

# An Open-label, Single-arm Study of CRYO2 for Debulking at the Site of Central Airway Obstruction or Stenosis

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**Abstract.** *Background: An open-label, single-arm study was conducted to assess the safety of a cryosurgery unit named CRYO2 for debulking at the site of obstruction or stenosis. Patients and Methods: In order to treat central airway tumor-related stenosis, debulking at the stenotic site of the airway was performed using CRYO2 under general or local anesthesia. The primary endpoint was the incidence of moderate to massive hemorrhage. Results: Incidence of moderate to massive hemorrhage during surgery was 3.8% (1/26) (95% confidence interval(CI)=0.1-19.6%). Technical success was 96.2% (25/26), with a 95% confidence interval of 80.4-99.9%. Conclusion: CRYO2 for debulking at the site of obstruction or stenosis can be performed safely.*

Argon-plasma coagulation (APC), high-frequency treatment, laser therapy, microwave treatment, and coring by rigid bronchoscopic tube are all therapeutic options for reducing tumor-related stenosis of the central airway. These treatments may cause airway fire under a high oxygen concentration, so the fraction of inspiratory oxygen (FiO<sub>2</sub>) levels must be kept at 40% or less. This limitation may be dangerous when treating patients with respiratory failure, such as dyspnea or hypoxemia. The cryosurgery unit, CRYO2 (Erbe Elektromedizin GmbH, Tübingen, Germany) facilitates treatment under a FiO<sub>2</sub> level of 100%, safely reducing this risk.

However, tumor resection with CRYO2 can cause bleeding from the tumor or peripheral tissue while removing frozen tissue. It has not yet been established whether the associated risks outweigh the above-mentioned benefits.

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In the United States and Europe, this cryosurgery unit was approved with the brand name ERBE-CRYO2 in 2015 (Erbecryo2 in 2012) for the purposes of cryobiopsy, debulking at the site of obstruction or stenosis, and foreign body removal. The import of this unit to Japan as a medical device was approved in 2017 for cryobiopsy and foreign body removal. In contrast to Europe, however, it has not yet been approved in Japan for debulking at the site of obstruction or stenosis, due to lack of sufficient evidence.

According to a study in Europe (1, 2), recanalization of the central airway was achieved under an oxygen concentration of 100%, and the degree of hemorrhage was moderate or slight in most cases. To expand indications for this unit in Japan, we conducted this study to evaluate the safety of CRYO2 for patients with central airway mass-related stenosis of the airway requiring emergency airway maintenance.

## Patients and Methods

*Study design.* This open-label, single-arm study for patients with central airway mass-related stenosis of the airway requiring treatment for symptoms was conducted to evaluate safety of CRYO2. Major inclusion criteria were (i) patients with central airway mass-related stenosis of the airway requiring treatment for symptoms such as dyspnea, hypoxemia, and stridor, and (ii) those who may tolerate bronchoscopy. Detailed information of the study protocol was reported previously (3). This study was approved by the Institutional Review Board of the National Hospital Organization Nagoya Medical Center. Written informed consent was obtained from every patient prior to participation. This study was registered in the Clinical Trial Registry (jRCTs042180175).

*Interventions.* Debulking at the airway stenotic site was performed using CRYO2 under general or local anesthesia in patients with central airway tumor-related stenosis. We defined the day of surgery as day 1, and days 2 to 7 to be an observation period. During the study period, combination therapies including airway dilation and aspiration for safety assurance were performed according to the attending physician's judgement.

*Device.* Cryosurgery units provide a gas or liquid refrigerant to heated tissues directly or indirectly, such as through contact with a probe that is cooled with a cryogen. We used CRYO2 in this study

(Figure 1). The cooled probe part was placed in contact with the target site (the bronchus and its peripheral tissue) or object (intra-bronchial alien bodies including sputum and blood clots) to be cooled/frozen. Then, biopsy tissues were obtained or alien bodies were removed.

**Endpoints.** The primary endpoint was the incidence of moderate to severe and massive hemorrhage. The degree of hemorrhage was evaluated using the American College of Radiology ACR Appropriateness Criteria (4) as follows: Minor, blood loss volume within 24 hours of less than 30 ml; moderate to severe, blood loss volume within 24 hours of between 30 and 300 ml; and massive, blood loss volume within 24 hours of more than 300 ml. Secondary endpoints included the proportion of technical success, adverse events, and proportion of patients, whose intraoperative pulse oxygen saturation (SpO<sub>2</sub>) value was 95% or less than. The definition of technical success is as follows: the amelioration of airway stenosis, successful stenting, or improved sputum excretion. The severity of adverse events was evaluated using the Common Terminology Criteria for Adverse Events (Ver. 4.0) (5).

**Statistical methods.** Two studies had reported incidences of moderate and marked hemorrhage of 25 (10/40) (1) and 8.0% (18/225) (2), respectively. Assuming that the incidence of moderate to severe and massive hemorrhage may be 25%, 27 patients were required to establish a width from the lower limit of the 95% confidence interval to sample the estimate for the incidence of hemorrhage as <15%. Considering the possibility of dropouts, the sample size was set to 30.

The proportion of technical success, the proportion of patients with an intraoperative SpO<sub>2</sub> value of  $\leq 95\%$ , the incidence of moderate or marked intraoperative hemorrhage and their 95% confidence intervals were calculated. The incidence of moderate to severe and massive hemorrhage with respect to the presence or absence of a stent were calculated, along with the incidence of adverse events.

## Results

**Participants.** Between June 2018 and January 2019, 30 cases (28 patients) were enrolled in the study. Two patients were enrolled and underwent intervention twice because they had different central airway mass-related stenosis twice. Four patients did not undergo study treatment and other modalities were performed. Twenty-six cases (24 patients) successfully completed treatment and were included in the statistical analysis.

**Baseline characteristics.** The baseline characteristics of patients are shown in Table I. The median age was 67.5 (range=37-81) years, and 16 (61.5%) were men. For those with primary metastatic lung cancer, there was one case each of renal cell carcinoma; alveolar soft part sarcoma of the left femur; cancer of the rectum, ovary, esophagus, breast, and stomach; and advanced esophageal cancer. Other malignant tumors comprised one case each of renal cell carcinoma, and of the breast, left main bronchus, ovary, and esophagus. Eastern Cooperative Oncology Group performance status was 2 or more in 13 cases. Muscle relaxants were used in 73.1% (19/26).

Table I. Baseline characteristics and treatment procedure (N=26) for patients included in this study.

Characteristic	Value
Age, years	
Median (IQR)	67.5 (37-81)
Gender, n (%)	
Male	16 (61.5)
Primary lung cancer, n (%)	
Adenocarcinoma	2 (7.7)
Squamous cell carcinoma	2 (7.7)
Small cell lung cancer	1 (3.8)
Undiagnosed/suspected	1 (3.8)
Metastatic lung cancer, n (%)	
Yes	10 (38.5)
Malignant tumor, n (%)	
Other	11 (42.3)
Bleeding tendency, n (%)	
Yes	1 (3.8)
Administration of anticoagulant, n (%)	
Yes	0 (0.0)
ECOG PS	
0	2 (7.7)
1	11 (42.3)
2	7 (26.9)
3	4 (15.4)
4	2 (7.7)
Muscle relaxants	
Yes	19 (73.1)
Oxygen administration	
Yes	5 (19.2)
Amount of oxygen (l/m) (n=5)	
Median (IQR)	2 (1-10)
SpO <sub>2</sub> (%)	
Median (IQR)	95 (92-100)
Treatment procedure for airway dilation	
APC (n=24)	7 (29.2)
High-frequency snare (n=23)	5 (21.7)
Mechanical debulking (n=25)	5 (20.0)
Other (n=25)	5 (20.0)

APC: Argon-plasma coagulation; ECOG PS: Eastern Cooperative Oncology Group performance status; IQR: interquartile range; SpO<sub>2</sub>: pulse oxygen saturation.

**Treatment.** Treatment procedures for airway dilation were performed in 16 cases. Among them, two procedures were used for six cases, and one procedure for 10 cases. For each procedure, comprised APC was used in seven (29.2%) cases, high-frequency snare in five (21.7%) cases and mechanical debulking in five (20.0%) cases.

**Outcome.** Technical success was achieved in 96.2% (25/26) (95% confidence interval=80.4-99.9%) and led to improved sputum excretion, amelioration of airway stenosis, and successful stenting in 29.2% (7/26), 88.5% (23/26), and 84.6% (22/26), respectively. The proportion of patients whose



Figure 1. ERBE-CRYO2 (ERBE Elektromedizin GmbH) cryosurgery unit.

Table II. Adverse events (intraoperative/postoperative) experienced by patients with tumor-related stenosis who underwent debulking at the stenotic site of the airway using CRYO2 (N=26).

Adverse event	Grade	N	%
Mediastinal emphysema	-	0	0.0
Hemoptysis	-	1	3.8
Hypoxia	2	1	3.8
	3	1	3.8
Dyspnea	1	6	23.1
	2	1	3.8
Bronchospasm	-	0	0.0
Atrial fibrillation	-	1	3.8
Intraoperative cardiopulmonary arrest	-	0	0.0
Hemorrhage	Minor	19	73.1
	Moderate to severe	1	3.8

intraoperative SpO<sub>2</sub> value was  $\leq 95\%$  was 11.5% (3/26) (95% confidence interval=2.4-30.2%).

In regard to hemorrhage, minor hemorrhage was found in 88.5% (23/26). Moderate to severe hemorrhage occurred in one patient with a stent. Incidence of moderate to severe and massive hemorrhage was 3.8% (1/26) with 95% confidence interval=0.1-19.6.

**Adverse events.** Adverse events intraoperatively/postoperatively are given in Table II. The most frequent was minor hemorrhage in 19 (73.1%) cases; moderate-to-severe hemorrhage only occurred in one case (3.8%).

Regarding hypoxia, seven cases had hypoxia at baseline, but only two at final assessment on day 7. Twenty-one cases had dyspnea at baseline, but seven did at final assessment (Table III).

Table III. The need for oxygen and incidence of hypoxia and dyspnea at baseline at follow-up by patients with tumor-related stenosis who underwent debulking at the stenotic site of the airway using CRYO2 (N=26).

Symptom	Baseline	Final (day 7)
Oxygen administration, n (%)		
Required	5 (19.2)	2 (7.7)
Oxygen (l/min)		
Median (IQR)	2 (1-10)	5.5 (1-10)
SpO <sub>2</sub> (%)		
Median (IQR)	95 (92-100)	96 (86-99)
Hypoxia, n (%)		
Grade 0	19 (73.1)	24 (92.3)
Grade 2	2 (7.7)	1 (3.8)
Grade 3	3 (11.5)	1 (3.8)
Grade 4	2 (7.7)	0 (0.0)
Dyspnea, n (%)		
Grade 0	5 (19.2)	19 (73.1)
Grade 1	14 (53.8)	6 (23.1)
Grade 2	2 (7.7)	1 (3.8)
Grade 3	1 (3.8)	0 (0.0)
Grade 4	4 (15.4)	0 (0.0)

IQR: Interquartile range; SpO<sub>2</sub>: pulse oxygen saturation.

Besides these adverse events, two serious adverse events occurred in the same patient, namely neutropenia and blood clot.

## Discussion

This is the first study in Japan to show safety data of CRYO2 for debulking at the site of central airway obstruction or stenosis. The incidence of moderate to massive hemorrhage intraoperatively/postoperatively in this study was 3.8%. This

seems to be lower than in previous reports, whose incidences were reported as 25% and 8.0% (1,2).

In this study, technical success was achieved in 96.2% (95% confidence interval=80.4-99.9%), and seemed to be similar to previous studies. There were three retrospective studies and five prospective studies, not randomized controlled trials, that examined the effects of debulking using a previous generation of cryoprobe. In those studies, the proportion of technical success was 72.5% to 100% (1, 2, 6-11).

Since this study was not a randomized controlled trial, it is difficult to conclude whether the bleeding events were less frequent in the procedure with CRYO2 compared to that with APC and coring methods.

### Conflicts of Interest

The Authors declare that they have no competing interests in regard to this study.

### Author's Contributions

HS gave final approval of the protocol and oversaw the entire study. HS and MO were directly involved in the collection and management of data. AK was responsible for the statistical analysis. AMS performed data management and monitoring of this study. All Authors have read and approved this article.

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### References

- 1 Yilmaz A, Aktaş Z, Alici IO, Çağlar A, Sazak H and Ulus F: Cryorecanalization: keys to success. *Surg Endosc* 26(10): 2969–2974, 2012. DOI: 10.1007/s00464-012-2260-1
- 2 Schumann C, Hetzel M, Babiak AJ, Hetzel J, Merk T, Wibmer T, Lepper PM and Krüger S: J Endobronchial tumor debulking with a flexible cryoprobe for immediate treatment of malignant stenosis. *Thorac Cardiovasc Surg* 139(4): 997-1000, 2010. PMID: 19716140. DOI: 10.1016/j.jtcvs.2009.06.023
- 3 Saka H and Kada A: An open-label, single-arm study of CRYO2 for tissue removal at the site of central airway obstruction or stenosis: study protocol. *Nagoya J Med Sci* 80(3): 411-415, 2018. PMID: 30214090. DOI: 10.18999/nagjms.80.3.411
- 4 American College of Radiology ACR Appropriateness Criteria@ hemoptysis: 1995 (revised 2014). Available at: <https://acsearch.acr.org/docs/69449/Narrative/>. Accessed March 5, 2019.
- 5 National Cancer Institute: Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0. Available at: <http://evs.nci.nih.gov/ftp1/CTCAE/About.html>. Accessed June 6, 2019.
- 6 Mu D, Nan D, Li W, Fu E, Xie Y, Liu T and Jin F: Efficacy and safety of bronchoscopic cryotherapy for granular endobronchial tuberculosis. *Respiration* 82(3): 268-272, 2011. PMID: 21150172. DOI: 10.1159/000322142
- 7 Bertolotti L, Elleuch R, Kaczmarek D, Jean-François R and Vergnon JM: Bronchoscopic cryotherapy treatment of isolated endoluminal typical carcinoid tumor. *Chest* 130(5): 1405-11, 2006. PMID: 17099017. DOI: 10.1378/chest.130.5.1405
- 8 Hetzel M, Hetzel J, Schumann C, Marx N and Babiak A: Cryorecanalization: a new approach for the immediate management of acute airway obstruction. *J Thorac Cardiovasc Surg* 127(5): 1427-1431, 2004. PMID: 15116003. DOI: 10.1016/j.jtcvs.2003.12.032
- 9 Deygas N, Froudarakis M, Ozenne G and Vergnon JM: Cryotherapy in early superficial bronchogenic carcinoma. *Chest* 120(1): 26-31, 2001. PMID: 11451811. DOI: 10.1378/chest.120.1.26
- 10 Noppen M, Meysman M, Van Herreweghe R, Lamote J, D'Haese J and Vincken W: Bronchoscopic cryotherapy: preliminary experience. *Acta Clin Belg* 56(2): 73-7, 2001. PMID: 11383315. DOI: 10.1179/acb.2001.013
- 11 Mathur PN, Wolf KM, Busk MF, Briete WM and Datzman M: Fiberoptic bronchoscopic cryotherapy in the management of tracheobronchial obstruction. *Chest* 110(3): 718-23, 1996. PMID: 8797417. DOI: 10.1378/chest.110.3.718

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