Outcome and risk factors of recurrence after thoracoscopic bullectomy in young adults with primary spontaneous pneumothorax

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Abstract

Purpose To investigate the risk factors of recurrence of pneumothorax following thoracoscopic bullectomy in young adults.

Methods: Between January, 2005 and September, 2015, 167 patients aged ≤40 years old underwent initial thoracoscopic bullectomy for primary spontaneous pneumothorax (PSP) at our hospital. Recurrence-free probability was calculated from the date of surgery to recurrence or last follow-up, using the Kaplan–Meier method.

Results Sixteen (9.6%) of the 167 patients suffered a recurrence (collective total, 16 recurrences). The recurrence-free intervals were 3–107 months (median 25.8 months) and the 5-year recurrence-free probability was 85.9 %. Multivariate Cox analysis demonstrated that age ≤ 23 years (p=0.029) and a history of ipsilateral pneumothorax before surgery (p=0.029) were significantly associated with higher risk of recurrence. The 5-year recurrence-free probability was 72.3 % for patients aged ≤23 years and a history of ipsilateral pneumothorax before surgery, and 94.1 % for those with neither of these factors (p=0.001). Recurrence developed within 3 years after surgery in 14 of the 16 patients.

Conclusions Patients ≤23 years of age with a history of ipsilateral pneumothorax before surgery are at significantly high risk of its recurrence, frequently within 3 years; thus, the risk of postoperative recurrence of a pneumothorax must be kept in mind.

Key words Pneumothorax, Bullectomy, Recurrence, Predictor

Introduction

Primary spontaneous pneumothorax (PSP) is the most common type of pneumothorax, especially in young men [1], and can have a serious social and economic impact. PSP is defined as the occurrence of pneumothorax in the absence of any obvious underlying pathogenesis, such as pulmonary emphysema, endometriosis, Marfan syndrome, pulmonary lymphangioleiomyomatosis, Ehlers-Danlos syndrome, histiocytosis X, or Birt-Hogg-Dubé syndrome [2]. PSP rarely occurs in people older than 40 years of age [3, 4]. Bullectomy is generally considered the definitive treatment for PSP.

Thoracoscopic bullectomy has been performed with increasing frequency in recent decades. Whereas the recurrence of pneumothorax after thoracoscopic surgery ranges from 2% to 14% [1], the overall raw recurrence after thoracoscopic bullectomy was reported at 5.4 % in a meta-analysis by Barker et al. [5], being four times higher than that after open bullectomy. To prevent postoperative recurrence, some surgeons have performed additional procedures, such as staple line coverage [6–8], pleural ablasion [9], and pleurectomy [10] after bullectomy. The risk factors of recurrence after thoracoscopic bullectomy are not well understood, although we selected candidates for a randomized study to prove the efficacy of additional procedures, based on supposed risk factors. To this end, we aimed to investigate the rate of recurrence after thoracoscopic bullectomy and its risk factors.

Patients and methods

We reviewed, retrospectively, 167 consecutive patients aged ≤40 years who underwent initial thoracoscopic bullectomy at the Department of General Thoracic Surgery, Teikyo University School of Medicine Hospital between January, 2005 and September, 2015. No patient presented with synchronous bilateral PSP. Asynchronous bilateral PSP was counted as one PSP on each side. We excluded patients who underwent only looping of a bleb and those with follow-up of <3 months. All patients had computed tomography (CT) of the chest done routinely. For a diagnosis of PSP, we excluded secondary pneumothorax based on the following criteria: a history of chronic lung disease or suspected chronic lung disease on chest CT; and catamenial, iatrogenic pneumothorax or a recent history of trauma. We also excluded patients who had undergone thoracic bullectomy for ipsilateral pneumothorax at other hospitals. After PSP was diagnosed, the surgical indication was decided by the Surgery Board based on our policy, which recognizes that patients with recurrent PSP following conservative treatment such as thoracentesis and indwelling chest tube drainage, and persistent air leakage for >3 days, are good candidates for thoracic bullectomy.

We performed thoracoscopic bullectomy using an endoscopic stapler (Echelon, Cincinnati, OH) via three intercostal port accesses (5–12 mm) for all bullae detected intraoperatively. Since April 2010, we have covered the stapling lines with absorbable

polyglycol acid sheets (Neoveil®, 10×5 cm; Gunze Ltd, Kyoto, Japan) and then applied fibrin glue (Bolheal®; Chemo-Sero-Therapeutic Research Institute, Kumamoto, Japan) to make the sheets adhere tightly to the stapling lines and pleural surface. All patients were followed up for at least 2 months, but usually for 4 months postoperatively, on an outpatient basis, even if their postoperative course was uneventful.

We reviewed the medical records of each patient to obtain clinical and perioperative information, including sex, age (dichotomized by a median of 23 years), body mass index (BMI; dichotomized by a median of 19.1 kg/m^2), smoking habits (non-smoker vs ever-smoker), laterality, history of PSP before surgery, number of staples (dichotomized by a median of 2 staples), number of resected bulla or bullae, stapling line coverage, operation time (dichotomized by a median of 46 min) , and postoperative drainage duration (dichotomized by a median of 1 postoperative day). To investigate outcomes after surgery precisely, we conducted telephone interviews for all patients up to September, 2015. Postoperative recurrence was defined as ipsilateral PSP after thoracoscopic bullectomy, regardless of where the air was located. The recurrence-free period was defined as the interval between the date of surgery and the date of recurrence or the most recent date that the patient was examined.

Recurrence-free probability was calculated using the Kaplan–Meier method and comparisons were drawn using the log-rank test in a univariate analysis. To identify independent

risk factors, a multivariate analysis was conducted with the Cox proportional hazard model using backward stepwise procedures. The annual recurrence rate was calculated by dividing the number of recurrences during a certain year (r) by the sum of the following: the number of patients without recurrence for the entire year (p), the number of patients with recurrence during the year (r), and half of the number of patients without recurrence who were followed up for less than the entire year (c), according to the following formula by the Cutler Ederer method [11–13]: annual recurrence rate = $r / (p+r+0.5c)$.

All tests were two-sided, and values $p<0.05$ were considered to indicate significance. Statistical analysis was performed using SAS® 9.4 software (SAS Institute Inc., Cary, NC, USA).

Results

Table 1 shows the clinical and perioperative characteristics of the 167 patients (154 men and 13 women; median age, 23 years). Among them, 111 (66.5 %) did not have a smoking history, 83 (49.7 %) had a history of ipsilateral PSP before surgery, and 38 (22.8 %) had a history of preoperative contralateral PSP. In 105 (62.9%) of the patients, staples were used once or twice and 120 (71.9%) underwent resection of a single bulla or bullae. During the study period, there were 16 (9.6 %) recurrences in a collective 16 patients. The recurrence-free intervals ranged

from 3 to 107 months (median, 25.8 months). The follow-up rate was 92.6%. Overall, the 5-year recurrence-free probability was 85.9 %. Table 2 shows the 5-year recurrence-free probabilities, according to clinical and perioperative factors. On univariate analysis, age ≤23 years (p=0.007), a history of ipsilateral PSP before surgery (p=0.002), and a history of contralateral PSP before surgery (p=0.034) were shown to be significant risk factors for recurrence after surgery. The recurrence-free probability was not significantly different between the groups stratified by sex, BMI, smoking history, and all perioperative factors.

Next, we performed a multivariate analysis using the Cox proportional hazard model, to identify the independent predictors of recurrence after thoracoscopic bullectomy. Table 3 shows that age ≤23 years (hazard ratio (HR) 4.064; 95 % confidence interval (95 % CI) 1.152–14.33, p=0.029) and a history of ipsilateral PSP before surgery (HR 9.671; 95 % CI 1.255–74.53, p=0.029) were independent predictors of postoperative recurrence.

We defined the high-risk group as patients aged ≤ 23 years with a history of ipsilateral PSP before surgery and the non-high risk group as patients with neither of these factors. Overall, 51 patients were classified as the high-risk group, and 116 as the non-high-risk group. Twelve of the 16 patients with recurrence were from the high-risk group and the other 4 were from the non-high risk group. The 5-year recurrence-free probability of the high-risk group was 72.3 %, whereas that of the non-high-risk group was 94.1 % (p=0.001; Fig. 1).

Fig. 2 shows that the recurrence rate per year had a bimodal distribution, with peaks 2 and 6 years after thoracoscopic bullectomy. Fourteen (87.5 %) of the 16 cases of postoperative recurrent PSP were found within 3 years after surgery, with 12 (75.0 %) of these occurring within 2 years after surgery. The other two (12.5 %) recurrences were found more than 4 years after surgery.

Discussion

Generally, PSP is not considered a fatal disease, with the exceptions of synchronous bilateral pneumothorax and tension pneumothorax. However, it can compromise the patient's quality of life, socially and economically, especially if it is recurrent. For patients treated conservatively, by observation, thoracentesis, or indwelling chest tube drainage, the recurrence rate has been reported to range from 16–52 % [1, 14]. Thoracoscopic bullectomy is considered a definitive treatment choice for recurrent PSP after conservative therapy [1]. However, the actual mechanisms of onset of postoperative recurrent PSP and the risk factors for postoperative recurrence are not well understood. It is difficult to obtain long-term follow-up data to investigate recurrence after bullectomy because most patients are followed up only in the short term following bullectomy. Thus, we investigated recurrence after thoracoscopic bullectomy and conducted telephone interviews of all patients to gather more information on longer follow-

up data.

The recurrence rate after thoracoscopic bullectomy in our cohort was 9.6 %, which is comparable with previously reported rates of 2–14 % [1]. We found that an age ≤23 years and a history of ipsilateral PSP before surgery were independent risk factors for recurrence after bullectomy. Younger age has been reported as a risk factor of PSP [1]. Choi et al. [15] also reported that younger age is a predictor of worse prognosis after thoracoscopic bullectomy for PSP. Newly grown bullae, possibly more common in younger patients and associated with growth of the chest cavity, might be a cause of recurrent PSP after surgery [16]. Similarly, Moriyama et al. [17] reported that bullae might not develop de novo in patients >25 years of age, which supports the current findings. We also found that a history of ipsilateral pneumothorax before surgery was an independent risk factor for recurrence after surgery, as has been reported after conservative treatment [18]. It might also imply a relatively high risk for de novo bullae. In fact, most of these patients had multiple bullae in their resected specimen (data not shown). On the other hand, it has been reported that low BMI [19], female sex [20], and prolonged air leak before surgery [20] were risk factors for recurrence after surgery, although they did not reach statistical differences in our analyses. Thus, our findings should be followed up through further large-scale, prospective studies.

The annual recurrence rate revealed a bimodal distribution, with peaks 2 and 6 years after surgery. To the best of our knowledge, this is the first report to investigate annual recurrence rates, characterized by possible recurrent PSP over 5 years after surgery. A possible explanation for this is newly developed bullae and blebs or emphysema, but the actual mechanism is not clear. The available CT findings of patients with recurrence did not reveal anything significant. To this end, our study should be followed up by further analysis because the number of recurrences in this series was small.

The current findings will prove useful in a clinical setting and we could modify our follow-up plan for high-risk patients based on the current findings. We should also make all patients aware of the risk of recurrence, manifesting even more than 5 years after thoracoscopic bullectomy. On the other hand, we did not show the efficacy of covering the stapling line with absorbable polyglycol acid mesh and fibrin glue, which is still controversial. One randomized trial reported that it had a negative effect [21], even though additional procedures such as stapling line coverage, mechanical or chemical pleurodesis, pleurectomy were applied to prevent postoperative recurrence in clinical practice [6–10, 14]. Overall, no additional procedures to combine with thoracoscopic bullectomy have proven effective, and their efficacy should be investigated in a prospective trial. However, the risk factors can be used to select or randomize candidates in clinical trials.

The major limitations of the current study are caused by its retrospective nature and relatively small study population, which might create both selection and information bias. We should be aware of these possible biases before generalizing our findings.

Conclusion

Pneumothorax recurred in 16 (9.6 %) of the 167 young patients following thoracoscopic bullectomy in this series. Our findings showed that patients aged ≤23 years and a history of ipsilateral pneumothorax before surgery harbor significant risks of postoperative recurrence. Of the 16 recurrences, 12 were associated with the known risks. Although recurrence is commonly seen within 3 years postoperatively, we should bear in mind the risk of recurrence in the longer term.

Conflict of statement

We have no competing interests to disclose.

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Table 1. Clinical characteristics of the 167 patients who underwent thoracoscopic bullectomy

Characteristics	No. of Patients (%)
Overall number	167
Median Age (yr)	23
≤23	83 (49.7)
>23	84 (50.3)
Gender	
Male	154 (92.2)
Female	13 (7.8)
Median BMI (kg/m^2)	19.1
≤19.1	85 (50.9)
>19.1	81 (49.1)
Smoking habits	
Non-smoker	111 (66.5)
Ever-smoker	56 (33.5)
Laterality	
Right	76 (45.5)
Left	91 (55.5)
History of ipsilateral PSP before surgery	
Yes	83 (49.7)
No	84 (50.3)
History of contralateral PSP before surgery	
Yes	38 (22.8)
No	129 (77.2)
Median number of used staples	2
≤2	105 (62.9)
>2	62 (37.1)
Number of resected bulla or bullae	
Single	120 (71.9)
Multiple	47 (28.1)
Staple line coverage	
Done	104 (62.3)
Not	63 (37.7)
Median operation time (minute)	46
≤46	87 (52.1)
>46	80 (47.9)

Postoperative drainage duration (day)		
≤1	147	(88.0)
>1	20	(12.0)

BMI: Body mass index, PSP: Primary spontaneous pneumothorax

Table 2 Clinical characteristics and recurrence-free probability after thoracoscopic bullectomy

Characteristics	5year-RFP (%)	p-value[a]
Age (yr)		
≤23	78.1	
>23	93.8	0.007
Gender		
Male	88.4	
Female	64.3	0.144
BMI (kg/m^2)		
≤19.1	81.2	
>19.1	90.7	0.278
Smoking habits		
Non-smoker	84.1	
Ever-smoker	90.8	0.289
Laterality		
Right	81.3	
Left	91.6	0.519
History of ipsilateral PSP before surgery		
Yes	77.7	
No	98.8	0.002
History of contralateral PSP before surgery		
Yes	76.8	
No	88.6	0.034
Number of used staples		
≤2	83.8	
>2	88.0	0.910
Number of resected bulla or bullae		
Single	85.2	
Multiple	86.9	0.864
Stapling line coverage		
Yes	91.5	
No	82.7	0.278
Operation time (minute)		
≤46	88.8	
>46	89.0	0.203
Postoperative drainage duration (day)		

≤1	83.4	
>1	94.4	0.246

[a] Log-rank test, RFP: Recurrence free probability, BMI: Body mass index, PSP: Primary spontaneous pneumothorax

Table 3 Multivariate analysis of risk factors for recurrence

Factors	Unfavorable	Favorable	Hazard Ratio (95% CI)	p-value[a]
Age (yr)	≤23	>23	4.064 (1.152-14.33)	0.029
History of ipsilateral PSP before surgery	Yes	No	9.671 (1.255-74.53)	0.029
History of contralateral PSP before surgery	Yes	No	2.373 (0.879-6.406)	0.088

[a] Cox proportional hazard model, PSP: Primary spontaneous pneumothorax

Fig. 1

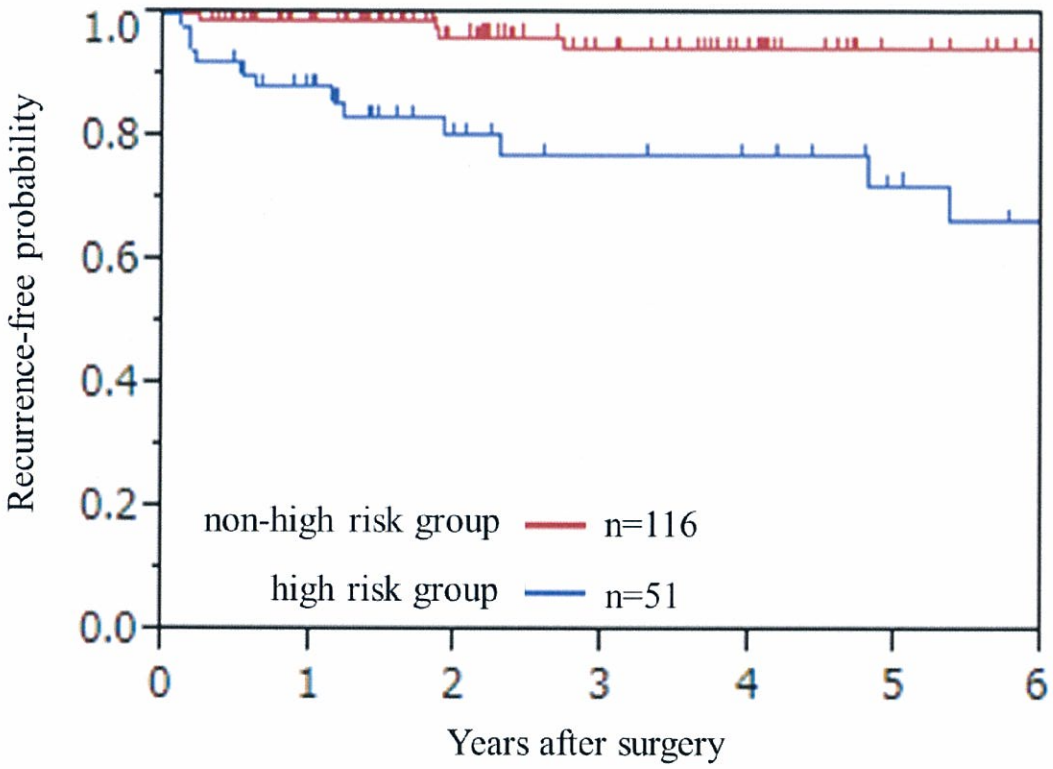
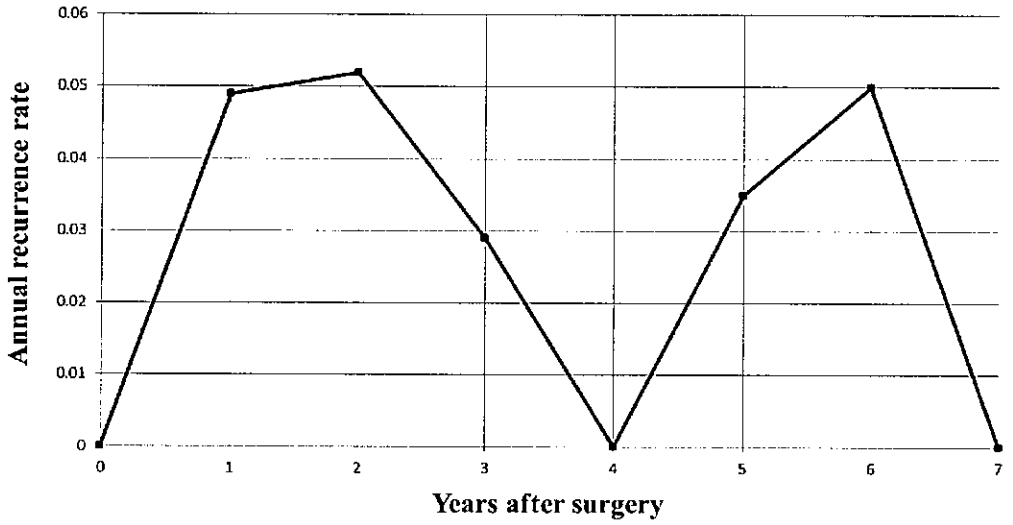

1.0
0.8
0.6
0.4
0.2
0.0
Recurrence-free probability
non-high risk group
n=116
high risk group
n=51
0
1
2
3
4
5
6
Years after surgery

Fig. 2



Patients at risk

167	134	89	64	40	25	17	15

Figure legends

Fig. 1

Recurrence-free probability after surgery, according to the risk factors. The high-risk group included patients aged ≤23 years and those with a history of ipsilateral primary spontaneous pneumothorax. The low risk group had neither of these.

Fig. 2

Estimated annual recurrence rates after surgery, for the entire cohort.