Airway Spray Cryotherapy: Initial Outcomes From a Multiinstitutional Registry

David J. Finley, MD, Joe Dycoco, BS, Saiyad Sarkar, MD, William S. Krimsky, MD, John T. Sherwood, MD, Dominic Dekeratry, MD, Gordon Downie, MD, PhD, Joel Atwood, BS, Hiran C. Fernando, MD, and Valerie W. Rusch, MD

Department of Surgery, Memorial Sloan-Kettering, New York, New York; Division of Pulmonary Medicine, Franklin Square Hospital, Baltimore, Maryland; Cardiovascular and Thoracic Surgery, Mary Washington Hospital, Fredericksburg, Virginia; Pulmonary Medicine, Georgetown Hospital, Austin, Texas; Division of Interventional Pulmonology, Titus Regional Medical Center, Mt. Pleasant, Texas; and Department of Cardiothoracic Surgery, Boston University Medical Center, Boston, Massachusetts

Background. **Spray cryotherapy (SCT) uses a noncontact system to deliver liquid nitrogen (2 to 4 psi) through an endoscopic catheter. Rapid freezing and thawing of tissue causes cellular death and is also hemostatic. We report the preliminary results from 6 institutions in which SCT was used for the treatment of malignant airway tumors.**

Methods. **SCT was performed on patients with symptomatic airway tumors and reviewed retrospectively. Airway narrowing was graded as 25% or smaller, 26% to 50%, 51% to 75%, and exceeding 75%. All events were documented and assessed.**

Results. **Eighty patients (45 male [56%]) underwent 114 treatments. Median age was 66 years (range, 15 to 90 years). All patients were treated with minimal blood loss. Fifty-eight percent of the cases were outpatient procedures. Airway obstruction exceeded 75% in most of the lesions treated. There were 21 intraoperative events (19%), including hypotension, bradycardia and tachycardia, ST segment changes, desaturation, and an airway tear. Three pneumothoraces occurred, one requiring emergency chest tube placement. Two intraoperative deaths were associated with bradycardia. Three postoperative deaths occurred in patients who were transitioned to comfort care. All but 1 patient had airway patency after treatment.**

Conclusions. **SCT can be used in patients with highly vascular tumors, with reduced bleeding complications and a low overall complication rate. Caution is needed before SCT is used on a widespread basis, given the intraoperative complications. Although the potential benefit of SCT is considerable, this needs to be confirmed in larger studies.**

(Ann Thorac Surg 2012;94:199–204)

Malignant airway tumors (MAT) cause significant morbidity and mortality. In non-small cell lung cancer alone, up to 30% of patients can have central airway obstruction due to MAT [1]. These lesions often lead to shortness of breath, postobstructive pneumonia, hemoptysis, and ultimately, respiratory failure and death. Life expectancy with untreated symptomatic MAT is typically 4 to 8 weeks.

Treatment of these lesions is difficult. A variety of local modalities are used, including mechanical debridement, laser, argon plasma or electrocautery ablation, endoluminal brachytherapy, photodynamic therapy, and stents. Spray cryotherapy (SCT) is a new modality with encouraging results in the treatment of esophageal lesions, including esophageal cancer [2–6]. It uses a noncontact low-pressure (2 to 4 psi) spray of liquid nitrogen to induce cell death. Initial reports suggest that SCT is safe and effective in the management of benign stenoses of the airway [7–9]. Little data exist regarding the use of SCT for MAT. This report describes early multi-institutional experience with SCT for the treatment of MAT.

Material and Methods

We conducted a retrospective review of patients treated for MAT at 6 institutions known to use SCT. The study excluded patients with benign strictures. Patients who had other treatment modalities at the same time as SCT were included. All data were deidentified before collection and entered into Excel software (Microsoft Corp, Redmond, WA), for analysis. Patient demographics were collected.

Airway obstruction was graded in quartiles: 25% or smaller, 26% to 50%, 51% to 75%, and exceeding 75% before and after treatment, using an estimate of cross-sectional area to determine the percentage of obstruction.

Drs Sarkar, Krimsky, and Fernando disclose that they have financial relationships with CSA Medical.

Accepted for publication Jan 6, 2012.

Presented at the Forty-seventh Annual Meeting of The Society of Thoracic Surgeons, San Diego, CA, Jan 31–Feb 2, 2011.

Address correspondence to Dr Finley, Surgery, Thoracic Service, Memorial Sloan-Kettering Cancer Center, 1275 York Ave, New York, NY 10065; e-mail: finleyd1@mskcc.org.

Published by Elsevier Inc

0003-4975/$36.00
http://dx.doi.org/10.1016/j.athoracsur.2012.01.112

Complications were recorded and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0 (http://ctep.cancer.gov/reporting/ctc.html). Permission from the Institutional Review Boards at each participating center was obtained for this study.

SCT was performed with the CryoSpray Ablation System (CSA System, Model CC2-NAM, CSA Medical Inc, Baltimore, MD) through a 7F disposable catheter. The catheter is advanced to the target tissue using the working channel (minimum 28-mm diameter) of a therapeutic flexible bronchoscope. This device is approved for use through an endoscope with an active decompression tube. The use of this device through a bronchoscope is considered off-label because only passive venting of the gas is used.

Adequate venting of the gas is required due to the rapid expansion of nitrogen as it undergoes a phase change from a liquid to a gas (liquid-to-gas expansion ratio 1:694). This is confirmed during treatment with SCT by visualization of the gas exiting the airway, feeling the gas, and by hearing the gas escaping. Also, continued chest expansion is an indication of retained gas even if venting is confirmed. Any indication of inadequate venting aborted the SCT.

The application of SCT is usually performed under general anesthesia, although some patients were treated with sedation alone. Rigid bronchoscopy, endotracheal intubation, and laryngeal mask airway is used for patients undergoing general anesthesia. The flexible bronchoscope is advanced into the airway and used to direct the SCT toward the tissue to be treated. Ventilation is held during the period of SCT. An open circuit is confirmed in all patients before treatment. Cuff deflation of the endotracheal tube and detachment of the ventilator is used for all methods of ventilation. If unable to confirm an open circuit, SCT was aborted and an alternative approach to maintaining adequate venting was used.

The length of the SCT is determined by the amount of time the tissue is more than 50% frozen. Visible mucosal frost formation was used as a surrogate for frozen tissue, and the cycle started once this reached 50% of the local area view from the flexible bronchoscope. Most SCTs lasted 5 seconds, though some initial treatments were longer. Complete visible thaw of the tissue (complete resolution of frost), with a minimum of a 30-second waiting period between treatments, is required before proceeding to the next treatment. The number of treatments was determined by each physician. This procedure was standard and uniform amongst the physicians participating in this study, with slight variations in the total number of spray treatments and the number of airway sites treated during the same procedure.

Table 1. Patient Demographics

Variable	Median (range) No. (%)
Age, years	66 (15–90)
Male sex	45 (57)
Current or former smoker	58 (73.5)
Active alcohol use	8 (10)
Stage IV disease	58 (73.5)
Operative time, min	65 (15–176)
Outpatient procedure	65 (58)

Table 2. Histology of Tumors Treated With Spray Cryotherapy

Histology	Patients No. (%)
Metastasis	26 (32)
Squamous	20 (25)
Non-small cell lung cancer	17 (21.5)
Carcinoid	4 (5)
Small cell lung cancer	3 (4)
Head and neck malignancies	3 (4)
Adenoid cystic carcinoma	1 (1)
Thyroid carcinoma	2 (2.5)
Benign	2 (2.5)
Unknown	2 (2.5)

Results

From July 2008 to September 2010, 80 patients underwent 114 SCT treatments at 6 institutions. Patients were a median age of 66 years (range, 15 to 90 years), and 45 (56%) were male. More than 70% of the patients had stage IV carcinoma at the time of treatment. Median operative time was 65 minutes (range, 15 to 176 minutes; Table 1). By the American Society of Anesthesiologists (ASA) classification, 87% of patients were 3 or 4, and no patient was assessed as ASA 1. Two patients presented with benign disease that was behaving in a malignant fashion.

Metastatic lesions were the most common disease treated with SCT (Table 2). Comorbid conditions were present in 60 patients (75%) and included chronic obstructive pulmonary disease, postobstructive pneumonia, and diabetes (Table 3). Patients presented with shortness of breath, dyspnea on exertion, cough, or hemoptysis.

Table 3. Comorbid Conditions

Condition	Patients[a] No. (%)
Any comorbidity	60 (75)
Chronic obstructive pulmonary disease	43 (54)
Diabetes mellitus	10 (13)
Chronic renal insufficiency/chronic renal failure	5 (6)
Atrial fibrillation	7 (9)
Postobstructive pneumonia	24 (30)

[a] The total number of patients with any comorbid condition as well as by most common comorbidities. Patients may have more than one comorbid condition.

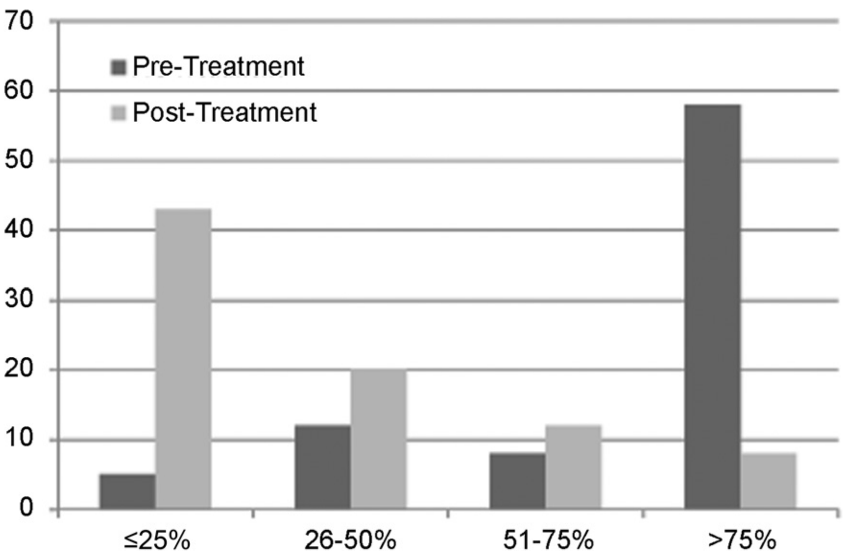

Fig 1. Airway narrowing is shown as the percentage of occlusion before treatment (dark bars) and after treatment (light bars). Only 1 patient did not achieve improved luminal patency after treatment (preoperative and postoperative data available on 73% of procedures).

Significant dyspnea was the most common presenting symptom.

Data on airway occlusion were available in 83 of the procedures performed. Pretreatment airway occlusion was graded as more than 75% in 74% of patients, but only 8 patients had more than 75% narrowing after treatment (Fig 1). Luminal patency was not achieved in 1 patient after treatment (100% pretreatment and posttreatment occlusion). Most patients underwent another form of endobronchial treatment at the time of SCT, most often mechanical debridement through a rigid scope and biopsy forceps.

Significant bleeding (> 50 mL) occurred in only one treatment and was treated successfully with SCT to control the bleeding. All other patients had minimal (< 20 mL) blood loss during the SCT and debridement procedures. No transfusions were given in the perioperative period for blood loss during the procedure.

Conscious sedation was used for 16 SCT procedures (14%). Rigid bronchoscopy was used in 52 SCT procedures (46%), and flexible bronchoscopy was used in 100% of patients. SCT was performed as an outpatient procedure in 58%.

Of the patients who were admitted after SCT, 33 (69%) were admitted to a standard hospital floor and 13 (27%) were admitted to intermediate level care or to the intensive care unit. All but 3 of these patients were discharged home, for a 95.6% discharge rate (109 of 114 procedures led to discharge).

Complications occurred in 22 of 114 procedures (19.3%), with 1 patient having complications during 2 separate procedures. Most complications were intraoperative and self-limiting, including hypotension, bradycardia and tachycardia, and desaturation (Table 4). A pneumothorax in 1 patient required chest tube placement. An analysis of tumor location and complications found no correlation between tumor location and type or incidence of complications (data not shown). Complications in 10 patients (8.8.%) were grade 3 or greater, including 5 deaths (4.4%). Two of these deaths were intraoperative. Three additional patients, who were transitioned to comfort care postoperatively (do not resuscitate/do not intubate palliative care only), died of respiratory failure at 1, 5, and 7 days after the procedure.

The intraoperative deaths were in patients, aged 79 and 55 years, with stage IV non-small and small cell lung cancers, and both were ASA 4 classification. One had coronary artery disease and both were former smokers. Neither death occurred during the SCT treatment, but occurred within 5 to 30 minutes after SCT was administered. There were no other preoperative or intraoperative factors that were similar between these patients.

In addition, there was one emergency chest tube placement, one airway tear during rigid mechanical debridement (no intervention required), one massive hemoptysis during mechanical debridement (treated successfully with SCT), and one cardiac arrest. The patient who had the intraoperative cardiac arrest was successfully resuscitated and discharged from the hospital after a brief stay in the intensive care unit.

The patients who had intraoperative arrest or death

Table 4. Complications

Variable	Patients No. (%)
Complications	22 (19.3)
Hypotension	13 (11.4)
Bradycardia	6 (5.3)
Desaturation	7 (6.1)
Massive hemoptysis	1
Pneumothorax	3
Chest tube placement	1
Grade 3 or greater	10 (8.8)
Intra-op death	2
Post-op death (comfort care)	3

had very similar preceding events, including profound bradycardia (10 to 20 beats/min), ST segment changes, hypoxemia, and ultimately, pulseless electrical activity arrest. Two of the patients were noted to have very low end-tidal carbon dioxide after reintubation, and there was concern for pulmonary embolism. The patient who survived had a myocardial infarction with no change in heart function by echocardiography.

Comment

SCT applies liquid nitrogen directly to the tissue with a noncontact low-pressure delivery system. The ability to deliver liquid nitrogen (−196°C) directly to the tissues allows for rapid freezing of the tissue, can be used to treat large areas rapidly, and provides uniform treatment. Its efficacy in the treatment of premalignant and malignant esophageal disease has been promising and suggested that similar results might be achieved in the treatment of MAT [2, 3, 6–8]. This report outlines the initial experience with SCT for the treatment of MAT.

Treatment of MAT has been shown to improve quality of life and survival, especially if undertaken before the onset of morbid symptoms [1, 9–11]. Most other modalities used to treat MAT have significant drawbacks. Laser therapy requires the patient to tolerate oxygen levels of less than 40% to reduce the risk of airway fires. SCT has no risk of airway fire and can be used in patients who require 100% oxygen therapy, which is common in these patients.

Mechanical debridement can often lead to significant airway hemorrhage, especially in highly vascular tumors such as renal cell carcinoma. The ability of laser therapy to control moderate to large airway hemorrhage is poor due to the scatter of the energy with large amounts of blood and the need to localize the bleeding, which is often difficult. Contact cryoprobes have an increased incidence of hemorrhage, some requiring bronchoscopic blocker placement for control [12]. SCT has hemostatic properties [13], and given that its effects are over a large area, one does not need to localize beyond the airway from which the bleeding emanates. SCT successfully controlled bleeding in 1 patient who had massive hemoptysis after mechanical debridement of a tumor. If this effect of SCT can be confirmed in larger studies, it may become a vital tool in patients with difficult to control hemoptysis.

Furthermore, laser therapy is relatively contraindicated in complete airway obstruction and is contraindicated in and around implants, such as stents, where there is a risk of ignition. Some physicians observed immediate tumor shrinkage after treatment with SCT, allowing navigation beyond the tumor and facilitating tumor debulking. In addition, SCT is safe to use in and around implants, such as stents, because there is no risk of ignition.

With rapid expansion of the liquid nitrogen into gas, the risk of pneumothorax was initially considered to be significant, but this did not seem to be the case in this cohort of patients. Pneumothoraces occurred in 3 patients, with only 1 requiring chest tube placement. With the rigid adherence to the outlined protocol for venting of gas, the risk of pneumothorax was 2.6%, and symptomatic pneumothorax was only 0.9%, which is similar to the incidence during jet ventilation and other interventional bronchoscopic procedures [10, 14].

In addition, a number of patients appeared to have durable results, including a number who had prior treatment with other ablative modalities without particular success. Several patients were noted to have complete regression of tumors, including a patient who had complete mucosal regrowth after treatment of an occluding left mainstem tumor. This cohort of patients does not have enough data to comment on this specifically, and again, a larger study is needed to confirm this observation. Durability of response would be of significant use in patients who no longer have other treatment options.

Overall, the outcomes in these patients were similar to other cohorts treated for MAT [9, 10, 15–17]. Intraoperative problems are expected in this population of patients with multiple comorbidities, decreased functional status, and respiratory status that is often very marginal. Severe intraoperative complications occurred in 4 patients in this cohort that seemed to be related to cardiovascular compromise, including bradycardia, hypoxemia, and pulseless electrical activity arrest. As such, before SCT is used on a widespread basis, caution must be used. To that end, we presently recommend that Investigational Review Board approval or a separate consent be obtained if SCT is to be undertaken.

Further studies to gain a better understanding of the mechanism by which these complications may be occurring are warranted. Increased surveillance of patients intraoperatively, including arterial catheter placement should be considered.

The ability to determine which patient will have a significant complication from any airway procedure is very important, especially in this patient population. Preoperative and intraoperative factors associated with significant complications, including death, would help in the decision of who should be taken to the operating room. Razi and colleagues [17] suggested that patients with an Eastern Cooperative Oncology Group performance status of 4 had no real benefit from treatment of MAT. In the current study, ASA classification did not predict perioperative complications (data not shown). Any future studies that evaluate this patient population should focus on factors that will help predict outcomes and optimize patient selection.

In conclusion, SCT can be used in patients who require oxygen levels exceeding 40%, in highly vascular tumors with reduced bleeding complications, and has a low overall complication rate that is similar to other endoluminal treatments. SCT is often used in conjunction with mechanical debridement, with excellent luminal patency rates. Caution is needed before SCT is used on a widespread basis, given the intraoperative complications. Although the potential benefit of SCT is considerable, this needs to be confirmed in larger studies.

References

1. Ernst A, Feller-Kopman D, Becker HD, Mehta AC. Central airway obstruction. Am J Respir Crit Care Med 2004;169: 1278–97.
2. Dumot JA, Vargo JJ 2nd, Falk GW, Frey L, Lopez R, Rice TW. An open-label, prospective trial of cryospray ablation for Barrett's esophagus high-grade dysplasia and early esophageal cancer in high-risk patients. Gastrointest Endosc 2009; 70:635–44.
3. Greenwald BD, Dumot JA, Abrams JA, et al. Endoscopic spray cryotherapy for esophageal cancer: safety and efficacy. Gastrointest Endosc 2010;71:686–93.
4. Greenwald BD, Dumot JA, Horwhat JD, Lightdale CJ, Abrams JA. Safety, tolerability, and efficacy of endoscopic low-pressure liquid nitrogen spray cryotherapy in the esophagus. Dis Esophagus 2010;23:13–9.
5. Halsey KD, Greenwald BD. Cryotherapy in the management of esophageal dysplasia and malignancy. Gastrointest Endosc Clin N Am 2010;20:75–87, vi-vii.
6. Johnston MH, Eastone JA, Horwhat JD, Cartledge J, Mathews JS, Foggy JR. Cryoablation of Barrett's esophagus: a pilot study. Gastrointest Endosc 2005;62:842–8.
7. Johnston CM, Schoenfeld LP, Mysore JV, Dubois A. Endoscopic spray cryotherapy: a new technique for mucosal ablation in the esophagus. Gastrointest Endosc 1999;50:86–92.
8. Shaheen NJ, Greenwald BD, Peery AF, et al. Safety and efficacy of endoscopic spray cryotherapy for Barrett's esophagus with high-grade dysplasia. Gastrointest Endosc 2010; 71:680–5.
9. Jeon K, Kim H, Yu C-M, et al. Rigid bronchoscopic intervention in patients with respiratory failure caused by malignant central airway obstruction. J Thorac Oncol 2006;1:319–23.
10. Oviatt PL, Stather DR, Michaud G, Maceachern P, Tremblay A. Exercise capacity, lung function, and quality of life after interventional bronchoscopy. J Thorac Oncol 2011;6:38–42.
11. Stephens KE, Wood DE. Bronchoscopic management of central airway obstruction. J Thorac Cardiovasc Surg 2000; 119:289–96.
12. Schumann C, Hetzel M, Babiak AJ, et al. Endobronchial tumor debulking with a flexible cryoprobe for immediate treatment of malignant stenosis. J Thorac Cardiovasc Surg 2010;139:997–1000.
13. Pasricha PJ, Hill S, Wadwa KS, et al. Endoscopic cryotherapy: experimental results and first clinical use. Gastrointest Endosc 1999;49:627–31.
14. Patel A, Randhawa N, Semenov RA. Transtracheal high frequency jet ventilation and iatrogenic injury. Br J Anaesth 2002;89:184.
15. Bolliger CT, Sutedja TG, Strausz J, Freitag L. Therapeutic bronchoscopy with immediate effect: laser, electrocautery, argon plasma coagulation and stents. Eur Respir J 2006;27: 1258–71.
16. Chhajed PN, Somandin S, Baty F, et al. Therapeutic bronchoscopy for malignant airway stenoses: choice of modality and survival. J Cancer Res Ther 2010;6:204–9.
17. Razi SS, Lebovics RS, Schwartz G, et al. Timely airway stenting improves survival in patients with malignant central airway obstruction. Ann Thorac Surg 2010;90:1088–93.

DISCUSSION

DR RAFAEL S. ANDRADE (Minneapolis, MN): It was a very nice presentation. It was a nice series of patients. The question I have is the average operative time was pretty long, 76 minutes, and in our own personal experience, if we do a rigid bronchoscopy for coring out or laser, it's usually 15-minute cases. Can you elaborate a little on that?

DR FINLEY: Yes. Actually, that was one thing that struck me when we were looking through the data, and what I found was that the majority of these patients had more than one tumor treated. About 3 tumors in most of these patients were treated, and there was significant disease burden. And then about 50% of them had to be stented due to external compression.

So it wasn't just a simple coring that we go through. The spraying itself, the majority of the patients had about five 5-second cycles, so the spray cryotherapy itself adds a minimal amount of time on to the total procedure.

DR ANDRADE: And my second question was when you have compared other modalities, such as rigid or laser, for instance, how does this mortality compare with those procedures?

DR FINLEY: I don't have all of the mortality data. There's more procedures that have been done nationally, and we don't have all of these data, so I don't have the exact numbers. But from what I have here, it is equivalent in terms of mortality for doing rigid bronchoscopy. Actually, if you look at some of the older data from the '80s, any kind of airway tumor has a 30-day mortality up to 20% when dealt with. So the mortality here that we have, which is about 8%, is much lower than that.

DR ANDRADE: Thank you.

DR DAVID P. PARK MASON (Cleveland, OH): I think one of the arrests was actually at our own institution. I wasn't there at the time, but I had heard about it, so I don't want to speak too much to the specifics of it other than to say it was felt to be a direct consequence of the technique. It was clearly directly related to the cryotherapy. I think the patient either had a pneumothorax or massive pneumoperitoneum related to the amount and flow associated with the actual application of the treatment. So I have little doubt that those arrests and deaths were also related to this cryo technique. What can we do in terms of rolling this out and increasing the safety component of this therapy?

DR FINLEY: Exactly. I have actually performed 5 pig experiments, and I am doing my sixth next week. And we are trying to look at the physiologic changes that are going on with both right and left heart catheters, and we are doing ultrasound through a thoracotomy to see whether or not something is going on. So we are trying to get that data. But I agree with you. I think it is directly related. They are sick patients, and I think in the 3 patients who went to comfort care, it had nothing to do with it. It is the intraoperative events that concern me most.

DR ANDRADE: Just one last question. Do you have a hint of what patients we should avoid to do this on in terms of location, anything?

DR FINLEY: So that was the thing that I have tried to answer. The ages of the patients have ranged from 40 to 88 years old that have had intraoperative complications, including the hypotension and bradycardia, that did not lead to arrests or other sequela. Tumor locations included pretty much any airway, right bronchus intermedius, left main stem, distal left lower lobe, and right lower lobe.

We initially thought that it would be secondary to maybe cold on the heart, a vagal response. Clearly this is not what is going on. It has something to do with either the proximity of the spray catheter to the tissue that you are spraying or it is the venting. We know that pneumothoraces can occur. There was one death from a tension pneumothorax during the procedure, but that doesn't seem to be the problem in any of these other deaths. So as I said, we haven't figured it out yet, but that is kind of my plan. And once we figure it out, believe me, I'll let everyone know.

DR KAZUHIRO YASUFUKU (Toronto, Ontario, Canada): I have just one question. From your own experience in using the spray cryotherapy, how does it compare to other ablative modalities, such as YAG laser. What is your opinion on treating big tumors in the airway? How effective is it?

DR FINLEY: Dr Bains and Dr Rusch trained me, and you put the rigid scope in and you core the tumor out, and you can get great results. The thing that I have noticed with doing Spray Cryotherapy is that I have had a couple of patients, specifically with renal cell, where instead of spending 45 minutes to an hour trying to clean up all of the blood, you spray the tumor, you core it out, it doesn't bleed. I have also had some patients who have been unable to have treatment any other way, so no radiation or any kind of chemo, and they have had significant prolonged response with really bulky tumors within the mediastinum.

And the last thing is that you always know there are tumors that you can't get to because of the angle. With this technology you can actually spray them, and they have regression over a couple of weeks. So you can spray a left-upper-lobe tumor that is nearly occluding it, and then you come back and see them in 2 or 3 weeks and the tumor is nearly gone. It is actually pretty impressive.

Member and Individual Subscriber Access to the Online *Annals*

The address of the electronic edition of *The Annals* is http://ats.ctsnetjournals.org. If you are an STS or STSA member or a non-member personal subscriber to the print issue of *The Annals,* you automatically have a subscription to the online *Annals,* which entitles you to access the full-text of all articles. To gain full-text access, you will need your **CTSNet user name and password.**

Society members and non-members alike who do not know their CTSNet user name and password should follow the link "Forgot your user name or password?" that appears below the boxes where you are asked to enter this information when you try to gain full-text access. Your user name and password will be e-mailed to the e-mail address you designate.

In lieu of the above procedure, if you have forgotten your CTSNet username and/or password, you can always send an email to CTSNet via the feedback button from the left navigation menu on the homepage of the online *Annals* or go directly to http://ats.ctsnetjournals.org/cgi/feedback.

We hope that you will view the online *Annals* and take advantage of the many features available to our subscribers as part of the CTSNet Journals Online. These include inter-journal linking from within the reference sections of *Annals'* articles to over 350 journals available through the HighWire Press collection (HighWire provides the platform for the delivery of the online *Annals*). There is also cross-journal advanced searching, eTOC Alerts, Subject Alerts, Cite-Track, and much more. A listing of these features can be found at http://ats.ctsnetjournals.org/help/features.dtl.

We encourage you to visit the online *Annals* at http://ats.ctsnetjournals.org and explore.

Published by Elsevier Inc
Ann Thorac Surg 2012;94:204 • 0003-4975/$36.00