A Higher Restenosis Rate of Benign Endobronchial Mass after Cryotherapy in Endobronchial Tuberculosis

Fu-Tsai Chung[#,1,3], Hao-Cheng Chen[#,2], and Chun-Liang Chou[3]

[1]Department of Thoracic Medicine, Saint Paul's Hospital, Taoyuan, Taiwan;
[2]Department of General Medicine, Saint Paul's Hospital, Taoyuan, Taiwan;
[3]Department of Thoracic Medicine, Chang Gung Memorial Hospital at Linkou, Chang Gung University, College of Medicine, Taipei, Taiwan

Abstract

Management of benign endobronchial mass with central airway obstruction remains challenging. The benefits and outcomes of cryotherapy in benign diseases are not clear, especially endobronchial tuberculosis. We collected medical records of patients with benign endobronchial mass who received cryotherapy and refused surgery as the first choice of treatment. Between 2007 and 2011, 16 patients were included. The leading diagnosis was endobronchial tuberculosis (n = 9, 56.25%), followed by non-tuberculosis granuloma (n = 2, 12.5%), leiomyoma (n = 2, 12.5%), foreign body (n = 2, 12.5%), and chondroma (n = 1, 6.25%). The overall incidence of endobronchial lesion re-stenosis post-cryotherapy was 31.25% (5/16 patients). Patients with endobronchial tuberculosis had a higher re-stenosis rate, necessitating management, than patients with other diagnoses (56.25% vs. 0%; *p* value, 0.0174). The median follow-up duration of the patients was 15.25 months (n = 16; interquartile range, 7-36.13 months). The cumulative re-stenosis rate of endobronchial lesions was also higher in patients with endobronchial tuberculosis (80%; median duration, 17 months; *p* value, 0.036). Cryotherapy is feasible for the management of benign endobronchial mass. Among patients with endobronchial tuberculosis after cryotherapy removal, completed anti-tuberculosis treatment and regular follow-up are mandatory for higher restenosis rate. However, surgical treatment provides a rescue therapy among these patients when restenosis. (J Intern Med Taiwan 2015; 26: 99-106)

Key Words: Cryotherapy, Endobronchial tuberculosis, Benign endobronchial mass, Relapse rate

Background

Obstruction of the central airways, the trachea and main bronchi, can result from a variety of disease processes and lead to significant morbidity and mortality. Although the actual incidence and prevalence of central airway obstruction (CAO) are unknown, the etiologies of central airway obstruction may be from a variety of malignant and nonmalignant processes such as sarcoidosis, tuberculosis, etc[1,2,3]. The management of endobronchial mass with central airway obstruction

Reprint requests and correspondence：Dr. Fu-Tsai Chung
Address：Department of Thoracic Medicine, Saint Paul's Hospital, No. 123, Chien-Hsin Street, Taoyuan, Taiwan; Chang Gung Memorial Hospital, No. 5, Fushin Street, Taoyuan, Taiwan
[#]Drs. F.T. Chung and H.C. Chen share equal contribution.

remains challenging and treatments including dilation of the airways (Bronchoplasty), electrocautery, argon plasma coagulation, laser therapy, photodynamic therapy (PDT), and surgical resection have been widely used for symptom relief[1,2,3]. Recently, results from patients with central airway obstruction caused by benign diseases treated by placement of airway stents using a flexible bronchoscope under sedation and local anesthesia, have been reported[4,5]. However, notable complications including granulation tissue formation, stent fracture, and recurrent stent obstruction by the lumen were also reported[6-8].

In patients with obstruction of central airway including the trachea and the main bronchi, respiratory failure is the one of the most severe complications. Due to the advances in airway re-canalization techniques, interventional bronchoscopic procedures have been reported to treat these patients with central airway obstruction[9]. For patients with central airway obstruction caused respiratory distress, the primary goal of therapy is to relieve the obstruction in the central airway. Treatment options include laser ablation, photodynamic therapy, and cryotherapy[10,11]. Cryotherapy, using flexible or rigid bronchoscopy, has a relatively long history of use, and quickly freezes endobronchial mass to -70°C prior to removal[11-13]. Previous studies[11-13] have mentioned that cryotherapy is useful to relieve symptoms of central airway obstruction in patients with malignant diseases. However, there is insufficient data of cryotherapy in patients with benign obstructive lesions.

The aim of this study is designed to analyze the baseline characteristics, clinical response, and re-stenosis rate after cryotherapy in patients with benign central airway obstruction.

Patients and methods

Design

This was a retrospective study. Informed consent was obtained from all patients or their representatives, prior to cryotherapy. The methodology, assurance of patient confidentiality, and design of the project were all approved by our institutional review board (IRB No.:100-3211B).

Patients

From December 2007 to December 2011, consecutive patients from Linkou Chang Gung Memorial Hospital with benign endobronchial mass that received cryotherapy via a flexible bronchoscope were included in this study. Most patients were referred from local hospital such as Taoyuan Saint Paul's Hospital. Because of illness severity, high surgical risk, or surgical refusal, patients in our study did not select surgery as the first choice of treatment.

Clinical data, complications, and outcomes of cryotherapy

Clinical data including age, gender, pathologic diagnosis, location of endobronchial mass, follow-up duration, and occurrence of relapse after cryotherapy, were obtained from patient records.

Cryotherapy

A cryoprobe, with carbon dioxide as the cryogen, was used. A temperature of approximately -70°C is achieved at the probe tip. All patients in our study received cryotherapy via flexible bronchoscopy under sedation, as previously described[14-15]. Briefly, patients received sedation with intravenous midazolam or propofol under bispectral index for consciousness monitoring and a local anesthetic with 2% xylocaine solution during the bronchoscopy[14]. Oxygen saturation, blood pressure, and electrocardiography were monitored during the bronchoscopy.

The bronchoscope was advanced through a mouth guard into the tracheal or bronchial lumen and was inserted at the proximal end of the lesion (Figure 1A). The probe was inserted via the bronchoscope to contact the mass. CO_2 cryotherapy at -70°C was performed for 20-60 s (evaluated by the operator) at the lesion site (Figure 1B); in cases with large mass lesions, the procedure was repeated. We removed the mass in the outward direction with the bronchoscope after cryotherapy and re-warmed the mass with room temperature water to detach it from the probe (Figure 1C). Next, we reintroduced the bronchoscope to check for airway patency (Figure 1D).

Statistical analysis

All data are expressed as median values and interquartile ranges (IQRs) or as numeric values (%). Categorical variables were compared using the Chi-square test. Unpaired *t*-tests were used to compare continuous variables. The level of statistical significance was set at $p < 0.05$. Time to endobronchial lesion relapse was defined as the duration between the date of cryotherapy and relapse detection. The Kaplan–Meier test was used to determine the relapse rate. The rate curves of endobronchial lesion relapse between patients with endobronchial tuberculosis (TB) and those with endobronchial

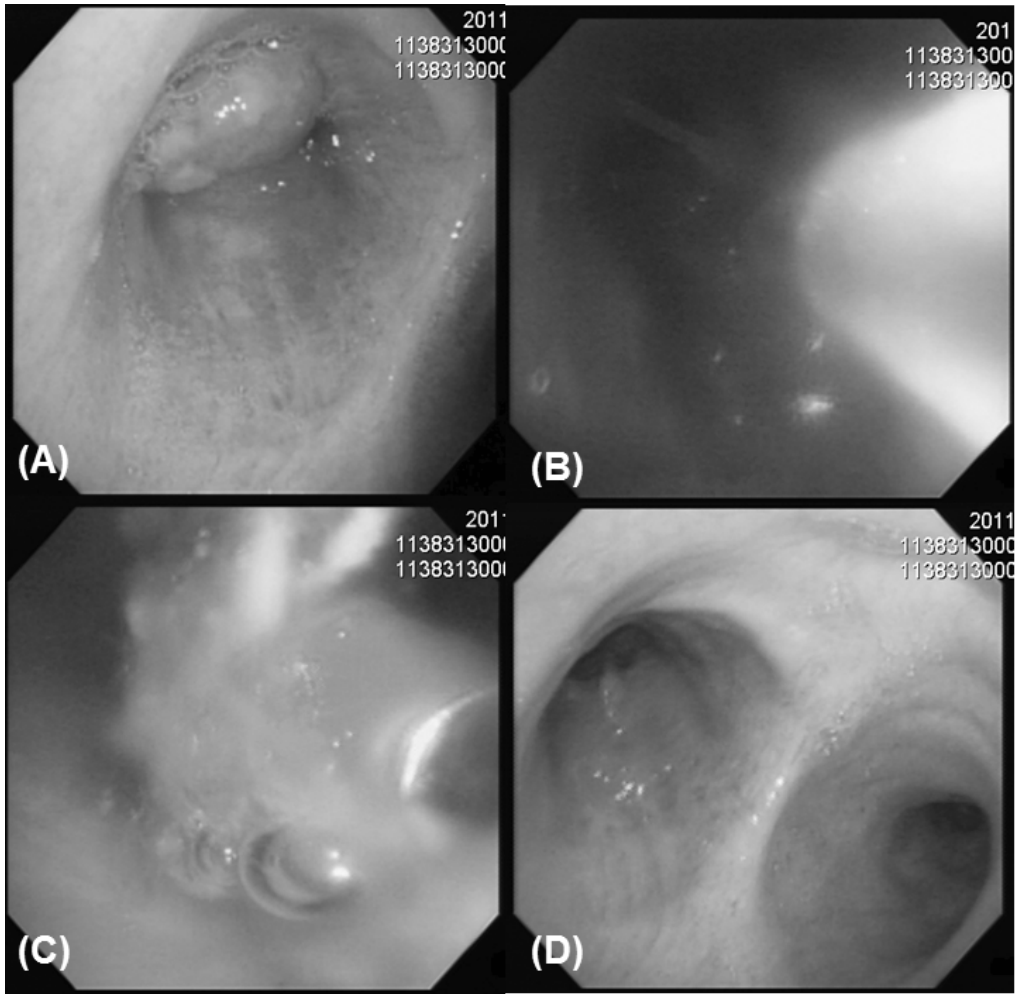

Figure 1. Cryotherapy procedures. (A) The bronchoscope was inserted at the proximal end of the lesion; (B) The probe was inserted via the bronchoscope to contact the mass. CO2 cryotherapy at -70°C was performed for 20-60 s (evaluated by the operator) at the lesion site; (C) The benign mass was removed outward with the bronchoscope after cryotherapy, and re-warmed with water at room temperature; (D) After removal of the mass by cryotherapy, the bronchoscope was reintroduced to check for airway patency.

mass other than TB, were compared using the log rank test. All analyses were conducted using SPSS software (version 13.0, SPSS, Chicago, IL), and Prism 5 for Windows (version 5.03, GraphPad Software Inc., San Diego, CA).

Results

From 2007 to 2011, 16 patients (median age, 58 years; IQR, 29-76 years) with benign airway disease and central airway obstruction received cryotherapy. Patient demographics are presented in Table 1; there were 10 women (62.5%). Endobronchial TB was the most common diagnosis (n = 9, 56.25%), followed by non-TB granuloma (n = 2, 12.5%), leiomyoma (n = 2, 12.5%), foreign body (n = 2, 12.5%), and chondroma (n = 1, 6.25%).

The cases are presented in table 2. The location of the endobronchial masses were as follows: trachea (n = 5), left main bronchus (n = 4), right intermediate bronchus (n = 4), right lower lobe bronchus (n = 1), left lower lobe bronchus (n = 1), and right middle lobe bronchus (n = 1). The overall incidence of re-stenosis from endobronchial mass post-cryotherapy was 31.25% (5/16 patients). Of the 9

Table 1. Patient demographics, n = 16

Age, years	58 (29-76)
Gender, Male/Female	6/10
Diagnoses of endobronchial masses	
Endobronchial TB	9
Non-TB granuloma	2
Leiomyoma	2
Foreign body	2
Chondroma	1

Abbreviations: TB, tuberculosis.

Table 2. Case presentation

	Age	Gender	Diagnosis	Location	Time to Re-stenosis	Management of re-stenosis	Follow-up duration, months	Follow-up or loss
Case 1	53	M	Leiomyoma	LM	x	x	25	f/u
Case 2	29	F	Endobronchial TB	RIB	3 months later	Dumon stent	7	f/u
Case 3	18	M	Endobronchial TB	LM	x	x	48	f/u
Case 4	69	M	Endobronchial TB	T	1 month later	Dumon stent	6.5	f/u
Case 5	82	F	Non-TB-granuloma	T	x	x	29	f/u
Case 6	25	F	Leiomyoma	RIB	x	x	20	f/u
Case 7	30	F	Endobronchial TB	LM	17 months later	Dumon stent	40	f/u
Case 8	79	F	Endobronchial TB	T	x	x	5.5	loss
Case 9	72	F	Endobronchial TB	T	x	x	2.5	loss
Case 10	41	M	Endobronchial TB	T	x	x	12	loss
Case 11	31	F	Endobronchial TB	RLL	2.5 months later	Dumon stent	38.5	f/u
Case 12	82	M	Foreign body	LL	x	x	7	loss
Case 13	77	F	Non-TB-granuloma	RML	x	x	9.3	loss
Case 14	68	M	Chondroma	RIB	x	x	18.5	f/u
Case 15	63	F	Foreign body	RIB	x	x	11	f/u
Case 16	28	F	Endobronchial TB	LM	36 months later	Dumon stent	43	f/u

Abbreviations: M, male; F, female; TB, tuberculosis; LM, left main bronchus; RIB, right intermediate bronchus; RLL, right lower lobes bronchus; LLL, left lower lobe bronchus; RML, right middle lobe bronchus;
f/u, follow up; loss, lost to follow up; x, none.

patients with endobronchial TB, 5 had a re-stenosis and received Dumon stent placement. Of the 16 patients with benign airway disease who received cryotherapy, 13 (81.25%) were followed up at the outpatient department, and 3 (18.75%) were lost to follow-up.

All patients with restenosis from endobronchial mass after cryotherapy were endobronchial TB cases. In addition, patients with endobronchial TB had a higher re-stenosis rate than that of patients with non-TB endobronchial mass after cryotherapy (56.25% vs. 0%; relative risk, 2.75; 95% confidence interval [CI], 1.258-6.011; *p* value, 0.0174) from the current study.

The median follow-up duration of all patients was 15.25 months (n = 16; IQR, 7-36.13 months). The cumulative endobronchial lesion restenosis rate was also higher in patients with endobronchial TB (80%; median duration, 17 months; hazard ratio, 6.65; 95% CI, 1.1-39.1; $p = 0.036$), as determined by the log rank test (Fig. 2)

Discussion

Despite management of central airway obstruction remains challenging, restenosis of central airway obstruction after treatment is also an important issue in these patients with endobronchial mass. The restenosis of central airway in these patients may be caused by granulation tissue formation in benign airway diseases after local treatment[1,4,16]. However, the mechanism of this re-stenosis remains undetermined. This study shows that endobronchial TB may contribute to restenosis of central airway after cryotherapy despite standard anti-tuberculosis treatment completed! It's interesting that all restenosis endobronchial mass from previously diagnosed endobronchial tuberculosis after cryotherapy had no evidences of tuberculosis during endobronchial lesions recurrence and restenosis of airway lumen including acid fast stain positive, mycobacteria tuberculosis grew from culture and caseous granuloma. The pathologic finding of these re-stenosis endobronchial mass was granulation tissue formation.

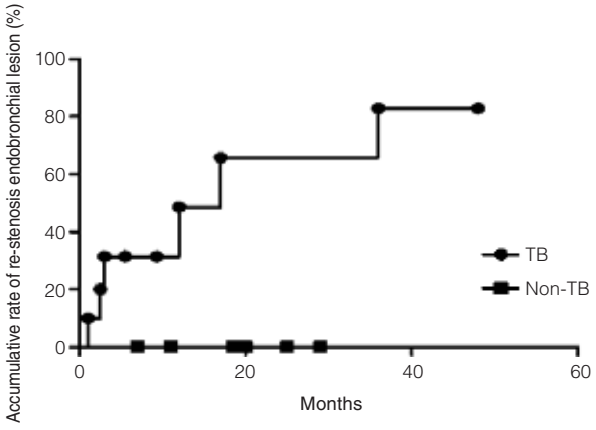

Figure 2. Logistic regression analysis of the cumulative incidence of endobronchial lesion re-stenosis after cryotherapy. The endobronchial lesion re-stenosis rate was higher in patients with endobronchial TB (80%; median duration, 17 months; hazard ratio, 6.65; 95% CI, 1.1-39.1; $p = 0.036$.), as determined by the log rank test.

In general practice, bronchoscopy is not routinely performed to all patients with pulmonary tuberculosis. Therefore, actual incidence of endobronchial tuberculosis could not be well evaluated. For this reason, the proportion of endobronchial involvement in active pulmonary tuberculosis is variable according to the literature. In a study, it was reported that 5.88% of pulmonary tuberculosis cases were shown to have endobronchial tuberculosis[17]; in another study this ratio was reported to be 10-40%[18] and in other two studies this ratio was shown to be 50%[19-20]. Chung classified forms of endobronchial tuberculosis into seven subtypes by bronchoscopic finding: actively caseating, edematous-hyperemic, fibrostenotic, tumorous, granular, ulcerative, and nonspecific bronchitic[21]. Endobronchial tuberculosis is a severe situation with high bacilli load, and may cause complications with high morbidity like bronchial stenosis; early diagnosis and treatment is therefore mandatory[17,20,22]. The course and prognosis of endobronchial TB are

variable, ranging from complete clearance to severe bronchostenosis[23].

Our previous studies have reported underlying structural obstruction of the trachea to be an independent predictor of obstructive granulation tissue formation and restenosis of the airway[6]. Here, we further showed that endobronchial TB causes a nearly 3-fold increase in the risk of endobronchial lesion restenosis than the other benign airway diseases, such as non-TB granuloma, leiomyoma, foreign body, and chondroma. Patients with endobronchial TB also had a higher restenosis rate after cryotherapy during follow up. Thus, patients with endobronchial TB should receive regular radiologic and bronchoscopic follow-up, since the median duration of restenosis in these patients was 17 months (Fig. 2). We suggest that regular radiologic and bronchoscopic examination should be mandatory in patients after cryotherapy, particularly for those with endobronchial TB.

Our results suggest that cryotherapy may induce a higher rate of restenosis in patients with endobronchial TB after cryotherapy. Although 80% of these endobronchial tuberculosis patients did develop endobronchial re-stenosis during the follow-up duration, the use of cryotherapy in patients with endobronchial-TB should be carefully considered. However, in those with benign airway diseases other than TB, including non-TB granuloma, leiomyoma, foreign body, and chondroma, it may completely cure the airway obstruction without recurrence, as seen during our follow-up duration of up to 29 months (Table 2).

The higher incidence of re-stenosis in patients with endobronchial TB after cryotherapy means that cryotherapy may be an alternative treatment in patients suitable for surgery (but initially refused surgical treatment when diagnosed). Surgical treatment in patients with benign airway diseases should be the first option, unless patients are unsuitable for surgical intervention due to poor lung function, co-morbidities, or refusal to undergo surgery[7]. Moreover, the balance between the clinical benefit vs. the risk for re-stenosis should be seriously considered prior to cryotherapy. In patients with endobronchial TB with a follow-up duration of > 17 months after cryotherapy, it should be mandatory to have regular radiologic or bronchoscopic examinations. In endobronchial TB patients with a restenosis of endobronchial mass, surgical treatment after cryotherapy may be beneficial.

On the other hand, cryotherapy provided a less-invasive treatment option than surgery in the patients with airway obstruction due to endobronchial TB. If patients refused surgical intervention initially, bronchoscopy-guided cryotherapy should be performed when no other treatment options (such as electrocautery, laser therapy, stent placement… etc.) wre available. Furthermore, the patients should be closely monitored by radiologic or bronchoscopic examination for the development of restenosis endobronchial mass. Cryotherapy may cure airway obstruction without the risk of restenosis in patients with benign airway diseases other than endobronchial TB.

Our study has several limitations. First, we did not include control patients that did not receive cryotherapy. However, we did not find any obvious diversity signifying that cryotherapy did not worsen the survival. However, in clinical practice, it is difficult to perform blinded, randomized controlled trials on these subjects. Second, other treatments for airway obstruction caused by benign airway disease such as surgery, laser therapy, and photodynamic therapy are reported. However, we only studied patients that received cryotherapy. Other treatments, besides surgery, were not available at our institution. Finally, although our study revealed a higher rate of re-stenosis endobronchial lesions in patients with endobronchial TB, the factors contributing to a re-stenosis of endobronchial lesions in benign airway diseases may be complex.

In conclusion, management of central airway obstruction caused by benign airway disease remains challenging. However, cryotherapy is a feasible and safe option for the management of this condition and may be most effective in patients with benign diseases other than endobronchial TB. Among patients with endobronchial tuberculosis after cryotherapy removal, completed anti-tuberculosis treatment and regular follow-up are mandatory for higher restenosis rate. However, surgical treatment provides a rescue therapy among these patients when restenosis.

Acknowledgments and Funding

We thank the staff of the bronchoscopy examination room at St. Paul's Hospital and Chang Gung Memorial Hospital. This study was partly supported by grants from Chang Gung Memorial Hospital (CMRPG391211, CMRPG391221 and CMRPG3B0981-3). The sponsors had no role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript.

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良性支氣管內腫瘤在冷凍治療後支氣管內結核有較高的復發率

鍾福財[#,1,3] 陳豪成[#,2] 周俊良[3]

沙爾德聖保祿修女會醫療財團法人聖保祿醫院 [1]胸腔內科 [2]一般內科
[3]長庚醫療財團法人林口長庚紀念醫院 胸腔內科

摘 要

良性的支氣管內腫塊致中央氣道阻塞的處理仍然具有挑戰性。好處和冷凍治療良性疾病的結果是不明確的，尤其是支氣管內結核。收集拒絕手術作為治療首選之良性支氣管內腫塊患者有接受冷凍治療醫療記錄。2007年至2011年，16例支氣管內腫瘤的病患。診斷序分別是支氣管結核(N= 9，56.25%)，其次是非結核性肉芽腫(n = 2的12.5%)，平滑肌瘤(n = 2時，12.5%)，異物(n = 2的12.5%)和軟骨瘤(n = 1的6.25%)。冷凍治療支氣管病變後復發再阻塞的總發生率為31.25% (5/16例)。支氣管結核有較高的復發再阻塞率，因此需要處理，比其他良性支氣管內腫瘤高(56.25%對0%；P值，0.0174)。患者的追蹤時間中位數為15.25個月(N=16；四分範圍，7-36.13個月)。良性支氣管內腫瘤的累積復發再阻塞率在支氣管內結核患者也較高(80%以上；中位時間17個月；P =0.036)。冷凍療法是治療良性支氣管內腫瘤一個可行的方法。其中支氣管結核有較高的復發率，因此需要處理。除了完整的抗結核藥物治療外，手術治療提供了在這些病人在氣管內腫塊復發時候的救援治療。

(#鍾福財、陳豪成為共同第一作者。)