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Percutaneous Cryoablation for Clinical Stage I Non-Small Cell Lung Cancer: Histology, Results, and Safety

Frank A Baciewicz Jr[1,2], Hakob Kocharyan[3], Deborah Hackstock[2], Lance Heilbrun[2], Hussein D Aoun[4], Fulvio Lonardo[2,5] and Peter J Littrup[6]*

[1]Department of Cardiothoracic Surgery, Wayne State University, USA

[2]Karmanos Cancer Institute, USA

[3]Department of Radiology, Detroit Medical Center/Wayne State University, USA

[4]Department of Radiology, Karmanos Cancer Institute/Wayne State University, USA

[5]Department of Pathology, Wayne State University, USA

[6]Department of Diagnostic Imaging, Ascension Medical Center, Rochester, USA

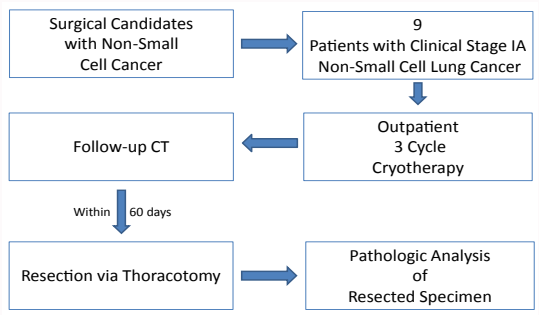
Abstract

Objectives: Lobectomy for clinical stage I lung cancer has an 80% to 90% 5-year survival rate but has morbidity and mortality risks. Not all clinical stage I patients are surgical candidates and some refuse surgery. This study's primary endpoint was to describe the histologic outcome of stage I lung cancer patients treated by percutaneous CT guided cryoablation (PCA).

Methods: Histologically confirmed, clinically staged stage I tumors underwent PCA with standard cryo probes (Endocare, Irvine, Cal). Intraprocedure CT documentation of visible ice (-0 degree Celsius) extending beyond the tumor margins (~1 cm) was performed. Resection of the ablation zone/tumor and lymph node dissection with extensive histologic review was then performed.

Results: Nine patients (7 male, 2 female), median age 65.9 years (range 52 to 78) with mean CT scan tumor diameter 1.7 cm ± 0.3 cm underwent PCA for 4 right upper lobe, 4 left upper lobe and 1 right lower lobe tumors. There were 2 grade 3 CTCAE and 3 grade 1-2 CTCAE complications. Two patients required admission after PCA. Surgical resection via thoracotomy was performed a median of 64.6 days after PCA. Two resections showed only 1 microscopic focus of tumor (≤ 1 mm). Only one showed macroscopic residual tumor (1 cm) and the remaining 6 showed no tumor. The only patient with macroscopic residual disease had pathologic stage IIIB.

Conclusion: Outpatient PCA in clinical stage I Non-Small Cell Lung Cancer (NSCLC) offers a safe, feasible treatment with complete local tumor eradiation in 6/9 patients.



Graphical Abstract

Abbreviations

PCA: Percutaneous Cryoablation; NSCLC: Non-Small Cell Lung Cancer; SBRT: Stereotactic Body Radiation Therapy; RFA: Radiofrequency Ablation; HIPAA: Health Insurance Portability and Accountability; MRI: Magnetic Resonance Imaging; PET: Positron Emission Tomography; FVC: Forced Vital Capacity; FEV1: Forced Expiratory Volume in 1 second; DLCO: Lung Diffusing Capacity for Carbon Monoxide; CTCAE: Common Terminology Criteria for Adverse Events;

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Correspondence:
Frank A Baciewicz Jr, Department of Cardiothoracic Surgery, Wayne State University School of Medicine, 3990 John R, Detroit, MI 48201, USA, E-mail: fbaciewicz@dmc.org

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VATS: Video Assisted Thoracoscopy

Introduction

Surgical resection of clinical Stage I NSCLC demonstrates a one-year survival rate of more than 90% and a five-year survival rate of 70% to 90% [1,2]. Stage I NSCLC must be less than 3 cm in size and located 2 cm or more distal from the carina. These tumors have not involved regional or mediastinal lymph nodes and not invaded the visceral pleura [3]. Historically, surgical resection of clinical stage IA lung cancer has resulted in the best long-term outcomes compared with Stereotactic Body Radiation Therapy (SBRT), standard radiation or Radiofrequency Ablation (RFA). Standard radiation delivers a 40% two-year survival rate [4] and 35% three-year survival rate [5]. SBRT has demonstrated 22% complete response [6], and 32% to 56% three-year survival rate [7-9]. RFA provides a local control rate of 58% to 68% with short follow-up of 18 months and a three-year overall survival rate of 43% to 74% [10-12]. Two trials utilizing ablate and resect technique via open thoracotomy reported a complete cell necrosis in 37.5% with primary and metastatic lung neoplasms [13,14]. Complete cell necrosis was only achieved in tumors <2 cm [13]. Standard radiation, SBRT and RFA frequently leave residual tumor and recurrence rates range from 8% to 30% depending on tumor size and vessel proximity [6,11-16]. PCA has not undergone an immediate or delayed ablate and resect protocol.

The lethal effect of the cryoablation on the cell is based on formation of extracellular ice crystals which result in osmotic shift and dehydration. This process is at least partially reversible. However, if freezing occurs very quickly, the majority of fluid remains intracellular. Since there is insufficient time for the osmotic process, this result in formation of intracellular ice crystals. These have a destructive effect on the cell membrane and organelles. During thawing, water flows from the interstitium into the cells resulting in further cell damage [17].

We propose that outpatient percutaneous CT-guided cryoablation could achieve comparable local histologic tumor control to surgery while avoiding the morbidity/mortality of minimally invasive or open surgical resection [18,19]. PCA could be an alternative treatment for patients who could not tolerate lung resection because of marked impairment of pulmonary function secondary to smoking [20-22].

Our prospective pilot project was designed to determine if percutaneous CT-guided cryoablation for clinical stage I NSCLC could have similar local control as standard surgical techniques. While resection provides 100% tumor eradication, we hypothesized close to 100% tumor eradication in a pilot PCA study. The primary objective was to analyze post PCA surgical resection specimens and assess for residual tumor on histologic review. The secondary objective was to assess the technical feasibility and safety of PCA for small lung tumors.

Materials and Methods

All cryoablation procedures were performed between 6/2009 and 7/2013 under an Institutional Review Board (IRB) approved protocol for prospective data collection, in compliance with the Health Insurance Portability and Accountability Act (HIPAA). The trial was registered with the clinical trials registry prior to enrollment in 6/2009. Patients were selected by thoracic oncologists and thoracic surgeon. Inclusion criteria included patients who were diagnosed with clinical stage I NSCLC by percutaneous transthoracic needle biopsy or transbronchial biopsy. All tumors were less than 3 cm and in the peripheral 1/3 of the lung. All patients were evaluated as candidates for surgical resection. Written informed consent for participation in the prospective trial including cryoablation and resection was obtained from all patients.

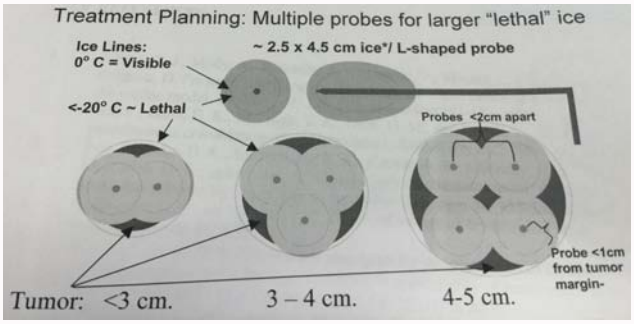

Figure 1: The 1-2 rule for cryoprobe placements according to tumor size (black circles). Using a single cryoprobe requires precise central placement to cover the tumor with ice (darker gray around each probe), let alone lethal ice (smaller dashed line ~5 mm inside ice). Conversely, when more probes are 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 ray circle) projects ~10 mm [30].

Patients underwent a CT scan of the chest, brain MRI and PET/CT to assess extent of disease and clinical stage [23-25]. Patients were excluded if the PET or brain MRI showed metastases. The nodal stage was determined by CT and PET scan. No mediastinoscopy was performed for staging as mediastinal lymph nodes were less than 1.0 cm and PET negative.

The ablation procedures were performed by two experienced interventional radiologists. All lung cryoablation patients received local lidocaine anesthesia (Fresenius Kabi USA, Lake Zurich, IL) and moderate sedation as needed during the procedure per anesthesia staff. Intraprocedure routine monitoring of patients' vital signs with pulse oximetry and standard technique was performed per anesthesia team. Intravenous antibiotic prophylaxis (e.g. Cefazolin 1gm, WG Critical Care, Paramus, NJ) was routinely administered prior to cryoablation. Patients were placed in supine or lateral oblique position for comfort (e.g., right decubitus for left lung tumor access). No patient was required to be in the prone position during ablation. All procedures were performed under CT-fluoroscopic guidance (Siemens plus 4 with Care-Vision fluoroscopy package Erlangen, Germany). CT documentation of ice progression during the procedure relied primarily upon intermittent CT fluoroscopy. Helical scans, having less quantum mottle, were also obtained for greater clarity at the completion of the first freeze cycle and post procedure to evaluate for potential complications.

The ablations were performed with a system using the Joule Thomson gas effect of argon (freezing) and helium (thawing) (Endocare HealthTronics, Austin, TX). The system was Food and Drug Administration (FDA) cleared for soft tissue ablation with variable probe sizes (i.e.: 1.7 mm or 2.4 mm).

Cryoprobes were placed according to the 1 to 2 probe placement rule (Figure 1) and no case was performed with a single cryoprobe to avoid non-lethal isotherms [26,27].

A triple freeze protocol of 3 minutes included a three-minute freeze which was followed by a three-minute stick freeze (passive

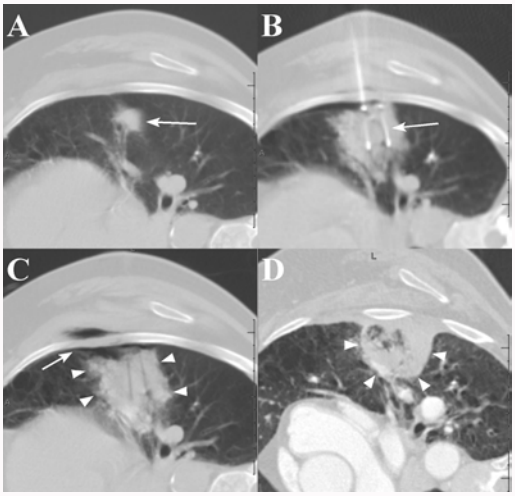

Figure 2: CT scans showing lung lesion (A), lung lesion with PCA probes in place (B), post PCA iceball on CT (C), pre-thoracotomy ablation zone on CT (D).

thaw) to generate a thermally conductive [28], hemorrhagic/edematous cloud encompassing the tumor. This was followed by two additional freeze sticks, cycles of up to10 min freeze, 5 min stick and 5 min freeze. The length of the second freeze cycle was determined by intermittent CT fluoroscopy showing low density ice extending greater than 1 cm beyond visible tumor margins, as well as a helical acquisition at approximately 5 min. CT images of final ice dimensions were recorded from the post-procedure scans immediately after rapid probe removal (~2 min after thaw), thereby eliminating beam-hardening artifact from the cryoprobes (Figure 2). The ablation zone diameter was determined by the treating interventional radiologist.

Within 60 days after completion of the percutaneous cryoablation the patients had CT of the thorax, assessing tumor dimension and surrounding parenchymal changes. All patients were found to have large freeze zone around tumor. As all included patients were undergoing tumor resection, no PET scan was done to evaluate for disease progression. Patients then underwent thoracotomy for lobectomy or segmental resection of the primary lung carcinoma. The proposed interval between the ablation and resection was 60 days. This 60 day interval was chosen to determine the intermediate term local tumor control with PCA and to evaluate intermediate term lung injury. Intraoperatively, patients had standard staging by mediastinal node dissection at the time of operation with multiple lymph node stations assessed. The ablated tissue and regional lymph nodes within the resected specimens underwent hematoxylin and eosin stains and were subject to histologic review of individual sections.

Statistics

The primary statistical objective was to estimate the PCA success rate (p). The pilot study hypothesis was that all tumors would be eradicated *via* PCA, i.e., that p would be 100%.

It was desired to estimate p to within 0.200 of its true value with 80% confidence. Hence, the half-width of the 80% Confidence Interval (CI) should be <0.200. That would require N=10 patients to achieve, as calculated from the PASS 2011 software program "Confidence Intervals for One proportion- New". The largest precision (i.e., CI half width) would then be 0.188, if p=0.500. The study was halted after enrolling 9 patients, as patients resisted waiting 60 days for tumor resection. The maximum precision in the estimate of the PCA success rate (p) with 9 patients was then 0.197 still <0.200.

Results

Patient outcomes

Nine patients, 7 males and 2 females, were enrolled in the study with a mean age of 65.7 years (range: 52 to 78). Average pack years smoked was 40.3 years, ranging from 0pack/years to 110 pack/years. Mean FVC, FEV1 and DLCO were 3.5 ± 0.73 L (mean ± standard deviation), 2.28 ± 0.62 L/sec and 15.21 ± 3.20 mL/mmHg/min, respectively (Table 1). Preoperatively, tumor had a mean diameter of 1.7 ± 0.3 (standard deviation) cm by CT scan. All tumors were solid with no ground glass component. The mean for the maximum standard uptake value (SUVmax) was 6.4 ± 3.5 on the preoperative PET scans (Table 2). Histologic types included 7 adenocarcinomas and 2 squamous cell carcinomas.

The iceball diameters had an overall mean diameter of 3.7 cm ± 0.5 cm on immediate post PCA procedure CT.

CT scans obtained within 60 days following percutaneous cryoablation demonstrated an ablation zone and resorbing area with a smooth consolidative rim. No enhancement was noted within the ablation zones or margin to suggest residual tumor.

The ablation zone mean diameter on CT was 3.1 cm ± 0.7 cm consistent with expected early ablation zone resorption and the necrotic central area in the pathologic specimen. The ablated surgical tissue specimen had a mean diameter of 3.10 cm ± 1.76 cm. The ablation zone was larger than the original tumor size consistent with the expected extension of lethal isotherm margin (Figure 2).

There were two grade 3 CTCAE complication. One patient had

Table 1: Average pack years smoked.

PT. #	AGE	SEX	PMH	PACKS YEARS SMOKED	PFT'S (% PREDICTED)		
					FVC	FEV1	DLC
1	75	M	CAD (Stent 2001) right leg bypass 1997, psoriasis	110	3.86 (99)	2.78 (68)	17.6 (60)
2	65	M	Gout, HPB, hyperlipidemia, decortication right lung	33	3.44 (73)	1.80 (48)	16.3 (63)
3	54	M	Carotid Stent, HPB, laryngeal cancer	60	4.93 (103)	3.58 (98)	16.0 (92)
4	72	M	CAD, DM, HBP	15	3.18 (90)	2.26 (82)	15.4 (78)
5	52	F	Colon Cancer, Left lung cancer 2007	30	2.26 (86)	1.53 (73)	12.5 (52)
6	64	M	CVA, schizophrenia, BPH, CRF	22	3.72 (71)	2.09 (52)	15.5 (62)
7	78	F	Atrial Fib, Polio	37	2.98 (104)	2.44 (114)	18.0 (84)
8	68	M	DM, MI (stent) cirrhosis	0	3.27 (82)	2.28 (75)	18.6 (91)
9	64	M	HPB, Drug use, hyperlipidemia, BPH	56	3.83 (103)	1.77 (62)	17.0 (90)

Table 2: Preoperative PET scans.

Patient	Histology	Location	Size (cm)	SUV_{MAX}	CT PATTERN	Probes	Iceball size (cm)	Iceball/ Tumor	Days CT was done after ablation	Ablation zone (cm) on F/U CT
1	Adeno	RLL	1.57	2.1	SOLID, NO GGO	2×2.4	4.03	2.57	29	4.2
2	Adeno	LUL	2.1	9.5	SOLID, NO GGO	3×2.4	3.8	1.81	35	3.1
3	Squamous	LUL	2.1	12.1	SOLID, NO GGO	3×2.4	3.9	1.86	15	3.6
4	*Squamous	RUL	1.5	4.1	SOLID, NO GGO	3×1.7	3.1	2.07	NA	NA
5	Adeno	RUL	1.3	5	SOLID, NO GGO	3×1.7	3.17	2.44	37	2.9
6	Adeno	RUL	2.2	9.9	SOLID, NO GGO	3×2.4	4.5	2.08	59	3.6
7	Adeno	LUL	1.5	6.1	SOLID, NO GGO	3×1.7	3.5	2.33	49	2.7
8	Adeno, Level 5,7,8 positive lymph nodes	LUL	1.5	2.1	SOLID, NO GGO	3×1.7	3.17	2.11	40	2.1
9	*Adeno	RUL	1.9	6.9	SOLID, NO GGO	2×1.7 1×1.5	4.17	2.19	36	2.6

*Denotes patients with microfocus of disease on Histology

Table 3: Post-operatively, the patients remained in the ICU.

Patient	Complications post-cryo	Days Surgery was done after ablation	OPERATION	OPERATIVE COMPLICATIONS	ICU DAYS	HOSP DAYS	HOME O_2
1	Cough	34	Right upper lobectomy	Ileus, air Leak aspergillus in specimen not treated	5	9	Yes
2	Dyspnea, pneumonia, hemoptysis	197	Empyema, adhesion, left upper lobe bi-segmentectomy	Air leak	3	9	Yes
3	Dyspnea, chest wall pain, hemoptysis	48	Adhesions, left upper lobe	Pneumonia	2	17	Yes
4	Hemoptysis, pneumothorax, Right chest tube insertion	29	Right upper lobectomy	Atrial fib. reintubated mucus plugs	7	11	No
5	Atrial fibrillation	57	Adhesions, right upper lobe post segmentectomy	--	2	6	Yes
6	Pneumothorax, dyspnea	77	Right upper lobectomy	Pneumonia perc trach, PEG, pericarditis	23	23 rehab	Yes
7	Cough	55	Left upper lobectomy	Atrial fibrillation vocal cord dysfunction fever	8	9	No
8	-	42	Lingula bi-segmentectomy	Left vocal cord dysfunction	6	7	No
9	Pneumothorax	42	Right upper lobectomy	Atrial fibrillation, multiple bronch for atelectasis	6	10	Yes

Patient 2 - was hospitalized with inflammatory lung process
Patient 4 - pneumothorax resolved with aspiration *via* 8F catheter
Patient 5 - atrial fibrillation resolved without hospital admission
Patient 6 - pneumothorax resolved with aspiration *via* 8F catheter
Patient 9 - pneumothorax required chest tube 1 day hospital admission

new onset atrial fibrillation (resolved), and another dyspnea requiring hospitalization with treatment for presumptive pneumonia. The latter patient had an inflammatory lung response to the PCA, which delayed surgery for 169 days. The remaining PCA complications were CTCAE grade 1 to 2. Three patients had pneumothorax with 8F tube placement and aspiration in two of them, followed by immediate discharge. One patient with small pneumothorax returned with pneumothorax the following day and was hospitalized with chest tube for one day.

All 9 tumors were removed through a thoracotomy incision as this was a pilot study, and the extent and severity of adhesions at 60 days after PCA were unknown. One of the patients developed inflammatory lung condition after cryoablation which took months to resolve. This patient underwent thoracotomy 197 days after cryoablation. Patients underwent surgery an average of 64.6 days after percutaneous cryoablation. Soft, friable adhesions and mild inflammatory changes were noted at the time of surgery. One patient had a segmentectomy, two bi-segmentectomies, and 6 had lobectomies. No patient required transfusion during the operation, and all were extubated after the procedure. Post-operatively, the patients remained in the ICU for an average of 6.9 ± 6.4 days, and the total hospitalization averaged 11.2 ± 5.4 days (Table 3). One patient died 2.5 months after the surgery from *Aspergillus pneumonia*. The patient had *Aspergillus* organisms noted in the resected lung. Our interpretation was that the patient was colonized prior to treatment and that cryoablation and operation allowed the colonization to become clinically significant.

Histologic results

The typical gross appearance of a cryoablation site was a well circumscribed mass of brown-reddish, friable tissue, separated by a rim of firmer, grayish tissue from the adjacent lung (Figure 3A). The mass was extensively sampled for microscopic evidence of disease. No supravital dye was utilized for assessment of viability. Microscopic examination demonstrated a central area of necrotic tissue, where only the vague outlines of stroma and vessels, traversed by elastin fibers and focally admixed with yellow pigment, compatible with hemosiderin, were seen (Figure 3B). Admixed with it were scattered nuclear debris and neutrophils, forming diffuse micro-abscesses in one case, which represented the only viable cells, identified. One case showed cavitation and colonization by *Aspergillus*. The edge between this necrotic core and the adjacent lung was occupied by mature granulation tissue, frequently containing recanalized intravascular thrombi and bronchi with squamous metaplasia.

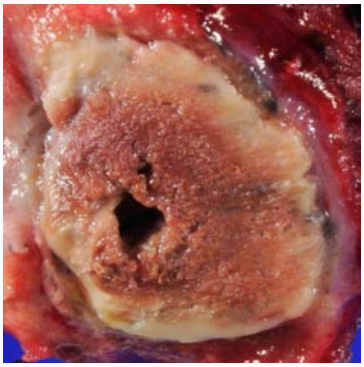

Figure 3A: Representative gross picture of lung tumor after cryotherapy, showing a brown-reddish, friable, granular center with focal cavitation and an outer rim of grayish, firmer tissue.

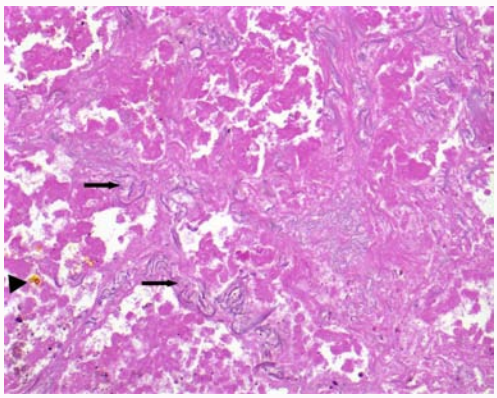

Figure 3B: Representative micrograph of the necrotic center of tissue subject to cryotherapy (200x magnification), showing effaced architecture with no viable cells. Only the ill-defined, ghostly outline of septa, traversed by elastin fibers (arrows), and scattered hemosiderin deposits (arrow head) are identified.

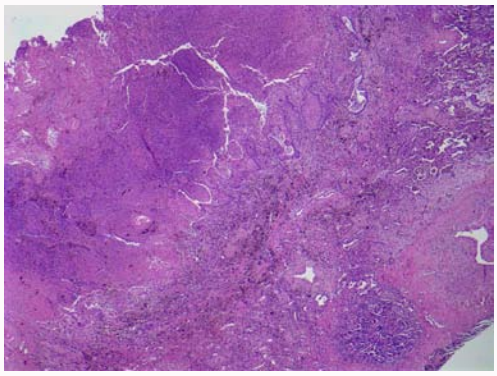

Figure 4: Low magnification micrograph (20x) shows the typical zones seen histologically after cryotherapy, with a necrotic core (upper half), followed by granulation tissue (lower half). Viable microscopic tumor was typically found in this area, as in this case (circled area).

Three cases showed tumor. These were represented by a single microscopic focus, measuring 0.5 mm in one case, a 1 mm focus in a second case (patients 4, 9) and a large focus, measuring 1 cm in one case (patient 8). The two microscopic tumor foci were single isolated foci and were localized at the edge with normal lung, admixed to granulation tissue (Figure 4, 5). The third case showed viable tumor (1 cm) occurring both admixed with granulation tissue as well as at the

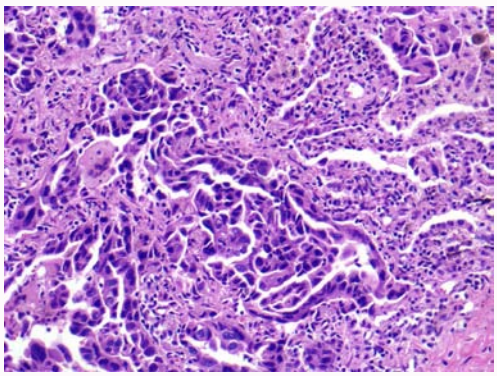

Figure 5: Higher magnification (20x) of area in inset of previous picture, showing microscopic focus of residual viable adenocarcinoma.

center of the cryoablation area without changes suggestive of therapy effect. The case also featured extensive angio-lymphatic emboli of viable tumor both within the lung parenchyma proper, in the pleura and multistation lymph node metastases. All other cases revealed no evidence of microscopic metastases in mediastinal lymph nodes. There was no difference in time interval between PCA and resection, pre-op lesion diameter or iceball/tumor diameter in patients with residual tumor compared to those with complete eradication (Table 2). Patient 8 with positive pleural lymph nodes and positive pleura was pathologic stage IIIB. All other patients were pathologic stage IA1.

Discussion

In our prospective ablate and resect trial we determined the lethal effect of cryoablation on malignant lung tissue an average of 64.6 days after PCA. Two patients had single tumor foci less than 1 mm and one had macroscopic disease. The 3-year overall survival and cancer free survival after PCA has been reported as 77% and 45.6% respectively, suggesting residual disease [29]. This study offers histologic confirmation that residual tumor following PCA may account for the superiority of resection to PCA.

The thorough histologic analysis of tissue (6 to 19 slides/case) demonstrated rare microscopic tumor in 2 of 9 patients, and extensive disease in 1 of 9 patients. In 6 patients, no tumor was evidenced on extensive histologic examination. One patient had a single 0.5 mm focus of tumor, and one had a single 1.0 mm tumor focus. In addition, the microscopic tumor was seen in the rim between the necrotic center and the granular rim suggesting that a larger "iceball" may have killed all tumors in pathologic stage IA patients. The clinical relevance of a 0.5 mm or 1.0 mm foci is uncertain. Subsequently, the ischemic surrounding tissue may have caused these foci to die. In addition, the immunologic response with cryotherapy may have eradicated these foci. Because of the surrounding area of ischemia and secondary immune response, the lethal effect of cryoablation may be greater than the effect of freezing. Extending the lethal margin or using additional cryo probes may have eradicated even these miniscule foci.

The only patient with extensive residual disease after cryoablation was incorrectly staged and rather than clinical Stage I disease, had multi-station mediastinal lymph node and pleural involvement resulting in pathologic Stage IIIB disease. The patient underwent routine screening per protocol having CT chest and PET scan which were negative for enlarged or PET positive nodes. The ablation was routine by confirming presence of a greater than 1 cm ice

ball around the tumor. The lung resection demonstrated a 2.5 cm adenocarcinoma in the lingua in addition to malignant lymph nodes in multiple stations. This patient is thought to be one of 10% patients who are inaccurately staged false negative on CT and PET scans [30,31]. If the staging evaluation had demonstrated lymph node or pleural involvement, cryoablation would not have been offered to this patient. The duration between PCA and resection for this patient was 42 days, no different from the remainder of the study subjects.

Cryoablation has been shown to ramp up the human immune response with increased levels of CD4 T cells, CD8 T cells, 1L-1ß, 1L-2, IL-6, TNF-alpha, and IFN [32] and *in vitro* studies have demonstrated elevated soluble interleukin 2 receptor and IL-6 levels [32]. These boosts of the immune response with PCA could improve long term outcomes compared to present surgical therapy for stage IA disease. Our group's cryoablation experience forecast better outcome stage-for-stage for all organs receiving open or percutaneous cryoablation [33-35]. One explanation would be the systemic immune boost from the inflammatory effect of cryoablation. The FUDA Cancer Hospital Group has shown longer survival for advanced stage lung cancer when cryoablation was added to chemo/immunotherapy [36].

The adverse events of cryoablation experienced by the 9 patients were almost exclusively managed as outpatients. The complications from the outpatient cryoablation procedure, which lasted approximately 3 h, resulted in hospitalization for two patients (patient 2, patient 9).

One hospitalization was secondary to pneumothorax treated with chest tube insertion. A second patient developed dyspnea and an inflammatory lung process which necessitated hospitalization, and delayed resection until day 197. Our minor complication rate was 56% compared to 70.5% in Inoue's study [29]. PCA related causes of death pulmonary embolus and ARDS were not seen.

The average 6-day ICU stay and 11-day hospitalization were not uncommon in 2009 to 2013 when the study was done. In addition, the 17-day hospitalization for patient 2 with the PCA induced inflammatory lung process, which delayed surgery until post PCA day 197, and patient 9 requiring 23 days for placement to rehab skewed ICU and inpatient hospitalization length of stays.

The pre-op comorbidities of our urban inner city patient population typically contribute to longer than average hospital stays.

Our study has limitations: one patient was incorrectly staged and enrolled in the study. Staging of the hilar and mediastinal nodes could be done with endobronchial ultrasound, thus ensuring that only clinical stage I patients are entered. We did not utilize supravital dye when evaluating for residual tumor in the resected specimens. The patient with aspergillosis might have benefited from treatment of the infection, if the diagnosis had been made prior to the resection. Stricter enrollment criteria with assessment of preoperative health status and more invasive preoperative mediastinal lymph node evaluation may alter the outcomes of PCA. We have not presented long term survival data as the surgical resection rather than cryotherapy was responsible for long term outcomes.

In brief, this is the first human study evaluating local tumor control by PCA. While limitations are acknowledged, this outpatient procedure provided a minimally invasive approach for local control in clinical stage I lung cancer at 64.6 days after PCA in 6 of 9 patients. The PCA technique was demonstrated to be a single outpatient procedure which was safe and feasible.

Acknowledgement

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