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Bronchoscopically Delivered Thermal Vapor Ablation of Human Lung Lesions

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Background: **The discovery that early diagnosis can reduce the mortality of lung cancer provides firm evidence that early surgical intervention is effective. However, surgical resection is available only to those who are healthy enough to tolerate the procedure. Vapor ablation may provide an additional method of treating the lung cancer patient, and has been studied in humans for emphysema treatment. In swine, we previously demonstrated that bronchoscopically delivered thermal vapor ablation (BTVA) could be accurately applied, was uniform, anatomically confined, and was tolerated by the animal. To provide evidence that BTVA may be a feasible method of treatment in humans, and since human and swine lungs have differing airway and segmental anatomy, we extended our studies to deceased human lungs to determine if anatomically confined and uniform ablations could be obtained with levels of energy comparable with our swine and human emphysema studies.**

Methods: **We obtained fresh, deceased human lungs and performed BTVA with increasing energy in subsegmental regions of lung containing tumors as well as non–tumor-containing areas in order to determine if uniform ablations with sharp boundaries could be obtained in human lung.**

Results: **We found that all ablations were anatomically contained. The frequency of uniform ablation effect was dependent on the total energy delivered and was achieved at a greater frequency than those with sharp boundaries. If a lung tumor was contained within the anatomy of the subsegment, the ablation zone completely surrounded the tumor.**

Conclusion: **We conclude that BTVA may have a future role in the treatment of lung cancer and should be investigated further in clinical trials.**

Key Words: lung cancer, bronchoscopy, ablation

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Lung cancer kills more people than any other cancer in men and women. It is estimated that there will be >234,000 new cases of lung cancer in the United States and 154,000 deaths in 2018.[1] Although these numbers portend a disease with marked importance, research funding and research activity in lung cancer has lagged behind other types of cancer for some time.[2] In the last few years; however, advances in knowledge of lung cancer pathogenesis and the improvement in mortality with early diagnosis demonstrated by the National Lung Screening Trial,[3] clinicians have seen a renewed interest in the disease. Just in the last several years multiple new drugs and candidate drugs have been developed that have led to the concept of personalized therapy for lung cancer.[4]

National Lung Screening Trial demonstrated that annual low-dose computerized tomography screening reduced the mortality of lung cancer by 20% compared with standard chest x-ray in high-risk subjects.[3] These data indicate that early diagnosis can reduce mortality, and suggest that effective therapy exists for early disease. In spite of these encouraging results, the therapy for early (stage I) disease can be problematic because of surgical morbidity and mortality, patient selection and comorbidity, and disparities in treatments among socioeconomic regional groups.[5,6]

For those patients who are not surgical candidates because of medical conditions that increase the risk, or those who choose not to undergo surgery, ablation of tumors has been performed as a means of primary treatment. Some centers use stereotactic ablative radiotherapy as an alternative to surgery and small studies suggest that this is an effective form of therapy in selected patients. However, stereotactic ablative radiotherapy use is

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limited to some degree by lung toxicity and other injuries,[7] and is not widely available outside of developed countries.

Other forms of ablation such as, radiofrequency, microwave, and cryoablation of lung tumors have all been used clinically with some success, but are limited in applicability due to complications likely related to the percutaneous approach and inconsistent energy delivery resulting in incomplete ablations.[8] Each of these energy sources have advantages and disadvantages that investigators leverage to develop consistent ablations, minimizing some of the problems with energy delivery. It is possible that endobronchial delivery of ablative energy would mitigate most of the complications associated with percutaneous approaches.[9]

Vapor ablation for lung volume reduction has been used safely in patients with severe lung disease and is applied through a standard bronchoscope.[10] We hypothesized that lung tumors could be effectively treated using bronchoscopically delivered thermal vapor ablation, as this therapy has the capacity to transfer sufficient heat energy ablating segments and subsegments of lung, and avoiding the percutaneous complications associated with other forms of energy.

In a prior study,[11] we demonstrated that in a live porcine model, vapor ablates subsegments of the lung in a pattern predictable by the total energy used, has a low complication rate, and is well tolerated by the animals. Gross pathologic assessments showed uniform and nonuniform ablations by color and texture change. There were pneumatoceles present in many segments that were treated with higher energy levels. The gross pathologic changes corresponded to consistent histopathologic changes consisting primarily of necrosis of alveolar tissue with additional damage to bronchi and blood vessels. Ablations were anatomically limited because of the pattern of gas flow in the lung. However, in the porcine model, pigs do not have collateral ventilation (CV) between lung segments, but CV is relatively common in humans.[12] We hypothesized that CV in humans may alter the vapor ablations since gas may transfer through air passages, leading to ablations that cross anatomic boundaries. In this study, we used fresh (< 48 h) deceased human donor lungs and performed ablations in subsegmental locations. Our primary objective for this study was to determine if vapor ablation in human lungs crossed anatomic boundaries. Our secondary objectives were to determine if the energy characteristics in the deceased donor were similar to those in the live pig, and to begin to develop methods to study this treatment clinically.

MATERIALS AND METHODS

Vapor ablation across a range of power was applied to ex vivo human lung tissue. The primary observation was uniformity of the ablation zone. Lungs were treated bilaterally up to 10 times in each lung with a range of energy levels. After ablation, the tissue was fixed and then sliced in a bread loaf manner. The effect of ablation was evaluated by observing areas of ablation, which presented as visibly altered areas that are firmer in texture and lighter in color compared with nonablated tissue. Microscopic examination was not performed since the tissue was nonliving, ex vivo.

Acquisition and Preparation of Human Lungs

Nontransplantable human lungs excised en bloc were obtained from a tissue procurement agency (MedCure, Portland, OR). The tissue requests were approved by an external feasibility committee. Lungs with primary and secondary cancer lesions were included, as well as normal lungs and lungs with various states of emphysema tissue destruction. No conditions were placed on the donor's age, sex, or height. Lungs were excluded from the study if they had significant fluid accumulation or did not inflate properly. During lung preparation, nonlung tissue, such as large blood vessels and adipose tissue, was removed. Lungs were suspended from a modified trachea tube with an adapter for a flexible bronchoscope and inflated with air to 15 ± 5 cm H_2O. Lungs were studied within 48 hours of receipt.

Device Description

The vapor ablation system (Uptake Medical, Seattle, WA) is comprised of a water vapor (steam) generator with disposable catheter. The catheter tip with occlusion balloon was placed in the target airway via the working channel of a flexible bronchoscope (Fig. 1). The proximal end of the catheter is attached to the vapor generator, which delivers a precise electronically controlled amount of vapor through the catheter to the target region of the lung. The water vapor is 100° C and 1 atm as it exits the catheter and dissipates energy to the lung tissue. The ablation system is similar to the commercial system being used for emphysema segmental volume reduction, but has a longer and thinner catheter compatible with a 2.0-mm working channel, and independent control of flow and energy.[10,11]

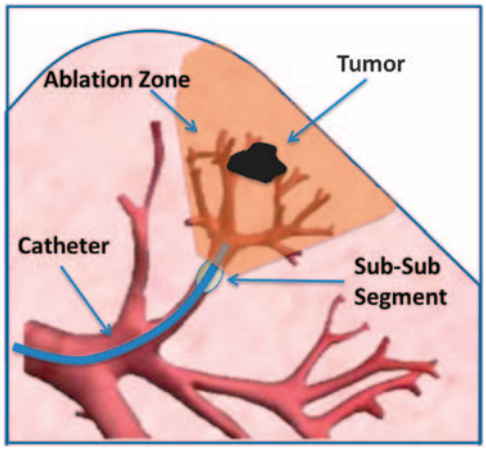

FIGURE 1. A schematic representation of a small peripheral tumor, placement of the catheter, and the resulting ablation zone.

Vapor Application

Vapor was applied to 8 to 12 nonadjacent subsegments in each lung. Subsegment airways with basal diameters of 2 to 4.0 mm were included for treatment. For each subsegment, the following steps were performed: (1) the bronchoscope was inserted into the inflated lung and navigated to the selected airway, (2) the catheter was advanced through the bronchoscope working channel, (3) the catheter balloon was inflated to occlude the airway, (4) an energy setting and treatment time was programmed into the generator, (5) the catheter was attached to the handpiece of the generator, and (6) vapor was delivered to the targeted airway.

Dosing

Energy levels that were previously evaluated in an in vivo porcine model[11] were evaluated in this ex vivo model. These were 125, 270, 330, 390, and 450 cal in an 8-second period.

Tissue Preparation

During each vapor delivery, the lung surface was monitored with an infrared camera.[13] The location of maximum temperature change was marked with a numbered pin to label the ablation and guide dissection. When all deliveries were complete, the en bloc lung was placed in a 10% formalin bath and inflated with 10% formalin overnight. After fixation, each lobe was bread loaf sliced perpendicular to the main airways stems in 5 to 10 mm thickness, tracking from the proximal extent of the ablation to the marking pin. The slices were placed on trays and allowed to settle for at least 20 minutes. The ablation zone of each vapor delivery was identified and photographed. Each ablation zone was inspected and characterized for uniformity of collagen denaturation, presence of complete boundary, and presence of pneumatocele. Any other unexpected effects of treatment and dissection were noted.

RESULTS

Vapor Ablations in Human Lungs Did Not Cross Fissures

Ten human lungs received a total of 107 ablation treatments at 1 of 5 energy levels from 125 to 450 cal. In each ablation, the energy was delivered over 8 seconds to a subsegment (2 to 5 mm diameter). On average, each lung received 10.7 treatments of nonadjacent subsegments. While examining the lungs immediately post-ablation and with dissection, none of the ablations crossed lobar boundaries or fissures. There was no evidence of collateral ablation effect in any of the 10 explanted human lungs.

Uniform Ablations and Sharp Ablation Boundaries are Associated With Total Energy Delivery and Airway Diameter

Between 125 and 450 cal, the majority of ablations were uniform (79/107). However, the frequency of uniform ablations ranged from 54% to 93% and was associated with increasing energy (Table 1). Nonuniform ablations were only commonly observed at 270 cal and less.

We found that the ability to achieve sharp ablation boundaries was also dependent on the total energy delivery, although the frequency of achieving a sharp boundary was somewhat less than achieving uniformity (Table 1). However, at 330 cal and above, $\geq$67% of the ablations achieved a sharp boundary, and these boundaries were demarcated by subsegmental anatomy (Fig. 2).

The ability to achieve uniform ablations and sharp boundaries appeared to correlate with airway size. Relative to other variables, smaller

TABLE 1. Frequency of Uniform Ablation and Sharp Ablation Boundary by Energy Level

	[N/n (%)]	
Energy (Cal)	**Uniform Ablation**	**Sharp Ablation Boundary**
125 ± 20	2/3 (67)	1/3 (33)
270 ± 20	15/28 (54)	13/28 (46)
330 ± 20	26/36 (72)	24/36 (67)
390 ± 20	22/25 (88)	17/25 (68)
450 ± 20	14/15 (93)	13/15 (87)

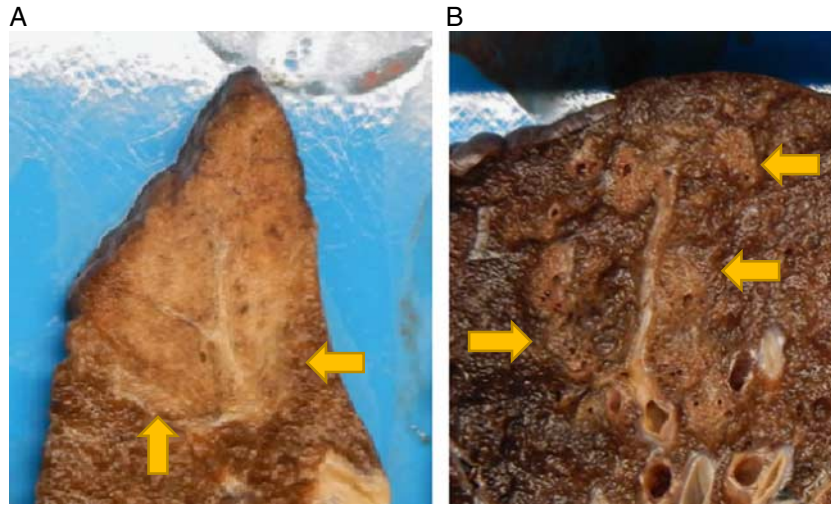

FIGURE 2. A, A complete ablation that is uniform with sharp boundaries (yellow block arrow). B, A nonuniform ablation with indistinct boundaries (yellow block arrows).

airway diameters were associated with more complete, uniform, and demarcated ablations, likely reflecting segmental and subsegmental anatomy. For the larger airway sizes ($\geq$4.0 mm) or lower airway generations the ablation size, uniformity, and boundaries were less consistent and complete (Table 2). Similarly, airway generation, which is related to size, appeared to correlate with uniformity and boundaries (data not shown).

Pneumatocele Formation was Infrequent

Only 4 pneumatoceles were detected in 107 treatments. There was 1 at 270 cal (1/28), one at 390 cal (1/25), and 2 at 450 cal (2/15). None of the 4 pneumatoceles extended to the pleural surface. No pneumatoceles were observed in nonablated lung.

TABLE 2. Frequency of Uniform Ablation and Sharp Ablation Boundary by Airway Diameter

Energy (Cal)	[N/n (%)]				
	2.0 mm	2.5 mm	3.0 mm	3.5 mm	4.0 mm
Uniform ablations by airway diameter					
125 ± 20			1/1 (100)		1/2 (50)
270 ± 20	0/1 (0)	1/4 (25)	10/15 (67)		4/8 (50)
330 ± 20		1/1 (100)	19/26 (73)	3/3 (100)	3/6 (50)
390 ± 20		1/1 (100)	16/18 (89)		5/6 (83)
450 ± 20		1/1 (100)	5/6 (83)	1/1 (100)	7/7 (100)
Sharp boundaries by airway diameter					
125 ± 20			1/1 (100)		0/2 (0)
270 ± 20	0/1 (0)	1/4 (25)	10/15 (67)		2/8 (25)
330 ± 20		1/1 (100)	18/26 (69)	3/3 (100)	2/6 (33)
390 ± 20		1/1 (100)	12/18 (67)		4/6 (67)
450 ± 20		1/1 (100)	5/6 (83)	1/1 (100)	6/7 (86)

Uniform Ablations Were Possible in Lungs With Primary and Metastatic Tumors

Five lungs had single or multiple nodules. Although imaging was not used to determine the precise location of the tumors, palpation was able to determine the location in some cases. In these instances, visual inspection during dissection demonstrated that the nodules were completely contained within the ablation zone (Fig. 3).

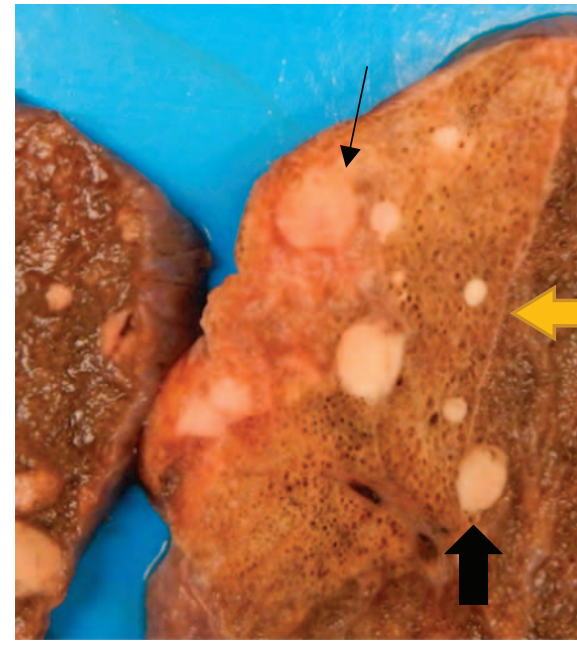

FIGURE 3. Lesions (black arrows) are shown within (line arrow) and outside (block arrow) an ablation that has a sharp boundary (yellow arrow) at a fissure.

DISCUSSION

This study adds to our previous work and provides evidence that in human lung, vapor ablations can be conducted that are confined to the targeted subsegments, and do not appear to be propagated to adjacent lobes, or adjacent subsegments. These ablations are confined anatomically in the human lung, which often has CV as opposed to the pig lung that does not have CV. In addition, this study provides evidence that ablation size, uniformity, and completeness are related to the total energy applied during the ablation and the diameter of the target airway.

As we have demonstrated in pigs, vapor ablation in the human lung is confined to the targeted subsegment of the lung within defined energy parameters. With increasing energy, the ablations were observed to be more uniform with increasingly sharp boundaries. It is likely that the confinement of the ablation and the uniformity within a targeted subsegment or is related to the airway anatomy. Since steam can move through air-containing spaces, and dissipation of heat is related to tissue structure, boundaries, tissue density, and regional blood volume, we would expect that targeted ventilated areas of the lung would be ablated, while nontargeted lung, not receiving the steam would not undergo ablation. This mechanism is distinct from other methods of heat ablation, such as radiofrequency ablation, which depends on the electrical resistance and conductance of the tissue, and microwave, which depends on water content of the mass. Irrespective of the mechanism, confinement of the ablation to a subsegment may have certain advantages in treating tumors while attempting to preserve healthy lung.

As opposed to our prior work in the pig lung, in the human lung high-energy ablations while anatomically confined, led to the formation of only 4 small pneumatoceles that did not extend to the pleural surface or cause visceral pleural rupture. Pig lung and human lung differ in lobular structure and conducting airway anatomy. Human lung appears to have branching but interconnecting airways so that the airspace is quite large allowing greater expansion, while the pig lung has branching and nonconnecting airways that all terminate at their own lobular unit.[12] When a volume of gas is delivered to the airway in pigs, there may be a more limited displacement volume than the human.

We found that the uniformity of the ablation was inversely related to the airway diameter. With increasing size of the airway, higher energy levels were required to achieve uniform ablations. The size of the airway is relative to the size or amount of tissue that it serves. Since larger airways deliver gas to larger volumes of lung, it stands to reason that for the same ablation size, a larger airway will require more energy since there is a larger mass of tissue to ablate and larger volume of airspace to move steam through.

We found that single and multiple nodules in the lung were completely contained within the ablation boundary when specific areas of the lung were targeted. When nodules crossed boundaries however, the ablation appeared to be incomplete with respect to the nodule. Since the ablations are contained to anatomic boundaries, cancers that cross boundaries will likely require additional planning to ensure complete necrosis or thermal fixation.[14]

There are limitations to this study. This was a study in human explanted lung. Although the tissue was fresh, it was nevertheless nonliving. There was no natural ventilation or blood volume. Because we occlude the airway with a balloon during vapor application, ventilation likely plays little role in heat transfer. Vascular perfusion and the total blood volume likely has a larger effect on heat dissipation since blood is a heatsink and is constantly replenished. This may have the effect of reducing the total energy delivery to the tissue. In the pig lung, less energy was required for ablation of living lung tissue, but this could be species related. However, as opposed to microwave and radiofrequency ablation requiring minutes, vapor ablation is very fast at 8 seconds in this and prior studies. This short time to achieve ablation in our models, may result in less heatsink effect attributable to circulation. When extrapolating to the living human, initial dosimetry experiments will be required.

An additional limitation is that while we have shown that complete ablations of subsegments containing nodules is readily attainable, we have not yet demonstrated death of viable tumor. Demonstration of this objective will require a "treat and resect" trial in a large animal model or in humans.

The data presented in this study are important because successful ablation in the living human requires a degree of precision and predictability. As opposed to microwave, radiofrequency, and cryoablation, vapor is the only method of ablation we are aware of that is propagated along airway channels. Propagation of vapor within the airway would be predicted to be limited by diffusion into

the airspaces of the lung, and would dissipate with the distance from the conducting airway up to the point of complete subsegmental ablation. In this respect, vapor is "airway centric" and might be useful for bronchogenic tumors.

In summary, we found that in human explanted lung, uniform ablations and sharp boundaries were directly related to energy delivery, while appearing to cause less pneumatocele formation and pleural rupture than in the pig lung in prior studies. Ablations were anatomically confined to segments and subsegments, and involved entire lung nodules if the nodule was also contained in the boundary. This study provides evidence that ablation of lung tumors using steam may be feasible for human studies.

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