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Stellenwert der Video-assistierten Thorakoskopischen Chirurgie (VATS) in der Therapie des Primären und Sekundären Spontanpneumothorax

Habilitationsschrift
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Abbreviations

ACCP	American college of chest physicians
BMI	body mass index
BTS	British thoracic society
Ch.	Charrière
CI	confidence interval
COPD	chronic obstructive pulmonary disease
CT	chest tube
CT scan	computerized tomography scan
DRG	diagnosis related groups
ECOG	eastern cooperative oncology group
FEV1	forced expiratory volume-one second
Fig.	figure
FVC	forced vital capacity
HR	hazard ratio
HR-QoL	health-related quality of life
LLN	lower limit of normal
LOS	length of hospital stay
MCS	mental component score
PA	posterioranterior
PCS	physical component score
PSP	primary spontaneous pneumothorax
RFS	recurrence-free survival
SF-36	short-form 36
SSP	secondary spontaneous pneumothorax
VATS	video-assisted thoracoscopic surgery
VBPP	VATS bullectomy with partial pleurectomy
VPPB	VATS mit partieller Pleurektomie und Bullektomie
2-P (2P-) VATS	two-port VATS
3-P (3P-) VATS	three-port VATS

Figures

1. Introduction

1.1 Primary spontaneous pneumothorax (PSP)

Primary spontaneous pneumothorax (PSP) describes the presence of air within the pleural space of young patients (usually under 45 years of age) without preceding trauma or underlying pulmonary disease [1]. To date, PSP remains a significant global health problem, as it is associated with high rates of hospital readmission due to recurrent disease and considerable associated healthcare costs. It is a rare disease with a reported incidence of 1-9.8 cases per 100.000 individuals per year in females and 7-24 cases per 100.000 individuals per year in males [2, 3].

1.1.1. Etiology and predisposition factors

The exact etiology of primary spontaneous pneumothorax (PSP) is hitherto unknown. In most cases, PSP occurs from the rupture of a small subpleural bleb or, of a bulla. However, the pathogenesis of blebs or bullae and cause of their rupture remains controversial. In a recent study, distension of emphysematous bullae was reported to cause extreme thinning and reduction of the surface tension of their walls and thus promoting rupture [4]. Although the rupture of a subpleural bleb or, of bulla is the most reported cause of PSP, alternative explanations such as degradation of elastic fibres of the lungs due to smoking-related influx of neutrophils and macrophages are available [2, 5].

Primary spontaneous pneumothorax (PSP) typically occur in tall, thin young patients [6]. Interestingly, in the literature, several clinicopathological parameters have been well-reported as potential risk factors contributing to the occurrence of PSP. One of the most important risk factor is tobacco smoking. In large

retrospective studies [2, 7] tobacco smokers were reported with significantly increased risk of spontaneous pneumothorax occurrence compared with non-smokers. Additionally, male sex was observed in these studies as potential risk factor compared to female sex. Other reported predisposition factors include cannabis smoking [8, 9], anatomical abnormalities of the bronchial tree [10], hereditary predisposition [11], thoracic scoliosis [12], ectomorphic physiognomy with more negative intrapleural pressures [13], low body mass index and caloric restriction [14, 15] and abnormal connective tissue [16, 17].

1.1.2. Clinical presentation and diagnosis of primary spontaneous pneumothorax (PSP)

The onset of clinical symptoms commonly occur while the patients are at rest. In most cases, ipsilateral pleuritic chest pain or acute dyspnea are the predominant symptoms. The chest pain may be minimal or severe, and might resolve within 24 hour even if the pneumothorax remains untreated [2]. In some cases, the chest pain are absent. Depending on the size of the pneumothorax, affected patients might have either a normal clinical examination (in case of a small pneumothorax) or clinical conspicuities such as hyperresonant percussion note, decreased movement of the chest wall, reduced fremitus (in case of large pneumothorax) as well as hemodynamic compromise such as tachycardia and hypotension (a case of a tension pneumothorax). To determine the size of the pneumothorax, the actual German S3 guidelines [1] recommend the regression formula derived from the method of Collins [18] (Figure 1). According to the guidelines, a spontaneous pneumothorax (SP) is considered as large when the sum of the interpleural distances derived from the Collins method is ≥4 cm (≥ 20 %).

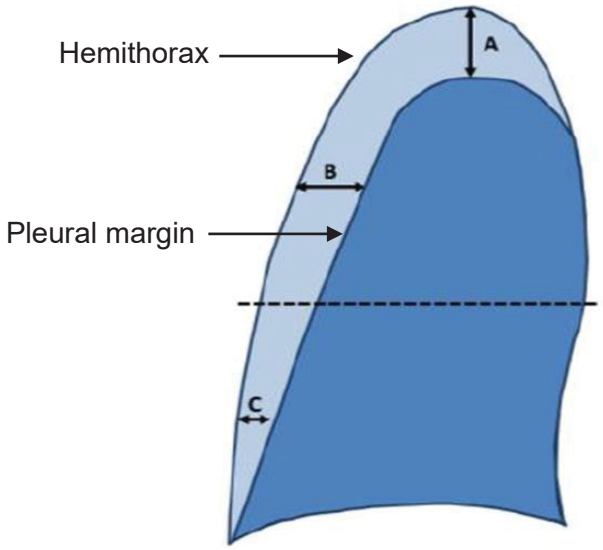

Figure 1: *Diagram showing location of interpleural distance measurements. Sum of interpleural distances = A+B+C. Accurate estimation of percentage pneumothorax size is calculated from the Collins formula: percentage (%) = 4.2 + [4.7 x (A+ B+ C)]. Modified from [18].*

For patients with suspected PSP, the actual guidelines [1, 19-21] recommend at presentation a posterioranterior (PA) inspiratory chest radiograph obtained with the patient in an upright position. Although a computed tomography (CT scan) is more sensitive than a chest radiograph in the detection of a pneumothorax, it is not required in the most cases, as the diagnosis can be clearly made on a chest radiograph [21]. Additionally, high radiation dose should be avoided, especially due the young patient population. However, a CT scan is recommended for complicated

cases (persistent air leak after chest tube drainage, initial hemopneumothorax or recurrent disease) and prior to surgery to determine the extent of a bullous disease.

1.2. Secondary spontaneous pneumothorax (SSP)

In contrast to primary spontaneous pneumothorax (PSP), secondary spontaneous pneumothorax (SSP) affects patients with an underlying pulmonary disease. The most common cause, accounting for approximately 57% of the cases is the chronic obstructive pulmonary disease (COPD) [22]. In most cases, the patients are 45 years of age or older [1]. The risk of SSP seems to increase with higher COPD stage, with highest risk reported particularly in cases with emphysema and cystic fibrosis [23]. Compared with PPS, SSP is associated with high morbidity and mortality rates due to the underlying pulmonary disease. The incidence of SSP has been reported with approximately 2.0 and 6.3 cases per 100,000 individuals per year in females and males, respectively [24].

1.2.1. Etiological causes of secondary spontaneous pneumothorax (SSP)

As described above, chronic obstructive pulmonary disease (COPD) is the main etiological cause of SSP. Other causes of SSP are summarized in Table 1.

Table 1. Other typical causes of SSP

Category	**Underlying pulmonary disease**
Airway disease	Severe asthma Cystic fibrosis
Infectious lung disease	Pneumocystis carinii pneumonia Tuberculosis

	Necrotising pneumonia
Interstitial lung disease	Idiopathic pulmonary fibrosis Sarcoidosis Histiocytosis X Lymphangioleiomyomatosis
Malignant disease	Lung cancer Sarcoma
Connective tissue disease	Rheumatoid arthritis Scleroderma Ankylosing spondylitis Marfan's syndrome Ehlers Danlos syndrom

***Table** 1 shows other frequent or typical causes of secondary spontaneous pneumothorax. Modified from [5].*

1.2.2 Clinical presentation and diagnosis of secondary Spontaneous pneumothorax (SSP)

Compared with primary spontaneous pneumothorax (PSP), secondary spontaneous pneumothorax (SSP) is a potential life-threatening condition due to its cardiopulmonary compromise [25, 26]. Therefore, immediate diagnosis and treatment is mandatory. At presentation, dyspnea is the main clinical symptom. Other clinical symptoms such as chest pain, hypoxaemia, cyanosis and hypercapnia might be present.

Similar to primary spontaneous pneumothorax (PSP), a PA chest radiograph confirms the diagnosis in most cases. However, for patients with large or giant bullae, diagnosis of pneumothorax on a chest radiograph might be difficult,

necessitating a computed tomography (CT scan) for confirmation. Of note, the actual German S3 guidelines [1] recommend a CT scan for diagnosis of SSP, as it is more sensitive to detect the etiological cause of SSP.

1.3. Risk factors for recurrent disease in primary and secondary spontaneous pneumothorax

Rates of recurrent primary spontaneous pneumothorax (PSP) are heterogeneously reported in the literature. Recurrences rates range from 16 to 54% depending on the initial treatment, with most recurrences occurring within the first two year [27-29]. For PSP, smoking (tobacco and cannabis) has been extensively reported to correlate with high risk of disease recurrence [26, 28]. Further reported risk factors for recurrent disease of PSP include male gender, a large pneumothorax size, history of contralateral pneumothorax and treatment modality as well as the pleurodesis technique implemented [27, 30-34].

For patients with secondary spontaneous pneumothorax (SPS), recurrent disease depends on the extent of the underlying pulmonary disease. Due to the underlying pulmonary disease, patients with SSP experience more recurrent disease compared with PSP patients. For SSP, recurrence rates of up to 80% have been reported [28, 35, 36]. However, patients with chronic obstructive pulmonary disease (COPD) are more affected by recurrent disease and the rate of recurrence seems to increases with higher COPD stage [23].

1.4. Treatment modality and treatment goals

a) Primary spontaneous pneumothorax (PSP)

At first episode of PSP, the primary treatment goal is the evacuation of air from the pleural space (if necessary) with consecutive relief of pain or dyspnea. Secondly, measures to prevent recurrence should be undertaken.

1. The role of conservative treatment

The role of a conservative approach (clinical observation without intervention) to manage PSP depends not only on the clinical symptoms of the patients, but also on the size of the pneumothorax. However, the recommendation for conservative approach differs within the international guidelines. The current guidelines of the British Thoracic Society [19] and a recently published report (publication year 2020) in *The New England Journal of Medicine* of Brown et al [37] predominantly recommend conservative treatment based strongly on the clinical symptoms and not on the size of the pneumothorax. In contrast, the actual German S3 guidelines [1] strongly recommend interventional treatment (needle aspiration or thoracic drain) for PSP patients with dyspnea irrespective of the initial pneumothorax size. Only for patients without respiratory distress and with a small size of the pneumothorax measured according to the regression formula of Collins [18], a conservative approach is recommended. Moreover, the American College of Chest Physicians (ACCP) Delphi consensus statement [20] recommend irrespective of the symptoms, chest tube drain placement for any pneumothorax larger than 20% of the hemithorax.

2. The role of percutaneous needle aspiration and thoracic drain

The evacuation of air from the pleural space can be performed with percutaneous needle aspiration or placement of a chest drain. The actual German S3 guidelines [1] recommend both needle aspiration and a small-bore chest drain as initial treatment for symptomatic PSP patients. The British Thoracic Society (BTS) emphasise on needle aspiration as initial intervention in patients with large or symptomatic PSP [21]. Interestingly, the American College of Chest Physicians (ACCP) Delphi consensus statement does not recommend needle aspiration for any patient. Of note, treatment failure following needle aspiration is high has been reported with rates between 25-50%.[38, 39]. After unsuccessful treatment with needle aspiration, the above guidelines recommend the insertion of a chest drain [1, 19]. However, treatment with a chest tube drain has been reported frequently to be associated with high rates of PSP recurrence [30, 33, 34, 40].

3. The role of surgical treatment (Thoracotomy and VATS)

The primary goal of surgery is to prevent recurrent disease. According to the international guidelines [1, 19-21] surgery should be recommended for patients with recurrent disease or persistent air leak after chest tube drain placement. Acute indication for initial surgical treatment include hemopneumothorax and bilateral pneumothorax. The surgical treatment should be cost-effective and evidence based. In the literature several surgical and pleurodesis techniques to prevent recurrence have been reported. Depending on the surgical method implemented, different recurrence rates and patient outcomes including

morbidity, postoperative pain, length of hospital stay (LOS) and quality of life have been reported.

In the last decades, surgical treatment has evolved from the traditionally used open thoracotomy to nowadays well-established video-assisted thoracoscopic surgery (VATS). In previous studies, open thoracotomy for PSP was reported with lower recurrence rates (0-5%) compared to VATS alone (0-10%) [1]. However, open thoracotomy was associated with significantly high rates of morbidity and mortality and increased postoperative pain as well as prolonged length of hospital stay (LOS).

Due to the low recurrence rates and favourable postoperative patient outcome, the actual German S3 guidelines, British Thoracic Society (BTS) guidelines and American College of Chest Physicians (ACCP) Delphi consensus statement recommend for surgical treatment of PSP, VATS in combination with a pleurodesis technique to prevent recurrence. The aim of pleurodesis is to achieve pleural symphysis and thus preventing recurrence. Pleurodesis can be performed chemically or mechanically. For chemical pleurodesis, a chemical irritant is applied during VATS. There are several chemical agents suitable for chemical pleurodesis (e.g. talc, tetracycline, minocycline, blood patch, iodine, picibanil (OK432)). However, the most commonly used chemical agent in Europe is talc, which can be administered as poudrage [21]. Mechanical pleurodesis can be achieved by performing mechanical abrasion and apical or partial pleurectomy. Depending on which type of pleurodesis used during VATS, reported recurrence rates vary from 0-29.2%, with Talc poudrage and partial pleurectomy yielding the best results [1, 31, 41, 42].

To date, it is still a matter of debate, whether VATS (in combination with pleurodesis) should be offered at first episode of PSP. Although not recommended as initial treatment in international guidelines, several studies have reported better outcomes and reduced socioeconomic burden for the patients and healthcare system following initial VATS instead of chest tube treatment [43-47]. However, further studies are certainly needed to support these observations and to establish them in the guidelines.

4. *The role of VATS with mechanical pleurodesis as definitive treatment and recurrence prevention*

According to the international guidelines, VATS should be combined with a pleurodesis technique to reduce recurrence. Regarding mechanical pleurodesis, various methods for its achievement such as apical pleurectomy, pleural abrasion and partial pleurectomy are described in the literature. Of all these mechanical pleurodesis techniques, VATS in combination with partial pleurectomy and bullectomy when blebs or bullae are evident have been reported with the lowest (short and medium term) rate of recurrence [1, 31, 41, 42]. However, long-term studies that elucidate the efficacy of VATS – partial pleurectomy are limited in the literature. Nonetheless, the actual German S3 guidelines strongly recommend partial pleurectomy or talc poudrage (to reduce the risk of recurrence in VATS) with bullectomy for blebs as surgical treatment of PSP. Therefore, further long-term studies are needed to confirm the above observation after VATS – partial pleurectomy and bullectomy.

5. Role of the number of port - access for VATS

In the last years, VATS (video-assisted thoracoscopic surgery) for PSP has evolved from the standard three- port-access (three port VATS) to a lower number of port-access (two- port VATS and uniportal VATS). Although three port VATS offers better feasibility in some cases, it has been described to be associated with more postoperative pain, prolonged length of hospital stay and with unfavourable surgical outcome in some cases compared with uniportal or two port VATS [48-52]. In summary, the evolving treatment strategy nowadays is to treat PSP patient with less port - accesses while performing VATS due to better postoperative outcomes and higher patient satisfaction.

b) Secondary spontaneous pneumothorax (SSP)

The treatment of patients with SSP requires a multimodal therapy concept. The challenging therapy aspect relies not only on the treatment of the pneumothorax, but also on the treatment of the underlying pulmonary disease [53]. The main treatment goal at presentation is the immediately evacuation of air from the pleural space, as these patients commonly present with chest pain, dyspnea and reduced cardiopulmonary reserve.

1. The role of conservative, needle aspiration and chest tube treatment

Due to the underlying pulmonary disease and mostly acute symptoms with cardiopulmonary compromise, conservative treatment is not recommended. The British Thoracic Society (BTS) guidelines recommend needle aspiration for asymptomatic secondary pneumothorax measuring 1-2 cm at the hilum [26].

The German S3 guidelines recommend chest tube (small-bore chest tube ≤ 14 French) treatment and oxygen supplementation at presentation of SSP [1, 19]. Although SSP can be treated initially with a chest tube drainage, high rates of recurrent disease, morbidity and mortality have been reported [54, 55]. Certainly, the latter depends on the underlying pulmonary disease. For patients with complicated SSP who are unsuitable for surgery, the above guidelines recommend pleurodesis via chest tube and less invasive treatment strategy. Indication to perform surgery should be taken interdisciplinary considering the underlying pulmonary disorder.

2. The role of surgery (VATS) and pleurodesis

According to the German S3 guidelines [1], surgery should be recommended for cases with persistent air leak after chest tube treatment or recurrent disease. However, indication for surgery should be taken individually depending on the comorbidity and underlying pulmonary disease as well as the patient's choice, as these factors might significantly impact morbidity, mortality and surgical outcome. For surgical treatment of SSP, the current guidelines [1, 19] also recommend video-assisted thoracoscopic surgery (VATS) in combination with a pleurodesis technique to reduce the risk of recurrence. Similar to primary spontaneous pneumothorax, pleurodesis can be performed either chemically (e.g., with Talc poudrage, tetracycline, Iodine, minocycline and blood patch) or mechanically (partial pleurectomy, pleural abrasion, apical pleurectomy). Depending on the pleurodesis technique implemented, different outcomes and recurrence rates are reported in the literature [1]. Although most of the studies reported in the literature implemented chemical pleurodesis, only a few reported

outcome following mechanical pleurodesis [53, 56-58]. Moreover, studies reporting the outcome of less port accesses after VATS for SSP are lacking in the literature. Similar to PSP, the knowledge about the outcomes following VATS with three-, two port or one port might significantly influence future treatment strategies for patients with SSP.

1.5. Scientific aims and clinical relevance

As recommended by international guidelines, video-assisted thoracoscopic surgery (VATS) in combination with a pleurodesis technique should be offered in patients with complicated (persistent air leak or recurrent disease) primary and secondary spontaneous pneumothorax. At first episode of spontaneous pneumothorax (PSP and SSP), the guidelines recommend for symptomatic patients, chest tube treatment. However, recurrence rates following chest tube treatment are high. VATS in combination with partial pleurectomy and bullectomy for blebs/bullae has been reported in some few studies to be associated with significantly low rates of recurrence compared to VATS - bullectomy alone, VATS – apical pleurectomy and VATS - pleural abrasion. However, studies that evaluate long-term outcomes following VATS – partial pleurectomy (± bullectomy) are limited. Additionally, studies that investigate postoperative quality of life, pulmonary function, postoperative pain and independent risk factor for pneumothorax recurrence following VATS - partial pleurectomy (± bullectomy) are scarce.

The aim of my work was primarily to investigate the efficacy of VATS - partial pleurectomy and bullectomy (VPPB) in the treatment of patients with primary and secondary spontaneous pneumothorax in our institution. I investigated long-term recurrence rates and clinicopathological parameters to identify potential risk factors

for disease recurrence. Moreover, I investigated postoperative quality life and pulmonary function as well as the socioeconomic outcomes following VPPB to identify potential factors that could be adversely affected by this treatment. I compared our results of surgery (VPPB) with those our patients initially successfully treated by chest tube drainage only in our institution. Furthermore, I analyzed the postoperative surgical and clinical outcomes after two-port and three-port VATS for PSP and SSP in our institution to determine which surgical technique might be safer and more effective for our patients.

2. Results and discussion

With my work presented here, I provided further insight into the effectiveness of video-assisted thoracoscopic surgery (VATS) in the treatment of primary (PSP) and secondary (SSP) spontaneous pneumothorax. I could demonstrate that VATS combined with partial pleurectomy and bullectomy (VPPB), as recommended in the German S3 guidelines, significantly reduces the long-term risk of disease recurrence in patients with PSP and SSP. For both conditions (PSP and SSP), I clearly elucidated that treatment by chest tube only is an independent risk factor for disease recurrence. Additionally, I proved that a large pneumothorax size is an independent risk factor for pneumothorax recurrence in PSP patients irrespective of the initial treatment. Due to this observation, I concluded that, PSP patients with a large pneumothorax size should be closely monitored, as they are at risk for disease recurrence. Moreover, I highlighted the observation that, male sex is a potential risk for disease recurrence of SSP. In the treatment of patients with PSP, I showed for the first time that VATS in combination with partial pleurectomy, which causes pleural symphysis, has no adverse effect on postoperative pulmonary function and

health-related quality of life. Furthermore, I could demonstrate that VPPB is associated with a reduced socioeconomic burden for PSP patients and the health-care system due to its significantly lower recurrence rats compared with chest tube treatment. Therefore, in this study, I have contributed to answer the question of whether VATS should be considered at first episode of PSP (instead of chest tube drainage as recommended in the guidelines). Lastly, I could demonstrate that performing VATS with a two-port approach (two-port VATS) is safer and more effective compared with the standard three-port approach. Two-port VATS for PSP and SSP was associated with less postoperative pain, short length of hospital stay and less postoperative morbidity compared with three-port VATS.

2.1. Effectiveness of video-Assisted thoracoscopic surgery with bullectomy and partial pleurectomy in the treatment of primary spontaneous pneumothorax - a retrospective long-term single-center analysis (Appendix 1 [30])

Video-assisted thoracoscopic surgery (VATS) with bullectomy and partial pleurectomy (VBPP) is an increasingly used and well-established surgical treatment for primary spontaneous pneumothorax (PSP). However, reports on its effectiveness and long-term outcomes are limited. The aim of this study was to assess and compare long-term recurrence rates following VBPP and chest tube (CT) treatment and to identify potential risk factors for disease recurrence in patients with PSP. Data of 120 patients with PSP treated either by VATS bullectomy with partial pleurectomy (VBPP) or by chest tube (CT) only between January 2008 and December 2020 in our institution were retrospectively reviewed. Patient demographics, including age, sex, body mass index (BMI), smoking status, length

of hospital stay (LOS), duration of surgery, time until recurrence, treatment modality, complications, and size of the pneumothorax, were retrieved from medical records. The size of the pneumothorax was assessed using the regression formula derived from the method of Collins [18]. Four patients were lost during follow-up and were excluded from this analysis.

A total of 116 patients with a median age of 24 years (range 18-41) were included in this study. Sixty-two patients underwent VBPP, whereas 54 patients received CT treatment. At first presentation of spontaneous pneumothorax (SP), identified patients received chest tube (CT) treatment. Patients who were initially successfully treated with CT during our study period were classified in the CT group. Indication for surgery (VBPP) included persistent air leak for more than 5 days following CT treatment (n=20), first ipsilateral recurrent pneumothorax (recurrence of pneumothorax on the previously treated side, n=32), synchronous bilateral spontaneous pneumothorax (n=8), and spontaneous hemopneumothorax (n=2). Our specialized team of thoracic surgeons performed all surgical procedures and postoperative patient follow-up. For long-term follow-up, patients were contacted and assessed with a questionnaire.

At presentation, the mean pneumothorax sizes estimated according to Collins method were 13.4 cm and 13.9 cm in the VBPP and CT groups, respectively, indicating a large pneumothorax size for both patient cohorts. Clinical variables, such as age, gender, BMI, and pneumothorax size and chest tube duration, were similar in both groups. During a median follow-up period of 76.5 months (range 1–155 months), patients who underwent CT treatment experienced a significantly higher recurrence rate compared with patients following VBPP (VBPP vs. CT: 9.7% vs. 64.8%; $p<0.0001$). This high rate of recurrence in the CT group occurred mainly

within the first year after treatment (CT vs. VBPP: 9.6 months (range 2-26) vs. 59 months (range 6-110); p<0.001). Interestingly, patients with a large pneumothorax size (Collins ≥ 4 cm) suffered a significantly higher rate of recurrence compared with patients with a small pneumothorax size (Collins < 4 cm vs. Collins ≥ 4 cm: 9.1% vs. 37%; p=0.010). Univariate analysis revealed that treatment of PSP patients with VBPP (VBPP vs. CT: HR 0.056; CI: 0.023-0.14; p<0.001) and a small size of the initial pneumothorax (Collins ≥ 4 cm vs. Collins < 4 cm: HR 4.602; CI: 1.106-19.151; p=0.020) were significantly associated with a lower risk of pneumothorax recurrence (Fig. 2A, B). Both factors, namely the therapeutic procedure chosen (VBPP vs. CT: HR 0.047; CI: 0.017-0.132; p<0.001) and the baseline pneumothorax size (Collins ≥ 4 cm vs. Collins < 4 cm: HR 6.325; CI: 1.372-29.162; p=0.018), were confirmed as independent predictive markers of pneumothorax recurrence in multivariate regression analysis.

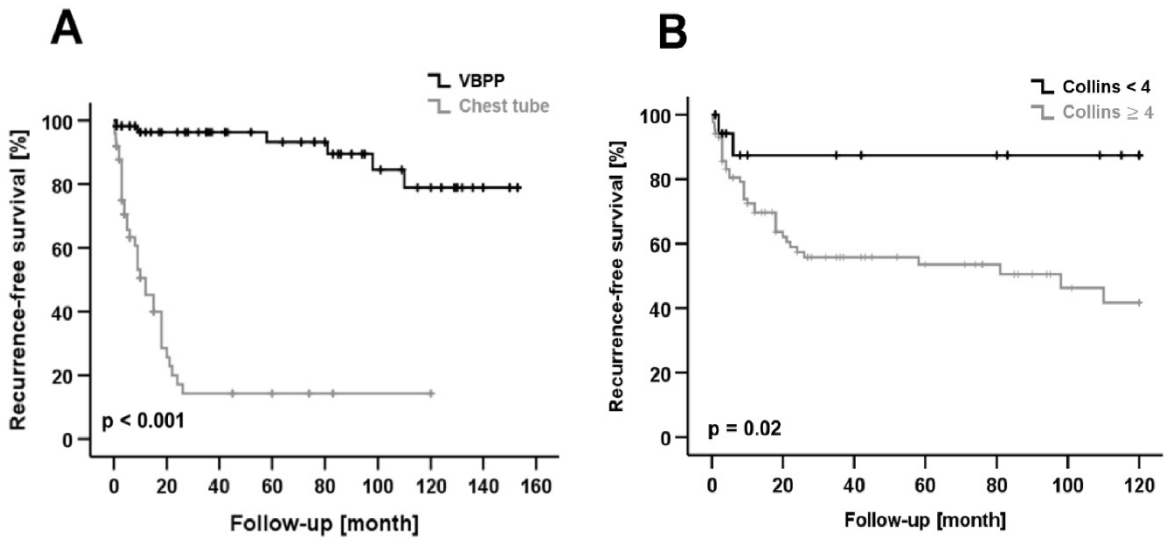

Figure 2. *(**A**) Kaplan–Meier curve shows recurrence-free survival (RFS) after treatment by surgery (VBPP) or chest tube (CT). VBPP was associated with significantly better RFS compared to CT treatment. (**B**) Patients with a large*

pneumothorax size (Collins ≥ 4 cm) had a significantly reduced RFS compared to patients with a small pneumothorax size (Collins < 4 cm). Modified from [30].

Our result demonstrate that VBPP is associated with an increased recurrence-free survival compared to CT treatment. These results also highlight the high efficacy of VBPP in the treatment of patients with PSP and the clinical importance of the initial pneumothorax size as a significant risk factor for disease recurrence. The recurrence rate of 9.7% of our VBPP cohort is slightly higher than some studies described in the literature. In the study of Imperatori, A. et al.[59] with 134 patients, VATS blebectomy and parietal pleurectomy had a recurrence rate of 6%. The median follow-up was 79 months (range: 36-187 months). Shaikhrezai, K et al. [24] observed no recurrent pneumothorax of 44 PSP patients operated by VATS bullectomy and partial pleurectomy during a median follow-up of 73 months. In a recent study of Caecilia Ng et al. [25], in which 73 PSP patients underwent VATS partial pleurectomy, a recurrence rate of 1.4% at a median follow-up period of 58.5 months was reported. Although the above recurrence rates are lower than the recurrence rate of our VBPP cohort, none of them evaluated the pneumothorax size as a potential risk factor for PSP recurrence. In our study, the patients presented with a large pneumothorax size estimated according to the method of Collins. The mean pneumothorax size of the VBPP group was 13.4 cm and 13.9 cm for the CT group. As reported in earlier studies, a large pneumothorax size is a risk factor for PSP recurrence [60-62]. Therefore, we assumed that the large pneumothorax size of our PSP cohort influenced our comparatively high rate of recurrence.

In conclusion, our data demonstrate that the risk of recurrent pneumothorax can be significantly reduced by VBPP. In addition, our data highlight the fact that a large initial pneumothorax size is associated with a markedly increased risk of

pneumothorax recurrence. Therefore, the option of VBPP should be discussed early for PSP patients treated with a large pneumothorax size, and close follow-ups should be performed due to the high risk of recurrence.

2.2. Video-assisted thoracoscopic surgery with bullectomy and partial pleurectomy versus chest tube drainage for treatment of secondary spontaneous pneumothorax – a retrospective single-center analysis (Appendix 2 [53])

Current guidelines recommend chest tube (CT) drainage as the initial treatment of secondary spontaneous pneumothorax (SSP). Surgery should be considered in cases of persistent air leak or recurrent disease. Video-assisted thoracoscopic surgery (VATS) is nowadays an established surgical treatment for complicated spontaneous pneumothorax. However, reports on VATS-bullectomy with partial pleurectomy (VBPP) for treatment of secondary spontaneous pneumothorax (SSP) are limited. The primary aim of this study was to evaluate and compare the clinical outcomes of patients with secondary pneumothorax treated either by VBPP or CT drainage in our institution. Secondly, we assessed underlying clinical parameters to identify potential risk factors for SSP recurrence.

We retrospectively reviewed the data of 82 patients with secondary spontaneous pneumothorax (SSP), treated either by VATS-bullectomy with partial pleurectomy (VBPP) or by chest tube (CT) only between January 2008 and December 2020 in our institution. Patient demographics, including age, sex, body mass index (BMI), COPD stage, ECOG status, Charlson Comorbidity Index score, treatment modality, etiological cause of SSP, post-treatment complications, length of hospital stay (LOS), and size of the pneumothorax, were retrieved from medical records. The size of the pneumothorax was assessed using the regression formula derived from the method of Collins [18].

At the initial presentation of SSP, identified patients received chest tube (CT) treatment. Patients who were initially successfully treated with CT or were unsuitable for surgery (high Charlson Comorbidity Index score or poor ECOG status) and underwent only CT treatment during our study period were classified in the CT group. For patients suitable for surgery, indication for surgical therapy (VBPP) included persistent air leak for more than 5 days following CT treatment (n = 16) and ipsilateral or contralateral recurrent pneumothorax (n=20). Prior to surgery, a computer tomography of the chest was performed to detect the cause of SSP and to determine the extent of a bullous disease. A team of specialized thoracic surgeons made indication for surgery. Of note, indication for surgery was made individually depending on the comorbidity and underlying pulmonary disease as well as the patient's choice. Patients with incomplete follow-up data and patients who received other treatment modalities (e.g., thoracotomy, apical pleurectomy, observation, needle aspiration) were excluded from this study. For long-term follow-up, patients were contacted and assessed with a questionnaire.

Eight patients were lost during follow-up and were excluded from this study. A total of 82 patients with a median age of 65 years (range 41-86) were included in this study. Thirty-six patients underwent VBPP, while 46 patients received CT treatment. Clinical variables, such as age, gender, BMI, pneumothorax size, COPD stage, ECOG status and Charlson Comorbidity Index, were similar in both groups. Post-treatment complications such hemothorax (VBPP vs. CT: 13.9% vs. 2.8%, p=0.43) and acute pneumonia (VBPP vs. CT: 30.6% vs. 10.9%, p=0.026) were significantly more common in the VBPP cohort. Three patients who suffered a hemothorax in the VBPP group were successfully treated conservatively, while two patients underwent re-VATS. The patient who suffered a hemothorax after CT treatment was

conservatively treated. In both groups, patients with acute pneumonia were treated successfully with our standard regimen of antibiotics. The high rate of acute pneumonia in the VBPP group seems to be related to postoperative pain, which might have impaired breathing exercises during the first postoperative days. During the clinical course, none of the patients died after treatment in both groups. Additionally, the mean length of hospital stay (LOS) was significantly longer in the VBPP group compared with the CT group (VBPP vs. CT: 9.3/14.1; p=0.006).

During a median follow-up period of 76.5 months (range 1-155 months), patients who underwent CT treatment experienced a significantly higher recurrence rate compared with patients following VBPP (VBPP vs. CT: 16.7% vs. 41.3%; p=0.016). Interestingly, male gender was associated with a significantly higher rate of recurrence compared to female gender (male vs. female: 41.3% vs. 16.7%; p=0.016). Univariate analysis revealed that the treatment of SSP with VBPP (CT vs. VBPP: HR 0.196; CI: 0.077-0.498; p<0.001) and female sex (female vs. male: HR 2.803; CI: 1.118-7.030; p=0.021) were associated with a significantly lower risk of SSP recurrence (Figure 3A, B). Interestingly, the treatment modality chosen (CT vs. VBPP: HR 0.151; CI: 0.051-0.441; p=0.001) was confirmed as the only independent predictive marker of SSP recurrence in the multivariate Cox regression Analysis.

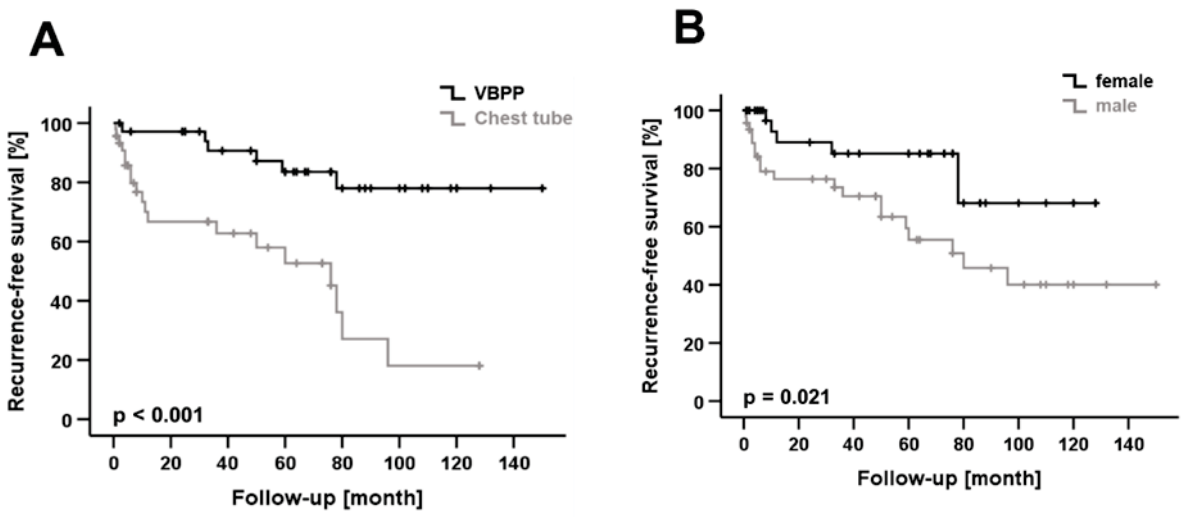

Figure 3. *(**A**) Kaplan–Meier curve shows recurrence-free survival (RFS) after treatment by VATS-bullectomy with partial pleurectomy (VBPP) or chest tube (CT). VBPP was associated with significantly better RFS compared to CT treatment. (**B**) Male sex was associated with a significantly shorter RFS compared with female sex. Modified from [53].*

In this study, chronic obstructive pulmonary disease (COPD) was the main cause of SSP (n=64), followed by tuberculosis (n=11) and lung cancer (n=7). The high number of COPD patients in our study confirms the observations of the current guidelines that COPD is the main etiological cause of SSP [1, 19, 21]. Interestingly, during a median follow-up period of 76.5 months (range 1-55 months), patients who underwent CT treatment experienced a significantly higher recurrence rate compared with patients following VBPP. This difference was statistically significant in the univariate and multivariate Cox regression analyses. These results confirm that treatment by VBPP is associated with significantly lower SSP recurrence. Of note, the rate of SSP recurrence after VBPP in our study was significantly lower than the only comparable long-term study we found in the literature [56]. In this study of Shaikhrezai K et al [56], five SSP patients underwent VBPP, of which two (40%)

patients recurred during a median follow-up period of 73 months. Interestingly, our results of recurrence after VATS with mechanical pleurodesis (VBPP) is similar to the results of a previously reported study by Kim SJ et al. [57]. In this study, 22 patients after VATS-chemical pleurodesis (Talc–pleurodesis) displayed a significantly low rate of recurrence compared to 32 patients who underwent chemical pleurodesis via chest tube only. Our results and those of Kim SJ et al. confirm the efficacy of VATS with additional pleurodesis (chemical or mechanical) as a surgical technique to reduce recurrent disease and demonstrate the ineffectiveness of chest tube drainage only as well as pleurodesis via chest tube drainage as treatment techniques to prevent recurrence.

Compared with the CT group, patients in the VBPP group had a significantly longer length of hospital stay (LOS) and higher post-treatment complications (five patients suffered a hemothorax and two patients had an acute pneumonia). The LOS in the VBPP group was significantly prolonged by the number of hospital days until surgery was performed (mean of 7.1 days). Additionally, a long recovery period after surgery due to the underlying pulmonary disease and the high rates of post-treatment complications certainly affected the LOS in the VBPP group. The LOS in both groups was comparable to previously reported studies in the literature [56, 63]. With regard to complication rates, the number of patients who suffered a hemothorax was significantly higher in the VBPP group compared to patients after CT treatment. We assume that the extent of pleurectomy during VBPP markedly influenced the occurrence of hemothorax. We also observed a significantly higher rate of acute pneumonia in the VBPP group compared with the CT group. This high rate of acute pneumonia in the VBPP group could be related to post-treatment pain, which might have impaired early breathing exercises and mobilization during the first

postoperative days. During the clinical course, we observed no cases of in-hospital mortality in either group. Analyses of potential risk factors for SSP recurrence, such as pneumothorax size, age, gender, BMI, COPD, smoking status, and treatment modality, revealed that male sex was associated with a high risk of disease recurrence.

In conclusion, our results demonstrate that VBPP is suitable surgical treatment for SSP. It is associated with a very low risk of disease recurrence. Therefore, VBPP should be offered as a treatment modality for patients with complicated SSP (recurrence or persistent air leak). However, prior to surgery, the underlying pulmonary disease, Charlson Comorbidity Index, and ECOG status should be considered, as these factors might prolong the length of hospital stay and negatively impact the patient as well as the surgical outcome.

2.3. Does video-assisted thoracoscopic surgery with bullectomy and partial pleurectomy for primary spontaneous pneumothorax impair health-related quality of life and pulmonary function? (Appendix 3 [64])

Video-assisted thoracoscopic surgery (VATS) with partial pleurectomy is an established treatment for primary spontaneous pneumothorax (PSP). However, postoperative pulmonary function and health-related quality of life (HR-QoL) after VATS–bullectomy with partial pleurectomy (VBPP) have not been elucidated. Eligible patients were assessed for HR-QoL using the Short-Form 36 (SF-36) health survey. Pulmonary function (PF) was evaluated by spirometry. We compared the results of the VBPP cohort with the German national norms, and with a similar cohort of patients successfully treated by chest tube (CT) only. This was a prospective non-randomized single-centre study performed between January 2017 and December 2019. During our study period, 34 patients underwent VATS–bullectomy with partial pleurectomy due to PSP in our hospital. Of these patients, 25 patients with a mean age of 26.1 years (range 17-42) completed the survey and were included in this study; 15 of those 25 patients presented in our outpatient clinic, and were assessed for pulmonary function by spirometry. For comparability, and to explore the impact of VBPP on pulmonary function and HR-QoL, a control group of 25 eligible patients with mean age of 27 years (range 19–40), who underwent successful chest tube (CT) treatment between January 2018 and April 2020, were included in this study. For pulmonary function, data on 15 patients were evaluated. Likewise, these patients were contacted one year after CT treatment and assessed for HR-QoL and pulmonary function at our outpatient clinic.

We found no significant differences in FVC (forced vital capacity) or FEV1 (forced expiratory volume in one second), nor in the FEV1/FVC ratio, between the VBPP

and CT groups. Interestingly, in both groups, the estimated FVC, FEV1, and FEV1/FVC ratio were higher than the matched LLN values (Table 2), indicating normal pulmonary function after VBPP. This suggests that partial pleurectomy, which causes adhesion of the visceral pleura to the inner surface of the thoracic cavity in order to prevent recurrent pneumothorax, has no restrictive effect on lung function. Furthermore, these results indicate no obstructive pattern (both FVC and FEV1/FVC > LLN). Together, these results demonstrate that VBPP does not adversely affect the pulmonary function of PSP patients, while it was previously shown to be highly effective at reducing the risk of recurrence of PSP.

Table 2. Comparison of lung function after VBPP and CT treatment (n = 15 patients per group).

	FVC (L)			FEV1 (L)			FEV1/FVC (%)		
	Predicted	% Predicted	LLN	Predicted	% Predicted	LLN	Predicted	% Predicted	LLN
VBPP Mean (SD)	4.89 (0.35)	90.95 (5.34)	4.20 (0.76)	4.09 (0.41)	88.48 (5.71)	3.28 (0.87)	83.66 (5.88)	97.09 (2.22)	74 (0.76)
CT Mean (SD)	4.88 (0.33)	91.19 (4.86)	4.31 (0.77)	3.82 (0.44)	89.64 (4.12)	3.3 (0.89)	78.54 (9.01)	98.47 (4.58)	73.8 (0.74)
p-Value	0.9364	0.8985	0.6967	0.0931	0.5286	0.9018	0.0759	0.3026	0.4713

Table 2: Comparison of lung function after VBPP and CT treatment (n=15 patients per group). *All data are presented as mean and standard deviation (SD). FVC: forced vital capacity; FEV1: forced expiratory volume in one second; FEV1/FVC ratio: the percentage of the FVC expired in one second; LLN: lower limit of normal (defined as below the fifth percentile of spirometry data obtained from the Third National Health and Nutrition Examination Survey); L: litre; VBPP: VATS–bullectomy with partial pleurectomy; CT: chest tube. A p-value < 0.05 indicates statistical significance. Modified from [64].*

Moreover, we used the well-established SF-36 health survey to evaluate the HR-QoL [65, 66]. Of 34 patients, 25 completed the SF-36 questionnaire (9 patients were excluded due to an incomplete questionnaire). We compared our results with a control group of patients successfully treated by chest tube only at our institution, and with the normative data from the general German population, as published by Morfeld et al. [67]. For our VBPP cohort, the physical component summary (PCS) scores were similar to the scores of the general German population, indicating that VBPP does not impair physical health. However, the mental component summary (MCS) scores of our patients were significantly lower (score −4.5, p=0.0049) than those of the general German population, indicating high psychological distress for VBPP patients. This may be due to increased stress and post-traumatic anxiety of a possible relapse after surgery. Moreover, we compared the results of the SF-36 survey of the VBPP and CT groups. Interestingly, we found no significant statistical differences between the eight domains and summary scores of the SF-36 survey.

Although limited by the lack of baseline data and the lack of a surgical control group (e.g., patients treated by VATS without pleurectomy and/or bullectomy), this study is the first to report on the impact of VBPP on the HR-QoL and pulmonary function of PSP patients after surgery and chest tube treatment. Our data demonstrate that VATS–bullectomy with partial pleurectomy (VBPP) for primary spontaneous pneumothorax (PSP) has no adverse impact on pulmonary function, and is associated with stable physical health. However, psychological distress and measures to counteract its impact should be considered after surgical treatment.

2.4. Socioeconomic impact of recurrent primary spontaneous pneumothorax: Should video-assisted thoracoscopic surgery be considered at first episode of primary spontaneous pneumothorax? (Appendix 4 [43])

Current guidelines recommend video-assisted thoracoscopic surgery (VATS) for recurrent primary spontaneous pneumothorax (PSP) and for cases with persistent air leak after chest tube treatment. The socioeconomic impact of recurrent PSP on the healthcare system is insufficiently reported.

We retrospectively reviewed the data of 96 patients with PSP treated in our institution either by CT or VATS between January 2010 and January 2020. Patients' clinical data, including age, gender, weight, height, body mass index (BMI), length of hospital stay (LOS), duration of chest tube, postoperative complications and length of air leakage were retrieved from the medical records. One group underwent immediate surgery (VATS) (39 males and 9 females) during primary hospitalization; the other group received CT treatment only (40 males, 8 females). The mean age of the patients treated using VATS was 24.8 years (range 18–39), and was 26.2 years (range 18–40) for those who underwent CT treatment. Patients in the VATS group underwent immediate surgery due to the following conditions: occurrence of second ipsilateral or contralateral pneumothorax (recurrence) (n=38), synchronous bilateral spontaneous pneumothorax (n=6) and spontaneous hemopneumothorax (n=4). Patients in the CT group received chest tube drainage only upon first episode of unilateral PSP. Patients initially planned for CT treatment but suffering prolonged air leak (>5 days) underwent secondary VATS during first hospitalization. Although secondary VATS was performed, we assigned these patients for comparability to the CT group based on their initial treatment. In both groups, low-dose computer tomography of the lungs was performed prior to surgery to detect any bullous

disease. VATS consisted of partial pleurectomy and bullectomy when blebs were evident. Patients who relapsed after CT treatment or VATS underwent VATS or re-VATS, respectively. After discharge, all patients were closely monitored for complications as outpatients. Follow-up consisted of 3-monthly consultations for one year. For long-term follow-up, the patients were contacted and assessed with a questionnaire. For all patients, the mean follow-up period was 46.2 months (range 1–119).

The mean LOS during primary hospitalization was 6 days in both groups. After VATS for recurrence, the mean LOS of the second hospitalization was also 6 days. Duration of chest tube drainage was shorter in the VATS group (5 days) compared to the CT group (6 days). After VATS for recurrence, the mean duration of chest tube drainage in both groups was 5 days. Regarding complications, one patient (2.1%) in the VATS group developed postoperative hemothorax and was re-operated on by VATS. In the VATS group, six (12.5%) patients had persistent air leak, which resolved spontaneously on postoperative day 6 or 7. Prolonged air leak was also observed in 11 (22.9%) patients of the CT group. Ten (20.8%) patients of this group underwent VATS and one resolved spontaneously on postoperative day 8

As defined in the German diagnosis-related groups (DRG) catalogue, the cost of a hospital stay per day for patients with PSP is calculated at EUR 148. The cost of surgical materials for VATS or chest tube placement under local anaesthesia is EUR 465 and EUR 77, respectively. As previously mentioned above, one patient in the VATS group underwent re-VATS for hemothorax and 10 patients in the CT group underwent VATS due to prolonged and persistent air leakage. The costs of treatment for these 10 patients were assigned to the CT group and not to the VATS

group due to their initial treatment. The combined cost of treatment for these cases was EUR 1353 for the VATS group and EUR 13,530 for the CT group. With a mean hospital stay of 6 days in both groups, the total treatment cost (including material, hospitalization and complication treatment costs) prior to recurrence, excluding additional medication for comorbidities, was calculated at EUR 1.360 and EUR 1.247 per patient for the VATS and CT group, respectively.

During follow-up period of 46.2 months, 4 (8.3%) and 25 (52.1%) patients of the VATS and CT group presented with recurrent PSP ($p<0.001$), respectively. All patients underwent re-VATS or VATS, according to the previous treatment, incurring a further cost of EUR 1.353 per patient. Including treatment cost for recurrence, the total management cost per patient was EUR 1.473 in the VATS group and EUR 1.952 for the CT group (Δ = EUR 479). The total management cost increased to EUR 1.501 and EUR 2.233 per patient in the VATS and CT group, respectively, after adding treatment costs for complications (Δ = EUR 732) (Table 3)

Variables	VATS (*n* = 48)	Chest Tube (*n* = 48)
Primary treatment costs (pg)	EUR 65.288	EUR 59.850
Recurrence treatment costs (pg)	EUR 5.412	EUR 33.825
Total management costs (pg)	EUR 70.700	EUR 93.675
Total management costs (pp)	EUR 1.473	EUR 1.952
Total management and complication costs (pg)	EUR 72.053	EUR 107.205
Total management and complication costs (pp)	EUR 1.501	EUR 2.233

Table 3: Total management cost. *VATS: video-assisted thoracoscopic surgery; pp = per patient; pg = per group. The cost of surgical materials and cost of a hospital stay per day may differ across hospitals. Modified from [43].*

To date, chest tube drainage is still a recommended treatment for the first episode of PSP. According to the current guidelines, VATS should be considered at recurrence or in case of persistent air leak after CT treatment. Similar to our results, various studies have proven VATS to be superior to CT treatment in terms of recurrence rates, even at first episode of PSP [40, 68, 69]. VATS has also been reported to be associated with shorter hospitalization rates and better quality of life.[34, 70]. In a previous study, Schramel FM et al. [46] analyzed the cost effectiveness of VATS versus conservative treatment for first time or recurrent spontaneous pneumothorax. They reported VATS to be cost effective and associated with less morbidity compared to conservative therapy. In another study, Torresini G et al. [47] reported a cost reduction due to VATS in patients with the first episode of spontaneous pneumothorax compared to CT treatment. Moreover, in a recent meta-analysis of Daemen JHT et al. [40], VATS was reported to be associated with significantly reduced ipsilateral recurrence rates and shorter length of hospitalization compared with CT treatment. In our study. CT treatment was associated with higher overall treatment cost compared with treatment by VATS. The main causes for the increased economic burden in the CT group were the high recurrence rate and the high rate of persistent air leaks after CT treatment, both requiring secondary VATS. This resulted in an overall 48.8% increase (EUR 732 per case) in total management and complication cost of the CT group versus the VATS group.

In conclusion, performing VATS upon first PSP seems to be associated with reduced socioeconomic burden, not only for the patients, but also for the healthcare system.

2.5. Two-port versus three-port video-assisted thoracoscopic surgery for primary spontaneous pneumothorax: feasibility, postoperative outcome and long-term recurrence rates (Appendix 5 [48])

Two-port VATS (2-P-VATS) and three-port VATS (3-P-VATS) are well-established techniques for surgical therapy of primary spontaneous pneumothorax (PSP). However, comparisons of both techniques in terms of postoperative outcome and recurrence are limited. From January 2010 to March 2020, we retrospectively reviewed data of 58 PSP patients who underwent VATS in our institution. For statistical analysis, categorical and continuous variables were compared by chi-square test or Fisher's exact test and the Student´s t-test, respectively. Twenty-eight patients underwent 2-P-VATS and 30 were treated with 3-P-VATS. Operation time, length of hospital stay (LOS), total dose of analgesics per stay (opioids and non-opioids), duration of chest tube drainage, pleurectomy volume (PV), postoperative complications and recurrence rates were compared between both groups. Of note, all patients received the same surgical treatment, consisting of partial pleurectomy and bullectomy when blebs were evident.

Clinical and surgical characteristics including mean age, gender, Body-Mass-Index (BMI), pneumothorax size, smoking behaviour, history of contralateral pneumothorax, side of pneumothorax, pleurectomy volume and number of resected segments were similar in both groups. The mean operation time, LOS and total postoperative opioid and non-opioid dose was significantly higher in the 3-P-VATS group compared with the 2-P-VATS group. Despite not being statistically significant, duration of chest tube was longer in the 3-P-VATS group compared with the 2-P-VATS group. In terms of postoperative complications, the occurrence of hemothorax was significantly higher in the 3-P-VATS group (3-P-VATS vs. 2-P-VATS; p=0.001).

During a median follow-up period of 61.6 months, there was no significant statistical difference in recurrence rates in both groups (2/28 (16.7%) vs. 5/30 (7.1%); p=0.274).

In the last decades, thoracic surgery has evolved from thoracotomies to video assisted thoracoscopic surgery (VATS) as the gold standard. While three port VATS still remains the standard-of-care in most centres due to the accessibility, recent technical developments are leading to a reduction in access ports. While this may improve postoperative performance such as reduced paraesthesia, analgesic use and LOS, the more limited access may reduce the operative results. While single-port VATS has been heralded as new minimal access VATS in selected indications and specialized centres, two- and three-port VATS remains the gold standard in most settings. Yet, comparisons of 3-P-VATS with 2-P-VATS have been rarely reported and the impact on postoperative performance as well as effectiveness of the surgical therapy remain elusive. In this study, we observed a significant difference in operation time, LOS and postoperative dose of analgesic between both groups. Patients operated by 2-P-VATS had a significantly reduced LOS, less postoperative pain and shorter operation time compared with patients operated by 3-P-VATS. In terms of postoperative complications, we observed a significantly higher rate of hemothorax in the 3-P-VATS group. Although not reaching statistical significance, the larger volume of resected parietal pleura in the 3-P-VATS groups, as well as the additional port access, may have contributed to the higher rate of hemothorax in the 3-P-VATS group. In this study, we used the cumulative postoperative dosage of opioid and non-opioid analgesics per patient as an objective surrogate for postoperative pain. Unlike the VAS (visual analogue scale) score, which may give a one-time measurement including the patient's emotional

and psychological state, the quantification of applied analgesics allows to assess average pain levels over a longer period. We found a significantly reduced opioid and non-opioid dosage in the 2-P-VATS group, most likely due to the reduced port access. To our knowledge, our study is the first study that elucidates pain-related analgesic use after VATS for patients with PSP.

In conclusion, our results demonstrate that 2-P-VATS is safer and as effective as 3-P-VATS in the treatment of PSP. It leads to a better postoperative outcome and earlier recovery compared with the conventional 3-P-VATS. 2-P-VATS should be considered standard-of-care in the treatment of PSP.

2.6. Postoperative pain and clinical outcome following two- and three-port video-assisted thoracoscopic surgery for secondary spontaneous pneumothorax (Appendix 6 [71])

Two-port (2P) and three-port (3P) video-assisted thoracoscopic surgery (VATS) are well-established surgical methods for the treatment of complicated spontaneous pneumothorax (SP). However, a comparison between both techniques, in terms of clinical outcomes in patients with secondary spontaneous pneumothorax (SSP), is unreported. The aim of this study was to evaluate and compare postoperative pain, as well as clinical outcome, following 2P and 3P VATS for SSP in our institution. Between January 2008 and December 2020, we retrospectively analyzed the data of 115 SSP patients treated by VATS in our institution. Fifty-two patients underwent 2P-VATS, while 63 patients were treated by 3P-VATS. The total dose of analgesic use per stay (opioid and non-opioid), length of hospital stay (LOS), operation time, total area of pleurectomy, recurrence rates and postoperative complications were compared between both groups.

The 3P-VATS group had a significantly higher total dose of analgesic use compared with the 2P-VATS patients. The LOS and mean operation time were significantly shorter in the 2P-VATS group. A larger area of pleurectomy was resected using 3P-VATS compared to 2P-VATS. The postoperative complications and recurrence of SSP during a median follow-up period of 76.5 months were similar in both groups.

To date, reports on the outcomes following surgery for secondary spontaneous pneumothorax (SSP) are limited in the literature. Although surgery is associated with low rates of recurrence, high rates of morbidity and mortality after surgical treatment have been reported [72, 73]. These high rates of morbidity and mortality are certainly not only impacted by the underlying pulmonary disease, but also by the

surgical technique used. In the last decade, thoracic surgery has evolved from open thoracotomy to video-assisted thoracoscopic surgery (VATS), as the gold standard. While three-port VATS (3P-VATS) still remains the standard of care in most centers, due to its accessibility, recent surgical and technical developments are leading to a reduction in access ports. While there are abundant reports on the surgical performance and benefits of limited port access, in terms of postoperative pain, paraesthesia and length of hospital stay (LOS), for the treatment of primary spontaneous pneumothorax (PSP), there is a lack of information on VATS for the treatment of SSP in such reports.

In this retrospective study, patients in the 2P-VATs group had a significantly lower total dose of analgesics administered per stay compared to the patients operated on with 3P-VATS, indicating less postoperative pain. In addition, following 2P-VATS, the mean operation time and the LOS were significantly shorter. In terms of postoperative complications, the 2P-VATS patients had a low rate of hemothorax and pneumonia compared to the 3P-VATS patients. We suggest that the high rate of hemothorax in the 3P-VATS group was related not only to the large area of pleurectomy resected during this procedure, but also to the additional port access. Similarly, we assume that the high rate of acute postoperative pneumonia in the 3P-VATS group was related to a higher postoperative pain level, which might have impaired breathing exercises during the first postoperative days. We believe that the high rate of postoperative complications also prolonged the LOS in the 3P-VATS group. Interestingly, during follow-up there was no significant difference in recurrence rates between both groups (2P-VATS 9.6% vs. 3P-VATS 11.1%; p=1.000).

Although this study is limited due to its retrospective nature, it is the first study that analyses and compares postoperative pain and treatment outcome following 2P- and 3P-VATS for SSP patients. The results of our study demonstrate that treatment of SSP by 2P-VATS is associated with less postoperative pain, low morbidity rates and earlier patient recovery compared to the conventional 3P-VATS. Therefore, 2P-VATS should be preferred for the surgical treatment of SSP. Nonetheless, this observation should be verified in a prospective trial with a larger number of patients.

3. Summary (German)

Die aktuellen internationalen Leitlinien [19, 20] sowie die aktuelle Deutsche S3-Leitlinie zur Diagnostik und Therapie des Spontanpneumothorax [1] empfehlen die Anlage einer kleinlumigen (≤ 14Ch.) Thoraxdrainage zur Therapie der ersten Episode eines symptomatischen primären (PSP) oder sekundären (SSP) Spontanpneumothorax. Für beiden Erkrankungen (PSP und SSP) wurde jedoch in der Literatur umfassend berichtet, dass die alleinige Therapie mit einer Thoraxdrainage mit einer erhöhten Rezidivrate verbunden ist. Leitliniengemäß wird bei persistierender Luftleckage (üblicherweise nach 3 bis 5 Tagen) oder unvollständiger Re-expansion der Lunge unter Sogtherapie sowie beim Rezidiv eines Spontanpneumothorax nach Aspiration oder Thoraxdrainagenbehandlung, eine chirurgische Therapie empfohlen. Für die operative Behandlung des PSP und SSP empfehlen die aktuellen Leitlinien die video-assistierte thorakoskopische Chirurgie (VATS). Zusätzlich empfehlen die aktuellen Leitlinien ein gleichzeitiges Pleurodese-Verfahren (Verklebung der Pleura mit der Thoraxwand) zur Prävention eines Rezidivs. Die Deutsche S3-Leitlinien empfehlen die Anwendung einer Talkumpoudrage (chemische Pleurodese) oder die Durchführung einer partiellen Pleurektomie (mechanische Pleurodese). In den letzten Jahrzehnten wurden in der Literatur verschiedene Substanzen zur chemischen Pleurodese (zum Beispiel Tetrazykline, Minozykline, Talkum, autologes Blut, Povidon-Jod, Picibanil) sowie verschiedenen Techniken zur mechanischen Pleurodese (Beispielsweise die apikale Pleurektomie, die Pleura-Abrasio und die partielle Pleurektomie) untersucht. Je nach Pleurodese-Verfahren während der VATS wurden unterschiedliche Rezidivraten bei Patienten mit PSP und SSP beschrieben. In Bezug auf VATS mit mechanischer Pleurodese zeigten aktuelle Studien, dass die VATS mit partieller

Pleurektomie und fakultativer Bullektomie (eine Bullektomie wird durchgeführt, wenn eine Bulla vorhanden ist) eine signifikant niedrigere Rezidivrate aufweist, als die VATS mit alleiniger Bullektomie, die VATS mit apikaler Pleurektomie oder die VATS mit Pleura-Abrasio [1, 31, 41, 42]. Allerdings gibt es in der Literatur nur wenige Studien, die sich mit den Langzeitergebnissen nach VATS mit partieller Pleurektomie (±Bullektomie) befassen. Darüber hinaus gibt es nur wenige Studien, die die postoperative Lebensqualität, die postoperative Lungenfunktion, die postoperativen Schmerzen und die unabhängigen Risikofaktoren für einen Rezidivpneumothorax nach VATS mit partieller Pleurektomie (±Bullektomie) untersuchen. Daher war mein primäres Forschungsziel, den Stellenwert der VATS in der Therapie des primären und sekundären Spontanpneumothorax und die Effektivität in Kombination mit einer partiellen Pleurektomie und Bullektomie zu untersuchen. Hierbei ermittelte ich retrospektiv die Langzeit-Rezidivrate (>10 Jahre Beobachtungszeit) und untersuchte die vorhandenen klinisch-pathologischen Parameter, um potentielle Risikofaktoren für das Wiederauftreten eines PSP oder SSP zu identifizieren. Darüber hinaus untersuchte ich die postoperative Lebensqualität und Lungenfunktion sowie die sozioökonomischen Ergebnisse nach VATS mit partieller Pleurektomie und Bullektomie, um potenzielle Faktoren zu ermitteln, die durch diese Behandlung beeinträchtigt werden könnten. Ich verglich ebenfalls die Ergebnisse nach VATS mit partieller Pleurektomie und Bullektomie mit den Ergebnissen unserer PSP und SSP Patienten, die erfolgreich nur mit einer Thoraxdrainage behandelt wurden.

Um zu ermitteln welche Technik bei der VATS für unsere PSP und SSP Patienten von klinischem Vorteil sein können, untersuchte und verglich ich das postoperative klinische sowie das chirurgische Outcome nach standardmäßig durchgeführter

three-port Technik (VATS über 3 Zugänge) mit der two-port Technik (VATS über 2 Zugänge).

Mit dieser Forschungsarbeit habe ich einen weiteren Einblick in die Effektivität der video-assistierten thorakoskopischen Chirurgie (VATS) für die Behandlung des primären (PSP) und sekundären (SSP) Spontanpneumothorax gegeben. Ich konnte zeigen, dass die VATS in Kombination mit einer partiellen Pleurektomie und Bullektomie das Langzeitrisiko eines Krankheitsrezidivs bei Patienten mit PSP und SSP deutlich reduziert. Für beide Erkrankungen (PSP und SSP) konnte ich eindeutig nachweisen, dass die alleinige Behandlung mit einer Thoraxdrainage ein unabhängiger Risikofaktor für das Wiederauftreten der Erkrankung ist. Außerdem konnte ich zeigen, dass ein großer Pneumothorax ein unabhängiger Risikofaktor für ein Pneumothorax-Rezidiv bei PSP-Patienten ist, und zwar unabhängig von der initialen Behandlung. Aufgrund dieser Beobachtung kam ich zur Schlussfolgerung, dass Patienten mit PSP, die mit einem großen Pneumothorax diagnostiziert und behandelt werden, engmaschig im Verlauf kontrolliert werden sollten, weil sie ein erhöhtes Risiko haben ein Rezidiv zur erleiden. Des Weiteren habe ich verdeutlichen können, dass das männliche Geschlecht bei SSP Patienten ein potenzieller Risikofaktor ist, einen Rezidivpneumothorax zu erleiden. Bei Patienten mit PSP konnte ich weiterhin zum ersten Mal zeigen, dass die VATS mit einer partiellen Pleurektomie keine negativen Auswirkungen auf die postoperative Lungenfunktion und die gesundheitsbezogene Lebensqualität hat. Im Vergleich zur Therapie mit einer Thoraxdrainage konnte ich zeigen, dass die Therapie mit VATS und partieller Pleurektomie und Bullektomie mit einer deutlich geringeren sozioökonomischen Belastung für den Patienten und für das Gesundheitssystem verbunden ist (aufgrund der sehr niedrigen Rezidivrate). Schließlich konnte ich

zeigen, dass die Durchführung einer VATS über zwei Zugänge (two-port VATS) sicherer und effektiver ist, als der aktuelle Standard einer VATS über drei Zugänge (three-port VATS). Die VATS über zwei Zugänge war mit weniger postoperativen Schmerzen, einer kürzeren Dauer des Krankenhausaufenthalts und geringeren postoperativen Komplikationen verbunden.

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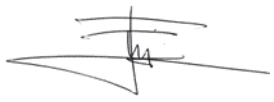
6. Eidesstattliche Versicherung

Ich versichere an Eides statt, dass diese Habilitationsschrift selbstständig und ohne unzulässige fremde Hilfe erstellt worden ist.

Die hier vorgelegte Arbeit wurde nicht von einer anderen Medizinischen Fakultät abgelehnt und ich habe keine anderen Habilitationsverfahren begonnen oder abgebrochen.

Bei den hier vorgelegten wissenschaftlichen Arbeiten wurden die ethischen Grundsätze und die Grundsätze und Empfehlungen zur Sicherung guter wissenschaftlicher Praxis beachtet. Für alle Forschungsvorhaben wurde vor Beginn ein positives Ethikvotum der Ethikkommission der Heinrich-Heine-Universität Düsseldorf eingeholt.

Die Vorgaben des Bundesdatenschutzgesetzes wurden bei allen Arbeiten in der jeweils aktuellen Version eingehalten.



Dr. med. Stephen Ngum Fung

7. Anhang

Die Habilitationsschrift basiert auf den folgenden Arbeiten:

Appendix 1:

Fung, S*.; Ashmawy, H.; Safi, S.-A.; Schauer, M.; Krieg, A.; Schauer, A.; Kivilis, M.; Ziayee, F.; Rehders, A.; Dizdar, L.; Knoefel, W.-T. Effectiveness of Video-Assisted Thoracoscopic Surgery with Bullectomy and Partial Pleurectomy in the Treatment of Primary Spontaneous Pneumothorax—A Retrospective Long-Term Single-Center Analysis. Healthcare 2022, 10, 410

Appendix 2:

Fung, S*.; Kivilis, M.; Krieg, A.; Schauer, A.; Rehders, A.; Dizdar, L.; Knoefel, W.-T. Video-Assisted Thoracoscopic Surgery with Bullectomy and Partial Pleurectomy versus Chest Tube Drainage for Treatment of Secondary Spontaneous Pneumothorax—A Retrospective Single-Center Analysis. Medicina 2022, 58, 354.

Appendix 3:

Fung S*, Ashmawy H, Schauer A, Eichler M, Safi S, Dizdar L, Rehders A, Knoefel WT, Fluegen G. Does Video-Assisted Thoracoscopic Surgery with Bullectomy and Partial Pleurectomy for Primary Spontaneous Pneumothorax Impair Health-Related Quality of Life and Pulmonary Function? Healthcare (Basel). 2021 Oct 29;9 (11):1463.

Appendix 4:

Fung S*, Alexander A, Ashmawy H, Dizdar L, Safi S, Rehders A, Fluegen G, Knoefel WT. Socioeconomic Impact of Recurrent Primary Spontaneous Pneumothorax: Should Video-Assisted Thoracoscopic Surgery Be Considered at First Episode of Primary Spontaneous Pneumothorax? Healthcare (Basel). 2021 Sep 19;9(9):1236.

Appendix 5:

Fung S*, Ashmawy H, Safi S, Schauer A, Rehders A, Dizdar L, Fluegen G, Knoefel WT. Two-port versus three-port video-assisted thoracoscopic surgery for primary spontaneous pneumothorax: feasibility, postoperative outcome and long-term recurrence rates. BMC Surg. 2021 Dec 18;21(1):428

Appendix 6:

Fung, S*.; Jaber, K.; Kivilis, M.; Rehders, A.; Schauer, A.; Dizdar, L.; Knoefel, W.-T. Postoperative Pain and Clinical Outcome Following Two- and Three-Port Video-Assisted Thoracoscopic Surgery for Secondary Spontaneous Pneumothorax. J. Clin. Med.2022,11, 1404.

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Effectiveness of Video-Assisted Thoracoscopic Surgery with Bullectomy and Partial Pleurectomy in the Treatment of Primary Spontaneous Pneumothorax—A Retrospective Long-Term Single-Center Analysis

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Abstract: Background: Video-assisted thoracoscopic surgery (VATS) with bullectomy and partial pleurectomy (VBPP) is an increasingly used and well-established surgical treatment for primary spontaneous pneumothorax (PSP). However, reports on its effectiveness and long-term outcomes are limited. The aim of this study was to assess and compare long-term recurrence rates following VBPP and chest tube (CT) treatment and to identify potential risk factors for disease recurrence in patients with PSP. Methods: A total of 116 patients treated either by VBPP or CT were included in this study. Long-term recurrence rates and associations between clinical parameters and recurrence of pneumothorax were analyzed. Results: Sixty-two patients (53.4%) underwent VBPP, whereas 54 (46.6%) patients underwent CT treatment only. During a median follow-up period of 76.5 months, VBPP patients experienced a significantly lower recurrence rate compared to CT patients (6/62 vs. 35/54; $p < 0.0001$). CT treatment (VBPP vs. CT; $p < 0.001$) and a large initial pneumothorax size (Collins < 4 vs. Collins $\geq$ 4; $p = 0.018$) were independent risk factors for pneumothorax recurrence. Conclusion: VBPP is an effective and safe surgical treatment for PSP. Therefore, patients with a large pneumothorax size might benefit from VBPP, as they are at high risk for disease recurrence.

Keywords: VATS bullectomy; partial pleurectomy; chest tube; recurrence; PSP

1. Introduction

According to the German S3 guidelines, primary spontaneous pneumothorax (PSP) describes the presence of air without preceding trauma or underlying pulmonary disease within the pleural space of patients under 45 years of age [1]. The incidence of PSP has been reported with approximately 1–9.8 and 7–24 cases per 100,000 individuals per year in females and males, respectively [2,3]. In most cases, PSP results from the rupture of subpleural blebs and bullae, predominantly in young, thin males [4,5]. Despite unknown etiology of PSP, associated risk factors for its occurrence and recurrence, such as male sex, tall stature, nicotine abuse, size of pneumothorax, and a family history of pneumothorax, have been reported [6–9].

According to the current guidelines, the initial treatment algorithm depending on the patient's clinical condition includes observation, oxygen supplementation, needle aspiration, and chest tube drainage [1,10,11]. Although PSP often resolves by observational conservative approach or by chest tube drainage [12,13], high rates of recurrence after these treatment modalities have been described [14–17]. For cases with ipsilateral recurrence of PSP and those with persistent air leak following chest tube (CT) treatment, the guidelines [1,10,11] recommend video-assisted thoracoscopic surgery (VATS). In previous studies, VATS with bullectomy alone was demonstrated to have recurrence rates up to 20% [18,19]. When combined with pleurectomy, the short- and medium-term recurrence rates were reported to reduce to 1–6% [20–22]. For long-term results, only a few studies are described in the literature [23–25].

Therefore, the primary aim of this study was to evaluate the long-term recurrence rates following VBPP and to compare these results with those of patients successfully treated by CT only at our institution. Secondly, we analyzed underlying clinical features to determine potential risk factors for pneumothorax recurrence in our PSP cohort.

2. Materials and Methods

We retrospectively reviewed data of 120 patients with primary spontaneous pneumothorax (PSP) treated either by VATS bullectomy with partial pleurectomy (VBPP) or by chest tube (CT) only between January 2008 and December 2020 in our institution. Patient demographics, including age, sex, body mass index (BMI), smoking status, length of hospital stay (LOS), duration of surgery, time until recurrence, treatment modality, complications, and size of the pneumothorax, were retrieved from medical records. The size of the pneumothorax was assessed using the regression formula derived from the method of Collins [26]. According to the actual German S3 guidelines for management of spontaneous pneumothorax and post-interventional pneumothorax, a spontaneous pneumothorax (SP) is considered as large when the sum of the interpleural distances derived from Collins method is $\geq$4 cm [1]. Hence, in this study, we considered a spontaneous pneumothorax to be large at a size of $\geq$4 cm.

At first presentation of spontaneous pneumothorax (SP), identified patients received chest tube (CT) treatment. Patients who were initially successfully treated with CT during our study period were classified in the CT group. Indication for surgery (VBPP) included persistent air leak for more than 5 days following CT treatment (n = 20), first ipsilateral recurrent pneumothorax (recurrence of pneumothorax on the previously treated side, n = 32), synchronous bilateral spontaneous pneumothorax (n = 8), and spontaneous hemopneumothorax (n = 2). Of note, patients who received VBPP for recurrence either underwent initial CT treatment at our institution before our study period or had received CT treatment at another hospital and subsequently presented in our institution with recurrence. Prior to surgery, a computer tomography of the chest was performed to detect any bullous disease. A team of three specialized thoracic surgeons (WTK, AS, AR) made indication for surgery. Patients with incomplete follow-up data and patients who received other treatment modalities (e.g., thoracotomy, apical pleurectomy (pleurectomy of the apex of the pleural cavity only), observation, needle aspiration) were excluded from this study. The primary objectives of this study were to assess and compare long-term recurrence rates after treatment with VBPP and CT in our institution and to identify potential risk factors for pneumothorax recurrence. Recurrence was described as an ipsilateral pneumothorax detected on a chest radiograph at presentation in our emergency room after surgical treatment by VBPP or chest tube drainage. The local ethic committee of the Heinrich-Heine University Clinic of Duesseldorf approved this study (study no.: 2020-1271).

2.1. Surgical Technique: VATS Bullectomy with Partial Pleurectomy (VBPP)

Our specialized team of thoracic surgeons (A.S., A.R., and W.T.K.) performed all surgical procedures and postoperative patient follow-up. All the patients were treated under general anesthesia with a double-lumen tube intubation and single-lung ventilation.

After lateral positioning of the patient, video-assisted thoracoscopic surgery (VATS) was performed in the conventional two- or three-port approach. Initial thoracoscopy was undertaken for thorough inspection of the visceral and parietal pleura. Bullectomy was carried out when blebs or bullae were identified by wedge resection using an endoscopic stapling device (Autosuture GIA Universal; COVIDIEN^{TM}, Mansfield, MA, USA). Partial pleurectomy was performed beginning from the apex of the pleural cavity. During this procedure, the parietal pleura was carefully separated from the endothoracic fascia while sparing the region of the subclavian artery and vein to avoid injury of these structures. Pleurectomy was performed up to the 7th or 8th intercostal space in a blunt manner. After cautious hemostasis of the endothoracic fascia using electrocautery to reduce the risk of hemothorax, one 24-Fr. chest tube was inserted and connected to a digital underwater seal system (Thopaz+, Medela AG, Baar, Switzerland) with a suction of −20 mm Hg. During postoperative care, the chest tube drain was removed when no clinical signs of air leak and a drain output of less than 200 mL after 24 h were evident. After chest tube removal, a chest radiograph was taken to verify full expansion of the lung. All the patients (VBPP and CT treated patients) received our standard postoperative medication regime of analgesia (non-opioid, orally or intravenously). The patients received either metamizole-natrium 1000 mg, paracetamol 1000 mg, or ibuprofen 600 mg four times per day. In cases of persistent pain using the standard pain medication regime, we applied piritramide (opioid) 7.5 mg intravenously every 4–6 h on patient request.

2.2. Outpatient Care and Follow-Up

One week after discharge, the patients visited our outpatient clinic for postoperative control and follow-up. These visits continued at a 3-month interval for one year. A chest radiograph was taken at each visit. The patients were advised to visit our emergency room at any time they had symptoms related to recurrent pneumothorax, such as dyspnea, chest pain, or cough. Recurrent pneumothorax was identified clinically in each case with a chest radiograph. For patients who recurred after CT or VBPP treatment, VBPP or re-VATS was performed, respectively. For long-term follow-up, patients were contacted and assessed with a questionnaire.

2.3. Statistical Analysis

All data were analyzed with the SPSS 25.0 software program (Statistical Package for Social Sciences; SPSS Inc., Chicago, IL, USA). Patients' data were expressed as numbers, mean or median. Continuous variables were compared using a Mann–Whitney U test, and the chi-square test was implemented for categorical data. Recurrence-free survival (RFS) was defined as the period between initial treatment by surgery (VBPP) or chest tube (CT) and ipsilateral recurrent pneumothorax. Kaplan–Meier curves were generated and evaluated with the log-rank test (Mantel–Cox test), and hazard ratios (HRs) were estimated with 95% confidence intervals (CIs). For multivariate analysis, all variables were included in a logistic regression analysis. Statistical significance was considered at $p < 0.05$.

3. Results

Between January 2008 and December 2020, 120 patients with primary spontaneous pneumothorax (PSP) were treated either by VATS-bullectomy with partial pleurectomy (VBPP) or by chest tube (CT) in our institution. Four patients were lost during follow-up and were excluded from this analysis. A total of 116 patients with a median age of 24 years (range 18–41) were included in this study. Sixty-two patients underwent VBPP, whereas 54 patients received CT treatment. The clinical characteristics of the patients are summarized in Table 1.

At presentation, the mean pneumothorax sizes estimated according to Collins method were 13.4 cm and 13.9 cm in the VBPP and CT groups, respectively, indicating a large pneumothorax size for both patient cohorts. Clinical variables, such as age, gender, BMI, and pneumothorax size and chest tube duration, were similar in both groups (Table 1).

Three patients suffered a hemothorax in the VBPP group. Of these patients, two were successfully treated conservatively, while one patient underwent re-VATS. Likewise, 24 patients suffered a prolonged air leak following VBPP. In all the cases, the patients were successfully treated conservatively. Significant differences were found between the two groups in terms of patients' smoking behaviour and the length of hospital stay (LOS). The proportion of smokers was significantly higher and the LOS significantly longer in the VBPP group compared to the CT group. However, it must be considered that the LOS in the VBPP group was significantly prolonged by the preoperative period until surgery was performed (mean of 4.1 days).

Table 1. Clinical characteristics of the VBPP and CT group.

Variables	VBPP n = 62 (%)	CT n = 54 (%)	p-Value
Gender			
Male	48 (77.4)	38 (70.4)	
Female	14 (22.6)	16 (29.6)	0.376
Smoking status			
Smokers (current and past)	19 (30.6)	8 (14.8)	
Non-smokers	43 (69.4)	46 (85.2)	0.028 *
Pneumothorax size (cm)			
Initial size at presentation (mean)	13.4	13.9	0.778
Collins < 4 cm (n)	13 (21.0)	9 (16.7)	
Collins ≥ 4 cm (n)	47 (75.8)	42 (77.8)	
Missing (n)	2 (3.2)	3 (5.5)	0.527
Age (y)			
Median (Mean)	23 (24.6)	24.(25.3)	0.537
Height (m)			
Median (Mean)	1.8 (1.8)	1.8 (1.8)	1.000
Weight (kg)			
Median (Mean)	64.5 (67.1)	70 (68.6)	0.332
BMI (kg/m^2)			
Median (Mean)	20.5 (20.7)	21.4 (21.0)	0.348
Length of hospital stay (LOS) (days)			
Mean (range)	6.1 (3−13)	4.8 (2−7)	<0.001 *
Days until operation			
Mean (range)	4.1 (0−11)	/	/
Operation time (min)			
Mean (range)	79.4 (45–130)	/	/
Chest tube duration (days)			
Mean (range)	5.5 (3−8)	5.2 (2−6)	0.836
Time until recurrence (months)			
Mean (range)	59 (6−110)	9.6 (2−26)	<0.001 *
Complications (n)			
Hemothorax	3 (4.8)	0 (0.0%)	0.103
Prolonged air leak after surgery	24 (38.7)	/	/

Data are presented as mean, median, numbers (n) and percentages, BMI, body mass index; kg, kilogram; LOS, length of hospital stay; CT, chest tube; min, minutes; VBPP, VATS bullectomy with partial pleurectomy; m, meter; cm, centimeter; y, years. * p-value < 0.05 indicates statistical significance.

During a median follow-up period of 76.5 months (range 1–155 months), patients who underwent CT treatment experienced a significantly higher recurrence rate compared with patients following VBPP (VBPP vs. CT: 9.7% vs. 64.8%; $p < 0.0001$). This high rate of recurrence in the CT group occurred mainly within the first year after treatment (CT vs. VBPP: 9.6 months (range 2–26) vs. 59 months (range 6–110); $p < 0.001$). Interestingly, patients with a large pneumothorax size (Collins ≥ 4 cm) suffered a significantly higher rate of recurrence compared with patients with a small pneumothorax size (Collins < 4 cm vs. Collins ≥ 4 cm: 9.1% vs. 37%; $p = 0.010$) (Table 2).

Table 2. Patient clinical characteristics and recurrence rates of PSP.

Variable	Recurrence *n* (%)	*p*-Value
Gender		
Male	29 (33.7)	0.323
Female	12 (40.0)	
Age		
≤24 years	22 (33.4)	0.756
>24 years	19 (36.5)	
BMI		
≤20.85 kg/m^2	20 (35.5)	0.843
>20.85 kg/m^2	21 (36.2)	
Smoking status		
Smokers (current and past)	6 (22.2)	0.186
Non-smokers	35 (39.3)	
Treatment		
VBPP	6 (9.7)	<0.0001 *
CT	35 (64.8)	
Pneumothorax size (cm)		
Collins < 4 cm	2 (9.1)	0.010 *
Collins ≥ 4 cm	37 (41.6)	

Kg, kilogram; m, meter, VBPP, VATS bullectomy with partial pleurectomy; CT, chest tube; BMI, body mass index. * *p*-value < 0.05 indicates statistical significance.

Next, we investigated potential risk factors for recurrent pneumothorax in our patient cohort. Univariate analysis revealed that treatment of PSP patients with VBPP (VBPP vs. CT: HR 0.056; CI: 0.023–0.14; $p < 0.001$) and a small size of the initial pneumothorax (Collins ≥ 4 cm vs. Collins < 4 cm: HR 4.602; CI: 1.106–19.151; $p = 0.020$) were significantly associated with a lower risk of pneumothorax recurrence (Table 3; Figure 1A,B). Both factors, namely the therapeutic procedure chosen (VBPP vs. CT: HR 0.047; CI: 0.017–0.132; $p < 0.001$) and the baseline pneumothorax size (Collins ≥ 4 cm vs. Collins < 4 cm: HR 6.325; CI: 1.372–29.162; $p = 0.018$), were confirmed as independent predictive markers of pneumothorax recurrence in multivariate regression analysis (Table 4).

Table 3. Univariate analysis of potential risk factors for recurrence of PSP.

Risk Factor	Hazard Ratio	95% CI	*p*-Value
Gender			
Male vs. female	0.864	0.44–1.695	0.668
Age			
>median vs. ≤median	1.088	0.588–2.011	0.787
BMI			
>median vs. ≤median	1.155	0.623–2.139	0.644
Smoking status			
Smoker vs. non-smokers	0.536	0.220–1.246	0.133
Treatment			
VBPP vs. CT	0.056	0.023–0.14	<0.001 *
Pneumothorax size			
Collins ≥ 4 vs. Collins < 4	4.602	1.106–19.151	0.020 *

Univariate analysis displays potential risk factors that might influence recurrence-free survival (RFS). Patients with a large pneumothorax size (Collin ≥ 4) and those treated by chest tube (CT) have a significantly low RFS. * *p*-value < 0.05 indicates statistical significance. VBPP, VATS bullectomy with partial pleurectomy; BMI, body mass index; CI, confidential interval.

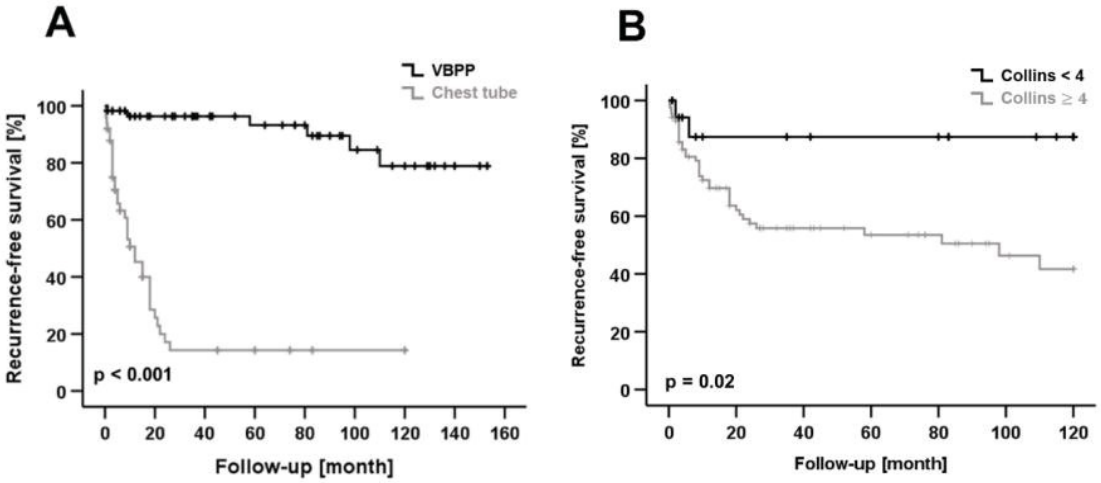

Figure 1. (**A**) Kaplan–Meier curve shows recurrence-free survival (RFS) after treatment by surgery (VBPP) or chest tube (CT). VBPP was associated with significantly better RFS compared to CT treatment. (**B**) Patients with a large pneumothorax size (Collins ≥ 4 cm) had a significantly reduced RFS compared to patients with a small pneumothorax size (Collins < 4 cm).

Table 4. Multivariate analysis of potential risk factors for recurrence of PSP.

Risk Factor	Hazard Ratio	95% CI	*p*-Value
Treatment			
VBPP vs. CT	0.047	0.017–0.132	<0.001 *
Pneumothorax size			
Collins ≥ 4 vs. Collins < 4	6.325	1.372–29.162	0.018 *

Multivariate analysis displayed initial pneumothorax size and administered treatment as independent risk factors for PSP recurrence. Chest tube (CT) treatment and a large pneumothorax size (Collins ≥ 4) were associated with a significantly reduced recurrence-free survival. * *p*-value < 0.05 indicates statistical significance. VBPP, VATS bullectomy with partial pleurectomy; CI, confidential interval.

4. Discussion

Nowadays, VATS–bullectomy with partial pleurectomy (VBPP) is a well-established and increasingly used surgical treatment for primary spontaneous pneumothorax (PSP). Recently, VBPP has been reported with superior performance and low rates of recurrence compared to VATS bullectomy alone [20,21,24,25]. However, only a few studies elucidate its effectiveness in terms of long-term outcomes. Additionally, studies that examine potential risk factors for PSP recurrence following surgical treatment are rare. In this study, we evaluated the long-term recurrence rates of patients treated with VBPP or CT in our institution. Moreover, we examined underlying clinical factors that might influence disease recurrence in our patient cohort.

In our study, 62 patients with a mean age of 24.6 years underwent VBPP, while 54 patients (mean age 25.3 years) (Table 1) were successfully treated by chest tube. Compared to some previous studies in the literature with a high number of smokers in their PSP collective [12,16,17], we had a significantly low number of smokers in both groups of our patient cohort (Table 1). This might be due to the increased awareness campaigns and information about the negative effects of smoking on human health over the last years. Interestingly, the length of hospital stay (LOS) of patients in the VBPP group was significantly longer than in the CT group. Although the LOS in the VBPP group was consistent with previous studies reporting the hospitalization time after VATS in the literature [27,28], this result was significantly prolonged by the number of hospital days until surgery was performed (Table 1).

During a follow-up period of 76.5 months (range 1–155 months), six (9.7%) patients suffered a recurrence following VBPP. Compared to the VBPP group, the CT group experienced

a higher recurrence rate of 64.8% (35 patients recurred, Table 2). This difference was statistically significant in the univariate (VBPP vs. CT: HR 0.056; CI: 0.023–0.14; $p < 0.001$) and multivariate analyses (VBPP vs. CT: HR 0.047; CI: 0.017–0.132; $p < 0.001$) (Tables 3 and 4). These results demonstrate that VBPP is associated with an increased recurrence-free survival compared to CT treatment. The recurrence rate of 9.7% of our VBPP cohort is slightly higher than some studies described in the literature. In the study of Imperatori, A. et al. [23] with 134 patients, VATS blebectomy and parietal pleurectomy had a recurrence rate of 6%. The median follow-up was 79 months (range: 36–187 months). Shaikhrezai, K et al. [24] observed no recurrent pneumothorax of 44 PSP patients operated by VATS bullectomy and partial pleurectomy during a median follow-up of 73 months. In a recent study of Caecilia Ng et al. [25], in which 73 PSP patients underwent VATS partial pleurectomy, a recurrence rate of 1.4% at a median follow-up period of 58.5 months was reported. Although the above recurrence rates are lower than the recurrence rate of our VBPP cohort, none of them evaluated the pneumothorax size as a potential risk factor for PSP recurrence. In our study, the patients presented with a large pneumothorax size estimated according to the method of Collins. The mean pneumothorax size of the VBPP group was 13.4 cm and 13.9 cm for the CT group. As reported in earlier studies, a large pneumothorax size is a risk factor for PSP recurrence [9,29,30]. Therefore, we assumed that the large pneumothorax size of our PSP cohort influenced our comparatively high rate of recurrence.

To determine potential risk factors for recurrence, we analyzed the impact of clinical factors, such as gender, age, BMI, smoking status, pneumothorax size, and the treatment modality on PSP recurrence. Treatment by CT placement (VBPP vs. CT: HR 0.047; CI: 0.017–0.132; $p < 0.001$) and a large pneumothorax size (Collins $\geq$ 4 cm vs. Collins < 4 cm: HR 6.325; CI: 1.372–29.162; $p = 0.018$) proved to be independent risk factors for disease recurrence in our PSP patient cohort. These results highlight the high efficacy of VBPP in the treatment of patients with PSP and the clinical importance of the initial pneumothorax size as a significant risk factor for disease recurrence. Noteworthy, other potential risk factors for disease recurrence, such as family history of pneumothorax, presence of connective tissue disorders, cannabis consumption, and scoliosis, were also investigated. However, the small number of patients with these risk factors limited the statistical analysis, and thus, they were not included as risk factors in this study.

The indication to perform surgery (VBPP) might differ internationally. However, our data demonstrate that the risk of recurrent pneumothorax can be significantly reduced by VBPP. In addition, our data highlight the fact that a large initial pneumothorax size is associated with a markedly increased risk of pneumothorax recurrence. Obviously, the power of our study is limited due to its retrospective design and the small number of patients included, but the logical consequence based on our observations would be to prefer VBPP to simple chest drainage in patients with a large pneumothorax size. However, this observation should be verified in large prospective randomized trials.

5. Conclusions

Our data confirm that VBPP is an effective and safe surgical treatment for PSP. It is associated with a very low risk of disease recurrence. A large pneumothorax size is an independent risk factor for recurrence of PSP. Therefore, the option of VBPP should be discussed early for PSP patients treated with a large pneumothorax size, and close follow-ups should be performed due to the high risk of recurrence.

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Video-Assisted Thoracoscopic Surgery with Bullectomy and Partial Pleurectomy versus Chest Tube Drainage for Treatment of Secondary Spontaneous Pneumothorax—A Retrospective Single-Center Analysis

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Abstract: *Background and objective:* Current guidelines recommend chest tube (CT) drainage as the initial treatment of secondary spontaneous pneumothorax (SSP). Surgery should be considered in cases of persistent air leak or recurrent disease. Video-assisted thoracoscopic surgery (VATS) is nowadays an established surgical treatment for complicated spontaneous pneumothorax. However, reports on VATS-bullectomy with partial pleurectomy (VBPP) for treatment of secondary spontaneous pneumothorax (SSP) are limited. The primary aim of this study was to evaluate and compare the clinical outcomes of patients with secondary pneumothorax treated either by VBPP or CT drainage in our institution. Secondly, we assessed underlying clinical parameters to identify potential risk factors for SSP recurrence. *Materials and Methods:* Eighty-two patients were included in this study. Long-term recurrence rates and potential risk factors for SSP recurrence were analyzed. *Results:* Thirty-six patients (43.9%) underwent VBPP, whereas 46 (56.1%) patients subsequently underwent CT treatment. During a median follow-up period of 76.5 months, VBPP patients experienced a significantly low recurrence rate compared to CT patients (VBPP vs. CT: 16.7% vs. 41.3%; $p = 0.016$). However, VBPP was associated with a higher complication rate and significantly longer length of hospital stay (LOS). Male sex (male vs. female: $p = 0.021$) and CT treatment (VBPP vs. CT: $p < 0.001$) were identified as potential risk factors for SSP recurrence. *Conclusions:* VBPP is a suitable surgical treatment for SSP. However, prolonged LOS and possible complications should be discussed prior to VBPP.

Keywords: VATS-bullectomy; partial pleurectomy; chest tube; recurrence; SSP

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1. Introduction

Spontaneous pneumothorax (SP) describes the presence of air without preceding trauma within the pleural space. SP in patients with an underlying pulmonary disease, commonly chronic obstructive pulmonary disease (COPD), is classified as secondary spontaneous pneumothorax (SSP). In most cases, the patients are 45 years of age or more [1]. The incidence of SSP has been reported with approximately 2.0 and 6.3 cases per 100,000 individuals per year in females and males, respectively [2].

In contrast to patients with primary spontaneous pneumothorax (PSP), secondary spontaneous pneumothorax is a potential life-threatening condition due to its cardiopulmonary compromise [3,4]. Therefore, immediate diagnosis and treatment of SSP is mandatory. At the initial presentation of SSP, current guidelines recommend, depending on the patient's clinical condition, oxygen supplementation, needle-aspiration, and chest tube (CT)

drainage [1,5,6]. Despite high rates of treatment failure, CT drainage is still the most commonly used initial treatment [1,5,6]. In most cases, surgery is recommended for persistent air leak after CT drain placement and for patients with recurrent disease. However, due to the underlying clinical disease, patients with SSP are more likely to experience treatment failure and in-hospital mortality even after surgery [7,8].

In previous studies [3,9,10], surgery for SSP (VATS-talc pleurodesis, open thoracotomy, VATS-apical pleurectomy, VATS-pleural abrasion) was reported to be associated with a reduced risk of recurrence. However, data reporting the outcome of SSP after VATS-bullectomy with partial pleurectomy (VBPP) are limited. Moreover, studies that evaluate risk factors for SSP recurrence are lacking.

Therefore, the primary aim of this study was to evaluate and compare the outcomes and long-term recurrence rates of patients following VBPP and CT treatment in our institution. Secondly, we analyzed underlying clinical factors to determine potential predictors for SSP recurrence in our patient cohort.

2. Materials and Methods

We retrospectively reviewed the data of 82 patients with secondary spontaneous pneumothorax (SSP), treated either by VATS-bullectomy with partial pleurectomy (VBPP) or by chest tube (CT) only between January 2008 and December 2020 in our institution. Patient demographics, including age, sex, body mass index (BMI), COPD stage, ECOG status, Charlson Comorbidity Index score, treatment modality, etiological cause of SSP, post-treatment complications, length of hospital stay (LOS), and size of the pneumothorax, were retrieved from medical records. The size of the pneumothorax was assessed using the regression formula derived from the method of Collins [11]. According to the actual German S3 guidelines, a spontaneous pneumothorax (SP) is considered as large when the sum of the interpleural distances derived from the Collins method is $\geq$4 cm [1]. Hence, in this study, we considered a spontaneous pneumothorax to be large at a size of $\geq$4 cm.

At the initial presentation of SSP, identified patients received chest tube (CT) treatment. Patients who were initially successfully treated with CT or were unsuitable for surgery (high Charlson Comorbidity Index score or poor ECOG status) and underwent only CT treatment during our study period were classified in the CT group. For patients suitable for surgery, indication for surgical therapy (VBPP) included persistent air leak for more than 5 days following CT treatment (n = 16) and ipsilateral or contralateral recurrent pneumothorax (n = 20). Prior to surgery, a computer tomography of the chest was performed to detect the cause of SSP and to determine the extent of a bullous disease. A team of three specialized thoracic surgeons (W.-T.K., A.S., A.R.) made an indication for surgery. Of note, indication for surgery was made individually depending on the comorbidity and underlying pulmonary disease as well as the patient's choice. Patients with incomplete follow-up data and patients who received other treatment modalities (e.g., thoracotomy, apical pleurectomy, observation, needle aspiration) were excluded from this study. The primary endpoint of this study was to assess and compare the clinical outcomes and long-term recurrence rates after VBPP and CT treatment in our institution. Additionally, we analyzed underlying clinical parameters to determine potential risk factors for disease recurrence in our patient cohort. Recurrence was described as an ipsilateral or contralateral pneumothorax detected on a chest radiograph or computed tomography of the lung at presentation in our emergency room after treatment by VBPP or CT. The local ethics committee of the Heinrich-Heine University Clinic of Duesseldorf approved this study (study-no: 2020-1271, date of approval: 11.01.2021).

2.1. Surgical Technique: VATS-Bullectomy with Partial Pleurectomy (VBPP)

A team of three thoracic surgeons (A.S., A.R., and W.-T.K.) performed all surgical procedures and postoperative patient follow-up. All the patients were treated under general anesthesia with a double-lumen tube intubation and single-lung ventilation. After lateral positioning of the patient, video-assisted thoracoscopic surgery (VATS) was performed in

the conventional two- or three-port approach. The initial thoracoscopy was undertaken for thorough inspection of the visceral and parietal pleura. The bullectomy was carried out by wedge resection using an endoscopic stapling device (Autosuture GIA Universal; COVIDIEN^{TM}, Mansfield, MA, USA) when a ruptured bleb or bulla was identified. (For patients with extensive bullous disease, only the ruptured bleb/bulla and ultrathin bulla with a high risk of rupture were resected.) Only one patient underwent anatomical lung resection for stage I lung cancer. A partial pleurectomy was performed beginning from the apex of the pleural cavity. During this procedure, the parietal pleura was carefully separated from the endothoracic fascia while sparing the region of the subclavian artery and vein to avoid injury of these structures. A pleurectomy was performed up to the 7th or 8th intercostal space in a blunt manner. After cautious haemostasis of the endothoracic fascia using electrocautery to reduce the risk of hemothorax, one 24 Fr. chest tube was inserted and connected to a digital underwater seal system (Thopaz^{+}, Medela AG, Baar, Switzerland) with a suction of −20 mm Hg. During postoperative care, the chest tube drain was removed when no clinical signs of air leak and a drain output of less than 200 mL after 24 h was evident. After the chest tube removal, a chest radiograph was taken to verify full expansion of the lung. All the patients received our standard postoperative medication regimen of analgesia (non-opioid, orally, or intravenously). The patients received either Metamizol-Natrium 1000 mg, Paracetamol 1000 mg, or Ibuprofen 600 mg four times per day. In cases of persistent pain using the standard pain medication regimen, we applied Piritramide (opioid) 7.5 mg intravenously every 4–6 h on patient request.

2.2. Outpatient Care and Follow-Up

One week after discharge, the patients visited our outpatient clinic for postoperative control and follow-up. These visits continued at 3-month intervals for one year. A chest radiograph was taken at each visit. Patients were advised to visit our emergency room at any time they had symptoms related to recurrent pneumothorax, such as dyspnoea or chest pain. Recurrent pneumothorax was identified clinically in each case with a chest radiograph and a computed tomography of the lung. For patients who recurred after CT or VBPP treatment, a VBPP or re-VATS was performed, respectively, depending on the patient's clinical condition, underlying pulmonary disease, and the patient's choice. For long-term follow-up, patients were contacted and assessed with a questionnaire.

2.3. Statistical Analysis

Continuous data were tested for normal distribution using the Shapiro–Wilk test. Subsequently, the two-sample *t*-test was used for normally distributed data. For comparison of non-normally distributed data, the Mann–Whitney U test was applied. For categorical data, the chi-square test was used. Recurrence-free survival (RFS) was defined as the time between initial treatment by surgery (VBPP) or chest tube drainage (CT) and the ipsilateral or contralateral occurrence of recurrent pneumothorax. To identify potential risk factors for recurrent pneumothorax, Kaplan–Meier curves were generated and evaluated using the log-rank test. In addition, hazard ratios (HRs) with 95% confidence intervals (CIs) were estimated using a univariate Cox regression analysis. All variables potentially relevant to the development of recurrent secondary pneumothorax from a clinical point of view were then included into a multivariate Cox regression analysis. Statistical significance was assumed at $p < 0.05$. All data were analyzed using the SPSS 25.0 software program (Statistical Package for Social Sciences; SPSS Inc., Chicago, IL, USA).

3. Results

Between January 2008 and December 2020, 90 patients with secondary spontaneous pneumothorax (SSP) were treated either by VATS-bullectomy with partial pleurectomy (VBPP) or by chest tube (CT) in our institution. Eight patients were lost during follow-up and were excluded from this study. A total of 82 patients with a median age of 65 years (range 41–86) were included in this study. Thirty-six patients underwent VBPP, while

46 patients received CT treatment. The clinical characteristics of the patients and etiological causes of the SSP are summarized in Table 1.

Table 1. Clinical characteristics and cause of SSP of the VBPP and CT groups.

Variables	VBPP (n = 36)	CT (n = 46)	p-Value
Gender			
Male	19 (52.8%)	27 (58.7%)	
Female	17 (47.2%)	19 (41.3%)	0.592
Smoking status			
Smokers (current and past)	30 (83.3%)	31 (67.4%)	
Non-smokers	6 (16.7%)	15 (32.6%)	0.101
Pneumothorax size (cm)			
Collins < 4 cm	5 (13.9%)	4 (8.7%)	
Collins ≥ 4 cm	30 (83.3%)	41 (89.1%)	
Missing	1 (2.8%)	1 (2.2%)	0.449
Age (yrs.)			
Median (Range)	65 (41–87)	60.5 (41–92)	0.144
Height (m)			
Mean (SD)	1.73 (0.08)	1.72 (0.08)	0.498
Weight (kg)			
Mean (SD)	65.8 (10.51)	64.7 (11.39)	0.655
BMI (kg/m^2)			
Median (Mean)	21.5 (22)	20.8 (21.8)	0.483
ECOG status			
Grade 0–1	27 (75%)	23 (50%)	
Grade 2–3	8 (22.2%)	12 (26.1%)	
Grade 4	1 (2.8%)	11 (23.9%)	0.238
Charlson Comorbidity Index (score)			
1–2	20 (55.6%)	24 (52.2%)	
3–4	14 (38.9%)	12 (23.1%)	
5	2 (5.5%)	10 (24.7%)	0.302
Length of hospital stay (LOS) (days)			
Mean (SD)	14.1 (8.99)	9.3 (4.82)	0.006 *
Days until operation			
Mean (SD)	7.1 (2.65)	/	/
Complications			
Hemothorax	5 (13.9%)	1 (2.8%)	0.043 *
Acute pneumonia	11 (30.6%)	5 (10.9%)	0.026 *
Clavien-Dindo grade			
Grade I	0 (0%)	0 (0%)	
Grade II	14 (87.5%)	6 (100%)	
Grade IIIa	2 (12.5%)	0 (0%)	0.375
In-hospital mortality	0 (0%)	0 (0%)	1.00
COPD stage			
No COPD	7 (19.4%)	11(23.9%)	
COPD Gold I	5 (13.9%)	2 (4.3%)	
COPD Gold II	6 (16.7%)	3 (6.5%)	
COPD Gold III	13 (36.1%)	21 (45.7%)	
COPD Gold IV	5 (13.9%)	9 (19.6%)	0.282
Cause of SSP			**Total (N)**
COPD	29 (80.6%)	35 (76.1%)	64
Tuberculosis	6 (16.7%)	5 (10.9%)	11
Lung cancer	1 (2.7%)	6 (13%)	7

Data are presented as numbers and percent or median and mean. kg: kilogram, COPD: chronic obstructive pulmonary disease, m: metre, cm.: centimetre, yrs.: years, CT: chest tube, SSP: secondary spontaneous pneumothorax, VBPP: VATS-bullectomy with partial pleurectomy, N = sum of the number of patients in both groups. * p-value < 0.05 indicates statistical significance.

Clinical variables, such as age, gender, BMI, pneumothorax size, COPD stage, ECOG status and Charlson Comorbidity Index, were similar in both groups (Table 1). However, two patients underwent VBPP, whereas 10 patients received CT treatment despite a Charlson Comorbidity Index score of five. VBPP was performed in this case on the patient's choice despite the associated high risk of one-year mortality. Post-treatment complications such hemothorax (VBPP vs. CT: 13.9% vs. 2.8%, $p = 0.43$) and acute pneumonia (VBPP vs. CT: 30.6% vs. 10.9%, $p = 0.026$) were significantly more common in the VBPP cohort. Three patients who suffered a hemothorax in the VBPP group were successfully treated conservatively, while two patients underwent re-VATS. The patient who suffered a hemothorax after CT treatment was conservatively treated. In both groups, patients with acute pneumonia were treated successfully with our standard regimen of antibiotics. The high rate of acute pneumonia in the VBPP group seems to be related to postoperative pain, which might have impaired breathing exercises during the first postoperative days. During the clinical course, none of the patients died after treatment in both groups. Additionally, the mean length of hospital stay (LOS) was significantly longer in the VBPP group compared with the CT group (VBPP vs. CT: 9.3/14.1; $p = 0.006$). However, it should be considered that the LOS in the VBPP group was significantly prolonged by the preoperative period until surgery was performed (mean of 7.1 days) (Table 1).

During a median follow-up period of 76.5 months (range 1–155 months), patients who underwent CT treatment experienced a significantly higher recurrence rate compared with patients following VBPP (VBPP vs. CT: 16.7% vs. 41.3%; $p = 0.016$). Interestingly, male gender was associated with a significantly higher rate of recurrence compared to female gender (male vs. female: 41.3% vs. 16.7%; $p = 0.016$) (Table 2).

Table 2. Patient clinical characteristics and recurrence rates of SSP.

Variable	Recurrence *n* (%)	*p*-Value
Gender		
Male	19 (41.3)	
Female	6 (16.7)	0.016 *
Age		
≤median (63 years)	14 (31.8)	
>median (63 years)	11 (28.9)	0.778
BMI		
≤median (21.1 kg/m^2)	13 (31.0)	
>median (21.1 kg/m^2)	12 (30.0)	0.925
Smoking status		
Smokers (past and current)	8 (38.1)	
Non-smokers	17 (27.3)	0.380
Treatment		
VBPP	6 (16.7)	
CT	19 (41.3)	0.016 *
Pneumothorax size		
Collins < 4 cm	3 (33.3)	
Collins ≥ 4 cm	20 (28.2)	0.747
Side of recurrence at presentation		
Ipsilateral	12 (60)	
Contralateral	8 (40)	0.211
COPD stage		
No COPD	4 (22.2)	
COPD Gold I-IV	21 (32.8)	0.389
Other causes of SSP		
Tuberculosis	4 (22.2)	
Lung cancer	0 (77.8)	0.024 *

Data are presented as numbers and percent, median and range (for non-normally distributed data) and mean and standard deviation (SD) (for normally distributed data). kg: kilogram, COPD: chronic obstructive pulmonary disease, m: metre, cm.: centimetre, yrs.: years, CT: chest tube, VBPP: VATS-bullectomy with partial pleurectomy, N = sum of the number of patients in both groups. * p-value < 0.05 indicates statistical significance.

Moreover, we investigated the potential risk factors for the recurrence of secondary spontaneous pneumothorax (SSP) in our patient cohort. A univariate analysis revealed that the treatment of SSP with VBPP (CT vs. VBPP: HR 0.196; CI: 0.077–0.498; $p < 0.001$) and female sex (female vs. male: HR 2.803; CI: 1.118–7.030; $p = 0.021$) were associated with a significantly lower risk of SSP recurrence (Table 3; Figure 1A,B). Interestingly, the treatment modality chosen (CT vs. VBPP: HR 0.151; CI: 0.051–0.441; $p = 0.001$) was confirmed as the only independent predictive marker of SSP recurrence in the multivariate Cox regression analysis (Table 4).

Table 3. Univariate analysis of potential risk factors for recurrence of SSP.

Risk Factor	Hazard Ratio	95% CI	*p*-Value
Gender			
Female vs. Male	2.803	1.118–7.030	0.021 *
Age			
≤63 years vs. >63 years	0.811	0.368–1.790	0.602
BMI			
≤21.1 kg/m^2 vs. >21.1 kg/m^2	1.073	0.489–2.355	0.861
Smoking status			
Non-Smokers vs. Smokers	0.690	0.297–1.601	0.382
Treatment			
CT vs. VBPP	0.196	0.077–0.498	<0.001 *
Pneumothorax size (cm)			
Collins < 4 vs. Collins ≥4	1.075	0.318–3.630	0.907
COPD stage			
COPD vs. no COPD	1.051	0.358–3.082	0.927

Univariate analysis displays potential risk factors for the recurrence of SSP. Patients treated by chest tube (CT) and male patients had a significantly higher risk of SSP recurrence. * *p*-value < 0.05 indicates statistical significance. VBPP: VATS-bullectomy with partial pleurectomy, COPD: chronic obstructive pulmonary disease, BMI: body mass index, CI: confidential interval, SSP: secondary spontaneous pneumothorax.

Table 4. Multivariate Cox regression analysis of potential risk factors for recurrence of SSP.

Risk Factor	B	SE	Wald	Hazard Ratio	95% CI	*p*-Value
Gender						
Female vs. Male	0.931	0.494	3.544	2.536	0.962–6.684	0.060
Age						
≤63 years vs. >63 years	0.005	0.018	0.065	1.005	0.969–1.041	0.799
BMI						
≤21.1 kg/m^2 vs. >21.1 kg/m^2	0.237	0.487	0.237	1.268	0.488–3.294	0.627
Smoking status						
Non-smokers vs. Smokers	−0.090	0.500	0.032	0.914	0.343–2.437	0.857
Treatment						
CT vs. VBPP	−1.893	0.548	11.938	0.151	0.051–0.441	0.001 *
Pneumothorax size (cm)						
Collins < 4 vs. Collins ≥ 4	−0.433	0.738	0.345	0.648	0.153–2.755	0.557
COPD						
no COPD vs. COPD	0.610	0.685	0.793	1.840	0.481–7.041	0.373

Multivariate Cox regression analysis displayed the treatment modality chosen (CT or VBPP) as the only independent risk factor for SSP recurrence. VATS-bullectomy with partial pleurectomy (VBPP) treatment was associated with a significantly lower risk of SSP recurrence. * *p*-value < 0.05 indicates statistical significance. VBPP: VATS-bullectomy with partial pleurectomy, CI: confidential interval, BMI: body mass index, B: coefficient beta, SE: standard error, Wald: Wald's statistics.

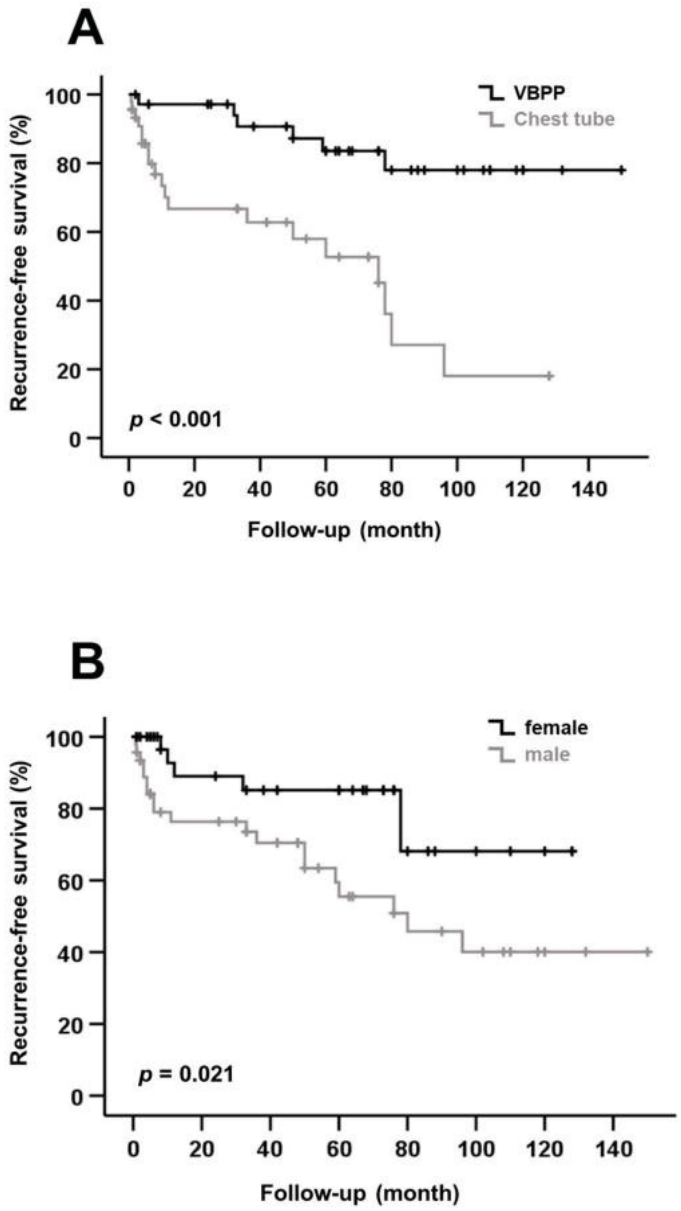

Figure 1. (**A**) Kaplan–Meier curve shows recurrence-free survival (RFS) after treatment by VATS-bullectomy with partial pleurectomy (VBPP) or chest tube (CT). VBPP was associated with significantly better RFS compared to CT treatment. (**B**) Male sex was associated with a significantly shorter RFS compared with female sex.

4. Discussion

Due to the underlying pulmonary disease, secondary spontaneous pneumothorax (SSP) treatment requires a multimodal therapy concept. The challenging therapy aspect relies not only on the treatment of the pneumothorax, but also on the treatment of the underlying pulmonary disease. The actual guidelines recommend chest tube (CT) treatment for the initial SSP therapy. However, CT treatment has been reported to be associated with a high morbidity and recurrence rate [12,13]. Even after surgery, high morbidity and mortality rates have been reported [3,10,14]. This high morbidity and mortality rate depends not only on the underlying pulmonary disease, but also on the surgical technique implemented. Nowadays, VATS-bullectomy with partial pleurectomy (VBPP) is an increasingly used und well-established surgical technique for complicated spontaneous pneumothorax. In the treatment of primary spontaneous pneumothorax (PSP), VBPP has been well-reported to be

effective and is associated with low rates of recurrence compared to VATS-apical pleurectomy, VATS-talc pleurodesis and bullectomy alone [15–18]. For treatment of SSP, reports on clinical outcomes and recurrence rates following VBPP are rare. Additionally, studies that evaluate potential risk factors for SSP recurrence are lacking in the literature. Therefore, the primary aim of this study was to evaluate and compare the long-term recurrence rates of patients treated either by VBPP or by CT in our institution. Moreover, we examined underlying clinical factors that might influence SSP recurrence in our patient cohort.

In our study, a total of 82 SSP patients were included. Chronic obstructive pulmonary disease (COPD) was the main cause of SSP (n = 64), followed by tuberculosis (n = 11) and lung cancer (n = 7). The high number of COPD patients in our study confirms the observations of the current guidelines that COPD is the main etiological cause of SSP [1,5,6]. Thirty-six patients with a median age of 65 years underwent VATS-bullectomy with partial pleurectomy (VBPP), while 46 patients (median age of 60.5 years) were successfully treated by chest tube (CT) only. During a median follow-up period of 76.5 months (range 1–155 months), patients who underwent CT treatment experienced a significantly higher recurrence rate compared with patients following VBPP (VBPP vs. CT: 16.7% vs. 41.3%; $p = 0.016$). This difference was statistically significant in the univariate (CT vs. VBPP: HR 0.196; CI: 0.077–0.498; $p < 0.001$) and multivariate Cox regression analyses (CT vs. VBPP: B: −1.893; SE: 0.548; HR 0.151; CI: 0.051–0.441; $p = 0.001$). These results confirm that treatment by VBPP is associated with significantly lower SSP recurrence. The rate of SSP recurrence after VBPP in our study was significantly lower than the only comparable long-term study we found in the literature [17]. In this study of Shaikhrezai K et al. [17], five SSP patients underwent VBPP, of which two (40%) patients recurred during a median follow-up period of 73 months. Interestingly, our results of recurrence after VATS with mechanical pleurodesis (VBPP) is similar to the results of a previously reported study by Kim SJ et al. [19]. In this study, 22 patients after VATS-chemical pleurodesis (Talc–pleurodesis) displayed a significantly low rate of recurrence compared to 32 patients who underwent chemical pleurodesis via chest tube only. Our results and those of Kim SJ et al. confirm the efficacy of VATS with additional pleurodesis (chemical or mechanical) as a surgical technique to reduce recurrent disease and also demonstrate the ineffectiveness of chest tube drainage only as well as pleurodesis via chest tube drainage as treatment techniques to prevent recurrence.

Compared with the CT group, patients in the VBPP group had a significantly longer length of hospital stay (LOS) (VBPP vs. CT: 14.1 days vs. 9.3 days, $p = 0.006$) and higher post-treatment complications (five patients suffered a hemothorax and two patients had an acute pneumonia; Table 1). The LOS in the VBPP group was significantly prolonged by the number of hospital days until surgery was performed (mean of 7.1 days). Additionally, a long recovery period after surgery due to the underlying pulmonary disease and the high rates of post-treatment complications certainly affected the LOS in the VBPP group. The LOS in both groups was comparable to previously reported studies in the literature [17,20]. With regard to complication rates, the number of patients who suffered a hemothorax was significantly higher in the VBPP group compared to patients after CT treatment (VBPP vs. CT: 13.9% vs. 2.8%, $p = 0.043$). We assume that the extent of pleurectomy during VBPP markedly influenced the occurrence of hemothorax. Two patients underwent re-VATS for hemothorax in the VBPP group, whereas three patients were successfully treated conservatively. We also observed a significantly higher rate of acute pneumonia in the VBPP group compared with the CT group (VBPP vs. CT: 30.6% vs. 10.9%, $p = 0.026$). This high rate of acute pneumonia in the VBPP group could be related to post-treatment pain, which might have impaired early breathing exercises and mobilization during the first postoperative days. In both groups, the patients were successfully treated with our standard regimen of antibiotics. During the clinical course, we observed no cases of in-hospital mortality in either group.

Analyses of potential risk factors for SSP recurrence, such as pneumothorax size, age, gender, BMI, COPD, smoking status, and treatment modality, revealed that male sex and

treatment by chest tube (CT) were associated with a high risk of disease recurrence. As mentioned above, only treatment by CT was proven to be an independent risk factor for SSP recurrence in the multivariate Cox regression analysis.

The power of our study is limited due to its retrospective design, the lack of a surgical control group (e.g., VATS-apical pleurectomy, VATS-pleural abrasion) or a control group following chemical pleurodesis (e.g., VATS-Talc pleurodesis, chest tube-Talc/Doxycycline pleurodesis). Additionally, the small number of patients included limited possible subgroup analyses. Nevertheless, our results suggest that treating SSP patients with VATS-bullectomy and partial pleurectomy (VBPP) significantly reduces the long-term risk of disease recurrence compared with chest tube placement alone. It is associated with very low in-hospital mortality (in our study 0%). However, this advantage seems to be bought by a higher complication rate and a longer length of hospital stay. A prospective randomized trial with a large number of patients is needed to verify this observation

5. Conclusions

VBPP is a suitable surgical treatment for SSP. It is associated with a very low risk of disease recurrence. Therefore, VBPP should be offered as a treatment modality for patients with complicated SSP (recurrence or persistent air leak). However, prior to surgery, the underlying pulmonary disease, Charlson Comorbidity Index, and ECOG status should be considered, as these factors might prolong the length of hospital stay and negatively impact the patient as well as the surgical outcome.

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Does Video-Assisted Thoracoscopic Surgery with Bullectomy and Partial Pleurectomy for Primary Spontaneous Pneumothorax Impair Health-Related Quality of Life and Pulmonary Function?

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Abstract: Background: Video-assisted thoracoscopic surgery (VATS) with partial pleurectomy is an established treatment for primary spontaneous pneumothorax (PSP). However, postoperative pulmonary function and health-related quality of life (HR-QoL) after VATS–bullectomy with partial pleurectomy (VBPP) have not been elucidated. Methods: Eligible patients were assessed for HR-QoL using the Short-Form 36 (SF-36) health survey. Pulmonary function (PF) was evaluated by spirometry. We compared the results of the VBPP cohort with the German national norms, and with a similar cohort of patients successfully treated by chest tube (CT) only. Results: A total of 25 VBPP patients completed the SF-36 health survey, of whom 15 presented for PF assessment. Between the VBPP and CT groups, the mean forced vital capacity (FVC), forced expiratory volume in one second (FEV1), and FEV1/FVC ratio were not statistically significantly different. However, in both groups, FVC, FEV1, and FEV1/FVC were above the lower limit of normal (LLN), suggesting no restrictive or obstructive patterns. Compared with the sex- and age-matched normal German population, patients who underwent VBPP displayed a similar physical component summary score and a significantly decreased mental component summary score. Interestingly, comparison of the SF-36 domains between the VBPP and CT groups showed no statistical difference. Conclusion: VBPP is a suitable surgical treatment for PSP, with no apparent adverse impacts on pulmonary or physical function. However, psychological distress and measures to counteract its impact should be considered.

Keywords: VATS; quality of life; pulmonary function

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1. Introduction

According to the German S3 guidelines, primary spontaneous pneumothorax (PSP) describes the presence of air within the pleural space of patients under 45 years of age, without preceding trauma or underlying pulmonary disease [1]. The incidence of PSP has been reported at 1–9.8 and 7–24 cases per 100,000 individuals per year in females and males, respectively [2,3]. Due to the low recurrence and morbidity rates, current guidelines recommend video-assisted thoracic surgery (VATS) for surgical treatment of PSP in cases with ipsilateral recurrence or persistent air leakage after pleural drainage [1,4,5].

VATS is a safe and well-established technique for surgical management of PSP [6]. In previous studies, VATS–bullectomy alone for PSP was demonstrated to have recurrence

rates of up to 20% [7,8]. When combined with pleurectomy, the short- and long-term recurrence rates were reduced to 1–6% [6,9–11]. To date, studies that evaluate preoperative lung function of patients at first presentation of PSP are lacking. This is most likely due to the acute symptoms at presentation, which might be life-threatening and may require emergency treatment. Additionally, reports that elucidate the impact of VATS, particularly in combination with bullectomy and pleurectomy on pulmonary function after treatment are lacking. It is thus still unknown whether wedge resection of blebs or pleurectomy to ensure tight adhesion of the affected lung to the thoracic wall cause restrictive pulmonary function impairment. Due to the acute symptoms at presentation, pretreatment data were not collected in this study. Thus, we assessed the pulmonary function of our patients following VBPP and CT treatment.

Moreover, any treatment that impairs the social, mental, and physical health of a patient may severely affect their quality of life (QoL). Various surveys have been developed to evaluate the health status and quality of life of patients affected by administered treatments. The SF-36 health survey is a well-established and reliable survey suitable for use in clinical practice and for research [12,13]; it has been widely used in patients of various ages, diagnoses, and nationalities to compare the effects of diseases and the benefits of various treatments [14–16]. Regarding surgical treatment of PSP, changes in quality of life after VATS have rarely been reported [17]. Furthermore, the impact of additional bullectomy and partial pleurectomy on the health-related quality of life (HR-QoL) remains unknown.

Therefore, the aim of this study was to evaluate the HR-QoL and postoperative pulmonary function of PSP patients following VBPP in our institution, and to compare our results with a similar group of patients successfully treated with chest tube drainage only. Additionally, we compared the results of our VBPP cohort with the sex- and age-matched normative data from the general German population.

2. Materials and Methods

This was a prospective non-randomized single-centre study. The local Institutional Review Board of the Heinrich Heine University Clinic Dusseldorf approved this study (ref Nr: 2020-1271). Between January 2017 and December 2019, 34 patients underwent VATS–bullectomy with partial pleurectomy due to PSP in our hospital. All patients presented in our emergency room with severe symptoms, and were scheduled for emergency or expedited operation. The patients were contacted one year after surgery and assessed for HR-QoL and pulmonary function at our outpatient clinic. Of these patients, 25 patients with a mean age of 26.1 years (range 17–42) completed the survey and were included in this study; 15 of those 25 patients presented in our outpatient clinic, and were assessed for pulmonary function. For comparability, and to explore the impact of VBPP on pulmonary function and HR-QoL, a control group of 25 eligible patients with mean age of 27 years (range 19–40), who underwent successful chest tube (CT) treatment between January 2018 and April 2020, were included in this study. For pulmonary function, data on 15 patients were evaluated. Likewise, these patients were contacted one year after CT treatment and assessed for HR-QoL and pulmonary function at our outpatient clinic

2.1. Surgical Procedure: VATS–Bullectomy with Partial Pleurectomy

All patients in this study underwent the same surgical procedure. In all cases, partial pleurectomy and bullectomy of one or more lung segments was performed. VATS was carried out under general anaesthesia with a double-lumen tube intubation and single lung ventilation. After lateral positioning of the patient, thoracoscopy was performed in the conventional two- or three-port approach. Bullectomy was carried out via wedge resection using an endoscopic stapling device (Autosuture GIA Universal; COVIDIEN™, Mansfield, MA, USA). Partial pleurectomy was performed beginning from the apex of the pleural cavity up to the 7th or 8th intercostal space. An underwater air-leak test was carried out to verify the lack of residual air leaks. One 24 French (Fr) chest tube (COVIDIEN™, Mansfield, MA, USA) placed at the apex of the thoracic cavity was inserted through the

Table 1. Clinical characteristics of the VBPP and CT groups.

	VBPP Group (n = 25)	CT Group (n = 25)
Gender		
Male	20 (80)	22 (88)
Female	5 (20)	3 (12)
Age mean (range) years	26.1 (18–42)	27 (19–40)
Height (m)	1.8	1.8
Weight (Kg)	64.9	65.7
BMI (kg/m^2)	19.9	20.1
Smoking history		
Smokers	3 (12)	5 (20)
Non-smokers	22 (88)	20 (80)
History of pneumothorax		
First episode	19 (76)	21 (84)
Recurrence	6 (24)	4 (16)
Complications		
Hemothorax	1 (4)	0 (0)
Prolonged air leak	5 (20)	3 (12)
None	19 (76)	22 (88)

Data are given as mean and percentages. kg: kilogram; m: metres.

3.1. Pulmonary Function

A summary of the pulmonary function data is presented in Table 2. Comparison of the calculated values of FVC, FEV1, and FEV1/FVC ratio between the VBPP and CT groups displayed no statistically significant differences. Interestingly, the values of FVC, FEV1, and FEV1/FVC in both groups were higher than the corresponding estimated LLN values (Table 2), suggesting no restrictive or obstructive pulmonary function impairment with either treatment modality.

Table 2. Comparison of lung function after VBPP and CT treatment (n = 15 patients per group).

	FVC (L)			FEV1 (L)			FEV1/FVC (%)		
	Predicted	**% Predicted**	**LLN**	**Predicted**	**% Predicted**	**LLN**	**Predicted**	**% Predicted**	**LLN**
VBPP	4.89	90.95	4.20	4.09	88.48	3.28	83.66	97.09	74
Mean (SD)	(0.35)	(5.34)	(0.76)	(0.41)	(5.71)	(0.87)	(5.88)	(2.22)	(0.76)
CT	4.88	91.19	4.31	3.82	89.64	3.3	78.54	98.47	73.8
Mean (SD)	(0.33)	(4.86)	(0.77)	(0.44)	(4.12)	(0.89)	(9.01)	(4.58)	(0.74)
p-Value	0.9364	0.8985	0.6967	0.0931	0.5286	0.9018	0.0759	0.3026	0.4713

All data are presented as mean and standard deviation (SD). FVC: forced vital capacity; FEV1: forced expiratory volume in one second; FEV1/FVC ratio: the percentage of the FVC expired in one second; LLN: lower limit of normal (defined as below the fifth percentile of spirometry data obtained from the Third National Health and Nutrition Examination Survey); L: litre; VBPP: VATS–bullectomy with partial pleurectomy; CT: chest tube. A p-value < 0.05 indicates statistical significance.

3.2. SF-36 Scores of Patients Who Underwent VBPP

Seven of the eight domains of the SF-36 health survey of our VBPP cohort were lower compared to those of the general German population. The affected domains included PF, GH, VT, SF, RF, RE, and MH. For these domains, the following differences were evaluated: PF = −3.8, GH = −3.2, VT = −7.0, SF = −0.5, RP = −3.8, RE = −3.2, and MH = −7.0 (Table 3). However, only the domains vitality (VT) (p = 0.0460) and mental health (MH) (p = 0.0271) were statistically significant. Interestingly, the physical component summary (PCS) scores were similar, whereas the mental component summary (MCS) score was significantly lower (p = 0.0049) in our patient cohort compared to the general German population (Table 3). Additionally, there were no significant changes in quality of life between the VBPP and CT groups.

Table 3. SF-36 results of patients who underwent VBPP compared to CT patients and the normative data from the general German population.

SF-36 Domains	VBPP Group (n = 25) Mean (SD)	CT Group (n = 25) Mean (SD)	p-Value	German Normative Data Mean (SD)	p-Value (Difference) VBPP vs. German Normative Data
Physical functioning (PF)	90.6 (9.5)	91.2(7.4)	0.8043	94.4 (10.8)	0.0841 (−3.8)
Role physical (RP)	87.0 (26.1)	88.25(24.1)	0.887	90.8 (24.6)	0.4510 (−3.8)
Bodily pain (BP)	78.8 (23.2)	81.96 (22.3)	0.6260	75.4 (22.5)	0.4604 (+3.4)
General health (GH)	69.8 (15.6)	73.28 (15.0)	0.4227	73.0 (16.8)	0.3502 (−3.2)
Vitality (VT)	54.4 (20.2)	58.24 (17.5)	0.4760	61.4 (17.0)	0.0460 * (−7.0)
Social functioning (SF)	88.5 (13.5)	87.66 (13.0)	0.8319	89.0 (16.4)	0.8807 (−0.5)
Role emotion (RE)	89.3 (18.6)	88.25 (15.6)	0.8297	92.5 (20.6)	0.4456 (−3.2)
Mental health (MH)	67.2 (14.5)	69.4(13.8)	0.5920	74.2 (15.5)	0.0271 * (−7.0)
Physical component summary score (PCS)	52.4 (6.3)	53.47 (8.5)	0.6154	52.3 (6.9)	0.9433 (+0.1)
Mental component summary score (MCS)	46.1 (7.9)	47.65 (7.2)	0.4578	50.6 (7.8)	0.0049 * (−4.5)

Data are given as mean and standard deviation (SD). A * p value < 0.05 displays statistical significance. SF-36: Short -Form 36; VBPP: VATS–bullectomy with partial pleurectomy; PCS includes RP, GH, PF, and BP; MCS includes SF, RE, MH, and VT.

4. Discussion

VATS–bullectomy with partial pleurectomy (VBPP) for blebs is a well-established and increasingly used surgical treatment for PSP. Recent studies have reported superior performance of VATS–bullectomy with partial pleurectomy (VBPP), with low rates of recurrence compared to VATS–bullectomy alone [6,9–11]. However, the impact of VBPP on the quality of life and pulmonary function of PSP patients is hitherto unknown. In the literature, various studies have reported the impact of VATS and lung resection on HR-QoL and pulmonary function after treatment of malignant diseases such as lung cancer. Avery et al. [21] reported a considerable detrimental impact on patients' HR-QoL following VATS with lung resection for lung cancer, which was not fully resolved 12 months post-surgery. Veronesi et al. [22] reported a better quality of life for the first year after VATS for lung cancer. Moreover, in two recent studies [23,24], VATS with sublobar resection for lung cancer was associated with preserved lung function. To date, only one study by Balduyck et al. [17] has evaluated the QoL following VATS for a benign disease; in this non-randomized prospective study of 20 patients, VATS and anterolateral thoracotomy for wedge resection and apical pleurectomy achieved comparable results in terms of QoL [17].

In our study, 25 patients who underwent VATS–bullectomy with partial pleurectomy (VBPP) were included. The aim of our study was to verify the impact of VBPP on pulmonary function and HR-QoL one year after surgery. We compared our results with patients successfully treated by chest tube only in our institution, and with normative data from the general German population.

Of the VBPP cohort, we were able to evaluate the lung function of 15 patients at our outpatient clinic (10 patients declined to participate). We found no significant differences in FVC or FEV1, nor in the FEV1/FVC ratio, between the VBPP and CT groups. Interestingly, in both groups, the estimated FVC, FEV1, and FEV1/FVC ratio were higher than the matched LLN values (Table 2), indicating normal pulmonary function after VBPP. This suggests that partial pleurectomy, which causes adhesion of the visceral pleura to the inner surface of the thoracic cavity in order to prevent recurrent pneumothorax, has no restrictive effect on lung function. Furthermore, these results indicate no obstructive pattern (both FVC and FEV1/FVC > LLN). Together, these results demonstrate that VBPP does not adversely affect the pulmonary function of PSP patients, while it was previously shown to be highly effective at reducing the risk of recurrence of PSP.

We used the well-established SF-36 health survey to evaluate the HR-QoL [12,13]. Of 34 patients, 25 completed the SF-36 questionnaire (9 patients were excluded due to

an incomplete questionnaire). We compared our results with a control group of patients successfully treated by chest tube only at our institution, and with the normative data from the general German population, as published by Morfeld et al. [20]. For our VBPP cohort, the physical component summary (PCS) scores were similar to the scores of the general German population, indicating that VBPP does not impair physical health. However, the mental component summary (MCS) scores of our patients were significantly lower (score −4.5, $p = 0.0049$) than those of the general German population, indicating high psychological distress for VBPP patients. This may be due to increased stress and post-traumatic anxiety of a possible relapse after surgery. Moreover, we compared the results of the SF-36 survey of the VBPP and CT groups. Interestingly, we found no significant statistical differences between the eight domains and summary scores of the SF-36 survey.

This study is limited by the lack of baseline data (both SF-36 and pulmonary function) and the lack of a surgical control group (e.g., patients treated by VATS without pleurectomy and/or bullectomy). We assessed HR-QoL and pulmonary function in our cohorts one year after surgery/chest tube treatment, and not at different intervals (e.g., 3, 6, and 12 months); this limits our results to a specific period. Additionally, due to the severe symptoms of the PSP patients who presented in our emergency room, a preoperative SF-36 health survey would not have been feasible.

Nevertheless, this study is the first to report on the impact of VBPP on the HR-QoL and pulmonary function of PSP patients after surgery and chest tube treatment. More prospective studies with a larger number of patients are needed in order to evaluate similar outcomes.

5. Conclusions

Our data demonstrate for the first time that VATS–bullectomy with partial pleurectomy (VBPP) for primary spontaneous pneumothorax (PSP) has no adverse impact on pulmonary function, and is associated with stable physical health. However, psychological distress and measures to counteract its impact should be considered after surgical treatment.

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Socioeconomic Impact of Recurrent Primary Spontaneous Pneumothorax: Should Video-Assisted Thoracoscopic Surgery Be Considered at First Episode of Primary Spontaneous Pneumothorax?

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Abstract: Background: Current guidelines recommend video-assisted thoracoscopic surgery (VATS) for recurrent primary spontaneous pneumothorax (PSP) and for cases with persistent air leak after chest tube treatment. The socioeconomic impact of recurrent PSP on the healthcare system is insufficiently reported. Methods: Ninety-six patients treated for PSP between 01/2010 and 01/2020 were included. Forty-eight patients underwent primary VATS, while the second group received chest tube (CT) treatment only. Length of hospital stay (LOS), duration of chest tube, prolonged air leak, postoperative complications, recurrences and treatment costs were analyzed. Results: Prolonged air leaks were evident in 12.5% and 22.9% patients of the VATS and CT group, respectively. Ten (20.8%) patients in the CT group underwent VATS for persistent air leakage. During follow-up, the VATS group recurred at 8.3% compared to 52.1% in the CT group. The total cost of treatment per patient, including treatment cost due to recurrence, was EUR 1.501 in the VATS group and EUR 2.233 in the CT group. Conclusions: Primary treatment of PSP by CT is associated with an increased socioeconomic burden for patients and the healthcare system due to high recurrence rates. This burden may be reduced if VATS is considered at the first episode of PSP.

Keywords: primary spontaneous pneumothorax; recurrence; socioeconomic impact

1. Introduction

According to the German S3 guidelines [1], primary spontaneous pneumothorax (PSP) describes the presence of air without preceding trauma or underlying pulmonary disease within the pleural space of patients under 45 years of age. The incidence of PSP has been reported as approximately 1–9.8 and 7–24 cases per 100,000 individuals per year in females and males, respectively [2,3]. According to the current guidelines [1,4–6], the initial treatment algorithm depending on the patient's clinical condition includes observation, oxygen supplementation and chest tube drainage. Although PSP often resolves by chest tube drainage, high rates of recurrence after this treatment have been described [7–10]. In cases with ipsilateral or contralateral recurrence of PSP and for those with persistent air leak following chest tube (CT) treatment, the guidelines [1,4–6] recommend video-assisted thoracoscopic surgery (VATS). In various studies, VATS bullectomy with or without pleurectomy was associated with very low rates of recurrence and a short length of hospitalization, even at first episode of PSP [10–14]. Therefore, we wondered if preventive surgical intervention might be a suitable alternative to reduce the recurrence rates and associated economic

burden, as well as to mitigate the negative psychological impact that results from anxiety about a potential recurrence [15]. To date, the economic and social impact due to hospital readmission for recurrent PSP on both patients and on the healthcare system is scarcely elucidated. Thus, the aim of this study was to retrospectively analyze the socioeconomic impact of recurrent PSP following VATS and CT treatment in our institution.

2. Materials and Methods

We retrospectively reviewed the data of 96 patients with PSP treated in our institution either by CT or VATS between January 2010 and January 2020. Patients' clinical data, including age, gender, weight, height, body mass index (BMI), length of hospital stay (LOS), duration of chest tube, postoperative complications and length of air leakage were retrieved from the medical records. One group underwent immediate surgery (VATS) (39 males and 9 females) during primary hospitalization; the other group received CT treatment only (40 males, 8 females). The mean age of the patients treated using VATS was 24.8 years (range 18–39), and was 26.2 years (range 18–40) for those who underwent CT treatment.

Patients in the VATS group underwent immediate surgery (these patients underwent VATS after a mean period of 2 days (range 1–4 days) after presentation in our emergency room upon first hospitalization) due to the following conditions: occurrence of second ipsilateral or contralateral pneumothorax (recurrence) (n = 38), synchronous bilateral spontaneous pneumothorax (n = 6) and spontaneous hemopneumothorax (n = 4). Patients in the CT group received chest tube drainage only upon first episode of unilateral PSP. Patients initially planned for CT treatment but suffering prolonged air leak (>5 days) underwent secondary VATS during first hospitalization. Although secondary VATS was performed, we assigned these patients for comparability to the CT group based on their initial treatment. In both groups, low-dose computer tomography of the lungs was performed prior to surgery to detect any bullous disease.

Patients who relapsed after CT treatment or VATS underwent VATS or re-VATS, respectively. After discharge, all patients were closely monitored for complications as outpatients. Follow-up consisted of 3-monthly consultations for one year. For long-term follow-up, the patients were contacted and assessed with a questionnaire. For all patients, the mean follow-up period was 46.2 months (range 1–119).

The local Institutional Review Board of the Heinrich Heine University Clinic of Duesseldorf approved this study (Study Nr: 2020-1271).

2.1. Surgical Procedure—VATS

All patients underwent the same surgical treatment, consisting of partial pleurectomy and bullectomy when blebs were evident. VATS was performed under general anesthesia with double-lumen tube intubation and single-lung ventilation. After the lateral positioning of the patient, VATS was performed by the conventional two- or three-port approach. Following initial thoracoscopy and thorough inspection of the visceral and parietal pleura, bullectomy was carried out where blebs or bullae were identified by wedge resection using an endoscopic stapling device (Autosuture GIA Universal; Covidien, Mansfield, MA, USA). Partial pleurectomy was performed in all patients beginning from the apex of the pleura cavity up to the 7th or 8th intercostal space. An underwater air leak test was performed to verify the lack of residual air leaks. One 24 French (Fr) chest tube (COVIDIEN^{TM}) placed at the apex of the thorax cavity was inserted through the trocar incisions at the 5th intercostal space. The chest tube was connected to a digital chest drainage system (Thopaz+, Medela AG, Baar, Switzerland) with a suction of -20 cmH_2O.

2.2. Chest Tube (CT) Treatment

In the CT group, one chest tube drainage (COVIDIEN^{TM}, 24 Fr) was used. This was inserted under local anesthesia by thoracostomic access in the mid axillary line at the level

of the 4th or 5th intercostal space. The chest tube was connected to a digital chest drainage system (Thopaz+, Medela AG, Baar, Switzerland) with a suction of −20 cmH_2O.

2.3. Statistical Analysis

Simple descriptive statistics were used. Data were expressed as mean value, range and percentages. Mean values of continuous variables between groups were compared with a Mann–Whitney U test and categorical variables with a chi-square test. Statistical significance was considered at $p < 0.05$. Statistical analysis was performed in Microsoft Excel and SPSS 25.0 (IBM Corp, released 2017. IBM SPSS Statistics for Windows, Version 25.0., IBM, Armonk, New York, NY, USA).

3. Results

Ninety-six PSP patients were included in this study, of whom 48 patients underwent primary VATS and 48 patients received CT treatment. Table 1 shows patients' demographic data. None of the patients were lost during follow-up. Patients treated by thoracotomy, needle aspiration or observation were initially excluded from this study.

Table 1. Demographics.

Variables	VATS (n = 48)	Chest Tube (n = 48)
Gender		
Male	39 (81.3)	40 (83.3)
Female	9 (18.7)	8 (16.7)
Age (mean)	24.8 (range 18–39)	26.2 (range 18–40)
BMI (kg/m^2)	20.2	21.1
Height (cm)	180	180
Weight (kg)	65.5	70

Unless otherwise specified, all data are presented as the mean (range) and are based on the total patient cohort (n = 48 per group). BMI: body mass index; VATS: video-assisted thoracoscopic surgery.

For both groups, the following parameters were analyzed from the medical records.

3.1. Length of Hospital Stay (LOS)

The mean LOS during primary hospitalization was 6 days in both groups. After VATS for recurrence, the mean LOS of the second hospitalization was also 6 days (Tables 2 and 3).

3.2. Duration of Chest Tube Drainage

Duration of chest tube drainage was shorter in the VATS group (5 days) compared to the CT group (6 days). After VATS for recurrence, the mean duration of chest tube drainage in both groups was 5 days (Tables 2 and 3).

Table 2. Postoperative parameters.

Variables	VATS (n = 48)	Chest Tube (n = 48)	p-Value
Duration of chest tube (days)	5	6	0.06
Mean LOS (days)	6	6	1.00
Prolonged air leak > 5 days (n)	6 (12.5%)	11 (22.9%)	0.181
Operation due to prolonged air leak *	0 (0%)	10 (20.8%)	0.001 *
Hemothorax (n)	1 (2.1%)	0 (0%)	0.315
Recurrence during follow-up (n) *	4 (8.3%)	25 (52.1%)	<0.001 *

Unless otherwise specified, all data are presented as mean and are based on the total patient cohort. * p-value < 0.05 displays statistical significance. LOS: length of hospital stay; VATS: video-assisted thoracoscopic surgery.

Table 3. Management costs of recurrence.

Variables	VATS (n = 4)	Chest Tube (n = 25)
Mean LOS at recurrence (days)	6	6
Duration of chest tube (days)	5	5
Cost of hospital day, as per DRG	EUR 148	EUR 148
Total LOS costs (pp/pg)	EUR 888/EUR 3.552	EUR 888/EUR 22.200
Surgical material cost (pp/pg)	EUR 465/EUR 1.860	EUR 465/EUR 11.625
Recurrence treatment costs (pg)	EUR 5.412	EUR 33.825
Recurrence treatment costs (pp)	EUR 1.353	EUR 1.353

VATS: video-assisted thoracoscopic surgery. All patients received VATS or re-VATS depending on their initial treatment. pp = per patient; pg = per group; LOS: length of hospital stay; DRG: diagnosis related group. The cost of surgical materials and cost of a hospital stay per day may differ across hospitals.

3.3. Treatment of Complications

One patient (2.1%) in the VATS group developed postoperative hemothorax and was reoperated on by VATS. Air leaks were considered as prolonged when evident for more than 5 days after treatment (VATS or CT). In the VATS group, six (12.5%) patients had persistent air leak, which resolved spontaneously on postoperative day 6 or 7. Prolonged air leak was also observed in 11 (22.9%) patients of the CT group. Ten (20.8%) patients of this group underwent VATS and one resolved spontaneously on postoperative day 8 (Table 2).

3.4. Management Costs

As defined in the German diagnosis-related groups (DRG) catalogue, the cost of a hospital stay per day for patients with PSP is calculated at EUR 148. The cost of surgical materials for VATS or chest tube placement under local anesthesia is EUR 465 and EUR 77, respectively (Table 4).

Table 4. Primary management costs.

Variables	VATS (n = 48)	Chest Tube (n = 48)
Mean LOS (days)	6	6
Cost of hospital day, as per DRG	EUR 148	EUR 148
Total LOS costs (pp/pg)	EUR 888/EUR 42.624	EUR 888/EUR 42.624
Surgical material cost (pp/pg)	EUR 465/EUR 22.320	EUR 77/EUR 3.696
Primary treatment costs (pp)	EUR 1.360	EUR 1.247
Primary treatment costs (pg)	EUR 65.288	EUR 59.850

pp = per patient; pg = per group; LOS: length of hospital stay; DRG: diagnosis-related group; VATS: video-assisted thoracoscopic surgery. The cost of surgical materials and the cost of a hospital stay per day may differ across hospitals.

One patient in the VATS group underwent re-VATS for hemothorax and 10 patients in the CT group underwent VATS due to prolonged and persistent air leakage. The costs of treatment for these 10 patients were assigned to the CT group and not to the VATS group due to their initial treatment. The combined cost of treatment for these cases was EUR 1353 for the VATS group and EUR 13,530 for the CT group (Table 5). With a mean hospital stay of 6 days in both groups (p = 1.00), the total treatment cost (including material, hospitalization and complication treatment costs) prior to recurrence, excluding additional medication for comorbidities, was calculated at EUR 1.360 and EUR 1.247 per patient for the VATS and CT group, respectively (Table 4).

Table 5. Complication management costs (secondary VATS).

Variables	VATS (Hemothorax, *n* = 1)	Chest Tube (Prolonged Air Leak, *n* = 10)
Mean LOS (days)	6	6
Cost of hospital day, as per DRG	EUR 148	EUR 148
Total LOS costs (pp/pg)	EUR 888/EUR 888	EUR 888/EUR 8880
Surgical material cost (pp/pg)	EUR 465/EUR 465	EUR 465/EUR 4650
Treatment costs (pp)	EUR 1.353	EUR 1.353
Treatment costs (pg)	EUR 1.353	EUR 13.530

VATS: video-assisted thoracoscopic surgery. All patients received VATS or re-VATS depending on their initial treatment. pp = per patient; pg = per group; LOS: length of hospital stay; DRG: diagnosis-related group. The cost of surgical materials and cost of a hospital stay per day may differ across hospitals.

During a mean follow-up period of 46.2 months, 4 (8.3%) and 25 (52.1%) patients of the VATS and CT group presented with recurrent PSP ($p < 0.001$), respectively. All patients underwent re-VATS or VATS, according to the previous treatment, incurring a further cost of EUR 1.353 per patient (Table 3). Including treatment cost for recurrence, the total management cost per patient was EUR 1.473 in the VATS group and EUR 1.952 for the CT group (Δ = EUR 479, Table 6). The total management cost increased to EUR 1.501 and EUR 2.233 per patient in the VATS and CT group, respectively, after adding treatment costs for complications (Δ = EUR 732; Table 6).

Table 6. Total management costs.

Variables	VATS (*n* = 48)	Chest Tube (*n* = 48)
Primary treatment costs (pg)	EUR 65.288	EUR 59.850
Recurrence treatment costs (pg)	EUR 5.412	EUR 33.825
Total management costs (pg)	EUR 70.700	EUR 93.675
Total management costs (pp)	EUR 1.473	EUR 1.952
Total management and complication costs (pg)	EUR 72.053	EUR 107.205
Total management and complication costs (pp)	EUR 1.501	EUR 2.233

VATS: video-assisted thoracoscopic surgery; pp = per patient; pg = per group. The cost of surgical materials and cost of a hospital stay per day may differ across hospitals.

4. Discussion

To date, chest tube drainage is still a recommended treatment for the first episode of PSP. According to the current guidelines [1,4–6], VATS should be considered at recurrence or in case of persistent air leak after CT treatment. Similar to our results, various studies have proven VATS to be superior to CT treatment in terms of recurrence rates, even at first episode of PSP [12–14]. VATS has also been reported to be associated with shorter hospitalization rates and better quality of life [10–13,16]. To date, the economic and social impact of recurrent PSP, especially due to hospital readmission, is rarely reported.

In a previous study, Schramel FM et al. [17] analyzed the cost effectiveness of VATS versus conservative treatment for first time or recurrent spontaneous pneumothorax. They reported VATS to be cost effective and associated with less morbidity compared to conservative therapy. In another study, Torresini G et al. [18] reported a cost reduction due to VATS in patients with the first episode of spontaneous pneumothorax compared to CT treatment. Moreover, in a recent meta-analysis of Daemen JHT et al. [14], VATS was reported to be associated with significantly reduced ipsilateral recurrence rates and shorter length of hospitalization compared to CT treatment.

In our study, 48 patients were initially treated with CT. In this group, persistent air leak for more than 5 days was evident in 11 patients (22.9%), of whom 10 (20.8%) had to receive VATS during first hospital admission. The primary treatment cost in the CT group, including hospitalization and surgical material, was calculated at EUR 1.247 (Table 4). The total management cost of the 10 patients who underwent secondary VATS for prolonged air

leak was calculated at EUR 13.530 (Table 5). Recurrent pneumothorax occurred in 25 of the CT patients, who were subsequently operated on using VATS. The management cost for these 25 patients was assessed at EUR 33,825, or EUR 1.353 per patient (Table 3). Overall, the total management cost of primary and recurrence treatment for the CT group was thus calculated to be EUR 93.675, with a cost per patient of EUR 1.952 (Table 6). The total management cost in this group increased to EUR 2.233 per patient after adding treatment costs for complications (prolonged air leak).

Likewise, 48 patients in our study cohort underwent primary VATS (VATS group) upon presentation at our hospital. One patient (2.1%) suffered a hemothorax and was reoperated by VATS. This complication rate is in line with previous reports [17,19]. The overall treatment cost of this complication as calculated at EUR 1.353 (Table 5). Interestingly, the primary treatment costs per patient, including hospitalization and surgical material in the VATS group, was higher (EUR 1.360) compared to the CT group (EUR 1.247). This difference was due to the higher cost of surgical materials for VATS (EUR 465 vs. EUR 77) (Table 4). In contrast with the CT group, significantly fewer patients (n = 4, 8.3%) suffered recurrence in the VATS group, which is similar to recently published data [10,14]. These patients subsequently underwent re-VATS. Due to the low rate of recurrence, overall cost for recurrence treatment was lower in the VATS group (EUR 5.412) than in the CT group (EUR 33.825). This disparity resulted in a considerably lower total management cost per patient in the VATS group (EUR 1.473) compared with the CT group (EUR 1. 952) (Table 6). Interestingly, this disparity increased considerably after addition of the treatment cost for complications (VATS: EUR 1.501 vs. CT: EUR 2.233; Table 6).

In this study, the mean LOS before and after treatment for recurrence was similar in both groups (Tables 2 and 3). The main causes for the increased economic burden in the CT group were the high recurrence rate and the high rate of persistent air leaks after CT treatment, both requiring secondary VATS. This resulted in an overall 48.8% increase (EUR 732 per case) in total management and complication cost of the CT group versus the VATS group.

This study has limitations, primarily due to its retrospective nature and lack of randomization. Therefore, future prospective randomized controlled trials with a large number of patients are needed. Secondarily, the calculated costs are those specific to our clinic. These costs may vary (especially due to varying surgical material costs and the cost of a hospital stay) between hospitals in Germany and internationally.

Furthermore, there might be a selection bias due to the various indications for immediate surgery (in the VATS group, not all the patients underwent surgery for the same reason). Lastly, the treatment modality we used might not be the same in other countries, e.g., observation or needle aspiration instead of chest tube treatment, as described in previous studies. However, this study displays significant results concerning the socioeconomic impact of both treatment modalities in PSP patients. These results should not be considered to compare the effectiveness of VATS and CT treatment for a first episode of PSP, but can be used to compare their socioeconomic impact on patients and the healthcare system.

5. Conclusions

In conclusion, performing VATS upon first PSP seems to be associated with reduced socioeconomic burden, not only for the patients, but also for the healthcare system.

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Informed Consent Statement: Informed consent to participate was waived because no data regarding the cases were disclosed.

Data Availability Statement: The data presented are included in this study; additional data may be provided by the corresponding author on request.

Conflicts of Interest: The authors declare no conflict of interest.

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RESEARCH ARTICLE Open Access

Two-port versus three-port video-assisted thoracoscopic surgery for primary spontaneous pneumothorax: feasibility, postoperative outcome and long-term recurrence rates

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Abstract

Background: Two-port VATS (2-P-VATS) and three-port VATS (3-P-VATS) are well-established techniques for surgical therapy of primary spontaneous pneumothorax (PSP). However, comparisons of both techniques in terms of postoperative outcome and recurrence are limited.

Methods: From January 2010 to March 2020, we retrospectively reviewed data of 58 PSP patients who underwent VATS in our institution. For statistical analysis, categorical and continuous variables were compared by chi-square test or Fisher's exact test and the Student´s t-test, respectively. Twenty-eight patients underwent 2-P-VATS and 30 were treated with 3-P-VATS. Operation time, length of hospital stay (LOS), total dose of analgesics per stay (opioids and non-opioids), duration of chest tube drainage, pleurectomy volume (PV), postoperative complications and recurrence rates were compared between both groups.

Results: Clinical and surgical characteristics including mean age, gender, Body-Mass-Index (BMI), pneumothorax size, smoking behaviour, history of contralateral pneumothorax, side of pneumothorax, pleurectomy volume and number of resected segments were similar in both groups. The mean operation time, LOS and total postoperative opioid and non-opioid dose was significantly higher in the 3-P-VATS group compared with the 2-P-VATS group. Despite not being statistically significant, duration of chest tube was longer in the 3-P-VATS group compared with the 2-P-VATS group. In terms of postoperative complications, the occurrence of hemothorax was significantly higher in the 3-P-VATS group (3-P-VATS vs. 2-P-VATS; $p = 0.001$). During a median follow-up period of 61.6 months, there was no significant statistical difference in recurrence rates in both groups (2/28 (16.7%) vs. 5/30 (7.1%); $p = 0.274$).

Conclusion: Our data demonstrate that 2-P-VATS is safer and effective. It is associated with reduced length of hospital stay and decreased postoperative pain resulting in less analgesic use.

Keywords: Two-port VATS, Three-port VATS, Outcome, PSP

Background

As defined in the current German S3 guidelines, primary spontaneous pneumothorax (PSP) describes the presence of air without preceding trauma or underlying pulmonary disease within the pleural space of young patients under 45 years of age [1] The incidence of PSP

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has been reported with approximately 1–9.8 and 7–24 cases per 100,000 individuals per year in females and males respectively [2, 3] Due to the low recurrence und morbidity rates, current guidelines [1, 4, 5] recommend VATS for surgical treatment of PSP. In the last decades, thoracic surgery has evolved from thoracotomy to video-assisted thoracoscopic surgery (VATS). While three-port VATS (3-P-VATS) remains the gold standard for PSP treatment, recent publications have demonstrated the advantages of uniportal VATS in terms of postoperative pain and paraesthesia, analgesic use, length of hospital stay, cosmetic results and patient satisfaction scores in specialized settings [6–11]. However, only a few studies have analysed and compared the postoperative outcome of the widely implemented two-port VATS (2-P-VATS) with 3-P-VATS [8, 12]. Therefore, the aim of this study was to evaluate and compare the outcome and long-term recurrence rates of PSP patients treated with 2-P-VATS and 3-P-VATS in our institution.

Material and methods

Patients

We retrospectively analysed data of 58 patients who underwent video-assisted thoracoscopic surgery (VATS) for primary spontaneous pneumothorax (PSP) in our institution between January 2010 and March 2020. Twenty-eight patients were treated using 2-P-VATS and 30 patients underwent the conventional 3-P-VATS. Indication for surgery was persistent air leak for more than 5 days after chest tube treatment on first episode (2-P-VATS: N = 8; 3-P-VATS: N = 10), second ipsilateral pneumothorax (2-P-VATS: N = 12; 3-P-VATS: N = 15), synchronous bilateral spontaneous pneumothorax (2-P-VATS: N = 5; 3-P-VATS: N = 3), and spontaneous hemopneumothorax (2-P-VATS: N = 3; 3-P-VATS: N = 2). Prior to surgery, all the patients received a CT (computer tomography) scan of the thorax to detect any bullous disease. For each patient, medical charts were reviewed to retrieve the following variables: age, sex, body mass index (BMI), side of pneumothorax, pneumothorax size, smoking behaviour, number of resected lung segments (if any), volume of resected parietal pleura, length of hospital stay (days), duration of chest drainage (days), total dose of opioid and non-opioid use per stay, operation time and postoperative complications (Tables 1 and 2). Only PSP patients with completed follow-up data were included in this study. All the patients underwent VATS with partial pleurectomy and bullectomy when blebs where evident. Patients who underwent other treatment modalities such as thoracotomy, apical pleurectomy or suffered a different pneumothorax type (e.g. secondary spontaneous pneumothorax, catamenial pneumothorax, iatrogenic pneumothorax) were excluded from this study.

The pneumothorax size was assessed using the regression formula derived from Collins et al. [13]. The volume of the resected parietal pleura was measured in cubic centimeter (cm^3) as noted in the pathology results. The operation time (minutes) was defined as the time from incision to the end of skin closure. A postoperative prolonged air leak was defined as a persistent air leakage for more than 5 days. Recurrence was described as pneumothorax detected on a chest radiograph at presentation in

Table 1 Clinical characteristics

Variables	Two-port VATS N = 28	Three-port VATS N = 30	*p*-value
Age (years)	23 (range 18–40)	22 (range 18–39)	0.49
Sex (n; %)			0.97
Female	5 (17.9%)	5 (16.7)	
Male	23 (82.1%)	25 (83.3%)	
Weight (kg)	70	63	0.53
Height (m)	1.80	1.80	0.77
BMI (kg/m^2)	21.35	20.15	0.51
Side of pneumothorax			0.54
Right	22 (78.6%)	15 (50%)	
Left	6 (21.4%)	15 (50%)	
Collins (A + B + C) (cm)	8.99	9.4	0.95
Active smoker			0.445
Yes	7 (25%)	5 (16.7)	
No	21 (75%)	25 (83.3%)	
History of pneumothorax	1	3	0.336

Unless otherwise specified, all data are presented as mean value. *BMI* Body-Mass-Index, *cm* centimetre, *Kg* kilogram, *m* metre, A **p*-value < 0.05 indicates statistical significance. Collins (A + B + C) = sum of the intrapleural distances (cm) according to the regression formula derived from Collins et al. (13)

Table 2 Surgical characteristics

Variables	Two-port VATS N = 28	Three-port VATS N = 30	*p*-value
Chest tube duration (days)	5,5	7	0.228
LOS (days)	7	9	**0.012***
Piritramide dosage / stay (mg)	15	30	**0.012***
Non-opioid dosage / stay (g)	16	20	**0.010***
Operation time (min)	65	90	**0.001***
Length of air leak (days)	5	6	0.135
Pleurectomy volume (cm^3)	12.8	14.3	0.450
Postoperative complications			
Hemothorax (n, %)	0	3 (10%)	**0.001***
Prolonged air leak (n, %)	9 (32.1%)	15 (50.0%)	0.136
Recurrence (n, %)	2 (7.1%)	5 (16.7%)	0.274

Unless otherwise specified, all data are presented as mean value. cm^3 cubic centimetre, *min* minutes, *mg* milligram, *g* gram, *LOS* length of hospital stay. A *p-value < 0.05 indicates statistical significance

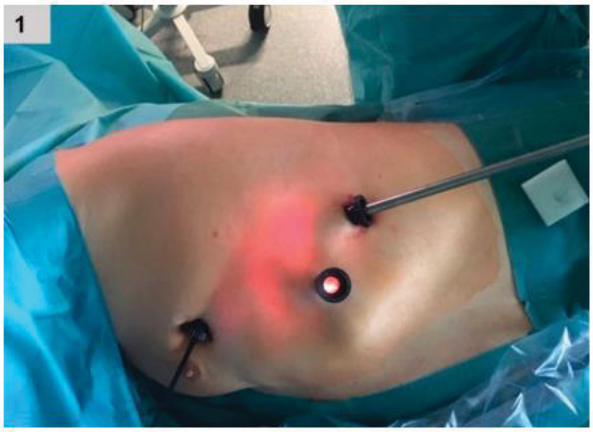

Fig. 1 Trocar position during three-port VATS

our emergency room after surgical treatment by VATS or chest tube drainage. Our standard postoperative medication regime of analgesia (non-opioid) was administered intravenously or orally. The patients received either Metamizol-Natrium 1000 mg, Paracetamol 1000 mg or Ibuprofen 600 mg four times per day. In case of persistent pain using the standard pain medication regime, we applied Piritramide (opioid) 7.5 mg intravenously every 4–6 h on patient request. For each patient, the total opioid- and non-opioid dose per stay was evaluated and documented.

One week after discharge from the hospital, the patients visited our outpatient clinic for postoperative control and follow-up. These visits continued in 3 months intervals for one year. For long-term follow-up, the patients were contacted (by telephone call or mail) and assed with a questionnaire. The median follow-up period was 61.6 (range 5–119) months.

The local Institutional Review Board of the Heinrich-Heine University Hospital of Duesseldorf approved this study (study Nr: 2020-1271).

Surgical procedures

Excluding the amount of surgical ports, all patients received the same surgical treatment, consisting of partial pleurectomy and bullectomy when blebs were evident. All operations were performed under general anaesthesia and one lung-ventilation. The patients were placed in a lateral position and the table flexed up to 35° to open up the intercostal spaces.

Three-Port VATS (Fig. 1)

For 3-P-VATS, the first 1.5 cm skin incision was performed at the level of the 5th intercostal space in the anterior axillary line. After placement of an 11 mm trocar and insertion of the video-thoracoscope, explorative thoracoscopy was performed for thorough inspection of the visceral and parietal pleura. If the patient already had a chest tube, this chest thoracostomy wound (mostly 5th or 6th intercostal space of the mid-axillary line) was used for the 11 mm optical trocar. Under thoracoscopic control, two additional 11 mm trocars were placed at the level of the 7th and 8th intercostal space in the mid- and posterior-axillary line, respectively (Fig. 1). In case of bullae or blebs, the video-thoracoscope was removed and reinserted through the trocar in the 8th intercostal space. Hereafter, an endograsper and an endoscopic stapling device (Autosuture GIA Universal; Covidien, Mansfield, MA, USA) were inserted through the trocars in the 5th and 7th intercostal space, respectively. After grasping the bullous area, bullectomy was undertaken with the stapling device. Partial pleurectomy was performed from the apex of the pleura cavity up to the 7th or 8th intercostal space in a blunt manner using an endograsper and a blunt dissector (Endo Peanut™ Auto suture™, COVIDIEN ®, Willow Lane, Mokena, IL), while sparing the regions of the subclavian and internal mammary vessels to avoid damage of these structures.

Two-Port VATS (Fig. 2)

Two 1.5 cm skin incisions were made at the level of the 5th and 8th intercostal space in the mid- and anterior axillary line, respectively (Fig. 2). Thoracoscopy and pleurectomy were performed as described in 3-P-VATS. For bullectomy, an endograsper was inserted without trocar-guidance through the skin incision in the 5th intercostal space, adjacent to the trocar of endoscopic stapling device. The video-thoracoscope was introduced through the trocar in the 8th intercostal space.

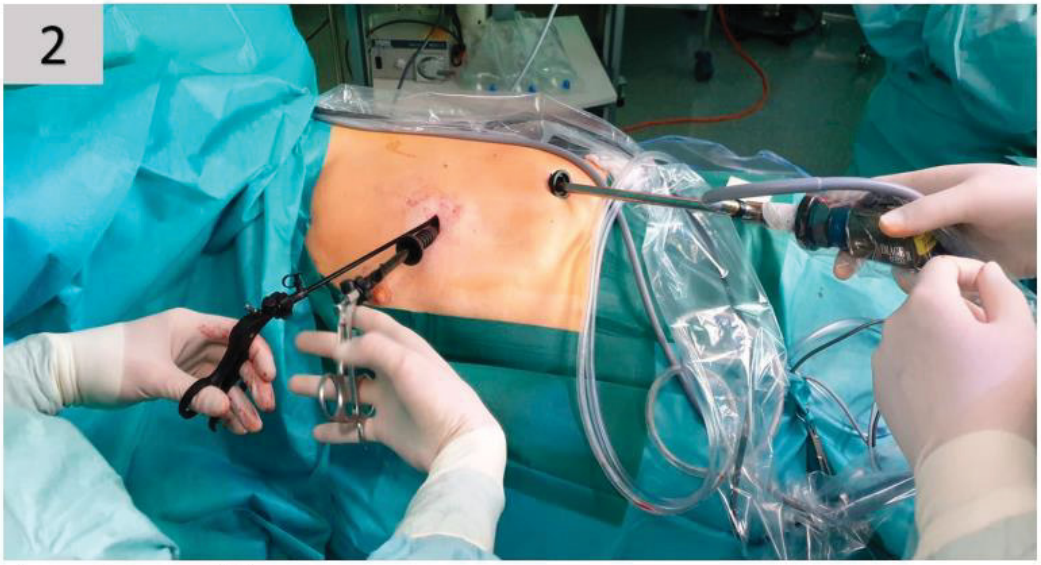

Fig. 2 Trocar placement for two-port VATS

In both procedures, an underwater air leak test was performed. Two 24 Fr chest tubes, placed at the apex of the thorax cavity and in the costodiaphragmatic recess, were inserted through the incisions in the 5th and 8th intercostal spaces, respectively, and connected to a digital chest drainage system (Thopaz+, Medela AG, Baar, Switzerland) with a suction equivalent to − 20 cm H_2O. During postoperative care, the chest tube drains were removed when no clinical signs of air leak and a drain output less than 200 ml after 24 h were evident. After chest tube removal, a chest radiograph was taken to verify full expansion of the lung.

Figure 3 shows a summary of the methodological approach of this study.

Statistical analysis

All data were analysed with the SPSS 25.0 software program (Statistical Package for Social Sciences; SPSS Inc., Chicago, IL, USA). Categorical variables were expressed as percentages and continuous variables were presented as mean. The means of categorical variables were compared by chi-square test or Fisher's exact test, and continuous variables were compared by Student's *t*-test. Statistical significance was considered at $p < 0.05$.

Results

Fifty-eight PSP patients were included in this study. The mean age of the patients was 25 years (range 18–48). Overall, there were 49 male and 9 female patients included. Thirty patients underwent 3-P-VATS, whereas 28 patients received 2-P-VATS. The mean age, sex, side of pneumothorax, smoking behaviour, BMI and pneumothorax size were similar in the 2-P-VATS group and the 3-P-VATS group. The clinical characteristics of the patients are summarised in Table 1.

Surgical characteristics of the two groups are listed in Table 2. There was no significant difference in the number of resected lung segments between both groups, suggesting a lack of selection bias based on the resected lung segments The mean operation time for the 2-Port-VATS was significantly shorter compared with the 3-P-VATS (65 min vs. 90 min, $p = 0.017$). Furthermore, patients operated using 3-P-VATS required a significantly higher total dose of opioid and non-opioid analgesics per stay, compared with patients treated by 2- P-VATS (opioid: 30 mg vs. 15 mg; $p = 0.021$; non-opioid: 16 g vs. 20 g; $p = 0.010$). 2- P-VATS patients had a significantly shorter LOS compared with 3-P-VATS patients (7 days vs. 9 days; $p = 0.012$). The duration of chest tube was longer in the 3-P-VATS group compared with the 2-P-VATS group, although this difference did not reach statistical significance (5.5 days vs. 7 days; $p = 0.228$). Three patients in the 3-P VATS group suffered a postoperative haemothorax, while none of the patients in the 2-P VATS group was affected. Although we observed no significant difference, the pleurectomy volume was larger in the 3-P-VATS patients compared to the patients who underwent 2-P-VATS. One of the patients with postoperative hemothorax required recurrent VATS, the other two patients were successfully treated conservatively. All patients with prolonged air leak received conservative treatment until full recovery. During a median follow-up period of 61.6 months, 5 (16.7%) patients in the 3-P-VATS group suffered a recurrence, whereas only 2 (7.1%) patients

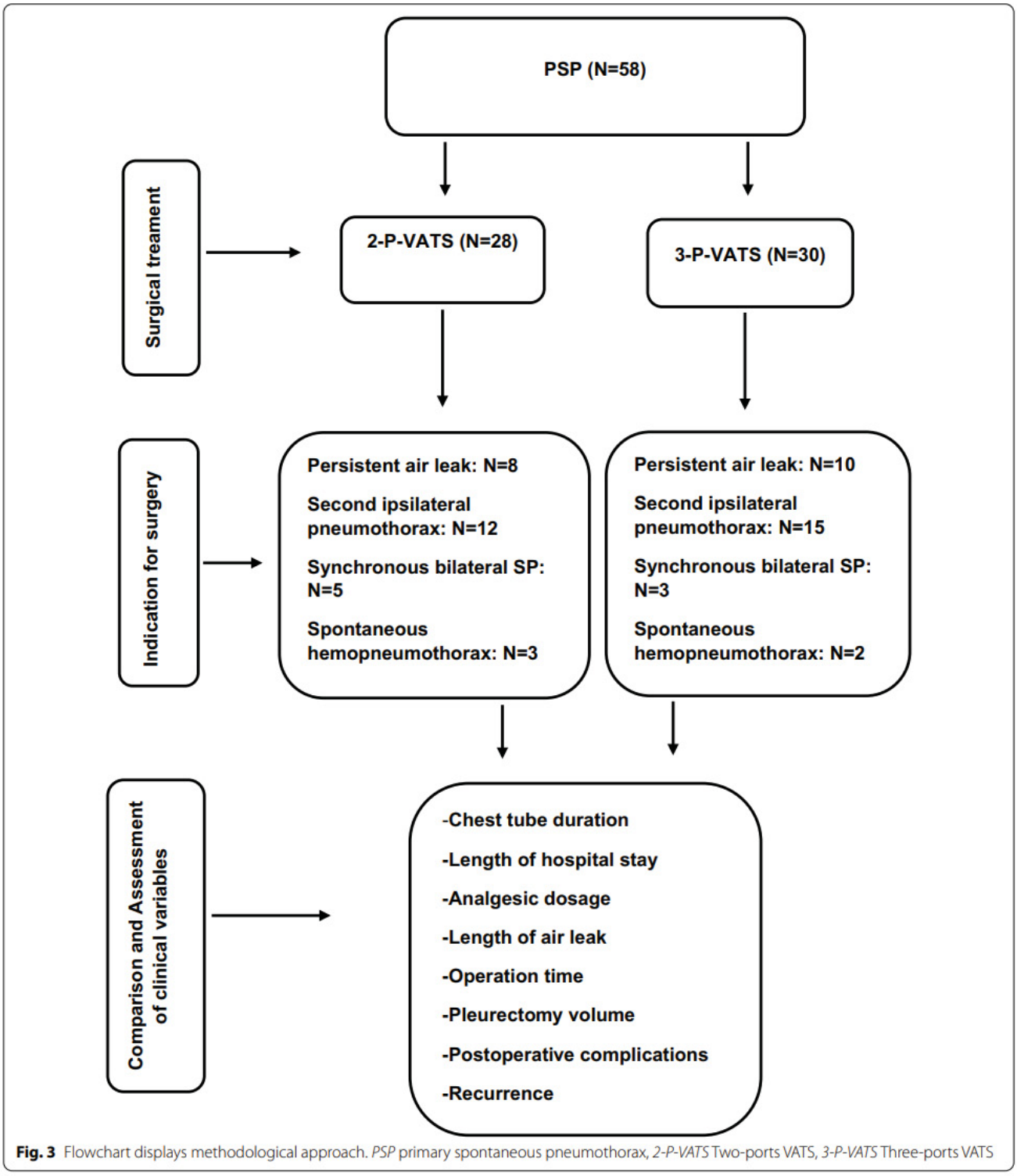

Fig. 3 Flowchart displays methodological approach. *PSP* primary spontaneous pneumothorax, *2-P-VATS* Two-ports VATS, *3-P-VATS* Three-ports VATS

in the 2-P-VATS group experienced recurrence. However, this difference did not reach statistical significance ($p=0.274$).

Discussion

In the last decades, thoracic surgery has evolved from thoracotomies to video assisted thoracoscopic surgery (VATS) as the gold standard. While three port VATS still remains the standard-of-care in most centres due to the

accessibility, recent technical developments are leading to a reduction in access ports. While this may improve postoperative performance such as reduced paraesthesia, analgesic use and LOS [6–11], the more limited access may reduce the operative results. While single-port VATS has been heralded as new minimal access VATS in selected indications and specialized centres, two- and three-port VATS remains the gold standard in most settings. Yet, comparisons of 3-P-VATS with 2-P-VATS have been rarely reported and the impact on postoperative performance as well as effectiveness of the surgical therapy remain elusive.

In the study of Lin F et al. [12] with 23 PSP patients who underwent 2-P-VATS and 73 patients with 3-P-VATS, mean operation time, average LOS and average postoperative chest tube duration were not significantly different between both groups. Similar to our results, postoperative pain was significantly lower in the 2-P-VATS group compared with the 3-P-VATS group. In another recent study of Kutluk AC et al. [8] including 45 patients operated by 2-P-VATS und 45 patients by 3-P-VATS, no significant difference was observed in mean operation time, LOS, duration of chest tube drainage, recurrence rates and postoperative pain.

In our study, 28 patients underwent 2-P-VATS and 30 patients received 3-P-VATS. In contrast to the above studies [8, 12], we observed a significant difference in operation time, LOS and postoperative dose of analgesic between both groups. Patients operated by 2-P-VATS had a significantly reduced LOS, less postoperative pain and shorter operation time compared with patients operated by 3-P-VATS. In terms of postoperative complications, we observed a significantly higher rate of hemothorax in the 3-P-VATS group. Although not reaching statistical significance, the larger volume of resected parietal pleura in the 3-P-VATS groups (14.3 vs. 12.8 cm^3), as well as the additional port access, may have contributed to the higher rate of hemothorax in the 3-P-VATS group. As described in previous studies, VATS with additional pleurectomy is associated with reduced recurrence rates [14–16]. However, the volume of pleurectomy seems to affect postoperative outcome in terms of complications and postoperative pain. Regarding our study groups, patients who underwent 3-P-VATS suffered a high complications rate and had a high analgesic use compared to patients after 2-P-VATS. We attributed these results to the high pleurectomy volume and the additional port access implemented during 3-P-VATS.

To assess the rate of recurrence, all patients were followed-up for a mean period of 61.6 months. During this period, 5 (16.7%) and 2 (7.1%) patients from the 3-P and 2-P VATS group, respectively, suffered a recurrence. Despite the lower volume of resected pleura in the 2-P-VATS group, there was no significant difference in terms of recurrence rates between both groups.

In previous studies [6–12], postoperative pain was assessed using the visual analogue scale (VAS), which is a subjective measure for pain. In our study, we used the cumulative postoperative dosage of opioid and non-opioid analgesics per patient as an objective surrogate for postoperative pain. Unlike the VAS score, which may give a one-time measurement including the patient's emotional and psychological state, the quantification of applied analgesics allows to assess average pain levels over a longer period. We found a significantly reduced opioid and non-opioid dosage in the 2-P-VATS group, most likely due to the reduced port access. To our knowledge, our study is the first study that elucidates pain-related analgesic use after VATS for patients with PSP.

Our results demonstrate that 2-P-VATS in the treatment of PSP leads to a better postoperative outcome and earlier recovery compared with the conventional 3-P-VATS.

As a retrospect analysis of a limited cohort, this study carries the limitations inherent to this approach. Due to the study period, not all operations were performed by the same surgeon. Nevertheless, our findings, especially the significantly higher rate of postoperative hemothorax observed in our cohort in the 3-P-VATS group, should be further elucidated in larger, randomized controlled trials.

Conclusion

Our data demonstrate that 2-P-VATS is safer and as effective as 3-P-VATS in the treatment of PSP. It is associated with decreased postoperative pain, reduced length of hospital stay and fewer postoperative complications, indicating that 2-P-VATS should be considered standard-of-care in the treatment of PSP.

Abbreviations

PSP: Primary spontaneous pneumothorax; VAS: Visual analog scale; VATS: Video-assisted thoracoscopic surgery; 3-P-VATS: Three-port VATS; 2-P-VATS: Two-port VATS; LOS: Length of hospital stay; PV: Pleurectomy volume; BMI: Body mass index.

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None.

Authors' contributions

Study conception, design and overall analysis and interpretation of data, drafting, revising the manuscript (SF, HA, SS, AS, AR, LD, GF, WTK), Data analysis and interpretation (SF, HA, AS, LD, GF, WTK) manuscript preparation (SF, GF), conceptual contributions and manuscript revision (SF, HA, SS, LD, AR, GF, WTK). All authors read and approved the final manuscript.

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Availability of data and materials
The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
This study was approved by the local institutional review board (Heinrich Heine University, Duesseldorf, Germany; study-no.: 2020-1271). All procedures performed in this study were in accordance with the ethical standards in the 1964 Declaration of Helsinki and its later amendments. Informed consent to participate was waived because no data regarding the cases were disclosed.

Consent for publication
Not applicable.

Competing interests
Drs. Stephen Fung, Hany Ashmawy, Sami Safi M.D, Anja Schauer, Alexander Rehders, Levent Dizdar, Georg Fluegen and Wolfram Trudo Knoefel have no conflicts of interest or financial ties to disclose.

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Postoperative Pain and Clinical Outcome Following Two- and Three-Port Video-Assisted Thoracoscopic Surgery for Secondary Spontaneous Pneumothorax

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Abstract: Background: Two-port (2P) and three-port (3P) video-assisted thoracoscopic surgery (VATS) are well-established surgical methods for the treatment of complicated spontaneous pneumothorax (SP). However, a comparison between both techniques, in terms of clinical outcomes in patients with secondary spontaneous pneumothorax (SSP), is unreported. The aim of this study was to evaluate and compare postoperative pain, as well as clinical outcome, following 2P and 3P VATS for SSP in our institution. Methods: Between January 2008 and December 2020, we retrospectively analyzed the data of 115 SSP patients treated by VATS in our institution. Fifty-two patients underwent 2P-VATS, while 63 patients were treated by 3P-VATS. The total dose of analgesic use per stay (opioid and non-opioid), length of hospital stay (LOS), operation time, total area of pleurectomy, recurrence rates and postoperative complications were compared between both groups. Results: The 3P-VATS group had a significantly higher total dose of analgesic use compared with the 2P-VATS patients. The LOS and mean operation time were significantly shorter in the 2P-VATS group. A larger area of pleurectomy was resected using 3P-VATS compared to 2P-VATS. The postoperative complications and recurrence of SSP during a median follow-up period of 76.5 months were similar in both groups. Conclusion: 2P-VATS is a safe surgical technique. It is associated with a short LOS and less postoperative pain, and, thus, low analgesic use.

Keywords: two-port VATS; three-port VATS; postoperative pain; clinical outcome

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1. Introduction

Spontaneous pneumothorax (SP) describes the presence of air, without preceding trauma, within the pleural space. SP in patients with an underlying pulmonary disease is defined as secondary spontaneous pneumothorax (SSP). In most cases, chronic obstructive pulmonary disease (COPD) is the etiological cause in patients who are 45 years of age or older [1]. The incidence of SSP has been reported as approximately 2.0 and 6.3 cases per 100,000 individuals per year in females and males, respectively [2]. For complicated SSP (persistent air leak following chest tube treatment, or recurrence), the current guidelines recommend VATS for the surgical treatment of operable cases [1,3,4]. However, high morbidity rates have been reported after surgery for SSP [5,6]. The high rates of morbidity depend not only on the underlying pulmonary disease, but also on the surgical technique used. Regarding the treatment of primary spontaneous pneumothorax (PSP), recent studies have reported low morbidity rates and less postoperative pain when using a low number of access ports for VATS [7–12]. Although, nowadays, three-port (3P) and two-port (2P) VATS

are well-established surgical techniques for the treatment of complicated SP; a comparison between both techniques, in terms of postoperative outcome following SSP treatment, is unreported. Thus, the aim of this study was to analyze and compare postoperative pain and clinical outcome after 2P-VATS and 3P-VATS for SSP in our institution.

2. Materials and Methods

We retrospectively reviewed the data of 115 patients with secondary spontaneous pneumothorax (SSP), treated either by two-port VATS (2P-VATS) or three-port VATS (3P-VATS) between January 2008 and December 2020 in our institution. Fifty-two patients underwent 2P-VATS, while 63 patients were treated with the conventional 3P-VATS. Indications for surgery included persistent air leaks for more than 5 days following chest tube treatment (n = 50) and second ipsilateral or first contralateral recurrent pneumothorax (n = 65). Prior to surgery, a computed tomography scan of the lungs was performed to detect the cause of the SSP, and to determine the extent of a bullous disease. A team of three specialized thoracic surgeons (WTK, AS and AR) made the indication for surgery. Notably, the indications for surgery were made individually, depending on the comorbidity and underlying pulmonary disease, as well as the patient's choice. Patients with incomplete follow-up data and patients who underwent other treatment modalities (e.g., thoracotomy, VATS pleural abrasion, observation, needle aspiration and chest tube drainage) were excluded from this study.

Patient clinical and surgical characteristics (Tables 1 and 2), including age, sex, body mass index (BMI), side of pneumothorax, COPD stage, size of pneumothorax, number of resected lung segments, total area of resected parietal pleura, length of hospital stay (LOS), operation time, postoperative length of air leak, postoperative complications, and total dose of opioid and non-opioid use per stay, were retrieved from medical records.

Table 1. Patient characteristics.

Variables	2P-VATS n = 52 (%)	3P-VATS n = 63 (%)	p-Value
Age (years)	67.7 (range 41–87)	68.6 (range 44–87)	0.808
Gender			
Male	35 (67.3)	32 (49.2)	
Female	17 (32.7)	32 (50.8)	0.060
Weight (kg)	66.1	64.1	0.223
Height (m)	1.72	1.73	0.297
BMI (kg/m^2)	22.4	21.2	0.036 *
Collins (A + B + C) (cm)	8.6	10.8	0.029 *
COPD stage			
Gold I–II	22 (42.3)	23 (36.5)	0.568.
Gold III–IV	21 (40.4)	30 (47.6)	0.457
No COPD	9 (17.3)	10 (15.9)	1.000
Side of pneumothorax			
Right	34 (65.4)	47 (74.6)	
Left	18 (41.2)	16 (25.4)	0.310

Data are presented as means, numbers and percentages. COPD: chronic obstructive pulmonary disease, BMI: body mass index, 2P-VATS: two-port video-assisted thoracoscopic surgery, 3P-VATS: three-port video-assisted thoracoscopic surgery, LOS: length of hospital stay, Collins (A + B + C) = sum of the intrapleural distances (cm) according to the regression formula derived from Collins et al. [13]. * p-value < 0.05 indicates statistical significance.

The pneumothorax size was assessed using the regression formula derived from Collins et al. [13]. The area of the resected pleura was measured in square centimeters (cm^2), as denoted in the pathology results. The operation time (in minutes) was defined as the time from skin incision to the end of skin closure. A postoperative prolonged air leak was defined as a persistent air leak for more than 5 days after VATS. Postoperative recurrence was described as a pneumothorax detected on a chest radiograph or computed tomography scan at presentation in our emergency room (ER) after treatment with 2P- or 3P-

VATS. All patients received our standard postoperative medication regimen of non-opioid analgesics administered intravenously or orally. The patients received either metamizol natrium 1000 mg, paracetamol 1000 mg or ibuprofen 600 mg four times per day. In case of persistent pain using the standard pain medication regimen, we applied piritramide (opioid) 7.5 mg intravenously every 4–6 h on patient request. For each patient, the total opioid and non-opioid doses per stay were calculated and documented.

Table 2. Surgical and postoperative characteristics.

Variables	2P-VATS $n = 52$ (%)	3P-VATS $n = 63$ (%)	p-Value
LOS (days)	10.7	14.3	<0.001 *
Opioid dosage/stay (mg)	24.5	41.6	<0.001 *
Non-opioid dosage/stay (g)	15.1	26.3	<0.001 *
Operation time (min)	70.3	91.4	<0.001 *
Length of air leak (days)	5.6	5.9	0.403
Area of pleurectomy (cm^2)	17.2	32.1	0.006 *
Number of resected segments			
One-segment	41 (78.8)	50 (79.4)	0.934
Multi-segment	11 (21.2)	13 (20.6)	0.934
Postoperative complications			
Hemothorax	3 (5.8)	9 (14.3)	0.220
Acute pneumonia	5 (9.6)	9 (14.3)	0.571
Recurrence	5 (9.6)	7 (11.1)	1.000

Data are presented as means, numbers and percentages. 2P-VATS: two-port video-assisted thoracoscopic surgery, 3P-VATS: three-port video-assisted thoracoscopic surgery, LOS: length of hospital stay, min: minutes. * p-value < 0.05 indicates statistical significance.

A week after discharge, the patients visited our outpatient clinic for postoperative control and follow-up. These visits were conducted at 3-month intervals for one year. A chest radiograph was taken at each visit. Patients were advised to visit our ER at any time they had symptoms related to recurrent pneumothorax (e.g., dyspnea, chest pain or cough). Recurrent pneumothorax was identified clinically in each case with a chest radiograph and a computed tomography scan of the lungs. For patients who recurred after VATS, repeated VATS or chest tube treatment was performed, depending on the underlying pulmonary disease, the patient's clinical condition, as well as the patient's choice. For long-term follow-up, patients were contacted and interviewed using a questionnaire.

The local ethics committee of the Heinrich-Heine University Clinic of Duesseldorf approved this study (study-no: 2020-1271).

2.1. Surgical Technique

Our specialized team of thoracic surgeons (A.S, A.R and WTK) performed all surgical procedures, consisting of a partial pleurectomy and bullectomy for ruptured bulla or blebs (for patients with extensive bullous disease, only the ruptured bleb/bulla and ultrathin bulla with high risk of rupture were resected). All the patients were treated under general anesthesia with a double-lumen tube intubation and single-lung ventilation. To open up the intercostal spaces, the patients were placed in a lateral position and the table was flexed up to 35°. Of note, the patients underwent either 2P-VATS or 3P-VATS initially, depending on the surgeon´s choice. However, in a few cases, the surgeons began surgery with 2P-VATS and then switched to 3P-VATS due to better accessibility and feasibility in these cases.

2.2. Three-Port VATS

The 3P-VATS was performed as previously described [7]. Briefly, three 11 mm ports were placed at the level of the 5th intercostal space in the anterior axillary line and at the level of the 7th and 8th intercostal spaces in the mid- and posterior axillary lines, respectively. An endoscopic stapler (Autosuture GIA Universal; COVIDIEN®, Mansfield, MA, USA) was used for bullectomies. Partial pleurectomy was performed from the apex

of the pleural cavity to the 7th or 8th intercostal space. To avoid vascular injury, the areas along the subclavian and internal mammary vessels were omitted (Figure 1).

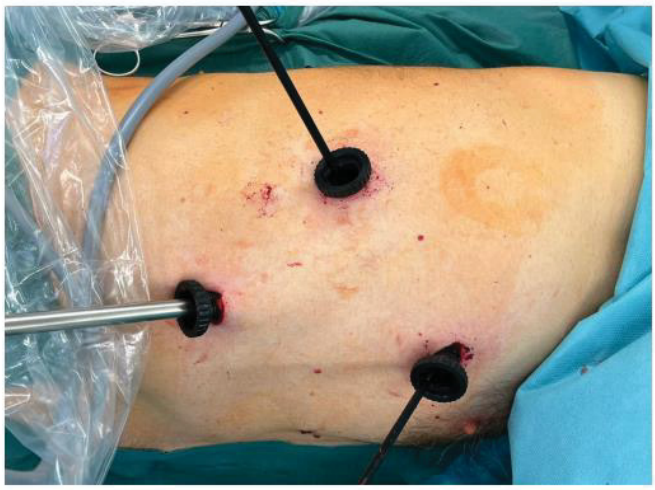

Figure 1. Trocar placement during 3P-VATS.

2.3. Two-Port VATS

The 2P-VATS was also performed as previously described [7]. In summary, two 11 mm ports were inserted at the level of the 5th and 8th intercostal space in the mid- and anterior axillary lines, respectively. For bullectomy, an endograsper and endoscopic stapling device were inserted side by side, without trocar guidance, via the incision in the 5th intercostal space [7] (Figure 2).

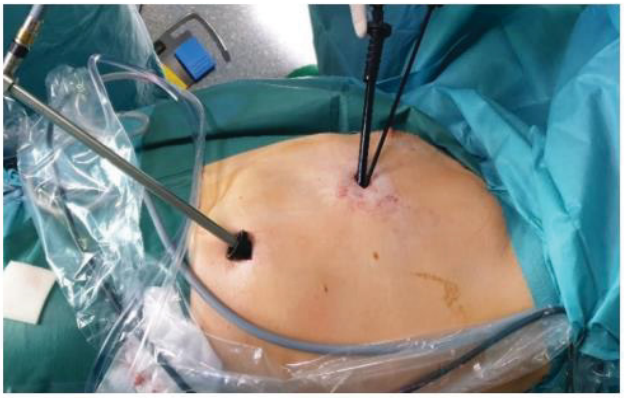

Figure 2. Trocar positioning for 2P-VATS.

For both techniques, an underwater air leak test was performed and a 24 Fr chest tube was placed via the incision in the 5th intercostal space, to which a chest drainage system (Thopaz+, Medela AG, Baar, Switzerland) with a suction equivalent of −20 cm H2O was connected. During the postoperative course, the chest tube drain was removed when there were no clinical signs of air leaks, and when the daily drain output was less than 200 mL. After chest tube removal, a chest radiograph was taken to verify full expansion of the lung.

2.4. Statistical Analysis

All data were evaluated using the SPSS 25.0 software program (Statistical Package for Social Sciences; SPSS Inc., Chicago, IL, USA). Categorical variables were expressed as numbers and percentages, and continuous variables were presented as means. Fisher's exact test was used to compare categorical data and the Mann–Whitney U test was applied for continuous data. Statistical significance was considered at $p < 0.05$.

3. Results

A total of 115 eligible patients were included in this study. Fifty-two patients, with a mean age of 67.7 years (range 41–87), underwent two-port VATS (2P-VATS), while 63 patients (mean age 68.6 years; range 44–87) were treated by three-port VATS (3P-VATS). The clinical characteristics (Table 1), such as mean age, gender, side of pneumothorax and COPD stage (I to IV), were similar in both groups. Between both groups, the BMI and initial size of the pneumothorax were significantly different (Table 1). Nine patients underwent 2P-VATS for other etiological causes (no COPD group: 7 patients had cavernous tuberculosis and 2 patients suffered from early stage I lung cancer (this patient underwent an anatomical lung resection)). Eight patients were treated with 3P-VATS for cavernous tuberculosis, one patient for early stage I lung cancer, and one patient for pneumocystis pneumonia.

Regarding the surgical characteristics (Table 2), there was no significant difference in the number of resected lung segments between both groups, suggesting a lack of selection bias, based on the resected lung segments. The mean operation time (70.3 min vs. 91.4 min; $p < 0.001$) and the length of hospital stay (LOS) (10.7 days vs. 14.3 days; $p = < 0.001$) were significantly shorter for patients in the 2P-VATS group compared with patients in the 3P-VATS group. Additionally, patients who underwent 3P-VATS required a significantly higher total dose of opioid (41.6 mg vs. 24.5 mg; $p < 0.001$) and non-opioid (26.3 mg vs. 15.1 mg; $p < 0.001$) analgesics per stay, compared to patients following 2P-VATS. Interestingly, the total area of resected pleura, during pleurectomy, was significantly larger in the 3P-VATS group compared with the 2P-VATS group. We assume that the additional port access in the 3P-VATS group allowed for better feasibility of pleurectomy, due to the three-dimensional placement of the working trocars, compared to the 2P-VATS group, with limited two-dimensional placement of the trocars. Nine patients in the 3P-VATS group suffered a postoperative hemothorax, whereas this was the case in only three patients in the 2P-VATS group. We assumed that the large area of pleurectomy, following 3P-VATS, contributed to this high rate of hemothorax. Three patients in the 3P-VATS group required repeated VATS, due to hemothorax; the other six patients, and the three patients in the 2P-VATS group, were successfully treated conservatively. Similarly, all the patients with prolonged air leaks received conservative treatment until full recovery. During the clinical course, 5 patients suffered from acute pneumonia in the 2P-VATS group, compared to 9 patients in the 3P-VATS group. During a median follow-up period of 76.5 months (range 1–155 months), there was no significant difference in recurrence rates between the two groups (2P-VATS vs. 3P-VATS: 9.6% vs. 11.1%; $p = 1.000$).

4. Discussion

To date, reports on the outcomes following surgery for secondary spontaneous pneumothorax (SSP) are limited in the literature. Although surgery is associated with low rates of recurrence, high rates of morbidity and mortality after surgical treatment have been reported [5,6].

These high rates of morbidity and mortality are certainly not only impacted by the underlying pulmonary disease, but also by the surgical technique used. In the last decade, thoracic surgery has evolved from open thoracotomy to video-assisted thoracoscopic surgery (VATS), as the gold standard. While three-port VATS (3P-VATS) still remains the standard of care in most centers, due to its accessibility, recent surgical and technical developments are leading to a reduction in access ports [7]. While there are abundant reports on the surgical performance and benefits of limited port access, in terms of postoperative pain, paresthesia and length of hospital stay (LOS), for the treatment of primary spontaneous pneumothorax (PSP) [8–12,14], there is a lack of information on VATS for the treatment of SSP in such reports. Therefore, the aim of our study was to analyze and compare postoperative pain, in terms of the total dose of analgesics used per stay, and clinical outcome following 2P-VATS and 3P-VATS for SSP in our institution.

In this retrospective study, 52 patients underwent 2P-VATS, while 63 patients received 3P-VATS. The patients in the 2P-VATs group had a significantly lower total dose of analgesics administered per stay compared to the patients operated on with 3P-VATS, indicating less postoperative pain. Compared to some previously reported studies [8–12,14] that assessed postoperative pain using the visual analogue scale (VAS score), we used the total dose of non-opioids and opioids per patient as an objective surrogate for postoperative pain. In contrast to the VAS score, which displays a one-time measurement, including the patient´s psychological and emotional state, the quantification of applied analgesics allows pain assessment over a long period of time, independent of the patient´s pschyco-emotional state.

In addition, following 2P-VATS, the mean operation time and the LOS were significantly shorter. In terms of postoperative complications, the 2P-VATS patients had a low rate of hemothorax and pneumonia compared to the 3P-VATS patients (Table 2). We suggest that the high rate of hemothorax in the 3P-VATS group was related not only to the large area of pleurectomy resected during this procedure, but also to the additional port access. Similarly, we assume that the high rate of acute postoperative pneumonia in the 3P-VATS group was related to a higher postoperative pain level, which might have impaired breathing exercises during the first postoperative days. We believe that the high rate of postoperative complications also prolonged the LOS in the 3P-VATS group. To assess recurrence rates following 2P- and 3P-VATS, all the patients were followed-up for a mean period of 76.5 months (range 1–155 months). Interestingly, there was no significant difference in recurrence rates between both groups (2P-VATS 9.6% vs. 3P-VATS 11.1%; $p = 1.000$).

The power of our study is limited due to its retrospective design and the small number of patients included. To the best of our knowledge, this is the first study that analyses and compares postoperative pain and treatment outcome following 2P- and 3P-VATS for SSP patients. Our study demonstrates that the treatment of SSP by 2P-VATS is associated with less postoperative pain, low morbidity rates and earlier patient recovery compared to the conventional 3P-VATS. Nonetheless, this observation should be verified in a prospective trial with a larger number of patients.

5. Conclusions

According to our results, 2P-VATS is a suitable and safe surgical technique for the treatment of SSP. When compared to 3P-VATS, it is associated with less postoperative pain, lower morbidity rates and faster patient recovery. Therefore, 2P-VATS should be preferred for the surgical treatment of SSP.

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Informed Consent Statement: Informed consent to participate was obtained prior to study begin.

Data Availability Statement: The data presented are included in this study; the corresponding author on request may provide additional data.

Conflicts of Interest: The authors declare no conflict of interest.

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