Risk of persistent air leaks following percutaneous cryoablation and microwave ablation of peripheral lung tumors

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ABSTRACT

Objectives: To compare the incidence of persistent air leak (PAL) following cryoablation vs MWA of lung tumors when the ablation zone includes the pleura.

Methods: This bi-institutional retrospective cohort study evaluated consecutive peripheral lung tumors treated with cryoablation or MWA from 2006-2021. PAL was defined as air leak for more than 24 hours after chest tube placement or an enlarging postprocedural pneumothorax requiring chest tube placement. The pleural area included by the ablation zone was quantified on CT using semi-automated segmentation. PAL incidence was compared between ablation modalities and a parsimonious multivariable model was developed to assess the odds of PAL using generalized estimating equations and purposeful selection of predefined covariates. Time-to-local tumor progression (LTP) was compared between ablation modalities using Fine-Gray models, with death as a competing risk.

Results: 260 tumors (mean diameter, 13.1 mm ±7.4; mean distance to pleura, 3.6 mm ±5.2) in 116 patients (mean age, 61.1 years ±15.3; 60 women) and 173 sessions (112 cryoablations, 61 MWA) were included. PAL occurred after 25/173 (15%) sessions. The incidence was significantly lower following cryoablation compared to MWA (10 [9%] vs 15 [25%]; p=.006). The odds of PAL adjusted for the number of treated tumors per session were 67% lower following cryoablation (odds ratio=0.33 [95% CI, 0.14-0.82]; p=.02) vs MWA. There was no significant difference in time-to-LTP between ablation modalities (p=.36).

Conclusions: Cryoablation of peripheral lung tumors bears a lower risk of PAL compared to MWA when the ablation zone includes the pleura, without adversely affecting time-to-LTP.

Key words:

1. cryoablation
2. microwaves
3. lung neoplasms
4. pleura
5. pneumothorax

Key points

1. The incidence of persistent air leaks after percutaneous ablation of peripheral lung tumors was lower following cryoablation compared to microwave ablation (9% vs 25%; p=.006).
2. The mean chest tube dwell time was 54% shorter following cryoablation compared to MWA (p=.04).
3. Local tumor progression did not differ between lung tumors treated with percutaneous cryoablation compared to microwave ablation (p=.36).

Abbreviations

CI – Confidence interval

HU – Hounsfield Units

IGTA – Image-guided thermal ablation

LTP – Local tumor progression

MWA – Microwave ablation

OR – Odds ratio

PAL – Persistent air leak

Introduction

Thermal and mechanical injury associated with image-guided thermal ablation (IGTA) of lung tumors can cause an abnormal communication of alveoli or airways with the pleural space resulting in an air leak [1]. Air leaks have been linked to heat-based IGTA when the ablation zone includes part of the pleura [1-6]. While most air leaks resolve spontaneously, some persist for more than 24 hours due to a fistula between the pleura and the alveoli or bronchial tree [7, 8]. Persistent air leaks are associated with significant morbidity, prolonged hospital length of stay, and mortality [2, 7, 9, 10].

When selecting a percutaneous thermal ablation modality, cryoablation has been recommended over heat-based microwave ablation (MWA) for peripheral lung tumors due to a purported lower risk of air leaks and the analgesic effect on the parietal pleura and chest wall soft tissues [5, 11-15]. However, data supporting this recommendation are lacking. The purpose of this bi-institutional cohort study was to retrospectively compare the incidence of persistent air leak (PAL) following cryoablation vs MWA of peripheral lung tumors when the ablation zone includes the pleura.

Materials and Methods

This HIPAA–compliant retrospective cohort study was approved by the institutional review board and the need for informed consent was waived.

Patient Selection

We reviewed prospectively maintained registries at two academic medical centers (Massachusetts General Hospital, Brigham and Women's Hospital) of percutaneous thermal lung ablations between May 2006 and December 2021. 90 tumors in 37 patients were part of prior investigations which focused on different aspects [16, 17]. We included consecutive percutaneous cryoablation or MWA sessions of one or more lung tumors with the goal of eradication (**Figure 1**). In each session, at least one ablation zone had to include part of the pleura. Sessions were excluded if a needle biopsy was performed together with the ablation, if an unintentional pneumothorax occurred before the application of energy, if pleural contact with the ablation zone could not be determined due to bleeding or image artifacts, or if follow-up was less than 30 days. Included intraprocedural pneumothoraxes for cryoablation sessions and MWA sessions targeting a single lesion occurred prior to applicator removal. For MWA sessions targeting multiple lesions with a single applicator, included intraprocedural pneumothoraxes occurred either prior to or following applicator removal.

Outcome Measures

The primary outcome was the incidence of PAL within 30 days after each ablation session. PAL was defined as an air leak for more than 24 hours after chest tube placement or an enlarging postprocedural pneumothorax (unintentional or intentional) requiring chest tube placement. Air leak after chest tube placement was defined as air bubbles in the water seal chamber of the chest drainage system. A pneumothorax was categorized as enlarging if the report of consecutive portable upright chest radiographs concluded that a preexisting pneumothorax had increased in size. Criteria for chest tube placement at both institutions were a moderate to large pneumothorax or respiratory distress caused by a pneumothorax.

Secondary outcomes were chest tube dwell time, hospital length of stay and time-to-local tumor progression (LTP). LTP was defined as reappearing viable tumor provided that at least one contrast-enhanced follow-up study did not reveal residual viable tumor at the ablative margin [18]. Time-to-LTP was only analyzed for tumors treated with primary technical success.

Data Collection and Image Analysis

We abstracted the incidence, time of onset, and duration of pneumothorax, chest tube placement and dwell time, air leak, and hospital length of stay from each center’s registry. A board-certified thoracic radiologist not involved with the ablation procedures reviewed procedural images and serial post procedure chest radiographs of all instances of enlarging postprocedural pneumothorax requiring chest tube placement to confirm that the air gap enlarged at least 2 cm prior to chest tube placement.

The registry also included age, sex, Eastern Cooperative Oncology Group performance status, smoking history, treatment history (prior lung resection or thoracotomy, systemic therapy), treatment goal (eradication, debulking, palliation), histology, axial tumor dimensions, tumor location, procedural characteristics (anesthesia type and ventilation strategy, number of probes, probe type, treatment protocol, number of tumors, concurrent needle biopsy). Fully automated lung densitometry of pretreatment diagnostic chest CT scans was performed using the Chest Imaging Platform extension of 3D Slicer (version 4.13.0) [23].

A trained analyst (M.A.K., one year of experience in lung ablation research), measured longest axial tumor diameter and shortest distance to pleura on planning CT images using electronic calipers and lung window settings (width, 1500 HU; level, –600 HU). The analyst also measured total length of aerated lung traversed by probes and categorized the pleural area included by ablation zones as costal, mediastinal, diaphragmatic, or cervical (**Figure 2**). The pleural area included by ablation zones was quantified using the open-source software package 3D Slicer (version 4.13.0) on lung window settings (width, 1500 HU; level, –600 HU). For cryoablation, the ablation zone was defined as the predicted -20C° isotherm in relation to the probe tip as per the manufacturer manual [19, 20] and visualized by superimposing a spherical 3D object onto intraprocedural CT images (**Figure 2**). For MWA, the ablation zone was defined as peritumoral ground glass and visualized by segmenting CT images obtained within 10 minutes after MWA with a lower threshold of –600 HU; no upper threshold was used [21, 22]. For sessions with multiple probes, the total (summated) length of aerated lung traversed, and the total (summated) pleural area included by ablation zones was calculated. Measurements were verified and corrected as necessary by a board-certified radiologist with 2 years of experience (M.C.M.).

All measurements were repeated for 10% of randomly selected cases by the analyst and a secondary analyst (J.A.S., one year of experience in lung ablation research) to assess inter- and intrareader agreement. Procedure time was defined as the time between the localizer image and the last intraprocedural CT acquisition.

Primary technical success, LTP, and prior ipsilateral lung resection or thoracotomy were assessed by a board-certified radiologist with 2 years of experience (M.C.M.) who was blinded to outcomes and not involved in the ablation procedures. Primary technical success was defined as completion of the planned ablation protocol and tumor coverage with a margin of at least 5 mm from the tumor edge to the edge of the ablation zone [18].

Patient Evaluation and Ablation Procedure

Patients were referred for ablation following evaluation by thoracic surgery, interventional radiology, radiation oncology, and medical oncology. Potential ablation targets were observed for at least 3 months to ensure that nodules did not decrease in size or increase in number. The diagnosis of lung metastases was established either by biopsy or based on new and enlarging lung nodules on CT in patients who had undergone resection of lung metastases or known metastases in other organs. Ablations were performed by one of 7 fellowship-trained radiologists with 2-12 years of experience. Ablation modality (cryoablation, MWA) was based on operator preference. Depending on comorbidities and technical considerations, moderate sedation, monitored anesthesia care, or general endotracheal anesthesia was used. Patients were placed in either prone, supine, or lateral decubitus position on the table of a CT scanner (LightSpeed [GE Healthcare] or Sensation Open [Siemens Healthineers]). Only one lung was treated per session. Under sterile precautions and local anesthesia, one or more applicators were introduced percutaneously under CT guidance. A single applicator was used during all MWA sessions, whereas one or more applicators were used during cryoablation sessions. One or more 22-gauge fine needles were placed to guide insertion in some cases. Applicator type and number, percutaneous entry route, and MWA treatment protocol were based on tumor size, number, and location. MWA was performed using the 2.45 GHz AMICA system (HS Hospital Service S.P.A.), 915 MHz MicroTherm X system (Siemens Healthineers) or 2.45 GHz Certus 140 system (Johnson and Johnson) using a 14- or 16-gauge AMICA (HS Hospital Service S.P.A.), 16-gauge SynchroWave® ST (Siemens Healthineers) or 17-gauge NEUWAVE™ PR XT (Johnson and Johnson) antennae. Cryoablations were performed using the Visual ICE system (Boston Scientific) or the Cryocare® (Siemens Healthineers) system using 14-gauge (IceForce 2.1 CX, IcePearl 2.1 CX), 17-gauge (IceRod 1.5 CX, IceSphere 1.5 CX, Boston Scientific), PERC-24 or PERC-17 probes (Siemens Healthineers). Of 129 cryoablations, 98 were performed with a triple freeze protocol and 30 with a dual freeze protocol. After the last freeze and before probe removal, either a passive thaw or a 0.5–5-minute active thaw was applied. No track ablation was performed following MWA. In 20 sessions, a pneumothorax was intentionally created to ensure protection of heart, nerves, and parietal pleura. Post ablation, patients were routinely admitted for overnight observation at one institution. At the other institution, 7 patients were discharged the same day.

Statistical Analysis

We calculated inter- and intraclass correlation coefficients to determine inter- and intrareader agreement for the longest axial tumor diameter, shortest distance to pleura, total length of aerated lung traversed by probes, and total pleural area included by ablation zones.

To explore risk factors for the incidence of PAL, we defined 11 candidate variables *a priori* on the basis of clinical experience and existing literature: ablation modality (explanatory variable), age, sex, number of targeted tumors, number of pleural punctures, number of pleural puncture sites included by ablation zones, total length of aerated lung traversed by applicators, ventilation strategy, total pleural area included by ablation zones, absence of prior ipsilateral lung resection or thoracotomy, chemotherapy within six weeks prior to ablation [1, 4, 6, 24, 25].

Because some patients underwent multiple sessions for the treatment of unique lung tumors, we explored associations of each candidate variable with the outcome using generalized estimating equations with an independence working covariance structure. We developed a parsimonious multivariable model using a purposeful selection approach as described by Bursac et al. [26, 27], followed by bootstrap resampling with 10,000 replicates [28, 29].

We used Fine-Gray models to estimate the association between the time-to-LTP and ablation modality on a per-tumor basis [30]. We included death as a competing risk and accounted for within-patient correlations using clustering. Patients without evidence of death based on the review of the electronic health record and online obituaries were censored at either the time of last contact or December 08, 2021, whichever occurred first.

A p-value $<.05$ was considered to indicate statistical significance. All analyses were performed using R Software Version 4.13.0 (Foundation for Statistical Computing) and supervised by D.A.P.

Results

Patient, Procedural, and Tumor Characteristics

Of 305 lung tumors treated in 210 sessions in 146 patients, we excluded 28 ablation sessions that were combined with biopsy, 6 sessions due to the development of unintentional pneumothorax prior to application of energy (3 cryoablation, 3 MWA), 3 sessions due to suboptimal imaging to assess pleural involvement and 1 session due to follow-up less than 30 days (**Figure 1**). A total of 260 lung tumors treated in 173 sessions (112 cryoablation, 61 MWA) in 116 patients (mean age, 63.8 years ±12.4; 60 women) were included (**Table 1**). There was no significant difference between the groups regarding the 15th percentile of lung attenuation (median -893 HU vs -897 HU; p=.14). Fifteen patients underwent both cryoablation and MWA in separate sessions. After exclusion of eight tumors ablated without primary technical success, we assessed LTP in a subset of 252 tumors treated in 167 sessions (107 cryoablation, 60 MWA) in 112 patients (**Figure 1**).

While the longest axial tumor diameter did not differ between cryoablation and MWA, tumors treated with cryoablation were significantly closer to the pleura (median 0 mm vs 4 mm; p<.001) (**Figure 2**, **Table 2**). High-frequency jet ventilation was more frequently used for cryoablations and cryoablation procedure times were longer (**Table 2**). Primary technical success did not differ significantly between ablation modalities and was achieved for 252 of 260 (97%) tumors, including 151 of 158 (96%) that underwent cryoablation and 101 of 102 (99%) that underwent MWA. The average cryoprobe was 15.8 gauge, the average MWA antenna was 15.9 gauge. The cryoablation zone did not manifest as focal consolidation following the third freeze in 3 of 112 instances (3%).

Inter- and intraclass correlation coefficients for the measurements of pleural area included by the ablation zone were excellent: the interclass correlation coefficient was 0.91 (95% CI, 0.67 –0.97) and the intraclass correlation coefficient was 0.95 (95% CI, 0.87–0.98). Inter- and intraclass correlation coefficients for the measurements of the longest axial tumor diameter, shortest distance to pleura, total length of aerated lung traversed by probes ranged from 0.85 to 0.98 (mean, 0.92).

Incidence of pneumothorax, persistent air leak, chest tube placement, chest tube dwell time, and hospital length of stay

An intentional intraprocedural pneumothorax was created in 13 of 112 (12%) cryoablations and 7 of 61 (11%) MWA sessions (p=.98). An unintentional intraprocedural pneumothorax occurred during 17 of 112 (15%) cryoablation and 20 of 61 (33%) MWA sessions (p=.007) (**Table 3**). During 11 MWA sessions targeting multiple lesions with a single applicator, one intraprocedural pneumothorax occurred prior to and 10 following applicator removal.

A post-procedure pneumothorax within 24 hours after ablation occurred after 17 of 112 (15%) cryoablation and ten of 61 (16%) MWA sessions (p=.83). A pneumothorax more than 24 hours after ablation occurred following four of 112 (4%) cryoablation and five of 61 (8%) MWA sessions (p=.21).

Chest tube placement for unintentional intraprocedural pneumothorax was required during 13 of 112 (12%) cryoablations and 12 of 61 (20%) MWA sessions (p=.16). Chest tube placement for enlarging postprocedural pneumothorax was required after six of 112 (5%) cryoablations and nine of 61 (15%) MWA sessions (p=.03). Independent review of procedural images and serial post procedure chest radiographs by a board-certified thoracic radiologist not involved with the ablation procedures confirmed air gap enlargement in all 15 instances (100%) prior to chest tube placement.

Two patients treated with MWA underwent chest tube placement for an unintentional intraprocedural pneumothorax which resolved initially but re-appeared and enlarged after chest tube removal. These patients underwent subsequent repeat chest tube placement.

An air leak in the chest drainage system 24 hours after chest tube placement was detected following five (4%) cryoablation and 11 (18%) MWA sessions (p=.007). Therefore, the primary outcome occurred after a total of 10 of 112 (9%) cryoablations and 15 of 61 (25%) MWA sessions (p=.006), of which six (24%) instances met both criteria for PAL.

Chest tube dwell time was 62% shorter for cryoablation compared to MWA (mean 1.3 days vs 3.5 days; p=.003). Hospital length of stay was 37% shorter for cryoablation compared to MWA (mean 1.21 days vs 1.90 days; p=.006). An average of 4 chest radiographs (standard deviation, 3.3) were obtained following each ablation session.

Univariable analysis showed no significant association between the 11 *a priori* defined risk factors and PAL other than ablation modality (p=.006) and number of targeted tumors per session (p=.004). Univariable analysis showed that the odds of PAL were 70% lower following cryoablation compared to MWA (odds ratio [OR], 0.30 [95% CI, 0.13–0.71]; p=.006) (**Table 4**). The number of pleural puncture sites included by ablation zones was not significantly associated with PAL (p=.84). However, insignificant trends were observed for decreased PAL when pleural puncture sites were included by cryoablation zones (OR, 0.77 [95% CI, 0.52–1.14]; p=.20) in comparison to increased odds of PAL when pleural puncture sites were included by microwave ablation zones (OR, 1.21 [95% CI, 0.65–2.23]; p=.55). Multivariable analysis showed that for the same number of lesions treated per session, the odds of PAL were 67% lower following cryoablation (OR, 0.33 [95% CI, 0.14–0.82]; p=.02) compared to MWA (**Table 4**). Predictors of univariable and multivariable analyses are reported together with bootstrapped CIs in **Table 4**.

Local Tumor Progression

Throughout the follow-up period of 5 years after ablation (range, 0-60 months; Q1, Q3, 6, 37), 57 of 252 tumors (23%) showed LTP at a median of 10 months (range, 2-82 months; Q1, Q3, 6, 21). Of these, 25 were treated with cryoablation and 32 with MWA. In the Fine-Gray model with ablation modality as the predictor and death as competing risk, ablation modality was insignificant (cryoablation vs MWA [Reference]: hazard ratio = 0.77 [95% CI 0.43-1.36]; p=.36) (**Figure 4**).

Discussion

Cryoablation has been recommended for percutaneous ablation of lung tumors close to the pleura due to a purported lower risk of PAL and bronchopleural fistulas compared to MWA [5, 11-13]. However, data supporting this recommendation are lacking. This bi-institutional retrospective cohort study of 260 lung tumors shows that after percutaneous ablation with ablation zones including the pleura, the incidence of PAL was significantly lower following cryoablation (9%) compared to MWA (25%) (p=.006). Adjusted for the number of tumors treated per session, cryoablation decreased the odds of PAL by 67% compared to MWA (p=.02). Furthermore, the mean chest tube dwell time was significantly shorter following cryoablation compared to MWA (p=.003). The pleural area included by the ablation zone was not significantly associated with PAL (p=.70).

Our findings support the recommendations made by several groups to use cryoablation for peripheral lung tumors, specifically whenever the ablation zone is expected to include the pleura [5, 11-13, 15]. Importantly, we did not observe a difference in LTP between cryoablation and MWA in this study (p=.36), suggesting that cryoablation, while safer than MWA in this setting, is equally effective.

In the surgical literature, PAL is defined as an air leak that lasts longer than 5 days [31]. This definition is based on the expected hospital length of stay following lobectomy but has not been clearly defined in the context of lung ablation [31]. Since patients are frequently discharged within 24 hours following percutaneous IGTA of lung tumors, we chose to define a PAL as any air leak prolonging the hospital length of stay, i.e., air leak for more than 24 hours after chest tube placement or an enlarging postprocedural pneumothorax requiring chest tube placement.

Case series of radiofrequency ablation and MWA have linked PALs to heat-based ablation of lung tumors located close to the pleura or ablation zones including the pleura [2, 32, 33], including four instances of bronchopleural fistula out of 1,000 lung radiofrequency ablation sessions (0.4%) [3]. Although most PALs resolve spontaneously, Sakurai et al. linked a death to a PAL complicated by pneumonia following lung radiofrequency ablation [2]. Managing PALs can be challenging, and treatments range from endobronchial valves, pleurodesis, to lung resection [10, 31-33]. The need for surgical intervention can be particularly problematic for patients referred for IGTA who often have poor cardiopulmonary reserve [32].

When an ablation zone includes the visceral pleura, thermal as well as mechanical injury can lead to communication of the alveoli or airways with the intrapleural space, resulting in a pneumothorax [1]. A potential reason for the higher risk of PAL following MWA could be dehydration which reduces the elasticity of lung parenchyma and results in tissue contraction [34]. The antenna insertion site may retract from the pleura and tissue channels may persist due to cauterization and airflow through the leaking track [1, 34]. Cryoablation, on the other hand, preserves the collagenous architecture of frozen tissue, potentially facilitating the natural closing of cryoprobe tracks and thus decreasing the risk of PAL [35] even when pleural tumors are targeted [36]. For thermal ablation of peripheral lung tumors, applicator insertion tangential to the pleura has been recommended to avoid having the ablation zone extend to the pleural puncture site [1, 5]. Our model therefore accounted not only for the total number of pleural punctures per session but also for the total number of pleural puncture sites included by the ablation zone. Neither variable was significantly associated with PAL, however. Compared to MWA, cryoablation sessions were longer and required more applicators. As a result, cryoablation may not be suited for all healthcare settings.

These data must be interpreted in the context of the study design. First, selection bias is a limitation in the absence of randomization to the ablation modality. However, these real-life data suggest high generalizability. Second, despite pooling prospectively collected data from two medical centers, multivariable analysis was limited due to a relatively low number of events. Third, while inter- and intrareader agreement showed that the semi-automated measurements of pleural area included by the ablation zone were objective and reliable, histopathologic correlation with pleural injury was not possible in this study. We relied on the predicted -20C° isotherm to estimate the cryoablation zone extent since peritumoral consolidation and ground glass does not necessarily reflect lethal ice given that cryoablation treatment protocols for lung tumors are specifically designed to induce alveolar hemorrhage.

In conclusion, the incidence of PAL after percutaneous IGTA of lung tumors with ablation zones including the pleura is lower following cryoablation compared to MWA, without adversely affecting LTP.

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2. ***Funding:***

The authors state that this work has not received any funding.

Compliance with Ethical Standards

3. ***Guarantor:***

The scientific guarantor of this publication is Florian J. Fintelmann.

4. ***Conflict of Interest:***

Florian J. Fintelmann received salary support from the William M. Wood Foundation for related research during the study period and is a consultant for Pfizer. The other authors have no relevant conflicts of interest to report.

5. ***Statistics and Biometry:***

One of the authors has significant statistical expertise.

6. ***Informed Consent:***

Written informed consent was waived by the Institutional Review Board.

7. ***Ethical Approval:***

Institutional Review Board approval was obtained.

8. ***Study subjects or cohorts overlap:***

The cohort (but not the analysis) of the current study overlaps with two previously published reports in that 125 tumors in 37 patients were part of prior investigations.

a) **Reference #16**

Comparison of Percutaneous Image-Guided Microwave Ablation and Cryoablation for Sarcoma Lung Metastases: A 10-Year Experience. AJR Am J Roentgenol. 2022 Mar;218(3):494-504. doi: 10.2214/AJR.21.26551. Epub 2021 Oct 6. Bourgouin PP, Wrobel MM, Mercaldo ND, Murphy MC, Leppelmann KS, Levesque VM, Muniappan A, Silverman SG, Shepard JO, Shyn PB, Fintelmann FJ.

Here we assessed overall survival and local tumor progression of pulmonary sarcoma metastases treated with percutaneous microwave and cryoablation.

b) **Reference #17**

Outcomes Following Percutaneous Microwave and Cryoablation of Lung Metastases from Adenoid Cystic Carcinoma of the Head and Neck: A Bi-Institutional Retrospective Cohort Study. Ann Surg Oncol. 2021 Oct;28(11):5829-5839. doi: 10.1245/s10434-021-09714-4. Epub 2021 Feb 23. Leppelmann KS, Levesque VM, Bunck AC, Cahalane AM, Lanuti M, Silverman SG, Shyn PB, Fintelmann FJ.

Here we assessed overall survival and local tumor progression of Adenoid Cystic Carcinoma of the Head and Neck metastases treated with percutaneous microwave and cryoablation.

The current study differs in that the focus is persistent air leaks following percutaneous lung ablation of peripheral lung tumors, regardless of histology.

9. ***Methodology***

- retrospective
- observational
- multicenter study

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Tables Legends

Table 1. Procedural Details and Characteristics of 116 Patients with 260 Lung Tumors Treated with the Intent of Eradication in 112 Cryoablation and 61 Microwave Ablation Sessions, Stratified per Ablation Session

Table 2. Procedural Details and Characteristics of 260 Lung Tumors in 116 Patients Treated with 112 Cryoablation and 61 Microwave Ablation Sessions, Stratified per Ablated Tumor

Table 3. Incidence of Pneumothorax, Persistent Air leak, Chest Tube Placement, Chest Tube Dwell Time, and Hospital Length of Stay After 112 Cryoablation and 61 Microwave Ablation Sessions of 260 Lung Tumors in 116 Patients, Stratified per Ablation Session

Table 4. Univariable and Multivariable Regression Models with Selected Predictors for the Incidence of Persistent Air Leaks After 112 Percutaneous Cryoablation and 61 Microwave Ablation Sessions of 260 Lung Tumors in 116 Patients.

Figure Legends

Figure 1. Flowchart shows study inclusion and exclusion criteria. Fifteen patients underwent both cryoablation and microwave ablation in separate sessions. MWA = microwave ablation

Figure 2. 33-year-old male who underwent percutaneous cryoablation of colorectal carcinoma metastases in the right upper lobe, right middle lobe, and right lower lobe. **Panel A**: Axial planning image obtained at the beginning of the procedure demonstrating a metastasis (arrow). **Panel B-C**: Axial (Panel B) and sagittal (Panel C) CT images show the -

20 °C isotherm (yellow) of the right upper lobe ablation zone in relation to the ablation probe and the included pleural area (red line). **Panel D**: 3D visualization of pleural area (red) included by the -20°C isotherms during cryoablation of the right upper lobe, right middle lobe, and right lower lobe metastases. Note that the right lower lobe tumor (blue) was not included in the study because the ablation zone did not include the pleura.

Figure 3. Location of lung tumors included in the study in relation to lobe and pleura**. Panel A**. Distribution of all tumors. **Panel B**. Distribution of the subset of tumors that resulted in a persistent air leak. Numbers in circles represent tumors treated with cryoablation (blue) and microwave ablation (red). Transparency encodes the distance from tumor margin to pleura with distance 0 to <10 mm in non-transparent circles and distance 10 to 25 mm in transparent circles.

Figure 4. Cumulative incidence curves of local tumor progression by ablation modality with death as competing risk. No significant difference in progression was detected between cryoablation and microwave ablation (p=.36).

Table 1. Procedural Details and Characteristics of 116 Patients with 260 Lung Tumors Treated with the Intent of Eradication in 112 Cryoablation and 61 Microwave Ablation Sessions, Stratified per Ablation Session

Characteristic	**All Sessions (n = 173)**	**Cryoablation Sessions (n =112)**	**MWA Sessions (n = 61)**	**p[a]**
Female sex	94 (54)	60 (54)	34 (56)	.80
Age at treatment (y), median [Q1, Q3]	65 [53, 71]	63 [50, 70]	65 [58, 71]	.12
ECOG performance status				.76
0	68 (39)	43 (38)	25 (41)	
≥1	105 (61)	69 (62)	36 (59)	
Smoking status				.29
Never smoker	67 (39)	47 (42)	20 (33)	
Former smoker	97 (56)	61 (54)	36 (59)	
Active Smoker	9 (5)	4 (4)	5 (8)	
15th percentile of lung attenuation value [Q1, Q3]	-893 [-912, -873]	-893 [-910, -873]	-897 [-918, -876]	.14
Pack years, median [Q1, Q3]	1.50 [0, 12.5]	1.50 [0, 10.6]	3.00 [0, 15.0]	.30
Diagnosis				.33
Non-small cell lung cancer	32 (18)	18 (16)	14 (23)	
Lung metastases from extrathoracic primary	141 (82)	94 (84)	47 (77)	
Chemotherapy within 6 weeks prior to ablation	13 (8)	9 (8)	4 (7)	.75
Prior ipsilateral lung resection or thoracotomy	73 (42)	53 (47)	20 (33)	.07
No. of targeted tumors, median [Q1, Q3]	1.0 [1.0, 2.0]	1.0 [1.0, 2.0]	1.0 [1.0, 2.0]	.23
1	100 (58)	61 (54)	39 (64)	
2-3	56 (32)	43 (38)	13 (21)	
> 3	17 (10)	8 (7)	9 (15)	
Total no. of pleural punctures, median [Q1, Q3]	2.0 [1.0, 3.0]	2.0 [2.0, 4.0]	1.0 [1.0, 2.0]	.08
1	57 (33)	22 (20)	35 (57)	
2-3	49 (28)	37 (33)	12 (20)	
> 3	67 (39)	53 (47)	14 (23)	
Total no. of applicators per session, median [Q1, Q3]	2 [1.0, 3.0]	2 [2.0, 3.0]	1 [1.0, 1.0]	**<.001**
No. of pleural punctures included by the ablation	1.0 [0.0, 1.0]	0.0 [0.0, 1.0]	1.0 [0.0, 1.0]	.84

zone, median [Q1, Q3]				
0	82 (47)	57 (51)	25 (41)	
1-2	76 (44)	45 (40)	31 (51)	
≥3	15 (9)	10 (9)	5 (8)	
Total length of aerated lung traversed by applicator (mm), median [Q1, Q3]	93.0 [49.9, 158.0]	107.0 [62.0, 188.0]	63.9 [40.9, 134.0]	.08
Location(s) of pleura included by the ablation zone*				
Costal	151	93	58	**.03**
Diaphragmatic	32	26	6	**.03**
Mediastinal	60	41	19	.48
Cervical	9	1	8	**.009**
Pleural area included by the ablation zone (cm^2), median [Q1, Q3]	7.1 [3.6, 12.7]	7.3 [4.7, 12.6]	6.4 [2.3, 13.1]	.93
Ventilation Support				**0.012**
None/Spontaneous breathing	64 (37)	35 (31)	29 (48)	
HFJV	29 (16)	28 (25)	1 (2)	
Positive pressure other than HFJV	80 (46)	49 (44)	31 (51)	
Total procedure time (min), median [Q1, Q3]	103.0 [80.0, 135.0]	111.0 [85.0, 156.0]	89.0 [61.0, 114.0]	**<.001**

Note— Unless otherwise indicated, values represent number of ablation sessions followed by percentage of ablation sessions in parentheses. Some percentages may not add up to 100 because of rounding.

ECOG, Eastern Cooperative Oncology Group; *HFJV*, high-frequency jet ventilation; *Q1*, first quartile; *Q3*, third quartile.

[a]Based on estimating modeling parameters with generalized estimating equations; boldface indicates that p value is statistically significant at $p < .05$.

*Ablation zone could contribute to more than one pleural location.

Table 2. Procedural Details and Characteristics of 260 Lung Tumors in 116 Patients Treated with 112 Cryoablation and 61 Microwave Ablation Sessions, Stratified per Ablated Tumor

Characteristic	Overall (n = 260)	Cryoablation (n = 158)	MWA (n = 102)	p[a]
Maximum axial tumor diameter (mm), mean ± SD	13.1 ± 7.44	13.2 ± 8.08	12.8 ± 6.37	.69
≤ 2cm	223 (86)	134 (85)	89 (87)	
> 2cm	37 (14)	24 (15)	13 (13)	
Distance to pleura (mm), median [Q1, Q3]	0.0 [0.0, 6.0]	0.0 [0.0, 4.0]	4.0 [0.0, 9.0]	**<.001**
Tumor location				**<.001**
Right upper lobe	61 (23)	18 (11)	43 (42)	
Right middle lobe	10 (4)	8 (5)	2 (2)	
Right lower lobe	70 (27)	55 (35)	15 (15)	
Left upper lobe	56 (22)	31 (20)	25 (25)	
Left lower lobe	63 (24)	46 (29)	17 (17)	
Histology				
Metastatic sarcoma	63 (24)	44 (28)	19 (19)	
Metastatic colorectal carcinoma	50 (19)	28 (18)	22 (22)	.46
Non–small cell lung cancer	40 (15)	23 (15)	17 (17)	.43
Metastatic neck and salivary gland carcinoma	15 (6)	8 (5)	7 (7)	.20
Other	92 (35)	55 (35)	37 (36)	.51
Cryoablation				
Final thaw mode				
Passive Thaw	…	66 (42)	…	…
Active Thaw/ Track ablation	…	92 (58)	…	…
Cryoablation protocol				
Dual freeze	…	30 (19)	…	…
Triple freeze	…	128 (81)	…	…
Total freeze time (min), median [Q1, Q3]	…	20.0 [20.0, 25.0]	…	…
Microwave ablation				
Maximum wattage, median [Q1, Q3]	…	…	40.0 [40.0, 60.0]	…
Duration of heat application (min), median [Q1, Q3]	…	…	6.00 [5.00, 10.0]	…
Primary technical success	252 (97)	151 (96)	101 (99)	.06

Note— Unless otherwise indicated, values represent number of ablation sessions followed by percentage of ablation sessions in parentheses. Some percentages may not add up to 100 because of rounding.

Q1, first quartile; *Q3*, third quartile; *SD*, standard deviation

[a]Based on estimating modeling parameters with generalized estimating equations; boldface indicates that p value is statistically significant at p < .05.

Table 3. Incidence of Pneumothorax, Persistent Air leak, Chest Tube Placement, Chest Tube Dwell Time, and Hospital Length of Stay After 112 Cryoablation and 61 Microwave Ablation Sessions of 260 Lung Tumors in 116 Patients, Stratified per Ablation Session

Event	**All Sessions (n = 173)**	**Cryoablation Sessions (n = 112)**	**MWA Sessions (n = 61)**	**p[a]**
Intentional pneumothorax	20 (12)	13 (12)	7 (12)	.98
Unintentional pneumothorax, by time of detection				
Intraprocedural	37 (21)	17 (15)	20 (33)	**.007**
Postprocedural, within 24 hours after ablation	27 (16)	17 (15)	10 (16)	.83
Postprocedural, more than 24 hours after ablation	9 (5)	4 (4)	5 (8)	.21
Persistent air leak	25 (14)	10 (9)	15 (25)	**.006**
Enlarging postprocedural pneumothorax requiring chest tube placement	15 (9)	6 (5)	9 (15)	**.03**
Air leak in chest tube drainage system > 24h after chest tube placement	16 (9)	5 (4)	11 (18)	**.007**
Chest tube placement for unintentional pneumothorax	37 (21)	19 (17)	18 (30)	.06
Chest tube dwell time in days, mean ± SD	2.38 ± 3.30	1.32 ± 0.58	3.50 ± 4.49	**.003**
Hospital length of stay in days, mean ± SD	1.45 ± 1.68	1.21 ± 0.70	1.90 ± 2.62	**.006**

Note— Unless otherwise indicated, values represent number of ablation sessions followed by percentage of ablation sessions in parentheses. Some percentages may not add up to 100 because of rounding.

SD, standard deviation

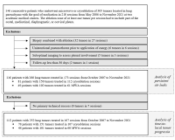
[a]Comparison of distribution of complications of any grade between the cryoablation and microwave ablation group based on estimating modeling parameters with generalized estimating equations using an independence correlation structure; boldface indicates that p value is statistically significant at $p < .05$.

Table 4. Univariable and Multivariable Regression Models with Selected Predictors for the Incidence of Persistent Air Leaks After 112 Percutaneous Cryoablation and 61 Microwave Ablation Sessions of 260 Lung Tumors in 116 Patients.

Predictor	PAL (n= 25)	Univariable Model			Multivariable Model		
		p[a]	Coeff[b]	Bootstrapped CI[c]	P[a]	Coeff[b]	Bootstrapped CI[c]
Ablation Modality		**.006**					
Microwave Ablation	15 (25)		…	…	Ref	…	
Cryoablation	10 (9)		-1.20 (-2.06, -0.34)	-2.23, -0.39	**.02**	-1.10 (-2.00, -0.19)	-2.16, -0.18
Age		.96	0.001 (-0.03, 0.03)	-0.03, 0.03			
Sex		.15					
Male	15 (19)		…	…			
Female	10 (11)		-0.68 (-1.61, 0.25)	-1.66, 0.21			
No. of targeted tumors		**.004**	0.35 (0.11, 0.58)	0.04, 0.67	**.03**	0.30 (0.03, 0.56)	0.00, 0.68
No. of pleural punctures		.42	0.08 (-0.11, 0.27)	-0.15, 0.27			
No. of pleural puncture sites included by ablation zones		.84	-0.03 (-0.35, 0.28)	-0.45, 0.28			
Total length of aerated lung traversed by applicators		.20	0.002 (-0.001, 0.01)	-0.002, 0.01			
Ventilation strategy		.58					
None/Spontaneous breathing	7 (11)		…	…			
HFJV	4 (14)		0.27 (-1.01, 1.54)	-1.71, 1.69			
Positive pressure	14		0.55	-0.40, 1.77			

other than HFJV	(18)		(-0.48, 1.57)				
Total pleural area included by ablation zones		.70	-0.0001 (-0.001, 0.0003)	-0.001, 0.0002			
Absence of prior ipsilateral lung resection or thoracotomy	18 (18)	.12	0.73 (-0.20, 1.65)	-1.94, 0.14			
Chemotherapy within six weeks prior to ablation	3 (23)	.47	0.63 (-1.09, 2.35)	-40.75, 1.93			

Note— Unless otherwise indicated, values represent number of ablation sessions followed by percentage of ablation sessions in parentheses. Some percentages may not add up to 100 because of rounding.
CI, Confidence Interval; *Coeff*, coefficient; *HFJV*, high-frequency jet ventilation; *PAL*, persistent air leak; *Ref*, reference.
[a]Boldface indicates that p value is statistically significant at p < .05.
[b]Numbers in parentheses are 95% CI.
[c]Numbers are 95% percentile CI.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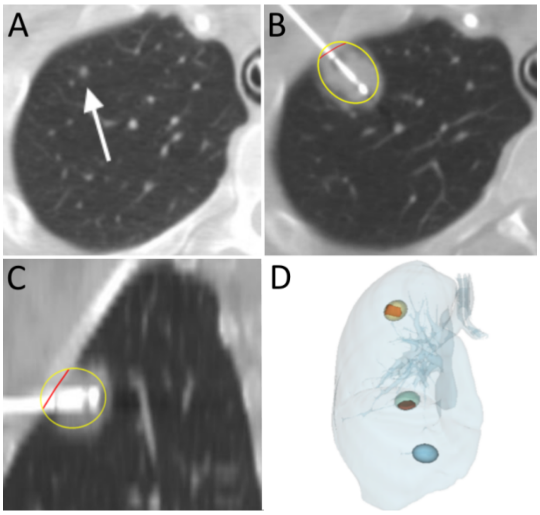
Exclusion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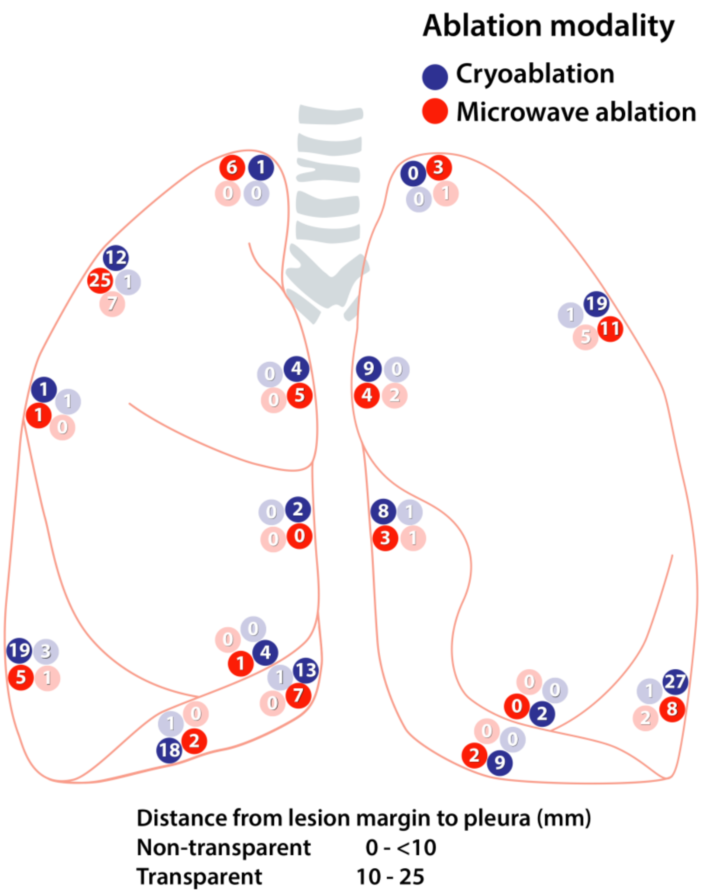
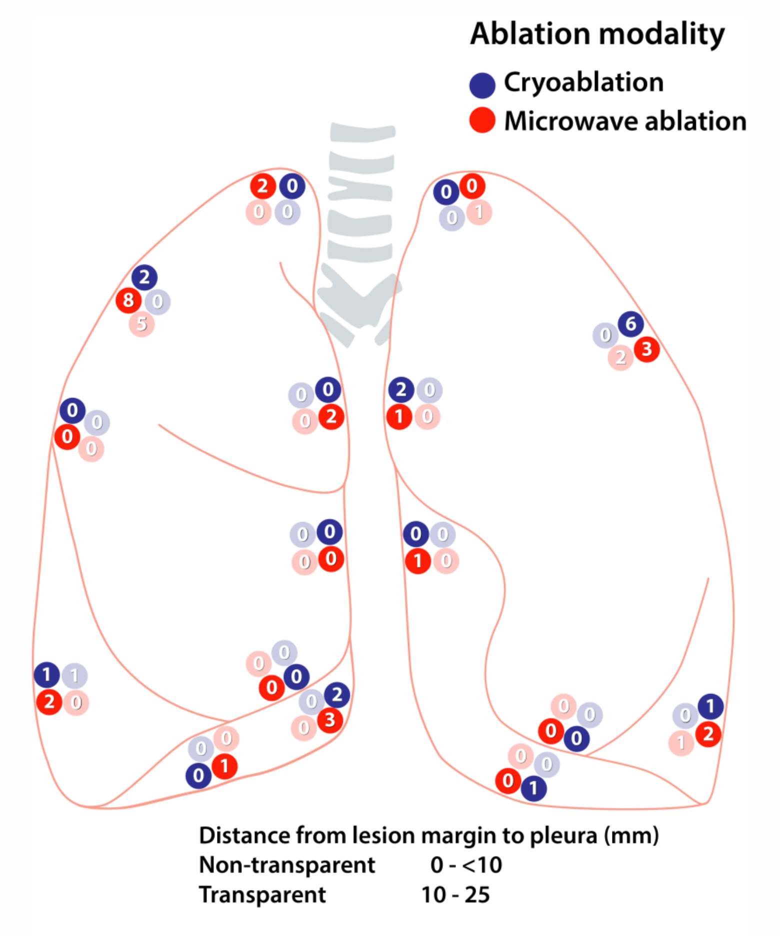

Ablation modality
Cryoablation
Microwave ablation
Distance from lesion margin to pleura (mm)
Non-transparent 0 - <10
Transparent 10 - 25


Ablation modality
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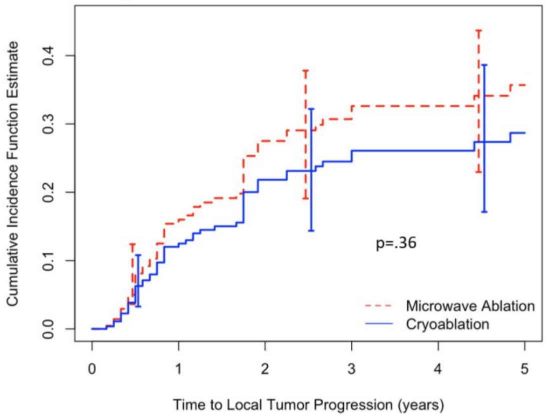
Microwave ablation
Distance from lesion margin to pleura (mm)
Non-transparent 0 - <10
Transparent 10 - 25



Cumulative Incidence Function Estimate
0.0
0.1
0.2
0.3
0.4
0
1
2
3
4
5
Time to Local Tumor Progression (years)
p=.36
Microwave Ablation
Cryoablation