Fibrobronchoscopic cryosurgery for secondary malignant tumors of the trachea and main bronchi
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Keywords
Airway obstruction; bronchoscopy; cryosurgery; secondary tracheobronchial tumors.

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Abstract
Background: Patients with secondary malignant tracheal and main bronchial tumors may suffer severe symptoms as a result of major airway obstruction. Curative surgical resection is usually not suitable because of the presence of metastatic disease and poor performance status. In this study, the use of bronchoscopic cryosurgery to reopen the airway is analyzed.

Methods: The clinical records of 37 patients who experienced secondary malignancies from December 2001 to January 2013 were retrospectively reviewed. Low temperature cryotherapy (−50°C to −70°C) was delivered to the central part of the tumor by cryoprobe for four to six minutes causing destruction of the tumor mass (Cryo-melt method). Subsequently, the edge of the tumor was frozen for 30 seconds to two minutes, followed by piecemeal removal of the frozen tumor tissue (Cryo-resection method).

Results: The endpoints of the study were degree of symptomatic improvement and survival. The rates of dramatic and partial symptomatic alleviation were 57.1% and 28.6%, respectively, there were no intraoperative deaths, and median survival was 16.0 months. Prolonged survival was significantly correlated to age (under 60 years of age 22.2% vs. over 60 100%, \(P = 0.011\)), tumor location (main bronchi 0% vs. trachea 77.8%, \(P = 0.003\)), and cryorecanalization times (once 33.3% vs. twice or more 80.0%, \(P = 0.037\)).

Conclusion: Bronchoscopic cryorecanalization is a safe, effective, non-invasive choice for improving the symptoms of malignant airway obstruction. In addition to achieving local-regional control, the technique may also contribute to improved survival.

Introduction
Secondary central airway carcinoma (involving the trachea and main bronchi) incidence is less than 2%, but the mortality associated with major airway obstruction without treatment is nearly 100% as a result of serious hypoxemia.1 Many patients die from subsequent complications, including atelectasis, pneumonia, hemoptysis, and acute respiratory failure. The percentage of candidates for radical surgery is low because of the presence of other metastatic disease, the high risk of recurrence even after resection, and poor performance status. Treatments available for the palliation of airway obstruction include external beam radiation (EBR), brachytherapy, neodymium-doped yttrium aluminium garnet (Nd:YAG) laser-debulking therapy, large biopsy forceps, photodynamic therapy, electrocoagulation, prostatic stents, and cryosurgery. Luminal cryoexsection for endobronchial tumors was first reported by Maiwand in 1986 and has since been used in more than 1000 patients.2 Nevertheless, few clinical studies on its application to secondary unresectable airway tumors have been conducted. Procedures intended for the preservation of pulmonary functions in these inoperable cases are considered very important. We analyze the use of bronchoscopic cryotherapy in patients with secondary malignant involvement of the major airway.

Methods
Patients
From December 2001 to January 2013, 226 patients with unresectable tracheobronchial tumor received cryorecanalization; 37 (16.4%) had secondary malignant tumors. Among the 37 patients, there were 22 men and six
women, with a mean age of 56 years (range: 22–81 years). Common presentations included increasing dyspnea, cough, fever, hemoptysis, chest pain, and hoarseness. Seven patients presented with acute respiratory distress and required urgent endoscopic resection. Five cases were supported by extracorporeal membrane oxygenation (ECMO), while the remaining two required endotracheal intubation.

Indications for cryosurgery were as follows:
1. Tracheobronchial lesion that developed stenosis or obstruction as a result of tumors. The tumors were located inside the airway (from the trachea to the entries to segmental bronchi) rather than in the lung tissue.
2. Distal airway patency was preserved. Pulmonary function and blood flow were preserved in the peripheral area with stenosis. The ventilation function could be improved immediately after the airway was reopened by endolumenal cryo resection.
3. The patient could endure anesthesia.
4. Cryorecanalization is indicated for emergency life-saving treatment in cases with serious ventilator insufficiency resulting from tracheobronchial obstruction, presenting a risk of asphyxia. ECMO support is available in emergency situations.
5. Palliative indications include: atelectasis and obstructive pneumonia as a result of advanced cancer, preparation for stenting, and hemostasis for bleeding from tumors.

Contraindications included: (i) the patient is already experiencing respiratory failure; (ii) the patient cannot endure general anesthesia; (iii) the tumors are located in the lung tissue, rather than in the airway; (iv) dyspnea symptoms do not respond to cryo-treatment; (v) pulmonary function and blood flow in the peripheral area are not preserved with stenosis; and (vi) tracheobronchial malacia resulting from previous treatment.

The development modes of secondary tumors were classified into two categories. Type I was defined as hematogenous or lymphatic tracheobronchial wall metastasis. This type of neoplasm was superficial with polypoid growth into the lumen with a predominant endoluminal component. The peripheral margin of the lesion can be identified and lesions could be solitary or multiple (Fig 1, 2). Type II resulted from the direct invasion of tracheobronchial structures by a parenchymal mass or mediastinal lymph node metastasis (Fig 3). Tracheobronchial stenosis was caused by extrinsic compression of outward tumor advancement beyond the tracheobronchial wall.

Lesions were located as follows: 45 of 63 lesions were recognized in the trachea (24 patients), 16 in the left main bronchus (11), and two in the right main bronchus (2). The cause of this predilection is unclear. Evidence of other metastases were multiple pulmonary nodules in 10 patients, right adrenal mass in two, and abdominal wall leiomyosarcoma in one. Fifteen patients received previous treatment in the form of external radiotherapy (8 patients), chemotherapy (5), or both (2).

The precise site and invasion extent of the neoplasm were evaluated through bronchoscopy and chest computed tomography (CT) with three-dimensional reconstruction of
the trachea and bronchus. Unless distal airway patency is preserved, patients should not be chosen as cryosurgical candidates. A pulmonary function test could not be performed preoperatively in all patients because of extreme shortness of breath. Pathologic diagnosis was made from bronchoscopic biopsies in all patients. Morphology was confirmed histologically, identical to a primary tumor.

**Cryoprobe**

We used Kooland 300 and 320 probes for cryorecanalization, 100 cm in length and 1.8, 2.0, 2.3, 2.5 mm in diameter (Beijing Kooland Medical Devices Co., Ltd., Beijing, China; Fig 4). The probe’s main body was flexible, with a metal head to facilitate exact guidance of the probe in the working channel.
of the bronchoscope (BF-IT20 or BF-260, Olympus, Fukushima, Japan). The metal tip of the probe was 5 mm in length, and could be frozen from −50°C to −70°C by means of carbon dioxide (CO₂) decompression.

**Procedures**

General intravenous anesthesia was applied to patients who were paralyzed by atracurium (0.5 mg/kg) without spontaneous respiration and then intubated with a 8.0 mm tube (Tyco Kendall-Gammatron, Bangkok, Thailand). Oxygen (1–2 L/min) was continuously insufflated through this tube. The whole procedure was performed during sedation with propofol (4–6 mg/kg/h). Patients were monitored with electrocardiography, pulse oximeter, and measurement of blood pressure every 10 minutes.

The flexible bronchoscope was placed 0.5 cm above the tumor. Guided by the bronchoscope’s working channel, the cryoprobe was delivered to the tumor tissue at a temperature from −50°C to −70°C. Initially, the basement and central part of tumor were frozen for four to six minutes causing destruction of the tumor mass. White ice crystal was coated on the tumor’s surface during this freezing process, and melted naturally when the body temperature returned to normal level. In most cases, this process, which we termed the “cryo-melt” method, was endoscopically visible. The application time of this method depended on the size of the endolumenal component of the tumor.

The next step was to freeze the edge of tumor for 30 seconds to two minutes, and then immediately tear the lesion piece by piece with the advantage of concretion between the frozen probe tip and the tumor tissue. The freezing process was maintained to ensure the extracted tissue could firmly stick to the tip of the cryoprobe. Extracted tissue cannot usually pass through the bronchoscopic working channel; therefore, tumor pieces must be pulled out of the ventilating tube, together with the bronchoscope. Frozen tumor tissue was then released from the probe tip using a warm water bath, which we termed the “cryo-resection” method. Occasionally, the frozen probe cannot be removed from the tracheal or bronchial wall because of accidental freezing of the surrounding normal tissues, such as cartilage rings. When facing this situation, do not strongly pull the probe. It can be easily removed a few seconds after releasing the freezing button. The aim of the recanalization was to repeat these two methods until no obvious obstruction remained. In some cases, it was time-consuming to create an adequate lumen.

Generally speaking, capillary hemorrhage could be spontaneously stopped after a few minutes of observation. Otherwise, argon plasma coagulation (APC), local spraying of adrenalin (1:1000), or hemocoagulase were options to treat bleeding after tumor debridement. In the case of airway perforation during the first treatment, some patients with residual lesions were scheduled to receive further interventions one week later. The average duration of cryorecanalization was 2.2 hours, (range: 1–11). In cases of massive bleeding, equipment for intubation and oxygen administration must always be provided at hand. Nineteen patients received APC because of obvious blood oozing from the wound surface after cryotherapy. The local heat effect of the argon knife could postpone recurrence, while local intraluminal adrenalin (1:1000) was used for small bleeding occurrences in 24 patients.

**Evaluation**

Responses to endobronchial cryosurgery were assessed by bronchoscopic examination and patients’ accounts of the symptoms before and after treatment. Therapeutic effects were classified by three degrees:

1. **Dramatic effect**: the obstructive airway was completely reopened and the endolumenal tumor was totally resected with dramatic symptomatic alleviation (Figs 1, 2, 5). This effect is usually obtained with type I lesions. In this group of patients, the tumor’s basement is like a “peduncle,” with more than 80% of the tumor located inside the airway. Airway obstruction symptoms are relieved immediately after endolumenal cryo-resection.

2. **Partial effect**: partial symptomatic alleviation refers to large basement tumors that are usually classified into type II disease. Only 30–60% could be removed at each intervention. Residual stenosis is detected by means of bronchoscopy. The patient’s performance is partially improved (Fig 3).

3. **No effect**: there were no changes to airway stenosis or clinical symptoms.

Follow-up checks were conducted at three-month intervals. All patients were fully informed of possible complications and provided written consent for treatment. This study was approved by the China-Japan Friendship Hospital ethics committee. Statistical analysis was performed with SPSS soft-
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Discussion

Cryorecanalization is an endoscopic technique utilized to ablade airway tumors by direct and controlled application of low temperature. For centuries, low temperature has been used to treat injuries and inflammation, and to reduce pain. Between 1845 and 1851, Arnott described the benefits of local cold application in the treatment of numerous conditions. Modern cryosurgery began in 1961 through the collaborative work of Cooper and Lee (a physician and an engineer, respectively), who built a cryosurgical probe allowing liquid nitrogen to be conducted without heat loss to the tip of a probe. In 1986, Maiwand reported that cryotherapy could provide effective and rapid control of symptoms caused by tracheobronchial carcinoma and improve quality of life and survival.

This study describes the clinical experience of combining two methods, cryo-melt and cryo-resection, to reopen the tracheobronchial lumen. Cryo-melt works by taking advantage of the destructive force of freezing temperature on cells. When their temperature sinks beyond a certain level, ice crystals begin forming inside the cells and, because of their lower density, eventually tear those cells apart. The water content of cartilage tissue is low; therefore, low temperature causes less cartilage necrosis than thermal energy. The transition zone from the tumor to surrounding normal tissue is believed to be the breaking point. This point can be broken down when...
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removing the probe and tumor tissues can be extracted at the same time.7 Thus, a healthy airway wall can be preserved when applying cryo-resection. Furthermore, low temperatures can lead to vasoconstriction and capillary micro thrombosis, which is likely to decrease the rate of bleeding complications.3

In contrast to the laser, cryorecanalization can be employed at high oxygen concentrations without increased risk and low instrument maintenance cost.6–10 In addition, for extensive and deep tumor invasion, edema after laser treatment is higher because of high local temperature, aggravating the symptoms of apnea. Furukawa et al. reported that laser vaporization, performed in 177 cases of obstructive advanced lung cancer, was effective in 143 cases (81%). Complications included massive hemorrhage in 10 cases (6%) and bronchial perforation in four (2.3%).11 Stenting is effective for stenosis by extrinsic compression because of outward tumor advancement beyond the tracheobronchial wall. Dramatic improvement of dyspnea can be achieved immediately after stent insertion; however, complications of airway stenting include migration and displacement in 12–17.5%, granulation in 6.3–15%, symptomatic retention of secretion in 6.3–38%, and restenosis in 36%.12–14 Because of these potential complications, the cryo approach is advocated as a safe, convenient, and economic method.

Patients with secondary malignant tumors of the airway have a heterogeneity of cancers with different behaviors and spread. It is difficult to analyze survival outcome, but survival after diagnosis is poor. As previously reported, the median survival periods for patients with endobronchial metastasis (EBM), malignant strictures, or unresectable tracheal bronchus squamous carcinoma, are nine months to one year, 5.2 months, and 8.8 months, respectively.15–19 If radiation therapy is applied, survival could be prolonged to 10 months.20 Katsimbri et al. also reported that five out of eight patients (62.5%) with EBM died within one year.21

In this study, survival after treatment was prolonged by cryotherapy, and dramatically improved life quality could be obtained after endobronchial cryosurgery. Treatment success was related to the localization of the tumor: 77.8% of patients with tracheal lesions survived more than two years, while 24.3% of patients with main bronchial tumors all died within 16 months.

Our findings suggest that cryosurgery palliates the immediate cause of death. This phenomenon is particularly obvious in patients older than 60 years of age who have received two or more cryotreatment sessions. A 64-year-old man (the patient shown in Fig 2) received 11 cryorecanalization sessions because of metachronous multiple tracheal lesions and remains alive 78 months after the first cryotherapy session. Palliative cryorecanalization does not necessarily preclude future tracheal resection. Another patient (the patient in Fig 3) with recurrent thyroid papillary carcinoma received complete tracheal tumor resection after an acute airway obstructive problem was resolved by cryosurgery. At present, 38 months after surgery, he is doing well with no sign of recurrence. Cryotherapy can probably achieve cure in some selected patients. In another patient, an endotracheal lesion arose 84 months after resection of esophageal squamous cancer. This patient survived 75 months after only one session of cryotherapy. Her death was a result of myocardial infarction. Long-term survival is likely a result of the naturally slow progression of these types of tumors, rather than the result of cryotherapy; however, further studies are required to confirm this.12

Prognosis is related to the number of lesions; however, both solitary and multiple lesions need to be considered together with the metastatic pathway. There are two classifications of metastases for secondary airway tumors. One is from blood circulation or the lymphatic system (type I), while the other is a result of direct invasion by extrinsic compression because of outward tumor advancement beyond the tracheobronchial wall (type II). In this study, the two-year survival in type I disease patients was better than in type II (71.4% vs 28.6%, P = 0.100). In a previous study, patients with

| Variable         | No | %   | Two-year survival (%) | P value |
|------------------|----|-----|-----------------------|---------|
| Gender           |    |     |                       |         |
| Male             | 22 | 59.5| 50.0                  | 0.648   |
| Female           | 15 | 40.5| 50.0                  |         |
| Age              |    |     |                       |         |
| ≤ 60 years       | 24 | 64.9| 22.2                  | 0.011   |
| > 60 years       | 13 | 35.1| 100                   |         |
| Primary site     |    |     |                       |         |
| Intrathoracic    | 26 | 70.3| 50.0                  | 0.752   |
| Extrathoracic    | 11 | 29.7| 50.0                  |         |
| Histologic type  |    |     |                       |         |
| Squamous         | 24 | 64.9| 44.4                  | 0.431   |
| Non-squamous     | 13 | 35.1| 60.0                  |         |
| Tumor location   |    |     |                       |         |
| Trachea          | 24 | 64.9| 77.8                  | 0.003   |
| Main bronchi     | 13 | 35.1| 0.0                   |         |
| Lesion number    |    |     |                       |         |
| Solitary         | 26 | 70.3| 40.0                  | 0.729   |
| Multiple         | 11 | 29.7| 75.0                  |         |
| Tumor type       |    |     |                       |         |
| Type I           | 19 | 51.4| 71.4                  | 0.100   |
| Type II          | 18 | 48.6| 28.6                  |         |
| Cryo frequency   |    |     |                       |         |
| Once             | 22 | 59.5| 33.3                  | 0.037   |
| Twice or more    | 15 | 40.5| 80.0                  |         |
| Treatment modality| |    |                       |         |
| Cryo             | 16 | 43.2| 33.3                  | 0.066   |
| Combined         | 21 | 56.8| 62.5                  |         |

Combined, cryorecanalization with radiation and/or chemotherapy; Cryo, cryorecanalization.

Table 1 Univariate analysis for two-year survival
solitary lesions were separated from those with multiple lesions. We found that two-year survival rates for patients with solitary lesions were worse than in those with multiple lesions (40% vs. 75%); however, the difference was not significant ($P = 0.729$). The probable explanation is that the percentage of type I disease patients in the multiple lesion group was higher than in the solitary lesion group (72.7% vs 42.3%, $P = 0.091$). Therefore, prognosis is more likely related to metastatic classification than the number of lesions and the response to available treatment and management.\textsuperscript{21} Metastatic classifications reflect a tumor’s biologic behavior. The biologic behavior of type I tumors is less aggressive than type II.

Patients treated by cryorecanalization can expect long-term survival as this method is used against localized disease. In addition, with the establishment of airway patency, effective therapy strategies, such as radiation, chemotherapy, and/or target therapy are often necessary to treat systemic disease.\textsuperscript{21} Treatment for tracheobronchial obstruction was achieved thorough evaluation of the etiology, physiology, diagnostic, and treatment options of the disease and a multidisciplinary team approach including anesthesiology, medical oncology, thoracic surgery, radiology, and interventional pulmonology. In this multidisciplinary team approach, all doctors should know interventional bronchoscopic methods, endobronchial treatment, and indications of these procedures.

**Conclusion**

Bronchoscopic cryosurgery of central airway obstructions can be achieved safely, noninvasively, and effectively by a combination of cryo-melt and cryo-resection methods. It can provide immediate symptomatic alleviation, prevent bleeding or death from asphyxiation, and provides a possibility for curative resection. In addition to high local-regional control rates, prolonged survival can also be obtained. This endoscopic procedure is a minimally invasive method based on respect for and improvement of patients’ quality of life.

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**Disclosure**

No authors report any conflict of interest.

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