


BMJ Open Multicentre, prospective, observational study investigating the most appropriate surgical option that can prevent the recurrence of primary spontaneous pneumothorax after surgery: the PATCH study, protocol

Yuka Kadomatsu ,¹ Hiromu Yoshioka,² Kikuo Shigemitsu,³ Yuji Nomata,⁴ Shunsuke Mori,⁵ Kyoko Hijiya,⁶ Hideki Motoyama,⁷ Yasuhisa Ichikawa,² Kuniyo Sueyoshi,⁸ Toshiki Okasaka,⁹ Ei Miyamoto,¹⁰ Masashi Kobayashi,¹¹ Mamoru Takahashi,¹² Takuji Fujinaga,¹³ Hiroko Takechi,¹⁴ Hiroya Yamagishi,¹⁵ Teruhisa Takuwa,¹⁶ Jun Kobayashi,¹⁷ Jin Sakamoto,¹⁸ Tetsuo Taniguchi,¹⁹ Nobuharu Hanaoka,²⁰ Yoko Kubo,²¹ Toyofumi F Chen-Yoshikawa¹

To cite: Kadomatsu Y, Yoshioka H, Shigemitsu K, *et al*. Multicentre, prospective, observational study investigating the most appropriate surgical option that can prevent the recurrence of primary spontaneous pneumothorax after surgery: the PATCH study, protocol. *BMJ Open* 2021;**11**:e052045. doi:10.1136/bmjopen-2021-052045

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (<http://dx.doi.org/10.1136/bmjopen-2021-052045>).

Received 05 April 2021
Accepted 18 November 2021



© Author(s) (or their employer(s)) 2021. Re-use permitted under CC BY-NC. No commercial re-use. See rights and permissions. Published by BMJ.

For numbered affiliations see end of article.

Correspondence to

Yuka Kadomatsu;
ykadomatsu@med.nagoya-u.ac.jp

ABSTRACT

Introduction Thoracoscopic surgery is performed for refractory or recurrent primary spontaneous pneumothorax (PSP). To reduce postoperative recurrence, additional treatment is occasionally adopted during surgery after bulla resection. However, the most effective method has not been fully elucidated. Furthermore, the preference for additional treatment varies among countries, and its efficacy in preventing recurrence must be evaluated based on settings tailored for the conditions of a specific country. The number of registries collecting detailed data about PSP surgery is limited. Therefore, to address this issue, a prospective multicentre observational study was performed.

Methods and analysis This multicentre, prospective, observational study will enrol 450 participants aged between 16 and 40 years who initially underwent PSP surgery. Data about demographic characteristics, disease and family history, surgical details, and CT scan findings will be collected. Follow-up must be conducted until 3 years after surgery or in the event of recurrence, whichever came first. Patients without recurrence will undergo annual follow-up until 3 years after surgery. The primary outcome is the rate of recurrence within 2 years after surgery. A multivariate analysis will be performed to compare the efficacy of different surgical options. Then, adverse outcomes correlated with various treatments and the feasibility of treatment methods will be compared.

Ethics and dissemination This study was approved by the local ethics committee of all participating centres. The findings will be available in 2025, and they can be used as a basis for clinical decision-making regarding appropriate options for the initial PSP surgery.

Trial registration number NCT04758143.

Strengths and limitations of this study

- This prospective, multicentre, observational study on the recurrence after spontaneous pneumothorax surgery has very detailed clinical, radiographic and surgical data at multiple time points.
- Patients with various additional procedures will be enrolled because treatment depends on the policy of each participating institution.
- Long-term recurrence data for 3 years after surgery and data on the second surgery will be collected through the web-based database to ensure a high-quality follow-up.
- As for limitations, this study is observational and subject to various risks of bias, which will be handled using multivariate analysis.

INTRODUCTION

Primary spontaneous pneumothorax (PSP) is a common disease among young adults. It is characterised by the accumulation of air in the pleural space, which is frequently due to the rupture of a fragile area in the pleura, referred to as bulla or focal regions of emphysema. Moreover, sudden dyspnoea and chest pain are frequently observed. For every 100 000 young people in the population, the incidence rates are 15.5 in men and 3.1 in women.¹ The cumulative probability of spontaneous pneumothorax recurrence rate of PSP within 5 years has been reported to be 20.6% in men and 21.6% in women.¹ Surgical treatment is indicated for intractable cases in which conservative treatment is not sufficient

and recurrence cases. Thoracoscopic wedge resection is the standard surgical procedure for pneumothorax. However, thoracoscopic surgery has a higher recurrence rate than conventional open surgery.² To prevent recurrence after surgery, additional treatments have been sometimes adopted during surgery.

Two previous meta-analyses focusing on additional procedures showed that pleurodesis was more effective than bullectomy alone in preventing recurrence.^{3 4} In Japan, the staple line coverage is the most common additional procedure and is used in approximately 65% of PSP surgeries.⁵ Staple line coverage is a technique to cover the stapling line with absorbable mesh after lung resection and was introduced in the European Respiratory Society task force statement for PSP published in 2015.⁶ There are two main methods: one is to apply the sheet-type absorbable mesh after normal surgical stapling and the other is to reload the absorbable mesh (eg, polyglycolic acid (PGA tube type) into the stapling device.^{7 8}

In Europe, the staple line coverage is not widely performed, and pleurectomy is the most preferred additional procedure, according to the national survey.⁹ Pleurectomy is performed in less than 1% of primary pneumothorax in Japan.⁵ The abovementioned meta-analysis included few studies about the staple line coverage, and its preventive effect was not comprehensively examined.

Prior to this study, we performed a meta-analysis to investigate the preventive effect of the staple line coverage against recurrence.¹⁰ Results showed that the procedure was associated with a reduced recurrence of postoperative pneumothorax in approximately one-quarter of patients. However, the number of prospective studies in this area is limited, and there is a risk of publication bias. Therefore, any additional treatment may have no statistically significant preventive effect on the recurrence of postoperative pneumothorax. Another limitation is that only a few studies had a sufficient follow-up duration, which may underestimate recurrence rates. In addition, complications associated with the coverage method were not reported. There was no detailed information about side effects; hence, further investigation should be conducted.

The strengths of this study are as follows: the annual recurrence check-up and an adequate follow-up period. Participants will be contacted annually to confirm whether there is recurrence of pneumothorax. A prospective randomised controlled trial is the most appropriate study for determining the actual efficacy of the additional procedure. However, a national registry for pneumothorax surgery is not currently available in Japan. To identify the current situation, observational research is the initial step. This study will be the largest trial about treatment options including the coverage method in PSP surgery and will provide comprehensive details about recurrence after surgery.

Objectives

- ▶ Details about pneumothorax surgery, including the coverage method, in Japan should be validated.
- ▶ The recurrence rate and side effects between major treatments will be compared, and the type of treatment considered most appropriate will be investigated.

METHODS AND ANALYSIS

Study design and setting

This multicentre, prospective, observational study was conducted in the department of thoracic surgery under 21 collaborating hospitals in Japan in October 2020. It will include 450 patients requiring PSP surgery. The enrolment of this study started in September 2020 and will end in September 2022. Follow-up of all the patients will be completed in September 2025, and the entire study protocol, including statistical analysis, will end in December 2027.

Informed consent was obtained from the patients. If patients were aged below 20 years, informed consent was obtained both from them and from their guardians as well. The study protocol was approved by the ethics committee of each hospital.

Screening and selection

The potential participants include patients with pneumothorax who will be scheduled to undergo pneumothorax surgery for the first time. Patients who have a history of conservatively treated or chest drainage are also eligible. Generally, indications for definitive treatment including surgery are (1) second episode of PSP, (2) persisting air leak >3–5 days, (3) haemopneumothorax, (4) bilateral pneumothorax and (5) professions at risk (aircraft personnel, divers, etc.).⁸ Based on this fundamental policy, each patient's treatment strategy is determined by the respiratory physician and thoracic surgeon, independent of this clinical trial. After the surgical treatment plan is decided, the attending physician in charge will select the candidates for participation according to the inclusion and exclusion criteria. They will be informed that their decision to participate or refuse the trial does not affect their clinical management, and they can withdraw from the study at any time without risks. Then, patients will be enrolled in the trial after informed consent is obtained.

Inclusion criteria

- ▶ Men and women aged 16–40 years at the date of registration. The upper age limit was set at 40 years due to the higher incidence of underlying lung diseases in patients over 40 years old.¹
- ▶ Patients with PSP, which is diagnosed via chest radiography or chest CT scan, who are scheduled initial surgery.

Exclusion criteria

- ▶ Patients with a history of ipsilateral chest surgery
- ▶ Patients with no lesions found to be treated and no intervention have performed during the surgery

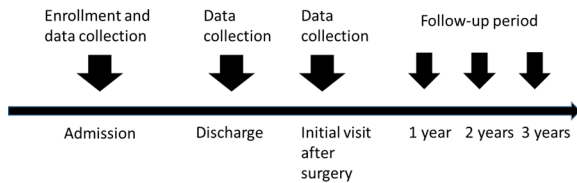


Figure 1 Overview of the PATCH study. Follow-up was performed until 3 years after surgery or in the event of recurrence, whichever came first. PATCH, most preventable surgical option for reducing the recurrence of primary spontaneous pneumothorax after surgery: a prospective cohort study.

- ▶ Secondary pneumothorax caused by acute trauma or iatrogenic or any underlying lung disease (eg, pulmonary emphysema, chronic obstructive pulmonary disease, asthma, etc.)
- ▶ Patients not willing or unable to provide consent for the study

Follow-up assessments

Follow-up will be conducted annually until 3 years after surgery or in the event of recurrence. Although the follow-up survey is performed via a telephone interview, reviewing of medical record and medical examination will be allowed (figure 1). Information about recurrence should be obtained from the patient directly. However, as an alternative, data can be obtained from the parents or guardians.

Study assessment

- ▶ Demographic characteristics such as age, sex, smoking history, comorbidities and medical history.
- ▶ History of treatment for pneumothorax.
- ▶ Family history of pneumothorax.
- ▶ Lesion details such as number and location on preoperative CT scan.
- ▶ Information about treatment for each lesion. To simplify the analysis, the answers were selected, and the following data can be included: bullectomy only, bullectomy using other materials (PGA sheet, pleural blood coating, fibrin glue and cellulose mesh), bullectomy with PGA tube type and material coverage without bullectomy. Surgical procedures that were not included in the predefined category were classified as other and the details of the procedure were collected as free descriptions.
- ▶ Surgical information, duration of surgery and volume of blood loss.
- ▶ Predefined complications
 - Persistent air leakage. Defined as the presence of a chest drain for 5 days or longer.
 - Prolonged fever. Defined as the presence of fever (38°C or higher) or use of an antipyretic for 3 days or longer. However, this excludes cases in which the cause (such as pneumonia, urinary tract infection and wound infection) is evident.

- Early recurrence of pneumothorax. Defined as radiographically confirmed pneumothorax on the same side within 30 days of surgery.

- ▶ Other complications
- ▶ Pneumothorax recurrence. Defined as radiographically confirmed pneumothorax on the same side 30 days after surgery.
- ▶ In recurrent cases, data on the following items were also collected:
 - ▶ Date of recurrence, treatment (chest tube drainage, surgery), chest CT scan findings during recurrence (presence or absence of new bullae on the pretreated site) and operative findings during recurrence (degree of adhesion between the previous resection site and the parietal pleura).

Primary outcome

The primary outcome is recurrence rate of pneumothorax 2 years after surgery for each surgical procedure. However, pneumothorax recurrence within 30 days after surgery is considered a postoperative complication. Recurrence was defined as all cases of pneumothorax on the ipsilateral side of the surgery on radiographic images.

Secondary outcomes

- ▶ Postoperative complications occurring within 30 days after surgery. These include persistent air leakage, presence of a chest drain for 5 days or longer, prolonged fever and recurrence of pneumothorax.
- ▶ Operative time and volume of blood loss
- ▶ Hospital bed days
- ▶ Rate of reoperation due to pneumothorax recurrence
- ▶ Degree of adhesion between the parietal and visceral pleura at the recurrence site of pneumothorax (no adhesion, partial and complete).
- ▶ Recurrence rate of pneumothorax 3 years after surgery for each surgical procedure

Data collection

The data of all participants are stored in a web-based database (REDCap) with limited access and identification code. The data manager checks for data accuracy, and a query is issued to the data entry person of each facility, as necessary. Data are stored until the end of the study, including the statistical analysis period. Then, data files will be deleted, and the REDCap database will no longer be accessible.

Statistical analysis

All continuous data are expressed as mean±SD or medians with IQRs based on the distribution. Categorical data are presented as proportions, frequencies or percentages. Continuous group data are compared using student's t-test or the Mann–Whitney U test in case of skewed variables. The frequencies of categorical variables are compared using the Pearson χ^2 test or Fisher's exact test, as appropriate. Kaplan–Meier curve analysis will be performed to compare the duration of recurrence-free survival.

The Cox proportional hazards for the HR of recurrence among treatment groups. Since this is an observational study, it is estimated that the patient background may vary from procedure to procedure. Therefore, we plan to adjust for sex, age and smoking rate as covariates in the Cox proportional hazards model for the primary outcome. If factors that may affect the choice of procedure will be identified during the data analysis, we will consider performing post-hoc analysis. Missing values will be complemented by contacting the data registrant before analysis if possible. Participants with missing data in the relevant items will be excluded from the analysis. In the analysis of primary outcome, the time-to-event outcome for patients with no/unknown events is censored at the time of the last follow-up. If there are missing variables to be adjusted in the multivariate analysis, the multiple imputation method will be used to supplement the data. A *p* value of <0.05 was considered significant.

Determination of sample size

The sample size calculation is based on the recurrence rate of pneumothorax in previous studies. Based on the annual report on PSP in Japan, we roughly assumed that there were two types of surgery for PSP: lung resection alone group and additional staple line coverage group.⁵ Two years after surgery, the relapse-free survival rates are assumed to be 95% in the staple line coverage group and 84% in the lung resection alone group.^{3,11,12} Moreover, according to the latest annual report, the proportion of each therapy was assumed to be 7:3.⁵ The recurrence within the last 2 years is assumed to be 8.6% based on the recurrence rate and the percentage of each procedure performed.

In the multivariate analysis, according to three fundamental factors (age, sex and smoking status) and additional techniques, 30 recurrent cases were considered necessary. The minimum number of the sample size for the calculation was 348. Considering the dropout rate of 20% during the study period and the fact that approximately 10% of the other techniques are adopted, the required sample size will be 450.

Ethics and dissemination

The study was approved by the local ethics committee of the participating hospitals. A written informed consent was obtained before enrollment. A list of all ethics approvals received as of 5 October 2021 is provided as an online supplemental file 1.

PATIENT and public involvement

The study did not involve any patients and the public in the development, design, conduct, or reporting of the study.

Author affiliations

¹Department of Thoracic Surgery, Nagoya University, Nagoya, Aichi, Japan

²Department of Thoracic Surgery, Japanese Red Cross Aichi Medical Center Nagoya Daini Hospital, Nagoya, Aichi, Japan

³Department of Thoracic Surgery, Ogaki Municipal Hospital, Ogaki, Gifu, Japan

⁴Department of Thoracic Surgery, Toyohashi Municipal Hospital, Toyohashi, Aichi, Japan

⁵Department of Thoracic Surgery, Yokkaichi Municipal Hospital, Yokkaichi, Mie, Japan

⁶Department of Thoracic Surgery, Shizuoka City Shizuoka Hospital, Shizuoka, Shizuoka, Japan

⁷Department of Thoracic Surgery, Kobe City Nishi-Kobe Medical Center, Kobe, Hyogo, Japan

⁸Department of Thoracic Surgery, St. Luke's International Hospital, Tokyo, Japan

⁹Department of Thoracic Surgery, Toyota Kosei Hospital, Toyota, Aichi, Japan

¹⁰Department of Thoracic Surgery, Tenri Hospital, Tenri, Nara, Japan

¹¹Department of Thoracic Surgery, Kurashiki Central Hospital, Kurashiki, Okayama, Japan

¹²Department of Thoracic Surgery, Kyoto Katsura Hospital, Kyoto, Kyoto, Japan

¹³Department of Thoracic Surgery, National Hospital Organization Nagara Medical Center, Gifu, Gifu, Japan

¹⁴Department of Thoracic Surgery, Hyogo Prefectural Amagasaki General Medical Center, Amagasaki, Hyogo, Japan

¹⁵Department of Chest Surgery, Japanese Red Cross Fukui Hospital, Fukui, Fukui, Japan

¹⁶Department of Thoracic Surgery, Osakafu Saiseikai Noe Hospital, Osaka, Japan

¹⁷Department of Thoracic Surgery, Shimada Municipal Hospital, Shimada, Shizuoka, Japan

¹⁸Department of Thoracic Surgery, Shimane Prefectural Central Hospital, Izumo, Shimane, Japan

¹⁹Department of Thoracic Surgery, Komaki City Hospital, Komaki, Aichi, Japan

²⁰Department of Thoracic Surgery, Osaka Medical College Hospital, Takatsuki, Osaka, Japan

²¹Department of Preventive Medicine, Nagoya University Graduate School of Medicine, Nagoya, Aichi, Japan

Contributors YK and TFC-Y conceived the idea for the study. YK wrote the original study protocol. HYo, KSh, YN, SM, KH, HM, YI, KSu, TO, EM, MK, MT, TF, HT, HYa, TT, JK, JS, TT and NH contributed reviewed and commented on study procedures, and collected data resources. YK contributed data curation and statistical management. TFC-Y supervised the study. All authors contributed to the writing of the manuscript and agreed with submission of the final version for publication.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

Supplemental material This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by BMJ. BMJ disclaims all liability and responsibility arising from any reliance placed on the content. Where the content includes any translated material, BMJ does not warrant the accuracy and reliability of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>.

ORCID iD

Yuka Kadomatsu <http://orcid.org/0000-0002-3045-9475>

REFERENCES

- Hallifax RJ, Goldacre R, Landray MJ, *et al*. Trends in the incidence and recurrence of Inpatient-Treated spontaneous pneumothorax, 1968-2016. *JAMA* 2018;320:1471-80.
- Nakanishi K. Long-term effect of a thoracoscopic stapled bullectomy alone for preventing the recurrence of primary spontaneous pneumothorax. *Surg Today* 2009;39:553-7.

- 3 Vuong NL, Elshafay A, Thao LP, *et al*. Efficacy of treatments in primary spontaneous pneumothorax: a systematic review and network meta-analysis of randomized clinical trials. *Respir Med* 2018;137:152–66.
- 4 Sudduth CL, Shinnick JK, Geng Z, *et al*. Optimal surgical technique in spontaneous pneumothorax: a systematic review and meta-analysis. *J Surg Res* 2017;210:32–46.
- 5 , Shimizu H, Okada M, *et al*. Committee for Scientific Affairs, The Japanese Association for Thoracic Surgery. Thoracic and cardiovascular surgeries in Japan during 2017 : Annual report by the Japanese Association for Thoracic Surgery. *Gen Thorac Cardiovasc Surg* 2020;68:414–49.
- 6 Tschopp J-M, Bintcliffe O, Astoul P, *et al*. ERS task force statement: diagnosis and treatment of primary spontaneous pneumothorax. *Eur Respir J* 2015;46:321–35.
- 7 Kim KS. Polyglycolic acid sheet with fibrin glue technique without pleural abrasion in uniportal VATS for primary spontaneous pneumothorax. *J Thorac Dis* 2020;12:690–5.
- 8 Nakamura T, Suzuki K, Mochizuki T, *et al*. An evaluation of the surgical morbidity of polyglycolic acid felt in pulmonary resections. *Surg Today* 2010;40:734–7.
- 9 Asghar Nawaz M, Apparau D, Zacharias J, *et al*. Approach to pneumothorax surgery: a national survey of current UK practice. *Asian Cardiovasc Thorac Ann* 2019;27:180–6.
- 10 Kadomatsu Y, Fukui T, Mori S, *et al*. Polyglycolic acid sheet covering to prevent recurrence after surgery for spontaneous pneumothorax: a meta-analysis. *Sci Rep* 2021;11:3392.
- 11 Hirai K, Kawashima T, Takeuchi S, *et al*. Covering the staple line with a polyglycolic acid sheet after bullectomy for primary spontaneous pneumothorax prevents postoperative recurrent pneumothorax. *J Thorac Dis* 2015;7:1978–85.
- 12 Ozawa Y, Sakai M, Ichimura H. Covering the staple line with polyglycolic acid sheet versus oxidized regenerated cellulose mesh after thoracoscopic bullectomy for primary spontaneous pneumothorax. *Gen Thorac Cardiovasc Surg* 2018;66:419–24.