Endoscopic spray cryotherapy for genitourinary malignancies: safety and efficacy in a porcine model

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Abstract:

Objective: To examine the effects and safety of using endoscopic spray cryotherapy (ESC) on bladder, ureteral, and renal pelvis urothelium in a live porcine model.

Subjects and methods: ESC treatments were systematically applied to urothelial sites in the bladder, ureter, and renal pelvis of eight female Yorkshire swine in a prospective trial. Freeze–thaw cycles ranged from 5 to 60 s/cycle for one to six cycles using a 7 French cryotherapy catheter. Tissue was evaluated histologically for treatment-related effects. Acute physiologic effects were evaluated with pulse oximetry, Doppler sonography, and postmortem findings.

Results: In bladder, treatment depth was inconsistent regardless of dose, demonstrating urothelial necrosis in one, muscularis propria depth necrosis in two, and full thickness necrosis in all remaining samples. In ureter, full thickness necrosis was seen in all samples, even with the shortest spray duration (5 s/cycle for six cycles or 30 s/cycle for one cycle). Treatment to the renal pelvis was complicated by adiabatic gas expansion of liquid nitrogen to its gaseous state, resulting in high intraluminal pressures requiring venting to avoid organ perforation, even at the lowest treatment settings. At a planned dose of 5 s/cycle for six cycles of the first renal pelvis animal, treatment was interrupted by sudden and unrecoverable cardiopulmonary failure after three cycles. Repeated studies replicated this event. Ultrasound and immediate necropsy confirmed the creation of a large gaseous embolism and reproducible cardiopulmonary effects.

Conclusion: ESC in a porcine urothelial treatment model results in full-thickness tissue necrosis in bladder, ureter, and renal pelvis at a minimal treatment settings of 5 s/cycle for six cycles. Adiabatic gas expansion may result in fatal pyelovenous gas embolism and collateral organ injury, as seen in both animals receiving treatment to the renal pelvis in this study. These results raise safety concerns for use of ESC as a treatment modality in urothelial tissues with current device settings.

Keywords: cryosurgery, endoscopic surgery, spray, minimally invasive surgery, cryotherapy, urothelial malignancy

Introduction

Conservative strategies in the treatment of urothelial malignancies of the bladder and upper urinary tract play an important role in disease management and depend upon effective endoscopic treatment modalities [Sowter *et al.* 2007; Thompson *et al.* 2008b]. Laser photoablation [holmium:yttrium-aluminum-garnet (YAG) and

neodymium:YAG] and electrosurgical energy are used with variable success for upper-tract urothelial cell carcinoma, most commonly in low-grade tumors [Sowter *et al.* 2007]. Control of treatment effects, including tissue penetration depth and uniformity over the treatment area, while providing effective local tumor control, visualization, and instrument maneuverability, can prove

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difficult with these techniques. Limitations abound, not the least of which is balancing the risks of complications from excessive tissue damage with the risk of undertreatment, which may play a role in the potential for disease recurrence and progression [McCarron *et al.* 1983; Sowter *et al.* 2007; Thompson *et al.* 2008a, 2008b]. Therefore, local treatment modalities are needed that can provide the means for safe yet effective superficial treatment.

Endoscopic spray cryotherapy (ESC) using liquid nitrogen is a recently developed technology that has been demonstrated to provide short-term efficacy without sacrificing safety and tolerability in the management of mucosal malignancies within hollow organs, including esophageal and airway lesions [Fernando *et al.* 2011; Greenwald *et al.* 2010a, 2010b; Johnston *et al.* 1999; Johnston *et al.* 2005; Krinsky *et al.* 2010a, 2010b; Shaheen *et al.* 2010]. ESC exhibits adiabatic nitrogen gas expansion that raises concerns about its safety. An adiabatic thermodynamic process occurs when there is conversion without input or release of heat within the system. The ESC adiabatic gas expansion can occur if the process is too rapid and there is no time to transfer heat, or if the system is very well insulated from its surroundings. Liquid nitrogen expands up to 25 times its volume at a very rapid rate using ESC technology, potentially causing significant complications with its use. Our objective was to apply ESC to an animal model of the urinary tract and examine the histologic effects and safety of treatment within the scope of this application.

Materials and methods

The Memorial Sloan-Kettering Cancer Center Institutional Animal Care and Use Committee approved the use of animals in this study. All procedures were conducted in accordance with the National Academies' Guide for the Care and Use of Laboratory Animals [National Research Council (US) Committee for the Update of the Guide for the Care and Use of Laboratory Animals *et al.* 2011]. Eight Yorkshire pigs (Archer Farms, Darlington, MD) weighing 55–60 kg were obtained and received food and water *ad libitum*. Our experimental protocol called for eight pigs to have the genitourinary organs treated with ESC as part of a larger protocol that treated a number of other organ systems. Due to the immediate deaths of the experimental animals, continuing the genitourinary experiments would have compromised

the results of the other organ systems treatment. In consultation with the experimental team, we elected to terminate the genitourinary subprotocol and report our results. The night before surgery, the pigs were fasted for 12 h but allowed water *ad libitum*. All pigs were sedated with tiletamine/zolazepam (4.4 mg/kg) and given glycopyrrolate (0.007 mg/kg) and buprenorphine (0.01 mg/kg). Each pig was intubated and maintained on isoflurane (1.5–2.5%) during the experiment. Each pig was monitored intraoperatively by pulse oximetry, end-tidal carbon dioxide, electrocardiography, noninvasive and invasive blood pressure, and temperature. The pigs were euthanized at the end of the study with an intravenous injection of euthasol (1 ml/4.5 kg, concentration of 390 mg/ml).

Vascular sonography and echocardiographic monitoring were utilized in a subpopulation of renal pelvis treated animals to analyze for central venous gas embolism during treatment.

Access to the bladder was provided by a small cystotomy and insertion of a 12 mm trocar (Endopath Xcel, Ethicon-Endo Surgery, Cincinnati, OH, USA) secured by suture. Cystoscopy was performed with a flexible digital video endoscope with 5.1 mm diameter tip and 2 mm diameter instrument channel (Olympus BF-Q180, Olympus America Inc., Center Valley, PA, USA). Passive gas venting was provided via the insufflation port. A specialized 7 French flexible catheter for the CryoSpray Ablation System (CSA Medical, Inc., Baltimore, MD, USA) was inserted through the endoscope. Treatments with liquid nitrogen stored at -196°C under ambient pressure of 2–4 psi were completed to the superficial bladder urothelium.

Access to the ureter was gained by transecting the ureter at the bladder with care to preserve periureteral vascularity. Retrograde endoscope insertion was performed with the CryoSpray catheter used for hemi-circumferential treatment. Access to the renal pelvis was similarly obtained via incision created at the ureteropelvic junction, and treatment was directed tangentially at the major calyx. Following completion of all treatments the animals were euthanized and tissues were harvested from treated animals and normal controls.

ESC treatments of all urothelial sites were performed via endoscopic visual guidance using the endoscopic instrument channel. The catheter was extended 1–2 cm from the tip of the endoscope

Table 1. Histology findings at necropsy after endoscopic spray cryotherapy.

Treated region	Animal	Specimen number	Time/cycle (s)	Number of cycles	Necrosis depth	Neutrophil intensity	Neutrophil location	Edema	Hemorrhage
Bladder	A	1	5	6	Urothelium	1	Serosa	1	1
		2	5	6	Adventitia	0		1	1
	B	3	5	6	Adventitia	1	Adventitia, mucosa	1	1
		4	10	3	Adventitia	1	Adventitia	1	1
		5	10	3	Adventitia	1	Adventitia, mucosa	1	1
		6	15	2	Adventitia	1	Adventitia	1	1
		7	15	2	Adventitia	1	Adventitia	1	1
		8	30	1	MP	0		1	1
		9	30	1	Adventitia	0		1	1
Ureter	B	10	5	6	Adventitia	0		1	1
	C	11	30	1	Adventitia	0		0	0
		12	30	1	Adventitia	0		0	0
Renal pelvis	B	13	5	3	MP	0		0	1
	C	14	60	1	Adventitia	0		1	0

MP, muscularis propria.

and kept 9–11 mm from the target urothelial tissue during application of spray cryotherapy. Dosage was controlled by varying the duration of spray and number of spray–thaw cycles based on the range of treatment settings used in pulmonary applications [Krimsky *et al.* 2010a]. All treated urothelial tissue exhibited a characteristic superficial white frost cryoburn during each treatment. The interval for tissue thaw was standardized to 60 s according to manufacturer recommendations.

Pathologic interpretation was completed by a single dedicated, large-animal comparative pathologist (SM). Tissue injury was assessed by the presence and extent of necrosis. Only depth of necrosis according to urothelial layer (and not according to a measured length) was reported in an attempt to control for nontreatment-related differences (i.e. pathological processing). The locations of all areas of treatment were standard among experimental animals and there were no obvious differences between them when adjacent normal tissue thickness was examined on gross pathological examination. Tissue inflammation was assessed by the presence of neutrophil, lymphocyte, and macrophage intensity and location, as well the presence of edema or hemorrhage.

Results

Treated bladder specimens underwent six, three, two, and one cycle of ESC for 5, 10, 15, and

30 s/cycle respectively for a total of nine bladder urothelial specimens (Table 1). Adiabatic gas expansion of the nitrogen spray provided a significant technical impediment at all doses tested. Continuous venting of the large volume of gas via the port-side channel was required to successfully prevent bladder perforation. Pathologic analysis demonstrated full thickness necrosis in seven tissue samples, muscularis propria depth necrosis in one, and urothelial necrosis in one (Figure 1). There was no correlation between depth of tissue destruction and duration or extent of ESC treatment. Six samples demonstrated mild neutrophil infiltration into the serosa, adventitia, or mucosal layers. The bladders were treated first, followed by the ureter and then the renal pelvis, and this could certainly explain the reason why neutrophils were seen only in the bladder specimens. A significant amount of time would have passed from treatment to harvesting of the bladder tissue compared with the ureter and renal pelvis. All samples showed edema and hemorrhage. There were no organ perforations.

Upper tract applications were performed by direct luminal access via incision without the aid of a port or sheath. Ureteral treatments (5 s/cycle for six cycles or 30 s/cycle for one cycle) resulted in full-thickness necrosis in all samples (Table 1, Figure 2). Adiabatic gas expansion of liquid nitrogen produced ureteral distention, and venting was provided distally around the endoscope

Figure 1. Photomicrograph of porcine bladder after endoscopic spray cryotherapy (40 × 500 μm) displaying full thickness necrosis (N) and transmural hemorrhage (H) and edema (E).

Figure 3. Photomicrograph of porcine renal pelvis after endoscopic spray cryotherapy (400 × 50 μm) displaying full thickness necrosis (N) and hemorrhage (H).

Figure 2. Photomicrograph of porcine ureter after endoscopic spray cryotherapy (100 × 200 μm) displaying full thickness necrosis (N).

Figure 4. Photomicrograph of porcine renal parenchyma after endoscopic spray cryotherapy (left side demonstrates intraparenchymal emphysema in the endoscopic spray cryotherapy treatment area, right side is untreated normal parenchyma) (40 × 500 μm).

to avoid organ perforation. Treatments to the renal pelvis were similarly managed with passive venting via pyelotomy. At a planned treatment dose of 5 s/cycle for six cycles, treatment was interrupted by sudden and unrecoverable cardiopulmonary failure after three cycles. Tissue necrosis to muscularis propria was identified with no parenchymal injury (Table 1, Figure 3). Evidence of retrograde pyelovenous air embolus was suggested at necropsy, which also identified regional renal emphysema and dilated tubules from the pelvis to the capsule corresponding to the treatment area with nondilated, normal appearing parenchyma on either side (Figure 4). A repeat experiment treating the renal pelvis replicated this event. Ultrasound of the cardiovascular system and immediate necropsy provided findings of a large gaseous embolism as evidenced by the sonographic appearance of gas bubbles in

the central venous system and a large gas-filled right ventricle.

Discussion

Endoscopic spray cryotherapy with liquid nitrogen was developed using endoluminal applications in animal models and subsequently demonstrated promising results in clinical use treating benign and malignant lesions in the esophagus and airway [Fernando *et al.* 2011; Greenwald *et al.* 2010a, 2010b; Halsey *et al.* 2011; Johnston *et al.* 1999, 2005; Krinsky *et al.* 2010a, 2010b; Shaheen *et al.* 2010]. The potential advantages of this form of therapy (as opposed to heat-related modalities), such as preserving underlying tissue architecture and extracellular matrix, which favors

wound healing, make it attractive as an investigative option. In particular, ESC offers advantages for tumors involving the superficial surface of hollow organs, such as urothelial cancers, although application of this form of treatment has not previously been studied in the genitourinary system. Our initial investigation of ESC in a porcine urinary tract model identifies significant associated safety concerns, namely the risk for gas pressure-mediated tissue damage and fatal embolization.

Liquid nitrogen expands to 25 times its volume during evaporation [Greenwald *et al.* 2010b]. This necessitates adequate venting during ESC treatment. However, at all genitourinary regions treated (bladder, ureter, and renal pelvis), the nitrogen gas expansion made it difficult to consistently treat areas that were not fixed *in situ*. Experimental modification allowed us to assess the efficacy of treating the different regions of the genitourinary tract. The current system, therefore, would require specific endoscopic technical changes if the urothelium is to be ablated using ESC.

Necrosis was seen at all dosimetry levels tested in the bladder, ureter, and renal pelvis. No correlation was observed between duration or extent of treatment and depth of invasion was observed. This may have been due to maximal tissue destruction occurring at the lowest ESC duration tested. There was significant adjacent normal control tissue change identified, however, likely due to gas expansion. The histologic changes were limited hemorrhage and edema but there was no evidence of necrosis. This suggests that only the area of direct ESC treatment experienced necrosis.

Perhaps most important, all animals treated with renal pelvis ESC developed sudden and unrecoverable cardiopulmonary failure secondary to air embolus as evidenced by ultrasound. The mechanism for air embolism only occurring in the renal pelvis ESC treatments is almost certainly related to pyelovenous backflow of gas escaping directly into the venous circulation through large branch vessels. Pyelovenous backflow is well known and is often seen in retrograde pyelography when filling of the renal pelvis with contrast under pressure can be seen to flow into the venous circulation. From Figure 4, the left-hand side of the photomicrograph demonstrates the trajectory of the gas expansion that likely infiltrated into the major branches of the renal vein. For the ureter

and bladder treatments, we did not observe a similar effect and speculate the surface of the urothelium in these organs is resistant to fluid and gas absorption by its lining of urothelium, despite elevated gas pressure. Any gas which diffuses through these surfaces also did not have access to large venous vessels. The proximity to major venous channels should be very carefully considered when using spray cryotherapy in other organ sites, particularly in esophageal and thoracic procedures.

Esophageal liquid nitrogen ESC has been used to treat Barrett's neoplasia (including high-grade dysplasia and early cancer), localized esophageal cancer, and palliative squamous cell carcinoma of the esophagus. The initial porcine pilot study involved ESC of the distal 2–3 cm of esophagus in 20 swine [Johnston *et al.* 1999]. The results were promising as a treatment for esophageal lesions because of the ability of spray cryotherapy to induce controlled mucosal necrosis. The complications reported were one aspiration pneumonia and three esophageal strictures (only in swine that had circumferential rather than hemi-circumferential cryotherapy). Other authors then attempted to define the optimal dosimetry in another nine pigs [Johnston and Johnston, 2006]. They confirmed that four cycles of 10 s/cycle were able to achieve submucosal necrosis, as were two cycles of 20 s/cycle.

The first primary ESC treatment in a human was in a 73-year-old man with recurrent squamous cell carcinoma of the esophagus that was deemed inoperable and not amenable to further radiation therapy [Cash *et al.* 2007]. He was treated with two cycles of 30 s/cycle of ESC and achieved a 24-month complete remission and exhibited no complications relating to the technique. Larger single-center studies followed, evaluating the safety and efficacy of ESC for treating dysplasia and cancer of the esophagus. Dumot and colleagues reported a prospective series of ESC esophageal procedures in 39 patients. Two patients experienced serious adverse events; one, with Marfan's syndrome, presented with gastric perforation on postoperative day 1 and another reported lip ulceration secondary to contact with the cold endoscope post treatment [Dumot *et al.* 2009]. Of note, the perforation occurred during treatment with the prototype version of the gas decompression tubing. Minor adverse events were limited to stricture disease.

The initial success in treating esophageal lesions with ESC has led researchers to study its potential utility in bronchoscopy. Krinsky and colleagues reported on 21 patients scheduled to undergo lung resection who were treated initially with two cycles of 5 s/cycle of liquid nitrogen ESC [Krinsky *et al.* 2010a]. Subsequently, Fernando and colleagues retrospectively analyzed a series of 35 patients with benign airway strictures who were treated with ESC over a 22-month period at seven institutions [Fernando *et al.* 2011]. After a mean follow up of 8.2 months, 28 of 33 evaluable patients had improved or were asymptomatic. Seventeen (49%), however, required reintervention with ESC. Major adverse events included tracheostomy insertion due to airway swelling in the ESC-treated region and a pneumothorax requiring placement of a chest tube.

Significant adverse events associated with the use of liquid nitrogen spray cryotherapy have been published. Dermatological lesions treated with spray cryotherapy can result in significant subcutaneous emphysema, particularly if the skin is ulcerated or curetted prior to treatment [Samlaska and Maggio, 1996]. The clinical course is usually benign unless bacteria are insufflated, which can lead to serious infections. The US Food and Drug Administration's Manufacturer and User Facility Device Experience (<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfmaude/search.cfm>) database lists adverse events and deaths related to the use of medical devices [Gurtcheff, 2008]. Specific to liquid nitrogen ESC in both airway and esophageal treatment, a total of 37 events (including six deaths) were recorded from 27 July 2007 to 19 December 2011. Two deaths were from cardiac arrest, one resulted from anoxic encephalopathy, and in three cases the cause was unknown. Adverse events included pneumothorax (10 events), gastrointestinal (GI) perforation (six events), subcutaneous emphysema (five events), pneumoperitoneum/pneumomediastinum (five events), local ulceration requiring blood transfusion (one event), GI bleed (one event), aspiration pneumonia (one event), and dysphagia (one event).

Of note, gas embolism has not been listed as an adverse event. In some cases this could be related to the difficulty in diagnosing a gas embolism, particularly if clinical suspicion is not high. Autopsy will fail to show embolic gas phenomenon as the cause of death, and unless specific monitoring techniques are employed intraoperatively (i.e. noninvasive Doppler ultrasound, trans-esophageal

echocardiography, pulmonary artery catheter, or mass spectrometer for end-tidal nitrogen), it may remain undiagnosed [Herron *et al.* 1999].

The authors do not believe the current ESC probe is amenable for transurethral use, even with adequate venting. Perhaps a large bore catheter could be inserted beside the endoscope to aid venting, if the probe was significantly modified from its current form. Additionally, monitoring of gas pressure within the organ system may be useful to avoid excessive pressures, though the limits of safety may be organ specific.

Conclusion

In this porcine model, the treatment of renal pelvis urothelium using liquid nitrogen ESC identified significant technical and safety considerations for its use in this setting. Adiabatic gas expansion resulted in collateral organ injury, including fatal gas embolism, while treating urothelium in the renal pelvis. Clinical suspicion of gas embolism should be considered if adverse events arise with the use of ESC.

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Conflict of interest statement

The authors declare no conflicts of interest in preparing this article.

References

- Cash, B., Johnston, L. and Johnston, M. (2007) Cryospray ablation (CSA) in the palliative treatment of squamous cell carcinoma of the esophagus. *World J Surg Oncol* 5: 34.
- Dumot, J., Vargo, J., II, Falk, G. *et al.* (2009) 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* 70: 635–644.
- Fernando, H., Dekeratty, D., Downie, G. *et al.* (2011) Feasibility of spray cryotherapy and balloon dilation for non-malignant strictures of the airway. *Eur J Cardiothorac Surg* 40: 1177–1180.

- Greenwald, B., Dumot, J., Abrams, J. *et al.* (2010a) Endoscopic spray cryotherapy for esophageal cancer: safety and efficacy. *Gastrointest Endosc* 71: 686–693.
- Greenwald, B., Dumot, J., Horwhat, J. *et al.* (2010b) Safety, tolerability, and efficacy of endoscopic low-pressure liquid nitrogen spray cryotherapy in the esophagus. *Dis Esophagus* 23: 13–19.
- Gurtcheff, S. (2008) Introduction to the MAUDE database. *Clin Obstet Gynecol* 51: 120–123.
- Halsey, K., Chang, J., Waldt, A. *et al.* (2011) Recurrent disease following endoscopic ablation of Barrett's high-grade dysplasia with spray cryotherapy. *Endoscopy* 43: 844–848.
- Herron, D., Vernon, J., Gryska, P. *et al.* (1999) Venous gas embolism during endoscopy. *Surg Endosc* 13: 276–279.
- Johnston, C., Schoenfeld, L., Mysore, J. *et al.* (1999) Endoscopic spray cryotherapy: a new technique for mucosal ablation in the esophagus. *Gastrointest Endosc* 50: 86–92.
- Johnston, L. and Johnston, M. (2006) Cryo spray ablation (CSA) in the esophagus: optimization of dosimetry. *Am J Gastroenterol* 101: S532–S533.
- Johnston, M., Eastone, J., Horwhat, J. *et al.* (2005) Cryoablation of Barrett's esophagus: a pilot study. *Gastrointest Endosc* 62: 842–848.
- Krinsky, W., Broussard, J., Sarkar, S. *et al.* (2010a) Bronchoscopic spray cryotherapy: assessment of safety and depth of airway injury. *J Thorac Cardiovasc Surg* 139: 781–782.
- Krinsky, W., Rodrigues, M., Malayaman, N. *et al.* (2010b) Spray cryotherapy for the treatment of glottic and subglottic stenosis. *Laryngoscope* 120: 473–477.
- McCarron, J., Mills, C. and Vaughn, E., Jr (1983) Tumors of the renal pelvis and ureter: current concepts and management. *Semin Urol* 1: 75–81.
- National Research Council (US) Committee for the Update of the Guide for the Care and Use of Laboratory Animals, Institute for Laboratory Animal Research (US) and National Academies Press (US) (2011) *Guide for the Care and Use of Laboratory Animals*. Washington, DC: National Academies Press.
- Samlaska, C. and Maggio, K. (1996) Subcutaneous emphysema. *Adv Dermatol* 11: 117–151; discussion 152.
- Shaheen, N., Greenwald, B., Peery, A. *et al.* (2010) Safety and efficacy of endoscopic spray cryotherapy for Barrett's esophagus with high-grade dysplasia. *Gastrointest Endosc* 71: 680–685.
- Sowter, S., Ilie, C., Efthimiou, I. *et al.* (2007) Endourologic management of patients with upper-tract transitional-cell carcinoma: long-term follow-up in a single center. *J Endourol* 21: 1005–1009.
- Thompson, R., Krambeck, A., Lohse, C. *et al.* (2008a) Elective endoscopic management of transitional cell carcinoma first diagnosed in the upper urinary tract. *BJU Int* 102: 1107–1110.
- Thompson, R., Krambeck, A., Lohse, C. *et al.* (2008b) Endoscopic management of upper tract transitional cell carcinoma in patients with normal contralateral kidneys. *Urology* 71: 713–717.

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