Original Article

Long-term outcomes of the bronchial artery embolization are diagnosis dependent

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ABSTRACT

Background: Bronchial artery embolization (BAE) is an established, safe, and effective procedure for the treatment of hemoptysis but long-term outcomes of the BAE have never been investigated before. **Objectives:** To retrospectively analyze long-term outcomes of the BAE. **Materials and Methods:** A retrospective chart analysis was done from the hospital central database for all patients undergoing the BAE over a consecutive 14-year period (January 2000-February 2014). A total of 58 patients were identified from the database. Eight patients were excluded due to the lack of follow-up. Data such as patient demographics, reason for hemoptysis, medical imaging results, bronchoscopy findings, recurrence rates, and morbidity/mortality rates after the BAE were collected. **Results:** Eighty three embolizations were performed in 50 patients. The median follow-up was of 2.2 years. Cystic fibrosis (CF) bronchiectasis was the most common etiology (21/50), followed by non-CF bronchiectasis (9/50). Cavitary lung disease occurred in 12/50 patients, an additional 4/50 had cancer (primary lung and metastatic), and one patient had antineutrophil cytoplasmic antibody (ANCA) vasculitis. In three patients the etiology was unknown. Postprocedural complications occurred in 5/83 (6%) patients, two patients with two major complications - stroke (one) and paraplegia (one) - and three patients with minor complications - chest pain (two) and bronchial artery dissection (one). A total of 15/50 patients died during the follow-up. Three patients died of hemoptysis, and the remaining deaths were unrelated to the procedure or hemoptysis. Twenty four patients had recurrent hemoptysis. A Kaplan-Meier analysis revealed an excellent long-term survival that was 85% at 10 years. **Conclusions:** The BAE is a safe and effective procedure with excellent overall long-term survival.

KEY WORDS: Bronchial artery embolization, cavitary lung disease, cystic fibrosis, hemoptysis

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INTRODUCTION

Hemoptysis is one of the most dreaded respiratory emergencies that occur due to a variety of underlying causes. Cystic fibrosis (CF) bronchiectasis, non-CF bronchiectasis, aspergilloma, tuberculosis, and lung cancer (primary and metastatic) lead to life-threatening hemoptysis. Ninety percent of massive hemoptysis originates from the bronchial arteries rather than the pulmonary circulation (5%).[1] Conservative management of massive hemoptysis carries a broad mortality range of 5-100%.[2]

The bronchial artery embolization (BAE) has long been considered a safe and effective intervention for the treatment of hemoptysis;[3,4] however, the long-term results have never been investigated before. The purpose of this study was to retrospectively analyze the long-term outcomes of the BAE with regard to hemoptysis recurrence

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rate, morbidity rate, and mortality rate. We assessed the long-term outcomes based on each disease state and the factors influencing the outcome of the BAE in our patient group and reviewed the available literature.

MATERIALS AND METHODS

Setting

This study was undertaken at the University of North Carolina Hospital, a tertiary care teaching hospital located in Chapel Hill, North Carolina, USA. This facility is a bronchiectasis and large CF center, with statewide and national referrals.

Study design

The study design was an Institutional Review Board approved retrospective analysis of cases. All the patients who underwent the BAE from January 1, 2000 through February 28, 2014 were included. None of the patients who reported in this study were reported in previous manuscripts.[5] A retrospective medical record review of all the patients who had bronchial arteriograms during this time frame was done where all the available medical records and radiographs were studied. All the laboratory tests including coagulation profile were noted. Lung-function tests at the time of admission or the most recent one was noted. We also divided the CF bronchiectasis patients according to their severity of lung disease according to the guidelines published by the American Thoracic Society.[6] For the purpose of study, the clinical severity of pulmonary disease was assessed by the degree of forced expiratory volume in 1 s (FEV1) impairment as follows: Mild (FEV1 65-79% predicted), moderate (FEV1 50-64% predicted), severe (FEV1 35-49% predicted), or very severe (FEV1 < 35% predicted).

Subjects

All patients who had the BAE in the study period were included.

The BAE technique

All BAEs were performed by board-certified interventional radiologists. Prior to embolization pertinent imaging was reviewed that included chest radiograph, computerized tomography (CT) scan of chest, and prior bronchial angiogram if done. The laterality of suspected bleeding was predetermined based on the results of bronchoscopy, CT findings, or best clinical judgment. A transfemoral artery puncture was made and the bronchial arteries cannulated with various 5 French catheters and 3 French microcatheters. Digital subtraction images were obtained after injection of iodinated contrast [Figure 1a]. Particle embolization was performed as distal as possible in order to avoid embolization of adjacent spinal arteries [Figure 1b]. Coil embolization was also performed when necessary. Patients received moderate conscious sedation or general anesthesia. The embolization procedure was determined complete with the appearance of vessel stasis or reaching a particle size and volume that was deemed satisfactory. Following the BAE patients returned to their inpatient rooms, either regular floor or intensive care unit.

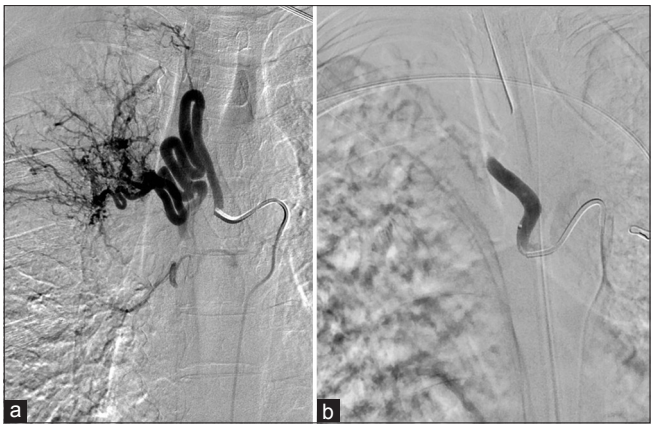

Figure 1: (a) Bronchial arteriogram: Massive tortuous right bronchial artery with irregular right upper lobe parenchymal branches, (b) Post-BAE with microcatheter injection in the main trunk demonstrates vessels stasis

The bronchial arteriogram morphologies found at the BAE were as follows: Vessel hypertrophy, engorgement, cork screw appearance, and tortuosity, with dilated vessels feeding the bronchiectasis area; extravasation of contrast in the lung parenchyma (six patients) or cavity and focal hyperemia or hyper-vascularity. Embolization of all abnormal bronchial arteries was performed if it correlated with the side of known or suspected bleeding (even though active bleeding was not visible) or side of abnormal lung parenchyma, and could be safely occluded by avoiding the spinal arteries.

The arteries embolized during the procedures were right/left bronchial artery, right/left internal mammary artery, right/left intercostal artery, inferior phrenic artery, and costocervical trunk. In 26 patients, only right-sided embolization was done that included combination of right bronchial artery (18), internal mammary artery (3), inferior phrenic artery (1), and intercostal artery (5); 8 patients had only left-sided embolization, 14 had embolization on both the sides, and 2 had embolization of the costobrachial trunk. The embolization particles were Embospheres (Merit Medical, South Jordan, UT) ranging from 300-1,200 μm, pushable fibered metal coils (COOK, Inc., Bloomington, IN), and Gelfoam gelatin slurry (Pfizer, New York, NY) were also used for vessel embolization. All 49 patients had immediate control of the bleeding post procedure and recurrences were due to additional collateral vasculature supplying the same area ($N = 19$) or new sites of bronchiectasis ($N = 4$).

Analysis

All data were expressed as mean ± standard deviation (SD) or 95% CI and number (%). Quantitative variables between two groups were compared using the Mann-Whitney test for continuous variables and the Fisher exact test for nominal variables. Kaplan-Meir curve was plotted to

analyze survival outcome. A two-sided *P* value of less than 0.05 was considered statistically significant. All analyses were conducted using the Statistical Package for the Social Sciences (SPSS) software (version 17.0; SPSS, Chicago, IL).

RESULTS

Clinical presentation

A total of 58 patients underwent the BAE from January 1, 2000 through February 28, 2014. Eight patients were not followed up and were excluded leaving 50 patients to be included in the study. A total of 83 procedures were done on 50 patients. The median follow-up was of 2.2 years (range 7-5,230 days). The mean age was 43 years ±19 (SD). Thirty patients were males and 20 were females, 25/50 had massive hemoptysis (as defined by hemoptysis >600 mL/24 h, requiring resuscitation with fluids/blood transfusions, and were hypoxic or required intubation). The average amount of hemoptysis was 250 mL in 24 h (range 30-1,000 mL/24 h). The most common presenting symptom was hemoptysis (25/50). The other presenting symptoms were shortness of breath, cough, and chest pain. All the patients eventually developed hemoptysis. A total of 47/50 patients had an abnormal chest radiograph and three had normal chest radiographs. Chest radiograph were suggestive of the etiology of hemoptysis in only 15 patients. A total of 9/50 patients underwent bronchoscopy prior to the BAE and in 6/9 the bleeding was localized. These nine patients had an abnormal chest radiograph. None of the patients were on anticoagulation. The platelet levels in all these patients were above 150 mm^3. The mean international normalized ratio (INR) was 1.2 ± 0.3 (SD) in patients from the CF and non-CF groups. Out of all the patients with CF, only three patients had INR >1.5 (one patient had INR of 1.9, the other two had INR of 1.5) and in the rest INR was below 1.5. In non-CF group, only one patient had INR of 1.8, in the rest INR was below 1.5 [Table 1].

Patient composition

We divided the patients into five major groups (CF bronchiectasis, non-CF bronchiectasis, malignant, nonmalignant cavities, and other groups). CF bronchiectasis was the most common etiology (21/50). In the non-CF bronchiectasis group, there were patients with idiopathic bronchiectasis (three patients), nontuberculous mycobacteria (two patients), sarcoidosis (two patients), and primary ciliary dyskinesia (PCD) (two patients). Of the patients with nonmalignant cavitary lung disease, 7/12 had sarcoidosis that was colonized with *Aspergillus* (i.e., fungal balls), 3/12 had preexisting right upper lobe cavities (from pervious infections) that were again colonized with *Aspergillus*, 1/12 had *Mycobacterium avium* complex (MAC) and 1/12 had granulomatosis with polyangiitis (colonized with *Aspergillus*). Ten out of 12 cavities that caused hemoptysis were infected with *Aspergillus*. A total of 4/50 patients had cancer, of which two had primary adenocarcinoma of the lung, one had small cell lung cancer and one had metastasis from renal cell carcinoma. In the other group, there were three patients with idiopathic hemoptysis and one patient with ANCA vasculitis. Although the BAE is not indicated in patients with diffuse alveolar hemorrhage, this patient underwent the BAE as a salvage procedure due to his young age and because it was refractory to other standard treatment options [Figure 2].

Table 1: Demographics

Etiology of hemoptysis (*n*)	Age (mean±SD)	*P* value*	FEV1% of predicted (mean±SD)	*P* value*
CF bronchiectasis (*n*=21)	26±8	<0.001	56±27	NS
Non-CF bronchiectasis (*n*=9)	55±14	<0.001	65±10	NS
Cavitary lung disease (*n*=11)	56±11	<0.001	44±8	NS
Cancer (*n*=4)	68±6	<0.001	70±10	NS
Others (*n*=4)	35±19	>0.05	60±20	NS

*$P \geq 0.05$ was considered not significant, *Mann-Whitney test. CF: Cystic fibrosis, FEV1: Forced expiratory volume in 1 s, SD: Standard deviation

Early (1 month) outcomes of the BAE: Efficacy and safety

We were able to achieve a 100% immediate control of hemoptysis with the BAE compared to the previously reported control rates of 75-90%.[3,7-9] Two patients had chest pain after procedure, one had nonflow limiting bronchial artery dissection, one had posterior circulation stroke (patient had multiple small infarcts with no long-term neurological sequel) and one patient developed lower extremity paraplegia after procedure (due to possible inadvertent spinal artery embolization) that was complicated by a preexisting aortic stent graft for aortic aneurysm. No BAE procedure related deaths were reported. Out of 15 deaths, 8 occurred within the 30-day period. One patient with CF had lung transplant 10 days after the BAE but she died of lung transplant complications the next day after the transplant. Out of four cancer patients who died, two with adenocarcinoma of lung died of complications from the underlying cancer within 30 days (at 7 days and 1 month). The patient with ANCA vasculitis, chronic bronchiectasis, and rapidly progressing glomerulonephritis died on day 30, after two BAEs. Three patients had cavitary sarcoidosis complicated byaspergillosis; they died on day 2, day 3, and day 30; none were surgical candidates due to poor lung function. One patient with idiopathic hemoptysis died of an unrelated aortic dissection on day 30.

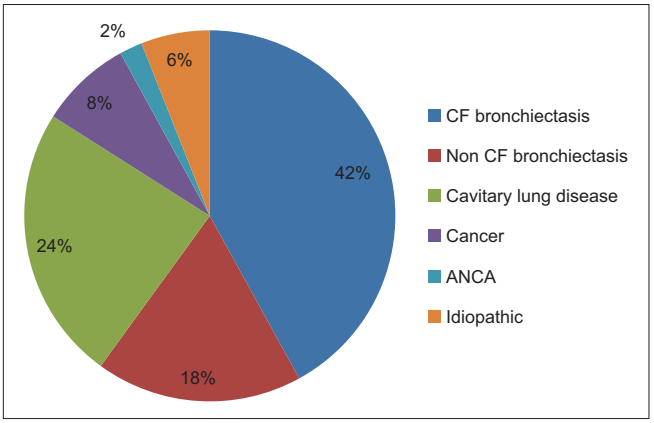

Figure 2: Etiology of hemoptysis

Recurrence of hemoptysis

There were a total of 24/50 patients with recurrent hemoptysis [Table 2], and Figure 3 shows the timeline for the recurrences. Of these, 11 were CF patients, 8 had cavities, 3 had non-CF bronchiectasis, 1 had ANCA, and 1 was idiopathic (P = NS between groups). Of the 11 recurrences in CF patients, 2 patients had spontaneous resolution of the hemoptysis. Six of the 11 patient required only one additional BAE procedure. Three patients required multiple procedures with one patient requiring a total of six BAEs and the other two requiring two more procedures. When the CF patients were divided according to the severity of lung function [Table 3], it appeared that patients with severely impaired lung function had more recurrences, but the sample sizes were too small to show statistical differences. Of all the non-CF bronchiectasis patients, three had recurrent hemoptysis at 2 weeks for PCD and at 9 months and 2 years, respectively, for idiopathic bronchiectasis. Eight patients with cavities had recurrent hemoptysis. No patients with malignancies had recurrences, procedural complications, or mortality from the BAE. Only one patient with idiopathic hemoptysis had recurrence on day 7 that resolved spontaneously and required no further intervention.

Definitive surgical treatment

The patients with cavitary lung disease with good pulmonary function tests were considered good surgical candidates and were referred for surgical evaluation for definite treatment (lobectomy) after the initial BAE. Three of the original 12 patients with cavities were considered poor surgical candidates and the rest nine elected to see if the BAE alone would control the hemoptysis. Five patients had long-term control with the BAE alone. Four patients with cavitary disease eventually (three with sarcoidosis and one with MAC) underwent thoracotomy and each had a right upper lobe lobectomy for cavity with mycetoma. One out of these four patients with sarcoidosis, following right upper lobe lobectomy, had a recurrence of hemoptysis with a cavity/mycetoma in the left upper lobe 10 years later. The hemoptysis recurred four times in this patient but she did not require repeat embolization as the bleeding resolved spontaneously; the patient was no longer a surgical candidate due to poor lung function. There were no surgery-related complications or mortality.

Table 2: Recurrences versus number of procedures

Etiology	Number of patients with recurrences	Number of patients requiring reembolization	Number of repeat procedure
CF bronchiectasis	11	09	17
Cavitary lung disease	08	07	12
Non-CF bronchiectasis	03	03	03
ANCA vasculitis	01	01	01
Idiopathic	01	00	00
Total	24	21	33

CF: Cystic fibrosis, ANCA: Antineutrophil cytoplasmic antibody

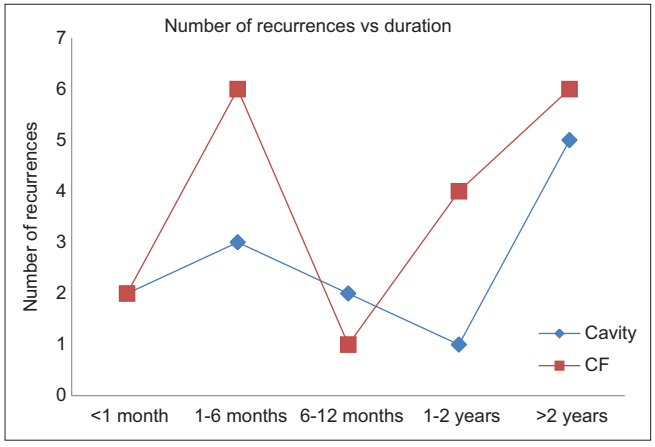

Figure 3: Timeline of recurrence in patients with cavitary lung disease and CF bronchiectasis

Long-term outcomes

We had 7/15 deaths after 30 days. Five out of these 7 patients presented with CF bronchiectasis. One patient died 4 months after procedure due to complications from lung transplant; she died within 10 days of lung transplant. While the rest four died of respiratory failure due to CF at 4 months, 2 years, 4 years, and 5 years after the BAE. One patient with small cell lung cancer died 2 months after the procedure and the patient with renal cell carcinoma died 51 months after the procedure due to complications of this metastatic disease.

DISCUSSION

Our results show, for the first time, that the BAE can be used as a durable long-term treatment in patients with CF and non-CF bronchiectasis. This is in contrast to the previous studies/views that largely viewed the BAE as a short-term intervention to palliate bleeding.[3,4] Our study can draw this conclusion because our median follow-up was of >2 years and our longest follow-up was of 13 years. We also observed that incidence of hemoptysis was not related to lung function [Table 3] in patients with CF bronchiectasis as suggested by previous studies[5] and the incidence of hemoptysis were similar in patients with severely impaired lung function and mildly impaired lung function. However, we found that the recurrence was higher in patients with severely impaired lung function but the BAE was still a durable and good long-term treatment.

Our immediate bleeding control rate was 100% after the BAE. The improved control rate compared to previous studies may have to do with the use of different and newer particle and microcatheter technology and more distal selective vessel catheterization compared to older studies. In addition, earlier embolization, cohort makeup, and preembolization imaging may account for the improved success. Our complication rate was low (only two patients had major complications). At our institute more selective BAE of the more terminal branches of the arterial tree beyond the origin of the spinal arteries are targeted, which decreases the complications. Spinal cord

Table 3: FEV1 and outcomes in CF bronchiectasis

FEV1 (% predicted)	Number of patients	Recurrence	Death
<35	7	6	1
35-49	1	1	0
50-64	3	1	1
65-79	7	3	0
≥80	3	0	0
Total	21	11	2

FEV1: Forced expiratory volume in 1 s, CF: Cystic fibrosis

injury, subintimal dissection of the aorta, transient thoracic pain, and transient dysphagia are all well described in the literature.[10]

Our study also highlights the point that not all hemoptysispatients behave in the same manner. The BAE outcome is excellent in patients with CF and non-CF bronchiectasis and indeed this intervention can be definitive in many patients. On the other hand, for patients with cavitary lung diseases this intervention only serves as a bridge to the definitive therapy that is surgical resection of the area involved. Similarly, in patients with cancers this is only a palliative procedure.

We compared our data with other published literature regarding the BAE that focused on the immediate bleeding control rate. According to the Mayo Clinic group, immediate control of bleeding was obtained in 94% of patients and the 30-day control was 85%.[4] In the Mayo group, 17 patients (31%) died while in our group there were 15 (30%) deaths, but our observation period was much longer. In the Mayo group, four patients died of massive hemoptysis versus three patients in our group. In the Mayo group, no follow-up information was available on 19 patients (35%); the remaining 18 patients had follow-up periods from 6 months to 6 years without evidence of recurrent hemoptysis. We followed our patients up to 13 years. Shigemura *et al*.[10] reported an 88% immediate success in controlling hemoptysis in a series of 55 patients. Their study had high mortality rate resulting from hemoptysis (8 patient died of hemoptysis out of a total of 50 patients who were followed up) compared to our study where we had only 3/50 deaths due to hemoptysis. They also lost a quarter of the patient (27%, 15/55) to follow up and the follow-up was only for 1 year, whereas we followed patient up to 13 years.

The other evidence in support of the BAE as a durable long-term intervention comes from the fact that despite a high (50%) recurrence of hemoptysis with CF, clinically significant hemoptysis requiring additional BAE was low (40%) and long-term outcomes were better (10 year survival =85%). Admittedly, some of the improvement in long-term outcomes in CF may have been due to better underlying CF care. Only 14% of CF patients required more than two BAE procedures. We had only one extreme case, requiring six procedures, while most of the CF group necessitated two procedures. The vast majority of patients that had recurrent hemoptysis requiring the BAE were due to bleeding in the same lung as the previous episode. Only one out of the nine patients, who had recurrent hemoptysis and required repeat BAE, was the one who was bleeding from the contralateral lung. This finding should assist interventional radiologists in addressing hemoptysis recurrence after initial BAE. There were two peaks of recurrence in CF. The first was between 1 month and 6 months after procedure that was possibly secondary to incomplete embolization and the second peak after 1-2 years, was likely due to development of bronchial artery collaterals [Figure 3].

In 2010, the CF foundation gave no clear recommendations for the BAE as the treatment of hemoptysis in CF due to lack of evidence even though this is a fairly common practice across the globe.[11,12] There was also no consensus on treating the clinically stable massive hemoptysis with the BAE due, again, to the lack of evidence. Finally, there was no consensus on embolization of all abnormal (dilated and tortuous) vessels versus just embolizing the actively bleeding vessel.

With regard to CF BAE, Brinson *et al*.[5] published the most comprehensive review to date by evaluating 18 patients who underwent a total of 36 procedures. The overall efficacy of the BAE for initial control of hemoptysis was 75% after one session. The follow-up was complicated because two patients died immediately, and of the remaining 16, three were lost to the follow-up. Figure 3 in their manuscript suggests a median follow-up of ~6 months for their cohort. Unfortunately, two patients died and three were transplanted making it difficult to ascertain what the success of the BAE alone would have been during a longer term follow-up. The overall recurrence rate was 46% and the mean time for recurrence was 12 months. There was a high incidence of bleeding from nonbronchial systemic collateral vessels among patients who had undergone a previous BAE. These results are similar to ours but there is a lack of long-term follow-up.

We had similar encouraging results in case of patients with non-CF bronchiectasis where only 3/9 patients had recurrent hemoptysis requiring another procedure. Similar to CF, bleeding usually originates from dilated bronchial arteries system (rather than pulmonary arteries). The BAE is again a durable long-term solution provided that the underlying disease processes are treated. Previous studies[13-15] have shown that hemoptysis is frequent (45-51%) in patients with non-CF bronchiectasis; and, in one of these studies,[14] blood-staining of sputum was seen in 27%, frank bleeding of up to 10 mL in 20%, and massive (>235 mL) bleeding in 4%. Massive hemoptysis may occur but is rarely a cause of death in this patient population.[11,16]

Our worse experience in terms of mortality was with patients who had non-malignant cavitary lung disease. We were initially able to control the hemoptysis in all these patients but they had early recurrence, and two patients died of hemoptysis as they were not surgical candidates for definitive treatment. Other cancers may be different but our experience is too small to draw any conclusions.

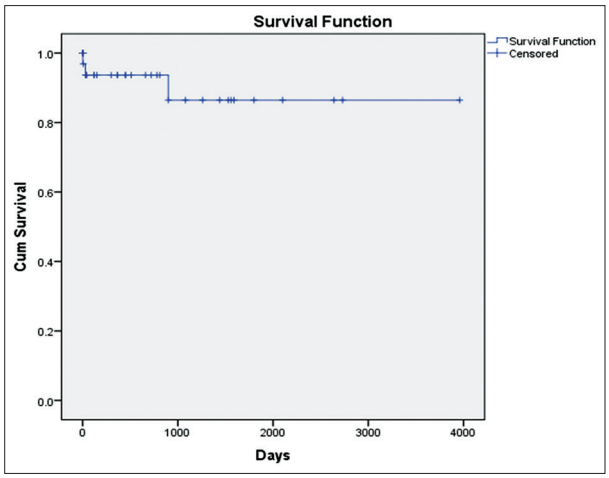

Figure 4: Follow-up in days and survival

We also believe that the BAE is proved to be an effective and safe procedure to control hemoptysis in patients with aspergilloma but because of the high rates of recurrences and mortality, we regard this procedure as palliative for this condition as well.[17] Our finding is similar to other reports.[7] Present guidelines recommend embolization for aspergilloma patients as a short-term treatment bridging these patients to more definite therapy, including surgery.[18] Recurrence rates after the BAE, based on our data and the published literature, are probably influenced by the etiology of hemoptysis such as what occurs with *Aspergillus spp.* CF and *Mycobacterium tuberculosis* infections.[8,19,20] Bleeding recurrence one-six months later is likely to be due to incomplete embolization or an undetected nonbronchial systemic arterial supply like the branches from inferior phrenic artery, intercostal arteries, neovascularization from the thyrocervical, or an internal mammary artery. Late recurrences (6-12 months after the BAE) have been reported in as many as 2-40% of patients, probably due to disease progression and collateral vessel formation.[21]

The limitations of this study were its retrospective nature and small sample size (especially in nonbronchiectasis patients), loss of some patients to follow up creating a possible selection bias toward reporting better outcomes (if some of the loss to follow up was due to patient death) and possible variations in the BAE techniques over the study period of over a decade. Larger, more comprehensive studies in the future will shed further light on the utility of this technique and better subgroup analysis may help discriminate which patient groups are most likely to benefit from the BAE.

CONCLUSION

We believe that the BAE is a safe, effective, and durable (with Kaplan-Meier survival near 85% at 10 years in CF patients, Figure 4) procedure in certain patient populations such as CF bronchiectasis, non-CF bronchiectasis, and idiopathic hemoptysis. In patients with cavitary lung disease, it serves as a bridge to surgery and is purely palliative in patients with advanced lung malignancy that needs to be explained to these patient groups.

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Conflicts of interest
There are no conflicts of interest.

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