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ASTHMA

Bronchial Thermoplasty Including the Middle Lobe Bronchus Significantly Improves Lung Function and Quality of Life in Patients Suffering from Severe Asthma

Stephan Eisenmann[1,2] · Wolfgang Schütte[3] · Faustina Funke[1] · Filiz Oezkan[1] · Shaheen Islam[4] · Kaid Darwiche[1]

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Abstract

Purpose Bronchial Thermoplasty (BT) is indicated in patients suffering from severe and symptomatic bronchial asthma despite maximal medical therapy. However, treatment of the right middle lobe (RML) bronchus is currently not recommended. The aim of this study was to investigate the safety and efficacy of BT if the RML bronchus is included.

Methods BT was performed in 17 consecutive patients, quality of life and pulmonary function were characterized before and 90 days after BT completion. Furthermore, we performed a clean-up bronchoscopy following every BT. This study was approved by the IRB of the University of Essen (No. 17-7356 BO) and registered as a retrospective observational study at the German Clinical Trials Registry (No. DRKS 00011550).

Results The median baseline values of FEV1 and Asthma Questionnaire of Life Quality (AQLQ) were 1.33 l (0.91; 1.73) and 3.01 (2.76; 3.61), respectively, and significantly improved 90 days after treatment with FEV 1 at 1.75 l (p-value 0.002) and AQLQ 3.8 (p-value < 0.05). Also the amount of oral corticosteroid necessity decreased significantly. No severe adverse events occurred due to the procedure. Clean-up bronchoscopies—when performed—revealed significant fibrinous exudation after every BT procedure.

Conclusion BT including the RML bronchus is feasible. Functionally limited patients with severe asthma could potentially profit. Due to the relevant fibrinous exudation, BT should be followed by clean-up bronchoscopy, not only after RML treatment.

Keywords Asthma · Bronchoscopy · Bronchial Thermoplasty · Middle lobe bronchus

Introduction

Bronchial asthma is one of the most common chronic diseases worldwide [1]. Although therapeutic strategies have been individualized, some patients suffer from recurrent symptoms and are characterized as "severe". Increasing possibilities to distinguish between different phenotypes may help a small number of patients with more individualized therapeutic options, e.g., anti-IgE- or anti-IL5-antibody treatment [2]. The majority of patients are still not eligible for such specific treatments [2]. Severe asthma has a negative impact on the patients' quality of life (QoL) and increases both social and economic burdens. Bronchial Thermoplasty (BT) is a new non-pharmaceutical therapeutic option for severe asthma. Through controlled bronchoscopic application of radiofrequency (RF) using the ALAIR®-system (Boston Scientific, Nattick, Massachusetts, USA), airway muscular tissue can be reduced [3, 4]. BT decreases bronchoconstriction, frequency of exacerbations, and the severity of asthma symptoms leading to more symptom-free-days and an improvement in QoL [5]. According to the AIR-2-study, a reduction of oral steroids is also expectable. In 2010, BT was FDA approved for severe asthma. Treatment of the RML bronchus is currently not recommended because of

✉ Stephan Eisenmann
stephan.eisenmann@uk-halle.de

1 Interventional Pneumology, Ruhrlandklinik-West German Lung Center, Essen, Germany

2 Department of Pulmonary Medicine, University of Halle-Wittenberg, Ernst-Grube-Straße 40, 06120 Halle, Germany

3 Martha-Maria Hospital Halle-Dölau, Halle, Germany

4 Interventional Pulmonology, Ohio State University, Columbus, USA

the fear of additional complications if BT was applied in the anatomically smaller and narrow RML bronchus [6].

The aim of this two-center retrospective trial was to investigate safety and efficacy of BT inclusive of the RML bronchus in the treatment algorithm.

Materials and Methods

Study Subjects and Design

All patients referred to our centers (Ruhrlandklinik Essen and Martha-Maria Halle-Dölau) between August 2013 and January 2016 were consecutively screened regarding their eligibility for BT. Both centers have a dedicated program for patients with severe asthma. Adult patients with an established diagnosis of severe, poorly controlled asthma were enrolled in this study. All received adequate maximum maintenance medication including high-dose inhaled corticosteroids (ICS), long-acting beta agonists (LABA), the long-acting muscarin antagonist (LAMA), tiotropium, Anti-IgE-antibody treatment, and oral corticosteroids (OCS) as needed. Patients were included if they were in a stable stage of disease and were free of exacerbations at least 4 weeks prior to BT. In contrast to former randomized-control (RCT) studies, permanent decline of FEV1 was no exclusion criteria. COPD was ruled out if no relevant smoking history (< 10 package years) was reported, radiographic signs of emphysema were absent and a positive reaction to bronchospastic agents was documented. Baseline investigation included total serum-IgE, absolute number of blood eosinophils, pulmonary function tests (PFT) with body plethysmography, and QoL-evaluation using the Asthma Questionnaire of Life Quality (AQLQ). A prior screening bronchoscopy was performed if additional factors of asthma persistence were to be excluded. Patients older than 40 years or those with reported mucus expectoration received chest computed tomogram (CT). Three-month follow-up after completion of BT included AQLQ, PFT and evaluation of need for OCS use.

Methods

BT was performed as described earlier [7]. Briefly: BT treatment consisted of three bronchoscopies, performed under total intravenous anesthesia (TIVA). BT bronchoscopies were performed at 4–8 week intervals. The RML was included in the treatment, whenever the inspection could be easily performed with a 6.2 mm diameter flexible bronchoscope. Treatment of the RML was performed with right lower lobe treatment in the first session. The second treatment session was conducted in the left lower lobe, the final treatment in both upper lobes.

For BT application, a bronchoscope with a maximum outer diameter of 4.2 mm and a working channel of 2.0 mm was used. After advancing the bronchoscope as peripheral as possible, the ALAIR®-catheter was placed into the particular subsegment. All bronchi with a diameter of 3–10 mm were treated by retracting the ALAIR®-catheter, guided by the 5-mm-marks on the catheter surface. The number of RF-activations was recorded. When BT was applied to the medial segment of the RML bronchus (RB 5), the ECG-patterns were additionally observed for cardiac arrhythmia. After RML treatment and in case of worsening of respiratory symptoms, a chest radiograph was obtained after 48 h after BT. A clean-up bronchoscopy was offered to all patients 48–72 h after the BT, even in case of a stable respiratory situation.

All patients were hospitalized for at least 3 days and received OCS (50 mg daily) starting 2 days prior to the procedure and continued until 2 days post procedure. Adverse events were recorded for 6 weeks after the BT and were identified as treatment-related. Informed consent was obtained from every patient. The study was approved by the local ethics committee of University of Duisburg-Essen (approval number. 6767-BO) and registered as a retrospective observational study at the German Clinical Trials Registry (No. DRKS 00011550).

Statistical Analyses

Kolmogorov–Smirnov-test was performed to characterize the parametric distribution. Student's *t*-test for paired samples was used to examine average differences from baseline to follow-up values. Wilcoxon tests were used for variables with non-parametric distribution. An increase of 0.5 points in AQLQ was considered necessary for minimal clinically important difference (MCID) [8]. A two-tailed *p*-value of less than 0.05 was considered statistically significant. Statistical analysis was performed with SPSS (Professional Version 17, 2010).

Results

42 patients were screened (see Table 1 for details), a total of 17 patients with a mean age of 50.7 years (± 12.7) were eligible for BT [15 females (87%) and 2 males (13%)]. Non eligibility resulted usually from non-optimal medical therapy, missing baseline information regarding allergy screening, and active nicotine consumption. All eligible patients had initially received maximum controller medication of ICS/LABA, nine of them additionally received LAMA. Ten patients required permanent OCS with a daily median dose of 20 mg (13.9). The median postbronchodilatator FEV1 was 1.33 L (47% pred.), Vital capacity (VC) and Airway

Table 1 Patients demographic and medication characteristics at baseline

Age	50.7 (12.7)
Women/men	15 / 2
BMI	29.9 (6.12)
Height (m)	1.65 (0.07)
Weight (kg)	81.4 (16.8)
Elevated IgE (> 100 IU/ml)	7 (41.2%)
Elevated eosinophils (absolute count > 300/µl)	3 (17.6%)
Omalizumab longer than 6 months	10 (58.8%)
Oral corticosteroid longer than 6 months	10 (58.8%)
Montelucast	6 (35.3%)
Tiotropium	9 (53%)
LABA/ICS at high dose	17 (100%)

Data are *n* or mean

BMI body mass index, *LABA* long-acting beta agonist, *ICS* inhaled corticosteroid

Table 2 Details of treatment and treatment-related side effects

Number of activations in right upper lobe	50 (23)
Number of activations in right lower lobe	67 (29.8)
Number of activations in middle lobe	14.3 (6.83)
Number of activations in left upper lobe (excl. lingula)	35.1 (13.8)
Number of activations in lingula	19.3 (9.36)
Number of activations in left lower lobe	61.1 (21.6)
Hemoptysis	0 (0%)
Wheezing after BT	34 (66.6%)
Musculosceletal disease	2 (3.9%)
Pneumonia[a]	1 (1.9%)
Longer duration of higher OCS dosage, but < 14 days	3 (5.8%)

Data are *n* (% of 51 procedures) or mean (SD)

OCS oral corticosteroid, *BT* Bronchial Thermoplasty

[a]One nosocomial pneumonia of the left lower lobe two weeks after Bronchial Thermoplasty (BT) of the right lower lobe was not considered to be BT related but counted as AE

resistance (Raw) were 2.35 L and 0.56 kPa*s/l, respectively. QoL was reduced to an average value of 3.07 points in AQLQ.

BT was performed in all 51 treatment sessions in these 17 patients under TIVA. RML treatment was possible in every patient (100%) and was complemented by right lower lobe treatment (Fig. 1, Table 2). Differences in exacerbation rates, asthma worsening, prolonged OCS, or reliever medication after RML treatment compared to procedures in other lobes were not noted. As the RML was always treated in the first BT session, all patients were automatically followed-up via bronchoscopy within the following 8–12 weeks during consecutive BT treatments. Visible long-lasting mucosal alterations, stenosis, or increased infections were not detected. Radiologic opacities in the RML without clinical signs of infection or impaired oxygenation were observed in five cases (33%). Chest radiographs were performed in fourteen patients after middle lobe treatment, three patients refused chest radiograph. No additional radiograph was obtained after the second and third treatment. Procedure-related complications, such as hemoptysis or severe asthmatic bronchoconstriction that required intravenous steroid or beta agonists were not observed. Abnormal heart rhythm or cardiac arrhythmias were not detected during treatment of RB5 (close to the pericardium).

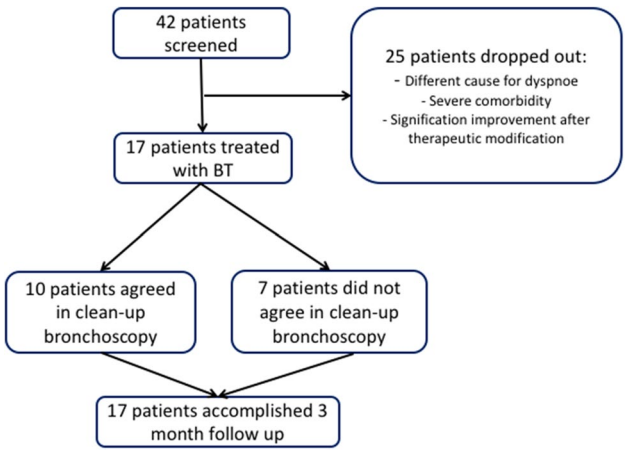

Fig. 1 Study enrolment

Ten patients received clean-up bronchoscopy after each of the three BT treatment interventions, while seven refused clean-up bronchoscopies. Clean-up procedures revealed significant fibrin plugs in the treated airways of each patient, either on the segmental or sub-segmental level. Fibrin plugs were removed with a 2.0 mm-forceps and applied suction (Fig. 1). Fibrin exudation was neither isolated nor any severe after RML treatment, but was observed in all treated airways. Exudation was independent from the number of activations and other individual parameters. None of the patients required antibiotics directly after BT.

In 34 of 51 BT treatments (66%) patients reported increased wheezing, that required intense application of reliever medication (salbutamol, iptratropiumbromide) for several days. A prolonged treatment with OCS was only necessary in six cases (11%), one out of these six cases occurred after RML treatment. One patient suffered from contralateral lower lobe pneumonia 12 days after first BT treatment that required hospitalization, antibiotic treatment and delayed the subsequent BT treatment. Clean-up bronchoscopy was not performed in this patient. The consecutive BT treatments did not lead to another infectious complication. Another patient suffered from acute gastrointestinal infection 3 weeks after the first treatment that resolved with conservative treatment. These two cases were not linked to BT treatment. See Table 2 for treatment and adverse event details.

90 days after completion of BT a statistically significant increase in median FEV1 by 0.42 L ($p=0.002$) and median VC by 0.39 L was observed. The reduction of median OCS dosage was statistically significant ($p=0.003$), as OCS could be terminated in seven patients (41%). Raw improved without reaching significant differences. QoL ameliorated significantly by 0.79 points ($p=0.0001$) in AQLQ. In 14 of 17 patients, an increase of AQLQ that exceeded the MCID of 0.5 points was observed. In the three cases without AQLQ improvement, a worsening of lung function, a decrease of QoL after BT, or the need for OCS escalation was not observed (Table 3).

Discussion

This is the first report of the safety and efficacy of patients receiving BT treatment inclusive of the RML bronchus in a retrospective two-center trial.

Patients in this study presented with severe functional limitations exceeding those of the earlier published RCTs. The AIR and AIR-2-studies included patients with preserved lung function. When compared to the RISA trial, the fixed obstruction of the patients enrolled in our study was more advanced. The average FEV1 in the BT group of 15 patients was 63% in the RISA trial, compared to 47% in the group analyzed in this study [9]. More recently, Doeing and Pretolani reported smaller studies describing safety of BT in severely limited patients. Their mean predicted FEV 1 was 50% (Doeing et al.) and 71% (Pretolani et al.), respectively. Mean OCS dosages were comparable to data of this study [10, 11]. Recent data of the post-market PAS2 study, with 190 patients with more severe asthma phenotype in comparison to the AIR2 trial, also reported comparable, 3 year stable treatment success that echoed the AIR2 results, but however without FEV1 improvement [12].

In our study, procedure-related complications were not observed. We used a 4.2 mm bronchoscope and noted a higher number of activations in each patient, when compared to equivocal studies [11]. However, neither of the AIR/RISA/AIR2-study reported their absolute number of activations, and it therefore remains speculative if the use of thinner bronchoscopes with more activations can result in a better functional outcome. Therefore, we can safely conclude that BT treatment including RML bronchus is a safe therapeutic option for asthma patients even with severe functional limitations. Further studies, ideally RCTs with larger patient cohorts including the RML treatment, are necessary for validation of these results.

The RML bronchus was historically excluded from BT treatment because of a potentially increased risk of infection and the functional relevance of RML was supposed to be negligible [5]. Long-term safety and absence of anatomical alterations in all other treated airways but the RML bronchus are known from 5-year results of the AIR2-study [13]. We found that, the RML could be treated without any complications in our cohort. Clinical, bronchoscopic and radiographic follow-ups, performed during the subsequent BT sessions revealed no additional side effects after RML integration. We, therefore, believe that the RML bronchus can be integrated without any increased risk into the treatment regimen of BT. Whether the pre-therapeutic measurement of the bronchus' diameter is essential to avoid local complications might be worth further evaluation in a RCT with larger patient cohorts. The functional contribution of RML, although difficult to measure independently, is supposed to be low [14]. However, to our best knowledge it has never been investigated in asthma patients and therefore we assume that the RML stabilization might contribute to an increase in benefit in functionally limited patients.

The increases of median FEV1, VC, and AQLQ as well as the decrease of OCS usage were statistically significant (Fig. 2, Table 3). Especially the FEV 1 increase was surprising, as it exceeded the effects reported in previous studies. Even though these are early results, 3 months after BT completion, we believe that they are robust enough as we

Table 3 Comparison of selected details at baseline and 90 days after Bronchial Thermoplasty

	Baseline Median [*Q*1, *Q*3] *n (%)*	Post-BT (90 days) Median [*Q*1, *Q*3] *n (%)*	Delta-*p*-value
FEV1 (l)	1.33 [0.91; 1.73]	1.75 [1.36; 2.30]	0.002
FEV1 % predicted	47.0 [36; 58.5]	63.6 [51.9; 76.3]	0.001
OCS	10 (66.6%)	3 (20%)	
OCS dose (mg)	20 [0; 25]	0 [0; 5]	0.003
AQLQ	3.01 [2.76; 3.61]	3.80 [3.44; 4.78]	0.000
VC (l)	2.35 [1.92; 2.81]	2.74 [2.15; 3.34]	0.028
Raw (kPa*s/l)	0.56 [0,31; 0.83]	0.53 [0.31; 0.94]	n.s.

Data are Median [percentile *Q*1, *Q*3] or **n* (%)

BT Bronchial Thermoplasty, *FEV* post bronchodilatatory forced expiratory volume in 1 s, *OCS* oral corticosteroid, *AQLQ* Asthma quality of life questionnaire, *VC* inspiratory vital capacity, *Raw* airway resistance

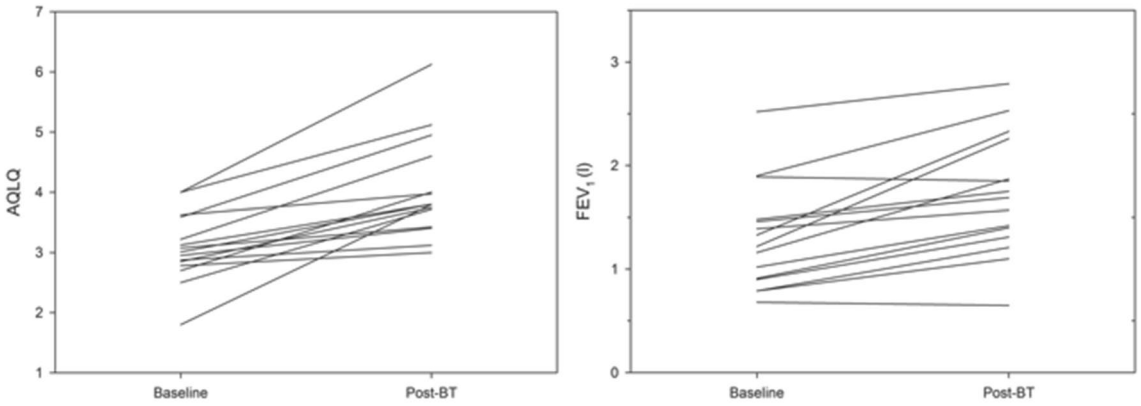

Fig. 2 Individual development of AQLQ and FEV1 before and post-BT BT. *AQLQ* Asthma Quality of Life Questionnaire, *BT* Bronchial Thermoplasty. *FEV 1* Forced expiratory volume in 1 s

included patients with severe fixed obstruction despite maximum medical therapy and the OCS use decreased already in the same period, which means that there was no additive anti-inflammatory and anti-obstructive concomitant medication. Pretolani et al. showed similar results with 3 and 12-month follow-up data, suggesting that BT benefits can be detected early and that it can last long [11]. The therapy control after 3 months seems therefore feasible. The RISA trial reported statistically significant improvements only of AQLQ but not of FEV1, after finishing the established prophylactic OCS treatment 8 weeks after BT completion [9]. Lack of PFT benefits in the AIR and AIR-2-studies and the recent post-market PSA2-trial could be explained by only moderate functional limitation in these patients [5, 12, 15]. The absence of statistically significant benefit of AQLQ-elevation in the sham-controlled AIR-2-study is also noteworthy [4, 15–17]. Although placebo effect plays a role in asthma treatment [18], we assume the AQLQ change in functionally limited patients is a robust marker, if FEV 1 increases consecutively, as documented in our study. None of the RCT that were performed prior to FDA approval could detect a significant FEV1 improvement [9]. If the additional ameliorating effect could be explained by the integration of RML treatment or the inclusion of severely limited patients remains unclear and requires further investigation in larger RCTs. However, two patients stood out with a moderate FEV 1 decline that did not correlate with an AQLQ decrease. This underlines that BT is not effective in every patient, but missing improvement will not consecutively lead to overall deterioration. FEV 1 reduction at this early follow-up might be also a result of prolonged post interventional decline due to BT that however is below the subjective patient's sensation. Additional clinical controls need to be performed.

There was no difference of parameters in patients receiving clean-up bronchoscopy compared to those who refused. However, we noticed a single case of nosocomial pneumonia of the left lower lobe 14 days after the treatment of the RML. This was radiologically defined as atypical pneumonia and not linked to an atelectasis. A clean-up bronchoscopy was not performed in this patient. After restitution consecutive BT treatments in this patient were performed without further events.

Clean-up bronchoscopies revealed fibrin plugs significantly obstructing the treated proximal lobar and segmental bronchi in every patient (Fig. 3). Fibrinous exudation is a well-known phenomenon in a broad spectrum of bronchoscopic interventions applying thermal energy or mechanical pressure to the mucosa [19]. Latest reports of the ongoing TASMA-trial show intense peribronchial inflammatory side effects on CT scans immediately after BT [20]. This would easily explain the amount of fibrin noted in our clean-up bronchoscopies and might be correlated to mucosal healing processes after the thermal treatment. To our knowledge, all studies in which BT was followed by early bronchoscopic control also reported these findings, both in the first human study by Miller and in case reports, about early pneumonia and abscess formation after BT [21–23]. As expected, the patients included in this study reported an increase in post procedural respiratory events that led to a more intense application of inhaled reliever medication. Regarding earlier studies this was believed to be caused by asthma aggravation, but fibrin plug removal usually resulted in amelioration of respiratory symptoms. Whether the lack of antibiotic treatment is linked to clean-up bronchoscopies requires further evaluation. However, we believe that BT especially when applied in functionally limited patients can be followed by a clean-up bronchoscopy, although not recommended as part of the current treatment algorithm. The subjective clinical improvement after fibrin plug removal is however impossible to quantify and it therefore remains speculative if a clean-up bronchoscopy is functionally necessary.

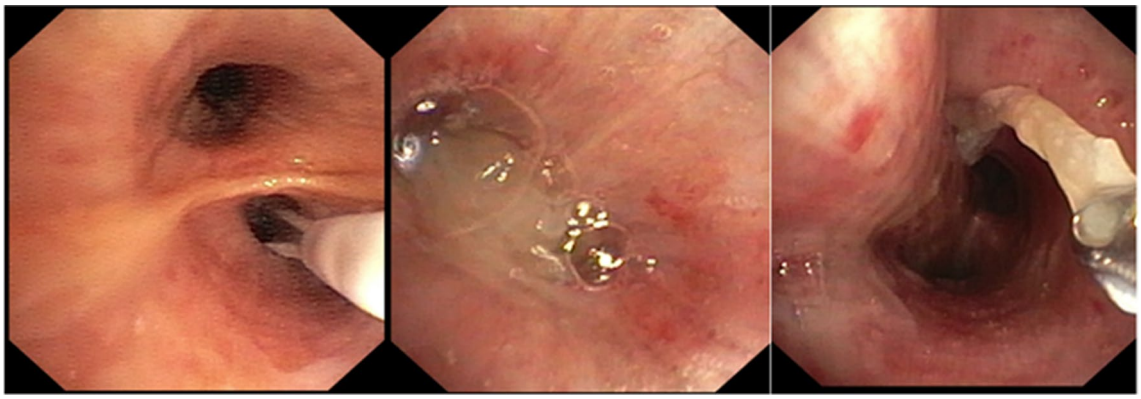

Fig. 3 Fibrin plugging in a patient after Bronchial Thermoplasty (BT). Left: BT in right lower lobe bronchus 9/10. Center: 2 days after BT: fibrin plug centrally in the right lower lobe bronchus on carina between B8 and B9/10. Right: fibrin removal by flexible forceps

It also uncertain open whether additional clean-up bronchoscopies might be useful. We did not notice prolonged or delayed respiratory problems after singular additional bronchoscopies and could not detect local endobronchial alterations during the consecutive BT procedures. Therefore, we do not see benefit from additional clean-up bronchoscopies.

The major limitation of this study is the retrospective nature and small sample size ($n = 17$). Further limitations are the lack of a control group and a relatively short-term follow-up. A longer follow-up period might reveal more information about long-term-efficacy, especially in initially impaired patients, and should be subject to further studies. As mentioned earlier a placebo effect is linked to this method and cannot be excluded without a control group.

Conclusion

BT including the RML bronchus is a safe therapeutic option for patients with severe asthma. Significant improvements of PFT and QoL can be achieved. Whether this could result in long-lasting success needs to be investigated in larger RCTs with long-term follow-up. As fibrinous exudation was frequently reported, a clean-up-bronchoscopy shortly after BT can be considered to prevent post-stenotic complications.

Author Contribution Conception, design: SE, WS, FF, FO, SI, KD. Procedure performance: SE, WS. Data acquisition: SE, WS. Analysis and interpretation: SE, KD, FO, FF, WS, SI.

Compliance with Ethical Standards

Conflicts of Interest The author declares that they have no conflict of interest.

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