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A PILOT STUDY OF PERCUTANEOUS CRYOTHERAPY AS TREATMENT FOR STAGE I LUNG CANCER OR SOLITARY METASTATIC LUNG CANCER

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1.0 SCHEMA

Prior to lung resection at three weeks after PTC, the patient will receive a dynamic enhanced (i.e., non-contrast, arterial and delayed phase) computed tomography(CT) of the chest. These preoperative studies will be compared with the histologic results from thoracotomy, obtained at least 2 days after PTC and no more than 2 months after PTC to assure thorough necrosis. Evaluations will include dimensions of the resected pathologic specimen's necrotic center and its peripheral rim, compared to the CT findings of vessel proximity, central cavitation and associated healing rim, noting the enhancement of the rim and overall ablation zone. The resected ablation zone will undergo histologic analyses of the tumor region near vasculature, as well as the anterior, posterior, superior, inferior, medial and lateral margins to determine if cancer is present and note the characteristics of the healing rim (e.g., inflammatory infiltrates). If cancer is present in any area, this will be compared to the similar ablation margin on CT to assess any differences in enhancement or nodularity.

Key Inclusion Criteria

1. The patient will be a candidate for a thoracotomy
2. The patient will have a peripheral lung tumor 3.0 cm or less in diameter
3. If primary lung cancer, non-invasive staging or mediastinoscopy will suggest the patient has Stage I disease. If patient has metastatic disease, the lungs will be the only site of metastases.
4. The patient will have a biopsy proven cancer before PTC and thoracotomy, including either a CT-guided needle biopsy diagnosis, a bronchoscopic or transbronchial biopsy.

Treatment Plan

1. The patient will undergo CT-guided PTC with the intent to eradicate the entire tumor(s).
3. The patient will have CXR at weeks 1 and 2 (±2 days).
4. Approximately 3 weeks after PTC, (2-53 days) chest CT and pulmonary function tests will be performed within 7 days of planned resection.
5. Approximately 3 weeks after PTC (2-60 days) the patient will undergo a thoracotomy with resection of the treated lung, consisting of lobectomy for primary lung cancer or wedge resection with adequate margin for a metastatic lesion. The mediastinal lymph nodes will undergo dissection.
6. The resected ablation zone(s) will be measured and histologic samples taken from all six margins and resected lymph nodes.
7. The pathology results will be compared with the preoperative, post-cryotherapy CTs.

2.0 OBJECTIVES

The primary objective of the study is to evaluate the histologic result of treating primary lung cancer or solitary metastatic lung cancer after PTC.

The secondary objective is to provide a qualitative assessment of the histology from the ablation and tumor margins, comparing histologic observations with imaging enhancement patterns by computed tomography (CT) before and after PTC. Post-cryotherapy, pre-surgical CT scan dimensions and characteristics (e.g., central necrosis and healing rim) will be qualitatively compared to similar areas of the surgical specimen. In addition, histology samples from anterior, posterior, superior, inferior, medial and lateral areas of the resected tumor will be compared to enhancement zones of the ablation margin for any residual cancer.

A tertiary objective is long term follow up for clinical outcome and overall survival.

A total of ten evaluable patients qualifying in either Cohort A or Cohort B will be included.

Cohort A. Patients who have been diagnosed with Stage I primary peripheral lung cancer less than 3.0 cm in average diameter without prior radiation or chemotherapy.

Cohort B. Patients with metastatic solitary or multiple (≤ 3) peripheral lung lesions less than 3.0 cm in average diameter which have not been treated with radiation or chemotherapy since the new metastatic lesion appeared.

3.0 BACKGROUND

3.1 NON-SMALL CELL LUNG CANCER

Lung cancer is the number one cause of cancer related death among both men and women in the United States. Approximately 200,000 new cases of lung cancer are diagnosed each year, representing 15% of new cancer cases. [1,2,3]

Nearly 180,000 people died of lung cancer in 2003, comprising 30% of all cancer deaths. At present the one-year survival is 40% while the overall five-year survival for all stages of lung cancer remains at only 14%. [4,5]

Following surgical resection for a Stage I non-small cell lung cancer there is a one-year survival of more than 80% and a five-year survival between 60-70%.[6,7] The best one year and five year survival data for Stage I non-small-cell lung cancer is achieved with surgical intervention. Stage I non-small cell cancer requires that no regional lymph nodes or mediastinal lymph nodes be involved. The tumor must be greater than 2.0 cm from the carina. TI tumors in Stage I are less than 3.0 cm and do not involve the visceral pleural while T2 tumors are greater than 3.0 cm or invade the visceral pleura.

Presently patients with probable Stage I non-small-cell lung cancers are offered operation if their preoperative staging, which usually includes MRI (magnetic resonance imaging)[8,9,10] of the brain and PET scan to rule out liver, bone, adrenal or mediastinal lymph nodes are negative. While operation results in the best long-term outcomes for Stage I lung cancer as opposed to radiation

and/or radiation-chemotherapy protocols, the thoracotomy or less invasive thoracoscopic approach does cause morbidity and mortality.

There is a 1-4%[11,12,13] mortality for thoracotomy and morbidity includes arrhythmias, wound infection, hemothorax, broncho-pleural fistula, pneumonia and deep venous thrombosis. In addition, the spreading of the intercostal spaces with thoracotomy or the insertion of intercostal trochars with manipulation of the intercostal nerves for thoracoscopy causes considerable discomfort.[14] Pain management is a significant problem following thoracotomy or thoracoscopy and postoperative pain is primarily managed with epidural catheter and infusion of Lidocaine, Demerol or morphine. Other techniques of pain management include intercostal nerve block during the thoracotomy or insertion of a catheter along the intercostal nerves to intermittently inject an anesthetic agent.

If a percutaneous CT-guided therapy could achieve the same results as an operative approach, it would revolutionize cancer treatment and options. In addition, it would markedly improve the pain control and the morbidity associated with thoracoscopy or thoracotomy. The percutaneous cancer treatment would have to demonstrate that the ablation efficacy is the same as with a thoracotomy while minimizing collateral damage and overall morbidity.

Percutaneous ablation would be an alternative treatment for patients who could not tolerate lung resection because of marked impairment of pulmonary function secondary to smoking.[15,16,17]Other medical contra-indications including recent myocardial infarction or impaired cardiac status would also allow patients who would not be surgical candidates to receive an equally efficacious treatment. Presently, the patient who is not a surgical candidate would receive chemotherapy or a chemotherapy-radiation protocol. These protocols have multiple side effects due to the chemotherapeutic agent and the radiation therapy delivered to the underlying organ. In addition, they require multiple visits to the radiation suite and the chemotherapy unit. The cryotherapy option is a single treatment option administered as an outpatient, or overnight monitoring.

With the introduction of endobronchial and trans-esophageal ultasound guided biopsy of mediastinal lymph nodes, one could envision treating the peripheral tumor with cryotherapy and staging the mediastinal nodes in a relatively non-invasive manner. This would allow accurate pathologic staging rather than image based staging and a true comparison of surgery, radiation and /or cryotherapy for similar stage lung cancers.

3.2 METASTATIC LUNG CANCER

A second cohort of patients who would be candidates for the protocol are those with limited (≤3) number of metastatic lesions, each less than 3.0 cm and resectable. These patients would satisfy the usual preoperative criteria for operations with metastatic neoplasms to the lung.[18]

These patients would meet the criteria that removal of all metastatic lung tumor is being achieved and retain good pulmonary function after surgical removal of the affected tissue. The primary tumor must have been treated or be under control. The definition of local control will vary depending on the primary tumor. These patients must have absence of metastases to other locations. The final requirement is that lung metastases have no alternative treatment available. Patients that meet these criteria would be offered the option for percutaneous cryotherapy.

Three weeks after treatment the patient would receive a CT scan and then undergo surgical resection with the mediastinal resection for staging purposes. Many authors have reported a five-year disease-free survival in the 30-45% range with resection[18] of pulmonary metastases using these criteria.[,19,20,21]

3.3 CRYOTHERAPY

Enthusiasm still exists for radiofrequency ablation (RFA) in multiple organs despite relatively high recurrence rates in lung[22-24] that we have not encountered with cryotherapy in our ongoing human trials at our institution. RFA appears particularly prone to failure for tumor sizes above 3cm and abutting adjacent vasculature. if a tumor abuts a vessel >3mm, RFA appears to produce a relatively consistent recurrence rate of ~50% in liver[25], kidney[26] and lung[22-24]. Despite these problems, the relatively low morbidity compared to resection and the improved survival rates[27-28] makes RFA an accepted treatment option. The apparent ability for cryotherapy to be more capable of thorough ablation even near vessels may require more definitive tissue confirmation in our proposed resection study.

Cryotherapy with the use of cytotoxic freezing temperatures for cancer treatment was first used in the early 1900's. Percutaneous cryotherapy was initiated when smaller probes were able to be accurately placed and monitored using ultrasound guidance for liver and prostate tumors[29-31]. Intraoperative ultrasound was able to monitor the leading edge of the ice ablation zone with millimeter accuracy. The ability to instantaneously initiate and terminate both freeze and thaw cycles with Argon gas systems also made cryotherapy more controllable. Cryotherapy for hepatic and prostate lesions has since become well established. Our center has also become the leading site for percutaneous cryotherapy of nearly any organ, including publications for breast, renal and lung tumors[32-34].

Percutaneous cryotherapy is administered with the application of 1.7 or 2.4 mm diameter cryo probes. Ice ball sizes vary between 1.5 and 3.0 cm in diameter, dependant on the vascularity or fibrous content of the tissue. For an example, tumors within the cirrhotic liver, which contains significant collagen fibers, or fibrous lesions of the prostate may require more numerous and closely spaced cryoprobes (e.g., <1.5cm apart) to adequately achieve cytotoxic temperatures (-40^{0}c). In addition, the high heat low load and/or low conductivity of lung tissue has been recently confirmed in an animal model, whereby cryoprobes spaced 2.0 cm apart did not generate lethal temperatures at the midpoint between the probes[35].

Lengths of the ice ball are consistent with both probe sizes and are approximately 4.5 cm. Maximal lethal ice dimensions for even multiple probes in high heat load tissue require a freeze/thaw/refreeze cycle of at least 15:10:10 minutes respectively. The general rule is that more than one cryotherapy probe is required for each centimeter of tumor diameter. A 2-3 cm lung tumor may thus require 3-4 probes, especially if the tumor abuts a vessel >3mm in diameter. Masses less than 2.0 cm in size may be easily treated by bracketing the tumor with two probes, rather than relying upon a highly accurate central single probe placement. However, if a tumor approaches 2 cm and lies near major vessels, even 3 cryoprobes may be needed with current technology to assure thorough lethal ice along all margins abutting vessels. Ice ball margins of multiple cryotherapy probes coalesce to form a larger volume as seen in Figure 1[34].

The patients selected for this protocol will not need multiple planning sessions and CT scans to assess tumor position in relation to other organs. Multiplanar reconstruction of the tumor to be

treated and the mapping of the appropriate probe requirement can be determined from the baseline CT scan. CT scan documentation of ice progression is required during the procedure as well as scanning after completion of the first and second thaw cycles.
Cryotherapy has achieved areas of complete necrosis without basic disruption of the underlying anatomic architecture since it is relatively sparing of collagen. In addition, the margins achieved with cryotherapy are more regular, thinner and better defined than with RFA. The radiotherapy appears to destroy underlying anatomic architecture or "melts" the tissue. In addition, the patients who undergo radiofrequency ablation require significantly more sedation as the burn from radiofrequency is quite painful and often results in overnight hospitalization for pain control for at least 24 hours. [36]

Significant numbers of patients who have developed lung cancer or secondary metastatic disease are not candidates for lung resection because of inadequate pulmonary function. These patients can presently be treated only with radiation or chemotherapy. One benefit of evaluating cryotherapy as the initial treatment for primary lung or metastatic disease is that patients previously considered unresectable would now be able to achieve a "non-surgical" resection using cryo surgery.

3.4 RATIONALE

Many patients with non-small cell lung cancer are not candidates for surgery secondary to inadequate pulmonary function for resection or poor cardiopulmonary reserve. The location of the tumor such that resection would require removal of vital structure (ex. superior vena cava, thoracic aorta) could also rule out a surgical approach.

In patients with metastatic lung disease, the ability to treat patients without thoracotomy would be an advantage since they frequently have recurrences requiring multiple thoracotomies. These patients also would benefit from preservation of as much lung tissue as possible, which would be maximized with a non-resective localized technique. Patients with metastatic lung cancer often have multiple lesions and are not a candidate for lung resection as they would have inadequate pulmonary function after operation. The impairment of cardiopulmonary reserve could rule out their candidacy for surgical resection.

A percutaneous approach, which would have comparable results to resection without its attendant morbidity and mortality, would also be attractive. In addition, an outpatient percutaneous approach would decrease hospitalization and overall healthcare costs. If similar treatment outcomes could be achieved on an outpatient basis with a several-hour treatment rather than a five to six day hospitalization required for thoracotomy or thoracoscopy, this would be a major advantage in medical costs.

Recent data has demonstrated that percutaneous cryotherapy can ablate lung tumors without loss of underlying architecture including blood vessels[32]. These techniques have also been successful in terms of ablating pain and have been used for patients with intractable discomfort. [32] Cryotherapy of the lung has usually been utilized only as a treatment of last resort in patients who cannot be offered surgical resection because of limited pulmonary status, cardiopulmonary reserve, advanced metastatic disease, advanced local disease and with debilitating pain syndromes[32].

There are no studies on the efficacy of percutaneous cryotherapy of lung tumors other than chest CT scan or by utilizing PET scan to demonstrate that no residual tumor is present.[37] There is no study that histologically demonstrates that the percutaneous cryoablation technique has been able to kill all viable tumor cells, including the potentially misleading breast cancer data which reports insufficient ablation of tumors >1.5 cm but only used 1 probe in all cases[38].

This study would resect the ablated lung tissue after a sufficient period of time to assure thorough necrosis by standard hematoxylin and eosin stains (i.e., >1 day), but not so long after cryotherapy that central necrosis can not be differentiated from healing rim (i.e., <60 days). This allows greater flexibility in the recruitment of patients surrounding their scheduled resection. The resected ablation zone will be measured to compare the average diameter in three dimensions with the CT scan dimensions. The diameter of the necrotic tumor and the ablated zone will be measured and compared with these areas on the CT scan. The ablative zone's regions of enhancement or nodularity (i.e., possible residual cancer) will be compared with regions (anterior, posterior, superior, inferior, medial and lateral) from the pathologic analysis of the tumor, including effects upon any adjacent bronchi and vasculature. We expect that all tumor will be eradicated with cryotherapy, but would define success as more than 75% of analyzed tissue being negative for cancer. Radiofrequency ablation frequently leaves residual tumor and recurrence rates range from 12-58%[22-24] depending on tumor size and vessel proximity. Our hope is that the percutaneous cryoablation technique will show more thorough destruction of cancer cells.

The usual clinical scenario is that the patient who is receiving percutaneous cryotherapy does not have an operation or cannot have an operation. This study would give us the unique opportunity to resect the tissue, which has received cryotherapy, and determine whether this is a viable treatment option as a primary treatment modality rather than as a last ditch treatment, or treatment of last resort.

4.0 PATIENT SELECTION

4.1 Eligibility Criteria

1. Patients must have histologically or cytology-demonstrated non-small cell carcinoma or metastatic lung disease. The diagnosis can be made by CT – guided needle biopsy, bronchoscopic biopsy, or transbronchial biopsy. Only patients who have a definitive diagnosis of cancer can be enrolled.

2. Patients must have measurable disease defined by one peripheral lung lesion that can be accurately measured in at least one dimension with the average diameter ≤ 3.0 cm on conventional CT scan techniques.

3. Patients with metastatic lung disease must have no more than 3 peripheral lung lesions (each ≤ 3.0 cm in average diameter) which have not been treated with radiation or chemotherapy since the new metastatic lesion appeared. Lung must be the only site of metastases.

4. Patients may not have received any prior chemotherapy or radiotherapy for this particular lesion prior to treatment with percutaneous cryotherapy.

5. Patients must be 18 years of age or greater

6. Patients must have adequate pulmonary function tests (as determined by the treating physician) to tolerate either the lobectomy or wedge resection required. This would entail that the patient have a FEV-1 following resection of at least 1.0 L/sec and pre-operative diffusing capacity of >50%.

7. Patient would have had a pre-therapy CT scan of the chest and PET scan as a baseline.

8. The patient must have neutrophil count of greater than 1,500 c/mL, a platelet count greater than 75,000 c/ml and INR ≤ 1.5.

9. Patients with metastatic lung disease must have their primary tumor under local control and have no evidence of metastatic disease other than the lung.

10. The patient must have the ability to understand and willing to sign a written informed consent document.

11. The patient must be registered with the Clinical Trials office at the Karmanos Cancer Center/Wayne State University.

4.2 Exclusion Criteria

1. The inability or unwillingness to interrupt aspirin, or other platelet inhibiting drugs, Coumadin or heparin prior to the study.

2. Uncontrolled or concurrent other illnesses, including active infection, heart failure, unstable angina, cardiac dysrhythmia, psychiatric illness or a social situation that would limit compliance with the study requirements.

3. Patients must agree to follow an acceptable method of birth control while participating in this study.

4. Women who are pregnant or lactating.

5. Patients in other ongoing experimental studies.

4.3 Inclusion of Women and Minorities

Both genders and members of all races are eligible for this trial.

4.4 Registration Procedures

All patients will be registered at the Clinical Trials Office (CTO) of the Karmanos Cancer Center/Wayne State University by Frank Baciewicz, MD or Peter Littrup, MD.

Registration and Data management for the protocol will comply with all Karmanos and National Cancer Institute regulations for research studies. The study coordination will be undertaken by trained personnel who meet the minimum criteria espoused by Karmanos

Cancer Institute and the National Cancer Institute. The personnel will include Barbara Adam, RN and her designees who are currently providing these services for Dr. Littrup's present cryotherapy protocols, and Pat St. Marie, Karmanos surgical PA who works in the cancer institute, the operating room and clinic with Dr. Baciewicz.

5.0 TREATMENT PLAN

All patients who have been diagnosed with primary Stage I lung cancer or limited metastatic disease, confirmed by percutaneous transthoracic needle biopsy or transbronchial biopsy will also have a CT scan of the chest, MRI of the brain and a PET scan. All patients will have no evidence of cerebral disease, no evidence of metastatic disease by the PET scan or the CT scan. This will include no evidence of satellite lesions on the CT scan of the chest, no mediastinal lymph nodes greater than 1.5 cm. There will be no hepatic or adrenal masses noted. MRI of the brain will not demonstrate evidence of metastatic disease. PET scan may show only significant uptake in the primary lung lesion. There will be no areas that have SUV of greater than 2.5 in any location other than a primary lesion considered under control in the metastatic subgroup. The lesion on the lung CT scan must be in the peripheral third of the lung.

The patients with metastatic lung cancer will have a solitary or limited number (≤ 3) of lesions less than 3.0 cm diameter. They will have prescreening MRI of the brain, which demonstrates no evidence of disease, the chest CT scan and PET scan will demonstrate no evidence of other metastatic disease and control of the primary tumor. Patients will then undergo treatment with percutaneous cryotherapy to the lesion. This will be performed on an outpatient basis.

The technique for local anesthesia will be 1% Lidocaine for the initial skin injection with 1% Lidocaine with Epinephrine (1:1000) for deeper injections. This will minimize bleeding and increase the duration of the Lidocaine. A 3.0-4.0 cm wide path of local anesthesia for each probe will be created by angulating the injection in several directions all the way to the tumor site. Intercostal nerve blocks will be achieved as needed with Lidocaine on each side of the lesions and on both sides of the affected rib.

The cryotherapy equipment (Endocare, Inc., Irvine, CA) will utilize application of 1.7 and/or 2.4 mm diameter cryoprobes. The ice ball size for these probes will vary between 1.5 – 3.0 cm in diameter depending on the vascularity and fibrous content of the underlying tissue and the tumor. The length of the ice ball will be consistent with the probe size at approximately 4.5 cm. Depending on the size of the tumor, a cluster of cryoprobes may be required to adequately achieve cytotoxic temperature (-40^{o} C). The individual probes will require a freeze/thaw/refreeze cycle of up to 15/10/10 minutes respectively. The use of a triple freeze will be at the discretion of the interventional oncologist, whereby the first freeze: thaw is of short duration to facilitate further ablation. The general rule is that there is more than one cryotherapy probe for each centimeter of tumor diameter as previously noted.

A central guidance needle (20 gage, 15 cm length) is first placed in order to define the ideal course and angulation. The cryoprobes are then placed with minimal repositioning and secondary tissue disruption. Saline injections of the overlying skin will prevent ice necrosis from extending into the epidermal layer as needed.

Cryotherapy procedures currently utilize the Siemens Somatome Plus 4 with the Care Vision fluoroscopy package. The patient will have an initial CT scan to assess tumor position in relation to adjacent tissue while he or she is placed in the anticipated prone or decubitus position for the procedure. Multi-planar reconstructions will be performed to map the approach and probe requirements. CT documentation of the ice ball progression during the procedure will include scans after the first and second freeze cycles. The CT image has better resolution than CT

fluoroscopy images and allows multiplanar reconstructions. The best final image on the final ice dimensions are produced by limited spiral scans after probe removal which eliminates the scatter artifact from the cyroprobe.

Approximately 3 weeks after completion of the percutaneous cryotherapy the patient will receive a CT scan of the chest. The CT scan will assess tumor dimension as well as any residual changes in the treated lung.

The patient will then undergo a standard thoracotomy for lobectomy for the primary lung carcinoma or a limited wedge resection for metastatic lung cancer. The resected tissue will be forwarded to pathology for analysis of remaining tumor. The patients will also have mediastinal node dissection at the time of operation, a standard staging procedure. The lymph node stations will also be assessed for residual tumor. Lung parenchyma surrounding the area of cryotherapy will also be assessed for any residual damage from the cryotherapy probes and treatment.

The histological analysis of the lung, tissue will then be compared with the CT scan. If there is any residual tumor, this will be correlated with the CT scan. In addition, the lung which had been resected will be assessed for damage from the cryotherapy technique.

Patients will have standard follow-up studies as per their primary lung oncologist. The patient will be requested to have a follow up CT scan of the chest and PET scan at six months for their long term follow up.

In addition to patients being followed by the treating physician at as needed clinic visits patients will be followed yearly for survival.

5.1 Concomitant Medication Therapy

Patients will be instructed to take Prednisone to prevent/alleviate any acute inflammation. The steroid should be taken:
20mg BID on the day of the cryotherapy procedure
20mg BID on the day after the procedure
20mg BID two days after the procedure
20mg AM and 10mg PM three days after the procedure
10mg AM and 10mg PM four days after the procedure
10mg five days after the procedure
5mg six days after the procedure

STUDY CALENDAR

	Pre-Cryotherapy	Cryotherapy	Week 1[H]	Week 2[H]	Week 3	Thoracotomy[J]	Month 6
Diagnosis	X						
Informed Consent	X						
Demographics	X						
Medical History	X						
Physical Exam[G]	X[C]						
Chest X-ray	X[B]	X	X	X			
CT scan of chest	X[B]				X[I]		X
PET scan	X[A]						X
MRI of brain	X[D]						
Pulmonary Function Tests (PFTs)	X[D]				X[I]		
EKG	X[D]						
CBC w/differential	X[C]						
Chem-7[F], alkaline phosphatase, SGOT, bilirubin	X[C]						
INR	X[E]						
Pregnancy test, urine or serum	X[E]						
Histology						X	

B: Must be performed within 42 days of cryotherapy
C. Must be within 6 weeks of cryotherapy
D: Must be within 12 weeks of cryotherapy
E: Must be within 1 week of cryotherapy

F: Chem-7 includes BUN, creatinine, glucose, and electrolytes

G: Physical exam to include heart, rate, blood pressure, respiratory rate, temperature and documentation of concurrent medication

H: +/- 2 days

I: 2-53 days following percutaneous cryotherapy; within 7 days of planned thoracotomy

J: Less than 12 weeks from percutaneous cryotherapy

6.0 ADVERSE EVENTS

Adverse event monitoring and reporting is a routine part of every clinical trial. The following list of adverse events and the characteristics of an observed adverse event will be expeditiously reported when the event occurs.

1. Pneumothorax - In the placement of cryoprobes, and after removal of the percutaneous probes, the patient may develop a pneumothorax in the treated area. This may be noted on a chest x-ray obtained following the percutaneous treatment. It may also be noted on subsequent chest x-rays. The patient may become short of breath. Only ~15% pneumothoraces have been reported after cryoablation of the lung[32], usually only on large masses located centrally.

2. Hemothorax –One of the advantages of cryotherapy is the preservation of the blood vessel architecture. A hemothorax may be more likely, if a central lesion was being treated. Treatment of more peripheral lesions makes this unlikely. Subsequent chest x-ray or complete blood counts may be indicated. A significant hemothorax would require either percutaneous drainage with a catheter or the patient might have his/her thoracotomy performed sooner than three weeks after operation.

3. Hemoptysis - This would more likely occur with central lesions rather than with this protocol. However, when the probes are used for cryotherapy, a pulmonary vessel could be penetrated and hemoptysis might result. If this developed prior to cryoablation, the therapy would not be administered. If the hemoptysis was self-limited, CBC would be obtained as well as chest x-ray and CT scans to primarily ensure that the hemoptysis has not resulted in secondary areas of consolidation other than the treated area. If the hemoptysis is significant, the patient would require a bronchoscopy and possibly operation prior to the three-week interval after therapy.

4. Nerve Damage - If cryotherapy was in the area of the phrenic nerve, recurrent laryngeal nerve or in the area of the brachial plexus, it is possible that nerve damage could result. Brachial damage would be demonstrated by anesthesia of the extremity affected, or any weakness in the motor strength of the affected extremity. Phrenic nerve damage would be noted by elevated diaphragm on the treated side. Further evaluation of the phrenic injury could be performed with fluoroscopy to determine if the diaphragm was able to contract. Recurrent laryngeal nerve damage would present as hoarseness but would be unlikely since masses in this study would not be near the aorto-pulmonary window.

Any of these adverse events would be reported. In addition, any event that requires hospitalization, placement of a tube, or any interventions such as bronchoscopy or early operation, would then be reported as protocol-specific adverse events.

7.0 CORRELATIVE / SPECIAL STUDIES

We propose to correlate the patient's CT scan before the operation with the final pathology result.

Any changes that are noted on the CT scan in relation to the pathologic specimen may have predictive value. Imaging studies such as chest CT scan, or PET scan will be a requirement to ensure that no tumor remains after therapy. Since future patients who are not operative candidates will require imaging studies to determine the presence or absence of tumor following therapy, any prediction value of imaging studies will be very important.

The PET scans will be performed and interpreted by Dr. Richard Joyrich (313-966-4397) of Karmanos Cancer Center/Wayne State University, 4100 John R., Detroit, MI 48201.

FDG(F-fluoro-deoxy-D-glucose)- is a radiolabelled glucose used in PET imaging that is transported into the cells. It is accumulated in neoplastic cells at a more rapid rate than normal tissue. Non-neoplastic disease such as granulomatous and inflammatory processes could also accumulate PDG and give false results, there a histologic analysis of cryotreated tissue (both neoplastic and inflammatory processes) needs to be done to evaluate the cryotherapy effect on the neoplasm.

FDG uptake will be measured as Standard Uptake Value (SUV). Standard Uptake Value is calculated by the following formula: SUV = radioactivity concentration in ROI (Region of Interest(μCi/ml) divided by injected dose (μ Ci)/body weight (kg). The SUV mean will be measured over the whole Region of Interest (ROI). The SUV max will be measured as the uptake in the hottest pixels in the same ROI.

7.1 Measurement of effect

Size of a lesion is defined as diameter in at least one dimension on chest x-ray or CT. The lesion would be a maximum of 3.0 cm or less by chest x-ray or X-ray.

7.2 Response Criteria

Complete response – CR disappearance of the entire target lesion.

Partial response – PR at least 30% decrease in the longest diameter of the target lesion using as a reference the baseline diameter.

7.3 Pathological Response

The tumor will be evaluated by a pathologist, Dr. Fulvio Lonardo (313-745-0630) in the Harper University Hospital , DMC/Wayne State University Pathology Department. The entire resected specimen and the lymph nodes will be re-evaluated for presence of tumor. In addition, the remainder of the treated lung will be analyzed for response to cryotherapy, including damage to lung parenchyma, connective tissue and blood vessel. Any area of hemorrhage will be noted.

7.4 Follow-Up

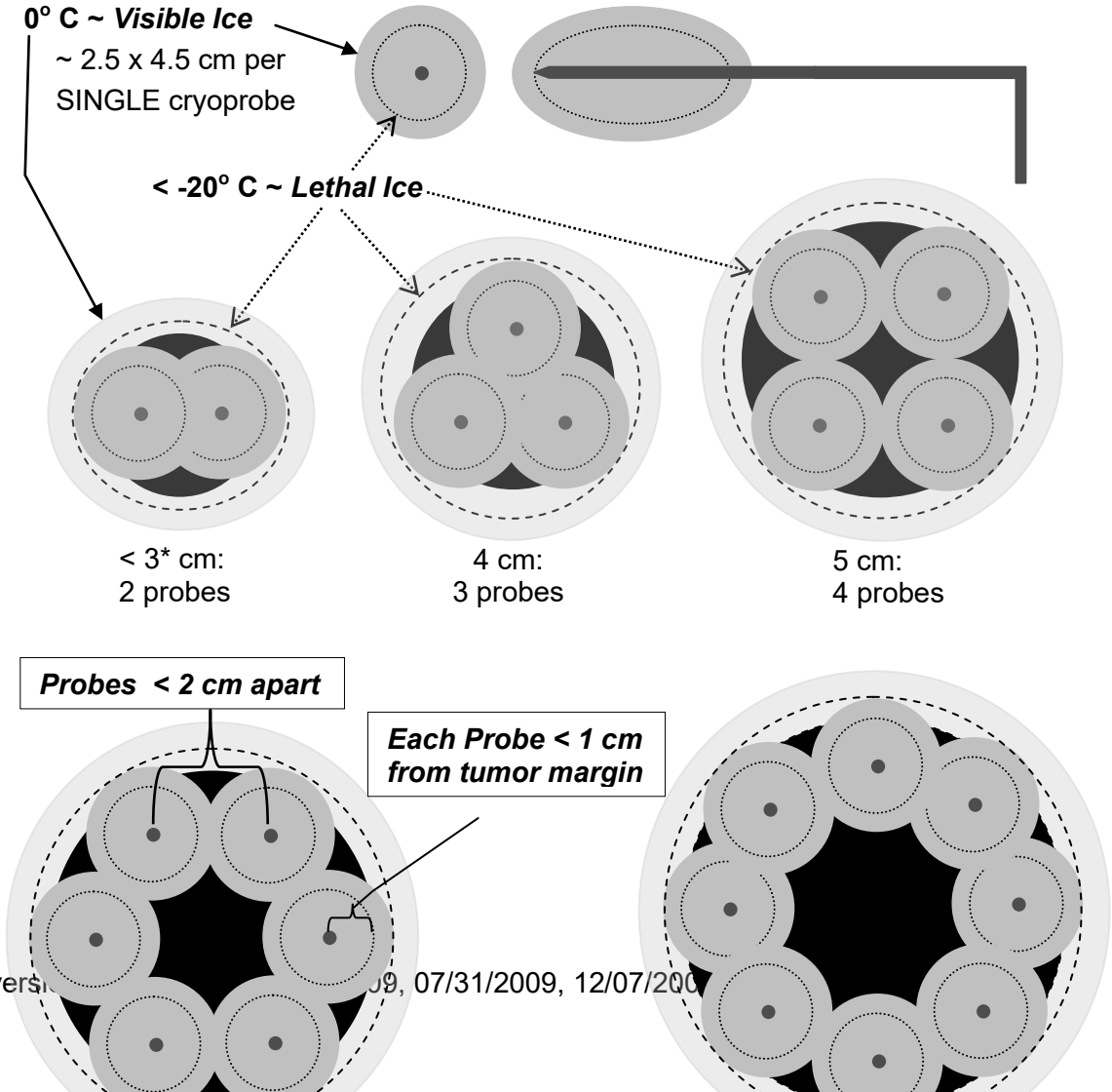
All patients who are registered to the trial wil be followed for survival regardless of whether the patient completed protocol treatment.
All adverse events and serious adverse events that are related to protocol treatment will be followed until resolution.

7.5 Evaluable patients.

To be evaluable for this pilot study, the patient must undergo the planned thoracotomy < 12 weeks from percutaneous cryotherapy, as noted in the Study Calendar. Inevaluable patients will be replaced until the statistically required sample size of 10 evaluable patients (as determined in Section 9.2) has been obtained.

8.0 ***Figure 1: The 1-2 rule for cryoprobe placements according to tumor size (black circles)***

Using a single cryoprobe requires precise central placement [22] to cover the tumor with ice (darker gray around each probe), let alone lethal ice (smaller dashed line ~5 mm inside ice). Conversely, when more probes are used, the sum of the individual ice projections (darker gray circles) synergistically expand, extending lethal ice (larger dashed line) ~ 5 mm beyond all tumor margins while visible ice (lighter gray circle) projects ~ 10 mm.



9.0 Statistical Considerations

9.1 Primary objective.

The primary objective of this pilot study is to evaluate the histologic result of treating primary lung cancer or solitary metastatic lung cancer after PTC. The primary statistical objective is to estimate the PTC success rate (p) as defined in Section 3.4, paragraph 6, i.e., that > 75% of the tissue analyzed histologically 3 weeks post-PTC is negative for cancer. The pilot study hypothesis is that all tumor will be eradicated via PTC.

9.2 Sample size.

The target sample size for this pilot study is 10 evaluable patients (defined in Section 7.5) , from Cohorts A and B combined. The 2 cohorts are defined in Section 2.0, and will not be distinguished in this small pilot study. It is expected that most (if not all) patients who enroll will be in Cohort A. Both point and 80% confidence interval (CI) estimates of p, and of the mean % of tissue which is found negative for cancer (TNC) histologically will be calculated. The precison (i.e, half-width of the CI) attainable in the estimate of (p) with N=10 evaluable patients will depend on the point estimate of the sample rate (p), in the following manner:

Rate	0.10	0.20	0.30	0.40	0.50	0.60	0.70	0.80	0.90
Precision	0.126	0.156	0.175	0.185	0.188	0.185	0.175	0.156	0.126

With 10 evaluable patients, (p) could be estimated to a precision of 0.188 or better (i.e., smaller) for most values of (p), with 80% confidence. The table values were computed using Wilson 80% confidence intervals in the PASS 2011 software program "Confidence Intervals for One Proportion – New". With 10 evaluable patients, the mean of a continuous endpoint (e.g., the mean % TNC) could be estimated to within 0.437 standard deviation (SD) units, with 80% confidence. Those are reasonable precision and confidence levels for a small pilot study, and should provide sufficiently precise estimates for use in planning a subsequent investigation.

9.3 Secondary objectives.

The secondary objectives are: 1) to provide a qualitative assessment of the histology from the ablation and tumor margins; and 2) to perform various correlative studies described in Section 7.0. Secondary objective (1) will not likely require statistical assessment. For secondary objective (2), summary statistics will be calculated, including point and interval estimates of either means or proportions as appropriate, for: PET SUVmean, PET SUVmax, (clinical CT) response rate (RR), and pathologic response rate (pRR). As per Section 7 (and its Study Calendar), the post-PTC CT results will be obtained at 3 weeks and at 6 months; the post-PTC PET results only at 6 months.

9.4 Toxicity (Adverse Event) and Safety Evaluation.

There are various types of adverse events (AEs) listed in Section 6.0. Any one of them could occur as a serious AE (SAE). Based on our prior clinical experience with cryotherapy, we anticipate that up to 20% of patients may have such complications, but that would not be regarded as reason to stop the study.

However, to prevent continuation of this trial in the face of an unacceptably high rate of SAE's (combining all types), we would consider stopping the trial if we see an early example(s) of that.

In addition, as part of our Data and Safety Monitoring Plan for this trial, we have devised a statistical monitoring plan for SAEs. This approach uses a 1-sided upper 80% confidence limit (CL) to determine the first opportunity at which the observed SAE rate provides evidence that the true (and unknown) SAE rate could be > 30%.

Using this statistical monitoring plan, if 1 patient in the first 9 patients are treated and none have an SAE, then we can be 80% confident that the true (and unknown) SAE rate is < 30%, because that is the smallest sample size for which the 1-sided upper 80% CL (0.268) is still < 30%.

The first statistically-based early stopping opportunity for safety reasons occurs if 1 patient has an SAE among the first 8 (or fewer) patients treated, in which case the 1-sided upper 80% confidence limit (0.303) just exceeds 0.30. The second such early stopping opportunity for safety reasons occurs if 2 patients have an SAE among the first 10 (or fewer) patients treated, in which case the 1-sided upper 80% confidence limit (0.327) just exceeds 0.30. Over the full range of the 10 patients intended for this pilot protocol study, we would recommend re-evalution of the study for safety reasons according to the statistical monitoring plan for toxicity given in Table 1.

Table 1. Statistical Monitoring Plan for Toxicity

We would recommend re-evalution of the study for safety reasons if there were X many SAE's among the first N (or fewer) patients treated:			
X	N	p	UCL
1	8	0.125	0.303
2	10	0.200	0.327

In Table 1, X = the cumulative number of SAE's observed thus far; N = the number of cryotherapy patients treated thus far; p = the observed (i.e., sample) SAE rate, combining SAE's of any type; and UCL = the exact 1-sided upper 80% binomial confidence limit for p.

9.5 Accrual rate, accrual duration, and study duration.

The expected accrual rate is 2 patients/year, hence it should take 60 months to enroll the intended 10 evaluable patients. Allowing for 6 months to obtain all endpoints for the last patient enrolled, the expected total duration of this pilot study is 66 months. It may require enrolling 12-15 patients in order to obtain 10 evaluable patients among them.

10.0 Data and Safety Monitoring

Data and safety monitoring of this clinical trial will be done through monthly meetings of, at a minimum, the principal investigator, study coordinators, data manager, and regulatory specialist. The co-investigators and biostatistician will attend when available. Registrations, accrual rate, adverse events, toxicity data, treatment received, response assessments, and data completeness will be reviewed for all patients on the trial. Concerns regarding the study, and modifications to the protocol, if needed, will be discussed with all investigators. A monthly report will be submitted to the KCI Data and Safety Monitoring Committee (DSMC).

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