Clinics in Oncology

Research Article
Published: 22 Jul, 2022

Cryoablation Using Liquid Nitrogen for Metastatic Lung Cancers

Hiroaki Nomori[1], Ikuo Yamazaki[2] and Takuya Adachi[3]*

[1]Department of General Thoracic Surgery, Kashiwa Kousei General Hospital, Japan

[2]Departments of Radiology, Kameda Medical Center, Japan

[3]Department of Radiology, Tokyo Medical and Dental University, Japan

Abstract

Background: While the cryoablation for tumors has been conducted using argon gas, the present study conducted cryoablation using liquid nitrogen for metastatic lung cancers. The study aim is to evaluate the suitability of cryoablation using liquid nitrogen for metastatic lung cancer and to compare preserved pulmonary function according to the number of treated tumors.

Methods: This was a retrospective observational study including 68 patients with 121 metastatic lung tumors that were treated with cryoablation using liquid nitrogen between 2013 and 2019. The treatment was performed with a single 10-G cryoprobe under computed tomography with local anesthesia. To penetrate the tumor with cryoprobe under spontaneous breathing, a guide needle kit consisting of a 21-G guide needle and an 8-G stainless-steel coaxial system was used. Cryoablation was generally performed with repeating freeze and thaw for 3 cycles. Primary outcome was the local control and incidence of pneumothorax. Secondary outcome was whether preserved pulmonary function 6 months after cryoablation varied according to number of treated tumors.

Results: Cryoprobe could reach all of the 121 tumors under computed tomography. Median follow-up period was 32 months. Histological types were carcinomas in 95 tumors and sarcoma in 26. The 3-year local control rate was 73% in all tumors, and 96% and 46% in tumors <2.2 cm and ≥ 2.2 cm, respectively. While the local control was not different in tumors <2.2 cm between carcinoma and sarcoma (p=0.43), sarcoma showed significantly poorer local control than carcinoma in tumors ≥ 2.2 cm, of which 3-year local control rate was 18% and 62%, respectively (p<0.001). The incidence of pneumothorax was 25%. While the average preserved pulmonary function was 98 ± 6% after cryoablation for 1 tumor, the treatment for multiple tumors was associated with significantly lower preservation of pulmonary function (p=0.002).

Conclusion: Cryoablation using liquid nitrogen would be one of the treatment methods for metastatic lung cancers <2.2 cm. Preserved pulmonary function declined significantly with an increasing number of treated tumors.

Keywords: Cryoablation; Liquid nitrogen; Argon gas; Metastatic lung cancer; Local control; Pneumothorax

Abbreviations

CT: Computed Tomography; FEV1: Forced Expiratory Volume in 1 Second; FVC: Forced Vital Capacity; %PPF: Percentage of Preserved Pulmonary Function

Introduction

For metastatic lung cancers, stereotactic body radiation therapy and percutaneous ablation therapies, including radiofrequency ablation and cryoablation, have recently been used as a substitute for surgery to minimize invasiveness [1-7]. Among these, cryoablation for lung cancer has been conducted using argon gas with two or more cryoprobes per tumor [6-9]. In 2010, a device for cryoablation using liquid nitrogen was developed, which was approved by the Food and Drug Administration of USA. Because it usually uses a single cryoprobe and the liquid nitrogen is much cheaper than argon gas, the cost of cryoablation using liquid nitrogen is lower than that using argon gas. Recently, the cryoablation using liquid nitrogen has reportedly provided satisfactory results for primary lung cancer [10], whereas it has not been reported for metastatic lung cancers, which frequently needs multiple treatments for multiple tumors. To evaluate the efficacy of the device

OPEN ACCESS

***Correspondence:**
Hiroaki Nomori, Department of General Thoracic Surgery, Kashiwa Kousei General Hospital, 617 Shikoda, Kashiwa City, 277-8551, Chiba, Japan,
E-mail: hnomori@qk9.so-net.ne.jp

Received Date: *20 Jun 2022*
Accepted Date: *13 Jul 2022*
Published Date: *22 Jul 2022*

Citation:
Nomori H, Yamazaki I, Adachi T. Cryoablation Using Liquid Nitrogen for Metastatic Lung Cancers. Clin Oncol. 2022; 7: 1932.

ISSN: 2474-1663

using liquid nitrogen for metastatic lung cancers, the present study evaluated local control after cryoablation using liquid nitrogen in 68 patients with 121 metastatic lung cancers. Treatment complications and preserved pulmonary function were also evaluated. We also discussed the appropriateness of cryoablation using liquid nitrogen for metastatic lung cancers in comparison with those in previously reported studies using argon gas.

Methods

Study design

This retrospective observational study evaluated 68 patients who underwent cryoablation for metastatic lung cancers between 2013 and 2019. The study was designed in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology Guidelines [11] and complied with the principles of the Declaration of Helsinki. The study was approved by the institutional ethics committee in January 2013 (approval number, 12-047).

Eligibility

Patients were considered eligible if they fulfilled the following criteria: (1) ≤ 6 new or growing pulmonary nodules with a history of malignancy; (2) surgery was not appropriate because the tumor was located deeply in lung parenchyma; and/or (3) the patient had refused surgery. The exclusion criteria were as follows: (1) a Karnofsky performance scale score of <60; (2) incurable primary or other metastatic tumors; and (3) tumors with a diameter of ≥ 5 cm, because it would exceed a "-20°C cytotoxic zone" even when using two cryoprobes. Treatment indication was decided at the in-hospital conference of the chest group, including departments of respiratory medicine, thoracic surgery, medical oncology, and radiology. All patients provided written informed consent after fully discussing the risks and benefits of cryoablation. A written consent for publication was obtained from all patients for every individual person's data included in the study.

Cryoablation procedure

The treatment was usually performed with a single 10-G cryoprobe (3.4 mm in diameter) using liquid nitrogen (IceSense 3; IceCure Medical Ltd., Caesarea, Israel) under Computed Tomography (CT) (Brilliance iCT SP; Philips Co., Amsterdam, Netherlands). However, two cryoprobes were used for tumors ≥ 3 cm employing two machines of IceSense 3, because one machine was available for one cryoprobe. To penetrate the tumor with cryoprobe under spontaneous breathing, a guide needle kit (Daimon coaxial system; Silux Co., Kawaguchi, Japan) consisting of a 21-G guide needle and an 8-G stainless-steel coaxial system was used (Figure 1).

After administration of pethidine hydrochloride (35 mg) and/or midazolam (2 mg to 3 mg), the patient was placed on a table of CT in supine or prone position according to the tumor location. For multiple tumors on one side lung, the cryoablation was conducted in one procedure, whereas for multiple tumors on both sides, the treatment was conducted separately. After local anesthesia, the guide needle was penetrated through the tumor under real-time CT imaging (Figure 2). The inner and outer sheaths were advanced over the guide needle. After the outer sheath penetrated the tumor, the guide needle and inner sheath were withdrawn and the cryoprobe was inserted into the outer sheath. Cryoablation was generally performed with 3 cycles using the following sequence: 5-min freeze, 8-min passive thaw, 8-min freeze, 10-min passive thaw, 8-min freeze, and finally 4-min active thaw, i.e., 43 min in total. Technical success was defined as a consolidated area or a zone of ground-glass appearance encompassing the tumor at least 5 mm of circumferential ablative margin (Figure 2d). After the cryoprobe was removed from the outer sheath, fibrin glue or a 33% of n-butyl-2-cyanoacrylate (B. Braun Aesculap Co., Tokyo, Japan) mixed with lipiodol was injected through the outer sheath to plug the needle tract for preventing pneumothorax.

Safety assessment

Adverse events that happened within 30 days of the treatment were graded with the Common Terminology for Adverse Criteria for Adverse Events (CTCAE version 4.03) [12]. Pneumothorax was defined as the adverse event when the thoracic drainage or puncture was required, because a transient free air space was sometimes seen around the insertion site of cryoprobe.

Follow-up

Follow-up was conducted by CT, which was performed every 3 to 4 months for the first 3 years after treatment; there after at least every 6 months. Local progression was defined as recurrence at the treated site. When the local recurrence was suspected on CT, needle aspiration biopsy was conducted for diagnosis. Local control period

Figure 1: The 10-G cryoprobe (diameter: 3.4 mm) and guide needle system, which consists of a guide needle, inner sheath, and 8-G outer sheath (diameter: 4.2 mm).

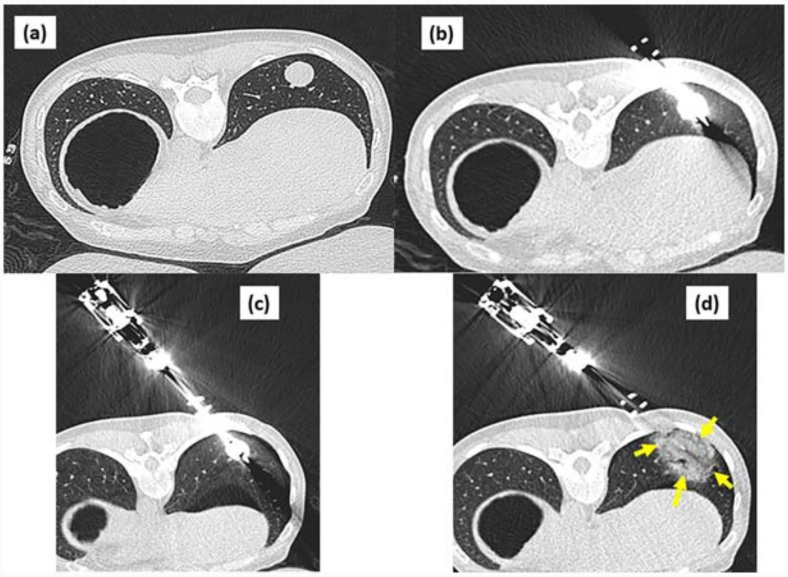

Figure 2: Metastatic sarcoma with diameter of 1.7 cm in the right lower lobe. (a) Cryoablation is conducted with patient in the prone position. (b) The guide needle system penetrates the tumor. (c) Cryoprobe is inserted into the outer sheath. (d) During cryoablation, the freezing zone exceeds the margin of tumor over 1 cm (indicated by arrows).

was evaluated based on the date of CT imaging. Medical records were searched in January 2021.

Evaluation of factors that predicted local control

Local control was evaluated based on tumor size, histology, location, and chemotherapy after cryoablation. Tumor histology was classified as carcinoma or sarcoma. Tumor location was classified as peripheral (<2 cm from pleura), intermediate (≥ 2 cm from pleura), or hilar (<1 cm from lobar artery or vein) on CT.

Evaluation of preserved pulmonary function

Forced Expiratory Volume in 1 sec (FEV1) and Forced Vital Capacity (FVC) were measured using a dry rolling-seal Spirometer (CHEST AC-8800; CHEST Ltd., Tokyo, Japan) before treatment and 6 months after treatment. The Percentage of Preserved Pulmonary Function (%PPF) was calculated using the following formula: [FEV1 after treatment/FEV1 before treatment] × 100(%). For patients who underwent cryoablations more than two times, the %PPF was evaluated at 6 months after the final treatment.

Evaluation of factors that predicted pneumothorax

The incidence of pneumothorax was evaluated based on age, sex, FEV1/FVC, number of treated tumors, tumor location, and number of needles used for each tumor ablation.

Study outcomes

Primary outcome was the local control and incidence of pneumothorax. Secondary outcome was whether preserved pulmonary function 6 months after cryoablation varied according to number of treated tumors.

Statistical analysis

Comorbidities were evaluated using the Charlson Comorbidity index [13]. The optimal cut-off value for tumor size to predict local recurrence was determined using a receiver-operating characteristic curve and the Youden's index. The Kaplan-Meier method was used to evaluate local control and overall survival period [14]. Variables that were significantly associated with local control in the univariate analyses were entered into a multivariate Cox regression model. The differences in %PPF for treatments for one tumor, 2 tumors, and ≥ 3 tumors were analyzed using an analysis of variance. Differences were considered statistically significant at p-values <0.05. All statistical analyses were performed using Microsoft Excel (version 10; Redmond, WA).

Results

During the study period, metastatic lung cancers were treated by surgery in 86 patients, stereotactic body radiation in 2 patients, and cryoablation in 68 patients. The characteristics of the 68 patients treated by cryoablation are shown in Table 1. Eleven patients (16%) had metastases in both lung sides, which were treated separately. Median follow-up period was 32 months (interquartile range, 21 to 46 months). Tumor histology was carcinoma in 53 patients (78%) and sarcoma in 15 patients (22%). Histological types of the tumors were various (Table 2).

Cryoprobe could reach all of the 121 tumors under CT. The ablation area was confirmed as sufficient at the end of treatment on CT in all of the 121 tumors. Table 3 shows the characteristics of the 121 treated tumors. The tumor histology was carcinomas in 95 tumors (79%) and sarcomas in 26 (21%). The tumor locations were peripheral in 81 tumors (67%), intermediate in 32 (26%), and hilar in 8 (%).

Ninety-three procedures were conducted for the 68 patients (Table 4). The number of treated tumors per procedure was 1 tumor in 69 procedures (74%), 2 tumors in 20 procedures (22%), and 3 tumors in 4 procedures (4%).

Local recurrence was experienced in 21 of the 121 tumors (17%). Table 5 shows the univariate and multivariate analyses of factors for local control. The multivariate analysis revealed that local control was significantly associated with tumor size (p=0.0014), and histology (carcinoma *vs.* sarcoma) (p=0.0015). The receiver-operating characteristic curve analysis of tumor size revealed that the optimal cut-off value for predicting local recurrence was 2.2 cm (area under

Table 1: Patient characteristics.

Number of patients (%)	68 (100)
Characteristics	**Value**
Age (y)	61 ± 15 (range, 25-85)
Sex= male	39 (57)
Charlson Comorbidity index	0.6 ± 1.1 (range, 0-5)
Tumor histology	
Carcinoma	53 (78)
Sarcoma	15 (22)
Side of tumors	
One side	57 (84)
Both sides	11 (16)
Number of metastases treated	
1	39 (57)
2	18 (26)
3	5 (7)
4	4 (6)
5	1 (1)
6	1 (1)
Number of cryoablation procedures	
1	52 (76)
2	9 (13)
3	5 (7)
4	2 (3)

Table 2: Histological type of tumors

Histological type	Number of patients (%)
Carcinoma (n=53)	
Colon/rectal cancer	18 (26.9)
Lung cancer	13 (19.4)
Renal cell cancer	4 (6.0)
Breast cancer	3 (4.5)
Hypopharyngeal cancer	2 (3.0)
Stomach cancer	2 (3.0)
Ovarian cancer	2 (3.0)
Urachal cancer	2 (3.0)
Others	6 (9.0)
Sarcoma (n=15)	
Leiomyosarcoma	12 (17.6)
Osteosarcoma	2 (3.0)
Synovial sarcoma	1 (1.5)

the curve, 0.87; 95% confidence interval, 0.80-0.93).

The 3-year local control rate for all tumors was 73%. There was a significant difference in local control between tumors <2.2 cm and those ≥ 2.2 cm (p<0.001), with 3-year local control rates of 96 and 49%, respectively. Figure 3 shows the local control curves in tumors <2.2 cm (69 carcinomas and 15 sarcomas) and those ≥ 2.2 cm (26 carcinomas and 11 sarcomas). For tumors <2.2 cm, there was no significant difference in local control between carcinoma and sarcoma (p=0.43), with 3-year local control rates of 97 and 93%, respectively. However, for tumors ≥ 2.2 cm, sarcomas were associated with significantly poorer local control than carcinomas (p<0.001),

Table 3: Tumor characteristics.

Number of tumors (%)	121 (100)
Characteristics	**Value**
Tumor size(cm)	
Mean	1.7 ± 1.1
Median (range)	1.3 (0.3-4.8)
Tumor histology	
Carcinoma	95 (79)
Sarcoma	26 (21)
Tumor location	
Peripheral	81 (67)
Intraparenchymal	32 (26)
Hilar	8 (7)
Number of used needles per tumor	
1	114 (94)
2	7 (6)
Chemotherapy after cryoablation	
Yes	100 (83)
No	21 (17)

Peripheral: <2 cm from pleura, intraparenchymal: ≥ 2 cm from pleura, hilar: <1 cm from lobar artery or vein

Table 4: Procedure characteristics.

Number of procedures (%)	93 (100)
Characteristics	**Value**
Number of tumors treated per procedure	
1	69 (74)
2	20 (22)
3	4(4)
Number of needles used per procedure	
1	64 (69)
2	25 (27)
3	4 (4)
Freezing cycles	
3	52 (56)
4	28 (30)
5	7 (8)
6	5 (5)
7	1 (1)

Table 5: Cox proportional hazard regression analyses for local control.

	Univariate analysis		Multivariate analysis	
Variables	HR (95% CI)	*P*	HR (95% CI)	*P*
Tumor size	1.8 (1.4-2.4)	<0.001	1.7 (1.2-2.3)	0.0014
Histology	4.5 (1.9-10.6)	<0.001	4.5 (1.8-11.4)	0.0015
Location	0.8 (0.4-1.7)	0.55	-	
Chemotherapy	2.0 (0.5-8.7)	0.34	-	

HR: Hazard Ratio; CI: Confidence Interval; Histology: Carcinoma *vs.* Sarcoma; Location: Peripheral *vs.* Intermediate *vs.* hilar; Chemotherapy: Chemotherapy after cryoablation

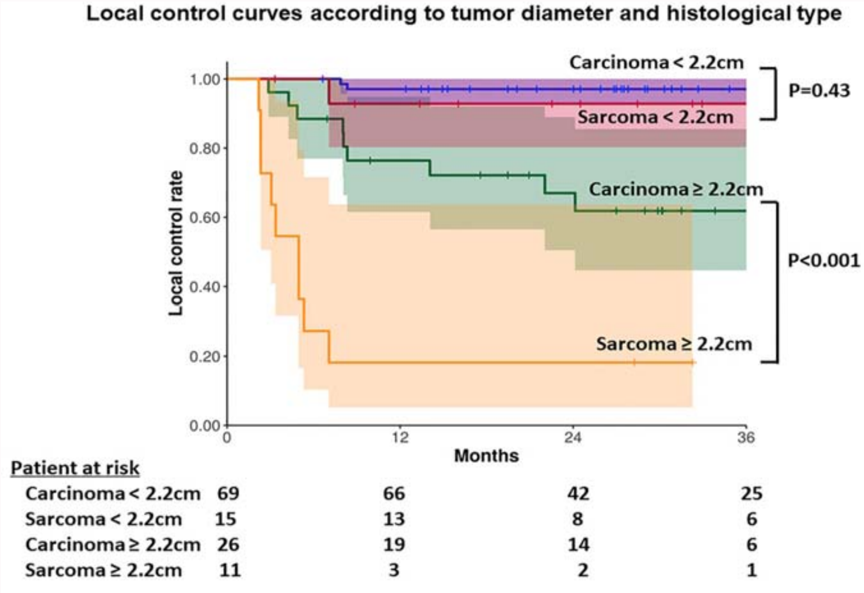

Figure 3: Local control curves according to tumor diameter and histological type. Among tumors with a diameter of ≥ 2.2 cm, sarcomas are associated with significantly poorer local control than carcinomas (p<0.001), although no significant difference is observed between the two types of tumors with a diameter of <2.2 cm (p=0.43).

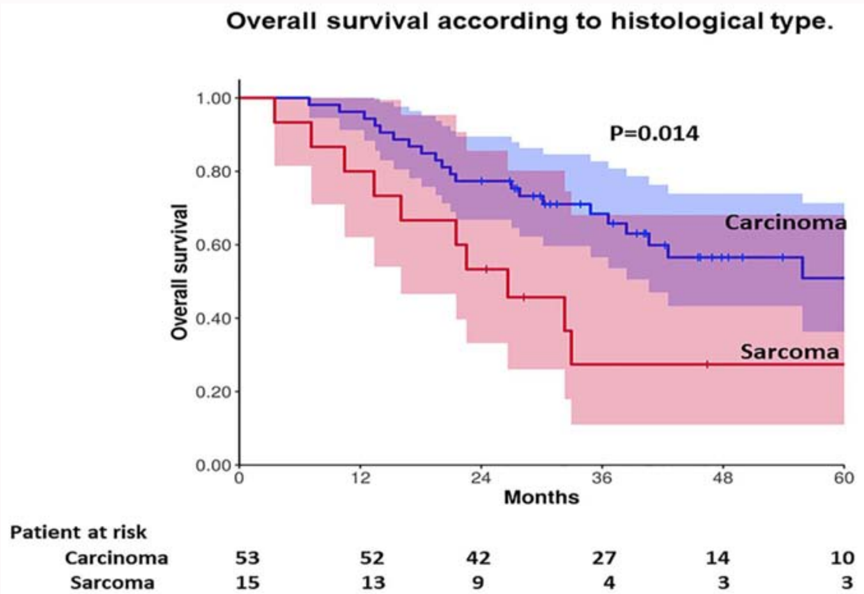

Figure 4: Overall survival according to histological type. Overall survival was significantly poorer for sarcoma than for carcinoma (p=0.014).

with 3-year local control rates of 18% and 62%, respectively.

For the 21 local recurrences, surgical treatment was conducted in 4, additional cryoablation in 3, bronchial arterial embolization in 2, while no other local treatment was done for the remaining 12, because of having another distant metastasis.

The 3-year overall survival rate in all patients was 56%; however, patients with sarcoma had significantly poorer overall survival than those with carcinoma (p=0.014), with 3-year survival rates of 28 and 67%, respectively (Figure 4).

Pulmonary function at 6 months after treatment could not be measured in 9 patients because of tumor recurrence (n=7), subsequent lung surgery (n=1), or patient's preference (n=1). Thus, pulmonary function after cryoablation could be evaluated in 59 of the 68 patients (87%). Figure 5 shows the %PPF, which significantly decreased with the increasing number of treated tumors: 98 ± 6% for 1 tumor (n=32), 95 ± 8% for 2 tumors (n=15), and 88 ± 7% for ≥ 3 tumors (n=11) (p=0.002).

No patients experienced treatment-related mortality. Pneumothorax was observed in 23 of 93 procedures (25%). The median chest tube drainage period was 1 day (interquartile range, 1 to 4 days) and 21 patients recovered without any further treatment (Clavien-Dindo grade I). However, 2 patients required chemical pleurodesis because of prolonged air leakage (Clavien-Dindo grade IIIa). Treatment complications other than pneumothorax were hemothorax requiring chest tube drainage (Clavien-Dindo

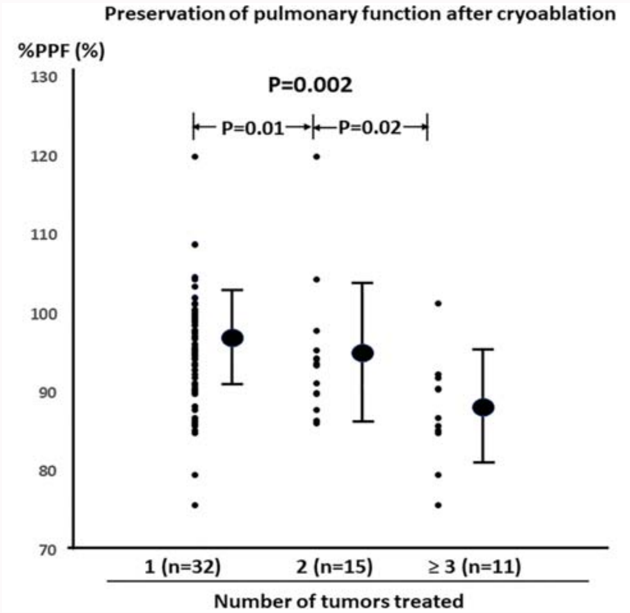

Figure 5: Percentage of preserved pulmonary function at 6 months after cryoablation according to the number of tumors. Significant differences are observed between all three groups (p=0.002), as well as between the groups with 1 tumor and 2 tumors (p=0.01) and the groups with 2 tumors and ≥ 3 tumors (p=0.02). %PPF: Percentage of Preserved Pulmonary Function.

Table 6: Comparison between previously published data on cryoablation using argon gas for malignant lung tumor with the present data using liquid nitrogen.

Author	Number of patients	Number of tumors	Tumor size	Local control rate	Median follow-up	Incidence of pneumothorax
Cryoablation using argon gas						
Yamauchi [18]	24	55 (all M)	≤ 1.5 cm	80% (3 years)	40 months	63%
Yashiro [6]	71	210 (P:11, M:199)	≤ 2 cm	70% (3 years)	15 months	Not described
			>2 cm	36% (3 years)		
McDevitt [17]	42	47 (P:25, M:22)	<3 cm	37% (3 years)	11 months	38%
Lyons [16]	42	67 (P:13, M:54)	≤ 5.9 cm	62% (3 years)	11 months	34%
Callstrom [7]	128	224 (all M)	≤ 3.5 cm	77% (2 years)	Not described	26%
de Baère [19]	40	60 (all M)	≤ 3.5 cm	88% (3 years)	Not described	8%
Cryoablation using liquid nitrogen						
Present study	68	121 (all M)	<2.2 cm	96% (3 years)	32 months	25%
			≥ 2.2 cm	49% (3 years)		
		All tumors		73% (3 years)		

grade I) (n=3) and hemoptysis requiring temporary breathing assistance (Clavien-Dindo grade I) (n=1). Median hospital stay after cryoablation was 4 days (interquartile range, 2 to 4 days).

Discussion

The present study revealed the following points: (1) the 3-year local control rate after cryoablation using liquid nitrogen for metastatic lung cancers was 73%; (2) local control was significantly associated with tumor size (<2.2 cm *vs.* ≥ 2.2 cm), and histology (carcinoma *vs.* sarcoma); (3) incidence rate of pneumothorax was 25%; and (4) pulmonary function decreased with the increasing number of treated tumors.

Several studies on cryoablation for lung cancers have indicated that the tumor size is significantly associated with local control. Yashiro et al. [6] reported that the 3-year local control rate was significantly higher for tumors ≤ 2 cm (84% for tumors ≤ 2 cm and 70% for tumors >2 cm). McDevitt et al. [15] reported that 3 cm was the cut-off value for predicting local control. The present study revealed a consistent result with these two reports, with 2.2 cm as the cut-off value for predicting local control.

In addition, among tumors ≥ 2.2 cm, sarcomas were associated with poorer local control than carcinomas. In contrast, Yashiro et al. [6] have reported that the local control rates were not significantly different between carcinomas and sarcomas; however, their study predominantly evaluated tumors that were ≤ 2.0 cm (158 of 167 tumors; 95%). Sarcomas are considered to be more resistant to cryoablation than carcinomas when tumor size is ≥ 2.2 cm.

An experimental study using liquid nitrogen revealed that extending the freezing time increased the size of the frozen area and decreased the temperature during 15 min of freezing [16]. While the present study usually conducted 8 min of freezing with 3 cycles, a prolonged freezing time might be appropriate for tumors ≥ 2.2 cm.

The present study results were compared to those in 6 studies on cryoablation for metastatic lung cancers using argon gas [6,7,15,17-19]. Table 6 shows the data of local control and incidence of pneumothorax after cryoablation using argon gas. Local control rates 2 or 3 years after the treatment were ranged from 36% to 88%, and the incidence of pneumothorax was ranged from 8% to 63%, which were similar with those in the present study, i.e., 73 % of 3-year local control rate and 25% of pneumothorax incidence.

While the 3-year local control rate and pneumothorax incidence in the present study using liquid nitrogen were almost the same as those with using argon gas, the cost of cryoablation using liquid nitrogen is cheaper than that using argon gas because of the followings: (1) while the cryoablation using liquid nitrogen usually uses one cryoprobe, that using argon gas requires 2 or more cryoprobes; and (2) liquid nitrogen is much cheaper than argon gas (approximately $10 *vs.* $1300 per procedure for one tumor). Therefore, cryoablation using liquid nitrogen is not only appropriate compared to that using argon gas but also is more cost effective than the latter.

Several authors, using argon gas, have speculated that the "-20°C cytotoxic zone" generally resides 4 mm to 10 mm inside the edge of an iceball [20-22]. A few reports have examined the temperature distribution in pig lung during cryoablation using argon gas [23,24]. Permpongkosol et al. [23] reported that the temperature at 1 cm diameter around the 17-Gcryoprobe using argon gas reached -28°C at the end of a second freezing period, whereas the temperature at 3 cm in diameter was +25°C, which is far above the freezing point. Hashimoto et al. [24] conducted a similar experiment using argon gas, reporting that the 17-Gcryoprobe produced a "-20°C zone" at "1.8 cm" in diameter at the end of a third freezing. In contrast, the experiment with the cryoablation using liquid nitrogen in pig lung showed that the 10-G cryoprobe produced "lower than -100°C zone" at "3 cm" in diameter at the end of a third freezing [16]. While the cryoablation using liquid nitrogen uses a thicker probe than that using argon gas (10-G *vs.* 17-G), it can produce a larger cytotoxic zone than the latter.

The incidence of pneumothorax in the present study was 25%. Cryoablation with liquid nitrogen usually uses a single thick needle (10-G), whereas that with argon gas uses multiple thin cryoprobes (17-G). However, the incidence of pneumothorax in the present study was similar to that in cryoablation using argon gas.

A recent study of cryoablation for a single stage I non-small cell lung cancer reported a %PPF of 97% [10]. Similarly, the %PPF after cryoablation for one tumor in the present study was 98%. However, the %PPF value was decreased with increasing number of treated tumors. Even though cryoablation has little damage on pulmonary function, it appears that treatment for multiple tumors has a cumulative effect on pulmonary function.

This study had some limitations. First, the retrospective design and lack of a control group precluded a conclusion regarding the causality of the relationship between cryoablation and outcomes. Second, the histological types were heterogenous, even for each carcinoma and sarcoma.

In conclusion, the present study revealed the followings: (1) cryoablation using liquid nitrogen would be one of the treatment methods for metastatic lung cancers <2.2 cm; and (2) pulmonary function decreased significantly when cryoablation was performed for an increasing number of tumors.

References

1. Mouli SK, Kurilova I, Kurilova I, Sofocleous CT, Lewandowski RJ. The role of percutaneous image-guided thermal ablation for the treatment of pulmonary malignancies. AJR Am J Roentgenol. 2017;209(4):740-51.
2. Sharma A, Duijm M, Oomen-de Hoop E, Aerts JG, Verhoef C, Hoogeman M, et al. Survival and prognostic factors of pulmonary oligometastases treated with stereotactic body radiotherapy. Acta Oncol. 2019;58(1):74-80.
3. Hess A, Palussière J, Goyers JF, Guth A, Aupérin A, de Baère T. Pulmonary radiofrequency ablation in patients with a single lung: Feasibility, efficacy, and tolerance. Radiology. 2011;258(2):635-42.
4. de Baère T, Aupérin A, Deschamps F, Chevallier P, Gaubert Y, Boige V, et al. Radiofrequency ablation is a valid treatment option for lung metastases: experience in 566 patients with 1037 metastases. Ann Oncol. 2015;26(5):987-91.
5. Vogl TJ, Naguib NN, Gruber-Rouh T, Koitka K, Lehnert T, Nour-Eldin NE. Microwave ablation therapy: Clinical utility in treatment of pulmonary metastases. Radiology. 2011;261(2):643-51.
6. Yashiro H, Nakatsuka S, Inoue M, Kawamura M, Tsukada N, Asakura K, et al. Factors affecting local progression after percutaneous cryoablation of lung tumors. J Vasc Interv Radiol. 2013;24(6):813-21.
7. Callstrom MR, Woodrum DA, Nichols FC, Palussiere J, Buy X, Suh RD, et al. Multicenter study of metastatic lung tumors targeted by interventional cryoablation evaluation (SOLSTICE). J Thorac Oncol. 2020;15(7):1200-9.
8. Nakatsuka S, Yashiro H, Inoue M, Kuribayashi S, Kawamura M, Izumi Y, et al. On freeze-thaw sequence of vital organ of assuming the cryoablation for malignant lung tumors by using cryoprobe as heat source. Cryobiology. 2010;61(3):317-26.
9. Ito N, Nakatsuka S, Inoue M, Yashiro H, Oguro S, Izumi Y, et al. Computed tomographic appearance of lung tumors treated with percutaneous cryoablation. J Vasc Interv Radiol. 2012;23(8):1043-52.
10. Nomori H, Yamazaki I, Shiraishi A, Adachi T, Kanno M. Cryoablation for T1N0M0 non-small cell lung cancer using liquid nitrogen. Eur J Radiol. 2020;133:109334.
11. Vandenvbroucke JP, von Elm E, Altman DG, Gøtzsche PC, Mulrow CD, Pocock SJ, et al. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): explanation and elaboration. Int J Surg. 2014;12(12):1500-24.
12. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: A new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg. 2004;240(2):205-13.
13. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis. 1987;40(5):373-83.
14. Kaplan EL, Meier P. Non-parametric estimation from incomplete observations. J Am Stat Assoc. 1958;53:457-8.
15. McDevitt JL, Mouli SK, Nemcek AA, Lewandowski RJ, Salem R, Sato KT. Percutaneous cryoablation for the treatment of primary and metastatic lung tumors: Identification of risk factors for recurrence and major complications. J Vasc Interv Radiol. 2016;27(9):1371-9.
16. Nomori H, Yamazaki I, Kondo T, Kanno M. The cryoablation of lung tissue using liquid nitrogen in gel and in the *ex vivo* pig lung. Surg Today. 2017;47(2):259-64.
17. Lyons GR, Askin G, Pua BB. Clinical outcomes after pulmonary cryoablation with the use of a triple freeze protocol. J Vasc Interv Radiol. 2018;29(5):714-21.
18. Yamauchi Y, Izumi Y, Kawamura M, Nakatsuka S, Yashiro H, Tsukada N, et al. Percutaneous cryoablation of pulmonary metastases from colorectal cancer. PLoS One. 2011;6(11):e27086.

19. de Baère T, Woodrum D, Tselikas L, Abtin F, Littrup P, Deschamps F, et al. The ECLIPSE study: Efficacy of cryoablation on metastatic lung tumors with a 5-year follow-up. J Thorac Oncol. 2021;16(11):1840-9.

20. Gage AA, Baust JM, Baust JG. Experimental cryosurgery investigations *in vivo*. Cryobiology. 2009;59(3):229-43.

21. Rewcastle JC, Sandison GA, Muldrew K, Saliken JC, Donnelly BJ. A model for the time dependent three-dimensional thermal distribution within iceballs surrounding multiple cryoprobes. Med Phys. 2001;28(6):1125-37.

22. Hinshaw JL, Littrup PJ, Durick N, Leung W, Lee FT Jr, Sampson L, et al. Optimizing the protocol for pulmonary cryoablation: A comparison of a Dual- and Triple-Freeze protocol. Cariovasc Intervent Radiol. 2010;33(6):1180-5.

23. Permpongkosol S, Nicol TL, Link RE, Varkarakis I, Khurana H, Zhai QJ, et al. Differences in ablation size in porcine kidney, liver, and lung after cryoablation using the same ablation protocol. AJR Am J Roentgenol. 2007;188(4):1028-32.

24. Hashimoto K, Izumi Y, Yamauchi Y, Yashiro H, Inoue M, Nakatsuka S, et al. Prediction of the critical thermal zone during pulmonary cryoablation on computed tomography from correlated experimental and clinical findings. J Thorac Cardiovasc Surg. 2013;145(3):832-8.