ORIGINAL ARTICLE

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 maglinancies 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, prosthetic stents, and cryosurgery. Luminal cryoresection 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 brochoscopic 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

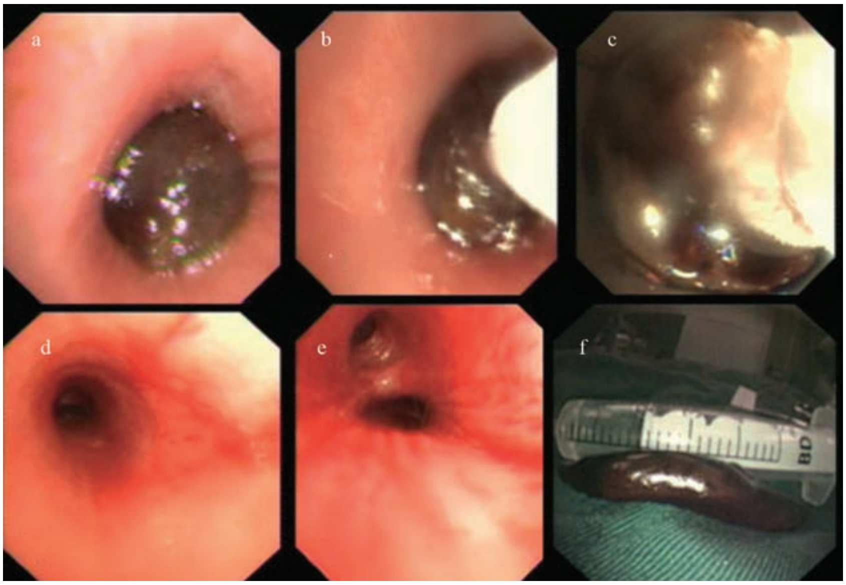

Figure 1 Cryorecanalization of the uterus leiomyosarcoma (type I). (a) Fibronchoscopy revealed a polypoid lesion totally obstructing the left main bronchus. (b) The tumor was frozen with the cryo-probe. (c) Cryo-melt and cryo-resection were combined to remove the tumor completely. (d,e) The left main bronchus was recanalized after extraction of the tumor. (f) Polypoid tumor tissue was smooth and soft with a pedicel on the internal bronchial wall. The size of the tumor was 6 cm × 1.5 cm.

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

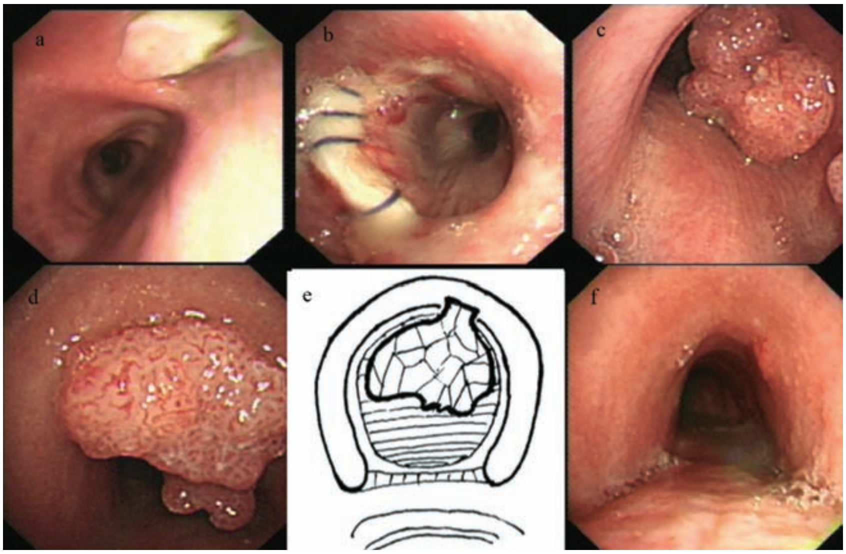

Figure 2 (a) A 64-year-old man with lung squamous cell carcinoma of the right upper lobe. Fibrobronchoscopy revealed a mass covered by necrotic tissue totally obstructing the right upper lobe. (b) There were no lesions on the anastomotic stoma 17 months after complete right upper lobe sleeve resection. (c,d) Multiple discrete lesions were found on the tracheal wall with exophytic propagation. (e) Illustration of type I disease. (f) Tracheal tumors were totally removed by cryoresection.

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.

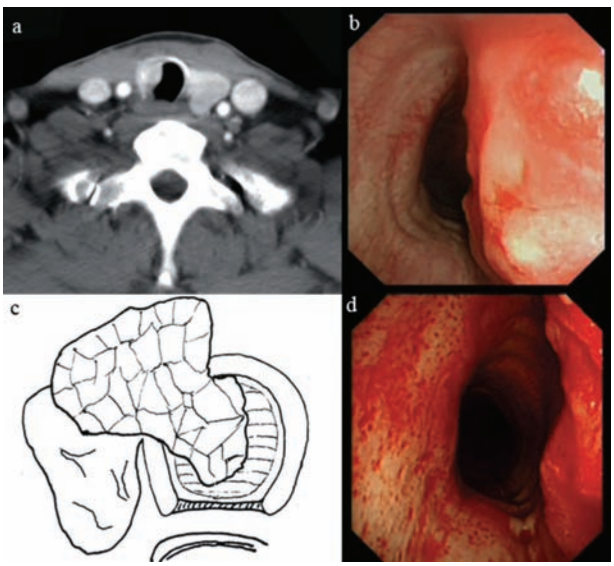

Figure 3 Cryorecanalization of the thyroid papillary carcinoma (type II). (a) Chest computed tomography revealed the right tracheal wall was invaded by recurrent thyroid papillary carcinoma. (b) Fibrotic bronchoscopy showed a submucosal mass protruding into the tracheal lumen. (c) Illustration of type II disease. (d) Eighty percent of the tumor was removed after cryotherapy, leaving a a wide tumor basement remaining.

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

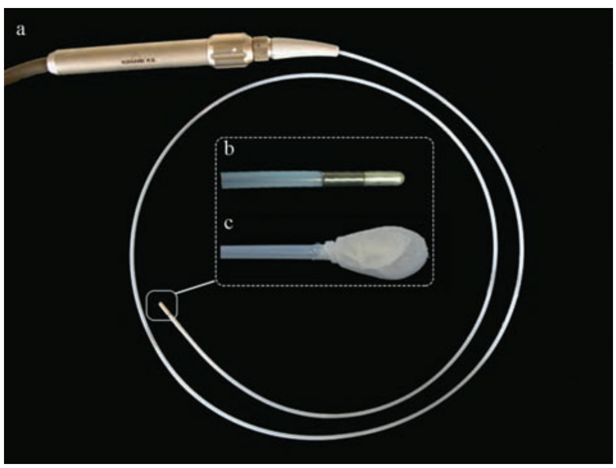

Figure 4 (a) Superfine curved cryosurgical probe. (b) The metal tip of the probe (5 mm). (c) Formation of an ice ball after 70 seconds of freezing.

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 (CO_2) decompression.[3]

Procedures

General intravenous anesthesia was applied to patients who were paralyzed by atracurum (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.

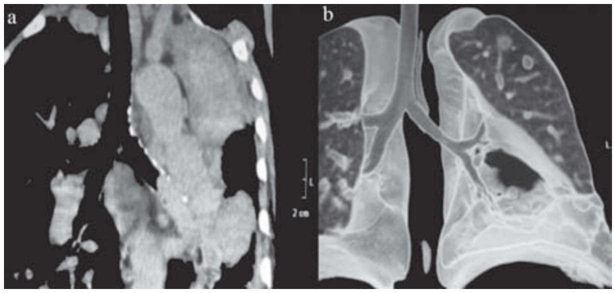

Figure 5 (a) Chest computed tomography revealed the left main bronchus was totally obstructed by left upper lobe atelectasis. (b) The left lung recovered spontaneously after cryorecanalization, and multiple pulmonary nodules were found in both lungs (the same patient as in Fig 1).

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 software, version 10.0 (SPSS Inc., Chicago, IL, USA). Statistic analysis is based on Fisher's exact test. One and two-year survival rates were calculated using a dichotomized outcome.

Results

Surgery duration ranged from 50 to 140 minutes. On average, 11 (range: 8–20) applications of the cryoprobe were required in one intervention. The average length of hospital stay was six days (range: 2–14). There were no intraoperative deaths, and none of the patients required mechanical ventilation after cryorecanalization. One patient became breathless, followed by atrial fibrillation, four hours after surgery. Repetitive bronchoscopy showed clots occluding the right main bronchus. The clots were immediately removed and bleeding was stopped by APC. Early death related to the procedure occurred in two cases at 17 and 23 days postoperatively. One patient died as a result of massive tracheal bleeding, the other of pulmonary infection and respiratory failure.

Urgent status in three patients became stable after airways were reopened. Dramatic effects were achieved in 22 patients (59.5%). The obstructed airway was reopened, and symptoms of dyspnea, atelectasis, and postobstructive pneumonia were immediately relieved. Twelve patients (32.4%) achieved partial effective status with residual strictures. There was no effect in three patients (8.1%). Tumor closures in these three patients turned out to be too extended. The sustentive cartilage structure was destroyed by compression of the predominant extralumenal tumor components. Although large quantities of tumor tissue were extracted, connection with the distal respiratory tract could not be achieved.

Symptom-specific relief rates were also analyzed. They were 78.6%, 83.3%, 33.3%, 75.0%, and 66.7% for dyspnea, cough, hemoptysis, fever, and chest pain, respectively.

Complications developing after endo-cryotherapy included damage to surrounding normal tissues. Because of the risk of bronchial perforation, especially in the area of the tracheobronchial membrane, it is crucial to set the cryo temperature from −50°C to −70°C. Considerable experience is required before performing accurate cryotherapy to lesions responding to the cough reflex of the patient. The most dangerous complication is massive bleeding.

Airway stents were attempted on five patients; however, the outcome was not satisfactory. These five patients suffered extreme pain and continuous dry coughing. Two stents slipped above the malignant stenosis, while in the other three cases, the patients or family members discontinued treatment because of granulation and/or symptomatic retention of secretion. The experience of stent implantation in our medical center is limited. Cryotherapy is an effective local treatment, and is recommended as a part of comprehensive therapy. In our study, 17 (45.9%) eligible cases received radiation therapy.

Follow-up information was obtained on all patients. The interval between intervention sessions was one to 24 weeks, while the mean recurrence interval (time from diagnosis of the primary tumor to diagnosis of the secondary tracheobronchial tumor) was 38.0 months. Considering different primary tumor sites, recurrence intervals were as follows: esophagus, 21.5 months (range: 1–84); lung 31.2 (range: 7–63); thyroid 46 (range: 8–84); colon 132; and uterus 28 months. Mean survival was 16.5 months (range: 0.56–75 months); 22 patients died during follow-up. Fifteen patients remain alive with mean survival of 36.4 months (range: 25–66).

The mean and median survival times were 36.2 (95% confidence interval [CI]: 17.3, 54.9) and 16.0 months (95% CI: 0, 43.5), respectively. 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 attempts (once 33.3% vs. twice or more 80.0%, $P = 0.037$), but not to gender, primary tumor site, histologic type, or lesion number. A trend toward a better outcome was observed in patients who had received combined treatments compared with cryosurgery only (2-year survival of 62.5% vs. 33.3%, $P = 0.066$). Patients with type I disease had a better outcome than those with type II disease (71.4% vs. 28.6%, $P = 0.100$; Table 1).

Discussion

Cryorecanalization is an endoscopic technique utilized to ablate 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.[4] 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.[5] 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.[2]

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.[6] The transition zone from the tumor to surrounding normal tissue is believed to be the breaking point. This point can be broken down when

Table 1 Univariate analysis for two-year survival

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

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

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.[8–10] 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 an 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.[22]

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 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.[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.[23] 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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