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Long term follow up after bronchoscopic lung volume reduction valve treatment for emphysema

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Take home message

A substantial amount of patients still experienced benefit 3 years after the lung volume reduction treatment with endobronchial valves. This benefit included quality of life which is an important outcome for these group of patients with end-stage COPD.

ABSTRACT

Background Multiple studies have shown that patients with severe emphysema can significantly benefit from the bronchoscopic lung volume reduction treatment with endobronchial valves (EBV) up to 1 year after treatment. However, hardly any data exists on longer term follow-up, especially on quality of life. Our aim was to investigate the long term follow-up after EBV treatment up to 3 years including quality of life in a real life routine clinical setting.

Methods We retrospectively included patients who underwent EBV treatment in our hospital at least 3 years ago. Patients were invited for annual visits to our hospital and spirometry, bodyplethysmography, 6-minute walk distance test (6MWD) and SGRQ-questionnaire were performed during these visits.

Results At one, two and three years of follow-up, data was available from 189, 146 and 112 patients, respectively. FEV_1, RV and SGRQ total score significantly improved as compared to baseline up to 3 years after treatment and 6MWD up to 2 years. In general, the magnitude of the improvements gradually decreased over time.

Conclusion Our results show that patients can benefit at least up to three years after the EBV treatment. For the first time we found that patients can also benefit in terms of quality of life in the long term which is an important outcome for these group of patients with end-stage COPD.

INTRODUCTION

The development of the bronchoscopic endobronchial valve treatment (EBV) for emphysema started approximately 20 years ago and the treatment was included in the Global initiative for Chronic Obstructive lung disease (GOLD) guideline in 2017.[1–3] This inclusion in treatment guidelines was based on the positive outcomes of the treatment on lung function, exercise capacity and quality of life in multiple randomised controlled trials.[4]

So far a handful of studies have published the results up to 1 year after treatment and all showed sustained positive effects of the treatment.[5–8] However, less is known about the longer term follow up. With the exception of the LIBERATE trial (NCT 01796392) which has an ongoing long term follow up of 5 years, the follow up duration of the other randomised clinical trials were 6 or 24 months. Therefore, data-registries from regular care settings are needed for long term outcomes.[7, 9–11] To our knowledge, the only longer term follow up analysis with a substantial amount of patients originates from a German data-registry.[12] This study included 256 treated patients and showed that although the clinical benefit gradually declined over time, a high number of patients still had a clinical significant response in hyperinflation and exercise capacity at 3 year follow up.[12] Due to the retrospective database design of this study, and the high number of drop-outs due to a study population with severe disease, additional data on long-term results after EBV treatment would be useful. Furthermore, this study did not include any information on quality of life, which is an important outcome, especially in the long term for this patient population with limited life expectancy.

Therefore, the aim of our study was to investigate the long term follow up after bronchoscopic lung volume reduction EBV treatment up to 3 year follow up including quality of life in a regular care setting.

METHODS

Study population

We retrospectively included patients with severe emphysema who were treated in our hospital with EBVs for lung volume reduction at least 3 years ago. Patients were either treated in clinical trials (CHARTIS, STELVIO, IMPACT, TRANSFORM or LIBERATE[7, 9–11, 13]), for compassionate use or in our regular care program BREATHE-NL (as of 2016, NCT02815683). All trials were approved by our local ethics committee and all patients signed written informed consent for use of their data.

Study design and measurements

After treatment, all patients were invited for a voluntary follow up visit in our hospital after 6 weeks, 6 months and afterwards yearly. During most of the visits to our hospital spirometry, bodyplethysmography, diffusion capacity and 6-minute walk distance test were measured according to the European Respiratory Society/American Thoracic Society (ERS/ATS) guidelines[14–17] In addition, the following questionnaires were completed: St. Georges Respiratory Questionnaire (SGRQ), COPD assessment test (CAT), modified Medical research council scale (mMRC) and the EuroQol-5D questionnaire (EQ5D).[18–21] Furthermore, blood gas measurement was performed at baseline and a chest computed tomography (CT) scan, on which a quantitative analysis was performed using LungQ software (Thirona, Nijmegen, The Netherlands) was performed at baseline and 2-6 months follow up.

Statistical analyses

Differences in clinical outcomes between baseline and follow up time points were tested with a paired sample t-test. To calculate the number of responders the following established minimal important differences (MIDs) were used: FEV_1: 100mL[22], 6MWD: 26 meter[23], RV: 310mL[24], SGRQ total score: 7.1 units[25], Target lobe volume reduction (TLVR): 563 mL and 22.4%[26]. The number of pneumothoraces, revision bronchoscopies and deaths were calculated together with the median time between the occurrence of the event and the date of the treatment. All statistical analyses were performed using IBM SPSS statistics version 23 (IBM, New York, NY, USA) and p-values below 0.05 were considered statistically significant.

RESULTS

Study population

In total, 322 patients underwent a bronchoscopy of which 280 patients were actually treated with EBVs between June 2008 and June 2018 in our hospital. The main reason for no treatment was presence of collateral ventilation. Table 1 shows the patient characteristics and the patient flow during the 3 year follow up can be found in the flowchart in Figure 1 (and Table S1 online supplement). Procedure details are shown in Table S2 in the online supplement.

Long term follow up

The $FEV_{1,}$ RV, SGRQ, mMRC score and EQ5D VAS score significantly improved at all time points compared to baseline (Table 2& Table S3 in online supplement show the results in all patients who completed the baseline and 3 year follow up visit, Table S7 shows the median values)). The 6MWD and CAT score were significantly higher compared to baseline up to 2 year follow up but not at 3 year follow up. In general, the magnitude of the improvements decreased over time. The number of responders are shown in Figure 2 and Table S4 (online supplement).

Target lobe volume reduction

A follow up CT scan after 2 or 6 months was performed in 226 patients, and the mean ± SD TLVR was -1281 ± 675 mL (relative reduction compared to baseline: -71 ± 32%) Eighty-six patients (38%) had a complete atelectasis (100%TLVR) and 193 patients (85%) had a clinically relevant reduction in target lobe volume according to the established MID of -563 mL (Table S4 online supplement). At 12 month follow up, patients with a complete atelectasis had a significant larger improvement in RV, FEV_1, SGRQ, CAT and 6MWD compared to patients who did not have a complete atelectasis (Table S5 online supplement).

Pneumothorax, revision bronchoscopy and survival

A pneumothorax occurred in 60 patients (21%) with a median of 1 day after treatment (range 0-660 days). In 13 (22%) patients no treatment was needed, in 43 (72%) of these cases a chest tube was placed, and 4 patients needed surgery. There were no differences in

outcomes at all timepoints between patients who developed a pneumothorax versus patients who did not. One-hundred and twenty-four patients (44%) underwent at least 1 revision bronchoscopy during follow up with a median of 140 days after treatment (IQR range 49-425 days). During the 3 year follow up 50 patients died (17.9%), with a median of 692 days after the treatment (range 39-1079 days) (see Figure S6 in online supplement).

DISCUSSION

Our results show that patients can benefit up to 3 years from bronchoscopic lung volume reduction treatment with endobronchial valves. After 3 years follow up, we still found significant improvements in terms of lung function, target lobe volume reduction, dyspnea severity and quality of life and up to 2 years in exercise capacity.

In line with the results of Gompelmann et al[12] we found significant improvements in exercise capacity up to 2 years after treatment and similar responder rates for the outcomes up to 3 year follow up. Furthermore, we also found significant improvements in dyspnea severity up to 3 year follow up. In contrast, we found a persistent significant improvement in FEV_1 up to 3 year follow up, while in the German registry the FEV_1 was only significantly higher up to 1 year follow up. Additionally, the number of FEV_1 responders was higher in our population. Also, in our patients, the residual volume was still significantly improved at 3 years follow up, in contrast with the German registry in which significant improvements were found until 2 years follow up. Remarkably, the responder rates of RV were higher in their population while even using a higher MID. To our knowledge, there are no papers with large sample sizes on the long term follow up after other bronchoscopic lung volume reduction techniques. Therefore, we were unable to compare our outcomes with other lung volume reduction techniques.

For the first time we investigated quality of life after EBV treatment in the long term. Our results show that quality of life measured using the SGRQ was still significantly higher up to 3 year after treatment. Moreover, at each time point the change in SGRQ was on or above the MID of -7.1 units. When comparing our results to lung volume reduction surgery (LVRS- NETT trial [27]) our responder rates were higher: respectively 57%/50%/46% vs 40%/32%/20% at

1, 2 and 3 year follow up. It should be noted that the NETT trial used a slightly higher MID-cut-off: -8 units versus -7.1 in our study and the NETT trial was performed more than 20 years ago and surgical treatment options further developed afterwards. In a previous study in which we investigated a small subgroup of patients treated with lung volume reduction coils we also found that on average the SGRQ was still higher than the MID of -7.1 units.[28]

Our results show that the size of the clinical improvement gradually declines over time, which could be an indication of a diminishing treatment effect. On the other hand, EBV treatment does not stop the natural disease progression of COPD, which may also be a likely explanation for the decline over time. Previously, we collected pre-treatment spirometry results in a small group of patients treated with lung volume reduction coil treatment to investigate the pre-treatment decline.[28] The decline before treatment was -0.08L/year, indicating that without treatment the FEV_1 would even be lower. Although probably the rate of decline will slow down when the FEV_1 decreases. The NETT trial, investigating lung volume reduction surgery was able to include a non-treated control group for the long term.[27] Their results showed that functional outcomes in the survivors in the control group worsened after approximately 6 months below baseline and continued to deteriorate afterwards.[27] For example, the SGRQ total score was +4.6 units after 3 year follow up (compared to -7.1 in our population treated with EBV). Thus, although the benefit gradually declines, it is likely that patients still have a clinical advantage compared to patients who did not undergo EBV treatment. Another important note is that the MIDs used were in general calculated for the short term (up to one year) and it is questionable whether these are applicable and not too strict to evaluate long term results.

The pneumothorax rate and number of revision bronchoscopies were comparable with previously reported results in literature. Furthermore, the survival rate at 3 year follow up was quite high (82%). Previously, we as well as Garner et al., found that bronchoscopically reducing lung volume in patients with severe hyperinflation can lead to a survival benefit as well[29, 30], which can also be an important indicator of long term treatment efficacy.

A limitation of our study is the high number of patients who were lost to follow up over time. This can be attributed to the retrospective data registry study design with voluntary

follow up visits, and also to the study population with very severe disease who already have a limited life expectancy, were not able to travel to our hospital, or underwent other treatments like lung transplantation. Our number of lost to follow up is in line or even slightly better than the study of Gompelmann et al.[12] and underlines the difficulty of performing real-clinical practice studies in comparison with controlled trials. However, we realize that patients who did complete the visits are more likely to be the better treatment-responders, which could have led to an overestimation of our results.

Unfortunately, it is difficult and expensive to perform clinical trials with long term follow up. The LIBERATE trial (NCT 01796392) is the only (still ongoing) trial with a follow up of 5 years after treatment. However, the follow up visits only include spirometry and safety reporting and therefore will not provide insight in changes in lung volumes, exercise capacity or quality of life in the long term. Furthermore, in the LIBERATE trial we still expect a substantial amount of patients who will be lost to follow up and additionally the patients were only randomized up to 1 year.

To conclude, our results indicate that a substantial amount of patients can still benefit from the bronchoscopic lung volume reduction treatment with endobronchial valves 3 years after treatment. The magnitude of the improvements gradually decreased over time which is probably also a consequence of the natural disease progression of COPD. For the first time we also showed that the quality of life of the patients is still better 3 years after treatment which is an important outcome for these group of patients with end-stage COPD.

CONFLICTS OF INTEREST STATEMENT

DJS reports: Grants or contracts from PulmonX Corp., USA, PneumRx/BTG/Boston Sc. USA, FreeFlowMedical, USA and Nuvaira, USA (PI and advisor to institution); consulting fees from PulmonX Corp., USA, PneumRx, USA and Nuvaira, USA; payment or honoraria for lectures from PulmonX Corp., USA, PneumRx, USA and Nuvaira, USA; support for attending meetings and/or travel from PulmonX Corp., USA, PneumRx, USA and Nuvaira, USA, Receipt of study material and medical devices to institution from PulmonX Corp., USA, PneumRx, USA and

Nuvaira, USA. KK reports payment or honoraria for lectures from PulmonX and Boehringer. All other authors have nothing to disclose.

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TABLES

Table 1: Baseline patient characteristics (n=280)

		N (valid)
Gender, male	89 (32%)	280
Age, *years*	60 ± 8.5	280
BMI, *kg/m^2*	23.9 ± 3.6	280
Pack years, *years*	39 (0-148)	263
LTOT use, yes(%)	75 (32%)	235
FEV_1, *Liter*	0.75 ± 0.27	280
FEV_1, *perc pred*	27.8 ± 8.0	280
RV, *Liter*	4.90 ± 1.06	278
RV, *perc pred*	234 ± 41	278
RV/TLC, %	63.5 ± 7.9	278
DLCO, *perc pred*	34.4 ± 11.3	219
PaO2, kPa	9.08 ± 1.3	252
PaCO2, kPa	5.32 ± 0.76	252
6WMD, *meter*	325 ± 95	266
mMRC, *score*	3.0 (1-4)	258
EQ5D, *VAS-score*	48.5 ± 16.7	243
SGRQ, *impact score*	47.5 ± 16.8	258
SGRQ, *activity score*	85.9 (38.7-100)	258
SGRQ, *symptom score*	48.4 ± 18.7	258
SGRQ, *total score*	59.3 ± 12.1	258
CAT, *total score*	22.2 ± 5.4	147
Target lobe volume, mL	1905 ± 638	273
Emphysema score*, target lobe, *%*	48.7 ± 9.8	273

Data are presented as n(%), mean ± standard deviation or median (range).
n:number, kg: kilogram, m: meter, FEV_1: forced expiratory volume in 1 second, perc pred: percentage of predicted, RV: residual volume, TLC: total lung capacity, DLCO: diffusing capacity for carbon monoxide, PaO2: partial pressure of oxygen, PaCO2: partial pressure of carbon dioxide, 6MWD: 6-minute walk distance, mMRC: modified Medical research council, EQ5D: EuroQol-5dimensions, VAS: visual analogue scale, SGRQ: St. George's Respiratory questionnaire, CAT: COPD assessment test. Emphysema score: percentage of voxels below the-950hounsfield units threshold*

Table 2: Changes in clinical outcomes compared to baseline up to 3 year after treatment

	6 week FU	*n*	p	6 month FU	*n*	p	12 month FU	*n*	p	24 month FU	*n*	p	36 month FU	*n*	p
Δ FEV_1, *Liter*	0.21 ± 0.18	*251*	**<0.001**	0.19 ± 0.19	*196*	**<0.001**	0.15 ± 0.19	*189*	**<0.001**	0.10 ± 0.20	*146*	**<0.001**	0.04 ± 0.18	*110*	**0.033**
Δ RV, *Liter*	-0.80 ± 0.64	*238*	**<0.001**	-0.69 ± 0.69	*189*	**<0.001**	-0.62 ± 0.63	*177*	**<0.001**	-0.44 ± 0.71	*123*	**<0.001**	-0.33 ± 0.69	*90*	**<0.001**
Δ 6MWD, *meter*	ND			57.9 ± 64	*197*	**<0.001**	45.6 ± 74	*173*	**<0.001**	36.1 ± 83	*94*	**<0.001**	8.8 ± 96	*86*	0.397
Δ SGRQ, *total score*	-18.0 ± 15.4	*220*	**<0.001**	-15.3 ± 16.3	*194*	**<0.001**	-11.0 ± 17.0	*184*	**<0.001**	-8.0 ± 15.7	*141*	**<0.001**	-7.1 ± 14.7	*112*	**<0.001**
Δ CAT, *total score*	-4.88 ± 6.46	*122*	**<0.001**	-3.42 ± 6.08	*115*	**<0.001**	-2.36 ± 6.63	*113*	**<0.001**	-1.5 ± 6.00	*72*	**0.037**	-1.40 ± 5.50	*60*	0.053
Δ EQ5D, *VAS score*	ND			ND			12.56 ± 20.8	*170*	**<0.001**	8.95 ± 19.6	*131*	**<0.001**	6.63 ± 21.3	*107*	**0.002**
Δ mMRC	-0.64 ± 0.76	*211*	**<0.001**	-0.54 ± 0.74	*198*	**<0.001**	-0.46 ± 0.76	*170*	**<0.001**	-0.38 ± 0.86	*126*	**<0.001**	-0.23 ± 0.81	*88*	**0.010**

Data are presented as mean ± standard deviation, number or p-value. Significant values using the Holm-Bonferroni method to adjust for multiple comparisons are depicted in bold. ND: test not done at that time point. Changes between baseline and follow up measurement were tested with a paired t-test. FU: follow up, n: number, p: p-value, Δ: change between baseline and follow up, FEV_1: forced expiratory volume in 1 second, RV: residual volume, 6MWD: 6-minute walk distance, SGRQ: St. George's respiratory questionnaire, CAT: COPD assessment test, EQ5D: EuroQol-5dimensions, VAS: visual analogue scale, mMRC: modified Medical research council.

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FIGURES LEGENDS

Figure 1: Flow chart of patients through study follow up

Figure legend: n: number, CV+: presence of collateral ventilation, FU: follow up.

Figure 2: Number of responders during FU

Figure legend: Figure shows the percentage of patients who exceeded the established MID per timepoint (6, 12, 24 and 36 months follow up).FEV_1: forced expiratory volume in 1 second, RV: residual volume, 6MWD: 6-minute walk distance, SGRQ: St. George's respiratory questionnaire.
MIDs used: FEV_1: 100mL, 6MWD: 26 meter, RV: 310mL and SGRQ total score: 7.1 units

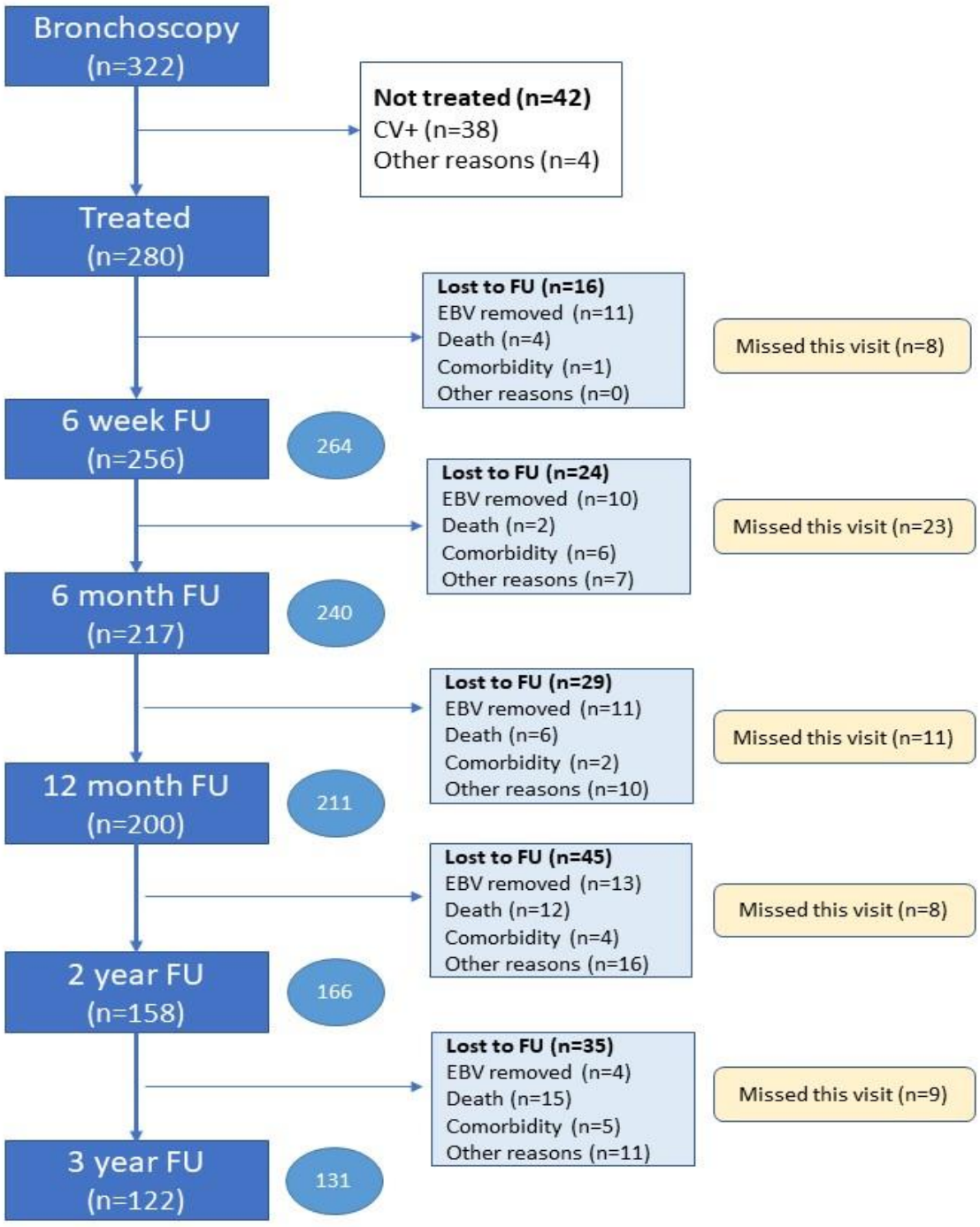
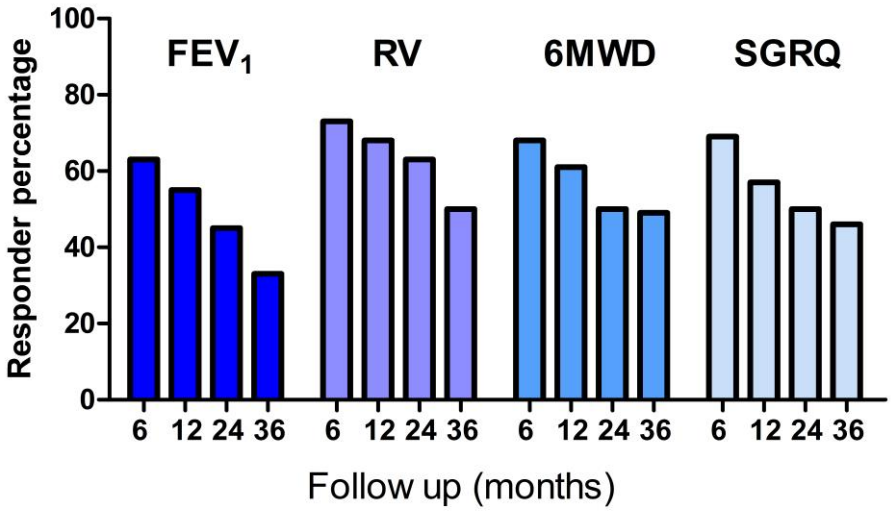


Figure 1: Flow chart of patients through study follow up Figure legend: n: number, CV+: presence of collateral ventilation, FU: follow up.



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ONLINE SUPPLEMENT

Three year follow up after bronchoscopic lung volume reduction valve treatment

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TABLE S1: Overview of the reasons of lost to follow up per visit

6 WEEK FU (n=24)				
Lost to FU	**n=16**		**Missed this visit**	**n=8**
EBV removed after pneumothorax	n=9		Revision bronchoscopy	n=3
EBV removed after kinked bronchus	n=2		Unknown reason	n=2
Death	n=4		Comorbidity	n=1
Comorbidity	n=1		Follow up in other hospital	n=1
			Hospitalization due to pneumothorax	n=1
6 MONTH FU (n=47)				
Lost to FU	**n=24**		**Missed this visit**	**n=23**
Lung transplantation	n=3		No part of study follow up	n=15
EBV removed, no benefit	n=10		Husband died	n=1
No benefit, end of follow up	n=1		Comorbidity	n=2
No regular follow up	n=1		Revision bronchoscopy	n=4
Death	n=2		Follow up in other hospital	n=1
Comorbidity	n=6			
Multiple reasons	n=1			
12 MONTH FU (n=40)				
Lost to FU	**n=29**		**Missed this visit**	**n=11**
Lung transplantation	n=2		Unknown reason	n=9
No regular follow up	n=6		Revision bronchoscopy	n=1
Lung volume reduction surgery	n=1		Comorbidity	n=1
VATS due to pneumothorax	n=1			
EBV removed	n=11			
Comorbidity	n=2			
Death	n=6			
24 MONTH FU (n=53)				
Lost to FU	**n=45**		**Missed this visit**	**n=8**
No benefit, end of follow up	n=1		Unknown reason	n=7
Death	n=12		Revision bronchoscopy	n=1
Lung volume reduction surgery	n=5			
EBV removed	n=13			
Patient's decision	n=7			
Comorbidity	n=5			
Revision bronchoscopy	n=2			
36 MONTH FU (n=44)				
Lost to FU	**n=35**		**Missed this visit**	**n=9**
End of follow up	n=9		Unknown reason	n=2
Additional treatment	n=1		Comorbidity	n=2
EBV removed	n=4		COVID-19	n=5
Death	n=15			
Comorbidity	n=5			
Lung transplantation	n=1			

FU: follow up, n: number

TABLE S2: EBV treatment details (n=280)

		n(%)	median (range)	*n (valid)*
Target lobe				*280*
	RUL	48 (17%)		
	RUL+RML	18 (6%)		
	RML	4 (1%)		
	RLL	51 (18%)		
	LUL	71 (25%)		
	LLL	87 (31%)		
	RUL+LUL	1 (0.4%)		
Valves				
Total			4 (1-9)	*280*
	EBV		4 (0-9)	
	IBV, n(%)	12 (4%)	0 (0-4)	
Procedure time, *minutes*			13 (0-75)	*253*
Hospitalization, *days after treatment*			4 (1-60)	*277*
Pneumothorax during hospitalization, *yes*		50 (18%)		*280*

Data are presented as n(%) or median (range).
RUL: right upper lobe, RML: right middle lobe, RLL: right lower lobe, LUL: left upper lobe, LLL: left lower lobe, EBV= endobronchial valve, IBV= intrabronchial valve, n= number, sd= standard deviation.

TABLE S3*:* Changes in clinical outcomes between baseline and follow up in patients who completed all study visits

	12 month FU	*n*	p	24 month FU	*n*	p	36 month FU	*n*	p
Δ FEV_1, *Liter*	0.19 ± 0.19	*88*	**<0.001**	0.12 ± 0.19	*88*	**<0.001**	0.04 ± 0.17	*88*	**0.046**
Δ RV, *Liter*	-0.68 ± 0.63	*68*	**<0.001**	-0.54 ± 0.65	*68*	**<0.001**	-0.27 ± 0.65	*68*	**0.001**
Δ 6MWD, *meter*	62.9 ± 76	*77*	**<0.001**	55.5 ± 77	*55*	**<0.001**	13.9 ± 94	*77*	0.200
Δ SGRQ, *total score*	-15.2 ± 16.5	*95*	**<0.001**	-9.83 ± 16.2	*95*	**<0.001**	-6.5 ± 15.0	*95*	**<0.001**
Δ CAT, *total score*	-3.72 ± 6.6	*50*	**<0.001**	-2.20 ± 6.4	*50*	**0.018**	-1.4 ± 5.4	*50*	0.072
Δ EQ5D, *VAS score*	14.8 ± 19.8	*91*	**<0.001**	9.8 ± 19.8	*91*	**<0.001**	5.5 ± 21.8	*91*	**0.019**
Δ mMRC	-0.59 ± 0.81	*69*	**<0.001**	-0.62 ± 0.84	*69*	**<0.001**	-0.29 ± 0.82	*69*	**0.005**

Patients were included when they had performed all follow up visits, and for 6MWD the 12 month and 36 month follow up because the 6MWD test was not always part of the 24 month follow up visit. Data are presented as mean ± standard deviation, number or p-value. Changes between baseline and follow up measurement were tested with a paired t-test. FU: follow up, n: number, p: p-value, Δ: change between baseline and follow up, FEV_1: forced expiratory volume in 1 second, RV: residual volume, 6MWD: 6-minute walk distance, SGRQ: St. George's respiratory questionnaire. CAT: COPD assessment test, EQ5D: EuroQol-5dimensions, VAS: visual analogue scale, mMRC: modified Medical research council.

TABLE S4: Number of responders during follow up

	6 week FU	6 month FU	12 month FU	24 month FU	36 month FU
Δ FEV_1 >100mL	174 (69%)	124 (63%)	104 (55%)	65 (45%)	36 (33%)
Δ RV < -310mL	178 (75%)	138 (73%)	121 (68%)	77 (63%)	45 (50%)
Δ 6MWD > 26 meter	NA	134 (68%)	106 (61%)	47 (50%)	42 (49%)
Δ SGRQ < -7.1 unit	165 (75%)	133 (69%)	105 (57%)	70 (50%)	51 (46%)
Δ TLVR < -563mL	193 (85%)	NA	NA	NA	NA
Δ TLVR < -22.4%	208 (92%)	NA	NA	NA	NA

Data are presented as number (%) and indicated the number of patients who exceeded the established minimal important difference (MID).

TABLE S5: Differences in change between baseline and 12 month follow up between patients who had a complete atelectasis versus patients who did not had a complete atelectasis

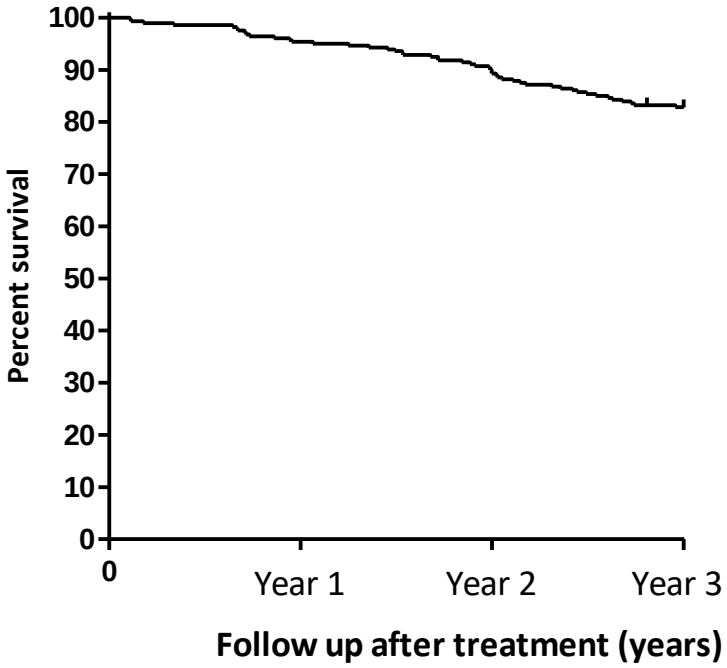
	Complete atelectasis	Not a complete atelectasis	p-value	N
Change in RV, *liter*	-0.80 ± 0.62	-0.50 ± 0.63	**0.003**	71/96
Change in FEV_1, *liter*	0.18 ± 0.18	0.12 ± 0.19	**0.042**	72/102
Change in SGRQ, *total score*	-14.6 ± 15.5	-8.0 ± 17.7	**0.012**	72/102
Change in 6MWD, *meter*	61.2 ± 73.0	32.1 ± 72.0	**0.011**	71/95
Change in CAT, *total score*	-4.13 ± 6.5	-1.56 ± 6.5	**0.049**	40/71
Change in EQ5D, *VAS score*	13.6 ± 18.8	11.5 ± 21.5	0.525	70/94
Change in mMRC	-0.49 ± 0.72	-0.44 ± 0.74	0.668	70/94

Data are presented as mean ± standard deviation, or n=number.

Complete atelectasis was defined as a Target lobe volume reduction measured on CT-scan ≥99.5% measured between 8 weeks-6 months follow up. RV: Residual volume, FEV1: Forced expiratory volume in 1 second, SGRQ: St. George's Respiratory Questionnaire, 6MWD: 6-minute walk distance. CAT: COPD assessment test, EQ5D: EuroQol-5dimensions, VAS: visual analogue scale, mMRC: modified Medical research council.

A regular follow up CT scan was only performed between 2-6 months after treatment and therefore we did not perform this analysis for the longer term as the presence of a complete atelectasis could not be verified at these time points.

FIGURE S6: Kaplan Meier curve of survival between treatment and 3 year follow up (n=280)



Legend: During the 3 year follow up in total 50 patients died (17.9%), with a median of 692 days after the treatment (range 39-1079 days).

TABLE S7: Changes in clinical outcomes compared to baseline up to 3 year after treatment (median values)

	12 month FU	*n*	24 month FU	*n*	36 month FU	*n*
Δ FEV_1, *Liter*	0.12 (0.01-0.25)	*189*	0.09 (-0.02- 0.20)	*146*	0.03 (-0.09- 0.13)	*110*
Δ RV, *Liter*	-0.63 (-1.01- -0.21)	*177*	-0.44 (-0.92- -0.06)	*123*	-0.32 (-0.76 - 0.11)	*90*
Δ 6MWD, *meter*	47 (5-98)	*173*	27.0 (-9.3- 78.3)	*94*	23.5 (-68.0- 65.5)	*86*
Δ SGRQ, *total score*	-10.5 (-22.2- 0.6)	*184*	-6.9 (-16.7- 1.5)	*141*	-4.0 (-15.7- 3.0)	*112*

Data are presented as median (inter quartile range), number. FU: follow up, n: number, Δ: change between baseline and follow up, FEV_1: forced expiratory volume in 1 second, RV: residual volume, 6MWD: 6-minute walk distance, SGRQ: St. George's respiratory questionnaire.