의학 석사 학위 논문

Bronchial Artery Embolization to Control Hemoptysis: Comparison of N-Butyl 2-Cyanoacrylate and Polyvinyl Alcohol Particles

-객혈 치료를 위한 기관지 동맥 색전술: 엔부틸시아노아크릴레이트와 폴리비닐 알코올 입자의 비교-

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서울대학교 대학원

의과대학 임상의과학과

우성민

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이 논문을 의학석사 학위논문으로 제출함

2013년 12월

서울대학교 대학원

의과대학 임상의과학과

우 성 민

우성민의 의학석사 학위논문을 인준함

2013년 12월

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학위논문 원문제공 서비스에 대한 동의서

본인의 학위논문에 대하여 서울대학교가 아래와 같이 학위논문 저작물을 제공하는 것에 동의합니다.

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①본인의 논문을 보존이나 인터넷 등을 통한 온라인 서비스 목적으로 복제할 경우 저작물의 내용을 변경하지 않는 범위 내에서의 복제를 허용합니다.

②본인의 논문을 디지털화하여 인터넷 등 정보통신망을 통한 논문의 일부 또는 전부의 복제.배포 및 전송 시 무료로 제공하는 것에 동의합니다.

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3. 서울대학교의 의무

①서울대학교는 본 논문을 외부에 제공할 경우 저작권 보호장치(DRM)를 사용하여야 합니다.

②서울대학교는 본 논문에 대한 공개의 유보나 해지 신청 시 즉시 처리해야 합니다.

논문제목: Bronchial Artery Embolization to Control Hemoptysis: Comparison of N-Butyl 2-Cyanoacrylate and Polyvinyl Alcohol Particles

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ABSTRACT

Introduction: The purpose of this was study was to retrospectively compare the safety and effectiveness of two embolic agents (polyvinyl alcohol [PVA] particles vs. n-butyl 2-cyanoacrylate [NBCA]) for bronchial artery embolization (BAE) for control of hemoptysis.

Methods: Institutional Review Board approved this retrospective study; informed consent was waived. From January 2005 to December 2008, 406 patients (M:F = 242:164; 6-92 years) with major hemoptysis underwent BAE using PVA particles (n = 293) or NBCA (n = 113). Technical and clinical success, complications, hemoptysis-free survival rates, the causes of recurrent hemoptysis were compared between PVA and NBCA groups. The differences in hemoptysis-free survival rates were also assessed between subgroups stratified to underlying diseases. The predictive factor for recurrent hemoptysis was identified with Cox proportional hazards regression model.

Results: Technical success was achieved in 93.9% (275 of 293) and 96.5% (109 of 113) of patients for PVA and NBCA, respectively (P = .463); clinical success was achieved in 92.2% (270 of 293) and 96.5% (109 of 113) of patients for PVA and NBCA, respectively (P = .180). The 1-, 3-, and 5-year hemoptysis-free survival

rates were, respectively, 77%, 68%, and 66% for PVA and 88%, 85%, and 83% for NBCA (P = .010). Recanalization of previously embolized vessels was more frequent in the PVA group (21.5%) than in the NBCA group (1.8%; P < .001). The NBCA group showed hemoptysis-free survival rates superior to the PVA group in patients with bronchiectasis (P = .016). The use of PVA (P = .050) and aspergilloma (P < .001) were predictive factors for recurrent hemoptysis.

Conclusions: BAE with NBCA provided higher hemoptysis-free survival rates compared with PVA particles without increasing complication rates. This improvement was evident in patients with bronchiectasis and seems to be caused by a more durable embolic effect than PVA particles.

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INTRODUCTION

Bronchial artery embolization (BAE) has been widely accepted as the most effective minimally invasive therapy alternative to surgery for massive and recurrent hemoptysis (1, 2). However, since BAE does not address the underlying disease, recurrence of hemoptysis is common, requiring frequent repeat embolization (3). To overcome this limitation, investigations have been performed to develop new embolic agents and thereby achieve more successful outcomes. For example, gelatin cross-linked particles (tris-acryl) have been demonstrated to prevent clumping within microcatheters due to their more uniform size and hydrophilic coating (4). In another study, thrombin was reported to be safely administered despite the insufficient engagement of the target bronchial artery (5). Although such advances in embolic materials and embolization techniques have led to some technical improvements, there has been no significant change in the overall recurrence rates since the 1970s (6, 7). Therefore, there is no consensus on which embolic material is best, and as of now, absorbable gelatin sponge particles or polyvinyl alcohol particles (PVA) are most widely used because of their inexpensiveness, easiness to handle, and controllability of embolic size (1, 7, 8).

Recently, n-butyl 2-cyanoacrylate (NBCA) has been gaining interest for control of bleeding from various organs such as the gastrointestinal tract, kidney, liver, uterus, adrenal gland, extremity, and chest wall (9-11). This may be attributed to several advantages of NBCA as an embolic agent. It occludes

target vessels rapidly and completely, which results in more reliable embolization and may reduce fluoroscopic and procedure time. By adjusting the ratio of NBCA and iodized oil, polymerization time the level of embolization within target vessels can be controlled (7, 9-13). Despite these advantages, the use of liquid embolic agents including NBCA has been avoided in BAE because of the concern that they carry a high risk for severe complications such as tissue necrosis and nontarget embolization from uncontrolled reflux (1, 14). Contrary to these concerns, a few investigators have recently suggested that NBCA is a promising embolic material for BAE (7, 13, 14). However, those studies were limited by an absence of a contemporaneous control group (7, 14) or short follow-up duration (mean, 11.7-14 months) (13, 14). Therefore, the purpose of our study was to retrospectively compare the safety and effectiveness of two embolic agents (polyvinyl alcohol [PVA] particles vs. n-butyl 2-cyanoacrylate [NBCA]) for BAE for control of hemoptysis.

MATERIALS AND METHODS

Baseline Characteristics

Institutional Review Board approval was obtained for this retrospective study; informed consent was waived. A computerized search of medical records from January 2005 to December 2008 identified 485 consecutive patients who underwent BAE for major hemoptysis. Major hemoptysis was defined according to the following criteria (15): a single event of massive (> 240 mL/d) bleeding (*n* = 118), moderate (> 100 mL/d) and recurrent bleeding for several days (*n* = 168), or small (≤ 100 mL/d) but limiting the patient's lifestyle for few weeks (*n* = 120). The exclusion criteria were as follows: previous history of BAE (*n* = 39); both PVA and NBCA (*n* = 12) or neither (*n* = 4) were used for BAE; significant missing data in the medical records (*n* = 8); iatrogenic cause of hemoptysis (*n* = 7); no abnormal findings on preprocedural imaging and angiography (*n* = 5). Ultimately, a total of 406 patients (age range, 6-92 years; mean age, 56 years ± 15) consisting of 242 men (age range, 6-92 years; mean age, 56 years ± 15) and 164 women (age range, 19-92 years; mean age, 56 years ± 13) who underwent BAE using PVA particles (*n* = 293) or NBCA (*n* = 113) were included in our study.

Prior to BAE, bronchoscopy and/or contrast-enhanced CT scans was performed to identify the underlying cause and extent of pulmonary diseases, to localize possible bleeding foci, and to predict culprit vessels. At our institution, it is routine to perform contrast-enhanced CT scans as a diagnostic step. However, in selected cases, such as when the patients were unstable, active bleeding required

endobronchial management, or when bilateral lung abnormalities limited the radiographic bleeding localization, a bronchoscopic approach was considered (16). Sixty-seven patients underwent bronchoscopy, of which in 41 patients, the bleeding focus was demonstrated. Of the 403 patients who underwent CT, the bleeding focus was indentified in 367 patients. The baseline data of the two groups including demographics, etiology and amount of hemoptysis were collected using the electronic medical records (EMR) and Picture Archiving & Communications Systems (PACS). The extent of the pulmonary disease was given a grade of 0-6 according to the number of pulmonary lobes with disease involvement on CT. All interpretation of imaging findings were performed under consensus between three authors (S.W., C.J.Y., and Y.J.K. with 2, 10 and 2 years of experience in BAE, respectively) blinded to the embolic agent used and clinical outcome.

Bronchial Artery Embolization Procedures

All angiographic procedures were performed by one of 3 interventional radiologists (C.J.Y., H.J.J., and H.C.K. with 10, 9, and 6 years' experience in BAE, respectively). After femoral arterial access was obtained with a 5-Fr sheath, aortography covering the thoracic and upper abdominal aorta was performed with a 5-French pigtail catheter with the tip located at the ascending aorta with a flow rate of 15 mL/sec during a 2-second injection, frame rate of 3 f/sec at anteroposterior position. Selective angiograms of the bronchial and nonbronchial systemic collateral arteries, which were helped to be identified on the basis of CT and

aortography, were obtained with 5-French angiographic catheters (Torcon NB, Cook, Bloomington, IN USA). The following findings were considered pathological on selective angiography: abnormal engorgement, parenchymal hypervascularity, bronchopulmonary shunting, and extravasation of the contrast agent (1). All pathological bronchial arteries and nonbronchial systemic collateral arteries were embolized. Microcatheters with a 3-F (Renegade, Boston Scientific), 2.4-F (Microferret; Cook,), or a 2.0-F (Progreat; Terumo, Tokyo, Japan) tip were introduced coaxially and advanced as distal as possible in order to avoid spinal feeders and reflux of the embolic material into the aorta. The choice between the embolic materials, NBCA and PVA, was not regimented but randomly determined by the attending interventional radiologists' discretion. Both embolic materials were routinely used during the study period without a transition period.

In the NBCA group, NBCA (Histoacryl, B-Braun, Melsungen, Germany) was mixed with iodized oil (Lipiodol Ultra Fluide, Guerbet) at a ratio of 1:2-1:4. After the microcatheter was flushed with 5% dextrose solution in order to avoid gluing and occlusion of the lumen during injection of NBCA, 0.5-2 mL of the mixture was carefully injected under fluoroscopic monitoring. The ratio, volume, and injection rate of the mixture were based on the size and flow of the embolized vessels. To avoid adhesion of the catheter tip to the vessel wall, the microcatheter was quickly removed after injection. Upon withdrawal, the microcatheter was flushed with 5% dextrose solution to be reused for subsequent embolization of the remaining pathologic arteries. In cases of PVA (Contour® PVA Embolization Particles; Boston Scientific, Natick, MA) embolization, particles larger than 250 μm

(250-355 or 355-500 μm), which were selected to avoid bronchial necrosis (17), were diluted with 15 ml contrast and 5 ml saline in a 20-ml reservoir syringe connected to a 1-ml delivery syringe via a three-way stopcock. Immediately before administration of the PVA particles, vigorous pumping between these two syringes was performed for re-suspension of the particles. The injection of PVA was ended when the forward flow of opacified embolic solution ceased. After completion of embolization, regardless of using NBCA or PVA, aortography was performed to confirm the absence of any other residual culprit arteries.

Assessment of Technical/Clinical Success and Follow-up

Technical success was defined as the complete embolization of bronchial and nonbronchial systemic collaterals in which embolization was attempted (3). Clinical success was defined as cessation of hemoptysis within 24 hours of BAE (3, 18). After discharge, the patients visited the outpatient department every 1-3 months for follow-up of the underlying condition and recurrent hemoptysis. If hemoptysis recurred, the patients were encouraged to visit the emergency department, where they would undergo a series of studies including complete blood count, chest CT, and otherwise required examinations. Thereafter, subsequent treatment (repeat BAE, emergency bronchoscopy, or surgery) was determined by multidisciplinary decision between the emergency physician, interventional radiologist, pulmonologist, and thoracic surgeon. For the patients who underwent repeat BAE, the causes of recurrence based on angiographic findings were categorized into the following:

recanalization of previously embolized vessels; missed culprit vessels on previous procedure; or recruitment of new collateral circulation (13). The follow-up period was defined as the duration until the last hospital visit or date of death.

Complications

Close observation for early complications of BAE was done during the procedure and post-procedural admission. Delayed complications were assessed at follow-up regardless of routine outpatient or emergency department visits due to recurrent events. Furthermore, the follow-up CT scans and bronchoscopic results in the EMR were reviewed by three authors (S.W., C.J.Y., and Y.J.K.) for CT findings of pulmonary ischemia or infarction, and CT or bronchoscopic findings of airway abnormalities including bronchial stenosis, necrosis and bronchoesophageal fistula (19, 20). Complications that required extended hospitalization, an advanced level of care or resulted in permanent adverse sequelae or death were classified as major complications (21); the remaining complications were considered minor.

Statistical Analysis

The baseline characteristics of the PVA and NBCA groups were compared using the Student *t*-test for parametric variables (patient age, amount of hemoptysis, disease extent, number of embolized vessels, and follow-up duration) and the Chi-square analysis for nonparametric variables (patient sex and the underlying causes of hemoptysis). Comparison of technical/clinical success, overall/major

complication rates, and the cause of recurrence on repeat angiograms between the two groups were evaluated using the Fisher's exact test. The hemoptysis-free survival rates were estimated using the Kaplan-Meier method and compared between the two groups using the log-rank test. We stratified the comparison of hemoptysis-free survival by underlying disease subgroup and examined predictive factors (patient age [dichotomized at the mean age], sex, cause, disease extent, amount of hemoptysis) of recurrent hemoptysis (which yielded a P value < .1 with the Kaplan-Meier method) through Cox proportional hazards regression models. Any factor that was different between the PVA group and NBCA group were to adjust the Cox proportional hazards regression model. Death was coded as censored independent of the occurrence of recurrent hemoptysis. The proportional hazard assumption and goodness-of-fit of the model were verified by using log-minus-log plot and Cox-Snell residuals, respectively. A P value < .05 was considered statistically significant. SPSS (version 18, SPSS Inc., Chicago, IL, USA) was used for data analysis.

RESULTS

Baseline Characteristics between PVA and NBCA Groups

The baseline characteristics of all patients are described in Table 1. Male:female ratio, age, and amount of hemoptysis were not significantly different in both groups. The common causes for hemoptysis were bronchiectasis (n = 117), sequelae of tuberculosis (n = 100), active tuberculosis (n = 49), nontuberculous mycobacterial infection (n = 32), aspergilloma (n = 29). In the remaining patients, the underlying diseases were lung cancer (n = 19), pneumonia (n = 9), metastasis of hepatocellular carcinoma (n = 6), actinomycosis (n = 4), chronic obstructive pulmonary disease (n = 4), lung abscess (n = 3), angioinvasive pulmonary aspergillosis (n = 3), radiation pneumonitis (n = 2), pneumoconiosis (n = 2), usage of anticoagulants (n = 2), congenital heart disease (n = 2), followed by pulmonary sequestration, anthracofibrosis, idiopathic pulmonary fibrosis, empyema, graft-versus-host disease, Wegener's granulomatosis, and infected bulla in one patient each. The cause of hemoptysis was not determined in 16 patients. There were no significant differences in the underlying causes of hemoptysis between the PVA and NBCA groups (P = 0.156). With regard to disease extent, the PVA (2.6 ± 1.5) and NBCA group (2.4 ± 1.3) did not show significant difference in the mean number of involved lobes (P =0.083). Regarding the location of the disease, the PVA group had a higher incidence in the non-lingular portion of the left upper lobe (P = 0.034) and the left lower lobe (P = 0.035). The mean follow-up period was 38.7 months ± 26.9 (range, 1 day-87 months) for PVA and 35.5 months ± 29.3 (range, 1 day-90

months) for NBCA ($P = 0.315$).

Characteristics and Technical/Clinical Success of BAE

Results of BAE procedures are summarized in Table 2. A total of 1244 arteries were embolized: 713 bronchial arteries (388 right, 325 left) and 531 nonbronchial systemic arteries for an average of 3.1 ± 2.2 arteries per patient. Thirty-nine bronchial arteries had an aberrant origin from the aortic arch (n = 17), subclavian artery ($n = 6$), thyrocervical artery ($n = 6$), internal mammary artery ($n = 9$) and inferior phrenic artery ($n = 1$). Nonbronchial systemic arteries embolized were intercostal ($n = 279$), internal mammary ($n = 84$), inferior phrenic ($n = 74$), lateral thoracic ($n = 36$), thoracoacromial ($n = 17$), thyrocervical ($n = 16$), superior thoracic ($n = 10$), subclavian ($n = 5$), thoracodorsal ($n = 5$), and costocervical ($n = 3$), long thoracic ($n = 2$). Between the two groups, there were no significant differences in the number of total and nonbronchial systemic arteries ($P = .644$ and $P = .617$, respectively): 3.0 ± 2.3 and 1.3 ± 2.0 for PVA and 3.1 ± 2.2 and 1.4 ± 2.0 for NBCA, respectively.

Technical success was achieved in 93.9% (275/293) for PVA and 96.5% (109/113) for NBCA ($P = .463$). The causes for technical failure were the following: failure of sufficient engagement of the microcatheter to the pathologic artery due to tortuosity ($n = 13$), dissection ($n = 3$), orifice stenosis ($n = 2$), small caliber ($n = 1$), or acute angle of branching ($n = 1$) and uncooperative patient condition such as irritability ($n = 1$) or an event of seizure ($n = 1$). Clinical success was achieved in

92.2% (270/293) for PVA and 96.5% (109/113) for NBCA (P = .180). In total, BAE did not control hemoptysis in 27 patients. Among them, 5 patients died due to uncontrolled hemoptysis; 7 patients underwent repeated sessions of BAE; 7 patients received operation for the underlying cause; and 10 patients who did not receive an additional session of BAE or operation were given an antifibrinolytic (Tranexamic acid, Huons, Hwaseong, Kyunggi, Korea) during and extended hospital stay.

Complications

The Early complications were observed in 33.3% (135/406) of the patients. Minor complications consisted of chest/shoulder discomfort in 13.6% (55/406), abdominal discomfort or nausea/vomiting in 5.9% (24/406), urticaria in 5.7% (23/406), neurological symptoms (headache and extremity weakness) in 4.4% (18/406), fever in 5.9% (24/406) and puncture site hematoma in 0.2% (1/406) of the patients. Abdominal and thoracic symptoms, as well as urticaria resolved spontaneously or with analgesics and anti-histamines. Blood cultures were negative for microorganisms in all patients with fever: 16 patients received antipyretics (n = 7) or empirical antibiotics (n = 9); the remaining 8 patients improved spontaneously. Puncture site hematoma resolved with manual compression. Among the neurologic complications, all patients with headache improved with analgesics. There was one major complication (0.2%, 1/406) in which the patient complained of lower extremity weakness after BAE. This patient who had received BAE with PVA was suspected of having cerebral infarction. However, further diagnostic work-up was

not possible due to uncontrolled hemoptysis which led to death 22 days after BAE. There were no significant difference of overall and major complication rates between the two groups (P = .559 and P = 1.000, respectively): 34.1% (100/293) and 0.3% (1/293) for PVA; 31.0% (35/113) and 0% (0/113) for NBCA, respectively (Table 3).

There were no delayed complications. Follow-up bronchoscopy (n = 179) and CT (n = 233) revealed no evidence of pulmonary parenchymal ischemia or airway abnormalities. There was no procedure-related mortality.

Hemoptysis-free Survival Rates

Of the 379 patients in which BAE was clinically successful, recurrence was observed in 94 (24.8%) patients (Figures 1-3) and death occurred in 31 (8.2%) patients of which only 0.5% (2/379) were directly related to recurrent hemoptysis. Among these patients, BAE, surgery (lobectomy [n = 19], segmentectomy [n = 6], and wedge resection [n = 4]), and emergency bronchoscopy was performed in 56, 15, and 3 patients, respectively, while 18 patients received a combination of these treatments. When stratified according to the embolic material, these rates were 29.6% (80/270) for PVA and 12.8% (14/109) for NBCA (P = .001). The 1-, 3-, and 5-year hemoptysis-free survival rates were 77%, 68%, and 66%, respectively for PVA and 88%, 85%, and 83%, respectively for NBCA (log-rank P = .01). The hemoptysis-free survival rates of the NBCA group were significantly higher than those of the PVA group (hazard ratio = 2.082; 95% CI = 1.174, 3.692; P = .012) (Figure 4).

When comparison of the hemoptysis-free survival was stratified by the underlying disease, only patients with underlying bronchiectasis showed significant difference in hemoptysis-free survival rates between the PVA and NBCA groups (log-rank $P = 0.016$). The corresponding 1-, 3-, and 5-year hemoptysis-free survival rates were 79%, 71%, and 69%, respectively for PVA and, 100%, 95%, and 95%, respectively for NBCA (hazard ratio = 7.991; 95% CI = 1.079, 59.186; $P = 0.042$) (Figure 5). These rates were not significantly different between the two groups for patients with tuberculous sequela ($P = .490$), active tuberculosis ($P = .545$), nontuberculous mycobacterial infection ($P = .784$), aspergilloma ($P = .852$), and other underlying causes ($P = .545$) (Figure 6).

Seventy-three patients underwent a total of 100 repeat BAEs: one session of repeat BAE was performed on 50 patients; two in 16 patients; three in 2 patients; and four in 3 patients. The causes of recurrence revealed on repeat angiograms are summarized in Table 4. The overall same-vessel recanalization rate was 15.8% (60/379). These figures were significantly ($P < .001$) higher in the PVA group (19.8%; 58/293) than the NBCA group (1.8%; 2/113). There were no significant difference regarding missed culprit vessels ($P = .145$) and new collateral circulation ($P = .824$).

The results of hemoptysis-free survival according to the possible predictive factors for recurrence are shown in Table 5. Other than type of embolic material, only the underlying disease ($P < .001$) was significantly associated with hemoptysis-free survival. Upon pairwise comparisons, aspergilloma was associated with earlier recurrence compared with all other causes ($P < .001$). In addition,

nontuberculous mycobacterial infection showed superior hemoptysis-free survival than tuberculous sequela (P = .03). There were no significant differences in the hemoptysis-free survival among the remaining underlying causes. Regarding the extent of the disease, although the mean disease extent were not different between the PVA and NBCA groups, the extent of ≥ 3 lobes was seen more frequently in the PVA group compared to the NBCA group (P = .035): 50.2% (147/293) vs 38.9% (44/113), respectively—therefore, an analysis of the disease extent ≥ 3 compared with that < 3 was performed and revealed that an involvement of 3 or more lobes showed a tendency (log-rank P = .052; hazard ratio = 1.523; 95% CI = 0.994, 2.335; P = 0.053) for earlier recurrence. Resultantly, the candidates for multivariate analysis were the type of embolic material, underlying disease, and extent of the disease (≥ 3 lobes or not). Cox proportional hazards analysis demonstrated that both underlying cause of aspergilloma (hazard ratio = 4.620; 95% CI = 2.480, 8.607, P < .001) and usage of PVA (hazard ratio = 1.787; 95% CI = 1.001, 3.189, P = .050) were independent predictors for recurrent hemoptysis (Table 6).

Table 1. Baseline Characteristics of 406 Patients Who Underwent Bronchial Artery Embolization Using NBCA and PVA Particles

Parameter	**NBCA group** (*n* = 113)	**PVA group** (*n* = 293)	***P* Value**
Age* (years)	54.77 ± 14.47 (23-92)	57.05 ± 14.54 (6-92)	.157
M/F ratio	64/49	178/115	.499
Hemoptysis amount (mL)			.322
>240	27 (23.9)	91 (31.1)	
100-240	52 (46.0)	116 (39.6)	
≤100	34 (30.1)	86 (29.4)	
Etiology			.156
Bronchiectasis	28 (24.8)	89 (30.4)	
Tuberculosis sequela	24 (21.2)	76 (25.9)	
Active tuberculosis	17 (15.0)	32 (10.9)	
NTM infection	13 (11.5)	19 (6.5)	
Aspergilloma	5 (4.4)	24 (8.2)	
Others	26 (23.0)	53 (18.1)	
Disease extent (lobes) *	2.4 ± 1.4 (0-6)	2.6 ± 1.5 (0-6)	.083
Disease location			
Right upper lobe	51 (45.1)	148 (50.5)	.376
Right middle lobe	51 (45.1)	114 (38.9)	.261
Right lower lobe	43 (38.1)	116 (39.6)	.821
Left upper lobe (non-lingular)	41 (36.3)	142 (48.5)	.034
Left upper lobe (lingular)	38 (33.6)	110 (37.5)	.492
Left lower lobe	41 (36.3)	141 (48.1)	.035
Follow-up duration (months) *	35.5± 29.3 (1day-90)	38.7 ± 26.9 (1 day-87)	.315

Note.—except where indicated, data are number of patients; data in parenthesis are percentages.

*Data are the mean ± standard deviation; data in parenthesis are the range.

Table 2. Characteristics of Bronchial Artery Embolization Procedures Using NBCA and PVA Particles

Parameter	NBCA group (n = 113)	PVA group (n = 293)	*P* Value
Total arteries*	3.1 ± 2.1 (1-12)	3.0 ± 2.3 (1-17)	.644
Nonbronchial systemic arteries*	1.4 ± 2.0 (0-9)	1.3 ± 2.0 (0-14)	.617
Technical success	109 (96.5)	275 (93.9)	.463
Clinical success	109 (96.5)	270 (92.2)	.180

Note.—except where indicated, data are number of patients; data in parenthesis are percentages.

*Data are the mean ± standard deviation; data in parenthesis are the range.

NBCA = n-butyl 2-cyanoacrylate, PVA = polyvinyl alcohol

Table 3. Complications after Bronchial Artery Embolization using NBCA and PVA particles

Parameter	NBCA group (n = 104)	PVA group (n = 289)	*P* Value
Treatment-related mortality	0 (0)	0 (0)	
Complications			
Major complication	0 (0)	1 (0.3)	1.000
All complication	35 (31.0)	100 (34.1)	0.559

Note.—data are number of patients; data in parenthesis are percentages.

NBCA = n-butyl 2-cyanoacrylate, PVA = polyvinyl alcohol

Table 4. Repeat Angiographic Findings of the Patients Who Initially Achieved Clinical Success After Bronchial Artery Embolization Using NBCA and PVA Particles

Repeat angiographic findings	**NBCA group** (*n* = 109)	**PVA group** (*n* = 270)	***P* Value**
Same-vessel recannalization	2 (1.8)	58 (21.5)	< .001
Missed culprit vessels	3 (2.8)	23 (8.5)	.145
New collateral circulation	8 (7.3)	18 (6.7)	.824

Note.—data are number of patients; data in parenthesis are percentages.

NBCA = n-butyl 2-cyanoacrylate, PVA = polyvinyl alcohol

Table 5. Univariate Analysis of Predictive Factors for Recurrence after Bronchial Artery Embolization

Parameter	No. of Patients	Hazard Ratio*	*P* Value†
Embolic material type			
PVA	270	2.082 (1.174, 3.692)	.012
NBCA	109	1	
Age (years)			
> 56	196	1	
≤ 56	183	1.096 (0.717, 1.674)	.672
Sex			
Men	221	1.008 (0.659, 1.541)	.971
Women	158	1	
Hemoptysis amount (mL)			.902
>250	107	1.024 (0.588, 1.783)	.934
100-250	163	0.917 (0.554, 1.519)	.737
≤100	109	1	
Etiology			<.001
Bronchiectasis	112	1	
Tuberculosis sequela	92	1.371 (0.773, 2.431)	.280
Active tuberculosis	47	0.845 (0.364, 1.962)	.845
NTM infection	32	0.394 (0.119, 1.308)	.128
Aspergilloma	25	5.013 (2.715, 9.256)	<.001
Others	71	0.947 (0.464, 1.935)	.947
Disease extent			
≥ 3 lobes	180	1.523 (0.994, 2.335)	.052
< 3 lobes	199	1	

*Data in parenthesis are 95% CIs.

†Determined with Cox regression.

NBCA = n-butyl 2-cyanoacrylate, PVA = polyvinyl alcohol

Table 6. Multivariate Analysis of Predictive Factors for Recurrence after Bronchial Artery Embolization

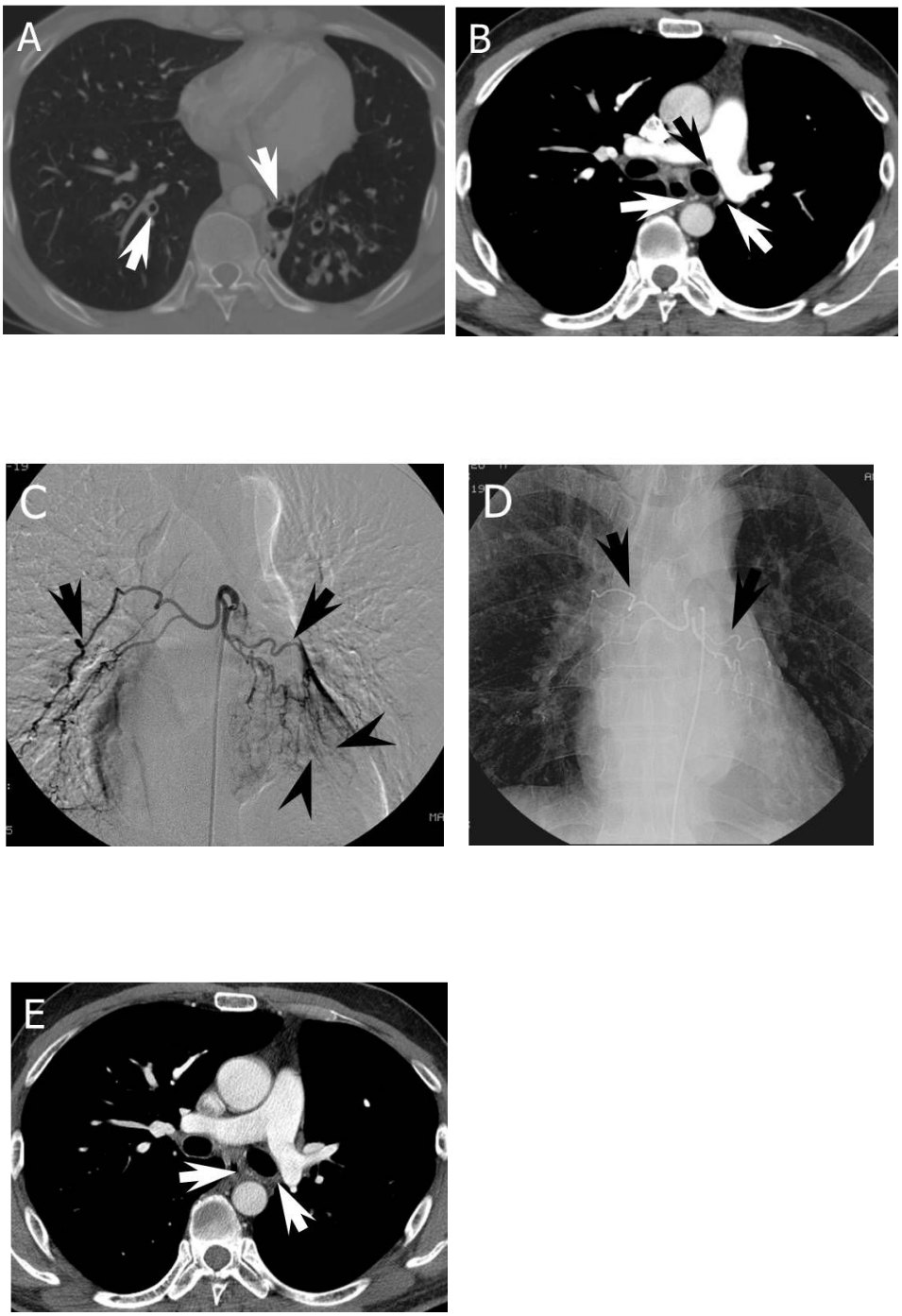
Parameter	**Hazard Ratio***	***P* Value**[†]
Embolic material type		
PVA	1.787 (1.001, 3.189)	.050
NBCA	1	
Etiology		<.001
Bronchiectasis	1	
Tuberculosis sequela	1.309 (0.736, 2.330)	.359
Active tuberculosis	0.929 (0.339, 2.164)	.865
NTM infection	0.415 (0.124, 1.386)	.153
Aspergilloma	4.620 (2.480, 8.607)	<.001
Others	0.984 (0.480, 2.016)	.965
Disease extent		
≥ 3 lobes	1.273 (0.817, 1.985)	.286
< 3 lobes	1	

*Data in parenthesis are 95% CIs.

†Determined with Cox regression.

NBCA = n-butyl 2-cyanoacrylate, PVA = polyvinyl alcohol

Figure 1. Images of hemoptysis caused by bronchiectasis in a 39-year-old man.



A. Lung window chest CT image shows bronchiectasis in both lower lobes (arrows), which were suspected to be the cause of hemoptysis.

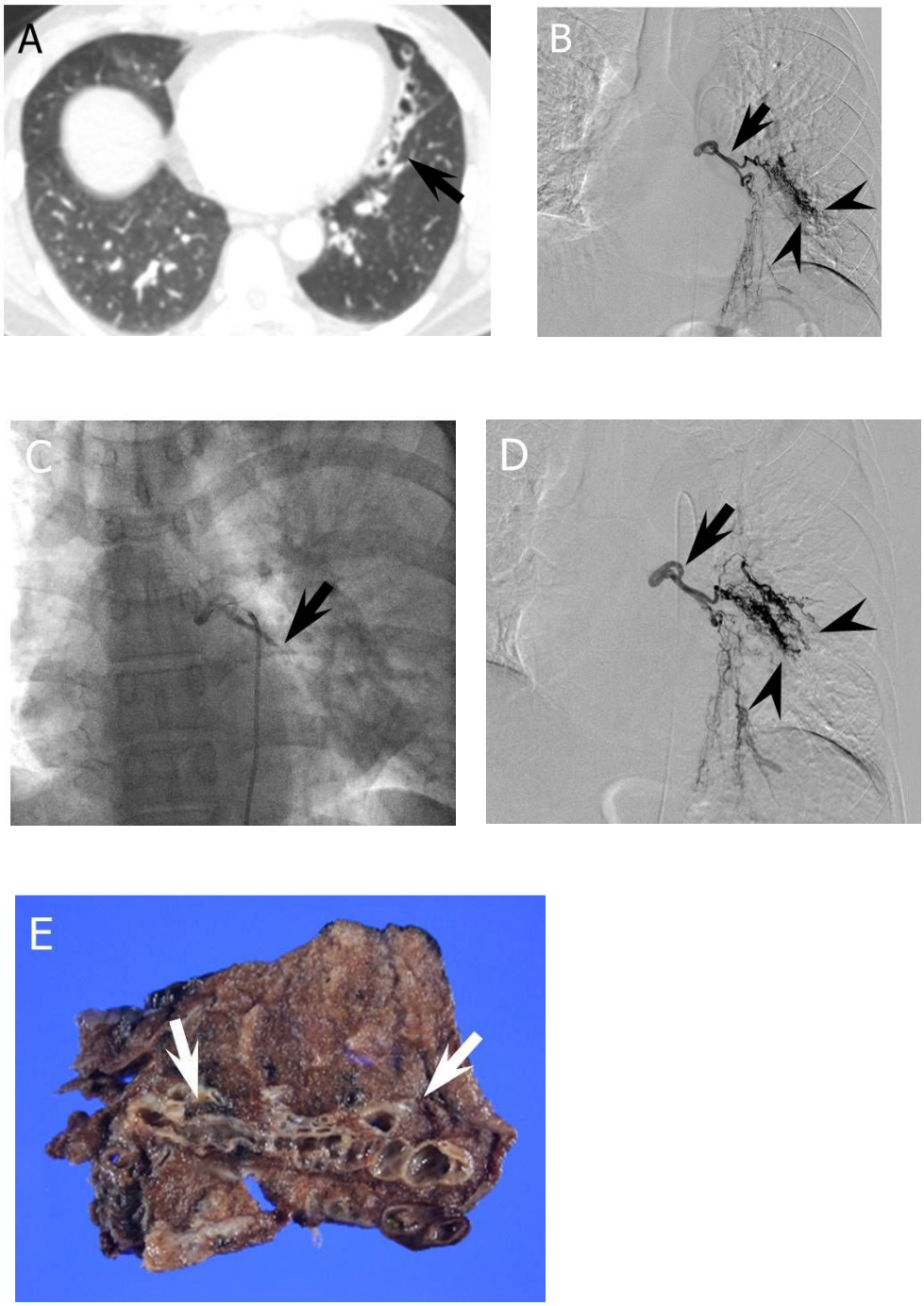
B. Engorged bronchial arteries around both main bronchi (arrows) with a mediastinal window setting.

C. Selective bronchial arteriogram shows engorgement of both bronchial arteries (arrows) that supply hypervascular inflammatory parenchymal lesions. Note opacification of distal parts of pulmonary arteries (arrowheads). Both bronchial arteries were separately embolized with NBCA and iodized oil mixture (ratio, 1:4) after sufficient engagement of the microcatheter in each bronchial artery just proximal to the first-order branch.

D. Radiograph immediately after embolization shows complete casting of both bronchial arteries (arrows) without filling the pulmonary arteries.

E. On follow-up chest CT scan obtained 3 years later, the engorged bronchial arteries on previous CT scan were completely obliterated (arrows). Patient has been doing well without recurrent hemoptysis for 5 years.

Figure 2. Images of hemoptysis caused by bronchiectasis in a 54-year-old man.



A. Chest CT scan reveals bronchiectasis in the lingular division of the left upper lobe (arrow).

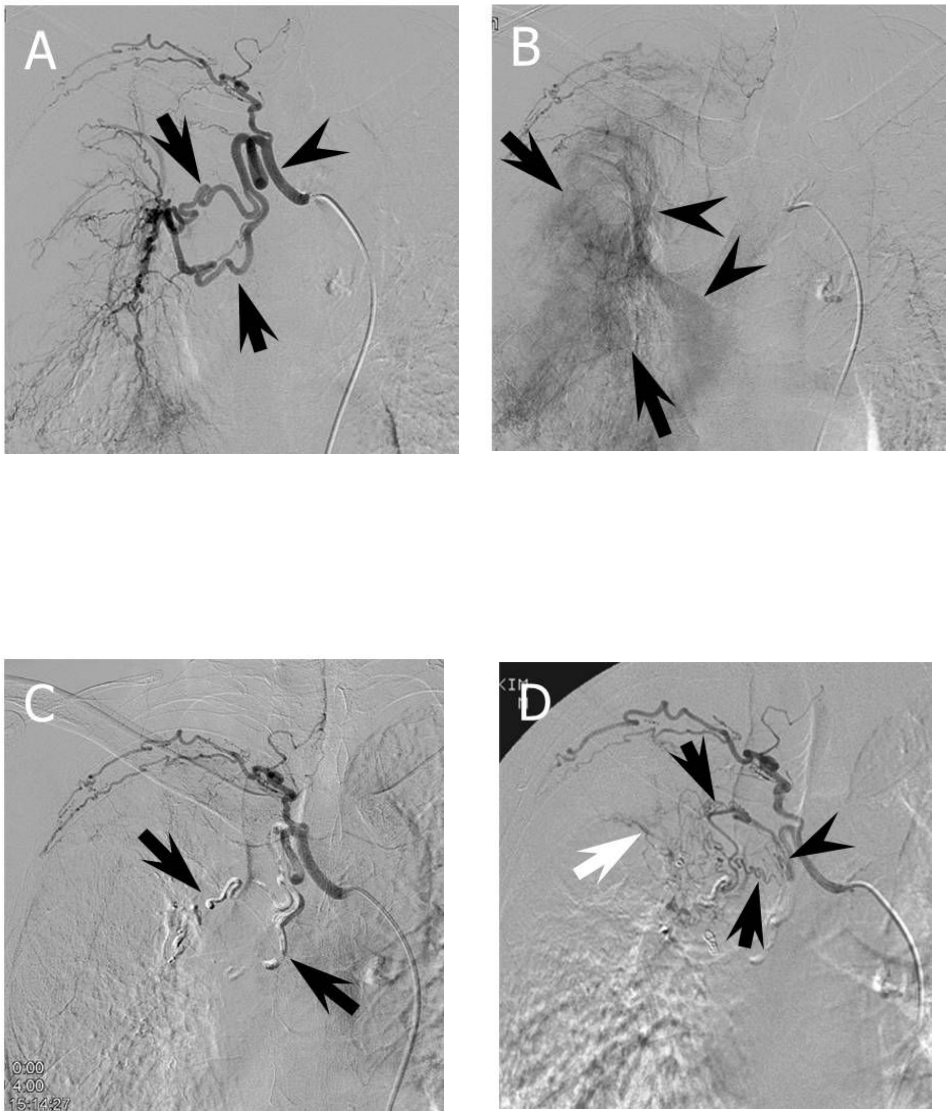
B. Selective arteriogram of the left bronchial artery shows engorgement of the left bronchial artery (arrow) and hypervascular staining in the left lower lung zone (arrowheads).

C. Stasis of contrast media is seen at selective left bronchial arteriogram after embolization with PVA particles sized 250-355 μm (arrow).

D. Left bronchial arteriography performed two years later at the second repeat bronchial artery embolization procedure reveals recanalization of the left bronchial artery (arrow) with residual hypervascular staining in the left lower lung zone (arrowheads).

E. Owing to recurrent hemoptysis, left upper lobe lingular segmentectomy was performed. Gross specimen reveals bronchiectasis (arrows).

Figure 3. Images of hemoptysis from pulmonary tuberculosis in a 77-year-old man.



A. Bronchial arteriogram shows an engorged right bronchial artery (arrows) issued from the intercostobronchial trunk (arrowhead).

B. On delayed image, ill-defined hypervascular parenchymal lesion (arrows) from bronchial-pulmonary shunting and filling of the pulmonary veins were observed (arrowheads).

C. The right bronchial artery is completely embolized with NBCA-iodized oil mixture (ratio 1:3) (arrows).

D. The patient had recurrent hemoptysis 15 months later. Bronchial arteriogram shows recruitment of new collateral circulation (black arrows) from the stump of previously embolized right bronchial artery (arrowhead). Note opacification of pulmonary shunt (white arrow).

Figure 4. Kaplan-Meier curves of the hemoptysis-free survival of the patients who were clinically successful after bronchial artery embolization stratified based on the embolic material used. (Hazard ratio: 2.082; 95% CI = 1.174, 3.692; $P = .012$ using Cox proportional regression analysis).

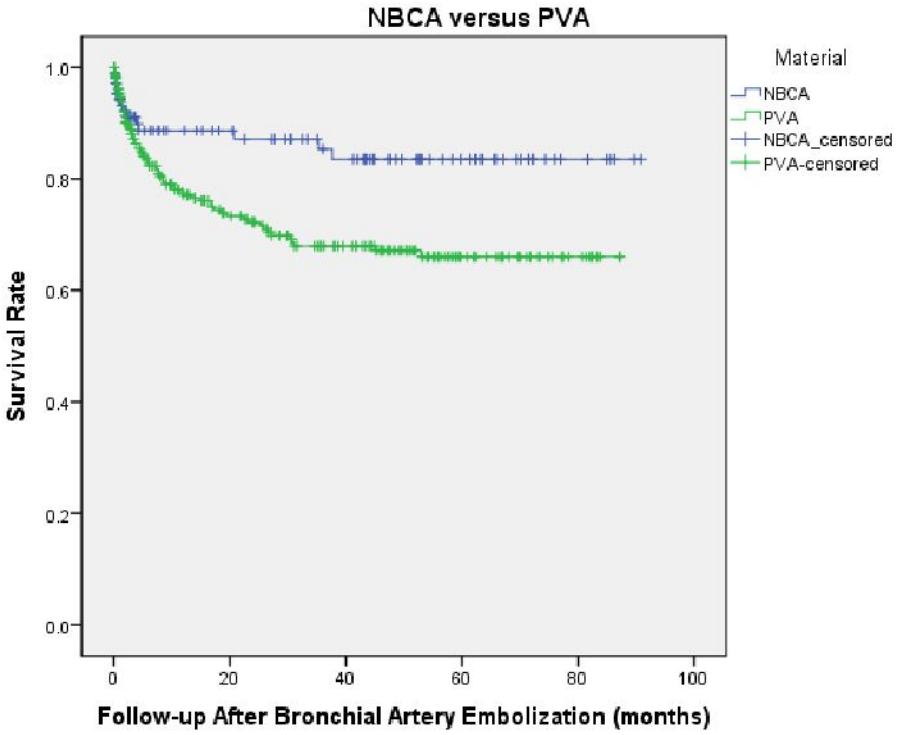


Figure 5. Kaplan-Meier subgroup analysis of the hemoptysis-free survival of patients with bronchiectasis stratified to the embolic material. (Hazard ratio: = 7.991; 95% CI = 1.079, 59.186; *P* = 0.042)

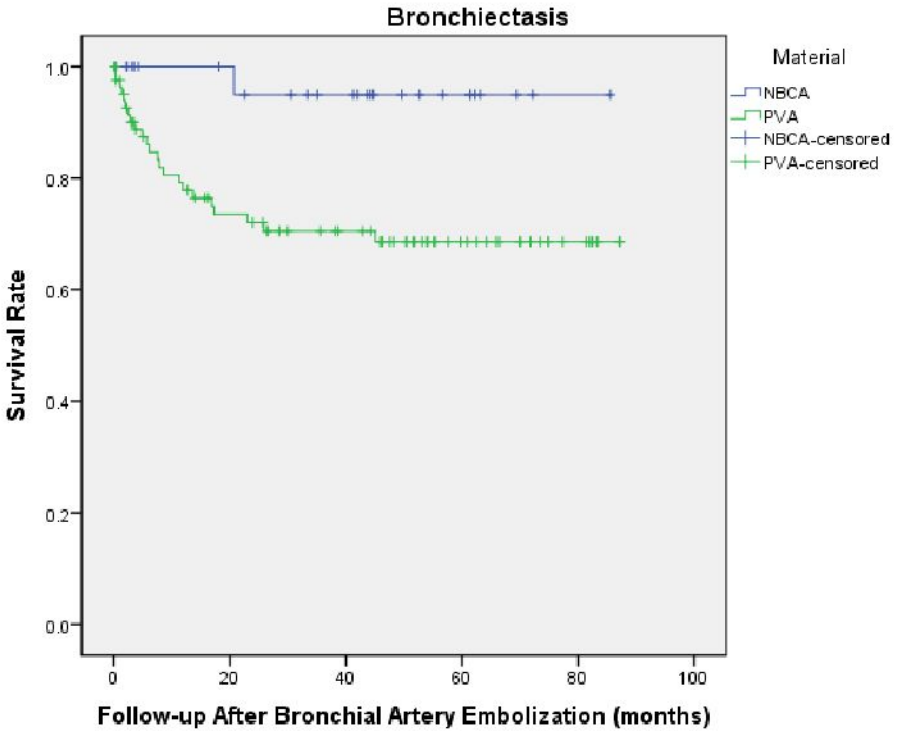
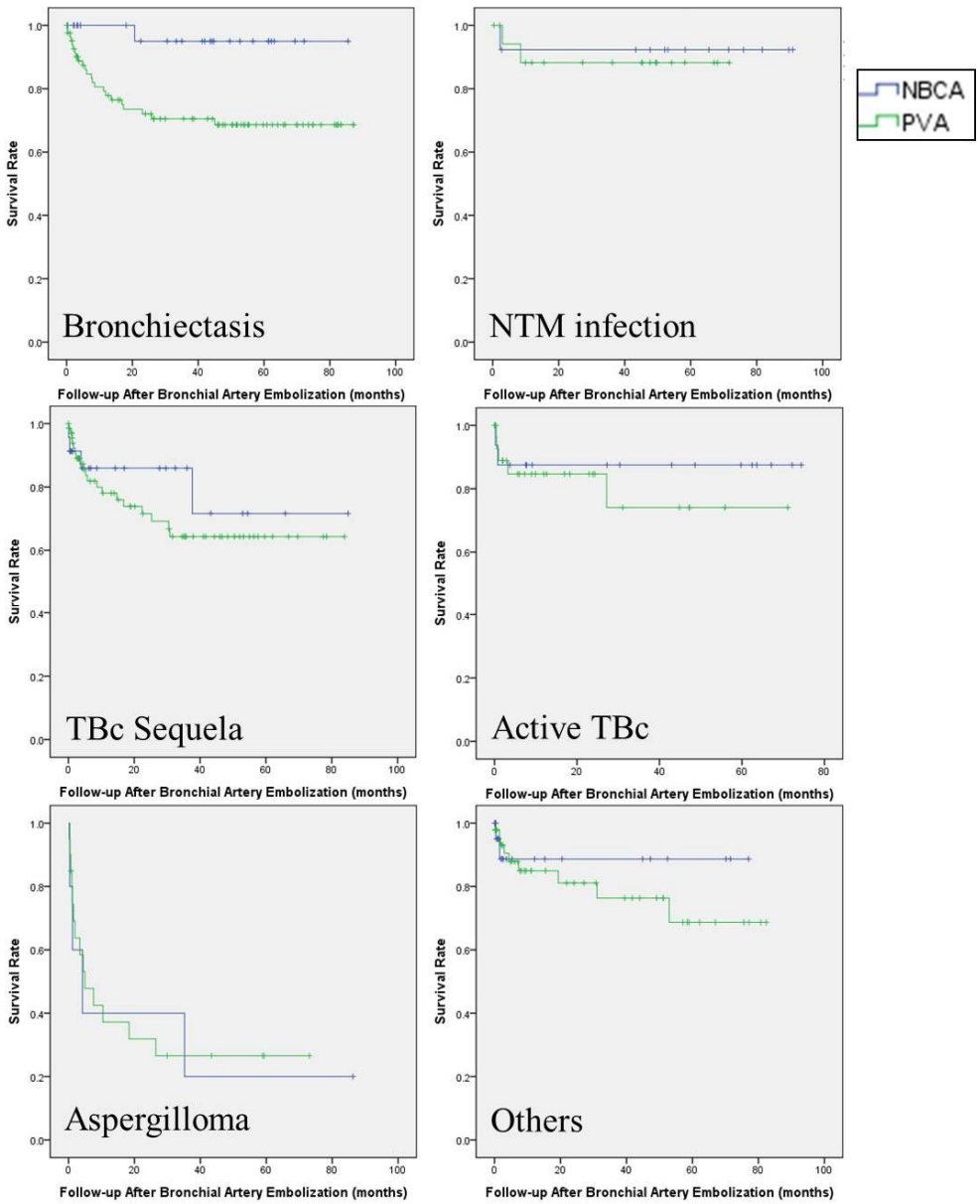


Figure 6. Kaplan-Meier subgroup analysis of the hemoptysis-free survival of patients with etiology other than bronchiectasis stratified to the embolic material. (Tuberculous sequel, P = .490; active tuberculosis, P = .545; nontuberculous mycobacterial infection, P = .784; aspergilloma, P = .852; and others, P = .545)



DISCUSSION

In our retrospective study, we evaluated NBCA as an embolic agent for BAE. The technical success was achieved in most patients (96.5%). Of note, instant hemostasis was achieved in all but one patient. This result supports previously published studies suggesting that NBCA is a promising embolic agent for BAE (7, 13, 14). The advantages of NBCA as an vascular embolic agent include: i) it is a potent embolic agent providing rapid and effective embolization, ii) it readily mixes with an iodized oil to become radiopaque for easy visualization on fluoroscopy, iii) the mixing ratio with iodized oil can be changed to adjust the time to polymerization, iv) emboli can be configured for vessels with multiple anastomoses (22, 23).

Our results demonstrated that NBCA was better than PVA in preventing recurrent hemoptysis. The 1-, 3-, and 5-year hemoptysis-free survival rates in the patients who received BAE using NBCA (88%, 85%, and 83%, respectively) were significantly higher than those using PVA (77%, 68%, and 66%, respectively). This benefit of NBCA was also evident on multivariate analysis, which indicated that the use of NBCA was an independent protective factor for recurrent hemoptysis (hazard ratio = 1.787; 95% CI = 1.001, 3.189 for using PVA). We believe that this enhanced effectiveness can be at least partly explained by the fact that NBCA was a more durable embolic material than PVA in our study. Angiography on repeat BAEs showed that the same-vessel recanalization rate was 19.0% in the PVA group and only 1.8% in the NBCA group, differences that were significant (P = .001). Our

results are in agreement with a previous report that demonstrated that NBCA (8 of 36 procedures) showed less frequent same-vessel re-embolization than PVA (1 of 12 procedures) (13). Similarly, other investigators reported that no recanalization was found in 319 arteries embolized with NBCA during a median follow-up of 28.5 months (7). The reason why BAE using NBCA resulted in a lower recanalization rates may be explained by the difference in level of embolization. NBCA, which is semi-fluid in character, comes out as droplets of 1-2mm from the microcatheter tip rendering it possible to reach and occlude the distal vascular beds. On the other hand, PVA particles, especially with sizes larger than 500μm, can aggregate and form plugs resulting in premature embolization proximal to the intended level (14).

At subgroup analysis stratified to the cause of hemoptysis, we observed that the use of NBCA was associated with longer hemoptysis-free survival only in patients with bronchiectasis. Among the underlying causes, patients with aspergilloma showed earlier recurrence than those with all other causes. In addition, the subgroup with tuberculous sequela showed earlier recurrence than those with nontuberculous mycobacterial infection. Our results agree with those in the previous reports which have also shown that aspergilloma and tuberculosis sequela were risk factors for recurrence (24-26). This may be attributed to the nature of these diseases. Chronic tuberculosis and aspergilloma are known for their aggressive and extensive disease process recruiting more feeding arteries, especially nonbronchial systemic collaterals than other pulmonary diseases. Therefore, when performing BAE, they often require embolization of a larger number of feeding vessels (24-26). This may be associated with our result that NBCA did not show longer hemoptysis-free

survival rates than PVA in these subgroups. Even though NBCA may resist recanalization for a longer duration, the benefit seems to be less likely to take effect in those diseases with frequent recruitment of new feeding vessels. In addition, complete embolization of all feeding vessels may be difficult to achieve in these subgroups than patients with bronchiectasis (27).

In our study, we found that the overall (31.0% and 34.1%, respectively) and major complication rates (0% and 0.3%, respectively) of the NBCA and PVA groups did not show significant differences. There was a single case that was considered a major complication, in which BAE using PVA resulted in lower extremity weakness. Such complications, probably due to nontarget embolization of the spinal artery or vertebral artery, are the most dreaded among the complications of BAE. There has been concern that liquid embolic materials including NBCA may increase the risk of nontarget embolization: with wedge positioning of the catheter in the target artery, interrupted antegrade flow may block the distal movement of liquid embolic material, and cause early back flow, leading to uncontrolled reflux into nontarget arteries (14). In addition, the polymerized NBCA that has adhered to the tip of the microcatheter could be detached during withdrawal of the microcatheter after NBCA injection (13). Although we did not experience those complications, extreme caution should be taken during the procedures.

Another concern regarding liquid embolic agents is the possibility of necrosis of tissues including the aorta or bronchi (1, 13, 28). However, no patient in our study experienced this. Furthermore, no evidence of lung parenchymal ischemia or airway abnormality was found on follow-up CT and bronchoscopy. This is in

agreement with recent studies that performed BAE using NBCA and reported no significant complications associated with tissue necrosis (7, 13, 14). Recently, Ikoma et al. (29) performed pathologic evaluation of a resected lung from a patient treated by BAE with NBCA and demonstrated that although NBCA was observed in bronchial arteries ≤ 300 μm in diameter, it caused no ischemic damage to the bronchial artery or pulmonary parenchyma. Therefore, unlike the conventional concern, we believe that NBCA is a safe embolic agent not causing tissue necrosis in BAE.

Our study has some limitations. First, it was a retrospective study, with all its inherent limitations. In addition, there were difference in baseline characteristics between the PVA group and the NBCA group, although not found to be statistically significant. In order to counterbalance this, we evaluated for the independent predictive factors with multivariate analysis, and also performed a subgroup analysis stratified to the cause of hemoptysis. Still, randomized controlled trials are required in order to confirm the benefit of NBCA compared to conventional embolic agents. Second, the choice between NBCA and PVA was determined by the attending interventional radiologists' discretion. Therefore, the indication of NBCA could not be well-defined, and this may have caused bias on our results. It must be pointed out that the etiology of hemoptysis may vary among different countries, and caution is required in extending our results to different institutions.

In conclusion, our study indicated that BAE using NBCA provided higher hemoptysis-free survival rates compared with that using PVA particles. This improvement was more evident in patients with bronchiectasis and seems to be

caused by a more durable embolic effect of NBCA than PVA. In addition, unlike the conventional concern regarding tissue ischemia, there was no evidence of increased complication related to NBCA.

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초 록 (국문)

서론: 객혈의 치료에 있어 엔부틸시아노아크릴레이트 (NBCA)와 폴리비닐 알코올 입자 (PVA)의 안전성과 효용성을 후향적으로 평가해 본다.

방법: 본 연구는 임상연구심의위원회 승인을 받았으며, 후향적 연구로서 사전 동의는 면제되었다. 2005년 1월부터 2008년 12월까지 대량 객혈로 406명의 환자 (남:녀 = 242:164; 평균 나이 = 6-92세)가 PVA (n = 293) 혹은 NBCA (n = 113)를 이용하여 기관지 동맥 색전술을 시행 받았다. 기술적 성공률, 임상적 성공률, 합병증, 무 객혈 생존율, 객혈 재발의 원인을 PVA와 NBCA 군 간에 비교하였다. 무 객혈 생존율의 차이는 기저 질환 군 별로 하위분석을 하였다. 객혈 재발에 대한 예측 인자는 콕스 비례 위험 회귀 모델을 이용하여 분석하였다.

결과: 기술적 성공률은 PVA와 NBCA 군에서 각각 93.9% (275/ 293)와 96.5% (109/113)으로 유의한 차이가 없었다 (P = 0.463). 임상적 성공률은 PVA와 NBCA 군에서 각각 92.2% (270/293)와 96.5% (109/ 113)으로 유의한 차이가 없었다 (P = 0.180). 1-, 3-, 5-년 무 객혈 생존율은 PVA 군에서 77%, 68%, 66%이었으며 NBCA 군에서는 88%, 85%, 83%이었다 (P = 0.010). 색전을 시행한 혈관의 재개통률은 PVA군 (21.5%)에서 NBCA 군 (1.8%)보다 유의하게 높았다 (P < 0.001). 기관지 확장증 환자의 하위군에서 NBCA 군이 PVA 군보다 높은 무 객혈 생존율을 보였다 (P = 0.016). PVA의 사용 (P = 0.050)과 아스페르길루스 종 (P < 0.001)은 객혈

재발의 유의한 예측 인자로 나타났다.

결론: NBCA를 사용한 기관지 동맥 색전술은 PVA를 사용하는 것 보다 합병증율을 증가시키지 않으면서도 더 높은 무 객혈 생존율을 보였다. 이는 특히 기관지 확장증 환자들에서 분명하였고, PVA 입자와 비교하였을 때 NBCA의 색전 효과가 내구성이 더 우수하기 때문으로 생각된다.

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주요어: 객혈, 기관지 동맥 색전술, N-butyl 2-cyanoacrylate, Polyvinyl alcohol 입자

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