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Original Article

Therapeutic Outcomes of 15 Postoperative Bronchopleural Fistulas Including Seven Endoscopic Interventions

Tsuyoshi Ueno[a]*, Yuho Maki[a], Ryujiro Sugimoto[a], Hiroshi Suehisa[a], Motohiro Yamashita[a], Daijiro Harada[b], Toshiyuki Kozuki[b], and Naoyuki Nogami[b]

Departments of [a]Thoracic Surgery and [b]Thoracic Oncology, National Hospital Organization, Shikoku Cancer Center, Matsuyama 791-0280, Japan

Therapeutic approaches to bronchopleural fistula (BPF) closure after lung resection are surgical or endoscopic interventions. We evaluated therapeutic outcomes to determine the optimal approach. We reviewed 15 patients who had developed BPF after lung resection for thoracic malignant diseases at our institution in the 10 years since 2008. The patients were 11 men and 4 women (mean age 68 years). We performed one pneumonectomy, 6 lobectomies, 7 segmentectomies, and one partial resection for malignant diseases. The median interval from lung resection to the BPF diagnosis was 46 days. The BPF-associated mortality rate was 26.7% (4/15). The rate of successful BPF closure was 66.6% (10/15). The endoscopic and surgical intervention success rates were 14.2% (1/7) and 69.2% (9/13), respectively ($p < 0.01$). Of 5 patients who had failed BPF treatments, 4 died, and one transferred out without BPF closure. The therapeutic outcomes were related to preoperative comorbidities, performance status at the BPF diagnosis, time intervals from lung resection to BPF diagnosis, and presence of active pneumonia. The difference between endoscopic and surgical outcomes was nonsignificant, although the surgical intervention success rate was somewhat higher. The selection of endoscopic or surgical intervention for BPF does not significantly affect therapeutic outcomes.

Key words: bronchopleural fistula, endoscopic intervention, surgical intervention

Bronchopleural fistula (BPF) is one of the serious potential complications following lung resection. Its incidence is reported to be 4.5-14.3% after pneumonectomy and 0.6-1.4% after lobectomy [1-4]. The reported mortality rate for BPF ranges from 11.1% to 71.2%, and BPF still represents a therapeutic challenge for thoracic surgeons [1, 2]. The most common cause of death among patients with a BPF is aspiration pneumonia with subsequent adult respiratory distress syndrome (ARDS). The risk factors for BPF are known; they include pneumonectomy, right-sided procedures, residual tumor on the bronchial stump, advanced age, male sex, diabetes, steroid therapy, preoperative radiotherapy, and perioperative infections [1, 5, 6].

The incidence of BPF peaks in the second or third postoperative week. The mortality rate of early BPF (*i.e.*, BPF that occurs within 30 days after lung resection) was found to be higher than that of late BPF [7]. Surgical intervention has been an established therapy for BPF, but an endoscopic procedure is the alternative for the closure of the fistula to avoid major surgery [8]. We analyzed the therapeutic outcomes of BPF at our institution to determine the optimal approach.

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*Corresponding author. Phone: +81-89-999-1111; Fax: +81-89-999-1100
E-mail: ueno.tsuyoshi.qz@mail.hosp.go.jp (T. Ueno)

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Patients and Methods

Fifteen patients underwent an endoscopic or surgical intervention for a postoperative BPF at the Shikoku Cancer Center between January 2008 and December 2017. The clinicopathologic data of these patients including their sex, age, performance status (PS) at the time of lung resection, primary disease, pathological stage, smoking history, comorbidities, preoperative treatment, extent and site of operation, technique of bronchial stump closure, use of reinforcement, and postoperative complications were collected. The TNM stage of lung cancer was estimated based on the eighth edition of the Lung Cancer Stage Classification. The information about BPF including the PS at the time of diagnosis, the time intervals from the lung resection to the diagnosis of BPF, the sizes of the fistulas, the presence of active pneumonia, infection of pleural effusion, therapeutic approaches, and outcomes were collected. In all patients, the diagnosis of BPF was confirmed by using bronchoscopy. We measured the size of each BPF in comparison to the diameter of the bronchoscope.

Endoscopic intervention was performed using a flexible bronchoscope. We used fibrin or cyanoacrylate glue, polyglycolic acid (PGA) sheet, an endobronchial Watanabe spigot (EWS), or silver nitrate to close the fistula. In the surgical intervention, the pedicled omentum or muscle flap was sutured to or eased into the edges of the BPF. Success was defined as the visual closure of the BPF without any air leak and the discharge of the patient without an *in situ* drain.

We used the JMP software program (SAS, Cary, NC, USA) for calculations, and the analysis was performed with log-rank statistics. The study was approved by the Institutional Review Board at the Shikoku Cancer Center, Matsuyama. Informed consent was not required for this retrospective study.

Results

Patient characteristics. The patient characteristics are summarized in Table 1. The patients were 11

Table 1 Patient characteristics

Characteristics	n=15		
Gender		Surgical approach	
Male/female	11/4	Thoracotomy	7
Age		Videothorcoscopy	8
Mean (SD), years	68 (6.7)	Operative procedure and location	
PS*		Pneumonectomy**	1
0/1	14/1	Right	1
Primary disease		Lobectomy	6
NSCLC	12	RU/RL	2/4
Metastic LC	2	Segmentectomy	7
MPM	1	RU/RL/LU/LL	1/1/3/2
NSCLC		Sublobar resection	1
pStage I/II/III	7/3/2	RU	1
Pathology Ad/Sq	11/1	Reinforcement	1
Smoking history	13	Postoperative complication***	
Past history of lung resection	6	Prolonged air leakage	5
Comorbidity		Pneumonia	5
Emphysema	4	Empyema	2
Tuberculosis	1	Atelectasis	1
Rheumatism	1	Pulmonary torsion	1
Preoperative therapy		AMI	1
Chemotherapy	1	Interval to the diagnosis of BPF****	
		Median (range), days	46 (12–1,123)

BPFs were more frequently observed in the right lower lobes (33.3%, 5/15). Ad, adenocarcinoma; AMI, acute myocardial infarction; BPF, bronchopleural fistula; LL, left lower; LU, left upper; NSCLC, non-small cell lung cancer; PS, performance status; RL, right lower; RU, right upper; SD, standard deviation; Sq, squamous cell carcinoma; PS*, PS at the time of lung resection; Pneumonectomy**, Extra-pleural pneumonectomy; Postoperative complication***, Postoperative complications at the first surgery; Interval to the diagnosis of BPF****, The time interval from the lung resection to the diagnosis of BPF.

men and four women with the mean age of 68±6.7 years. The primary disease at the initial operation was primary lung cancer in 12 patients, metastatic lung cancer in 2 (derived from primary colon cancer or submandibular gland cancer), and malignant pleural mesothelioma (MPM) in one. Six patients had previously undergone a pulmonary resection, because of metachronous primary lung cancers in 5 patients and lung metastases of submandibular gland cancer in the remaining patient. The patient with MPM had received preoperative chemotherapy with cisplatin and pemetrexed.

The therapeutic approaches in these cases were one pneumonectomy (extra-pleural pneumonectomy), 6 lobectomies, 7 segmentectomies, and one large sublobar resection. Right-sided resection was more frequent than left-sided (10 vs. 5). BPFs were more frequently observed in the right lower lobes (33.3%, 5/15). We used staples for bronchial closure in 14 patients; the other was the patient who underwent sublobar resection. In the single patient who underwent a pneumonectomy, the bronchial stump was covered with pericardial fat. One patient developed pulmonary torsion of the residual left upper division segment after a lingual segmentectomy, and he underwent a completion lobectomy. The median interval to the diagnosis of BPF after lung resection was 46 days (12-1,123 days).

Endoscopic and surgical interventions. The success rate of BPF closure was 66.6% (10/15). The mortality rate associated with BPF was 26.7% (4/15). Table 2 lists the therapeutic treatments and outcomes of BPF. We administered antibiotics and inserted the chest tube for all patients before treating their BPFs. We performed endoscopic interventions in 7 patients and surgical interventions in 13 patients. The success rates of the endoscopic and surgical interventions were 14.2% (1/7) and 69.2% (9/13), respectively ($p<0.01$). Endoscopic intervention was successful in only one patient, which was performed with cyanoacrylate glue. We often used fibrin glue (5/7) and PGA sheet (3/7).

Of the 13 patients who underwent surgical intervention, 9 underwent BPF closure with a pedicled omentum or muscle flap. One patient underwent only wound closure after an open-window thoracostomy because the BPF closed spontaneously. Another patient with BPF after a right lower lobectomy successfully underwent a completion middle and lower lobectomy. Two patients were unable to undergo BPF closure because of a poor nutritional status and physical condition after an open-window thoracostomy. Of the 5 patients who failed BPF treatments, 2 died of aspiration pneumonia with ARDS, one died of respiratory failure with narcosis 31 days after surgical intervention. One patient for whom we were unable to perform any intervention died of an acute myocardial infarction. One patient transferred to another hospital for rehabilitation without BPF closure because of the development of a cerebral infarction with subsequent hemiplegia. After a few years, 3 patients died of primary or other cancers, although they overcame their BPFs.

Table 2 Therapeutic approaches and outcomes of bronchopleural fistulas (BPFs)

	n=15
Endoscopic intervention	7
Success rate (%)	1 (14.2%)
Material	
Fibrin glue	5
PGA sheet	3
EWS	2
Cyanoacrylate glue	1
Others	2
Frequency	
Median (range)	2 (1–4)
Surgical intervention	13
Success rate (%)	9 (69.2%)
Operative procedure	
Pedicled omentopexy	7
Pedicled muscle flap	2
Others	2
Only OWT	2
Death (%)	4 (26.7%)
Aspiration pneumonia	2
Respiratory failure	1
AMI	1

The success rates of the endoscopic and surgical interventions were 14.2% (1/7) and 69.2% (9/13), respectively ($p<0.01$). The mortality rate was 26.7% (4/15). AMI, acute myocardial infarction; EWS, endobronchial Watanabe spigot; OWT, open-window thoracostomy; PGA, polyglycolic acid.

Important factors of the successful therapeutic outcome of BPF. Table 3 compares the patient characteristics and therapeutic outcomes between the patients who were successfully treated and those who failed. Preoperative comorbidities, poor PS at the time of the diagnosis of BPF, a short interval from the resection to the diagnosis of BPF, and the presence of active pneumonia each had a negative impact on therapeutic outcomes. No significant difference in outcomes was

Table 3 Comparison of the patients who were successfully treated and those who failed

	Success n=10	Failure n=5	*p*
Gender			
Male/female	6/4	5/0	0.10
Age			
Mean (SD), years	66 (5.5)	72 (6.7)	0.07
PS*			
0–2/3, 4	8/2	1/4	0.03
Smoking history	8	5	0.28
Past history of lung resection	4	2	1.00
Comorbidity			
Emphysema	1	3	0.03
Tuberculosis		1	
Rheumatism	1		
Primary operation			
Pneumonectomy and Lobectomy	5	2	0.71
Segmentectomy and Sublobar resection	5	3	
Operative side			
Right/left	7/3	4/1	0.70
Interval to the diagnosis of BPF**			
Median (range), days	144 (23–1,123)	16 (12–75)	0.02
Size of BPF			
Small (≤3 mm)	4	1	0.71
Intermediate (>3 and ≤6 mm)	4	3	
Large (>6 mm)	2	1	
Active pneumonia (%)	2 (20%)	5 (100%)	0.003
Positive infection of pleural effusion (%)	3 (30%)	1 (20%)	0.68
BPF treatment			
Endoscopic intervention	5	2	0.59
Surgical intervention	9	4	0.71
Death	0	4	0.001

The therapeutic outcome was related to preoperative comorbidities, the PS at the time of the diagnosis of BPF, the time interval from the lung resection to the diagnosis of BPF and the presence of active pneumonia; PS, performance status; PS*, PS at the time of diagnosis of BPF; Interval to the diagnosis of BPF**, The time interval from the lung resection to the diagnosis of BPF.

detected between the endoscopic and surgical intervention groups. Table 4 compares the patient characteristics and therapeutic outcomes between the patients with and without endoscopic intervention. No significant differences were shown in any factors. The selection of an endoscopic or surgical intervention showed no association with the therapeutic outcome.

Discussion

In the 10 years since 2008, we performed 1,976 lung resections for malignant lung disease such as primary and metastatic lung cancers and mesotheliomas at our institution. The incidence of BPF was 3.6% (1/28) after pneumonectomy, 0.4% (6/1,300) after lobectomy, 2.2% (7/314) after segmentectomy, and 0.3% (1/334) after sublobar resection. These results are consistent with the literature [1-4]. Right-sided pneumonectomy and right lower lobectomy are known to be associated with a high risk of BPF [2-4]. In the present study, a patient who had undergone a pneumonectomy had a right-sided bronchial fistula, and 4 of the 6 patients who had undergone a lobectomy had a BPF after a right lower lobectomy (66.6%). In the 7 segmentectomies and the single sublobar resection, the locations of BPF were dispersed.

Sonobe *et al.* reported that patients who had undergone a previous ipsilateral thoracotomy had a significantly higher incidence of BPF because of poor vascularity to the bronchial stump [3]. In the present study, 2 of the 6 patients with the previous thoracotomy underwent an ipsilateral lung resection. Likewise,

Table 4 Comparison between the patients with and without endoscopic intervention

	Endoscopic intervention		
	Yes (n=7)	No (n=7)	*p*
Gender			
Male/female	5/2	5/2	1.00
Age			
Mean (SD), years	69 (5.7)	68 (7.8)	0.78
PS*			
0-2/3, 4	5/2	3/4	0.58
Smoking history (%)	5 (71%)	7 (100%)	0.13
Past history of lung resection	4	2	0.28
Comorbidity	1	3	0.58
Primary operation			
Pneumonectomy and Lobectomy	2	4	0.28
Segmentectomy and Sublobar resection	5	3	
Operative side			
Right/left	4/3	5/2	0.58
Interval to the diagnosis of BPF**			
Median (range), days	160 (29–513)	37 (12–1,123)	0.98
Size of BPF			
Small (≤3 mm)	4	1	0.10
Intermediate (>3 and ≤6 mm)	3	3	
Large (>6 mm)	0	3	
Active pneumonia	2	4	0.28
Positive infection of pleural effusion (%)	2	1	0.51
Success of BPF treatment	5	5	1.00
Death	1	2	0.51

No significant differences in patient characteristics or therapeutic outcomes were revealed between the patients with and without endoscopic intervention. PS*, PS at the time of the diagnosis of BPF; Interval to the diagnosis of BPF**, The time interval from the lung resection to the diagnosis of BPF.

another patient developed a left lower BPF after 2 ipsilateral segmentectomies at the left upper division and S8+9 for metachronous lung cancer. Maintaining an adequate blood supply to the bronchial stump is a key factor in preventing BPFs.

Our analysis revealed that poor PS, the presence of preoperative comorbidities, a short interval between the lung resection and the diagnosis of BPF, and the presence of active pneumonia each had a negative impact on the therapeutic outcomes. We were thus unable to rescue the high-risk patients with active pneumonia. Peter *et al.* reported that the incidence of aspiration pneumonia dropped as the time interval between the operation and the fistula onset increased, and death from aspiration pneumonia was avoided when the fistula appeared ≥3 months after surgery. Jichen *et al.* reported that different treatments should be used for early and late BPFs because the mortality rate of early BPFs was significantly higher [7]. In the 2 present patients who died of active pneumonia, the time intervals between the lung resection and the diagnosis of BPF were 12 and 16 days, respectively. The selection of an endoscopic intervention or a surgical intervention had no significant impact on the therapeutic outcomes. It was more important to evaluate each patient's condition and control his/her pneumonia.

Some reports show that endoscopic intervention is useful and safe [4,8,9]. Conservative management is reported to be useful in post-lobectomy fistulas that are almost completely closed after the positioning of a chest tube for drainage. Endoscopic intervention associated with conservative therapy should be considered a safe and useful option [4]. If the patient's physical condition is stable, an endoscopic intervention might be effective.

One of the present patients underwent an endoscopic intervention that supported a surgical intervention; we diagnosed his BPF at 281 days after a segmentectomy of the left upper division. He had no pneumonia

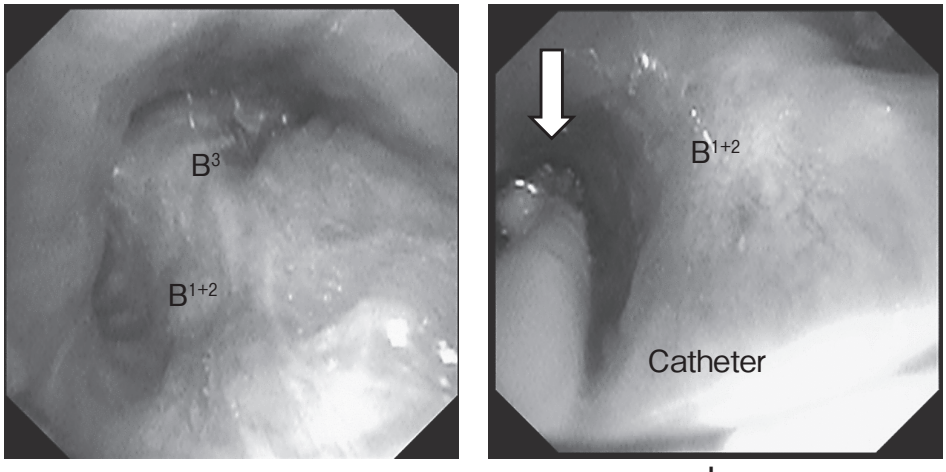

Fig. 1 a: Left B^{1+2} bronchial fistula. An endobronchial Watanabe spigot (EWS) successfully filled the fistula with the push-and-slide method in which a guide wire is inserted through the fistula with bronchoscopy, and an EWS (*white arrow*) through which the wire penetrates is pushed into the fistula with a catheter (b).

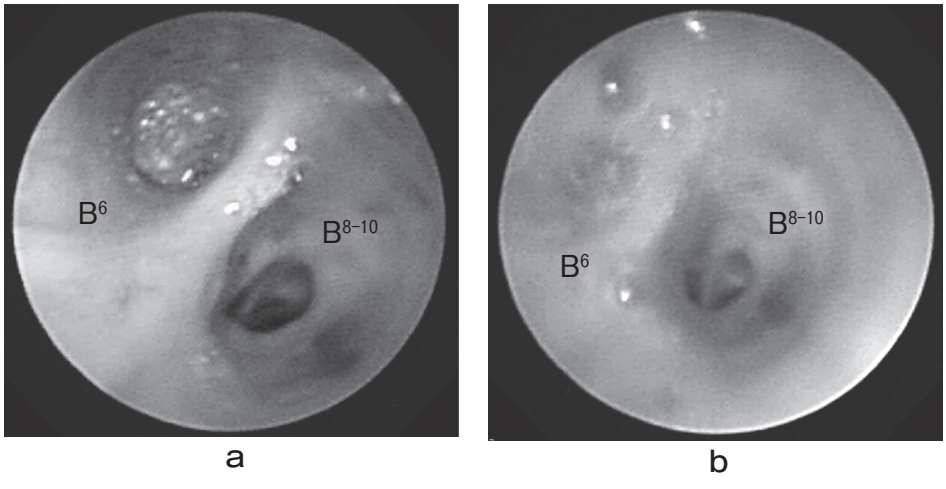

Fig. 2 After a polyglycolic acid (PGA) sheet was cut into pieces and rolled, it was inserted into the B^6 fistula (a) and stabilized with fibrin glue (b).

and his PS was 1. First, the endoscopic interventions with an EWS failed twice, and then an open-window thoracotomy was performed. The EWS successfully filled the left B^{1+2} fistula with the use of the push-and-slide method in which a guide wire is inserted through the fistula with bronchoscopy, and an EWS through which the wire penetrates is pushed into the fistula with a catheter (Fig. 1). We easily held the end of the wire projecting from the BPF in the chest cavity of the open window. Negative pressure wound therapy was performed for 1 month to minimize the cavity, which was then filled using pedicle omentopexy.

Our failure of endoscopic intervention may be partly because of our procedure for BPF closure. We often put some cut and rolled PGA sheets into a BPF with fibrin glue (Fig. 2). Although this patient's air leakage had disappeared for a few days, it developed again because the sheets were dislodged whenever the patient coughed.

Fuso *et al.* recommend cyanoacrylate glue rather than fibrin glue because the cyanoacrylate glue polymerizes quickly into a thin elastic film and adheres firmly

to the tissue [4]. Indeed, cyanoacrylate glue was used in our successful endoscopic intervention. According to the size, depth, and location of a BPF, an adequate filling material and/or method should be selected.

In summary, the selection of endoscopic intervention or surgical intervention for BPF did not affect the therapeutic outcomes. This study's main limitation is its retrospective design.

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