positive	3.21 (1.22–8.11)	.001	1.06 (0.38–2.98)	.909
	Negative	1 (ref)		1 (ref)	
Endobronchial lesion	Positive	11.37 (4.05–40.35)	<.001	3.97 (1.08–14.61)	.003
	Negative	1 (ref)		1 (ref)	

Abbreviations: OR: odds ratio, ref: reference, SCLC: small cell lung cancer.

*Others = Adenocarcinoma, Squamous cell carcinoma, NSCLC (non-small cell lung cancer)–NOS (not otherwise specified), large cell carcinoma, large cell neuroendocrine carcinoma, adenosquamous carcinoma, and carcinoid. †Others = stage I, II, IIIA, IIIB, and unknown. ‡Number of patients who required the use of adrenaline or cold saline to stop bleeding.

Table 4 Characteristics of lesions and pulmonary infectious complications in patients with endobronchial lesions

		With complications (<i>n</i> = 15)*	Without complications (<i>n</i> = 153)*	P-value
Type of endobronchial lesion	Exophytic mass	8	72	.781†
	Submucosal lesion	6	62	
	Extrinsic compression	1	19	
Procedures	EBB	11	78	.081‡
	Others	4	75	
Bleeding, <i>n</i> (%)§		8 (53)	71 (42)	.607†
Histology	Adenocarcinoma	3	60	.731‡
	Squamous cell carcinoma	7	48	
	SCLC	4	26	
	Others	1	19	

Abbreviations: *n*: number, EBB: endobronchial biopsy, SCLC: small cell lung cancer.

*Expressed as *n*. †From Pearson χ^2 test. ‡From Fisher's exact test. §Number of patients who required the use of adrenaline or cold saline to stop bleeding. ^{||}TBB and EBUS-TBNA.

Six patients did not receive anticancer treatment after recovery from the infection because of the following reasons: poor PS in five patients and the refusal for anticancer therapy in one patient. Out of five patients with poor PS, two patients manifested significant deterioration in their PS after infectious complications and therefore, did not receive anticancer treatment, whereas the remaining three had showed poor PS already before the FB.

DISCUSSION

In the present retrospective study, we compared the clinical characteristics and the CT and bronchoscopy findings between patient groups with infectious complications and those without them. We identified larger lesion sizes and the presence of endobronchial lesions as risk factors for the occurrence of post-bronchoscopy pulmonary infection.

In this study, the overall rate of infectious complications was 3.0%, with no deaths or disability resulting from them. In a nationwide survey conducted in Japan in 2010, Asano et al reported that the rates of pulmonary infectious complications associated with diagnostic bronchoscopy were 0.2% for forceps biopsy and 0.09% for transbronchial needle aspiration,⁶ respectively. However, other previous reports had described higher frequencies of pulmonary infectious complications after bronchoscopy.^{7,8,13} Fortin et al reported a rate of infectious complications after bronchoscopy by using peripheral endobronchial ultrasound of 4.0%, and that lesion heterogeneity was significantly associated with these complications.⁷ In a retrospective study by Takiguchi et al, the rates of post-bronchoscopy pneumonia in patients suffering from lung cancer were 4.1% and 6.3% in the derivation and validation samples, respectively.⁸ The authors also demonstrated that advanced age (≥ 70 years), current smoking habit, and centralized location of the tumor were independent risk factors associated with the development of pneumonia.⁸ However, advanced age was not associated with increasing pulmonary complications after bronchoscopy in previous studies and in our study.^{9,14,15}

We revealed that the presence of endobronchial lesions was significantly associated with the development of pulmonary infection. Pulmonary infection following bronchoscopy has been hypothesized to be caused by the introduction of organisms from the upper airway into the pulmonary lesion during the procedure.⁷ There might be a possibility that endobronchial biopsy or bleeding are risk factors of infectious complication rather than presence of endobronchial lesion. However, patients with endobronchial lesions significantly developed the complications more often than those without it among patients who underwent transbronchial biopsy (7.4% versus 0.5%, respectively; $p < 0.001$). Moreover, the number of patients who had bleeding was comparable between the complication and no-complication group among the patients with endobronchial lesions. The possible reason for the shorter procedure duration in the complication group was that the higher rate of endobronchial biopsy and lower rate of biopsy for small peripheral lesion. The pathogenic microorganisms of pulmonary infectious complications after FB include *Peptostreptococcus*, *Streptococcus anginosus*, Group A *Streptococcus*, *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, or *Haemophilus influenzae*, although a substantial number of pathogens remain unidentified.^{7,13,16} We found that a larger lesion size acted as an independent predisposing factor for pulmonary infection. We presume that a larger lesion may be associated with tumor necrosis or obstructive atelectasis around the lesion, factors that are associated with the development of local infection, even in patients without any abnormal endoscopic findings. The role of comorbidities in the development of infectious complications seems to be insignificant according to two reports.^{7,8} For instance, Fortin et al compared the prevalences of corticosteroids use, chronic obstructive pulmonary disease, chronic heart failure, diabetes mellitus, and immunosuppression between patients with and without pulmonary infections and found no significant differences.⁷ Similarly, Takiguchi et al showed the occurrence of post-bronchoscopy pneumonia did not significantly differ regardless of whether the patients had pulmonary emphysema or fibrosis.⁸ In the present study, we found no diabetes mellitus patients in the complication group and the rate of patients who received antibiotics was equivalent among the patients with and without diabetes mellitus (3.5% versus 4.8%, respectively; $p = 0.632$).

Clinical studies have failed to identify the significant benefits of prophylactic antibiotics in the prevention of infectious complications in patients after FB.¹⁷⁻²⁰ Although the rate of pulmonary complications did not differ significantly between patients with endobronchial lesions administered prophylactic antibiotics and those not given any in the present study, the number of patients who received prophylaxis was small and it is therefore difficult to assess the efficacy of prophylactic antibiotics. A study conducted by Kanazawa demonstrated that a 3 days course of azithromycin decreased the incidence of respiratory tract infections after bronchoscopic biopsy among patients with abnormal bronchoscopic findings.¹³ Antibiotic treatment was started just after the FB in the present and previous study^{13,19} and there is a possibility that prophylactic administration just before or during the procedure might to be more effective. These finding need to be studied in greater detail in the future.

We are aware of the limitations of our study. First, our results should not be generalized as the study was conducted at a single medical institution. Second, there is a possibility of physician bias in the selection of patients whose comorbidities were less severe to undergo FB, which may have affected the overall results. Third, the use of prophylactic antibiotics after the procedure depended on the decision of each physician and therefore there is a possibility that patients judged to be more infectious risk tended to receive the treatment. Forth, statistical limitation of this study was a low number of patients with infectious complication.

In conclusion, we identified the presence of endobronchial lesions and a larger lesion size as factors independently associated with the development of pulmonary infectious complications after diagnostic bronchoscopy. The occurrence of pulmonary infections may cause a delay or change in the anticancer treatment in patients with lung cancer. Therefore, it is important to realize that these factors increase risk of infectious complication and we need to carefully observe patients with predisposing factors after bronchoscopy.

CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest.

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