Original Article

Percutaneous Computed Tomography-guided Cryotherapy of Thoracic Masses in Nonsurgical Candidates: Experience in 19 Patients

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Background/Purpose: Percutaneous cryotherapy has become a minimally invasive treatment option for unresectable lung malignancies. We report the experience and outcomes with percutaneous computed tomography (CT)-guided cryotherapy of primary lung malignancies, as well as recurrence and metastases, in patients ineligible for surgery.

Methods: The procedure was performed after administration of local anesthesia on 23 tumors in 19 patients (10 male and 9 female patients; mean age, 58.7 years). None of the patients were surgical candidates and underwent CT-guided percutaneous cryotherapy for treatment of the malignant mass in the lung. Visualization of low-attenuation ice ball formation was performed using CT scanning after each cycle of freezing and thawing therapy. Subsequent CT scans were scheduled at 3-month intervals post-procedure to assess tumor control.

Results: No lethal complication, major bleeding or bronchial damage was observed in any of the 23 cryotherapy sessions performed. Three patients developed pneumothorax and one patient required chest tube insertion. Thirteen tumors (56.5%) regressed, including two complete responses, five tumors (21.7%) were stationary and the remaining five tumors (21.7%) were found to be progressing at the 3-month follow-ups. No recurrence was found in the 11 regressed tumors for 6 months, and there was also no recurrence in the two tumors that completely responded up to 12 months later with a satisfactory procedure.

Conclusion: Percutaneous cryotherapy for primary lung cancer, recurrence and metastatic lung tumors is feasible and safe for local control.

Key Words: computed tomography, cryotherapy, pulmonary nodules

Percutaneous cryotherapy is recommended for a range of anatomic and tumor treatment options because of its low pain, good ice visualization, and preservation of collagenous tissue architecture. Cryotherapy has been performed in the liver, prostate, kidney, and breast with good outcomes.1–4 In patients in whom the lung tumor is inaccessible through the tracheobronchial tree, and surgical

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resection is not indicated, oncological treatment of large tumors is often of limited benefit. Therefore, treatment options are severely restricted.\textsuperscript{1} Computed tomography (CT)-guided percutaneous cryotherapy of lung malignancy is considered for patients ineligible for surgery, and a metastatic tumor is associated with low procedural morbidity.\textsuperscript{5} Cryotherapy causes coagulation necrosis confined to the tissues within the region of probe application, and ice-ball formation occurs as a result of the dehydration caused by the intracellular ice crystals that form at very low temperatures. This leads to protein denaturation and solute toxicity within the cells.\textsuperscript{6,7} The extent and degree of tissue destruction correlate with the size of the ice ball and the temperature within it. The latest generation of cryotherapy machines use the Joule-Thomson effect, in which different gases undergo unique temperature changes when depressurized, according to unique gas coefficients. The properties of argon make it useful for cooling to below \(-180^\circ\text{C}\), whereas helium is ideal for thawing and re-warming. The use of gas allows for rapid transition from freezing to defrosting, which facilitates tighter control, as well as expedition of the procedure.\textsuperscript{8} Based on the biological effect of extreme cold, a lethal temperature of approximately \(-100^\circ\text{C}\) at the tumor level is required to achieve total destruction of tumors 2 cm or larger in diameter.\textsuperscript{9} We performed percutaneous cryotherapy under CT guidance with local anesthesia as a locally curative treatment for unresectable lung tumors. Twenty-three cryotherapy procedures were performed successfully in 19 patients, with tissue proof of unresected primary lung malignancy, recurrent lung malignancy and lung metastasis.

**Materials and Methods**

**Patients**

The institutional review board of our hospital approved this retrospective study and informed consent was waived due to the retrospective and anonymous nature of the analysis. A total of 23 pulmonary masses in 19 patients (10 male and 9 female patients; mean age, 58.7 years; age range, 19–77 years) were treated with cryotherapy between October 2007 and September 2009. Five patients had unresectable non-small cell lung cancer, six had non-small cell lung cancer after lobectomy with recurrence, and the remaining eight patients had lung metastasis. The patients were considered ineligible for surgery or had undergone other lung cancer therapies that were unsuccessful. All of the patients met at least one of the following inclusion criteria: (1) single or multiple peripheral lung masses larger than 1 cm but less than 5 cm in diameter, with previous therapies (radiation therapy, chemotherapy, and/or surgery) having failed; (2) a nonresectable central lung cancer (as determined by means of surgical consultation, according to size, stage or health status); (3) fewer than five metastatic tumors; and (4) a mass or adenopathy involving the mediastinum and/or the pericardium without distant metastasis. The latter was considered as an inclusion criterion only when it was associated with a distant measurable primary lung tumor.

**Cryotherapy technique**

The location and size of tumors were noted at preoperative evaluation. A tumor was considered a central mass if it abutted any of the mediastinal or hilar structures. Tumor measurements were obtained in two dimensions on CT images, at the level of the tumor’s most prominent appearance in the transverse plane. Patients were placed feet first into the CT gantry for better cryoprobe access.

Cryotherapy was performed after administration of local anesthesia by one thoracic surgeon and one radiologist. For sedation, the patients received 50 mg pethidine (Demoral; Roche, Basel, Switzerland) and 5 mg midazolam (Dormicum; Roche, Basel, Switzerland).

A 21-gauge 15-cm needle was inserted into the center of each mass under CT-guidance (Light speed VCT, GE Medical System, Milwaukee, WI, USA), and used as a guide for subsequent insertion of cryoprobes. The cryoprobe used was a PERC24 (Endocare, Irvine, CA, USA), it was 2.4 mm in diameter and it was inserted directly into the
Cryoablation is achieved using high-pressure argon and helium gas for freezing and thawing, respectively, based on the Joule-Thompson principle. Rapid freezing of tissue with a cryoprobe is based on the rapid expansion of argon gas in a sealed probe with a distal uninsulated portion. This process results in rapid cooling to $-100^\circ$C within a few seconds. Active thawing of the ice ball is achieved by introducing helium gas into the probes instead of argon gas. The cryoablation procedure we used consisted of two cycles of 10 minutes of freezing and a 5-minute active thaw between the cycles. During freezing, ice ball growth and tumor coverage were monitored at 5-minute intervals by CT scan. For a mass within the lung tissue, a 2.4-mm cryoprobe can generate an ice ball up to 3.7 cm in diameter and up to 5.7 cm along the probe shaft. For this reason, a single cryoprobe was placed for tumors 2 cm or less in diameter. An additional cryoprobe was used for larger tumors to ensure that an adequate freezing margin of 5–10 mm was achieved. After completion of the final freeze in the cryotherapy procedure, the cryoprobes were warmed by helium gas until the temperature was higher than 20$^\circ$C. The cryoprobes were then withdrawn.

**Post-procedural evaluation**

Immediately after the cryoprobes were removed, the patient was placed back into the CT gantry for scanning and measurement of the low-attenuation ice ball formation. All CT scans obtained after the percutaneous cryoablation were acquired within 2–3 minutes of termination of freezing; the visible size of the ice ball remains relatively unchanged during this time. A repeat CT scan was performed 24 hours after the procedure to evaluate the type and frequency of complications.

Follow-up helical CT scans of patients were performed at 3 months post-procedure. Changes in tumors following cryotherapy were measured using the Response Evaluation Criteria in Solid Tumors (RECIST) protocol, which is based on objective measurements of lesion size before and after treatment. "Complete response" (CR) indicates disappearance of the lesion, "partial response" (PR) is a decrease of at least 30% in the sum of the longest diameter of target lesions, "progressive disease" (PD) is an increase of at least 20% in the sum of the longest diameter of target lesions, and "stable disease" (SD) is neither sufficient shrinkage to qualify for partial response nor a sufficient increase to qualify for progressive disease.

**Results**

A total of 23 pulmonary masses in 19 patients were treated with cryotherapy. In all cases, cryotherapy was performed percutaneously under CT guidance with local anesthesia without major complications. Complications are listed in Table 1. The mean hospital stay after treatment was 2.8 days (range, 2–9 days). There were no treatment-related deaths or conversions to surgical intervention.

The responses to cryotherapy, measured using the RECIST protocol, are listed in Table 2. We observed a CR in two (8.7%) tumors, PR in 11 (47.8%) tumors, SD in five (21.7%) tumors and PD in five (21.7%) tumors, giving a response rate of 56.5% (Figures 1 and 2).

**Discussion**

Percutaneous cryotherapy of lung masses is technically feasible and may provide an important...
Percutaneous CT-guided cryotherapy of thoracic masses

14 The ability to visualize a low-attenuating ice ball as it thoroughly covers a soft tissue tumor mass during the freeze cycles is a potential benefit that is not available with heat-based treatment.

Cryotherapy kills cells and ablates tissue by direct cell injury resulting from ice crystal formation and related deleterious effects, as well as vascular stasis caused by microcirculatory failure. As temperatures fall, direct cellular injury occurs as a result of cellular metabolism failure. When the temperature reaches −20°C, water in the extracellular environment crystallizes into ice, and withdrawal of the water from the system results in a hyperosmotic extracellular environment. Consequently, denaturation and electrolyte imbalances occur.15,16 During thawing, ice crystals fuse to form larger crystals, which eventually disrupt the cell membrane, which is another pathway for causing cell injury. Gage and Baust recommend a minimum freezing temperature of −40°C for at least 3 minutes for complete eradication of the tumor and a minimum of two freeze-thaw cycles.15,16 This leads to modification of cryotherapy techniques, in turn leading to improved biochemical and histological outcomes.17

In our series, the response of the lung masses was evaluated using the RECIST protocol. In the 11 (47.8%) of 23 tumors diagnosed as PR, local

### Table 2. Radiographic response and clinical result

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Primary tumor</th>
<th>Nodules treated with cryotherapya</th>
<th>Each tumor’s response after 3 mo b</th>
<th>Clinical outcome (prognosis after initial cryotherapy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Alveolar soft part sarcoma of the thigh</td>
<td>2</td>
<td>CR</td>
<td>Stationary (24 POM)</td>
</tr>
<tr>
<td>2</td>
<td>Recurrent NSCLC</td>
<td>1</td>
<td>PR</td>
<td>Stationary (18 POM)</td>
</tr>
<tr>
<td>3</td>
<td>Recurrent NSCLC</td>
<td>1</td>
<td>PD</td>
<td>Progression (3 POM, 9 POM dead)</td>
</tr>
<tr>
<td>4</td>
<td>Recurrent NSCLC</td>
<td>1</td>
<td>SD</td>
<td>Liver metastasis (19 POM alive)</td>
</tr>
<tr>
<td>5</td>
<td>Recurrent NSCLC</td>
<td>1</td>
<td>PR</td>
<td>New pulmonary nodule (16 POM alive)</td>
</tr>
<tr>
<td>6</td>
<td>Liposarcoma of the chest wall</td>
<td>2</td>
<td>SD, SD</td>
<td>Stationary (17 POM)</td>
</tr>
<tr>
<td>7</td>
<td>Esophageal cancer</td>
<td>2</td>
<td>PR, PR</td>
<td>New pulmonary nodule (7 POM, 15 POM dead)</td>
</tr>
<tr>
<td>8</td>
<td>Rectal cancer</td>
<td>1</td>
<td>PR</td>
<td>Liver metastasis (7 POM alive under chemotherapy)</td>
</tr>
<tr>
<td>9</td>
<td>NSCLC</td>
<td>1</td>
<td>PR</td>
<td>New pulmonary nodule and multiple metastasis (10 POM, alive)</td>
</tr>
<tr>
<td>10</td>
<td>NSCLC</td>
<td>1</td>
<td>PR</td>
<td>Stationary (16 POM)</td>
</tr>
<tr>
<td>11</td>
<td>NSCLC</td>
<td>1</td>
<td>PR</td>
<td>Focal regression</td>
</tr>
<tr>
<td>12</td>
<td>NSCLC</td>
<td>1</td>
<td>PD</td>
<td>New pulmonary nodule (6 POM alive)</td>
</tr>
<tr>
<td>13</td>
<td>Recurrent NSCLC</td>
<td>1</td>
<td>CR</td>
<td>Died at 4 POM</td>
</tr>
<tr>
<td>14</td>
<td>Osteogenic sarcoma</td>
<td>2</td>
<td>PD, PD</td>
<td>Progression (3 POM alive)</td>
</tr>
<tr>
<td>15</td>
<td>NSCLC</td>
<td>1</td>
<td>SD</td>
<td>Stationary (6 POM)</td>
</tr>
<tr>
<td>16</td>
<td>Recurrent NSCLC</td>
<td>1</td>
<td>PD</td>
<td>Progression and new pulmonary nodule (3 POM alive)</td>
</tr>
<tr>
<td>17</td>
<td>Colon cancer</td>
<td>1</td>
<td>PR</td>
<td>Regression (6 POM)</td>
</tr>
<tr>
<td>18</td>
<td>High-grade sarcoma of the thigh</td>
<td>1</td>
<td>PR</td>
<td>Regression (6 POM)</td>
</tr>
<tr>
<td>19</td>
<td>Renal cell carcinoma</td>
<td>1</td>
<td>SD</td>
<td>Stationary (6 POM)</td>
</tr>
</tbody>
</table>

aTotal pulmonary nodules (n=23); bCR (n=2, 8.7%), PR (n=11, 47.8%), SD (n=5, 21.7%), and PD (n=5, 21.7%). CR = complete regression; PR = partial response; SD = stable disease; PD = progressive disease; POM = post operative months; NSCLC = non-small cell lung cancer.
recurrence did not occur during more than 6 months of follow-up. In the two (8.7%) of 23 tumors diagnosed as CR, there was no recurrence during 12 months of follow-up; therefore, our series had a response rate of 56.5%.

Cryotherapy offers the opportunity to have excellent healing and resistance to infection. The cryogenic lesion is an anesthetic lesion that initially shows minimal surrounding edema or inflammation.15,16 Because of this localized effect, cryotherapy is a well-tolerated procedure. These lesions, which have been found to be relatively resistant to infection, show excellent healing, with minimal scar formation and preservation of tissue planes.15,16

We achieved our major treatment goals of using local sedation during the procedures and preserving underlying tissue architecture with minimal complications. Because metastatic lung tumors may associate with other latent metastatic lesions in the lung, pulmonary reserve after treatment can be important. Greater pulmonary reserve is expected after cryotherapy, when applied to centrally located tumors than after surgical procedures such as lobectomy, which is usually required for resection of such tumors.

In conclusion, percutaneous CT-guided cryotherapy offers a viable alternative for a nonsurgical lung mass, because it is minimally invasive and uses local anesthesia, with satisfactory local control. It preserves respiratory function and is well tolerated by the patient. The procedure demands careful patient selection and technical expertise to achieve satisfactory cancer control, patient satisfaction, and acceptable quality of life.
Acknowledgments

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References


Figure 2. (A) A 3.5-cm lung mass in the RLL due to recurrent adenocarcinoma. (B) The mass is being treated from the posterior approach. Two cryoprobes are seen bracketing the mass. (C) Near-complete resolution of the RLL mass with linear scarring was observed 3 months post-procedure. (D) Retained linear scarring without recurrence or a residual tumor was observed at the 12-month follow-up.


