



Natural history of bulla neogenesis for primary spontaneous pneumothorax: a propensity score analysis

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Received: 20 September 2018 / Accepted: 25 November 2018 / Published online: 6 December 2018
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Abstract

Objective For patients with recurrent primary spontaneous pneumothorax, surgery has been thought to be an acceptable treatment. However, even if bulla is completely resected, postoperative recurrence is relatively common due to bulla neogenesis. Bulla neogenesis seems to develop naturally in younger patients compared with the elderly, as theorized till date. If the complete development of bulla neogenesis is confirmed, surgical resection can be performed as the radical treatment. Then, we evaluated the relationship between bulla neogenesis and age.

Methods Between February 2009 and July 2018, we consecutively enrolled 276 patients who underwent primary bullectomy for primary spontaneous pneumothorax in our hospital. Finally, high-resolution computed tomography findings/observations of 155 eligible patients were evaluated retrospectively. The relationship between bulla neogenesis and age was evaluated using univariate and multivariate analyses and an inverse probability of treatment-weighted method using the propensity score.

Results The study included 58 patients aged < 20 years and 97 aged ≥ 20 years. Bulla neogenesis was present in 34 patients (21.9%). Bulla neogenesis developed significantly at age < 20 compared with age ≥ 20 (44.8 vs. 8.2%). Univariate and multivariate analyses showed that age < 20 years was a significant factor associated with bulla neogenesis ($P < 0.001$ and $P = 0.018$, respectively). The inverse probability of treatment-weighted method showed that age < 20 years was a significant factor associated with bulla neogenesis ($P = 0.0057$, hazard ratio 4.79).

Conclusions Surgical treatment may be delayed in young patients (age < 20 years), because bulla neogenesis is not completely developed by this time for primary spontaneous pneumothorax.

Keywords Primary spontaneous pneumothorax · Bulla neogenesis · Age · Natural history · Propensity score

Introduction

Primary spontaneous pneumothorax (PSP) is a common disease, which develops in relatively young healthy individuals with no underlying lung disease. Conservative management is less invasive compared to surgical treatment; therefore, conservative management is often selected as the first choice of treatment in PSP [1–3]. However, conservative managements such as observation, simple aspiration, or chest tube drainage have a relatively high recurrence rate (29.2–54.2%)

[4, 5]. Therefore, for patients with recurrent PSP, surgical treatment such as video-assisted thoracoscopic surgery (VATS) bullectomy has been thought to be an acceptable treatment [1–3]. However, even if complete resection of the identified bulla and the reinforcement around the staple line by an absorbable covering sheet and/or the mechanical or chemical pleurodesis is performed during the VATS [6–11], postoperative recurrence is relatively common due to bulla neogenesis near the staple line and other locations, which were not related to the staple line [12–15]. VATS is less invasive than the traditional procedure of open thoracotomy. Nevertheless, there is more physical and mental damage in patients who undergo the VATS than in patients who undergo the conservative therapy; therefore, the VATS should be avoided until the patients are expected to benefit from the radical surgery.

It has been suggested that younger patients manifest a higher postoperative recurrence of the pneumothorax due

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to postoperative bulla neogenesis, even if the same procedures preventing the postoperative recurrence are performed [16–18]. There are guidelines for the management of the PSP [1, 2], which describe the management according to various conditions such as symptoms, findings of the chest X-ray, or air leakage. However, none of the guidelines describe age-related management of the PSP. Therefore, we aimed to describe the age-related management of the PSP in our study.

Bulla neogenesis seems to develop naturally in younger patients compared with the elderly, as hypothesized from the above reports. Therefore, we speculated that younger patients tend to develop natural bulla neogenesis regardless of the VATS, and the number of bullae may stop increasing by this time. If the time of completion of increasing natural bulla neogenesis is revealed, we can subsequently perform the VATS as the radical treatment. Unfortunately, the healthy individuals, whose lungs are untreated by the VATS, rarely undergo high-resolution computed tomography (HRCT) to identify natural bulla neogenesis. On the other hand, it is difficult to evaluate the history of the surgical side due to various changes such as reinforcement of the visceral pleura by an absorbable covering sheet and the presence of adhesions. However, HRCT can be performed for postoperative observation. Therefore, we evaluated the relationship between natural bulla neogenesis of the contralateral lung against the surgical side and age through retrospective observational analysis of HRCT images of patients who underwent VATS.

Methods

Between February 2009 and July 2018, we enrolled 276 patients of the PSP consecutively who underwent the primary VATS in our hospital. Patients with bilateral PSP treated with bilateral VATS and patients with lack of clinical data were excluded from our study. In total, 155 patients were considered eligible and underwent HRCT for the preoperative and postoperative evaluations.

The patients underwent the VATS according to the following indications: ipsilateral PSP recurrence, a persistent air leak after the chest tube drainage, hemopneumothorax, tension pneumothorax, and per the patient's request. All the procedures were performed by a single surgical team. The patient was placed in a lateral position under general anaesthesia with the ventilation of one lung. According to the difficulty involved in the surgery, the choice of the procedure (single-port or multi-port VATS) was made as we have described previously [19].

Natural bulla neogenesis was defined as the progression of the contralateral bulla against the ipsilateral VATS side, as evidenced from the preoperative to postoperative HRCT images. The follow-up period was defined as the time

between the preoperative and postoperative HRCT evaluation. If the postoperative HRCT was performed several times and the bulla was observed to increase continuously, the period that revealed the last increase of the bulla was defined as the follow-up period.

We performed preoperative HRCT to evaluate ipsilateral intrathoracic status including the position of the bulla and presence of adhesions and 12-month postoperative HRCT to evaluate the presence of ipsilateral bulla neogenesis, even when asymptomatic. In case of symptoms, the patients visited our institution without reservation and performed HRCT as necessary. Morbidity or mortality associated with our procedures was evaluated according to The Japan Clinical Oncology Group's postoperative complication criteria based on the Clavien-Dindo classification [20]. According to the criteria, grade IIIb or more is needed for the invasive procedures under general anaesthesia. The adverse events that corresponded to the grade IIIb or more were defined as severe morbidity.

As a primary analysis, the relationship between natural bulla neogenesis and age was evaluated using univariate analysis. Multivariate analysis and the inverse probability of treatment-weighted (IPTW) method using the propensity score were performed to correct for confounders. The confounders for natural bulla neogenesis included gender, smoking habits, body mass index (BMI), and the operational side. Statistical analyses were performed using the Welch test and Fisher's exact test. Continuous variables were presented as mean \pm standard deviation. Univariate analysis of the natural bulla neogenesis rate for the PSP was estimated based on the Kaplan–Meier method and was compared using the log-rank test. Multivariate analysis of the natural bulla neogenesis rate for the PSP was estimated based on the COX regression analysis using all factors. For the propensity score analysis, COX regression analysis using the IPTW method was performed. The cut-off point for age was determined using an ROC curve and was defined as 20 years [area under the curve 0.815 (95% CI 0.74–0.89), sensitivity 76.5%, specificity 73.6%]. A *P* value of <0.05 indicated statistical significance. The hazard ratio and 95% confidence intervals were calculated for each variable. An EZR software package (<http://www.jichi.ac.jp/saitama-sct/SaitamaHP.files/statmed.html>) was used for the statistical analyses.

This study was approved by the Institutional Review Board of Takasago Municipal Hospital (No. 2018-1), and informed consent was obtained from each patient.

Results

The study included 58 patients aged <20 years and 97 aged ≥ 20 years (Fig. 1). The mean age was 27.5 ± 13.5 years, with male predominance ($n = 136$, 87.7%) (Table 1).

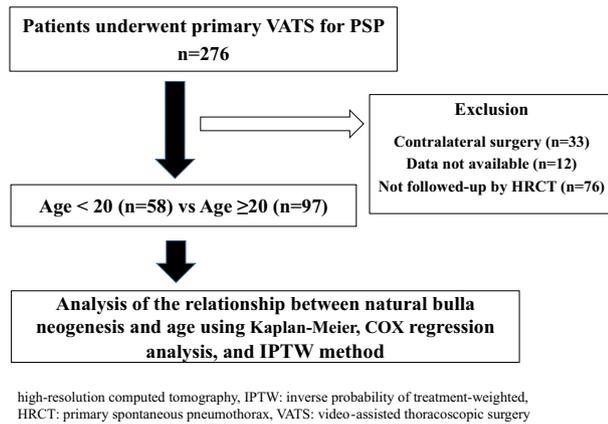


Fig. 1 Details of the patients enrolled for the study

Table 1 Clinical characteristics of the patients with the PSP who underwent the VATS

Variables	Clinical characteristics (<i>n</i> = 155)
Age (years)	27.5 ± 13.5
Male, <i>n</i> (%)	136 (87.7)
BMI	19.5 ± 2.2
Smoking history, <i>n</i> (%)	
Absent	94 (60.6)
Present	61 (39.4)
Operation side, <i>n</i> (%)	
Right	65 (41.9)
Left	90 (58.1)
The number of preoperative bullae	3.0 ± 3.9
The number of postoperative bullae	3.4 ± 4.0
Bulla neogenesis, <i>n</i> (%)	34 (21.9)
Follow-up period (days)	488.9 ± 445.6

BMI body mass index, *PSP* primary spontaneous pneumothorax, *VATS* video-assisted thoracoscopic surgery

The mean BMI was 19.5 ± 2.2 (Table 1). Smoking habit was present in 61 patients (39.4%) (Table 1). Sixty-five patients underwent the procedures on the right side (41.9%) (Table 1). The number of preoperative bulla was 3.0 ± 3.9 . The number of postoperative bulla was 3.4 ± 4.0 . Natural bulla neogenesis was present in 34 patients (21.9%). The mean follow-up period was 488.9 ± 445.6 days (Table 1).

Natural bulla neogenesis occurring at age < 20 and ≥ 20 years relatively developed (44.8 vs. 8.2%). According to the univariate analysis performed using the log-rank test, two factors including age < 20 years and smoking habit significantly favoured bulla neogenesis for the PSP (Table 2). Based on the COX regression analysis using all the factors, age < 20 years was a significant factor related to bulla neogenesis ($P = 0.018$; hazard ratio 4.73) (Table 2). For age < 20 years, an assumption of the proportional hazards was confirmed. The age-related background of the patients showed that there were significant differences in terms of BMI and smoking habit (Table 3). Based on the IPTW method, age < 20 years was a significant factor related to natural bulla neogenesis ($P = 0.0057$, hazard ratio 4.79) (Table 2). No severe morbidity and mortality were found.

Discussion

For the patients with recurrent PSP, surgical treatment such as VATS bullectomy has been thought to be an acceptable mode of radical management [1–3]. However, since VATS bullectomy alone has a high recurrence rate (16.3–24.1%) [7, 9], the following three methods have been mainly considered to reduce the postoperative recurrence rate mainly. First, an absorbable covering sheet for the reinforcement of the visceral pleura around the staple line has been thought to be one of the effective techniques in preventing the postoperative recurrence [6, 7]. In a prospective randomized controlled study by Lee et al., it was shown that the use of fibrin glue and absorbable oxidized regenerated cellulose mesh for the

Table 2 Assessment of the association between bulla neogenesis and age in the contralateral side for the PSP development using univariate and multivariate analyses and the IPTW method

	Bulla neo- genesis rate (%)	Univariate analysis			Multivariate analysis			IPTW method		
		HR	95% CI	<i>P</i> values	HR	95% CI	<i>P</i> values	HR	95% CI	<i>P</i> values
Age (< 20 vs. ≥ 20 years)	44.8 vs. 8.2	3.98	1.79–8.85	< 0.001	4.73	1.30–17.25	0.018	4.79	1.58–14.54	0.0057
Gender (male vs. female)	23.5 vs. 10.5	2.09	0.50–8.77	0.31	1.24	0.28–5.49	0.78			
BMI (< 18 vs. ≥ 18)	28.3 vs. 19.3	0.73	0.36–1.47	0.37	0.88	0.43–1.80	0.72			
Smoking habit (absent vs. present)	28.7 vs. 11.5	0.38	0.16–0.88	0.019	1.24	0.32–4.84	0.75			
Side (right vs. left)	24.6 vs. 20.0	1.56	0.77–3.16	0.22	1.70	0.81–3.56	0.16			

BMI body mass index, *CI* confidence interval, *HR* hazard ration, *IPTW* inverse probability of treatment-weighted, *PSP* primary spontaneous pneumothorax

Table 3 Age-related clinical characteristics of the patients with the PSP who underwent the VATS

Variables	Age < 20 (n = 58)	Age ≥ 20 (n = 97)	P values
Age (years)	16.9 ± 1.5	33.9 ± 13.4	< 0.001
Male, n (%)	53 (91.4)	83 (85.6)	0.32
BMI	18.8 ± 1.7	19.9 ± 2.3	< 0.001
Smoking history, n (%)			< 0.001
Absent	56 (96.6)	38 (39.2)	
Present	2 (3.4)	59 (60.8)	
Operation side, n (%)			0.31
Right	21 (36.2)	44 (45.4)	
Left	37 (63.8)	53 (54.6)	

BMI body mass index, PSP primary spontaneous pneumothorax, VATS video-assisted thoracoscopic surgery

reinforcement of the staple line after VATS bullectomy for the PSP is comparable to mechanical pleurodesis in terms of the prevention of the postoperative recurrence (13.8 vs. 14.2% in 1414 patients at 11 institutions) [6]. Hirai et al. and Hong et al. reported that VATS bullectomy with a polyglycolic acid (PGA) sheet and fibrin glue reduced the postoperative recurrence rate (3.3% in 279 patients and 8.6% in 116 patients, relatively). This method comparatively reduced the postoperative recurrence compared with bullectomy alone [7, 9]. Second, mechanical or chemical pleurodesis may be performed. Rena et al. reported the feasibility and safety of an intraoperative mechanical pleural abrasion for the PSP in 220 patients through a randomized controlled trial. The postoperative recurrence rate was 4.2% [10]. Cardillo et al. described the feasibility of VATS bullectomy and talc poudrage for the postoperative recurrence of the PSP in 861 patients retrospectively. The recurrence rate was 1.73% [8]. Third, hybrid procedures, which include all the above-mentioned methods, may be performed. We described a significant reduction in the postoperative recurrence rate of spontaneous pneumothorax by pleural coating method, using 50% glucose and an absorbable sheet, in 376 patients without severe complications. The recurrence rate was 8.3%. The IPTW method using the propensity score indicated that the procedure significantly prevented the postoperative recurrence ($P=0.014$, hazard ratio 0.15; and $P=0.0038$, hazard ratio 0.23, respectively) [19]. However, the postoperative recurrence was relatively common regardless of these procedures (1.22–14.2%) [6–11, 19]. In particular, the younger patients manifested a higher recurrence rate than the elderly, even if the same procedures were performed intraoperatively due to postoperative bulla neogenesis [16–18]. Nakayama et al. showed that after VATS bullectomy with an absorbable PGA sheet, the younger patients (age < 23 years) manifested a significantly lower postoperative 5-year recurrence-free probability as compared to those aged ≥ 23 years

(age < 23 years, 78.1%; age ≥ 23 years, 93.8%) [16]. Huang et al. described by performing a multivariate analysis that, the younger patients manifested a significant postoperative recurrence factor after VATS bullectomy with mechanical or chemical pleurodesis [17]. Noh et al. reported that the postoperative recurrence rate after a wedge resection was significantly higher in the patients aged ≤ 16 years than that in the elderly patients. They suggested that the VATS wedge resection method might be delayed in younger patients [18].

It has been reported that bulla neogenesis may occur on the staple line and other locations, which are not related to the staple line [12–15]. Cho et al. studied 76 patients who underwent repeated VATS for an ipsilateral recurrent PSP, and reported that, after VATS bullectomy with a covering technique or mechanical pleurodesis, the HRCT findings showed a bulla at the staple line in 26 (34%) patients and a new bulla at a location other than the staple line in 36 (47%) patients [14]. Muramatsu et al. studied 30 patients who manifested the postoperative recurrence after VATS bullectomy alone for the PSP and reported that, the most common factor was the new bulla formation that occurred in 28 patients, 16 of which were apparently related to the staple line and 12 were not related to the staple line [15]. We described that, on the HRCT images, the postoperative bulla neogenesis was detected on the staple line at 22 of 56 sites (39.3%), and 6 of 40 sites (15.0%) in the patients aged < 25 and ≥ 25 years, respectively, with this difference being statistically significant [13].

The tension of the staple line is thought to be the main cause for the development of the postoperative bulla neogenesis on the staple line [12, 13]. Meanwhile, the mechanism and characters of natural bulla neogenesis on other locations have not yet been clarified [3]. It is important that the natural history of bulla neogenesis for the PSP is revealed, so that its management can be decided. However, the healthy individuals, whose lungs are untreated by the VATS, are rarely evaluated by the HRCT to identify natural bulla neogenesis. Meanwhile, for the postoperative evaluation, the HRCT is performed several times on the patients who undergo the VATS. However, it is difficult to evaluate the history of the operational side due to various changes such as the reinforcement of the visceral pleura by the absorbable covering sheet, adhesion, and so on. Therefore, we evaluated the contralateral lung, which was not changed by the operation.

Till date, no classification of bulla neogenesis has been presented. Therefore, we observed from our results that, bulla neogenesis can be divided into two categories clearly: natural bulla neogenesis and postoperative bulla neogenesis near the staple line. Natural bulla neogenesis is defined as the increasing bulla neogenesis on other locations of the PSP, principally occurring in the patients aged < 20 years, regardless of the surgical treatments. Postoperative bulla neogenesis near the staple line is defined as bulla neogenesis,

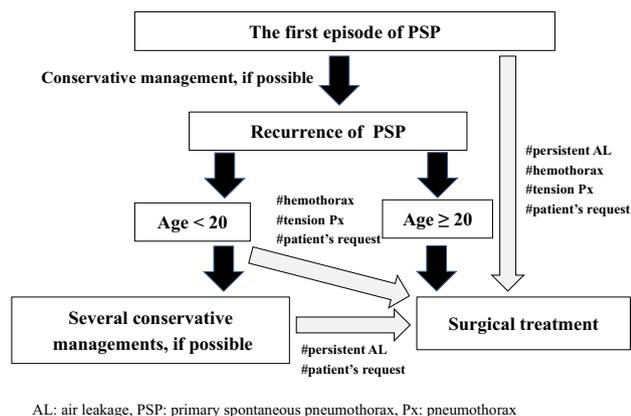


Fig. 2 Flow chart of the management of primary spontaneous pneumothorax

which develops due to the tension of the staple line after the bullectomy. We believe that, the postoperative bulla neogenesis near the staple line may be prevented to some extent by the pleural reinforcement procedures. However, it is difficult to prevent natural bulla neogenesis by the reinforcements until the age of 20 years, because it cannot be predicted where it will appear precisely. Furthermore, we believe that if the complete resection of the bulla and the reinforcement of the staple line are performed after the age of 20 years, the postoperative recurrence rate of the PSP may decrease greatly. Based on this idea, we made the flow chart for the management of the PSP at our institution (Fig. 2).

Our study revealed that the age < 20 years is a significant factor related to natural bulla neogenesis for the PSP. However, our study was retrospective, and there were significant differences in the patients' backgrounds between the ages < 20 and ≥ 20 years. Recently, for the retrospective study, the propensity score was used to adjust the patients' backgrounds [13, 19, 21]. Therefore, for the statistical analysis, the IPTW method using propensity score was employed to evaluate the relationship between natural bulla neogenesis and age, in addition to Kaplan–Meier and Cox regression analyses.

Our study had some limitations. It was carried out for the contralateral lung for those who underwent the ipsilateral VATS, and we adopted a retrospective design. Although we employed the IPTW method using the propensity score to adjust the patients' heterogeneous backgrounds, the unknown factors that might have affected natural bulla neogenesis could not be adjusted. Therefore, we believe that a prospective study of the management of the PSP may be required, which may include the patients aged < 20 years treated with conservative therapies as much as possible, and those aged ≥ 20 years treated with the VATS (Fig. 2).

In conclusion, we think that the surgical treatment may be delayed in the young patients aged < 20 years, because

natural bulla neogenesis is not completely developed by this time.

Acknowledgements The authors thank the staff of the Clinical and Translational Research Center, Kobe University Hospital, for statistical advice.

Funding None declared.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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