

東海大学大学院平成29年度博士論文

Post-bronchoscopy pneumonia in patients  
suffering from lung cancer: Development and  
validation of a risk prediction score  
(肺癌患者における気管支鏡後肺炎予測ス  
コアの検討)

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- This doctoral thesis was written on the basis of the original article published in “Respiratory Investigation”.
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## **Summary**

Flexible fiberoptic bronchoscopy has been accepted and widely used for the diagnosis and treatment of various respiratory diseases. Although it is a relatively safe procedure, diagnostic bronchoscopy may be complicated by a respiratory tract infection. After diagnostic bronchoscopy, fever and pneumonia develop in up to 26% and 5.6% of cases, respectively. Therefore, prevention and early management of post-bronchoscopy pneumonia are especially important in patients with lung cancer, as any delay in the treatment of the malignancy may have detrimental effects on prognosis. However, few studies have focused on the incidence, risk factors, or consequences of post-bronchoscopy pneumonia in these patients. The aim of this study was to elucidate the impact of post-bronchoscopy pneumonia on the subsequent treatment of lung cancer, and to develop and validate a post-bronchoscopy pneumonia risk prediction score for avoidance or prevention of this complication that compromises lung cancer prognosis. We retrospectively analyzed the data from 237 patients with lung cancer who underwent diagnostic bronchoscopy between April 2012 and July 2013 (derivation sample) and 241 patients diagnosed between August 2013 and July 2014 (validation sample) in a tertiary referral hospital in Japan. We defined post-bronchoscopy pneumonia as a respiratory infection that developed during the period between the bronchoscopy and

the first visit to the pulmonary clinic in the presence of 1)  $\geq 37^{\circ}\text{C}$  body temperature persisting for  $\geq 24$  hours, and 2) emergence or exacerbation of respiratory symptoms (cough, sputum, chest pain, or dyspnea) or an infiltrate on chest radiograph. The incident rate of pneumonia and its influence on the subsequent treatment of lung cancer within 30 days after bronchoscopy was evaluated. We also identified predictors of post-bronchoscopy pneumonia in the derivation sample and developed a pneumonia prediction score that was then tested using the validation sample.

Pneumonia developed after bronchoscopy in 6.3% and 4.1% of patients in the derivation and validation samples, respectively. Patients who developed post-bronchoscopy pneumonia changed or canceled their planned cancer therapy more frequently than those without pneumonia (56% vs. 6.3%;  $p < 0.001$ ). According to single-variable analysis in the derivation sample, the factors associated with an increased incidence of post-bronchoscopy pneumonia were current smoking ( $p = 0.028$ ), blood C-reactive protein concentration  $> 0.3$  mg/dL ( $p = 0.049$ ), central tumors on chest CT scan ( $p = 0.048$ ), endobronchial lesions ( $p = 0.041$ ), and histology of small cell lung carcinoma ( $p = 0.012$ ). A diagnosis of adenocarcinoma trended with a decreased incidence of pneumonia ( $p = 0.056$ ). Weaker relationships were observed in patients aged  $\geq 70$  years ( $p = 0.091$ ) with emphysematous change on chest CT scan ( $p = 0.091$ ) and hypoxia requiring supplementary oxygen during bronchoscopic procedure ( $p = 0.067$ ). According to multiple-variable analysis, an age of  $\geq 70$  years, current smoking, and central location of the tumor were independent predictors of pneumonia, which we used to develop our predictive score. In the derivation sample, the incidence of pneumonia associated with scores of 0, 1, and  $\geq 2$  was 0, 3.7, and 13.4%, respectively ( $p = 0.003$ ); the area under the ROC curve was 0.735. In the validation sample, the

incidence was 0, 2.9, and 9.7%, respectively ( $p = 0.016$ ), with an area under the ROC curve of 0.735. Goodness of fit was acceptable based on Hosmer-Lemeshow test results. This is the first study to highlight the incidence and predictors of post-bronchoscopy pneumonia in patients with lung cancer. It results in serious adverse events, including death and cancellation of planned oncologic treatment in > 50% of patients with lung cancer once pneumonia develops. Cigarette smoking causes mucosal inflammation/edema and compromised mucociliary clearance of the airways. Endobronchial mucosal lesions are associated with obstructive atelectasis and also impair airway clearance, predisposing to post-bronchoscopic adverse events. We found that central tumors identified by chest CT scan are equivalent pre-procedural predictors of post-bronchoscopy pneumonia as endobronchial lesions; areas under the ROC curve for prediction scores of central tumors or endobronchial lesions were 0.735 and 0.717 in the derivation sample and 0.713 and 0.763 in the validation sample, respectively. We therefore included central tumors on chest CT scan in the prediction scores because prediction of high-risk patients prior to the bronchoscopic procedure would be more beneficial. The incidence of post-bronchoscopy pneumonia could be lowered by choosing an alternative diagnostic approach other than bronchoscopy in high-risk patients identified by our prediction score  $\geq 2$  and would be beneficial to follow moderate-risk patients (prediction score = 1) closely after bronchoscopy to avoid delays in pneumonia treatment.

In conclusion, the incidence of post-bronchoscopy pneumonia in patients with lung cancer was high, and was associated with adverse effects on the clinical course. A simple 3-point predictive score identified patients with lung cancer at high risk of post-bronchoscopy pneumonia prior to the procedure.

## **Background and Introduction**

Since the introduction of flexible fiberoptic bronchoscopy by Ikeda in 1968, it has been accepted and widely used to diagnose and treat various respiratory diseases, including lung cancer and interstitial diseases and infections. Large surveys on the safety of bronchoscopy reported that the mortality rate and frequency of complication were 0.01-0.04% and 0.08-0.12%, respectively. Therefore, bronchoscopy is believed to be a relatively safe procedure. However, an increasing number of elderly patients who have undergone bronchoscopy in recent years might have experienced increased adverse effects, especially infectious complications with serious outcomes. In fact, there have been some reports of cases complicated with fetal respiratory tract infection after bronchoscopy, which prompt us to explore the factors that place patients at high risk of developing post-bronchoscopy pneumonia.

Respiratory tract infection complicated after diagnostic bronchoscopy is caused by the spread of pathogens from the oral cavity and upper airways to the sterile lower airways. Fever and pneumonia following diagnostic bronchoscopy develop in up to 26% and 5.6% of cases, respectively. Several studies suggest that the primary risk factors of post-bronchoscopic fever and respiratory infection are 1) older age, 2) abnormal findings in the bronchial lumen, 3) culture-positive bronchoalveolar lavage fluid, and 4) major bleeding. Prevention and early management of post-bronchoscopy pneumonia is especially important in patients suffering from lung cancer, as any delay in the treatment of the malignancy may have detrimental effects on prognosis. However, few studies have focused on the incidence, risk factors, or consequences of post-bronchoscopy pneumonia in these patients.

One possible strategy to reduce the risk of post-bronchoscopy pneumonia is the prophylactic administration of antibiotics. According to a nationwide survey of bronchoscopic practice in Japan, in 21% of the facilities accredited by the Japan Society for Respiratory Endoscopy, all patients receive prophylactic antibiotics at bronchoscopy. However, this strategy might be accompanied by increased medical costs, risks of adverse effects related to antibiotic treatment, and possible emergence of drug-resistant microorganisms. Furthermore, antibiotic treatment in the current practice is mostly performed after a bronchoscopic procedure. Clinical efficacy is doubtful, because administration of antibiotics should precede any surgical procedure. Appropriate prediction of high-risk patients and efficient prophylaxis of post-bronchoscopy pneumonia is highly demanded as a safer approach to diagnose lung cancer.

We retrospectively studied two separate groups of patients with lung cancer who underwent diagnostic bronchoscopy, and found that post-bronchoscopy pneumonia was not a rare complication and had a marked impact on the subsequent treatment for lung cancer. We then developed and validated a post-bronchoscopy pneumonia risk prediction score to avoid or prevent this complication that compromises prognosis in lung cancer.

## **Discussion**

In this retrospective analysis, the incidence of pneumonia developing after diagnostic bronchoscopy performed by certified and experienced specialists was consistent between the derivation and validation samples; 6.3% in 237 patients and 4.1% in 241 patients, respectively. This is, to the best of our knowledge, the first study that

demonstrates the incidence of post-bronchoscopy pneumonia in patients with lung cancer, which is compatible with the 1.6 to 5.6% incidence reported in the general population undergoing bronchoscopic examinations. However, once pneumonia had developed, serious adverse events, including death and cancellation of planned oncologic treatment, occurred in >50% of patients with lung cancer. Therefore, for these patients, an accurate prediction and effective prophylaxis of post-bronchoscopy pneumonia prior to bronchoscopy is highly desirable.

Fever developed after bronchoscopy in nearly 50% of our patients with lung cancer, as previously reported, though most of them were transient fever that resolved within 24 hours after the procedure without any antibiotic treatment, suggesting a cytokine-induced acute inflammatory response instead of an infectious manifestation, prompting us to develop and validate this prediction score. Using single variable analysis, current smoking, a central location of the tumor or a visible endobronchial lesion, high serum concentrations of C-reactive protein, histology other than adenocarcinoma, small cell in particular, were tentative predictors of pneumonia. Cigarette smoking, which causes mucosal inflammation/edema and compromised mucociliary clearance of the airways, has been shown to increase the risk of postoperative pulmonary complications. Endobronchial mucosal lesions are associated with obstructive atelectasis and impair the airway clearance, predisposing to post-bronchoscopic adverse events. We found that central tumors identified by chest CT scan are equivalent pre-procedural predictors of post-bronchoscopy pneumonia as endobronchial lesions; areas under ROC curve for prediction scores using central tumors or endobronchial lesions were 0.735 and 0.717 in derivation sample and 0.713 and 0.763 in validation sample, respectively. We, therefore, included central tumors on

chest CT scan, but not endobronchial lesions at bronchoscopy in the prediction scores because prediction of high-risk patients prior to bronchoscopic procedure would be more beneficial. It is noteworthy that only 2.0% of patients presenting with adenocarcinomas developed pneumonia, perhaps because of a lower prevalence of smokers and endobronchial lesions and the peripheral location of most primary tumors.

The incidence of post-bronchoscopy pneumonia could be lowered by choosing an alternative diagnostic approach to bronchoscopy in high-risk patients identified by our prediction score  $\geq 2$ . It would also be beneficial to follow up the moderate-risk patients (prediction score = 1) closely after bronchoscopy to avoid delays in the treatment of pneumonia. In contrast, there is little evidence on the efficacy of prophylactic antibiotics to prevent post-bronchoscopy pneumonia, and the results are mixed; one randomized controlled study reported that prophylactic antibiotics did not reduce the incidence of post-bronchoscopic fever and pneumonia, while Kanawaza et al. showed that the administration of azithromycin was effective for prevention of post-bronchoscopy pneumonia in patients with abnormal bronchoscopic findings. Although administration of antibiotics prior to the procedure is preferable, 90% of cases in a nationwide survey of bronchoscopic practice in Japan and in our study received antibiotics just after bronchoscopy. Our prediction score will be useful for identification of high-risk patients to enroll in upcoming studies of prophylactic antimicrobial therapy before bronchoscopy.

There are several limitations in our study. First, this study was conducted in a single medical institution. However, the bronchoscopic procedures were standardized and performed under the supervision by certified specialists. Second, since post-bronchoscopy pneumonia was retrospectively identified, it might have been

underestimated given its strict diagnostic criteria. We might have missed clinically mild cases of pneumonia, although they would be unlikely to have influenced the subsequent treatment for lung cancer. Third, this retrospective study included substantial number of patients who were pre-treated with antibiotics, and therefore, we may have underestimated the risk for pneumonia in these patients. However, the incidence of pneumonia was actually higher in the pre-treated patients (8.1% vs. 4.5%). It is because high-risk subjects for pneumonia had received prophylactic antibiotic treatment as presented in Table 2.

## **Conclusions**

Post-bronchoscopy pneumonia occurs in a sizable proportion of patients with lung cancer and influences their clinical outcomes. The risk of pneumonia can be predicted using a simple 3-point score comprised of the patient's age, smoking status, and the observations made on the pre-procedural chest CT scan. The prediction score will be useful in the future studies to test the effects of smoking cessation, close follow-up, and maximum antimicrobial prophylaxis to lower the incidence of post-bronchoscopy pneumonia.