

An open-label, single-arm study of CRYO2 for tissue removal at the site of central airway obstruction or stenosis: study protocol

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ABSTRACT

Argon-plasma coagulation, high-frequency electrosurgical snare, laser therapy, and microwave treatment are therapeutic options to reduce tumor-related stenosis of the central airway. These treatments may cause airway fire under a high concentration of oxygen, so FiO₂ levels must be ≤40%. This restriction may be dangerous when treating patients with respiratory failure. The cryosurgery unit, ERBE-CRYO2, facilitates treatment under an FiO₂ level of 100%, safely reducing this risk. In Japan, CRYO2 has been approved for cryobiopsy and foreign body removal, but not for tissue removal at the site of obstruction or stenosis due to lack of sufficient evidence. Since CRYO2 may be useful for reducing airway stenosis, the present study was designed to increase indications for this unit in Japan.

Keywords: obstruction, stenosis, cryosurgery unit, safety
Abbreviation: APC, Argon-Plasma Coagulation.

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INTRODUCTION

Argon-plasma coagulation (APC), high-frequency treatment, laser therapy, and microwave treatment 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 FiO₂ levels must be kept at 40% or less. This restriction may be dangerous when treating patients with respiratory failure, such as dyspnea and hypoxemia. The cryosurgery unit, CRYO2 (AMCO Inc., Tokyo, Japan) facilitates treatment under an FiO₂ level of 100%, safely reducing this risk. However, tumorectomy with CRYO2 may induce hemorrhage from the tumor or peripheral tissue as frozen/coagulated tissue is being removed. It has not yet been established whether the associated risk exceeds the above advantage.

In the United States and Europe, this unit was approved with the brand name “ERBE-CRYO2” in 2015 (“Erbecryo2” in 2012) for the purposes of cryobiopsy, tissue removal at the site of

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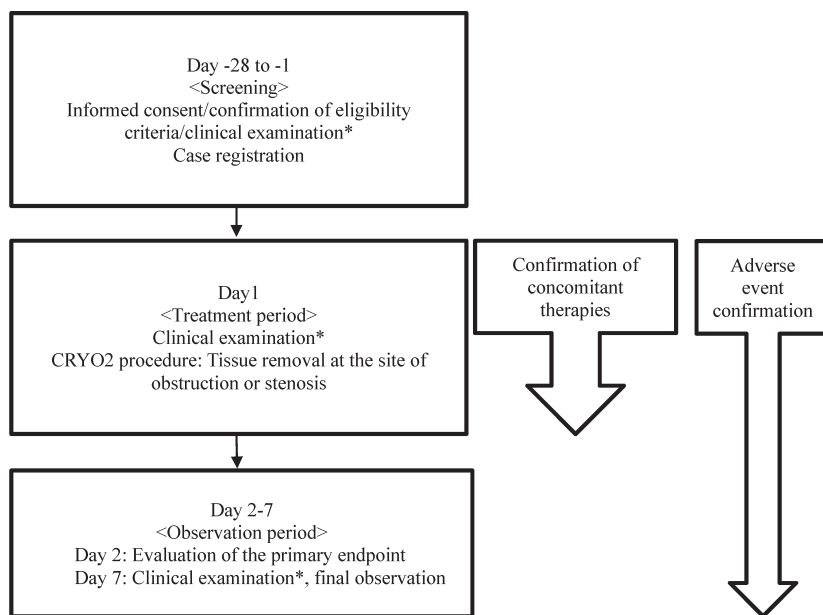
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obstruction or stenosis, and foreign body removal. The import of this unit to Japan as a medical device was approved for cryobiopsy and foreign body removal in 2017. However, in contrast to Europe, it has not yet been approved in Japan for tissue removal at the site of obstruction or stenosis, due to lack of sufficient evidence.

According to a study in Europe, 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. The present study was designed to increase indications for this unit in Japan.

METHODS / DESIGN

In order to treat central airway tumor-related stenosis, tissue removal at the stenotic site of the airway will be performed using CRYO2 under general or local anesthesia. Taking the day of surgery as Day 1, Days 2 to 7 are established as an observation period to evaluate primary endpoints and conduct clinical examinations (Refer to Figure 1). During the study period, combined therapies, such as airway-dilating procedures and aspiration for safety assurance, will be performed based on the attending physician's evaluation.



Clinical examination*:

Hematological parameters: Erythrocyte count, hemoglobin, hematocrit, leukocyte count, and platelet count
Blood biochemical parameters: Total protein, albumin, total bilirubin, AST, ALT, ALP, BUN, and Cr

Fig. 1 Study outline

1: Screening. 2: Informed consent/confirmation of eligibility criteria/clinical examination*. 3: Registration. 4: Treatment period. 5: Clinical examination*. 6: CRYO2 procedure; tissue removal at the site of obstruction or stenosis. 7: Observation period. 8: Day 2, Evaluation of the primary endpoint. 9: Day 7, Clinical examination*, final observation. 10: Confirmation of combined therapies. 11: Adverse event confirmation. 12: Clinical examination*. 13: Hematological parameters - erythrocyte count, hemoglobin, hematocrit, leukocyte count, and platelet count. 14: Blood biochemical parameters - total protein, albumin, total bilirubin, AST, ALT, ALP, BUN, and Cr.

Cryo2

Device

Cryosurgery units supply a gas or liquid refrigerant for target-tissue heat emission through direct cryogen supply or indirect contact with a probe cooled with a cryogen. CRYO2 will be employed in the present study (refer to Figure 2 for its shape/structure). This cryosurgery unit is used in the field of respiratory medicine; a probe cooled with a cryogen is brought into contact with the site to be operated on (the bronchus and peripheral tissue of the bronchus) or objective (intra-bronchial foreign bodies, such as sputum and blood clots) for cooling/freezing, and then biopsy specimens are collected or foreign bodies are removed.

*Eligibility criteria**Inclusion criteria*

- (1) Patients with central airway mass-related stenosis of the airway requiring treatment for symptoms such as dyspnea, hypoxemia, and stridor.
- (2) Those who may tolerate bronchoscopy.
- (3) Those who provide (or whose legal representatives provide) written informed consent to trial participation.

Exclusion criteria

- (1) Patients with unstable angina or a history of myocardial infarction within 6 months.
- (2) Those with a marked bleeding tendency.
- (3) Those with an aspartate transaminase or alanine aminotransferase level of ≥ 100 IU/L.
- (4) Women who are or may be pregnant.
- (5) Patients who are considered to be ineligible for this trial by the principal investigator or attending physicians.

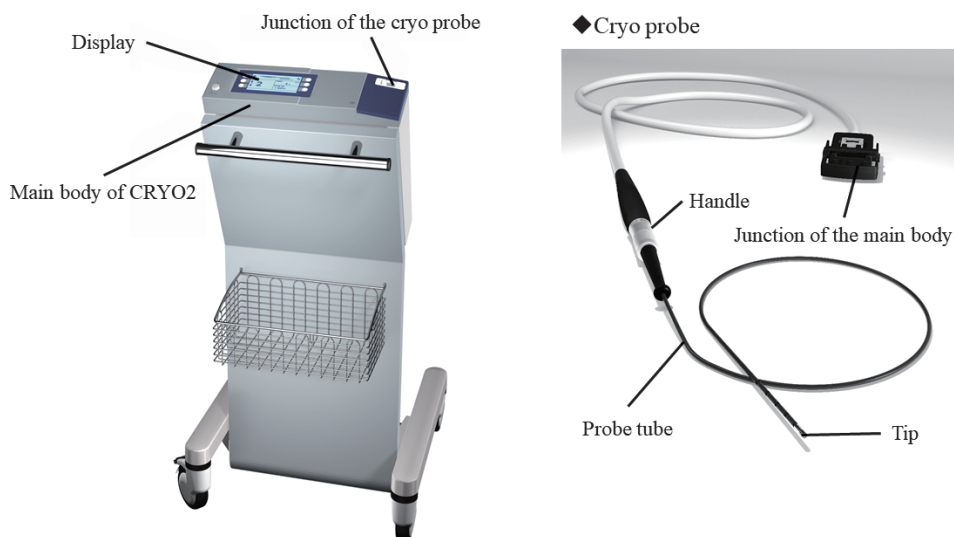


Fig. 2 Shape and structure of CRYO2

1: Display. 2: Main body of CRYO2. 3: Junction of the cryo probe. 4: Cryo probe. 5: Handle. 6: Junction of the main body. 7: Probe tube. 8: Tip.

Endpoints

The primary endpoint is the incidence of moderate to severe and massive hemorrhage. The degree of hemorrhage will be evaluated using the American College of Radiology ACR Appropriateness Criteria®¹⁾:

- Minor: blood loss volume within 24 hours, <30 cc
- Moderate to severe: blood loss volume within 24 hours, 30–300 cc
- Massive: blood loss volume within 24 hours, >300–400 cc

Secondary endpoints include the proportion of technical success, adverse events, and proportion of subjects with an intraoperative SpO₂ value ≤95. Patients with sputum excretion following its retention related to airway tumor dissection, the amelioration of airway stenosis, or successful stenting are regarded as achieving a technical success. The severity of adverse events will be evaluated using the Common Terminology Criteria for Adverse Events (Ver. 4.0).

Statistical analysis

Subjects meeting the main registration conditions and with at least one observation value after the start of the CRYO2 procedure will be regarded as a full analysis set. Furthermore, subjects in whom the CRYO2 procedure was started will be regarded as a safety analysis set.

In the full analysis set, the proportion of technical success and 95% confidence interval will be calculated. The proportion of subjects with an intraoperative SpO₂ value of ≤95 and 95% confidence interval will be calculated. In the safety analysis, the incidence of moderate or marked intraoperative hemorrhage in the safety analysis set and 95% confidence interval will be calculated. Furthermore, the incidence of moderate to severe and massive hemorrhage with respect to the presence or absence of a stent will be calculated, along with the incidence of adverse events.

Sample size

Two studies have reported the incidence of hemorrhage as an adverse event with respect to the severity in patients who underwent tissue removal with a CRYO probe at the site of obstruction or stenosis. The incidences of moderate and marked hemorrhage were 25 (10/40)²⁾ and 8.0% (18/225),³⁾ respectively. Assuming that the incidence of moderate to severe and massive hemorrhage may be 25%, 27 patients are 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.

DISCUSSION

The safety of CRYO2 for tissue removal at the site of obstruction or stenosis will be examined. According to a study in Europe, 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. This procedure may become a new, effective treatment method for patients with central airway mass-related stenosis of the airway requiring emergency airway maintenance.

DECLARATIONS

Ethics approval and consent to participate

The trial was approved by the Institutional Review Board of Nagoya Medical Center.

Written informed consent will be obtained from every patient prior to participation in the trial.

Trial registration

This study has been registered in the Clinical Trial Registry (UMIN-CTR) (UMIN000030492).

Competing interests

The authors declare that they have no competing interests.

Funding

Not applicable.

Authors' contributions

HS conceived the study, participated in its design and coordination, and drafted the manuscript. AK participated in the design of the study and the statistical analysis plan.

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