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Clinical Outcomes of Bronchoscopic Cryotherapy for Central Airway Obstruction in Adults: An 11-Years' Experience of a Single Center

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ABSTRACT

Background: Although bronchoscopic cryotherapy (BC) is a pragmatic modality for recanalization of central airway obstruction (CAO), the risk of complications, such as bleeding, remains a concern. This study aimed to present the clinical outcomes of BC and evaluate the factors associated with its complications.
Methods: In this retrospective study, we reviewed the medical records of patients who underwent BC for CAO at the Asan Medical Center, South Korea. Most sessions were conducted via flexible bronchoscopy under moderate sedation. A multivariate logistic regression analysis was used to identify the factors associated with the success rate and complications.
Results: BC was performed in 262 sessions in 208 patients between January 2009 and December 2020. The most common cause of cryotherapy was recanalization of the endobronchial tumor related CAO (233/262, 88.9%). More than partial re-establishment of airway patency was achieved in 211 of 233 (90.6%) sessions. The success rate did not differ significantly in the multivariate logistic regression analysis. The most common complication was intrabronchial bleeding (78/233, 35.5%); however, severe bleeding occurred only in one case (0.4%). Univariate and multivariate logistic regression analyses revealed that diabetes mellitus (odds ratio [OR] = 2.820, P = 0.011), respiratory failure before BC (OR = 3.546, P = 0.028), and presence of distal airway atelectasis (OR = 0.417, P = 0.021) were independently associated with moderate to severe intrabronchial bleeding, while the histologic type of tumor was not related to bleeding. BC for CAO caused by blood clot or foreign body was successful in most cases, and there were no complications.
Conclusion: BC is an efficient and relatively safe intervention for patients with CAO. Our findings suggest that diabetes, respiratory failure before BC, and the absence of distal airway atelectasis may be risk factors of moderate to severe intrabronchial bleeding.

Keywords: Cryotherapy; Recanalization; Central Airway Obstruction; Complication

INTRODUCTION

Airway obstruction commonly manifests as acute respiratory symptoms and is related to increased morbidity and mortality. It is mainly caused by malignancy such as primary

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endobronchial carcinoma or metastatic carcinoma of the airway. Furthermore, benign tumor, blood clot, and foreign body can cause airway obstruction.[1] It is known that approximately 30% of patients with lung cancer may experience an episode of airway obstruction with associated complications.[1-3] Clinical manifestations of airway obstruction vary depending on the location and the degree of airflow limitation, as well as the underlying causes. In the case of mild or peripheral airway obstruction, the patient tends to be asymptomatic. On the other hand, symptoms including cough, hemoptysis, wheezing, stridor and dyspnea can develop when the airflow limitation deteriorates, or obstruction occurs in the central airways. Even in severe cases, it can lead to atelectasis, obstructive pneumonia, and acute respiratory failure that may require urgent intervention.[4-6]

The core principle of management for central airway obstruction (CAO) is to relieve the patient's symptoms by re-establishing the airway patency. Multiple interventional techniques can be applied for restoration of airway patency including mechanical debulking by rigid bronchoscopy, electrocautery, laser therapy, airway stenting, argon plasma coagulation and cryotherapy.[7]

Endobronchial cryotherapy is a therapeutic technique that induces freezing of the tissue which can be removed from the lumen by direct application of extremely cold cryoprobe. It is mainly conducted through the working channel of a flexible or rigid bronchoscope. The tip of the cryoprobe is cooled by sudden expansion of the compressed gas cryogen such as nitrous oxide in accordance with the Joule-Thompson principle, and the cooling temperature reaches −89.5°C. The bronchoscopic cryotherapy (BC) is commonly used for biopsy, extraction of endobronchial exophytic tumor, and removal of blood clot or foreign body.[8,9] Further, Hetzel et al.[10] introduced an advanced technique in 2004 called cryorecanalization that enables rapid debulking of the occluded airways by specifically designed cryoprobe for recanalization. The BC can offer several merits, including high level of efficacy, easy to learn, inexpensive, and relatively safe.[9-11] Nonetheless, considering its invasive nature, risk of complications such as intrabronchial bleeding can be of great concern.

To our knowledge, there has been no data available on the factors associated with BC-related complications in patients with CAO. In our study, we aimed to describe the outcomes of diverse applications of BC performed at this tertiary referral center and evaluated various factors that could affect BC-related complication rate in patients with CAO.

METHODS

Study population

This study was a retrospective, single-center study at Asan Medical Center, Seoul, Republic of Korea, from January 2009 to December 2020. Eligible participants included patients who had undergone BC for various purposes such as recanalization of the obstructed airway lumen, biopsy, and foreign body removal. In addition to the BC, electrocoagulation knife, laser, rigid bronchoscopy, and extracorporeal membrane oxygenation (ECMO) were often applied simultaneously at the discretion of the interventional pulmonologist. Clinical data and baseline characteristics, including sex, age, underlying diseases, spirometry results, and smoking history were collected from medical records.

Cryotherapy process

Prior to the procedures, the interventional pulmonologists decided whether to apply flexible

or rigid bronchoscopy, general anesthesia or moderate sedation, and concomitant method such as ECMO in case of necessity, considering the condition of patients and the severity of airway obstruction. Most of the BC sessions were performed under moderate sedation using 3–5 mg of midazolam with occasional 50–100 micrograms of fentanyl intravenously. When mechanical ventilation was required because of respiratory failure or high oxygen demand before the procedure, BC was performed mainly using a rigid bronchoscope under general anesthesia. All patients were monitored through pulse oximetry, blood pressure, and electrocardiography during the procedure. For patients with uncorrectable thrombocytopenia or coagulation abnormalities, the procedure was not conducted. Moreover, all patients with a drug history of antiplatelets or anticoagulants were asked to stop these medications in advance before the procedure was initiated.

BC was mainly conducted via flexible bronchoscopy with a diameter of 5.9 mm (BF-1T260; Olympus, Tokyo, Japan); a cryoprobe (Erbokryo; ERBE, Tübingen, Germany) utilizes nitrous oxide which cools the probe tip very quickly to reach −89.5°C. During BC procedures, the bronchoscope was firstly located close to the target lesion, and then a cryoprobe was introduced through the working channel. The probe tip was placed into the exophytic mass and it froze the tissue for 15 to 60 seconds. After checking that the surrounding tissues were frozen enough through a monitor, both the frozen tissues attached to the cryoprobe and the bronchoscope were extracted simultaneously. Then, the extracted tissue was released from the tip of the cryoprobe after the procedure. This process was repeated until the obstructed airway lumen achieved a complete recanalization. After completing BC, a bronchoscopy was re-implemented to check for post-procedural airway patency and complications. **Fig. 1** shows the screen image during a BC session.

Clinical measurements

Survival after intervention was calculated as the duration from the time of the cryorecanalization session to the time of death or data collection. We examined the length of airway invasion by measuring the length of the exophytic portion on chest computed tomography. Distal airway atelectasis was defined as external compression of the distal airway lumen by the tumor or direct tumor invasion.[11] Symptom relief was defined as a medical record report of reduced oxygen requirements or improved subjective symptoms after BC. We excluded symptom relief when a patient had no oxygen requirement or subjective symptoms before the procedure.

Evaluation of outcome and safety

Re-establishment of airway patency after BC was classified into three grades[10]:

- Complete: No remaining mass or obstruction observed on bronchoscopy performed after the procedure.
- Partial: Debulked mass and partial remaining obstruction but passable with 5.9 mm bronchoscope performed after the procedure.
- None: Persistent obstruction and non-passable with 5.9 mm bronchoscope performed after the procedure.

We also classified procedure-related intrabronchial bleeding into three grades[12]:

- Mild: Bleeding which could be stopped by instillation of epinephrine solution (1mg/10mL normal saline) or cold 0.9% NaCl solution (2–4°C).
- Moderate: Bleeding which could be stopped by laser ablation or in case of administration of intravenous tranexamic acid due to hemoptysis after the procedure.

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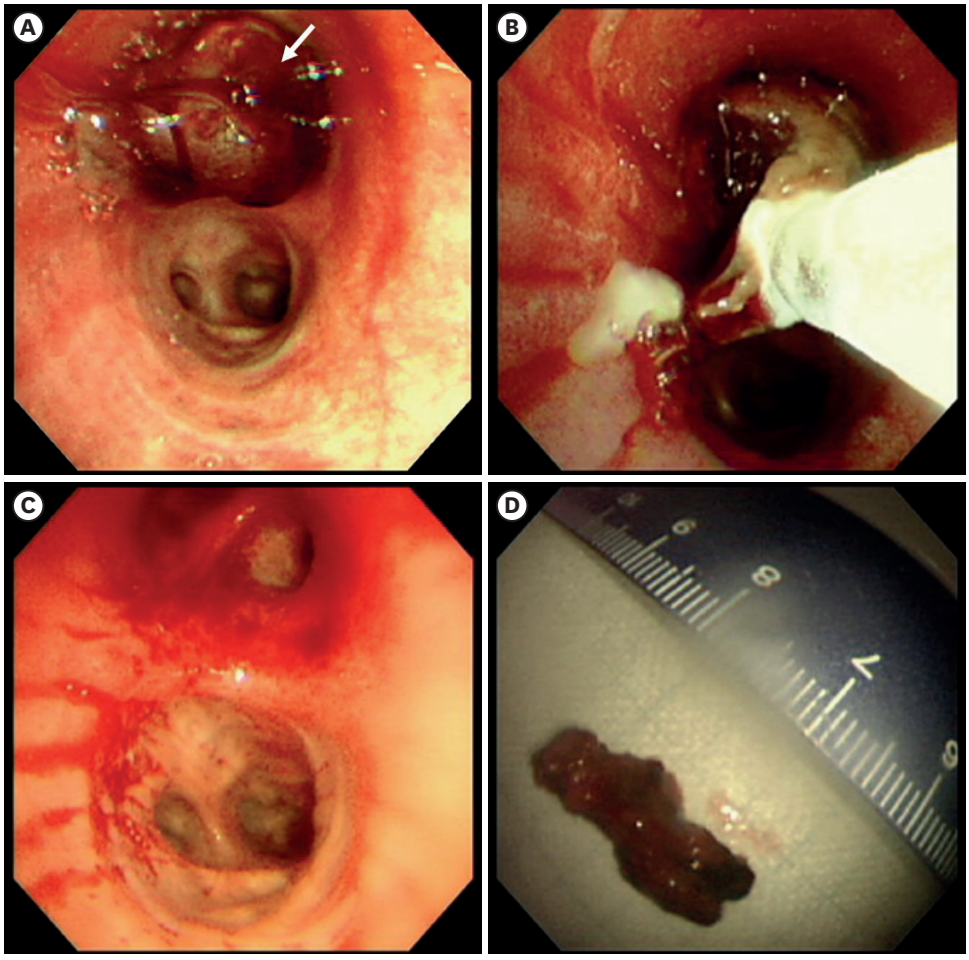
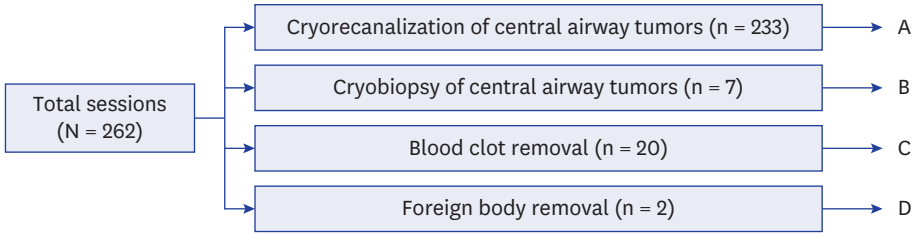


Fig. 1. Cryotherapy for endobronchial metastasis of renal cell carcinoma. (**A**) Huge exophytic tumor mass in left upper lobe bronchus (white arrow). (**B**) Freezing and extracting the tumor mass with cryoprobe. (**C**) Left upper lobe bronchus after cryotherapy. (**D**) Extracted tumor mass.

- Severe: Bleeding which required further management including transfusion of red blood cells or fresh frozen plasma, bronchial artery embolization, use of vasopressor, and application of mechanical ventilation.

We assessed the outcomes and analyses of factors associated with the success rate and moderate to severe intrabronchial bleeding. **Fig. 2** shows the flow diagram of BC sessions.



A: Analyses of factors associated with success rate (Table 3)
A + C: Assessment of outcomes according to etiology (Table 4)
A + B: Analyses of factors associated with moderate to severe intrabronchial bleedings (Table 6)

Fig. 2. Flow diagram of bronchoscopic cryotherapy sessions.

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Statistical analysis

Continuous data were described as median (interquartile range) or mean ± standard deviation, and categorical data were reported as numbers and percentage. Univariate logistic regression analysis was conducted to verify factors related to partial to complete reestablishment of airway patency and moderate to severe intrabronchial bleeding. Subsequently, multivariate logistic regression analysis was carried out on the variables whose *P* value was less than 0.1 on univariate analysis. The results were described as odd ratio (OR) with 95% confidence intervals (CIs). A Kaplan–Meier survival analysis with log-rank test was performed to evaluate survival patterns after intervention among patients with lung cancer, extrathoracic malignancies, and benign lesions. A statistical significance was considered if a *P* value was less than 0.05. Statistical analyses were implemented using Statistical Package for the Social Sciences (SPSS) version 21.0 (IBM Corporation, Armonk, NY, USA).

Ethics statement

The study protocol was approved by the Institutional Review Board of Asan Medical Center (approval No. 2021-1564). All patients provided informed consent before the BC.

RESULTS

Baseline characteristics of the patients

A total of 208 patients underwent BC at our tertiary referral center. The baseline characteristics of the patients are presented in **Table 1**. The median age was 63 years (interquartile range, 55–70 years), and 158 (76.0%) patients were men. Approximately two-thirds of the patients (n = 139, 66.8%) had a smoking history and the mean amount of smoking was 33.5 ± 18.6 pack years.

Table 1. Baseline characteristics of the study participants

Characteristics	Values
Total participants	208 (100.0)
Age, yr	63 [55–70]
Male sex	158 (76.0)
Smoking, pack-years	33.5 ± 18.6
Never	69 (33.2)
Ex-smoker	113 (54.3)
Current smoker	26 (12.5)
Pulmonary function (n = 167)[a]	
FVC, % of predicted	75.6 ± 17.7
FEV1, % of predicted	71.6 ± 18.9
FEV1/FVC ratio,	71.1 ± 13.4
DLCO, % of predicted (n = 123)[b]	68.5 ± 20.2
Underlying diseases	
History of malignancy	137 (65.9)
HTN	52 (25.0)
DM	36 (17.3)
COPD	14 (6.7)
Asthma	10 (4.8)
Chronic kidney disease	7 (3.4)
Liver cirrhosis	7 (3.4)
ILD	4 (1.9)

Values are presented as median [range], number (%), or mean ± standard deviation.
FVC = forced vital capacity, FEV1 = forced expiratory volume in 1 second, DLCO = diffusing capacity of the lung for carbon monoxide, HTN = hypertension, DM = diabetes mellitus, COPD = chronic obstructive pulmonary disease, ILD = interstitial lung disease.
[a]Data of 41 participants are missing because the patients could not undergo the pulmonary function test.
[b]Data of 85 participants are missing because the patients could not undergo the DLCO test.

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A baseline pulmonary function test was performed in most of the study participants (n = 167, 80.3%); the mean values of forced expiratory volume in 1 second (FEV1) and forced vital capacity (FVC) were 71.6 ± 18.9% and 75.6 ± 17.7%, respectively. Malignancy was the underlying disease involving the largest number of study participants (n = 137, 65.9%), followed by hypertension (HTN) (n = 52, 25%), diabetes mellitus (DM) (n = 36, 17.3%), and chronic obstructive pulmonary disease (n = 14, 6.7%).

Procedure characteristics of the cryotherapy sessions

A BC was implemented in a total of 262 sessions (**Table 2**). The most common reason for BC was cryorecanalization for tumor related CAO (n = 233, 88.9%), followed by blood clot (n = 20, 7.6%), cryobiopsy for central airway tumors (n = 7, 2.7%), and foreign body (n = 2, 0.8%). In about half of the BC sessions, the patients had dyspnea or an oxygen demand and, one out of five of them were subjected to mechanical ventilation before the procedure. Approximately 80% of BC sessions were conducted under moderate sedation, while the other sessions were conducted under general anesthesia. Total 232 sessions were performed using flexible bronchoscopy (88.5%), while the other 30 sessions were performed using rigid bronchoscopy (11.5%). Concomitant therapeutic methods included laser ablation in 54 sessions (20.6%), ECMO in 18 sessions (6.9%), stent placement in 12 sessions (4.6%), photodynamic therapy in 7 sessions (2.7%), and electrocoagulation knife in 6 sessions (2.3%).

Factors associated with the success rate of cryorecanalization for CAO

Table 3 presents the factors associated with partial to complete reestablishment of airway patency of cryorecanalization for CAO. A total of 233 cryorecanalization sessions were performed. Complete, partial, and no re-establishment of airway patency were achieved in 142 (60.9%), 69 (29.6%), and 22 sessions (9.4%), respectively. In the univariate logistic regression analysis, length of airway invasion > 2 cm was significantly associated with partial

Table 2. Procedure characteristics of cryotherapy sessions

Characteristics	Values (%)
Total number of sessions	262 (100.0)
Anesthesia	
Moderate sedation	209 (79.8)
General anesthesia	53 (20.2)
Respiratory failure before procedure	
No symptom	135 (51.5)
Dyspnea	37 (14.1)
Nasal O2 inhalation	64 (24.4)
Ventilator	26 (10.0)
Cause of cryotherapy	
Cryorecanalization of central airway tumors	233 (88.9)
Cryobiopsy of central airway lesions	7 (2.7)
Blood clot	20 (7.6)
Foreign body	2 (0.8)
Bronchoscopy	
Flexible bronchoscopy	232 (88.5)
Rigid bronchoscopy	30 (11.5)
Concomitant method	
Stent placement	12 (4.6)
Laser	54 (20.6)
Electrocoagulation knife	6 (2.3)
Photodynamic therapy	7 (2.7)
ECMO	18 (6.9)

Values are presented as number (%).
ECMO = extracorporeal membrane oxygenation.

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Table 3. Factors associated with success rate of cryorecanalization for central airway obstruction

Variables	Sessions	Reestablishment of airway patency			Univariate analysis[a]		Multivariate analysis[a]	
		Complete	Partial	None				
		No. (%)	No. (%)	No. (%)	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Total number of sessions	233	142 (60.9)	69 (29.6)	22 (9.4)				
Location								
Central[b]	178	109 (61.2)	54 (30.3)	15 (8.4)	Reference			
Peripheral[c]	55	33 (60.0)	15 (27.3)	7 (12.7)	0.631 (0.243–1.637)	0.344		
Distal airway atelectasis								
Absent	61	37 (60.7)	22 (36.1)	2 (3.3)	Reference		Reference	
Present	172	105 (61.0)	47 (27.3)	20 (11.6)	0.258 (0.058–1.137)	0.073	0.375 (0.076–1.842)	0.227
Length of airway invasion								
≤ 2 cm	101	67 (66.3)	29 (28.7)	5 (5.0)	Reference		Reference	
> 2 cm	132	75 (56.8)	40 (30.3)	17 (12.9)	0.352 (0.125–0.990)	0.048	0.486 (0.160–1.476)	0.203

OR = odds ratio, CI = confidence interval
[a]Factors associated with partial to complete reestablishment of airway patency were analyzed using univariate and multivariate logistic regression analyses.
[b]The location of the central type included the trachea, carina, both main bronchi, and right bronchus intermedius.
[c]The location of the peripheral type included the lobar bronchus.

to complete reestablishment of airway patency. However, the multivariate logistic regression analysis showed no statistical significance (OR = 0.486, *P* = 0.203).

Outcomes of cryotherapy for CAO according to the etiology

Table 4 shows the outcomes of cryotherapy for CAO according to etiology including blood clot. Post-procedural symptom relief was found in 93/125 (74.4%) sessions, and mean survival after intervention was 30.5 ± 39.2 months. In about half of all the sessions, the underlying etiology was non-small cell lung cancer (NSCLC); outcomes of re-establishment of airway patency and symptom relief were reported in 118/127 (92.9%) and 53/71 (74.6%) sessions, respectively, and the mean survival after intervention was 23.1 ± 34.3 months. The success rate of cryorecanalizaion for benign tumors was similar to the overall results (22/24, 91.7%). Blood clot extraction was performed in 20 sessions; it failed in only one session. In the Kaplan–Meier curve, the survival probability after intervention was significantly higher in patients with benign lesions (log-rank test $P < 0.001$; **Fig. 3**), while there was no significant difference in the survival probability between patients with lung cancer and those with extrathoracic malignancies (log-rank test $P = 0.446$; **Fig. 3**).

Table 4. Outcomes according to etiology of cryorecanalization for central airway obstruction

Variables	No. of sessions	Reestablishment of airway patency			Symptom relief[a]	No. of patients	Survival after intervention, mon[b]
		Complete	Partial	None			
		No. (%)	No. (%)	No. (%)	No. (%)		Mean ± SD
Total	253	161 (63.6)	69 (27.3)	23 (9.1)	93/125 (74.4)	202	30.5 ± 39.2
Malignancy							
NSCLC	127	81 (63.8)	37 (29.1)	9 (7.1)	53/71 (74.6)	100	23.1 ± 34.3
SCLC	6	3 (50.0)	2 (33.3)	1 (16.7)	2/4 (50.0)	4	6.7 ± 6.1
Metastasis of thyroid cancer	8	3 (37.5)	5 (62.5)	0 (0.0)	0/0	3	13.1 ± 11.6
Metastasis of colon cancer	7	5 (71.4)	2 (28.6)	0 (0.0)	2/2 (100.0)	6	14.7 ± 12.9
Metastasis of RCC	35	21 (60.0)	9 (25.7)	5 (14.3)	10/13 (76.9)	22	29.9 ± 29.4
Metastasis of HCC	8	4 (50.0)	4 (50.0)	0 (0.0)	6/6 (100.0)	7	7.9 ± 7.1
Other malignancy	18	10 (55.6)	3 (16.7)	5 (27.8)	5/8 (62.5)	16	40.1 ± 50.9
Benign lesion	24	15 (62.5)	7 (29.2)	2 (8.3)	5/6 (83.3)	24	72.3 ± 45.0
Blood clot	20	19 (95.0)	0 (0.0)	1 (5.0)	10/15 (66.7)	20	-

SD = standard deviation, NSCLC = non-small cell lung cancer, SCLC = small cell lung cancer, RCC = renal cell carcinoma, HCC = hepatocellular carcinoma.
[a]Data from 125 sessions are included, after excluding patients with no oxygen requirement or subjective symptoms of dyspnea before the procedure.
[b]For patients who underwent more than one intervention, calculations were based on the date of the first intervention. Patients with blood clots were excluded.

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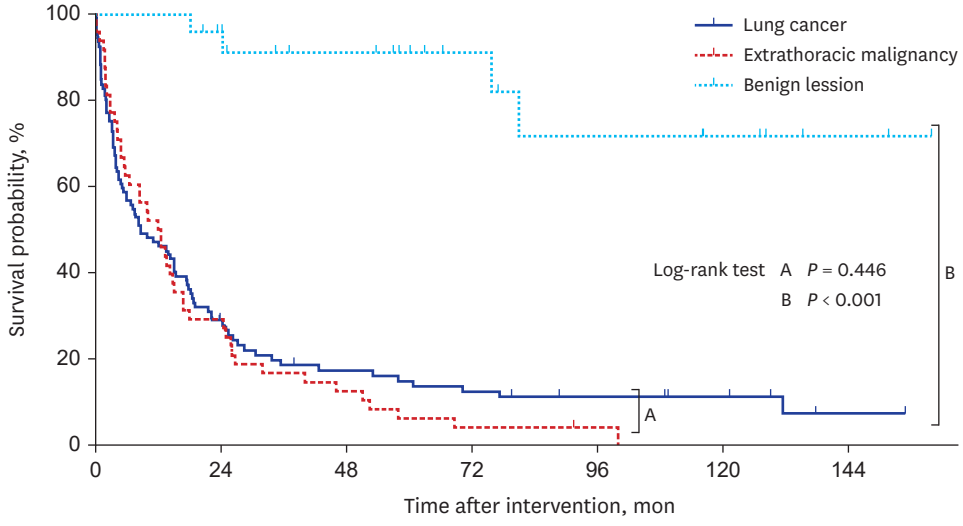

No. at risk[a]							
Lung cancer	104	26	14	10	7	5	1
Extrathoracic malignancy	48	14	6	2	1	0	0
Benign lession	24	21	16	10	7	5	2

Fig. 3. The Kaplan–Meier survival curve showing the survival patterns after intervention in patients with lung cancer, extrathoracic malignancies, and benign lesions.
[a]The initial number of patients was based on what is presented in **Table 4**. Six patients who could not be categorized were excluded.

Safety profile

The safety profile is described in **Table 5**. All the procedure-related complications occurred only in cryorecanalization sessions. Intrabronchial bleeding occurred in 78 of 233 sessions. One patient died of severe bleeding and respiratory failure after BC. No other complications were reported.

Factors associated with moderate to severe intrabronchial bleeding

Table 6 shows the factors associated with moderate to severe intrabronchial bleeding. In the univariate logistic regression analysis, old age (≥ 75 years), DM, HTN, location in upper lobe, stent placement, respiratory failure before BC, and the presence of distal airway atelectasis were associated with moderate to severe intrabronchial bleeding. The results of multivariate

Table 5. Safety profile

Variables	Values
Cryorecanalization	233
Total bleeding	78 (33.5)
Mild	12 (5.6)
Moderate	65 (27.9)
Severe	1 (0.4)
Respiratory failure	1 (0.4)
Death	1 (0.4)
Cryobiopsy	7
Complication	0 (0.0)
Blood clot	20
Complication	0 (0.0)
Foreign body	2
Complication	0 (0.0)

Values are presented as number (%).

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Table 6. Univariate and multivariate analyses of factors associated with moderate to severe intrabronchial bleeding (sessions N = 240)

Variables	Univariate analysis		Multivariate analysis	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Female sex	1.227 (0.626–2.402)	0.551		
Old age (≥ 75 years)	2.646 (1.067–6.565)	**0.036**	1.943 (0.714–5.290)	0.194
Smoking history (≥ 30 PYs)	0.872 (0.491–1.549)	0.641		
FEV1 < 50%	1.464 (0.635–3.378)	0.371		
Comorbidity				
DM	2.235 (1.124–4.446)	**0.022**	2.820 (1.273–6.247)	**0.011**
HTN	2.045 (1.103–3.791)	**0.023**	1.609 (0.798–3.242)	0.183
COPD	1.477 (0.798–2.734)	0.214		
Chronic kidney disease	1.056 (0.200–5.582)	0.949		
Liver cirrhosis	2.714 (0.534–13.800)	0.229		
Location				
Trachea & carina	Reference		Reference	
Right main bronchus	0.799 (0.375–1.702)	0.561	0.745 (0.318–1.745)	0.498
Left main bronchus	0.822 (0.356–1.900)	0.647	0.926 (0.366–2.347)	0.872
Upper lobe	0.305 (0.092–1.003)	**0.051**	0.356 (0.102–1.250)	0.107
Middle lobe	2.056 (0.377–11.213)	0.405	1.282 (0.216–7.606)	0.785
Lower lobe	0.685 (0.232–2.022)	0.493	0.757 (0.243–2.358)	0.631
Etiology				
NSCLC	Reference			
SCLC	0.500 (0.057–4.422)	0.533		
Metastasis of thyroid cancer	2.500 (0.595–10.510)	0.211		
Metastasis of colon cancer	0.417 (0.049–3.578)	0.425		
Metastasis of RCC	0.741 (0.309–1.775)	0.501		
Metastasis of HCC	2.500 (0.595–10.510)	0.211		
Benign	0.833 (0.307–2.260)	0.720		
Other malignancy	0.667 (0.208–2.138)	0.495		
Stent placement	2.800 (0.870–9.016)	**0.084**	2.921 (0.808–10.557)	0.102
Respiratory failure before BC	3.767 (1.341–10.578)	**0.012**	3.546 (1.148–10.951)	**0.028**
Distal airway atelectasis				
Absent	Reference		Reference	
Present	0.540 (0.291–1.003)	**0.051**	0.417 (0.199–0.875)	**0.021**
Length of airway invasion				
≤ 2 cm	Reference			
> 2 cm	0.715 (0.404–1.265)	0.249		

Bold-styled *P* values means statistically significant results.
OR = odds ratio, CI = confidence interval, PYs = pack-years, FEV1 = forced expiratory volume in 1 second, DM = diabetes mellitus, HTN = hypertension, COPD = chronic obstructive pulmonary disease, NSCLC = non-small cell lung cancer, SCLC = small cell lung cancer, RCC = renal cell carcinoma, HCC = hepatocellular carcinoma, BC = bronchoscopic cryotherapy.

logistic regression analysis revealed that DM, respiratory failure before BC, and the presence of distal airway atelectasis were independently associated with moderate to severe intrabronchial bleeding (OR = 2.820, *P* = 0.011; OR = 3.546, *P* = 0.028; OR = 0.417, *P* = 0.021, respectively).

DISCUSSION

In this retrospective study, more than partial success rate of re-establishment of airway patency through BC was 90.6%. The most common BC-related complication was intrabronchial bleeding. DM, respiratory failure before BC, and the absence of distal airway atelectasis were independently associated with higher risks of moderate to severe intrabronchial bleeding, whereas the tumor type was not related to bleeding complications.

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Several previous studies have reported that the success rates of restoration of airway patency after BC were 72.5–95%.[10-13] In this study, we found quite a remarkable success rate of 90.6% compared to that of previous findings. It is noteworthy that most sessions of our study were conducted under moderate sedation (79.8%) with flexible bronchoscope (88.5%), whereas the existing researches that have reported excellent outcomes mainly applied general anesthesia with rigid bronchoscope.[13] In addition, this study presented mostly satisfactory success rates regardless of anatomical locations and even in the case of a length of airway invasion > 2 cm.

Yilmaz et al.[11] reported successful recanalization after BC was independently associated with the absence of distal bronchial involvement and a duration of ≤ 6 weeks of obstruction. Hetzel et al.[10] also suggested that cryorecanalization usually failed when the tumor obstruction was extensive and the distal airway could not be reached. The present study showed no significant association in the success rate of cryorecanalization with the length of airway invasion or presence of distal airway atelectasis in the multivariate logistic regression analysis, although a statistical trend was found in the univariate analysis. Therefore, the present study suggests that even when airway invasion is fairly extensive or distal airway atelectasis is present, we can try cryorecanalization without significant differences in the success rate. Further well-designed clinical trials are required to validate these results.

In most previous studies of BC, there were no reports of severe complications related to the procedures, and the most common complication reported was intrabronchial bleeding.[14] Post-BC bleeding complications have been reported in 10.0–20.9% of the cases, in rare cases, pneumothorax, pneumomediastinum, and hypoxic respiratory failure followed after the procedure.[10,12,15,16] Similarly, in our study, the most common type of BC related complication was found to be intrabronchial hemorrhage, and the rate was 33.5%, which was relatively higher than that of the previous studies. Meanwhile, an interesting thing about the safety profile in this study was that no complications occurred during the BC sessions other than cryorecanalization such as cryobiopsy, and blood clot or foreign body removal. A severe complication was reported in only one patient of the total participants. The patient in whom both the main bronchi were obstructed due to metastatic tumor mass of renal cell carcinoma had undergone cryorecanalization; however, the post-procedural intrabronchial bleeding was not controlled although the recanalization was successfully conducted. After that mechanical ventilator and ECMO were applied since respiratory failure occurred, and eventually the patient died.

Diabetes mellitus is one of the most critical and widespread chronic metabolic disorder that can cause several complications, and sometimes can be life threatening.[17] The main complications associated with DM are macrovascular and microvascular diseases like nephropathy, retinopathy, and cardiovascular disease.[18] This study revealed that patients with DM have an increased risk of moderate to severe intrabronchial bleeding. To our knowledge, there is no previous study that has found the association between DM and BC related bleeding complications. In addition, the physiological mechanisms of increased bleeding risk in patient with DM are poorly understood. Some studies have described that long-lasting hyperglycemia can progressively damage vascular endothelium and eventually result in structural changes of blood vessels.[19] It can also cause increased level of chronic inflammation arising from excessive immune response that may be involved in diabetic angiopathy.[20] Considering the above two theories, it is reasonable to hypothesize that persistent vascular injury and inflammation in patients with DM can lead to increased risk of bleeding in BC. Further research is needed to validate this issue. Nonetheless, this is the first study to show that DM is an important factor for BC related bleeding complications,

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therefore, we need to check for the presence of DM during preoperative assessment in order to control predictable complications.

Respiratory failure before BC is another factor that is independently associated with increased procedure-related bleeding risk. In this study, since it was defined as the case of applying mechanical ventilator before procedure, there was a tendency for the patients to have a high tumor burden and severe airway obstruction. Therefore, the incidence of procedure-related intrabronchial bleeding might be increased because the intervention was inevitably conducted more invasively. A well-established upper airway by endotracheal tube and deep sedation can also be another reason in that it enables us to perform aggressive tumor debulking for a longer time.

In the present study, the risk of moderate to severe intrabronchial bleeding was significantly low when distal airway atelectasis was present. A previous study described that when lung atelectasis occurred, hypoxic pulmonary vasoconstriction occurred in response to alveolar hypoxia.[21] It is a compensatory mechanism to reduce pulmonary shunt and has been widely used in thoracic surgery to reduce blood flow to the nonventilated lung. Thus, the presence of distal airway atelectasis indicated the risk of intrabronchial bleeding during BC, which could decrease because hypoxic pulmonary vasoconstriction could reduce blood supply around the target lesion.

Based on prior researches, renal cell carcinoma which metastasized to the airway has been reported as a high risk of bleeding during intervention due to hyper-vascularity in pathology.[22,23] Even studies have been reported that bronchial arterial embolization prior to bronchoscopic intervention was performed in patients with metastatic renal cell carcinoma in order to reduce severe bleeding complications.[24,25] In our study, we conducted 35 sessions of BC for metastatic renal cell carcinoma; however, no increase in moderate to severe intrabronchial bleeding was found, although the only one post-BC death was the patient with renal cell carcinoma. Moreover, there was no significant association between the histologic type of tumor and moderate to severe intrabronchial bleeding. Another notable thing was that no complications occurred in the participants regarding BC for simple cryobiopsy, blood clot or foreign body removal apart from recanalization of tumor related airway obstruction. Further evaluation is needed through a large-scale prospective clinical trial in the future.

This study had some limitations. First, our study was performed as a retrospective and single-center study, so the possibility of selection bias could not be excluded. However, our center is one of the largest tertiary referral hospitals in the country; the sample size was relatively large compared to other previous studies. Second, since all the information was obtained based on medical records and images, there were some indeterminate cases in a few factors such as symptoms relief. However, we performed the analysis of all the cases without exception in most major factors, and recorded the number of valid cases separately for the factors with indeterminate cases. Third, the analysis of survival after intervention was incomplete. Patients who underwent BC, which was performed later in the study, had a relatively short follow-up duration; thus, the Kaplan–Meier survival analysis was conducted to complement this limitation. However, further evaluations, including survival gain related to BC, through a well-designed and large-scale prospective clinical trial are needed in the future.

In conclusion, BC is an efficient and relatively safe interventional technique to achieve a re-establishment of airway patency in patients with CAO. Considering that DM and respiratory

failure before BC were found to be risk factors of moderate to severe intrabronchial bleeding in this study, a careful preoperative assessment reflecting these factors can be important to reduce avoidable complications. Additionally, we could attempt cryorecanalization with safety and a comparable success rate even in the presence of distal airway atelectasis or extensive airway invasion.

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