Cryoablation Using Liquid Nitrogen for Metastatic Lung Cancers

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Case Report

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Abstract

Aims

To identify factors that were associated with local control after cryoablation for metastatic lung tumors and to compare preserved pulmonary function according to tumor number.

Methods

We retrospectively evaluated 68 patients with 121 metastatic lung tumors that were treated with cryoablation using liquid nitrogen during 2013–2019. Primary outcome was whether local control was related with tumor size, histology, location, and distance to a vessel with a diameter of ≥ 3 mm. Secondary outcome was whether preserved pulmonary function varied according to number of treated tumors.

Results

Median follow-up period was 32 months (range: 4–87 months).

Histological types were carcinomas in 95 tumors and sarcoma in 26 tumors. Multivariate analysis revealed that local control was significantly associated with tumor size ($p < 0.001$), histology ($p < 0.001$), and distance from a vessel with a diameter of ≥ 3 mm ($p = 0.03$). Among tumors with a diameter of ≥ 2.2 cm, poorer local control was observed for sarcomas ($p < 0.001$) and tumors that were ≤ 3 mm from the vessel ($p = 0.009$), although these relationships were not significant among tumors with a diameter of < 2.2 cm ($p = 0.44$ and $p = 0.16$). Relative to cryoablation for a single tumor, cryoablation for multiple tumors was associated with significantly lower preservation of pulmonary function ($p = 0.002$).

Conclusion

Poor local control after cryoablation was significantly associated with tumor size ≥ 2.2 cm, sarcoma histology, and tumors that were ≤ 3 mm from a vessel with a diameter of ≥ 3 mm. Preserved pulmonary function declined significantly with an increasing number of treated tumors.

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]. However, the stereotactic body radiation therapy can still cause a decrease in pulmonary function of approximately 8% decrease [8], which is a greater reduction than that after pulmonary segmentectomy [9]. Although percutaneous ablation therapies have been considered less invasive than surgery, the change of pulmonary function after the therapy is poorly understood.

Cryoablation for lung cancers has been performed with argon gas using two or more cryoprobes per tumor under computed tomography (CT) [10–12]. Recently, cryoablation with liquid nitrogen has become practical, which uses a single cryoprobe, of which cost is therefore cheaper. Recently, that device has been reported to provide satisfactory results for primary lung cancers [13]. However, the device using liquid nitrogen has not been reported for metastatic lung cancers, which frequently needs multiple treatments for multiple tumors. To evaluate the efficacy of this device for metastatic lung cancers, the present study evaluated factors that predicted local control after cryoablation using liquid nitrogen in 68 patients with 121 metastatic lung cancers. Treatment complications and preserved pulmonary function were also evaluated.

Methods

Study design

This retrospective study evaluated 68 patients who underwent cryoablation for metastatic lung cancers between 2013 and 2019 in Kameda Medical Center, which is an educational and cancer designated hospital. The study was designed in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology guidelines [14] 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) ≤ 3 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. Treatment 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 informed consent after fully discussing the risks and benefits of cryoablation.

Cryoablation procedure

Cryoablation was conducted by a radiologist (I.K.) who had 25 years of experience with interventional radiology. The treatment was usually performed with a single 13-G cryoprobe using liquid nitrogen (IceSense 3; IceCure Medical Ltd., Caesarea, Israel) under CT (Brilliance iCT SP; Philips Co., Amsterdam, Netherlands); however, two cryoprobes were used for tumors ≥ 3 cm with using 2 machines of IceSense3, because one cryoprobe was available for one IceSense 3. To penetrate the tumor with the 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 (**Fig. 1**).

After administration of pethidine hydrochloride (35 mg) and/or midazolam (2–3 mg), the patient was placed on a table of CT. After local anesthesia, the guide needle was inserted in the tumor under real-time CT imaging. The inner and outer sheaths were advanced over the guide needle to reach the tumor. After the outer sheath penetrated the tumor, the guide needle and inner sheath were withdrawn and the cryoprobe was inserted into the outer sheath (**Fig.S1**). Cryoablation was generally performed with 3 cycles as 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. After the cryoprobe was removed from the outer sheath, a 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.

Follow-up

Follow-up was conducted by CT with a slice thickness of 2 mm, which was performed every 3 to 4 months for the first 3 years after treatment; thereafter at least every 6 months. Local progression was defined as recurrence at the treated site. When the local recurrence was suspected on CT, the PET-CT or needle aspiration biopsy was conducted for the diagnosis. The local control period was evaluated based on the date of CT imaging. Medical records were searched in December 2020.

Outcomes

Outcomes were local control, preserved pulmonary function after treatment, and treatment complications.

Evaluation of factors that predicted local control

Local control was evaluated based on tumor size, histology, location, the distance from a vessel with a diameter of ≥ 3 mm, and chemotherapy after cryoablation. Tumor histology was classified as carcinoma or sarcoma. Tumor location was classified as peripheral (< 2 cm from pleura), intraparenchymal (≥ 2 cm from pleura), or hilar (< 1 cm from lobar artery or vein) on CT. The distance from the tumor to the closest vessel with a diameter of ≥ 3 mm was measured on CT, and categorized as > 3 mm or ≤ 3 mm based on the criteria reported by Yashiro et al. [6].

Evaluation of preserved pulmonary function

Forced expiratory volume in 1 second (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, since the pulmonary function after lung surgery has been reported to recover fully after 6 months and stabilize thereafter [15]. The percentage of preserved pulmonary function (%PPF) was calculated using the following formula: $[\text{FEV}_1 \text{ after treatment} / \text{FEV}_1 \text{ before treatment}] \times 100 (\%)$. For patients who underwent cryoablations more than once, 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, and number of needles used for each tumor.

Statistical analysis

Comorbidities were evaluated using the Charlson comorbidity index [16]. Postoperative complications were assessed using the Clavien-Dindo classification [17]. The optimal cut-off value for tumor size to predict local recurrence was determined using a receiver-operating characteristic curve and the Youden index. The Kaplan-Meier method was used to evaluate local control and overall survival period [18]. 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 $< .05$. 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 (range, 4–87 months). The patients were classified as having carcinoma (53 patients; 78%) or sarcoma (15 patients; 22%). Histological types of the tumors were various (**Table S1**).

Table 2 shows the characteristics of the 121 treated tumors, which were classified as carcinomas (95 tumors; 79%) or sarcomas (26 tumors; 21%). The tumor locations were classified as peripheral (81 tumors; 67%), intraparenchymal (32 tumors; 26%), or hilar (8 tumors; 7%). The distance from a vessel with a diameter of ≥ 3 mm was categorized as > 3 mm (74 tumors; 61%) or ≤ 3 mm (47 tumors; 39%). One tumor had tumor diameter < 5 cm, i.e., 6 cm, which was a metastasis of colon cancer and had rapidly grown after stereotactic radiation therapy. All the other tumors were less than 5 cm in diameter.

Ninety-three cryoablations were conducted for the 68 patients (**Table S2**). The number of treated tumors per procedure was 1 tumor for 69 procedures (74%), 2 tumors for 20 procedures (22%), and 3 tumors for 4 procedures (4%).

Table 3 shows the results of the univariate and multivariate analyses of factors for local control. The multivariate analysis revealed that local control was significantly associated with tumor size ($p = .0015$), histology ($p = .0014$), and distance from a vessel with a diameter of ≥ 3 mm ($p = .03$). 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 the curve, 0.87; 95% confidence interval, 0.80–0.93).

Local recurrence was experienced in 21 of the 121 tumors (17%). For the 21 local recurrences, surgical treatment was conducted for 4, additional cryoablation for 3, bronchial arterial embolization for 2, but no other local treatment for the remaining 12, because of having another distant metastasis. 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 tumors $\geq$ 2.2 cm ($p < .001$), with 3-year local control rates of 96% and 49%, respectively. Figure 2 shows the local control curves for tumors < 2.2 cm (69 carcinomas and 15 sarcomas) and tumors $\geq$ 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 ($p = .44$), with 3-year local control rates of 97% and 93%, respectively. However, for tumors $\geq$ 2.2 cm, sarcomas were associated with significantly poorer local control than carcinomas ($p < .001$), with 3-year local control rates of 18% and 62%, respectively.

Figure 3 shows the local control curves for tumors < 2.2 cm according to the distance to the vessel with a diameter of $\geq$ 3 mm (59 and 25 tumors with distance of > 3 mm and $\leq$ 3 mm, respectively) and for tumors $\geq$ 2.2 cm (15 and 22 tumors with distance of > 3 mm and $\leq$ 3 mm, respectively). For tumors < 2.2 cm, there was no significant difference between the distances of $\leq$ 3 mm and > 3 mm ($p = .16$), with 3-year local control rates of 98% and 92%, respectively. However, for tumors $\geq$ 2.2 cm, the distance of $\leq$ 3 mm from the vessel was associated with a significantly poorer local control than the distance of > 3 mm ($p = .009$), with 3-year local control rates of 31% and 77%, respectively.

The 3-year overall survival rate for all patients was 56%; however, patients with sarcoma had significantly poorer overall survival than those with carcinoma ($p = .02$), with 3-year survival rates of 28% and 67%, respectively (**Fig.S2**).

Pulmonary function at 6 months after treatment could not be measured for 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 4 shows the %PPF, which decreased with the increasing number of treated tumors: $98 \pm 6\%$ for 1 tumor ($n = 32$), $95 \pm 8\%$ for 2 tumors ($n = 15$), and $88 \pm 7\%$ for ≥ 3 tumors ($n = 11$) ($p = .002$).

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, 1–4 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). The univariate analysis revealed that the incidence of pneumothorax was significantly associated with FEV₁/FVC and the number of tumors treated per procedure (both $p < .001$); however, these relationships were not significant according to the multivariate analysis ($p = 0.62$ and $p = 0.32$, respectively) (**Table S3**). Treatment complications other than pneumothorax were hemothorax requiring chest tube drainage (Clavien-Dindo 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, 2–4 days).

Discussion

The present study revealed the following points: (1) the 3-year local control rate for metastatic lung cancers was 73%; (2) local control was significantly associated with tumor size (< 2.2 cm vs. ≥ 2.2 cm), histology (carcinoma vs. sarcoma), and distance from a vessel with a diameter of ≥ 3 mm (> 3 mm vs. ≤ 3 mm); (3) incidence rate of pneumothorax was 25%; and (4) pulmonary function decreased with the increasing number of treated tumors.

The 3-year local control rate (73%) for all tumors in the present study was similar to the 2-year or 3-year local control rates (range, 62–77%) associated with cryoablation using argon gas [6, 7, 19].

Several studies on cryoablation for lung cancers have indicated that the tumor size is significantly associated with local control. Yashiro et al. evaluated 8 primary lung cancers and 159 metastatic ones and 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). [6]. McDevitt et al. evaluated 25 primary lung cancers and 22 metastatic ones and reported that 3 cm as the cut-off value for predicting local control [20]. The present study revealed a consistent result, 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. 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%) [6]. Sarcomas are considered to be more resistant to cryoablation than carcinomas when tumor size is ≥ 2.2 cm.

Yashiro et al. have reported that the distance from the tumor to a vessel with a diameter of ≥ 3 mm was significantly associated with local progression after cryoablation [6]. The present study revealed a similar result, which might be attributable to the thermal sink effect [21]. An experimental study using liquid nitrogen revealed that extending the freezing time increased the size of the ablated area and decreased the temperature within it [22]. Therefore, a prolonged freezing time might be appropriate for tumors ≥ 2.2 cm when using liquid nitrogen.

The incidence rate of pneumothorax in the present study was 25%. Cryoablation with liquid nitrogen uses a single thick needle (13-G), whereas cryoablation with argon gas uses multiple thin cryoprobes (17-G). However, the incidence rate of pneumothorax in the present study was similar to that of cryoablation with argon gas (range, 25% to 34 %) [7, 19, 20].

A recent study of cryoablation for a single stage I non-small cell lung cancer revealed a %PPF of 97% [13]. Similarly, the %PPF after cryoablation for 1 tumor in the present study was 98%. However, the %PPF value decreased significantly after cryoablation for multiple tumors. Therefore, even though cryoablation has limited effect on pulmonary function, it appears that treatment for multiple tumors has a cumulative effect on pulmonary function.

While the cryoablation with argon gas usually uses 2 or more cryoprobes [10–12], the cryoablation with liquid nitrogen uses just one cryoprobe. In addition, the liquid nitrogen is even cheaper than the argon gas. Therefore, cryoablation using liquid nitrogen is not only as effective as that using argon gas but also is more cost effective than the latter.

This study had some important 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, which could have affected the overall survival.

In conclusion, the present study revealed that the cryoablation using liquid nitrogen for metastatic lung cancers resulted in similar local control and pneumothorax incidence as cryoablation using argon gas. However, pulmonary function decreased significantly when cryoablation was performed for an increasing number of tumors.

Declarations

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Tables

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)
Chemotherapy after cryoablation	
Yes	56 (82)
No	12 (18)

Table 2 Tumor characteristics.

Number of tumors (%)	121 (100)
Characteristics	Value
Tumor size	
Mean	1.7±1.1
Median (range)	1.3 (0.3 – 6.0)
Tumor histology	
Carcinoma	95 (79)
Sarcoma	26 (21)
Tumor location	
Peripheral	81 (67)
Intraparenchymal	32 (26)
Hilar	8 (7)
Distance from a vessel with a diameter of ≥ 3 mm	
> 3 mm	74 (61)
≤ 3 mm	47 (39)
Number of used needles	
1	114 (94)
2	7 (6)
Chemotherapy after cryoablation	
Yes	100 (83)
No	21 (17)

Table 3 Cox proportional hazard regression analyses for local control.

Variables	Univariate analysis		Multivariate analysis	
	HR (95% CI)	<i>P</i>	HR (95% CI)	<i>P</i>
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	—	
Distance from vessel	7.9 (2.7 – 23.6)	< 0.001	3.9 (1.2 – 12.6)	0.03
Chemotherapy	2.0 (0.5 – 8.7)	0.34	—	

HR: hazard ratio, CI: confidence interval.

Histology: carcinoma vs. sarcoma.

Location: peripheral vs. intraparenchymal vs. hilar.

Distance from vessel: > 3 mm vs. ≤ 3 mm from the vessel with a diameter of ≥ 3 mm.

Chemotherapy: chemotherapy after cryoablation.

Figures

Figure 1

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

Local control curves according to tumor diameter and histological type

Patient at risk

Carcinoma < 2.2cm	69	66	42	25
Sarcoma < 2.2cm	15	13	8	6
Carcinoma $\geq$ 2.2cm	26	19	14	6
Sarcoma $\geq$ 2.2cm	11	3	2	1

Figure 2

Local control curves according to tumor diameter and histological type. Among tumors with a diameter of ≥ 2.2 cm, sarcomas were associated with significantly poorer local control than carcinomas ($p < 0.001$), although no significant difference was observed among the tumors with a diameter of < 2.2 cm ($p = 0.44$).

Local control curves according to tumor diameter and distance to the vessel with a diameter of ≥ 3 mm.

Patient at risk

<2.2 cm with >3 mm to vessel	59	57	39	22
<2.2 cm with ≤ 3 mm to vessel	25	23	12	9
≥ 2.2 cm with >3 mm to vessel	15	12	8	3
≥ 2.2 cm with ≤ 3 mm to vessel	22	10	8	3

Figure 3

Local control curves according to tumor diameter and distance to the vessel with a diameter of ≥ 3 mm. Among tumors with a diameter of ≥ 2.2 cm, tumors that were ≤ 3 mm away from the vessel had significantly poorer local control ($p=0.009$), although no significant difference was observed among tumors with a diameter of <2.2 cm ($p=0.16$).

Figure 4

Percentage of preserved pulmonary function at 6 months after cryoablation according to the number of tumors. Significant differences were observed between all 3 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.

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