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Analysis of Risk Factors for Postpneumonectomy Bronchopleural Fistulas in Patients with Lung Cancer

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Abstract

Background: Bronchopleural fistula is a poentioally fatal complication of pulmonary resections, especially pneumonectomy.

Methods: Univariate and multivariate analyses of the development of bronchopleural fistula were performed in 12 patients with bronchopleural fistula and 102 patients without bronchopleural fistula who had undergone pneumonectomy from January 1983 through December 2005.

Results: Bronchopleural fistula developed after pneumonecotomy in 12 patients (8.5%). Seven (58.7%) of the 12 patients died of bronchopleural fistula. Univariate analysis showed that preoperative infection, right pneumonectomy, and pathological N2, 3 disease significantly contributed to the development of postpneumonectomy bronchopleural fistula (p=0.0002, p=0.0043, and p=0.0387, respectively). Multivariate analysis also showed that preoperative infection, right pneumonectomy, and pathological N2, 3 disease were significant risk factors for postpneumonectomy bronchopleural fistula.

Conclusions: Bronchopleural fistula is strongly associated with preoperative infection, right pneumonectomy, and pathological N2, 3 disease. Bronchial stump coverage with pedicled tissue flaps and preservation of the bronchial arteries during mediastinal lymphnode dissection are recommended to maintain the blood supply to the bronchial stump in patients at risk.
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Key words: lung cancer, bronchopleural fistula, pneumonecotmy

Introduction

Postpneumonectomy bronchopleural fistula (BPF) is a potentially fatal complication of respiratory surgery [1–9]. Analysis of risk factors for postpneumonectomy BPF is important to properly manage patients at risk and to prevent development of postpneumonectomy BPF. In 1996, we analyzed 76 patients with lung cancer and found that right pneumonectomy, preoperative infection, and metastasis to a subcarinal lymph node were risk

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Table 1 Clinical characteristics of the 12 patients with bronchopleural fistulas

Patient No.	Age/ Sex	Side of the thorax	PpoFEV1.0 (L)	Pack-years	Pathology	Pathological TN	Stage	Infection	Onset	Treatment (day)	Survival (day)
1.	69M	Right	0.66	70	Sq	pT3N2	Ⅲ	—	9	BSC (ICMF) +TP	87D
2.	74N	Left	1.39	100	Sq	pT4N2	Ⅲ	—	7	CTD	10D
3.	52M	Right	1.33	45	Sq	pT2N2	Ⅲ	—	16	BSC (OMF) after F	75D
4.	62M	Left	0.94	141	Sq	pT2N2	Ⅲ	AP	12	BSC (OMF) after F	582D
5.	47M	Right	1.46	40	Sq	pT3N2	Ⅲ	POP	10	BSC (LDF) after F	305D
6.	57M	Right	1.10	38	Sq	pT4N2	Ⅲ	Pyothorax	18	BSC (PMF) after F	37D
7.	59M	Right	1.16	34	Sq	pT2N2	Ⅲ	—	10	BSC (PMF) after F	96D
8.	56M	Right	1.13	50	Sq	pT2N2	Ⅲ	—	45	CTD	334D
9.	59M	Right	1.37	63	Ad	pN2N0	Ⅰ	—	17	CTD	378A
10.	72M	Left	1.34	105	Sq	pT4N2	Ⅲ	—	14	F	24D
11.	53F	Left	0.95	0	Ad	pT4N1	Ⅳ	Abscess	20	CTD	122D
12.	34M	Right	1.05	80	Other	pT4N2	Ⅳ	Abscess	10	F	10D

PpoFEV1.0=predicted postoperative forced expiratory volume in 1 second, Sq=squamous cell carcinoma, Ad=Adenocarcinoma, AP=aspiration pneumonia, POP=postobstructive pneumonia, CTD=chest tube drainage, F=fenestration, ICMF=intercostal muscle flap, TP=thoracoplasty, OMF=omental flap, LDF= latissimus dorsi flap, PMF=pectoralis muscle flap, D=dead, A=alive.

factors for postpneumonectomy BPF[3]. Since then, additional risk factors have been identified: previous ipsilateral thoracotomy[4], preoperative chemotherapy or radiotherapy or both[4], right pneumonectomy[5-7], mechanical ventilation[5,7], benign disease[6], lower preoperative forced expiratory volume in 1 second (FEV1.0)[6], diffusion capacity of lung to carbon monoxide[6], lower preoperative serum hemoglobin[6], bronchial stump coverage [6,7], completion pneumonectomy[6], timing of chest tube removal[6], increased intravenous fluid in the first 12 hours[6], blood transfusions[6], predicted postpneumonectomy FEV1.0[7], chronic obstructive pulmonary disease[7], and length of the resection margin[8]. Therefore, we reanalyzed risk factors for postpneumonectomy BPF in a larger series, adding some risk factors reported recently.

Materials and Methods

From January 1983 through December 2005, 142 patients underwent pneumonectomy for lung cancer at the Division of Respiratory Surgery, Department of Surgery, Nippon Medical School and the Department of Surgery, Nippon Medical School Musashi Kosugi Hospital. Twenty-eight patients without BPF were excluded due to the lack of detailed data. Therefore, 114 patients including 12 patients with BPF and 102 patients without BPF were subjected to univariate and multivariate analyses.

The postoperative pulmonary functions were predicted according to a simplified system, which we developed using plain chest roentgenograms of patients with primary lung cancer[9]. The predicted postoperative FEV1.0 (ppoFEV1.0) is (42-R)/(42-T) × preoperative FEV1.0, where R is the number of subsegments scheduled for lung resection and T is the number of tumor-related subsegments. T is determined as follows: a) if a tumor is located in the periphery of the lung, the T factor is equal to 1 in the case of a tumor 3 cm or less in its largest dimension and equal to 2 in the case of a tumor more than 3 cm in its largest dimension; and b) if a tumor obstructs large airways, the T factor is equal to the number of subsegments showing atelectasis or postobstructive pneumonia[9].

The lung cancers of all patients were staged

Table 2 Characteristics of patients with bronchopleural fistula (BPF) and non-BPF

	BPF	non-BPF	P value
Number of patients	12	102	
Age	58 ± 11	60 ± 11	0.5883
Sex Male	11 (92)	81 (79)	
Female	1 (8)	21 (21)	0.3089
Smoker and Ex-smoker	10 (83)	81 (79)	
Non-smoker	2 (17)	21 (21)	0.7488
Number of cigarette packyears	64 ± 38	45 ± 34	0.0717
Albumin	3.6 ± 0.6	3.8 ± 0.5	0.1105
Hemoglobin	12.6 ± 2.0	12.5 ± 1.8	0.8585
Diabetes mellitus	1 (8)	10 (10)	0.8704
PpoFEV1.0	1.2 ± 0.2	1.3 ± 0.4	0.2977
Preoperative treatment	0 (0)	12 (12)	0.1889
Preoperative infection	5 (42)	7 (7)	0.0002 *
Affected side of the thorax			
Right	8 (67)	27 (26)	
Left	4 (33)	75 (74)	0.0043 *
Operative time	325 ± 76	346 ± 124	0.5718
Volume of blood loss	1,104 ± 967	1,005 ± 992	0.7452
Method of bronchial closure			
Hans suture	8 (67)	64 (63)	
Mechanical	4 (33)	38 (37)	0.7899
Combined resection	5 (42)	41 (40)	0.9218
Pathological stage of lung cancer excluding MPLC			
I, II	1 (8)	28 (27)	
III, IV	11 (92)	74 (75)	0.1503
Pathological T factor			
T1, 2	5 (42)	46 (45)	
T3, 4	7 (58)	56 (55)	0.8211
Pathological N factor			
N0, 1	2 (17)	49 (48)	
N2, 3	10 (83)	53 (52)	0.0387 *
Histological type of lung cancer excluding MPLC			
Squamous cell carcinoma	9 (75)	58 (57)	
Adenocarcinoma	2 (17)	30 (29)	
Others	1 (8)	14 (14)	0.4820
Residual tumor at stump	1 (8)	4 (4)	0.4802

PpoFEV1.0=predicted postoperative forced expiratory volume in 1 second, [a]Data are shown as mean ± standard deviation; percentage given in parentheses, *Statistical significance

pathologically according to the International Union Against Cancer system[10]. Stapling devices we used were the Proximate Linear Stapler TLH30 (Ethicon, Cincinnati, OH, USA) and the Roticulator (U.S. Surgical Corp, Norwalk, CT, USA). Twenty-nine patients underwent bronchial stump coverage with an intercostal muscle flap (18 patients), pericardial flap (7 patients), or a thymus flap (3 patients). Usage and choice of pedicled tissue flaps were left to the surgeon's discretion in some cases even after 1996. Therefore, bronchial stump coverage was not included in the statistical analyses. Preoperative infection included aspiration pneumonia, pyothorax, postobstructive pneumonia, and lung abscess.

Statistical analyses were performed using the StatView 5.0J software package (SAS Institute, Inc, Cary, NC, USA). Univariate analyses between the groups were performed by means of an unpaired two-tailed t-tests or the chi-square test using age, sex, serum albumin concentration and serum hemoglobin concentration before operation, ppo%FEV1.0, smoking history (smoker and ex-

Table 3 Results of multivariate analysis related to development of bronchopleural fistula

	Odds ratio	95% confidence interval	P value
Preoperative infection	22.839	3.354 ～ 155.495	0.0014
Right pneumonectomy	0.168	0.037 ～ 0.751	0.0195
Pathological N2, 3	7.342	1.074 ～ 50.176	0.0420

smoker versus non-smoker), the number of cigarette pack-years, preoperative infection of the lung, diabetes mellitus, preoperative adjuvant treatment, affected side of the thorax, duration of surgery, volume of blood loss, bronchial closure technique (hand suturing, mechanical stapling), combined resection, residual carcinoma at bronchial stump, pathological stage (stage I or II versus stage III or IV), pathological t factor (T1, 2 versus T3, 4), pathological n factor (N0, 1 versus N2, 3), and histological type of lung cancer (squamous cell carcinoma, adenocarcinoma, and others). Multivariate logistic regression tests were performed with significant risk factors identified with univariate analyses. A $P<0.05$ was considered significant.

Results

Postpneumonectomy BPF developed in 12 (8.5%) of 142 patients who underwent a pneumonectomy for treatment of lung cancer (**Table 1**). The BPF developed in 8 (22.9%) of 35 patients after right pneumonectomy and in 4 (5.1%) of 79 patients after left pneumonectomy. The patients with BPF were 11 men and 1 woman. Nine patients had squamous cell carcinoma, 2 had adenocarcinoma, and 1 had large cell carcinoma. The BPF developed from 7 to 45 days (mean, 15.5 days) after pneumonectomy. The patient's average age was 57.8 years (range, 34～74 years). Five patients with postpneumonectomy BPF had preoperative infection. A 62-year-old man who underwent total resection of the tongue and reconstruction of the oral bed by right pedicled major pectoralis muscle flap had repeated aspiration pneumonia (Patient 4). A 47-year-old man with squamous cell carcinoma in right intermediate bronchus had postobstructive pneumonia (Patient 5). A 57-year-old man with squamous cell carcnoma in the right basilar bronchus had pleuritis carcinomatosa and pyothorax (Patient 6). A 53-year-old woman with adenocarcinoma in the left upper lobe had a lung abscess preoperatively (Patient 11), and a 34-year-old man with large cell carcinoma in the right upper lobe had lung abscess preoperatively (Patient 12).

Characteristics of patients with and without BPF who underwent pneumonectomy are shown in **Table 2**. Univariate analyses showed that preoperative infection, right pneumonectomy, and pathological N2, 3 disease significantly contributed to the development of postpneumonectomy BPF ($p=0.0002$, $p=0.0043$, and $p=0.0387$, respectively). Multivariate analysis also showed that preoperative infection, right pneumonectomy, and pathological N2, 3 disease were significant risk factors for postpneumonectomy BPF (**Table 3**).

Seven (58.7%) of 12 patients died of BPF. Treatment for BPF included bronchial stump coverage with pedicled tissue flaps after fenestration in 5 patients, chest tube drainage alone in 4 patients, fenestration alone in 2 patients, and bronchial stump coverage with pedicled tissue flap plus thoracoplasty in 1 patient. Three patients treated with bronchial stump coverage with pedicled tissue flap after fenestration died of BPF in the hospital (Patients 3, 6, and 7). Two patients treated with bronchial stump coverage with pedicled tissue flaps after fenestration died of lung cancer at home (Patients 4 and 5). Two patients treated with fenestration alone and one patient treated with chest tube drainage alone died of BPF within 30 days after pneumonectomy (Patients 2, 10, and 12). One patient treated with chest tube drainage alone died of lung cancer (Patient 8) and one patient treated with chest tube drainage alone survived (Patient 9). One patient treated with bronchial stump coverage with pedicled

tissue flap plus thoracoplasty died of BPF in the hospital (Patient 1).

Discussion

The incidence of postpneumonectomy BPF in the present study was 8.5%, which was comparable to the results of other recent series, in which the incidence ranged from 4.5% to 12.5%[1–8].

Multivariate analysis in the present study showed that preoperative infection was the most significant risk factor for postpneumonectomy BPF. Lung carcinoma causes BPF less frequently than do benign diseases[6]. However, lung carcinoma occasionally produces airway infection[3,11], postobstructive pneumonia[12], pyothorax[1], and abscess formation[11] before pneumonectomy. In addition, recurrent nerve paralysis due to tumor invasion and operative technique could cause aspiration pneumonia. In the present study 12 patients (10.5%) had preoperative infection, of whom 7 had postobstructive pneumonia, 2 had lung abscess and pyothorax, and 1 had aspiration pneumonia. Postpneumonectomy BPF developed in 6 (50%) of 12 patients. Postpneumonectomy BPF developed in all patients with aspiration pneumonia or lung abscess.

Multivariate analysis in the present study also showed that right pneumonectomy and pathological N2, 3 disease were significant risk factors for postpneumonectomy BPF. Right pneumonectomy has been the most common risk factor for BPF[1–9]. We suggested in 1996 that the bronchial stump protrudes into the pleural cavity and is not covered by tissue after right pneumonectomy, and that additional ligation of the bronchial arteries during mediastinal lymphnode dissection reduces the blood supply to the bronchial stump to a very low level and causes BPF[3]. Hollaus et al. have demonstrated that the diameter of the bronchial stump is a major risk factor for postpneumonectomy BPF, a finding that explains the predominance of the male sex, involvement of right side, and pneumonectomy[8]. Bronchial stump coverage with pedicled thymus and pericardial flaps prevents postpneumonectomy BPF[12,13]. Sarsam et al. devised a new technique for bronchial stump closure which minimizes protrusion into the pleural cavity and covers the stump with surrounding tissues, and effectively prevents postpneumonectomy BPF[14]. Sonobe et al. performed bronchial stump coverage in patients with concurrent pulmonary infection, preoperative adjuvant therapy, and impaired renal function, and was able to prevent postpneumonectomy BPF in these patients[4]. Therefore, we recommend bronchial stump coverage with pedicled tissue flaps and preservation of the bronchial arteries during mediastinal lymphnode dissection to maintain the blood supply to the bronchial stump in patients at risk.

Sirbu et al.[5] and Algar et al.[7] have identified artificial ventilation as a risk factor for BPF and recommended early extubation, but did not show how to reduce barotrauma to the bronchial stump. We saved one patient with postpneumonectomy BPF (Patient 5) by mechanical ventilation using a spiral tube. The tip of a spiral tube was located in the main bronchus of the unaffected lung to prevent barotrauma to the bronchial stump. The bronchial stump was covered with a pedicled latissimus dorsi flap. Therefore, future studies are expected to clarify the effectiveness of mechanical ventilation using a spiral tube for preventing postpneumonectomy BPF in patients at risk and for healing postpneumonectomy BPF.

In conclusion, BPF is strongly associated with preoperative infection, right pneumonectomy, and pathological N2, 3 disease. Bronchial stump coverage with pedicled tissue flaps and preservation of the bronchial arteries during mediastinal lymphnode dissection to maintain the blood supply to the bronchial stump are recommended in patients at risk.

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