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Long-Term Outcomes of Bronchial Artery Embolization for Patients with Non-Mycobacterial Non-Fungal Infection Bronchiectasis

Keita Takeda[a, b] Masahiro Kawashima[a] Kimihiko Masuda[a] Yuya Kimura[a] Shota Yamamoto[a] Yu Enomoto[a] Hiroshi Igei[a] Takahiro Ando[a] Osamu Narumoto[a] Yoshiteru Morio[a] Hirotoshi Matsui[a]

[a]Center for Pulmonary Diseases, National Hospital Organization Tokyo National Hospital, Tokyo, Japan; [b]Department of Basic Mycobacteriology, Graduate School of Biomedical Science, Nagasaki University, Nagasaki, Japan

Keywords
Bronchiectasis · Bronchial artery embolization · Haemoptysis · Long-term outcomes · Technical success

Abstract
Background: There is no study on the predictive factors of recurrent haemoptysis after bronchial artery embolization (BAE) with the long-term outcomes in patients with bronchiectasis (BE). ***Objectives:*** To evaluate the long-term outcomes of BAE in BE patients without accompanying refractory active infection of mycobacteriosis and aspergillosis with analysis for the predictive factors of recurrent haemoptysis. ***Methods:*** Data of 106 patients with BE who underwent BAE using coils between January 2011 and December 2018 were retrospectively reviewed. The cumulative haemoptysis control rate was estimated using Kaplan-Meier methods with log-rank tests to analyze differences in recurrence-free rate between groups based on technical success and failure, bacterial colonization status, number of BE lesions, and vessels embolized to bronchial arteries (BAs) or BAs + non-bronchial systemic arteries (NBSAs). ***Results:*** Bacterial colonization was detected in approximately 60% of patients. Computed tomography showed bronchiectatic lesions with 2.9 ± 1.4 lobes. In the first series of BAE, embolization was performed in the BAs alone and BAs + NBSAs in 65.1 and 34.9% of patients, respectively, with 2.4 ± 1.4 embolized vessels in total. The median follow-up period was 1,000 (7–2,790) days. The cumulative haemoptysis control rates were 91.3, 84.2, 81.5, and 78.9% at 1, 2, 3, and 5 years, respectively. The haemoptysis control rates were higher in the technical success group than in the technical failure group ($p = 0.029$). ***Conclusions:*** High haemoptysis control rates for long-term periods were obtained by embolization for all visualized abnormal arteries, regardless of the colonization status, number of bronchiectatic lobes, and target vessels, irrespective of NBSAs.

Introduction

Haemoptysis is defined as the expectoration of blood from the lungs or bronchial tree and, due to asphyxia and blood loss, is a life-threatening symptom [1, 2]. Haemoptysis can also impair patient's quality of life [3–5]. Treatment for haemoptysis includes haemostatic agents, bronchoscopy, bronchial artery embolization (BAE), and surgery [1, 5, 6]. BAE, a minimally invasive procedure for

karger@karger.com
www.karger.com/res

Keita Takeda
Center for Pulmonary Diseases
National Hospital Organization Tokyo National Hospital
3-1-1 Takeoka, Kiyose, Tokyo 204-8585 (Japan)
takeda.keita.ax@mail.hosp.go.jp

haemoptysis, is the first-line treatment for haemoptysis patients [6].

Bronchiectasis (BE) is one of the most common underlying pulmonary diseases that can cause haemoptysis [6]. BE is often associated with several pathological conditions, including idiopathic type, cystic fibrosis (CF), co- or post-infection with mycobacteria, and allergic bronchopulmonary aspergillosis [7–10]. While the pathological mechanisms in many of the non-CF forms of BE are often unclear, their clinical course is similar [11]. Patients develop chronic cough with purulent sputum, dyspnoea, and haemoptysis [12, 13]. Haemoptysis occurs in 20–37% of the patients with BE [14, 15]. When BE becomes complicated with chronic pulmonary infection, there is a higher risk for relapse of haemoptysis [16, 17]. Other predictive factors associated with the recurrent haemoptysis after BAE are unknown.

We have previously reported the BAE is efficacious for the control of haemoptysis in patients with *Mycobacterium avium* complex (MAC) infection, chronic pulmonary aspergillosis (CPA), and cryptogenic haemoptysis [18–20]. The cumulative haemoptysis control rates in 1 year, 1 year, and 20 months were 79.1, 65.8, and 97.0% among patients with MAC infection, CPA, and cryptogenic haemoptysis, respectively. This evidence suggests that repeat BAE is more frequently needed in patients with mycobacterial or fungal infection than in patients with other diseases, as other reports have indicated [5, 6, 18–23]. This is because it is difficult to control the active underlying pulmonary infection and exacerbation is associated with rebleeding after BAE [24]. In this study, we evaluated the 5-year recurrence rate of haemoptysis of BAE in BE patients without accompanying refractory active infection of mycobacteriosis and aspergillosis.

Methods

Patient Population

This retrospective study was approved by the Institutional Review Board of the National Hospital Organization (NHO) Tokyo National Hospital (approval date: 4 October 2019, approval no. 190038), and patient confidentiality was maintained. The requirement for the acquisition of informed consent was waived owing to the retrospective nature of the study.

Medical records of 126 consecutive BE patients without mycobacterial or fungal infection who underwent BAE at the NHO Tokyo National Hospital between January 2011 and December 2018 were retrospectively reviewed. BAE was performed in patients with episodes of massive or non-massive but recurrent haemoptysis [1, 6]. Massive haemoptysis was defined as bloody expectoration estimated to be >300 mL within 24 h [6]. A total of 106 BE patients were included in this study following the exclusion of (1) 10 cases who were treated with permanent embolic agents for BAE before our BAE procedure, and detailed information for BAE had not been obtained, (2) 7 cases in whom follow-up was discontinued after discharge, and (3) 3 cases with mycobacterial or fungal infection after BAE during follow-up (Fig. 1). The patients' characteristics (e.g., age, sex, aetiology of BE, and bacterial colonization status) were analyzed.

Computerized Tomography/BAE

Computerized tomography (CT) angiography was performed in all patients prior to BAE to assess the lung lesions as well as the arteries responsible for haemoptysis. Target vessels were considered responsible for the bleeding when they ran in the direction of the bleeding lesions [24]. When the bleeding lesions could not be determined by CT and bronchoscopy, the arteries responsible for haemoptysis were identified using angiographic findings, followed by engorgement, tortuosity, hypervascularity, systemic-pulmonary shunt, and extravasation of the contrast agent [25].

All angiography and embolization procedures were performed by a trained pulmonologist, as described previously [18–20]. In brief, a co-axial system using a guiding catheter and micro-catheter following a micro-guidewire was super-selectively adopted to embolize the responsible arteries. Embolization was performed using fluoroscopy and detachable or pushable coils (IDC or Interlock; Boston Scientific, Tokyo, Japan; Target; Stryker, Tokyo, Japan; C-STOPPER; PIOLAX, Yokohama, Japan), and the diameter of the coils ranged from 2 to 10 mm. During the first series of BAE, a second session of BAE was carried out for 15 (14.2%) out of 106 patients after the first session because the patients still experienced haemoptysis and the target vessels persisted at the first session for the following reasons: (1) an excess of the total dose of radiation or contrast medium or (2) a change in access from the femoral to the radial artery for embolization of the branches in the subclavian or axillary artery [19].

Outcomes of BAE

Technical success was defined as the successful embolization of all visualized abnormal arteries at the first series of BAE [6, 26]. Immediate clinical success was defined as complete cessation or a clinically significant reduction in haemoptysis after the first series of BAE [6, 26]. Recurrence was defined as haemoptysis requiring re-admission or treatment, including invasive interventions such as repeat embolization, bronchoscopy, or surgery [6]. Medical records and requested questionnaires were reviewed to evaluate recurrence. The primary endpoint was the 5-year recurrence rate of haemoptysis from the day of the last BAE session. Dead patients were censored at the time of death, whereas alive patients were censored at the time of their last follow-up.

Definition of Terms

Technical failure was defined as unsuccessful embolization of one or more visualized abnormal arteries. Cumulative haemoptysis control rate was defined as the proportion of individuals with non-recurrent haemoptysis at the start of a period, which recurred over that period.

Statistical Analysis

The χ^2 test for frequency measures and *t* test for continuous variables were used to analyze statistical differences in clinical characteristics between the recurrence and non-recurrence groups (the latter included individuals with non-recurrent haemoptysis after BAE). The 5-year cumulative haemoptysis control rate was

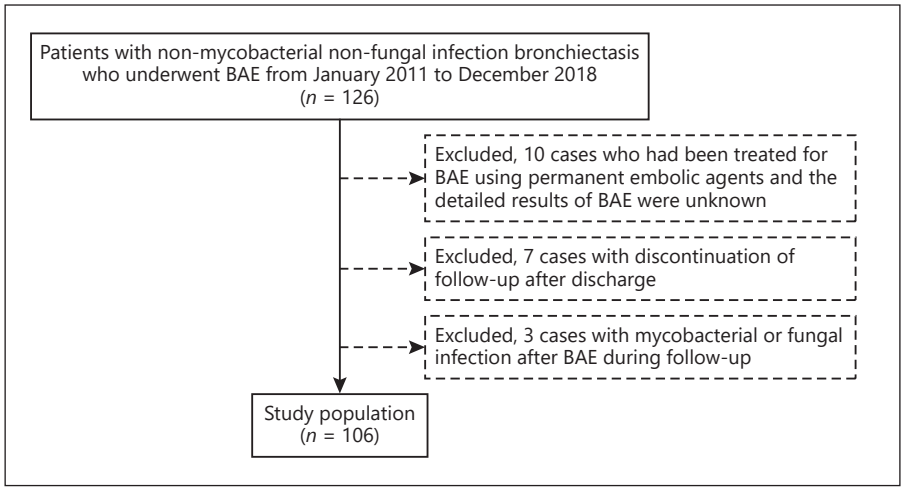

Fig. 1. Flowchart of patient selection. A total of 106 patients were included in this study after exclusion of cases that did not fulfil the selection criteria. BAE, bronchial artery embolization; BE, bronchiectasis.

Table 1. Characteristics of all patients and comparison of characteristics of recurrence and non-recurrence groups

	All patients (*N* = 106)	Recurrence (*n* = 19, 17.9%)	Non-recurrence (*n* = 87, 82.1%)	*p* value
Age, years	69.0 (22–85)	64.0 (44–85)	69.0 (22–84)	0.15
Sex, male, *n* (%)	27 (25.5)	4 (21.0)	23 (26.4)	0.57
BMI	19.6 (13.6–31.3)	19.5 (16.2–24.8)	19.6 (13.6–31.3)	0.76
MRC dyspnoea score (0/1/2/3/4)	5/85/9/6/1	0/16/1/2/0	5/69/8/4/1	0.79
Amount of haemoptysis				
Massive/non-massive	23/86	4/15	19/68	>0.99
Smoking history, *n* (%)	26 (24.5)	5 (26.3)	21 (24.1)	>0.99
Hypertension, *n* (%)	27 (25.5)	4 (21.1)	23 (26.4)	0.78
Anti-platelet or anti-coagulant agent use, *n* (%)	8 (7.5)	2 (10.5)	6 (6.9)	0.63
Aetiology of BE, *n* (%)				0.63
Idiopathic	76 (71.7)	12 (63.2)	64 (73.6)	0.40
Post-infection	23 (21.7)	6 (31.6)	17 (19.5)	0.36
Systemic inflammatory disease	5 (4.7)	1 (5.3)	4 (4.6)	>0.99
Diffuse panbronchiolitis	2 (1.9)	0	2 (2.3)	>0.99
Co-existence of chronic sinusitis, *n* (%)	33 (31.1)	7 (36.8)	26 (29.9)	0.59
Colonization with pathogenic organisms, *n* (%)	64 (60.4)	12 (63.2)	42 (48.3)	0.31
Pseudomonas colonization, *n* (%)	34/64 (53.1)	6/12 (50.0)	28/42 (66.7)	0.33
Macrolide antibiotic use, *n* (%)	70 (66.0)	11 (57.9)	59 (67.8)	0.43

Data are presented as *n* (%) or as median (range). BE, bronchiectasis; BMI, body mass index; MRC, Medical Research Council.

estimated using Kaplan-Meier methods. The proportion of recurrence-free patients for each year was estimated using Kaplan-Meier methods with log-rank tests to analyze differences in recurrence-free rate between groups of technical success and failure. The recurrence-free rate by technical success and failure, age, bacterial colonization status, number of BE lesions, and target vessels irrespective of NBSAs were compared by the Cox proportional hazards model. For the multivariate analysis, the Cox proportional hazards model followed by a backward selection (exclusion criteria $p > 0.10$) was used. A p value of <0.05 was considered statistically significant. Statistical analyses were performed using JMP 13.00 (SAS Institute Inc., Cary, NC, USA).

Results

Patient Characteristics

The clinical features of 106 BE patients are summarized in Table 1. The median age was 69.0 (22–85) years. The most frequent cause of BE was unknown (idiopathic, 71.7%), followed by post-infection (21.7%). There were 64 patients (60.4%) with bacterial colonization detected before the first series of BAE (*n* = 59) and during the follow-up periods (*n* = 5). No significant deference in clini-

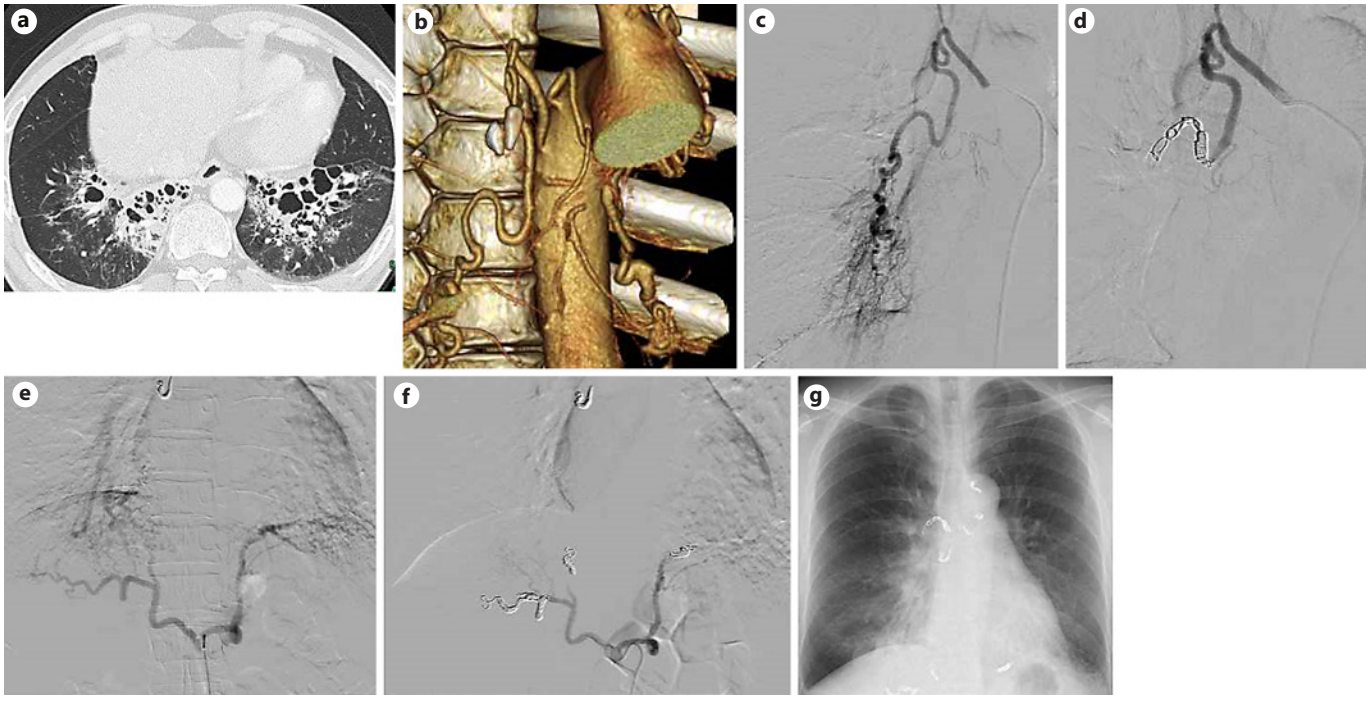

Fig. 2. Representative case of haemoptysis due to BE. **a** A chest CT shows bronchiectasis, consolidation, and ground-glass opacity, suggesting that haemoptysis occurred from the bilateral lower lobe. **b** CT angiography reveals a hypertrophic bronchial artery. **c** Angiography findings of the right bronchial artery reveals engorgement, tortuosity, and hypervascularity. **d** Angiography after embolization using coils shows the completely embolized right bronchial artery. **e** Angiography findings of the inferior phrenic artery reveals pulmonary artery shunt. **f** Angiography after embolization using coils shows the completely embolized bilateral inferior phrenic artery. **g** A chest X-ray after BAE. BE, bronchiectasis; CT, computerized tomography; BAE, bronchial artery embolization.

cal features was noted between the recurrent and non-recurrent haemoptysis groups (Table 1).

Radiological, Angiographic, and BAE Findings

Radiological and angiographic findings and results of BAE are presented in Table 2. The mean number of lung lobes developing BE was 2.9 ± 1.4, with 70.8% of patients exhibiting bilateral lesions. Hypervascularization was detected in all cases, and systemic-pulmonary shunting on angiography occurred in 58.5% of cases.

BAE Outcomes

Representative cases with CT and angiographic findings before and after BAE are shown in Figure 2. Technical success was achieved in 88.7% (n = 94) of patients at the first series of BAE. The reasons for technical failure in 11.3% (n = 12) of patients were as follows: (1) the diameter of the responsible artery was too narrow to embolize, compared with the diameter of the coil (n = 6); (2) it was not possible to embolize the responsible arteries branching off the subclavian or axillary artery from the femoral access in the first session of BAE (n = 4); and (3) it was impossible to achieve cannulation using guiding catheters (n = 2). The median number of embolized arteries was 2.4 ± 1.4 per session. In the first series of BAE, the embolized vessels were BAs alone in 65.1% of patients and BAs + NBSAs in the remaining 34.9% of patients.

Complications from the first series of BAE (n = 106) occurred in 18.9% (Table 2), including mild vascular injuries (8.5%), chest/back pain (3.8%), and allergic reactions to the contrast agent (2.8%). A major complication (mediastinal haematoma) occurred in 1 case (0.9%) with improvement following rest and blood pressure management.

Post-BAE Outcomes

The median follow-up period was 1,000 (7–2,790) days. The immediate clinical success rate was 98.1%. During the follow-up periods, 19 out of 106 patients (17.9%) had recurrence. The cumulative haemoptysis control rates were 91.3, 84.2, 81.5, and 78.9% at 1, 2, 3, and 5 years, respectively (Fig. 3a).

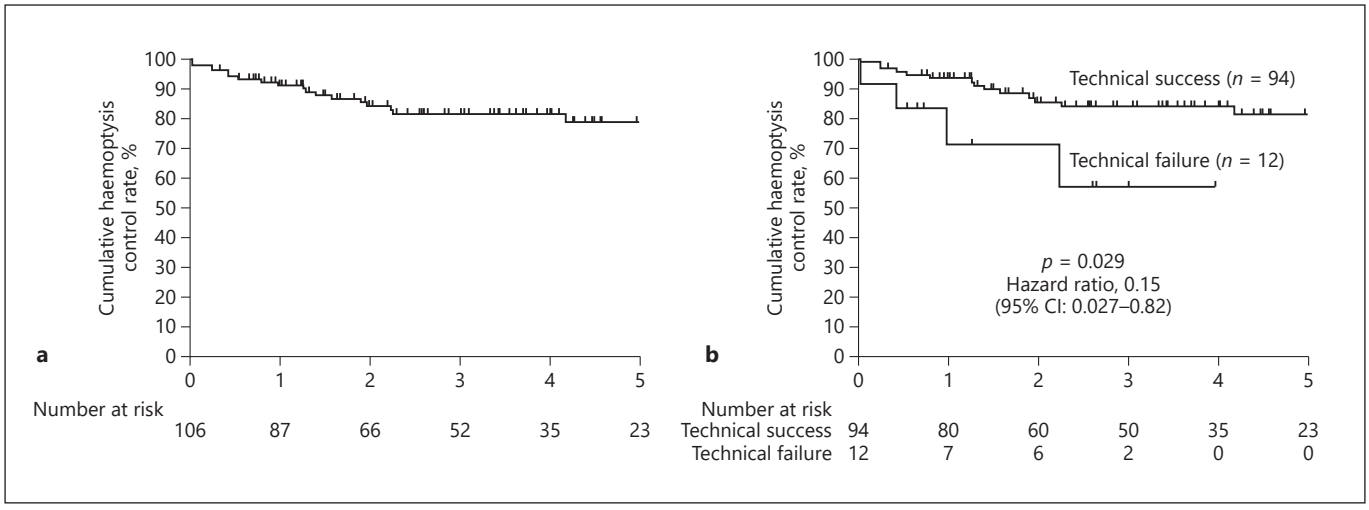

Fig. 3. a Cumulative haemoptysis control rate for all patients (N = 106). The recurrence-free rates were 91.3, 84.2, 81.5, and 78.9% at 1, 2, 3, and 5 years, respectively. The median follow-up period was 1,000 (7–2,790) days. **b** Cumulative haemoptysis control rates for the technical success group and technical failure group. The 1-, 2-, and 3-year recurrence-free rates were 93.5, 85.6, and 84.1% for the technical success group and 71.4, 71.4, and 57.1% for the technical failure group, respectively (p = 0.029).

The number of recurrences was 15 of 94 (16.0%) in the technical success group and 3 of 12 (33.3%) in the technical failure group. The haemoptysis control rates were higher in the technical success group than in the technical failure group (p = 0.029) (Fig. 3b). In other comparisons, bacterial colonization status, number of bronchiectatic lobes (≥3 lobes), and vessels embolized to BAs alone or BAs + NBSAs did not influence the control rates (Table 3).

The results of the multivariate Cox proportional hazards model are presented in Table 4. Technical success (hazard ratio: 0.22; 95% confidence interval: 0.073–0.83) and age (hazard ratio: 0.96; 95% confidence interval: 0.93–1.00) were statistically significant. After the backward selection, the following variables were excluded: bacterial colonization status, number of bronchiectatic lobes (≥3 lobes), and vessels embolized to BAs alone or BAs + NBSAs.

During the follow-up period, 5 patients died due to pneumonia, cancer, cerebral infarction, subarachnoid haemorrhage, and an unknown cause. No patients died of haemoptysis.

Clinical Course after Recurrence

Of 19 patients with haemoptysis recurrence, 13 underwent a second series of BAE. One patient underwent surgery, whereas another underwent endobronchial occlusion using bronchoscopy. The remaining 4 patients showed improvement with haemostatic agents; therefore, they did not undergo additional invasive procedures.

Table 2. Radiological and angiographic findings and results from the first series of BAE

	Patients (N = 106)
Radiological findings	
Lung lobes with BE, *n*	2.9±1.4
Bilateral lung lesions, *n* (%)	75 (70.8)
Angiographic findings, *n* (%)	
Hypervascularization	106 (100)
Systemic-pulmonary shunt	62 (58.5)
Results of BAE, *n* (%)	
Technical success	94 (88.7)
Technical failure	12 (11.3)
Embolized arteries, *n* (%)	
BAs alone	69 (65.1)
BAs + NBSAs	37 (34.9)
Embolized arteries, *n*	2.4±1.4
Complications of BAE, *n* (%)	20 (18.9)
Mild vascular injuries	9 (8.5)
Chest/back pain	4 (3.8)
Contrast agent allergy	3 (2.8)
Fever (≥38°C)	2 (1.9)
Pneumonia	1 (0.9)
Mediastinal haematoma	1 (0.9)

Data are presented as mean ± SD or as *n* (%). BAs, bronchial arteries; BAE, bronchial artery embolization; BE, bronchiectasis; NBSAs, non-bronchial systemic arteries.

Table 3. Results of univariate Cox analysis of predictive factors for recurrence

	Patients (N = 106)	Hazard ratio (95% confidence interval)	p value
BAE results			
Technical success	94	0.15 (0.073–0.83)	0.029
Technical failure	12		
Median age			
Age among patients of the recurrence group	64.0 (44–85)	1	0.10
Age among patients of the non-recurrence group	69.0 (22–84)	0.96 (0.94–1.00)	
Bacterial colonization status			
Colonization (–)	42	0.95 (0.38–2.40)	0.91
Colonization (+)	64	1	
Bronchiectatic lobes, *n*			
≤2 lobes	47	0.86 (0.35–2.18)	0.75
≥3 lobes	59	1	
Embolized vessels			
BAs alone	69	0.75 (0.30–1.95)	0.54
Bas + NSBAs	37	1	

BAE, bronchial artery embolization; BAs, bronchial arteries; NBSAs, non-bronchial systemic arteries.

Table 4. Results of the multivariate Cox proportional hazards model

	p value	Hazard ratio (95% confidence interval)
Technical success (Ref = technical failure)	0.013	0.22 (0.073–0.83)
Age	0.030	0.96 (0.93–1.00)

The Second Series of BAE Outcomes

In the second series of BAE (n = 13), the target vessels were most frequently the re-canalization vessels, which were embolized at the proximal site close to the embolized coils in the first series (n = 12, 92.3%). Among them, other mechanisms of the arteries responsible for haemoptysis were also revealed as follows: 6 cases (46.2%) had collaterals, 4 cases (30.8%) had new arteries responsible for haemoptysis, and 1 case (7.7%) had collaterals and new arteries responsible for haemoptysis without re-canalization. Furthermore, the remaining target vessels in the first series of BAE were embolized in 3 cases (23.1%).

Discussion

This study revealed the long-term outcomes of BAE in patients with non-CF BE without mycobacterial or fungal infection. The cumulative haemoptysis control rate was over 80% at 3 years and approximately 80% at 5 years. The high haemoptysis control rate was in accordance with the embolization of all visualized abnormal arteries, dependent on technical success but irrespective of bacterial colonization status, bronchiectatic condition, and target vessels, regardless of NBSAs.

It has been reported from other institutions that the overall cumulative haemoptysis control rates with BAE were 51–86.4% and 35.9–76.7% at 1 and 3 years, respectively [5, 8, 9, 24, 27–29]. The cumulative haemoptysis control rates in this study were relatively higher than those from previous reports, which may be explained by 2 potential reasons. First, the previous studies included subjects with various pulmonary diseases. The haemoptysis control rates depend on the causes of pulmonary diseases, and the rates among patients with BE in these studies were higher than those among patients with other pulmonary diseases except for cryptogenic haemoptysis [5, 6, 18–23]. Furthermore, patients with mycobacterial or fungal infection were excluded from this study. Other previous reports have suggested that BE with active

chronic pulmonary infection has a higher risk for haemoptysis relapse [16, 17]. Second, coils, which are permanent embolic agents, were used in this study. Among permanent materials, the long-term outcomes of BAE using coils, polyvinyl alcohol (PVA), and *n*-butyl-2-cyanoacrylate (NBCA) have been reported [5, 8]. The use of NBCA and coils might be related to the high haemoptysis control rates; nevertheless, no study has compared the outcomes of BAE using NBCA and coils [5, 8]. PVA and NBCA can be used for embolization at the distal site. PVA is more ineffective than NBCA for BAE, and NBCA might be associated with a risk of severe complications such as tissue necrosis and misembolization [8]. Coils have a high visibility and low risk for misembolization but with the possibility of embolization at proximal vessels [5]. On the other hand, a previous study reported that gelatin sponges, which are temporary embolic agents, may lead to recanalization of embolized vessels at a higher frequency [21]. Therefore, permanent materials should be used, particularly for haemoptysis due to chronic pulmonary diseases. Collectively, this evidence may explain the high haemoptysis control rates in this study.

At 3 years after BAE, the non-rebleeding rate was 63.3% among patients with MAC [18] and 47.9% among patients with CPA [19]. In contrast, the non-rebleeding rate was 97.0% among patients with cryptogenic haemoptysis in 20 months after BAE [20]. Under consistent procedures of BAE at our hospital, while mycobacterial or fungal infections worsened the outcomes, patients with cryptogenic haemoptysis showed better outcomes than BE patients in this study. These results might have been affected by the augmentation of angiogenesis through various cytokines (e.g., vascular endothelial growth factor) with chronic pulmonary infection [30, 31]. A large number of arteries responsible for haemoptysis were evermore embolized in patients with mycobacterial or fungal infections during BAE. The number of embolized vessels was 4.0 ± 2.9 and 2.7 ± 1.6 per session in the rebleeding group and in the non-rebleeding group, respectively, among patients with MAC and 5.24 ± 3.13 per session among patients with CPA.

Although BE was the primary or secondary underlying pulmonary disease indicated for BAE, with a prevalence of 1.3–38% [6], there are a few reports focussing on the long-term outcomes of BAE in BE patients [17, 22]. This study indicated that the detection of bacteria, number of bronchiectatic lobes, and presence of target vessels of NBSAs did not influence the haemoptysis control rates with respect to technical success. The technical failure that led to recurrence could be explained by the remaining responsible arteries branching off the subclavian or axillary artery due to the difficulty in approaching them from the femoral artery in the first session of BAE. To control haemoptysis, it should be emphasized that all responsible arteries detected must be embolized by changing the access route to the radial artery as necessary.

Younger age was also a variable that influenced the haemoptysis control rate in the multivariate Cox proportional hazards model, although there was no significant difference in the univariate analysis. The main reason for this might be the low number of individuals included in the recurrence group, coincidentally resulting in the variable being significant; hence, further analysis will be required.

Vascular injuries, including mild vascular injuries and mediastinal haematoma, were the most frequent complications of BAE. The percentage of vascular injuries with BAE was 9.4%: 8.5% of mild vascular injuries and 0.9% of mediastinal haematoma in this study (Table 2), aligning with previous reports, which included vasospasm, dissection, and perforation [6]. After vascular injury, the proximal side of the responsible arteries was embolized in most cases, leading to technical success. A major complication, mediastinal haematoma, occurred in 1 case. Other serious complications such as neurologic complications that could result from embolization of the spinal arteries might less frequently occur with coils than with the liquid embolic materials, owing to the good visibility of coils and the possibility of re-coiling [5].

This study has some limitations. First, this was a retrospective study conducted at a single centre. It is difficult to conduct a prospective study on haemoptysis patients; nonetheless, a multicentre analysis should be performed in future research. Second, the amount of haemoptysis was classified as either massive or non-massive; however, it is not possible to determine the precise amount of haemoptysis [32]. Third, the cause of BE might not have been meticulously investigated, resulting in a high proportion of "idiopathic" BE cases included in this study.

In conclusion, this study showed that BAE was effective in controlling haemoptysis in long term in patients with non-CF BE without mycobacterial or fungal infection. It is recommended that technical success in embolization should be achieved for all visualized abnormal arteries to reduce haemoptysis recurrence.

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Statement of Ethics

This retrospective study was approved by the Institutional Review Board of the National Hospital Organization (NHO) Tokyo National Hospital (approval date: 4 October 2019, approval no. 190038), and patient confidentiality was maintained. The requirement for acquisition of informed consent was waived owing to the retrospective nature of the study.

Conflict of Interest Statement

All authors declare that there are no conflicts of interest regarding the publication of this article.

Author Contributions

K.T. has full access to the data, takes responsibility for their integrity, and has the final responsibility for the decision to submit for publication. M.K., K.M., T.A., Y.M., and H.M. were responsible for the study concept and design. M.K., K.M., Y.K., S.Y., Y.E., H.I., T.A., O.N., Y.M., and H.M. were responsible for the acquisition, analysis, and interpretation of data. M.K., K.M., Y.M., and H.M. were responsible for drafting the manuscript. All authors were responsible for the critical revision of the manuscript.

Availability of Data and Material

Data are available on request due to privacy restrictions.

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