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Management of hemoptysis with bronchial artery embolization: Benign versus malignant indications

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ABSTRACT

Objectives: The purpose of this study is to compare the role of bronchial artery embolization (BAE) in hemoptysis due to malignant and non-malignant etiologies.

Material and Methods: Data from patients who underwent BAE at a tertiary care center from October 2002 to 2018 were retrospectively reviewed. Variables evaluated include procedural indication, technical success, clinical success, re-embolization, intensive care unit (ICU) admission, length of stay, and thirty-day readmission. Categorical and continuous variables were analyzed using Pearson's Chi-squared and two sample *t*-tests, respectively. Post-procedure survival and re-embolization were analyzed using Kaplan–Meier curves and Cox proportional hazard models.

Results: 114 BAE procedures from 93 unique patients with hemoptysis were identified, with 29.8% of procedures being performed for hemoptysis secondary to malignancy and 70.2% for benign causes. The technical and clinical success rates of the procedure were similar between benign and malignant etiologies (benign/malignant: 92.5% vs. 91.2% and 82.5% vs. 73.5%, respectively). There were no statistically significant differences in rates of need for re-embolization, ICU admission, 30-day readmission, mean hospital length of stay, or mortality between benign and malignant groups. Clinically successful embolization was protective against death (HR = 0.19, $P < 0.001$) and re-embolization (HR = 0.04, $P = 0.001$), while higher American Society of Anesthesiologists' (ASA) score, female sex, and primary pulmonary malignancy were associated with risk of death.

Conclusion: While patients with a malignant cause of hemoptysis had an increased risk of mortality and decreased survival time, BAE for malignant hemoptysis is effective with outcomes comparable to that for benign hemoptysis as indicated by high clinical and technical success rates and low rates of re-embolization.

Keywords: Bronchial artery embolization, Hemoptysis, Lung cancer, Malignancy

INTRODUCTION

Bronchial artery embolization (BAE) is an accepted treatment for the control of moderate-to-massive hemoptysis and has proven to be safe and efficacious.^[1-3] Viamonte was the first physician to perform a selective bronchial arteriogram in 1963, and Rémy *et al.* produced the first thorough description of embolization of the bronchial arteries for the treatment of hemoptysis in 1974.^[4,5] The most common indication for BAE world-wide is tuberculosis and post-tubercular

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inflammation.^[1] In the United States, benign conditions such as cystic fibrosis, bronchiectasis, sarcoidosis, and COPD are the most common indications for BAE.^[3]

Patients with lung cancer represent about 25% of those presenting with hemoptysis in the United States, and these patients have a high mortality rate without prompt treatment.^[6,7] Although the literature has not found a significant difference in the hemoptysis volume and imaging characteristics in patients with malignant or benign etiologies, the pathophysiology driving hemoptysis due to malignancy is unique and due to a combination of increased angiogenesis in addition to local necrosis and inflammation.^[8-12] The general approach to hemoptysis in patients with lung cancer is to secure and/or maintain an open airway, ensure hemodynamic stability, and further evaluate the underlying cause with subsequent bronchoscopy and/or computed tomography (CT).^[1,13] A variety of approaches have been studied in the palliation of hemoptysis, such as laser photocoagulation, endobronchial stenting, external radiotherapy, and BAE.^[1,14-16]

Although the safety and efficacy of BAE in patients with hemoptysis secondary to benign etiologies is well established, there is a relative paucity of data on outcomes in patients with hemoptysis due to underlying malignancy. The reported data on short- and long-term efficacy of BAE in patients with malignancy is variable, although several sources suggest poor outcomes in patients presenting with hemoptysis due to pulmonary neoplasm.^[17] In this study, we describe our experience with BAE, analyzing outcomes in patients with hemoptysis secondary to benign and malignant etiologies.

MATERIAL AND METHODS

Subject profile

This study was approved by the Institutional Review Board, completed with a waiver of consent, and HIPAA-compliant. We retrospectively reviewed consecutive BAE procedures performed for hemoptysis at our tertiary care center from October 2002 to October 2018. All patients who underwent BAE for hemoptysis and had post-procedural follow-up of at least 1 year or until death were included for analysis.

Data collection and definitions

All data were obtained from the electronic medical record. Given the COVID-19 crisis, data that overlapped with the pandemic were excluded to avoid potential confounding of the study objective. Procedural details including BAE indication, embolization agents used, arteries embolized, and radiation exposure were collected. Additional procedures, such as bronchoscopy and surgery, were noted if the patient received the intervention during their hospitalization in

which BAE was performed. Technical success was defined as successful bronchial artery catheterization, angiography, and radiographic stasis. Clinical success was defined as cessation of hemoptysis after the procedure, with no other interventions required for hemoptysis during the hospitalization. Need for intensive care unit (ICU) admission, length of stay, endovascular reintervention to the same or different artery, and readmission within 30-day were collected as well. Reported mortality values represent all-cause mortality.

Management of hemoptysis and technique of BAE

Patients presenting with hemoptysis were managed by an interdisciplinary subsection of interventional radiology, medicine, and surgery. The indication criteria for BAE and re-embolization are illustrated in [Figure 1].

Before performing each procedure, the risks, benefits, and alternatives of BAE were discussed with the patient, and informed consent was obtained. Briefly, the patient was brought to the angiography suite, and the right groin was prepared for right common femoral artery access. A 5 French vascular sheath was placed over a wire under fluoroscopic guidance. Selective right common femoral arteriography was performed to confirm puncture site within the common femoral artery. A 5 French catheter was then advanced over a wire into the aorta, and selection of the bronchial arteries was performed. If bleeding had been localized by CT or bronchoscopy to a lung laterality, only the bronchial arteries supplying that lung were embolized. Selective angiography was then performed of the bronchial arteries with a microcatheter to confirm catheter position and identify hypervascularity, vascular irregularity, and the presence of contrast extravasation, if any. Selected arteries were then embolized until radiographic stasis was achieved.

Statistical analysis

Data were analyzed with STATA 16.1 (StataCorp LLC, College Station, Texas); binary variables were compared with Pearson's Chi-squared. Continuous variables were compared with Student's *t*-tests. Kaplan–Meier survival curves were employed to analyze overall post-procedural survival and re-embolization-free survival, where survival time was started from the date of initial embolization. An event was initiated on the occurrence of death or the re-embolization/death composite variable for overall and re-embolization-free survival, respectively. Factors associated to death or re-embolization were calculated separately with a Cox-Proportional Hazards model. Factors selected for regression modeling included data on demographics, American Society of Anesthesiologists' (ASA) score, malignancy, ICU admission, and procedural success due to their potential to confound the risk of death and/or re-embolization. Demographic and survival data were analyzed

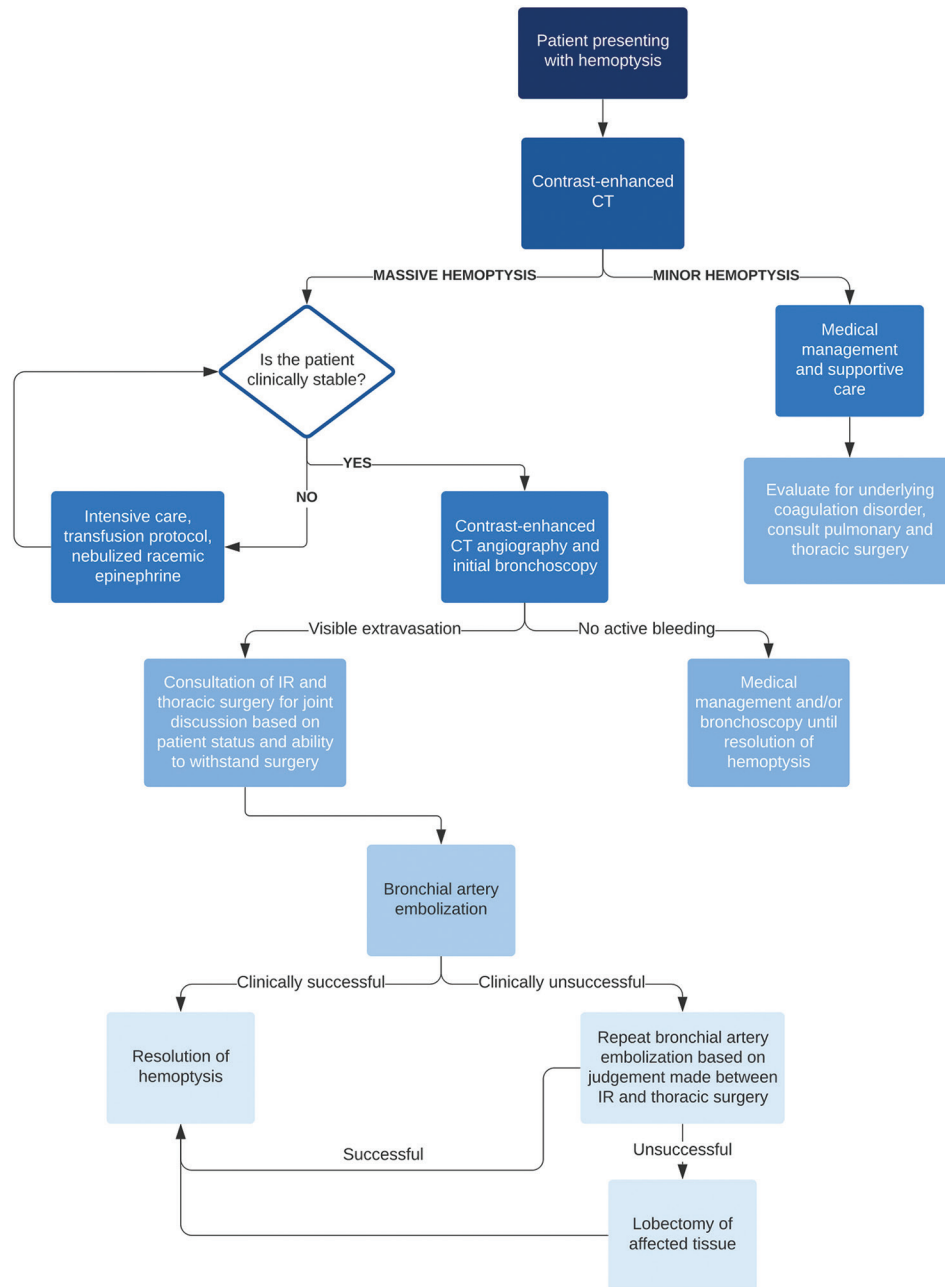


Figure 1: Indication criteria for bronchial artery embolization and re-embolization.

per unique patient at the time of initial embolization, while all other procedural characteristics and additional outcomes were analyzed per procedure. The end of follow-up for all patients was defined as the time of data collection.

RESULTS

Overall outcomes

There were 150 total BAE procedures performed over this period, with 114 procedures performed on 93 unique

patients who had sufficiently documented hospital and procedural notes from which the variables for this study could be drawn. There were 80 procedures among 64 unique patients with benign indications and 34 procedures in 29 unique patients with malignant indications. Overall patient characteristics are summarized in [Table 1]. The mean age was 54.8 years (\pm 17.9 years), and 47 (50.5%) patients were female. Of the 114 procedures, 71 were preceded by bronchoscopy (62.3%), and 38 (33.3%) were followed by further bronchoscopic evaluation. Upon

Table 1: Summary of unique patient characteristics (unique patients, n=93).

Characteristics	All patients (n=93)	Benign (n=64)	Malignancy (n=29)	P-value ^a (Benign vs. Malignant)
Mean age, years	54.8±17.9	53.6	57.4	0.364
Sex, n (%)				
Male	46 (49.5)	29 (45.3)	17 (58.7)	0.234
Female	47 (50.5)	35 (54.7)	12 (41.3)	-
ASA Score	3.21	3.3	3.04	0.067
Indications, n (%)				
Any pulmonary neoplasm	29 (31.2)	-	29 (100)	-
Primary pulmonary neoplasm	21 (22.6)	-	21 (72.4)	-
Metastatic lung malignancy	8 (8.6)	-	8 (27.6)	-
Cystic fibrosis	16 (17.2)	16 (25.0)	-	-
Pneumonia	9 (9.7)	9 (14.1)	-	-
Idiopathic	6 (6.5)	6 (9.4)	-	-
MAC	5 (5.4)	5 (7.8)	-	-
Tuberculosis	2 (2.2)	2 (3.1)	-	-
Aspergillosis	5 (5.4)	5 (7.8)	-	-
COPD	3 (3.2)	3 (4.7)	-	-
Vascular abnormality	2 (2.2)	2 (3.1)	-	-
Vasculitis	2 (2.2)	2 (3.1)	-	-
Coagulopathy/ITP	2 (2.2)	2 (3.1)	-	-
Berylliosis	1 (1.1)	1 (1.6)	-	-
Other	11 (11.8)	11 (17.2)	-	-
Overall clinical outcomes				
Survival (days)	1074.8	1359.0	447.4	0.005
Overall mortality	51 (54.8)	31 (48.4)	20 (69.0)	0.065

^aPearson's Chi²; Two-sample t-test, ASA: American society of anesthesiologists, ITP: Idiopathic thrombocytopenic purpura, MAC: Mycobacterium avium complex

angiographic evaluation, two patients were found to have a pseudoaneurysm, one found to have an arteriovenous malformation, and three found to have an arterio-venous shunt. The majority of procedures used *Embosphere*[®] microspheres as the embolization agent (68.4%), followed by coil (8.8%), polyvinyl alcohol (9.6%), and gel foam (3.5%) as the next most common embolization materials. The most common indications among individual patients for BAE within the benign and malignant groups were cystic fibrosis (16/64, 25%) and primary pulmonary malignancy (21/29, 72.4%), respectively. Patient and procedural details are summarized in [Tables 1 and 2].

The overall technical and clinical success rates for the benign and malignant groups were 92.1% and 79.8%, respectively. The average length of stay after BAE was 23.2 ± 70.8 days. About 73.0% of all patients were admitted to the ICU, and 12.3% of the patients were readmitted to the hospital within 30 days of being discharged. About 20.2% of patients underwent re-embolization. Of those, 47.8% needed re-embolization to the same artery. The mean follow-up time/survival was 1074.8 ± 1471 days. The Kaplan–Meier survival and re-embolization-free survival curves are shown in [Figure 2]. There were two major adverse events in the entire cohort; one patient had a stroke following their BAE

procedure, and another patient died intra-procedurally due to cardiac arrest.

Benign versus malignant outcomes

The average age (benign/malignant: 53.6 vs. 57.4 years, $P = 0.36$) and gender (45.3% male vs. 58.7% male, $P = 0.23$) were comparable between the malignant and benign groups [Table 1]. Within the malignant group, there were 29 unique patients and 34 total procedures. Twenty-one (72.4%) patients had primary pulmonary neoplasms, while 8 (27.6%) had metastatic neoplasms [Table 1]. Patients with benign etiologies of hemoptysis had more arteries embolized on average per procedure (1.75 vs. 1.21, $P = 0.009$), and the right bronchial arteries were embolized more often (70.0% vs. 47.1%, $P = 0.02$). The likelihood of receiving bronchoscopy post-BAE was higher in the malignant cohort (27.5% vs. 47.1%, $P = 0.047$; [Table 2]). Post-BAE bronchoscopies were primarily indicated for suction of residual blood clots and collection of sample, though there were two individuals in the benign cohort and three in the malignant cohort who required therapeutic intervention in the form of cauterization, stent placement, or blocker placement through bronchoscopy (2.5% vs. 8.8%, $P = 0.13$).

Table 2: Procedure characteristics (procedures, $n=114$).

Procedure characteristic	All procedures ($n=114$)	Benign ($n=80$)	Malignancy ($n=34$)	P-value ^a (Benign vs. Malignant)
Total # of arteries embolized**	181	140	41	0.009
Mean # of arteries embolized/procedure**	1.59	1.75	1.21	0.009
Radiation exposure/procedure				
Fluoroscopy time (min) (mean)	30.8	30.9	30.5	0.936
Dose (440mGym)	889.1	784.5	1132.4	0.099
DAP (440uGym2)	7461.4	6325.3	10101	0.098
Embolization Material ^c , n (%)				
Single embolization agent	90 (78.9)	66 (82.5)	23 (67.6)	0.080
Multiple embolization agents	20 (17.5)	12 (15.0)	8 (23.5)	0.287
None	4 (3.5)	1 (1.3)	3 (8.8)	0.044
Additional procedures, n (%)				
Pre-procedure bronchoscopy	71 (62.3)	47 (58.8)	24 (70.6)	0.233
Post-procedure bronchoscopy	38 (33.3)	22 (27.5)	16 (47.1)	0.047
Post-procedure surgery	7 (6.1)	3 (3.8)	4 (11.8)	0.103
Clinical outcomes per procedure, n (%)				
Technical success	105 (92.1)	74 (92.5)	31 (91.2)	0.811
Clinical success	91 (79.8)	66 (82.5)	25 (73.5)	0.275
ICU admission	73 (64.0)	47 (58.8)	26 (76.5)	0.071
30 day readmission	14 (12.3)	9 (11.3)	5 (14.7)	0.607
Mean length of stay (days)	23.2	19.3	32.3	0.373
^b Need for reembolization	23 (20.2)	18 (22.5)	5 (14.7)	0.343
^b Time to reembolization (days)	679.5	861.3	25.0	0.160

^aPearson's Chi²; Two-sample t-test, ^bRe-embolization analyzed for all procedures, ^cMore than one type per procedure may be used, DAP: Dose area product, ASA: American society of anesthesiologists physical status score, ICU: Intensive care unit

There were no statistically significant differences in embolization agent, fluoroscopy time, radiation dose, and dose area product between benign and malignant groups. There were no statistically significant differences in technical success (92.5% vs. 91.2%, $P = 0.82$), clinical success (82.5% vs. 73.5%, $P = 0.28$), need for re-embolization (22.5% vs. 14.7%, $P = 0.34$), need for surgery (3.8% vs. 11.8%, $P = 0.10$), length of stay (19.3 vs. 32.3 days, $P = 0.37$), 30-day readmission (11.3% vs. 14.7%, $P = 0.61$), need for ICU admission (58.8% vs. 76.5%, $P = 0.07$), or overall mortality (48.4% vs. 69.0%, $P = 0.065$; [Table 2]) between the benign and malignant indication cohorts. However, the overall survival time was significantly shorter among patients in the malignant indication cohort (447.4 vs. 1359.0 days, $P = 0.005$; [Table 1]).

Re-embolization-free survival and risk factors

Eighteen patients (18/93, 19.4%) underwent re-embolization, representing 23 total procedures (23/114, 20.2%). The overall rates of re-embolization among benign and malignant etiologies of hemoptysis were 22.5% and 14.7%, respectively. The average time to re-embolization was 678.9 days. Cystic fibrosis (7/23, 30.4%), metastatic lung malignancy (4/23, 17.4%), and pneumonia (4/23, 17.4%) were the most common etiologies within the re-embolization group,

while primary pulmonary neoplasms were significantly less common among the re-embolization group (non-re-embolization/re-embolization: 23.1% vs. 4.3%, $P = 0.04$). Of the procedures with a malignant indication for hemoptysis, primary pulmonary neoplasms were less likely to be in the re-embolization group compared to metastatic malignancy (primary/metastatic: 4.5% vs. 33.3%, $P = 0.02$). About 55.6% (10/18) of re-embolization procedures due to benign causes of hemoptysis involved re-embolization to the same artery, compared to 20% (1/5) due to malignant causes. There was no significant difference in technical success (non-re-embolization/re-embolization: 93.4% vs. 87.0%, $P = 0.31$) or clinical success (80.2% vs. 78.3%, $P = 0.834$). However, mean survival time was significantly lower in the non-re-embolization group (902.1 days vs. 1,577.7 days, $P = 0.04$).

Cox analysis [Tables 3 and 4] suggests that clinical success is protective against both death (HR = 0.19, 0.08–0.48, $P < 0.001$) and re-embolization (HR = 0.04, 0.005–0.28, $P = 0.001$), while higher ASA score (HR = 3.73, 2.19–6.36, $P < 0.001$), female sex (HR = 2.29, 1.15–4.55, $P = 0.02$), and primary pulmonary malignancy (HR 3.23, 1.03–10.19, $P = 0.045$) were associated with significant risk of death. Age, malignancy stage, technical success, and ICU admission status were not found to have a significant effect on the risk of death or re-embolization.

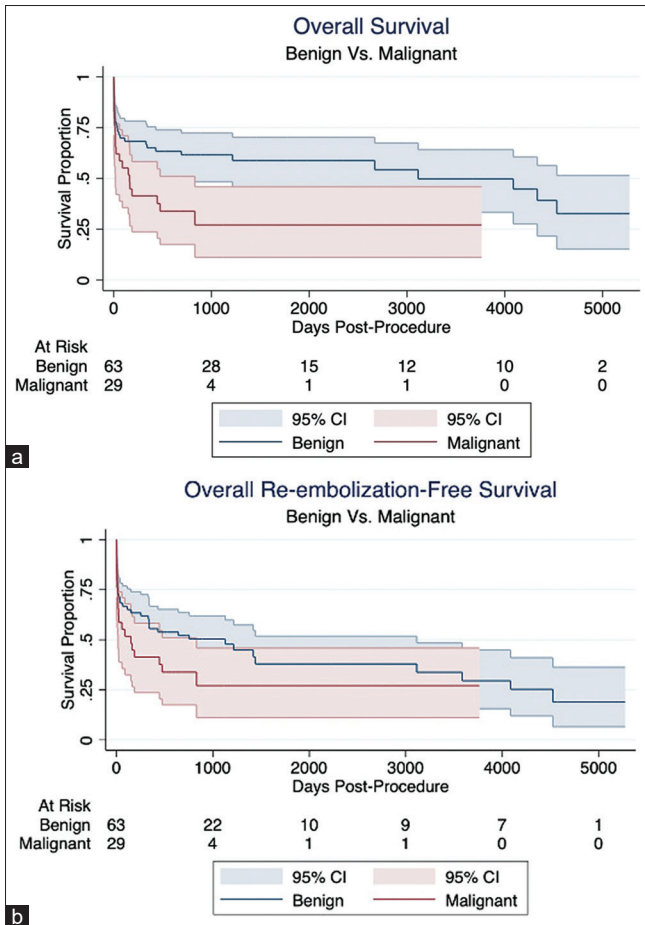


Figure 2: (a) Kaplan–Meier Survival Curves. (a) overall survival; (b) overall re-embolization-free survival.

DISCUSSION

The results of this study support the efficacy of BAE for malignant hemoptysis and provide a unique comparison of outcomes between patients with benign and malignant indications managed at the same institution. The overall technical (92.1%) and clinical (79.8%) success rates are within previously reported ranges for BAE for benign and malignant indications.^[1,10,18,19] The overall re-embolization rate of 20.2% in the present analysis also fell within previously reported values of ~20%, and malignant cases were not found to be at a higher risk of re-embolization relative to benign cases, unlike in other reported series.^[1,10,18] Technical (91.2%) and clinical (73.5%) success and re-embolization rates (14.7%) for the malignant group closely match previously published data on BAE in patients with malignant hemoptysis from Han *et al.*^[18] Chen *et al.* performed a similar study finding the overall clinical success rate to be 90.1%, with no significant differences between the malignant and benign groups.^[17]

The analysis identified several post-procedural outcome similarities between the two groups. There were no

Table 3: Risk factors for death.

Risk factor	Hazard ratio	95% CI	P-value ^a
Age	1.02	0.99–1.04	0.105
Female	2.29	1.15–4.55	0.018
ASA score	3.73	2.19–6.36	<0.001
Any malignancy	1.44	0.51–4.12	0.492
Primary pulmonary malignancy	3.23	1.03–10.19	0.045
ICU admission	1.36	0.55–3.34	0.506
Clinical success	0.19	0.08–0.48	<0.001
Technical success	1.38	0.46–4.19	0.567

^aCox-Proportional hazards analysis (Prob>Chi²=0.0000), ASA: American society of anesthesiologists physical status score, ICU: Intensive care unit

Table 4: Risk factors for re-embolization.

Risk factor	Hazard ratio	95% CI	P-value ^a
Age	1.02	0.99–1.05	0.303
Female	2.61	0.83–8.28	0.102
ASA score	2.26	0.80–6.37	0.123
Any malignancy	3.08	0.64–14.71	0.158
Primary pulmonary malignancy	0.38	0.03–4.23	0.433
ICU admission	0.64	0.15–2.80	0.553
Clinical success	0.04	0.005–0.28	0.001
Technical success	5.27	0.51–54.18	0.163

^aCox-proportional hazards analysis (Prob>Chi²=0.0081), ASA: American society of anesthesiologists physical status score, ICU: Intensive care unit

statistically significant differences in rates of technical success, clinical success, need for re-embolization, ICU admission, 30-day readmission, mean hospital length of stay, or mortality between benign and malignant groups [Table 2]. However, the difference in rate of ICU admission (58.8% vs. 76.5%, $P = 0.07$) may be interpreted as clinically significant, with lack of power likely accounting for lack of statistical significance. Similarly, a greater number of BAE procedures in the malignant cohort were followed by definitive treatment of hemoptysis in the form of surgery, though this difference did not come out to be statistically significant (3.7% vs. 1.8%, $P = 0.10$). BAE procedures indicated for a malignant cause of hemoptysis were also more likely to be followed by bronchoscopic evaluation (27.5% vs. 47.1%, $P = 0.047$), which were performed primarily for diagnostic evaluation and/or suction of remaining blood clots and secretions rather than for further therapeutic management of active hemoptysis. Altogether, the greater rates of ICU admission, post-procedure surgery, and post-procedure bronchoscopy among patients with malignancy suggest that hemoptysis due to malignancy may require additional immediate management in addition to BAE, expanding on Gershman *et al.*'s conclusion that diagnostic and treatment algorithms for hemoptysis of malignant versus non-malignant etiologies should be applied with care.^[13]

The observed survival time for patients with malignant hemoptysis is consistent with previously reported values.^[18,20,21] Cause of death in the present analysis for either group was not explored, though the decreased survival time in the malignant hemoptysis cohort was likely related to their underlying disease process.^[10] As expected, with regard to overall survival time, there was a significant difference of 911.6 days (1359 vs. 447.4 days, $P = 0.005$) between the benign and malignant groups, corresponding with an increase in overall mortality (48.4% vs. 69.0%, $P = 0.07$), which is a likely function of the underlying disease process. From the Kaplan–Meier survival curve, there was no short-term difference in mortality within 30 months post-procedure, suggesting no procedure-specific increase in mortality for patients with malignancy. Divergence in between 30 and 33 months is likely secondary to disease progression in the malignant group [Figure 2a]. Of the 14 patients with stage IV NSCLC, the median survival of patients post-BAE (5.7 months) is similar to the data reported in the literature of patients with stage IV NSCLC presenting with hemoptysis.^[22]

Further support for the efficacy of BAE in malignancy is demonstrated by the limited need for endovascular intervention in the form of re-embolization. As demonstrated in [Figure 2b], there was no statistically significant difference in re-embolization-free survival between the benign and malignant cohorts. Only one person with primary pulmonary malignancy required re-embolization of the same artery, comprising of only 4.3% of the cases of re-embolization in our study. Hemoptysis due to metastatic lung malignancy was more likely to undergo re-embolization compared to primary pulmonary neoplasms (33.3% vs. 4.5%). This finding is likely explained by multifocal tumor burden, as all four reinterventions (100%) due to metastatic malignancy were at different arteries, suggesting different tumor sites were being embolized per intervention.^[11] Patients who required re-embolization had similar overall mortality outcomes compared to patients who did not receive re-embolization (57.1% vs. 60.9%, $P = 0.746$).

Risk factors for re-embolization have been previously described, including presentation with massive hemoptysis, presence of a cavitary mass, and bronchial-pulmonary arterial shunts.^[9,18] Within this study, clinical success, defined as resolution of hemoptysis with no need for endovascular reintervention in the same hospital stay, was protective against all-cause mortality and re-embolization at any time during follow-up, while ASA score, primary pulmonary malignancy, and female sex were associated with significant risk of all-cause mortality. Age, technical success, and ICU admission status were not found to have a significant effect on the risk of death or re-embolization in our model. It is concerning that female sex status was associated with significantly higher risk of death and re-embolization in

our study, and further studies are needed to understand the factors that potentially contribute to this disparity.

This retrospective study has multiple limitations, including the modest number of patients, the retrospective nature, and loss to follow-up. The limited number of patients, particularly among the malignant etiology group, reduced the statistical power of our analyses. Therefore, certain clinically significant outcomes, such as increased rates of ICU admission and post-BAE surgery among patients with malignancy, were not statistically significant. Data collection was ended before 2019 to reduce possible confounding caused by the SARS-CoV-2 pandemic, and future studies analyzing how COVID-19 impacted rates of hemoptysis are indicated. Another limitation of this study was that re-embolization was used as an objective proxy for clinically significant recurrent hemoptysis, which does not accurately reflect cases in which re-embolization was not indicated despite recurrent hemoptysis. In addition, detailed staging data on all malignant cases were not available, so there may be variable outcomes for different stages of pulmonary malignancy. The exact degree of hemoptysis at presentation was similarly not included, preventing this study from being able to assess differences between major and minor hemoptysis. Furthermore, not all patients had follow-up data available beyond 1 year.

CONCLUSION

Analysis of outcomes after BAE performed in patients with hemoptysis due to various benign and malignant conditions suggests it is a safe and effective technique. There were no differences in periprocedural survival, technical success, clinical success, need for re-embolization, 30-day readmission, or mean hospital length of stay when BAE is performed for a benign or malignant indication. Endovascular intervention in the form of BAE for malignancy appears to be effective as seen by the limited requirement for re-embolization of the same artery and lack of statistically significant difference in re-embolization-free survival. As expected, patients presenting with hemoptysis due to malignancy undergo post-procedural bronchoscopy, surgery, and ICU admission as part of further management of the underlying malignancy.

Declaration of patient consent

Institutional Review Board (IRB) permission obtained for the study.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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