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CURRENT TOPICS REVIEW ARTICLE

Risk factor of bronchopleural fistula after general thoracic surgery: review article

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Abstract

Objective The aim of this article was to clarify recent risk factors for the early bronchopleural fistula after anatomical lung resection.

Methods Reports on early bronchopleural fistula after anatomical lung resection in adults, including information on risk factors, published between 2006 and 2016 were reviewed and our institutional data were evaluated. The early period was defined as within 30 days from surgery or as described early in the manuscript.

Results A total of seven retrospective observational articles were selected. Four articles investigated lobectomy and pneumonectomy, while the other three articles investigated only pneumonectomy. The surgical procedure, preoperative therapy, complications after surgery, right side, patient age, past history, and tumor residuals were mentioned as risk factors of bronchopleural fistula. Our data concluded that neoadjuvant therapy and a right lower lobe location were risk factors after a lobectomy, while a right side and complete pneumonectomy were risk factors after a pneumonectomy.

Conclusions Although recent studies have reached nearly the same conclusions as older reports, continuous research of potential risk factor is needed as therapeutic procedures continue to evolve.

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Abbreviations

BPF	Bronchopleural fistula
NSCLC	Non-small cell lung cancer
EGFR	Epithelial growth factor receptor
TKI	Tyrosine kinase inhibitor
ALK	Anaplastic lymphoma kinase
PD-L1	Programmed cell death ligand 1

Introduction

Bronchopleural fistula (BPF) is a rare but severe complication that can occur after anatomical lung resection. It exposes the clean pleural space to endobronchial bacterial flora, and the resulting pleural effusion can leak into the major airway and spread to the peripheral alveolar space. This situation causes severe aspiration pneumonia and/or empyema, which can be potentially fatal; in fact, the mortality rate for BPF after pneumonectomy is reported to be 18–50% [1–3].

BPF after general thoracic surgery requires emergency treatment, because affected patients usually have poor short-term respiratory function as a result of lung volume loss and/or surgical damage to the respiratory muscles. Recovery from early BPF symptoms is very much dependent on the urgent application of appropriate therapies.

Traditionally, a right-side pneumonectomy and right lower lobectomy are known to be associated with a high risk of BPF [2, 4], which is suspected to occur as a result of a decreased post-operative blood supply to the bronchial stump after lymph node dissection and preoperative therapies [3, 5–7]. Although the procedure used to suture the bronchial stump has been discussed as a risk factor for BPF, it is now considered that manual suturing and mechanical stapling are not significantly different [8].

Although anatomical and physiological factors of BPF should be investigated using older cases, factors that differ between older treatment periods and the present should not be discussed together. For example, the standard chemotherapy regimens for NSCLC, the use of energy devices using surgery, and the systems used for radiation therapy for NSCLC all differ between the 1990s and the 2010s.

Here, we reviewed recent literature to clarify the risk factors for BPF after anatomical lung resection to highlight areas where caution is needed.

Methods

All recent literature published between 2006 and 2016 and pertaining to early BPF after anatomical lung resection in adults, including information about risk factors, was reviewed. Our search was performed through Medline (PubMed: http://www.ncbi.nlm.nih.gov/PubMed) using the search keywords "bronchopleural fistula," "risk factor," and "lung resection." Papers describing radiofrequency ablation, microwave coagulation therapy, children or infants, and chronic BPF or with contents considered by the authors to be insufficient were excluded. In addition, references included in the collected literature and published during the same period were included, if appropriate.

Early BPF was defined as BPF occurring within 30 days from surgery or described as "early" in the literature.

Our institutional data were collected and analyzed for comparison as described below. The study candidates were 1114 consecutive NSCLC patients who had been undergone an anatomical lung resection between April 1999 and August 2015 at the Kagawa University Hospital. Risk factors (sex, age, past medical history, preoperative therapy, tumor location, histology, procedure, and reinforcement) were evaluated. Dichotomous variables were compared using the Fisher's exact test and categorical variables were compared using the Chi-squared test; continuous variables were compared using an unpaired Student's t test. Differences were considered significant at $p < 0.05$. Risk factors were analyzed using the logistic regression model. Factors shown to be significant using a univariate analysis at $p < 0.2$ were included in the multivariate analysis, in which independent prognostic factors were considered significant at $p < 0.05$. The results of our data are shown in Tables 1, 2, and 3.

Results

Original articles among the collected literature are listed in Table 4 [9–15]. Not all studies were included in the multivariate analysis. The reported risk factors for BPF included microscopically evident residual tumor, patient age, respiratory complications, procedure employed (pneumonectomy), preoperative therapy, previous medical history (diabetes mellitus), and acute exacerbation of interstitial pneumonia. Among studies of pneumonectomy, the completion of the pneumonectomy, neoadjuvant therapy, a patient age of over 70 years, diabetes mellitus, and the right side were described as significant risk factors. Studies of meta-analyses, reported mainly by Li et al. [1, 16–19], revealed that risk factors for BPF were residual tumor at the bronchial stump, use of neoadjuvant radiotherapy or chemoradiotherapy, and previous medical history (diabetes mellitus and chronic obstructive pulmonary disease).

Analyses of the risk factors at our institution are summarized in Table 2 (all cases, multivariate analysis) and Table 3 (lobectomy case and pneumonectomy case, multivariate analysis).

A male gender as a risk factor of BPF was not comparatively important, as its significance was shown in a univariate analysis [12] but not in a multivariate analysis [Table 2]. Patient age, however, was a considerable risk factor for BPF. In Japan, although not all patients underwent an anatomical lung resection, 85% of the surgically resected NSCLC patients were over 60 years old, and 53% were over 70 years old [7]. This result implied that surgery for NSCLC in Japan carries a potential risk of BPF.

A residual bronchial stump, as pointed out by Kawaguchi et al. [9], was a unique factor. Tumor regression or wound healing might contribute to BPF, and Kawaguchi et al. reported that a direct extension type, but not carcinoma in situ, was associated with BPF. A meta-analysis performed by Li [16] concluded a significant risk only for pneumonectomy.

Neoadjuvant therapy for NSCLC was the most notable risk factor for BPF, with several reports concluding the existence of a significant risk of BPF [11, 14, 17]. Chemotherapy or chemoradiotherapy followed by surgery might potentially disturb bronchial wound healing.

A past medical history, especially of diabetes mellitus, is a controversial risk factor. Hu et al. [14] and a meta-analysis [18] concluded the presence of a significant risk of BPF; however, the definition and degree of diabetes mellitus were not described, similar to our results. The presence of controlled or uncontrolled disease may be more important.

Respiratory complications like pneumonia or the acute exacerbation of interstitial pneumonia have been pointed out as risk factors of BPF [10, 15]. However, neither of these articles described an association between BPF formation and respiratory complications. Severe respiratory complications usually demand respirator ventilation, steroid pulse therapy, and numerous drug treatments. These situations occurring soon after anatomical lung resection may contribute to BPF formation. Aspiration pneumonia after anatomical lung

Table 1 Patient characteristics

Gender			Location		
Male	730		RU	364	32.7%
Female	384		RM	86	7.7%
Age	68	Range 26–92	RL	239	21.5%
Past medical history			LU	280	25.1%
CHF	23	2.0%	LL	145	13.0%
CRF	11	1.0%	Procedure		
CKD (HD)	35 (8)	3.1 (0.7)%	Lobectomy	1009	90.6%
Autoimmune disease	61	5.5%	Bilobectomy	28	2.5%
Malignant disease	132	11.8%	Pneumonectomy (completion)	77 (6)	6.9 (0.5)%
Hypertension	408	36.6%	Preoperative		
Diabetes mellitus	178	16.0%	None	954	85.6%
CAD	68	6.1%	NACRT	133	11.9%
CVD	97	8.7%	NAC	24	2.2%
Arrhythmia	72	6.5%	NART	3	
Asthma	52	4.7%	Reinforcement		
COPD	157	14.1%	None	911	81.8%
Interstitial pneumonia	71	6.4%	Muscle	41	3.7%
Tuberculosis	32	2.9%	Adipose tissue	162	14.5%
Steroid use	45	4.0%	BPF		
Radiation pneumonitis	8	0.7%	Yes	20	1.8%
Histology			No	1094	98.2%
Adenocarcinoma	730	65.5%			
Squamous cell carcinoma	285	25.6%			
Side					
Other	99	8.9%			
Right side	689	61.8%			
Left side	425	38.2%			

CDH chronic heart disease, *CRF* chronic respiratory failure, *CKD* chronic kidney disease, *HD* hemodialysis, *CAD* coronary arterial disease, *CVD* cerebrovascular disease, *COPD* chronic obstructive pulmonary disease, *RU* right upper, *RM* right middle, *RL* right lower, *LU* left upper, *LL* left lower, *NACRT* neoadjuvant chemoradiotherapy, *NAC* neoadjuvant chemotherapy, *NART* neoadjuvant radiotherapy, *BPF* bronchopleural fistula

resection, especially a right lower lobectomy, is a notable complication.

The diameter or thickness of the bronchial stump after a pneumonectomy is wider or thicker than those after a lobectomy. An analysis of the risk factors for BPF associated with both a lobectomy and a pneumonectomy tended to conclude that a pneumonectomy itself was a significant risk [10, 12]. Regarding BPF after anatomical lung resection, a pneumonectomy appeared to represent a situation that differed from a lobectomy; therefore, we analyzed the risk factors for BPF for each situation separately.

Lobectomy

A lobectomy is the surgical procedure used most frequently for the resection of bronchopulmonary carcinoma in Japan (27,584 cases, representing 72% of all lung cancer cases in 2014 [20]). BPF after lobectomy occurs in intermediate (right lower or right middle-lower lobectomy) or small-caliber bronchi (other lobectomy). Although a decrease in blood supply to the bronchial stump or damage to the bronchial stump (surgical procedure, electrical burn, destruction due to local infection, etc.) has been discussed as possibly causes of BPF [3, 5–7], no definitive conclusion has yet been reached.

Among lobectomy procedures, a right lower lobectomy and a right middle-lower bilobectomy have been considered to pose a significant risk. In addition, neoadjuvant therapy, especially radiation intervention, has been reported as a significant risk factor. Takahashi et al. reported dose-histogram parameters (irradiated lung volume ratio expressed percentage over 35 grays [V35g > 19%] and 40 grays [V40g > 16%]) for neoadjuvant chemoradiotherapy in relation to BPF [21]. However,

Table 2 Result of multivariate analysis of risk factor of BPF (all cases)

Risk factor of BPF	OR	95% CI	*p* value
Male gender	7.87	0.79–79.90	0.078
Past history (hypertension)	4.38	1.33–14.35	0.015
Past history (malignancy)	7.79	2.13–28.52	0.002
Past history (COPD)	2.34	0.76–7.25	0.140
Past history (tuberculosis)	2.32	0.36–14.96	0.378
Steroid use	3.59	0.56–22.99	0.177
Right middle lobe location	2.86	0.46–17.61	0.259
Right lower lobe location	5.48	1.57–19.07	0.008
Left upper lobe location	0.17	0.02–1.65	0.125
Procedure (pneumonectomy)	24.72	5.94–102.85	< 0.001
Histology	0.89	0.39–2.03	0.782
NACRT	2.96	0.79–11.03	0.107
Reinforcement	2.50	0.65–9.62	0.182

OR odds ratio, *95% CI* 95% confidence interval, *COPD* chronic obstructive pulmonary disease, *NACRT* neoadjuvant chemoradiotherapy

Table 3 Result of multivariate analysis of risk factor of BPF (lobectomy and pneumonectomy)

Risk factor of BPF	OR	95% CI	*p* value
Lobectomy			
Male gender	0.00	–	0.993
Past history (hypertension)	4.65	0.84–25.80	0.079
Past history (malignancy)	5.11	0.96–27.36	0.056
Past history (COPD)	1.86	0.38–9.20	0.448
Past history (tuberculosis)	0.00	–	0.998
Steroid use	3.12	0.34–28.79	0.315
Right middle lobe location	11.52	0.56–235.45	0.112
Right lower lobe location	16.07	1.69–152.36	0.016
Left upper lobe location	0.00	–	0.995
Histology	1.08	0.36–3.23	0.886
NACRT	11.86	1.45–96.84	0.021
Reinforcement	1.55	0.25–9.77	0.639
Pneumonectomy			
Past history (hypertension)	4.483	0.95–21.26	0.059
Right side	6.29	1.17–33.33	0.032
Completion pneumonectomy	8.67	1.10–68.23	0.040

RR odds ratio, *95% CI* 95% confidence interval, *COPD* chronic obstructive pulmonary disease, *NACRT* neoadjuvant chemoradiotherapy

a few recent studies have mentioned the risk factors for BPF after a lobectomy only. Further research on risk factors for BPF after a lobectomy is needed. Our institutional results showed that neoadjuvant chemoradiotherapy and a right lower location were significant risk factors after a lobectomy (Table 3).

Pneumonectomy

A pneumonectomy is a very invasive surgical procedure, and many papers have reported a high risk of BPF [3, 4, 10, 12], with a morbidity of about 6.3% (5.3–7.5%) [1]. In 2014, a total of 521 pneumonectomies were performed as radical procedures for NSCLC in Japan [20]. Right-side and complete pneumonectomy were associated with a high risk of BPF [12, 13], and neoadjuvant therapy, especially radiation therapy, was also a significant risk factor [14].

More articles have discussed the risk factors for BPF after a pneumonectomy, compared with articles regarding a lobectomy only. A complete pneumonectomy, which is one of the most invasive and dangerous surgical procedures performed in general thoracic surgery, was shown to be associated with a significant risk of BPF in a recent paper [13]. Our data concluded that a complete pneumonectomy and the right side were significant risk factors (Table 3).

Reinforcement

Although the prevention of BPF is an important issue, no rigorous procedures have been specifically recommended. Experience has shown that reinforcement of the stump and preservation of some of the bronchial blood supply at the time of lymph node dissection are important for preventing BPF.

Reinforcement of the bronchial stump is considered a common preventative measure for BPF, and many thoracic surgeons perform this step after anatomical lung resection despite a lack of evidence of any benefit. The most common materials used to reinforce the bronchial stump are adipose tissue and muscle. Adipose tissue is often derived from pedicled or free pericardial fat that can be easily harvested at the time of thoracic surgery [22, 23]. The omentum is considered to be the most effective material for preventing thoracic leakage, but a laparotomy or laparoscopy is needed to harvest this tissue [24, 25]. Intercostal muscle is usually used for muscle reinforcement of the bronchial stump. The use of an intercostal muscle flap at the time of thoracic surgery has the advantage of easy access and a convenient length [1, 26]. Other thoracic muscles, such as the latissimus dorsi, serratus anterior, and pectoralis major, are also candidates for reinforcement materials. However, muscles always shorten if they are not used for contraction and become lax. On the other hand, adipose tissue hardly degenerates over a long period, irrespective of whether it is used as a free or a pedicled flap. When a muscle flap is selected as the bronchial coverage material, atrophic shrinkage must be considered when determining the length to harvest; otherwise, unnecessary tension will build up at the bronchial stump (Fig. 1).

Table 4 Reviewed articles

Authors	Publication year	Study design	Incidence of BPF	Lobectomy/pneumonectomy	Risk factor (*p* value)
Kawaguchi et al. [9]	2008	ROS Univariate	6	57/17	R1 resection at bronchial stump (NA)
Jichen et al. [10]	2009	ROS Multivariate	Early 43 Late 23	4789/1450	Age > 60 year (0.020)[a] Pneumonia (0.003) Pneumonectomy (0.001)
d'Amato et al. [11]	2011	ROS Univariate	24	0/315	Neoadjuvant therapy and right side (0.028)
Uramoto et al. [12]	2011	ROS Univariate	19	1267/157	Male (< 0.001) Stage 2–4 NSCLC (0.006) Pneumonectomy (< 0.001)
Puri et al. [13]	2013	ROS Univariate	9	0/211	Completion pneumonectomy (0.004)
Hu et al. [14]	2013	ROS Mutivariate	30	0/684	Neoadjuvant therapy (< 0.001) Age > 70 year (0.017) Diabetes mellitus (0.033)
Kobayashi et al. [15]	2016	ROS Multivariate	14	758/25	Acute exacerbation of interstitial pneumonia (0.007)

ROS retrospective observational study, *NA* not available, *BPF* bronchopleural fistula

[a]Result only early BPF

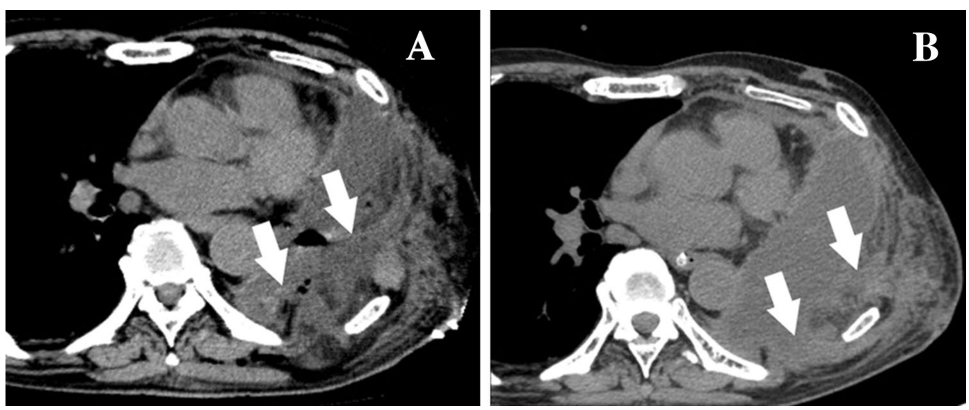

Fig. 1 Arrow shows pedicled muscular flap into the pleural cavity. **a** Rich volume of the flap existed at post-operative day 5. **b** Flap was already shrunken at post-operative day 21)

Comment

Many papers have described BPF as a severe and critical complication occurring after anatomical lung resection [2, 3, 27], with a reported incidence of about 0.6–4.4% [3, 4, 10, 12, 15, 20, 27] and a very high mortality rate (18–50% [2]). Various risk factors for BPF after anatomical lung resection have been reported. Two decades previously, right-side surgery, the pneumonectomy procedure employed, and neoadjuvant therapy were considered major risk factors [3, 4, 26], and recent studies have mostly reached the same conclusions. Recently, there has been an increased focus on radiation intervention in studies of neoadjuvant therapy followed by surgery in relation to BPF [12, 21]. In a study of chemotherapy, Uramoto et al. reported that only neoadjuvant therapy did not pose a significant risk [12].

In comparison with only a decade previously, various treatments have been developed for lung cancer. Molecular targeted therapies such as new-generation EGFR-TKI, ALK-inhibitors, immune-checkpoint inhibitors, or vascular epithelial growth factor agents did not exist in Japan in the early 2000s. The effectiveness of these new therapies, such as neoadjuvant therapy followed by surgery, remains inconclusive in relation to the risk of BPF. Salvage strategies for advanced non-small cell lung cancer have been frequently analyzed in recent studies [28, 29]. Salvage surgery is defined as surgery for residual tumors after definitive therapy for systemic advanced non-small cell lung cancer or surgery for relapsed lesions after a clinical complete response has been obtained using the previous therapies. The Japan Guidelines for Lung Cancer Therapy [30] state that agents should be selected according to the histologic type of the tumor and some biomarkers at an unresectable advanced stage. Treatments for advanced stage NSCLC can be selected from cytotoxic agents, EGFR-TKI, ALK inhibitor, immune-check point inhibitor, and endothelial growth factor inhibitor, for which adverse events include the development of fistulas. Therefore, strategies for salvage surgery after the use of newer systemic therapies may reveal other risk factors for BPF after anatomical lung resection.

As many thoracic surgeons tend to cover the bronchial stump in high-risk cases, a retrospective analysis of the effectiveness of bronchial reinforcement will almost certainly involve a collection bias. In a prospective study of pneumonectomy in patients with diabetes mellitus, Sfyridis et al. [26] reported that intercostal muscle flap coverage was significantly effective, and no BPF event occurred in the reinforcement arm. The low incidence of BPF was described as a limitation.

DiMagio et al. have reported that bronchial reinforcement is not significantly effective for the prevention of BPF [1], nor does it pose a risk of BPF. Our study reached the same results (Tables 2, 3). If, on ethical grounds, most thoracic surgeons perform reinforcement in high-risk cases, a prospective or randomized study of the effectiveness of reinforcement would be unnecessary, since no studies would likely investigate the disadvantages of bronchial reinforcement. Closer attention to cases with a high risk of BPF and urgent intervention when BPF occurs are considered more important issues.

In conclusion, BPF is one of the severest complications after general thoracic surgery, and no effective prophylactic procedure is available. Reinforcement of the bronchial stump may help to prevent BPF, but proof of its effectiveness is a difficult issue both ethically and experientially. Because reinforcement seems to pose no hazard at present, we do not discourage its use. An ongoing risk analysis of BPF will be necessary as therapeutic technologies related to general thoracic surgery continue to evolve.

Compliance with ethical standards

Conflict of interest There are no potential conflicts of interest.

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