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Evaluating Cryoablation of Metastatic Lung Tumors in Patients—Safety and Efficacy

The ECLIPSE Trial—Interim Analysis at 1 Year

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Introduction: To assess the feasibility, safety and local tumor control of cryoablation for treatment of pulmonary metastases.

Materials and Methods: This Health Insurance Portability and Accountability Act (HIPAA) compliant, IRB-approved, multicenter, prospective, single arm study included 40 patients with 60 lung metastases treated during 48 cryoablation sessions, with currently a minimum of 12 months of follow-up. Patients were enrolled according to the following key inclusion criteria: 1 to 5 metastases from extrapulmonary cancers, with a maximal diameter of 3.5 cm. Local tumor control, disease-specific and overall survival rates were estimated using the Kaplan–Meier method. Complications and changes in physical function and quality of life were also evaluated using Karnofsky performance scale, Eastern Cooperative Oncology Group performance status classification, and Short Form-12 health survey.

Results: Patients were 62.6±13.3 years old (26–83). The most common primary cancers were colon (40%), kidney (23%), and sarcomas (8%). Mean size of metastases was 1.4±0.7 cm (0.3–3.4), and metastases were bilateral in 20% of patients. Cryoablation was performed under general anesthesia (67%) or conscious sedation (33%). Local tumor control rates were 56 of 58 (96.6%) and 49 of 52 (94.2%) at 6 and 12 months, respectively. Patient's quality of life was unchanged over the follow-up period. One-year overall survival rate was 97.5%. The rate of pneumothorax requiring chest tube insertion was 18.8%. There were three Common Terminology Criteria for Adverse Events grade 3 procedural complications during the immediate follow-up period (pneumothorax requiring pleurodesis, noncardiac chest pain, and thrombosis of an arteriovenous fistula), with no grade 4 or 5 complications.

Conclusion: Cryoablation is a safe and effective treatment for pulmonary metastases with preserved quality of life following intervention.

Key words: Lung metastasis, Cryoablation, Percutaneous ablation, Tumor control, Safety.

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Lung metastases in patients with oligometastatic disease are managed with surgery, stereotactic body radiation therapy (SBRT), and ablative therapies.[1] Surgical resection is the standard of care for these patients when possible.[2] Surgery is not an option for many patients because of advanced age, comorbidities, limited respiratory function, prior pulmonary resection, or surgery refusal.[3,4] For these patients, image-guided ablation and radiation therapy are increasingly offered as alternative therapies.[3–9] Early reports, including case series and small clinical trials, demonstrate the potential of radiofrequency ablation (RFA), microwave ablation, and cryoablation for treatment of pulmonary tumors.[5,10–18] Cryoablation uniquely offers visibility of the ablation margin with cross-sectional imaging due to formation of an interstitial infiltrate or visible ice, which defines the ablation zone and allows for complete tumor ablation while avoiding adjacent normal tissues and can be used along the pleura without procedural pain.[15,19]

Limited case reports and series of the use of percutaneous cryoablation for treatment of pulmonary metastases are encouraging,[18] although data are limited to characterizing the safety of treatment. The objectives of this prospective clinical trial were to assess the feasibility and safety of cryoablation and local tumor control of lung metastases smaller than 3.5 cm. This report represents the first prospective clinical trial for the use of cryoablation for early efficacy of treatment of pulmonary metastases.

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MATERIALS AND METHODS

This Health Insurance Portability and Accountability Act (HIPAA) compliant, single arm, phase 1 multicenter prospective study was approved by the institutional review board for each center, and written consent was obtained from all patients.

Between January 2012 and March 2013, 40 patients qualified for the trial and underwent cryoablation for total of 60 metastases (Tables 1 and 2).

Patients were enrolled prospectively at four hospital centers (one in Europe and three in the United States). Inclusion criteria were age 18 years old or more, pulmonary metastatic disease, Eastern Cooperative Oncology Group (ECOG) score[20] of 0–2, Karnofsky performance scale (KPS) score[21] greater than or equal to 60, a maximum of three metastases unilaterally and total of five bilaterally, with a size of the largest metastasis of 3.5 cm or smaller on a computed tomography (CT) scan obtained within 4 weeks before the procedure, and no previous targeted local therapy to the currently targeted lung metastasis. All percutaneous cryoablations were reviewed and approved by an oncologist, a surgeon, and an interventional radiologist at the institution where the procedure was performed. Exclusion criteria included platelet count less than 50,000/mm^3 and International Normalized Ratio greater than 1.5, evidence of infection or neutropenia (absolute neutrophil count of less than 1000/ml).

Metastases to the lungs or pleura were either confirmed by biopsy or deemed eligible as new or growing nodules on sequential imaging (CT or positron emission tomography/CT) in patients with an already pathologically proven primary cancer.

Between January 2012 and March 2013, 40 patients qualified for the trial and underwent cryoablation for total of 60 metastases (Tables 1 and 2).

TABLE 1. Baseline Patient and Lesion Characteristics

Characteristic	Value
Age, yr[a] (±SD)	62.6 ± 13.3
Gender	
Male	24 (60%)
Female	16 (40%)
BMI (±SD)	26.7 ± 5.3
Primary tumor type histology	
Colorectal	17 (42.5%)
Renal cell carcinoma	7 (17.5%)
Sarcoma	4 (10%)
Other	12 (30%)
Previous focal treatments for other lung metastases	
Radiation surgery	5 (13%)
Surgery	14 (35%)
Cryoablation	3 (8%)
RFA	7 (18%)
Microwave	2 (5%)
Tumor characteristics	
Mean tumor diameter (cm)	1.4 ± 0.7 (range, 0.3–3.4)
Tumor size (cm)	
0.3–1.0	18 (30%)
1.1–2.0	30 (50%)
2.1–3.0	11 (18.3)
≥3.1	1 (1.7%)
Number of tumors treated per patient	1.8 ± 1.0 (range, 1.0–4.0)
Tumor distribution	
Unilateral	32 (80%)
Bilateral	8 (20%)

[a]Forty-eight cryoablation procedures.

TABLE 2. Cryoablation Procedure Characteristics

Characteristic	Value
Procedure time (min)[a]	101.2 ± 38.7
Freeze duration per tumor[b] (min)	21.2 ± 4.6
Anesthesia	
General	32 (67%)
Conscious sedation	15 (31%)
Regional	1 (2%)
Number of cryoablation needles per tumor (±SD)	1.6 ± 0.9
Mean hospital stay	1 day (range, 0–4), 25.3 ± 21 hr (7–99)

[a]Forty-eight cryoablation procedures.
[b]Sixty tumors, typically three freeze cycles.

Cryoablation Procedure

Ablation was performed under general anesthesia or conscious sedation based on the preoperative anesthesiologist evaluation and investigator preferences at each center.

Cryoablation needles, 1.5 mm or 2.4 mm in diameter (17 and 13 gauge), provided by Galil Medical, Inc. (Arden Hills, MN) were placed under CT-scan guidance (Fig. 1) strategically to cover the tumor with an adequate margin lethal ice. Number, type, and configuration of the needles were based on the necessity to maintain a distance between adjacent cryoablation needles (less than or equal to 15 mm) and not more than 10 mm from the tumor margin while avoiding or displacing adjacent normal anatomical structures.

Cryoablation was performed applying a three-cycle freeze–thaw phase protocol. The times for each phase were recorded and varied as a function of the size of the tumor (target times were 3-min freeze, 3-min thaw, 8-min freeze, 5-min stick, 8-min freeze followed by active thawing). Each procedure was monitored with noncontrast CT imaging at 3 to 5 minutes intervals to visualize the evolving ablation zone with the goal of achieving a circumferential margin beyond the tumor of 5 mm. After cryoablation needle(s) were removed, CT images were obtained to assess the overall ablation zone and any potential complications.

Follow-up

Patient-specific follow-up for the study was done within the first week, at 1, 3, 6, and 12 months. Within 1 week of a single procedure or the last of multiple procedures, patients had chest X-ray or a CT without intravenous contrast to assess for early complications. Patients were clinically evaluated at 1 month from the last ablation to assess safety of the

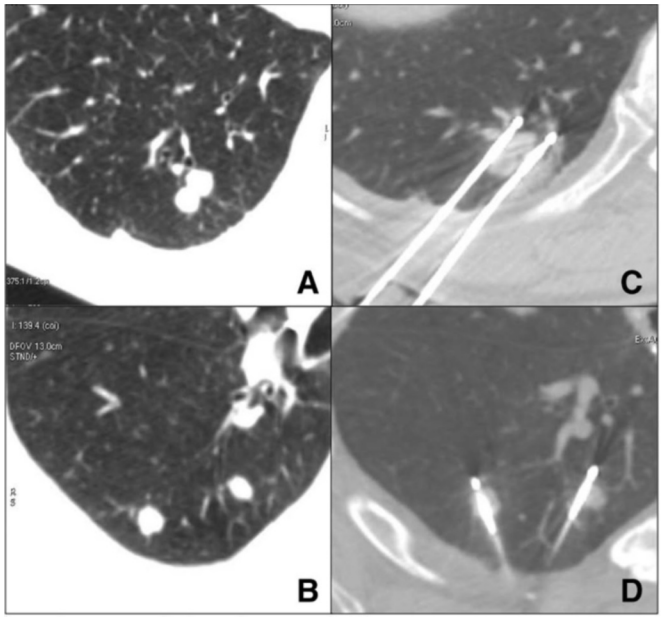

FIGURE 1. Percutaneous cryoablation under computed tomography (CT)-scan guidance. CT-scan images of the chest without contrast obtained before (*A* and *B*) and during (*C* and *D*) the cryoablation from a 71-year-old patient with right lower lobe lung metastases from a colon adenocarcinoma.

procedure and its impact on quality of life. Follow-up at 3, 6, and 12 months included clinical examination, chest CT with or without intravenous contrast material (Fig. 2), and quality of life evaluation. Follow-up will continue annually through 5 years.

Data Collection

Data were collected at each institution, anonymized and centralized to a web-based electronic data capture system (TrackIt2K, Acumen Healthcare Solutions, LLC, Plymouth, MN), compliant with FDA 21 CFR Part 11 guidance. Collected data included patient demographics, primary cancer histology, prior cancer treatment, number of metastases, tumor location, and maximal tumor dimensions. Procedural times, anesthesia type, the number and type of cryoablation needles, procedural complications and interventions, and the length of hospital stay were also recorded.

Treatment Outcome Measures

Technical success for each treated tumor was defined as a zone of ground glass opacity, or visible ice encompassing the targeted tumor with at least a 5-mm circumferential ablative margin on CT at end of the cryoablation. To be considered a technical success in each patient, all targeted tumors had to meet defined postablation technical success criteria.

Local tumor control assessment was based on imaging measures and ablation zone enhancement patterns at 6 and 12 months, using the appearance of the ablation zone at 3 months as comparative baseline. The 3-month follow-up imaging was selected to represent the baseline scan, as the ablation zone is larger than the targeted tumor. Assessment of tumor progression or incomplete ablation was based on changes in size and contrast enhancement relative to the 3-month baseline. Tumor response was calculated using the sum of the largest diameter of ablation zones and compared with baseline scan at 3 months. "Complete" response was defined as reduction of 75%, "partial" response as 30% to 75% decrease in size of the ablation zone, "stable disease" when there was less than 30% decrease and less than 20% increase in the size of the ablation zone, and "local failure" when an increase of greater than 20% compared with the smallest diameter (nadir) of the ablation zone or the appearance of nodular enhancement.

Time to tumor progression was defined as the time from cryoablation procedure to local failure.

Distant tumor progression was defined as the appearance of distant metastatic disease outside of the treatment area, either in the lung or outside the lung.

Disease specific survival and overall survival rates were calculated from the day of the ablation to time of death related to cancer and related to any cause, respectively.

Safety and Procedural Tolerance Assessment

Adverse events that occurred within 30 days of the procedure were reported considering causality and severity and were graded in accordance with the Common Terminology for Adverse Criteria for Adverse Events (CTCAE version 4.0) of the National Cancer Institute.[22] Subsequent hospital admission and surgical interventions were also recorded.

Changes in physical function and quality of life over time included physical performance (ECOG and KPS) and quality of life employing Short Form-12 (SF-12) assessment at baseline and during follow-up.[23]

Statistical Analysis

All subjects treated were included in the analyses (per protocol). Continuous variables are expressed as mean, standard deviation, number of patients, median, minimum, and maximum. Categorical variables including efficacy outcomes and adverse events are summarized by frequencies and percentages of patients in each category.

Survival rates are analyzed using Kaplan–Meier methodology. ECOG, Karnofsky, and SF-12 analyses used repeated measures analysis of variance models to examine differences. SAS version 9.3 (SAS Institute, Cary, NC) statistical software was used for analyses. *P* values less than 0.05 were considered as statistically significant.

RESULTS

Patients and Tumors

Patient and tumor characteristics are summarized in Table 1. Among the 40 enrolled patients, colorectal origin was the most frequent cancer, accounting for 40% of metastases. Thirty of 40 (75%) patients had prior focal treatment for other lung metastases but without prior treatment to the targeted lung metastases on this study. Seven of the 40 (18%) patients received systemic chemotherapy concurrently or after the cryoablation treatment. No patients received radiation therapy to the targeted tumors in this study after cryoablation. Three of 60 tumors (5%) had pleural contact, and no tumors had hilar involvement.

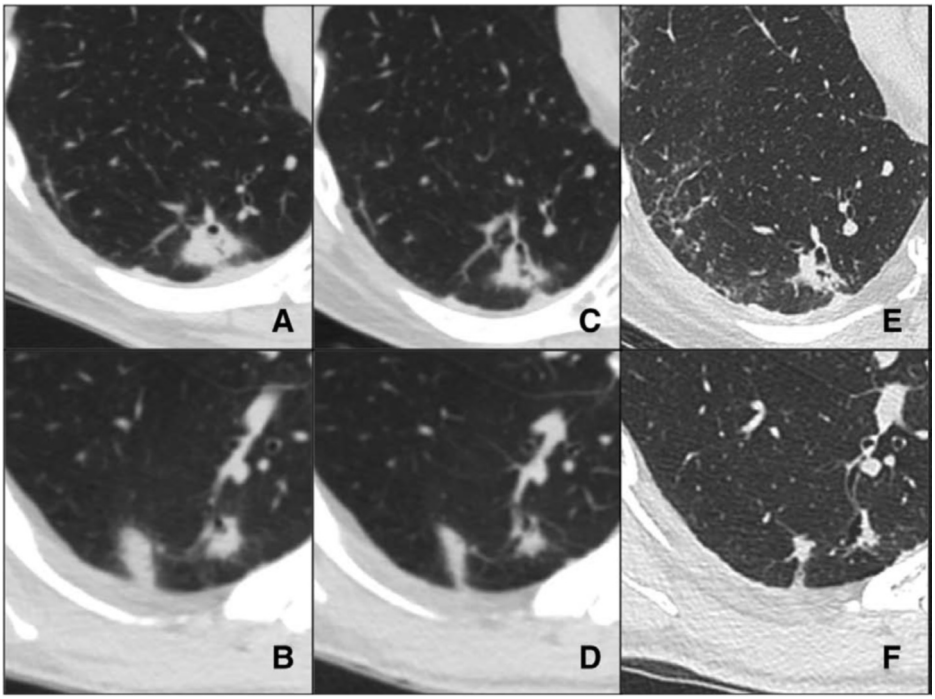

FIGURE 2. Follow-up after percutaneous cryoablation. Follow-up computed tomography (CT)-scans performed at 3 months (*A* and *B*), 6 months (*C* and *D*), and 1 year (*E* and *F*) after the cryoablation procedure showing a resorption of the ablation zone (same patient as Fig. 1).

Cryoablation

A total of 60 thoracic metastases were treated during 48 procedures in 40 patients. Treatment of bilateral disease on the same day was not allowed per protocol. The mean number of cryoablation needles used per procedure was 1.6 (range, 1–5). For tumors less than 2.0 cm in diameter, a mean of 1.7 probes with a range of 1 to 3 probes were used in treatment. For tumors larger than 2.0 cm in diameter, a mean of 2.3 probes with a range of 1 to 5 probes were used in treatment. Fifty-three of 60 (88%) tumors were treated with three freeze cycles, two tumors (3%) with two freeze cycles, and five (8%) tumors with four freeze cycles. Mean procedure time was 101.2 minutes (±38.7) including anesthesiology management, cryoprobe placement, ablation time, and postprocedural CT evaluation (Table 2). Immediate technical success was obtained in all 40 patients (100%) and 60 tumors (100%).

Treatment Efficacy

Primary efficacy is shown in Table 3. Thirty-five of 40 (90%) patients were included in the follow-up analysis. Of the five patients not available for the 12-month analysis, one patient had progression of disease outside the lung, which precluded further follow-up beyond 6 months, one patient had an unrelated death 5 months after treatment, one patient completed the 12-month visit but did not have imaging conducted, and two patients were lost to follow-up. Overall local tumor control after ablation at the 12-month analysis, for combined stable disease, partial, and complete response, was seen in 49 of 52 metastases (94.2%) and 32 of 35 patients (91.4%). Three of 52 metastases (5.8%) had local failure observed at 6 and 12 months with increasing size of the ablation zone. There was no significant difference in rate of tumor progression, or incomplete ablation, as a function of original treated tumor diameter ($p = 0.41$). For the remainder of the treated tumors that were followed in this study, no enlargement of the ablation zone or appearance of nodular enhancement were demonstrated during the 12-month follow-up (Fig. 2). Two of the three local progressions could be retreated with focal therapy (one cryoablation and one radiofrequency). The remaining local failure observed at 6 months was associated with widespread progression of metastatic disease, for which the patient received immunotherapy.

At 12 months, there was evidence of additional metastatic disease in 14 of 35 evaluable patients (40%), with a mean time to new metastases postcryoablation treatment of 10.7 months (SD ± 3.6). Fifteen of the 40 patients (38%) received new therapies during the study. Systemic treatment for diffuse metastatic disease (chemotherapy: n = 7 and immunotherapy: n = 1) was administrated to eight patients (20%), and 10 patients (25%) received other focal therapies for new

TABLE 3. Primary Efficacy Per Metastases

	6-mo Metastases = 58	12-mo Metastases = 52
Complete response	9 (15.5%)	11 (21.2%)
Partial response	20 (34.5%)	25 (48.1%)
Stable disease	27 (46.6%)	13 (25%)
Local failure	2 (3.4%)	3 (5.8%)

metastatic disease, among them six cryoablation procedures. One-year disease-specific survival and overall survival rates were 100% and 97.5%, respectively (Fig. 3).

Safety and Tolerance

Pneumothorax requiring chest tube placement occurred in 9 of the 48 procedures (18.8%), and chest tubes were removed after 1 day (n = 8) or 2 days (n = 1). CTCAE grade 3 adverse events within 30 days of the procedure occurred in 3 of 48 (6%) procedures including a delayed pneumothorax requiring pleurodesis, a thrombosis of a preexisting hemodialysis access arteriovenous fistula requiring thrombectomy, and a noncardiac chest pain, which spontaneously resolved. No grade 4 or 5 procedure-related adverse events occurred. No procedural-related delayed adverse events were observed. Hospital length of stay averaged 1 day (range, 0–4 days) but varied based on differences of international standard practices.

There was no significant change of ECOG or KPS at 1, 3, 6, or 12 months in comparison with baseline mean values. The SF-12 quality of life questionnaire revealed no clinically meaningful adverse impact on quality of life after cryoablation, though general health perception subscale showed statistical difference (63.9 versus 58.2 before cryoablation and at 12-month follow-up, $p = 0.047$; Table 4)

DISCUSSION

We report the first prospective, multicenter study of image-guided percutaneous cryoablation for the treatment of lung metastases. In this study, we found 94.6% local tumor control rate at 12 months follow-up, associated with a well-tolerated treatment.

A recent systematic review and a meta-analysis of patients with colorectal cancer lung metastases reported 5-year overall survival rates of 27% to 68% after complete surgical resection.[24,25]

But today, although surgical resection remains the standard procedure for lung metastases and despite advances in surgical techniques, many patients with lung metastases are not surgical candidates because of comorbidities or intolerance for further surgical resection. Percutaneous image-guided ablation offers the opportunity to treat nonsurgical candidates with limited tumor burden and preserve lung parenchyma for patients who have compromised respiratory function or who may need multiple interventions during the course of their disease management.[5,9] For the latter reason, thorough acceptance of surgical metastasectomy has been tempered given that up to 50% of patients recur.[26]

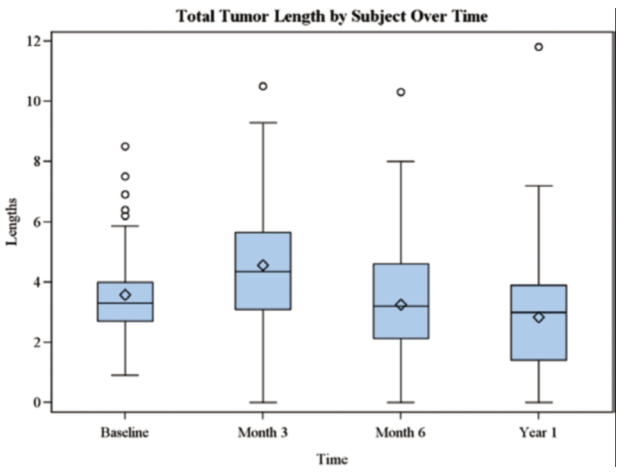

FIGURE 3. Tumor size evolution graph during 1-year follow-up.

The results of this trial compare favorably with the reported results utilizing other focal therapies including SBRT, RFA, microwave ablation, and cryoablation for the treatment of patients with metastatic lung disease.[6,8,9,13,19] Okunieff et al.[6] reported 83% local control with SBRT at a median of 18.7 months in the treatment of 50 patients with 125 tumors with a mean tumor diameter of 2.5 cm. Local control rate using RFA was 89% in a prospective study of 61 patients with metastatic lung disease with a mean follow-up of 15 months[9] and reported 4-year local efficacy 89% in a large prospective trial of 566 patients.[8] Local control rate of 73.1% is reported in the treatment of 130 metastatic lung tumors with microwave ablation with mean follow-up of 9 months.[13] We have to acknowledge that comparison of local control rates is difficult because this control rate depends on tumor diameter and location, even though the diameter of the tumors we treated in this prospective study (mean: 1.5 cm, range, 0.3–4.4) were within the range of what is described by other ablative techniques.[8,27–29]

Percutaneous cryoablation of lung and pleural tumors was well tolerated. The need for chest tube placement occurred in 18.8% of our procedures with 8 of 9 (89%) patients having the chest tube removed the day after the procedure. CTCAE grade 3 adverse events occurred in 6% of patients in this study, and no grade 4 or 5 adverse events. In addition, none of the patients undergoing cryoablation in this study experienced significant pain reported as grade 2 or greater during the postprocedural period. This low incidence of periprocedural and postprocedural pain has been widely recognized as one specific advantage of cryoablation over other thermal therapies.[17,30–32]

Cryoablation offers comparable, if not additional advantages, when compared to radiofrequency and microwave ablation. Current cryotechnology affords smaller (1.5 – 2.4 mm in diameter), more competitive, caliber cryoprobes compared with competing thermal modalities and segmental insulation for percutaneous application compared with early generation cryoprobes. In general, compared with the heat-based technologies, cryoablation treatment within the lung can be more easily monitored with CT imaging with the ablation zone defined by an interstitial infiltrate or low attenuation zone. A triple freeze–thaw cycle protocol was used in this study rather than the double freeze–thaw cycle more often used in kidney, liver, or soft tissue. This triple cycle exploits early focal edema and alveolar hemorrhage generated during the first thaw cycle resulting in better thermal conduction because of fluid beyond the margin of the targeted tumor.[33] Niu et al.[33] compared triple freeze–thaw cycle protocol (5-min freeze–5-min thaw–5-min freeze–5-min thaw–10-min freeze) and double freeze–thaw cycle protocol (10-min freeze–5-min thaw–10-min freeze) and concluded that triple freeze–thaw cycles may increase

TABLE 4. Quality of Life Evaluation

	Baseline	1 mo	3 mo	6 mo	12 mo	P[a]
ECOG	0.3 ± 0.5	0.1 ± 0.4	0.3 ± 0.5	0.3 ± 0.4	0.4 ± 0.6	0.6256
Karnofsky	95.5 ± 8.1	97.7 ± 6.1	95.9 ± 6.7	96.7 ± 6.1	95.5 ± 9.1	0.7017
SF-12[b]	63.9 ± 23.3	59.1 ± 19.1	64.8 ± 24	62.2 ± 19.6	58.2 ± 29.6	0.0474

Results are expressed as means ± standard deviation.
[a]*p* values using analysis of variance.
[b]General Health Perception item has been used to summarize SF-12 quality of life questionnaire.
ECOG, Eastern Cooperative Oncology Group; SF-12, short form-12.

ablation zone versus two freeze–thaw cycles and allow earlier visualization or treatment-induced changes. Because of the low incidence of associated procedural pain, cryoablation can be comfortably performed under conscious sedation, even when ablating targeted tumors are within the chest wall or subpleural and juxtapleural lung close to somatically innervated parietal pleura. Even for tumors within this location, cryoablation can be safely performed on tumors located in the lung periphery or involving the pleura with low risk for bronchopleural fistula.[31]

And finally, rapid involution in the size of the ablation zone on CT imaging (Fig. 3) facilitates identification of local treatment failure with most local tumor progression, or incomplete ablation visualized by 6-month CT.[5,34] In our study, 2 out of 3 local failures were detected on the 6-month evaluation.

Limitations of this study included a relatively small number of patients and a relatively short follow-up for assessment of local tumor control. Nonetheless, these early results are certainly encouraging with intermediate and long-term data for trial participants still being collected and based on our experience from this trial an expanded more comprehensive study is currently enrolling patients. The patients included in the herein reported trial have mixed primary histology and cancer-specific survival cannot be compared with sufficient statistical power. In addition, follow-up imaging to assess local tumor control in this study utilized the structure and size of the ablation zone at 3-month imaging as a baseline for comparison with subsequent imaging, and not pretreatment tumor size as standard in RECIST and other oncologic evaluations. Regardless, this methodology has been successfully utilized to assess treatment response in prior ablation studies[9] and in other applications of nonsurgical and nonsystemic local energies, specifically radiotherapy.

To summarize, and although percutaneous cryoablation for the treatment of lung metastases of 3.5 cm and smaller is safe and early local tumor control rates are promising and competitive with other contemporary technologies, large randomized controlled trials are needed to compare local therapies with the traditional standard surgical resection.[35]

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