Editorial Commentary

Primary spontaneous pneumothorax: time for surgery at first episode?

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Primary spontaneous pneumothorax (PSP) generally occurs in healthy young people between the ages of 10 and 30 years (1). It remains an important global health problem with an annual incidence of 7.4–18 (age-adjusted incidence) and 1.2–6 cases per 100,000 population, among men and women respectively. The pathogenesis of PSP is still unclear and the presence of blebs/bullae or macro/microscopical pleural modification (e.g., "pleural porosity") are currently the most accredited causes. Moreover, risk factors for PSP include tall-and-thin body habitus, male gender, and smoking (2). Without intervention, recurrence rates after PSP are variably reported, with studies quoting rates as low as 14% (3) and as high as 49% (4) at 1 year, up to 50% in patients followed-up for 5 years (5,6). According to Swedish cost analysis data, the economic burden of PSP approximates 130 million USD/year with around 20,000 individuals affected per year (7).

While the treatment of choice in case of recurrent or complicated spontaneous pneumothorax (PTX) is clearly established (8-10), the management of patients with PSP at the first episode is still an open debate.

In the first episodes of PSP, simple aspiration or pleural drainage are the current settled first line therapies with an immediate success rate of 59.3% and 68% respectively (11), whereas several studies have been conducted on the advantages and disadvantages of the conservative approach (thoracentesis and pleural drainage) versus surgery.

Analysing advantages and disadvantages of intercostal drainage (ITD) versus thoracentesis, a systematic review and meta-analysis by Kim *et al.*, and a Cochrane systematic review by Carson were conducted in 2017 (7,12). These studies showed that whereas ITD was more effective than simple aspiration in the timely resolution of PTX with higher rates of immediate success, the hospitalization was shorter with aspiration and the recurrence rate within 1 year did not vary between the initial approaches.

As regards the surgical approach, according to a recent systematic review and network meta-analysis of randomized clinical trials, in patients with persistent or recurrent PSP, pleural abrasion (mechanical pleurodesis) or pleurectomy performed by thoracotomy is the most effective treatment to prevent recurrent PTX and video-assisted thoracoscopic surgery (VATS) with talc poudrage (chemical pleurodesis) is related with noteworthy reduction in relapses compared to VATS with mechanical pleurodesis. However, VATS has significantly less complications compared with thoracotomy and is superior to it in terms of length of hospital stay, pain relief and compromised lung function (13).

The two most recent International guidelines, published

by The British Thoracic Society in 2010 and The European Respiratory Society in 2015, typically advocate surgical treatment for patients with non-resolving PTX, for a recurrent episode, haemopneumothorax, bilateral pneumothoraces or for occupations at risk. Several retrospective studies have revealed that, in patients with first episode PSP, VATS provide improved outcomes in terms of duration of chest tube, hospital stay and recurrence rates (14). Moreover, several authors have pointed out that young patients would willingly undergo surgery rather than live with the uncertainty of recurrences (15). Though in the future the indication for definitive treatment may enlarge to patients expected to have a high risk of recurrence after an initial episode, there is a lack of randomized clinical trial evidence.

Winnie Hedevang Olesen from Odense, Denmark, led a recently published randomized controlled, multicentre trial at three public university-based cardiothoracic departments (Odense University Hospital, Aarhus University Hospital, Aalborg University Hospital) to assess whether patients may benefit from surgery following their first PSP episode. Eligible patients were young and healthy individuals between 18 and 40 years of age admitted to the hospital within a 7-year period (01/08/2009–04/11/2016). On admittance at either of the hospitals, appointed local investigators oversaw the initial treatment of the first episode of PSP and they ascertained that chest tube drainage was indicated according to the standard of care for acute PTX. Then all patients were screened, the eligible ones were identified and informed by the investigators. Out of 457 patients admitted with PSP, 373 patients met the inclusion criteria, but ultimately only 181 were enrolled. In more detail 59/373 were not willing to take part in the trial; 81/373 eligible patients were inexplicably not requested to participate; 51/373 were excluded because referring to the regional cardiothoracic centre belatedly (>5 days after the episode); 1/373 patient underwent primary surgery without prior computed tomography (CT) because of an incomplete lung re-expansion after ITD and then was excluded. Of the 181 included patients, 151 were men and 30 women (ratio =5.0). According to the study protocol, all enrolled patients underwent multislice 64-row high-resolution computed tomography (HRCT) without contrast (spiral acquisition CT-scan) to discover the presence and actual size of blebs/bullae, that were defined as air-filled lesions <1 and ≥1 cm respectively. Eighty-eight patients showed blebs: 50 were randomly allocated to chest tube treatment and 38 to VATS. Ninety-three patients had bullae: 43 were randomly assigned to chest tube placing and 50 to VATS. Importantly it should be noted, because the authors did not use block randomization, the patients were not allocated equally between the 4 sub-groups.

VATS was performed according to a 3-port technique with a 10-mm inferior camera port and included bullectomy of all visible blebs/bullae, and if none were discovered, resection of the apical part of the upper lobe was executed; a mechanical pleurodesis of all visible parietal pleura was associated.

The analysed variables were recurrence (yes/no), allocated treatment (conventional chest tube treatment or VATS), bulla size (<1 or >1 cm) and referral cardiothoracic centre.

In 12 (13%) patients assigned to the conservative treatment arm, more than one chest tube was placed during their first admission, and in 38 (42%) patients, suction was applied to completely expand the lung. Eight patients crossed over from conservative arm to VATS due to prolonged air leakage even though proper ITD treatment. Three patients crossed from the surgical cohort to conservative one due to medical reasons. Two patients did not undergo surgery due to severe anxiety. The primary end point of the RCT was ipsilateral recurrent spontaneous PTX detected by chest radiography. Secondary end points were complications and length of hospital stay. The interim analysis reported in the paper was performed when the first 150 registered patients had concluded 1-year follow-up given that all four subgroups had at least 50% of the intended inclusions: the median follow-up of all 181 included patients was 59 (range, 9–97) months. Analysing the recurrence rate, 43 (23%) patients experimented ipsilateral recurrence: 32 (34%) patients in conservative treatment arm versus 11 (13%) patients in VATS arm. The multivariate analysis revealed that surgery had a significant impact on overall recurrence comparing with conventional chest tube treatment: 13% *vs.* 34% respectively (P=0.0012), with no differences between the three-referral cardiothoracic centres (P=0.35). The unadjusted Cox regression analysis stratified by the four subgroups revealed a risk reduction in recurrence in patients with bullae ≥1 cm who underwent primary VATS [hazard ratio (HR) 0.3, P=0.014], but only tendency towards statistical significance in patients with blebs <1 cm, indicating that the presence of large-scale dystrophic lesions may be an independent risk factor for recurrence.

Stratifying by approach, the authors detected a higher recurrence rate in patients with large bullae conservatively

treated. The Cox regression analysis adjusted by assigned treatment and bullae size of all conservatively managed patients versus surgically treated, showed that the allocation to conservative treatment was the only significant predictor of recurrence (P=0.0011).

The authors also detected a trend towards larger bullae being at higher risk of recurrence (HR 2.4, P=0.045): conservatively treated patients with bullae ≥2 cm were identified as high-risk population (HR 4.4, P=0.045). The presence of blebs and bullae on CT in predicting recurrence is controversial. Four previous studies have given conflicting results, with two finding no association (3,16) and two finding an association (17,18). A recent meta-analysis found that CT scoring systems could not reliably predict recurrence in PTX study (19). Interestingly, the scoring system with the most encouraging results, the dystrophic severity score (DSS), was not found to significantly predict recurrence in this study.

Length of hospital stay at first admittance was not significantly different (P=0.42) following either treatment: 4.1 days (95% CI: 3.4–4.8) in the surgical group and 3.8 days (95% CI: 3.0–4.3) after ITD management. It should be noted that when time in hospital for patients readmitted for their elective surgery was included, surgical patients had a significantly longer median length of stay of 7.1 days (95% CI: 6.4–7.9, P<0.001).

Surgery was not without complications, with three (3%) surgical patients undergoing reintervention due to bleeding from the intercostal arteries in one of the portholes. No patient related outcomes were reported, although it is stated that this will be published at a later date. Presently it is unclear if the amount of pain experience by the patients were comparable. Earlier observational work of 185 patients with PSP who underwent VATS demonstrated that 27% of patients had pain post-op, with 16.5% having pain for longer than 12 weeks (20).

Several aspects of the methodology deserve attention. Totally, 276 of the 457 (60%) of the patients assessed for eligibility were excluded, with 84 not meeting inclusion criteria and 81 omitted for unknown reasons. The protocol stated that patients who presented with small, asymptomatic pneumothoraces were treated with observation only, and it remains unclear how many were excluded for this reason. It has been proposed that the majority of PSPs can be managed with observation, with a recently completed randomised trial examining this issue due to be published shortly (21). Additionally, 51 patients were excluded if the patients were not referred for surgery for more than five days, and one patient was excluded due to inadequate lung re-expansion with initial chest tube drainage. The exclusion of these subjects are possible confounders, particularly as they did not receive a HRCT, and it is unclear whether the positive predictive value related to large bullae on HRCT is applicable to all patients. The paper suggests that surgery could be more cost-effective, despite longer length of stays, due to higher recurrence rates in the conservatively managed cohort. However, this is speculative, as no formal cost-effective analysis was performed, and further work is required. At interim analysis, the results strongly favoured VATS over conservative treatment in all three cardiothoracic centres, and according to the protocol, the Authors decided to stop enrolling patients for ethical reasons. This study showed VATS to be associated with a very low operative risk, surgical trauma, and complication rate with a short in hospital stay and a recurrence rate much lower than the standard treatment (ITD). Interestingly the rate of recurrence showed in the Danish RCT (13%) was higher than that reported in the literature (*Table 1*). In a paper reporting VATS talc poudrage in 1,415 patients with PSP, we showed a recurrence rate of 1.9% (5), other studies have reported a recurrence rate around 3–4% (*Table 1*) which compared to the high recurrence rate after drainage only (17–54%) (4,6), could give much more authority to the approach proposed by the present paper.

Olesen and his Danish co-workers should be commended for an excellent work, performing an RCT in a difficult study population, which has improved our understanding. Whilst these results are very encouraging, it must be recognised that the majority of patients with PSP will not develop a recurrence, with a recent meta-analysis of studies of medically managed patients (both first and subsequent presentation) demonstrating a recurrence rate of 32% (19). This study shows that with a number need to treat (NNT) of 4.8, five patients will have to undergo surgical procedure to avoid one recurrence. This information, together with the unpublished patient-related outcomes of pains and anxiety levels should help clinicians and patients make an informed decision.

In conclusion, the RCT by Olesen and co-workers demonstrates decreased recurrence rates with surgery at first occurrence of PSP (NNT 4.8) and identifies CT criteria, that could recognise which patients will benefit most. We eagerly await their publication of quality of life outcomes, which should help inform patient choice.

Table 1 Recurrence rate of PSP treated by VATS approach

Author	Year	Number of patients	Intervention	Follow-up (months)	Recurrence (%)	Journal, reference
Kutluk	2018	135	Wedge resection + pleurectomy		5	*Thorac Cardiovsc Surg* 2018;66:589-94
Cardillo	2016	720	Chemical pleurodesis	24	0.69	*Thorax* 2016;71:847-53
Cardillo	2016	618	Wedge resection + chemical pleurodesis	24	2.58	*Thorax* 2016;71:847-53
Imperatori	2015	134	Wedge resection + pleurectomy	79	5.97	*ICVTS* 2015;20:647-53
Min	2014	144	Wedge resection	18	6.25	*Ann Thorac Surg* 2014;98:1790-6
Min	2014	145	Wedge resection + pleural abrasion	18	5.52	*Ann Thorac Surg* 2014;98:1790-6
Lee	2013	128	Wedge resection + pleural abrasion	24	11.72	*Ann Thorac Surg* 2013;95:1919-23
Chen	2012	80	Wedge + pleurectomy	26.9	3.75	*Ann Surg* 2012;255:440-5
Chen	2012	80	Wedge resection + pleural abrasion + chemical pleurodesis	26.9	3.75	*Ann Surg* 2012;255:440-5
Chou	2012	89	Wedge resection + pleural abrasion	69.15	1.12	*MITAT* 2012;21:168-72
Park	2012	92	Wedge resection	92	6.52	*SLEPT* 2012;22:62-4
Park	2012	165	Wedge resection + pleural abrasion	66.2	7.27	*SLEPT* 2012;22:62-4
Muramatsu	2011	357	Wedge resection	51.2	8.40	*ASJSUR* 2011;34:69-73
Shaikhrezai	2011	41	Wedge resection + pleurectomy	73	0	*EJCTS* 2011;40:120-3
Shaikhrezai	2011	255	Wedge resection + pleural abrasion	73	3.14	*EJCTS* 2011;40:120-3
Shaikhrezai	2011	189	Wedge resection+ chemical pleurodesis	73	1.06	EJCTS 2011;40:120-3
Chou	2009	62	Wedge resection + pleural abrasion	34	0	*MITAT* 2009;18:4;221-4
Marcheix	2007	603	Wedge resection + chemical pleurodesis		1.49	*EJCTS* 2007;1106-9
Cardillo	2006	290	Chemical pleurodesis	96	2.41	*JTCVS* 2006;131:322-8
Cardillo	2006	515	Wedge resection + chemical pleurodesis	96	1.35	*JTCVS* 2006;131:322-8
Bobbio	2006	67	Wedge resection + pleural abrasion	76	2.99	*EJCTS* 2006 ;29:6-8
Chen	2004	51	Wedge resection + pleural abrasion	39	9.8	*Chest* 2004;125:50-5
Chen	2004	313	Wedge resection + pleural abrasion + chemical pleurodesis	39	2.88	*Chest* 2004;125:50-5
Gossot	2004	111	Wedge resection + pleural abrasion	36.5	3.60	*Surg End* 2004;18:466-71
Lang-Lazdunski	2003	182	Wedge resection + pleural abrasion	84	2.75	*Ann Thorac Surg* 2003;75:960-5
Margolis	2003	156	Wedge resection + pleural abrasion + chemical pleurodesis	62	0	*Ann Thorac Surg* 2003;76:1661-3
Cardillo	2000	122	Wedge resection + pleurectomy	38	9.8	*Ann Thorac Surg* 2000;69:357-62
Cardillo	2000	217	Wedge resection + chemical pleurodesis	38	0.9	*Ann Thorac Surg* 2000;69:357-62

PSP, primary spontaneous pneumothorax; VATS, video-assisted thoracoscopic surgery.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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