

Interventional Cryoneurolysis: What Is the Same, What Is Different, What Is New?

Ross W. Bittman, MD¹ Keywan Behbahani, BS¹ Felix Gonzalez, MD¹
J. David Prologo, MD, FSIR, ABOM-D¹

¹Department of Radiology and Imaging Sciences, Emory University School of Medicine, Atlanta, Georgia

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Address for correspondence Ross W. Bittman, MD, Department of Radiology and Imaging Sciences, Emory University School of Medicine, Emory University Hospital, 1364 Clifton Road, NE Suite D112, Atlanta, GA 30322 (e-mail: ross.bittman@emory.edu).

Abstract

Keywords

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Cryoneurolysis is the deliberate application of cold temperatures to nerves for therapeutic purposes. The idea of treating pain with this technique is thousands of years old and has evolved over time through the application of surgical techniques, nerve stimulation and/or landmark guidance, and through device development. Recent integration of the interventional radiology skill set to this space has unlocked a myriad of opportunities—primarily through a unique ability to percutaneously access deep structures in the body with accuracy and precision, and the capacity to monitor ablation zones. Understanding of the specific neurohistological process that follows targeted cryoneurolysis leads to new options for treating patients in pain without drugs and opens doors for the potential modification of a wide array of disease states.

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The integration of interventional radiology to the long-standing clinical concept of applying cold temperatures to nerves has illuminated several new procedural options and potential applications for the therapy. First, interventional radiology allows for percutaneous access to many nervous system structures in the body that are otherwise unreachable, or reachable only with significant associated costs and

morbidity (as with many surgical approaches) or risks (as with landmark or nerve stimulation-guided approaches). Second, the evolution of understanding regarding specific neuroregenerative processes that follow specific deliberate cryothermal insults to nerves allows for tailored therapies and potential applications of percutaneous image-guided cryoneurolysis that exist beyond pain.

What Is the Same?

The analgesic properties of cold for medicinal use date back to Hippocrates in 460 BC.^{1,2} Avicenna of Persia subsequently reported the use of cold to decrease pain related to surgery, and physicians from Napoleon's army noted decreased pain during amputation in soldiers exposed to extreme cold.³ Modern-day implementation of device-mediated cold to target pain generators began with a landmark report by Lloyd et al in 1976, during which investigators targeted a variety of peripheral nerves in 64 patients using a gas-cooled cryoprobe guided by an integrated nerve stimulator—noting that compared with other methods of nerve interruption, cryoneurolysis had the advantages of reversibility, repeatability, and decreased incidence of complications such as neuroma formation or neuritis.⁴

Over time, cryoablation of nerves under direct visualization has been widely reported in the setting of thoracotomy and/or during inguinal hernia repairs.⁵⁻⁷ For example, a recent randomized trial by Graves et al demonstrated that intercostal nerve cryoablation during surgical correction of pectus excavatum decreases length of hospital stay and opiate analgesic requirement compared with thoracic epidural analgesia, without complications.⁸ The cryoablation group's median length-of-stay was decreased by 2 days and opioid analgesic requirements were reduced by 52 to 82% compared with the thoracic epidural treatment group. A similar retrospective study of 26 patients drew similar conclusions.⁹ Pastor et al described a double-blind prospective randomized study of 100 patients undergoing posterolateral thoracotomy. Patients who underwent intercostal cryoanalgesia ($n = 55$) had significantly less pain, less analgesic requirement, and increased pulmonary function compared with those who did not.¹⁰

Similarly, Wood et al described cryoablation of the ilioinguinal nerve under direct visualization following hernia repair in 1979, with a follow-up three-arm randomized study in 1981 describing superior pain relief with cryoneurolysis.^{3,11,12} Fanelli et al demonstrated a 78% decrease in postoperative pain with associated decreased analgesic use and increased physical activity capacity following nerve cryoablation during herniorrhaphy.⁶ Several other open cryoablation investigations in this setting have also been published without clear statistically significant effect.^{3,13,14}

Nonsurgical targeting of nerves has been reported using anatomical landmark guidance. In 1981, Evans et al reported positioning of patients and cryoprobes to treat perineal pain by targeting lower sacral nerve roots based on anatomical landmarks. Forty patients underwent a total of 71 treatments for a variety of underlying conditions causing perineal pain, with 78% reporting significant improvement. "The treatment was more successful in relieving symptoms in patients suffering from pelvic cancer ... [and] best results were obtained in those patients who received numerous freeze applications or prolonged freezing."¹⁵ Radnovich et al described placement of cryoprobes targeting genicular nerves about painful, osteoarthritic knees in 2017 using only anatomical landmarks.¹⁶ Their randomized, double-blind, multicenter trial enrolled 180 patients, with 121 randomized to a cryoneurolysis group. Results demonstrated that percutaneous cryoneurolysis of the infrapatellar branch of the saphenous nerve is a safe and effective treatment for pain related to knee osteoarthritis with a statistically significant reduction in knee pain for up to 150 days posttreatment.

Percutaneous targeting of nerves has also been performed using stimulator guidance. A 2015 retrospective study by Kim et al demonstrated that cryoneurolysis of the occipital nerves, using surface landmarks and nerve stimulation to assist nerve targeting, is an effective therapy for occipital neuralgia.¹⁷ The 38-patient treatment group reported an average reduction in pain of 57.9% for an average duration of 6.1 months. Similarly, Moesker et al used nerve stimulator guidance to localize amputated nerves corresponding to phantom limb pain descriptions in five patients for cryoa-

blation. This study was a retrospective review with an average follow-up of 32 months postablation. No complications were found, three patients reported 90 to 100% pain relief, one patient reported a 40% pain relief, and one patient reported a 20% pain relief.¹⁸

What Is Different?

The integration of advanced imaging guidance through interventional radiology unlocks a myriad of potential applications for this technology using a percutaneous approach. The interventional radiologists routinely interact with oncologists, surgical oncologists, and palliative care physicians—relationships that may lead to opportunities for care of patients who may benefit from cryoneurolysis. For example, patients who suffer with pain related to neoplastic involvement of a nerve present a difficult clinical challenge. These patients are often not surgical candidates, cannot be radiated effectively and/or safely, and present with lesions deep in the body that cannot be safely reached using landmark or nerve stimulator guidance. The integration of advanced imaging guidance (computed tomography [CT], magnetic resonance imaging [MRI], and/or ultrasound) has helped overcome many of these challenges and allows for new treatment options, many times in a single session (►Figs. 1 and 2).

One illustrative example can be found with patients who are hospitalized with intractable pain secondary to locally advanced neoplastic disease in the pelvis. Palliative radiation therapy is often exhausted, direct ablation of the mass may not be feasible, and most of these patients are not surgical candidates—creating a formidable barrier to timely palliation.^{19,20} Given that the pudendal nerve transmits pain signals from the pelvis,²¹⁻²⁴ interruption of those signals may lead to palliation of intractable pelvic pain related to mass lesions, again providing a different option for patients with a difficult-to-manage clinical syndrome (►Fig. 3).

In the same way, nonneoplastic painful conditions may be managed percutaneously with cryoneurolysis if the interventional radiology skill set is applied. As examples, the use of CT guidance for percutaneous cryoneurolysis in amputees has been reported for the management of phantom limb pain.²⁵ Fritz and coworkers have described MRI-guided cryoneurolysis of the sural nerve and posterior femoral cutaneous nerves to manage pain.^{26,27} Kim and Ferrante reported using image guidance to cryoablate the obturator nerve for treatment of adductor spasticity.²⁸ Yoon et al reported the cryoneurolysis of peripheral nerves localized with ultrasound guidance for a variety of conditions.²⁹ Targeted nerves included the ilioinguinal, posterior tibial, saphenous, gluteal, sural, genicular, and digital nerves (and three plantar neuromas). Patients reported a significant decrease in self-reported pain scores following the cryoablation to 12 months—demonstrating the ability to reach nerves with imaging guidance for the purposes of cryoablation. In addition, ultrasound has been used to localize and cryoablate the peroneal, suprascapular, superior cluneal, femoral, sciatic, ilioinguinal, genitofemoral, and saphenous nerves,³⁰⁻³³ and several reports have described the safety and efficacy of

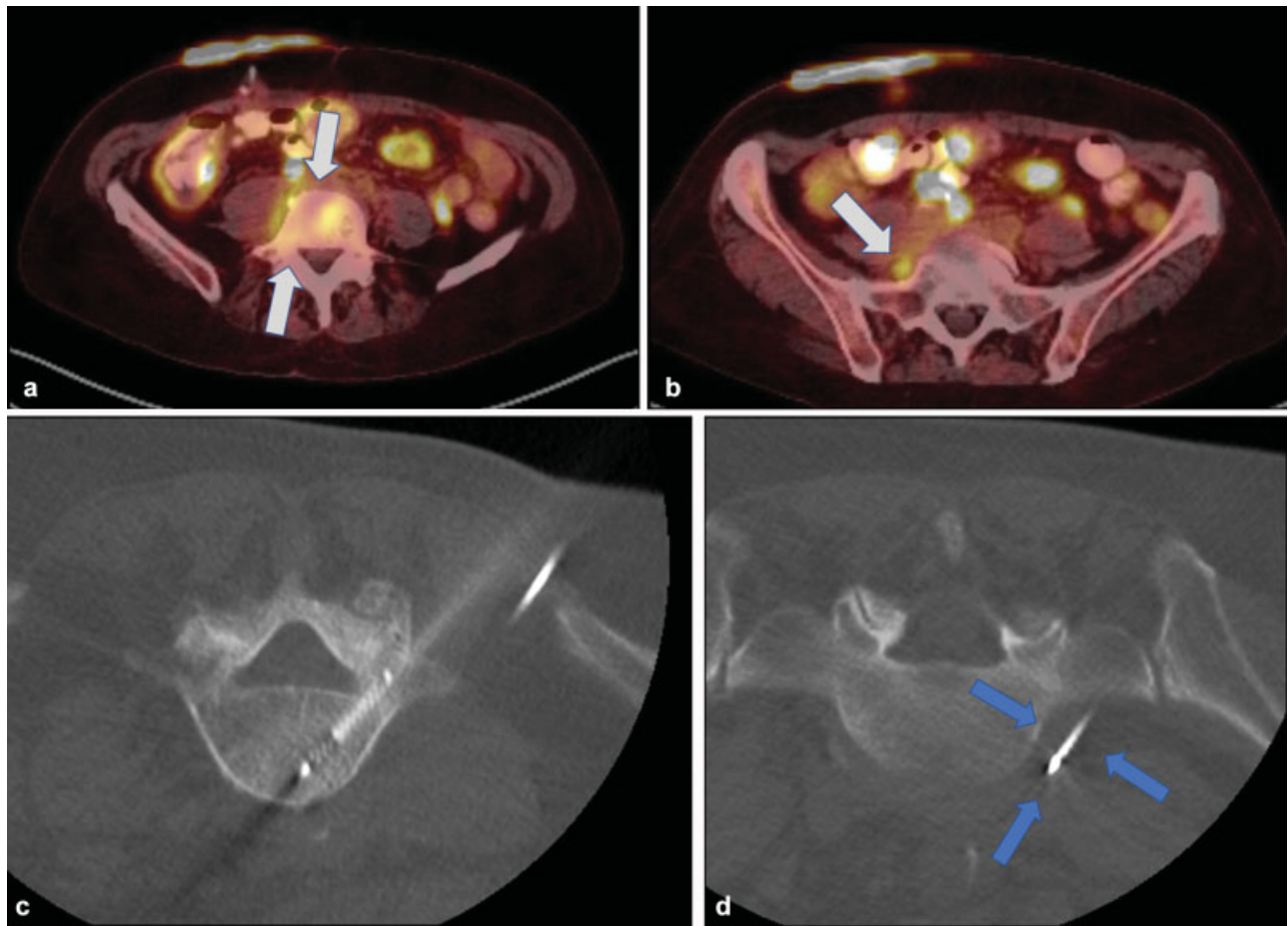


Fig. 1 (a) Single axial PET-CT image from a patient with metastatic urothelial cancer who presented with intractable right lower extremity pain demonstrates abnormal radiopharmaceutical activity involving the right portion of the L5 vertebral body and pedicle (arrows). (b) Slightly caudal image from the same exam demonstrates direct involvement of the right lumbosacral trunk (arrow). (c, d) Intraprocedural axial CT images demonstrate placement of a cryoablation probe via the right pedicle of L5 to the affected vertebral body as well as a second probe targeting the neoplastic focus involving the ipsilateral lumbosacral trunk (arrows indicate visualized ice).

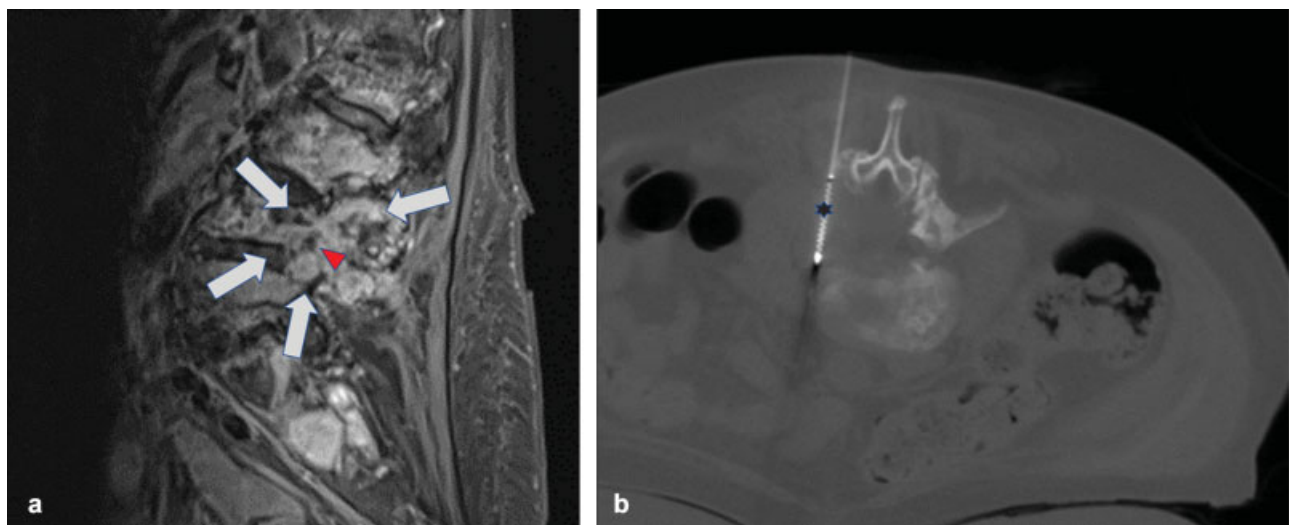


Fig. 2 (a) Sagittal T1-weighted fat-saturated post-contrast MRI image of the lumbar spine in a patient with metastatic breast cancer who presented with intractable L4 radiculopathy demonstrates an enhancing metastatic lesion involving the pedicle and vertebral body (arrows) impressing on the exiting nerve root (arrowhead). (b) Corresponding intraprocedural CT image demonstrates a cryoablation probe positioned to include the lesion and the exiting nerve root (star).

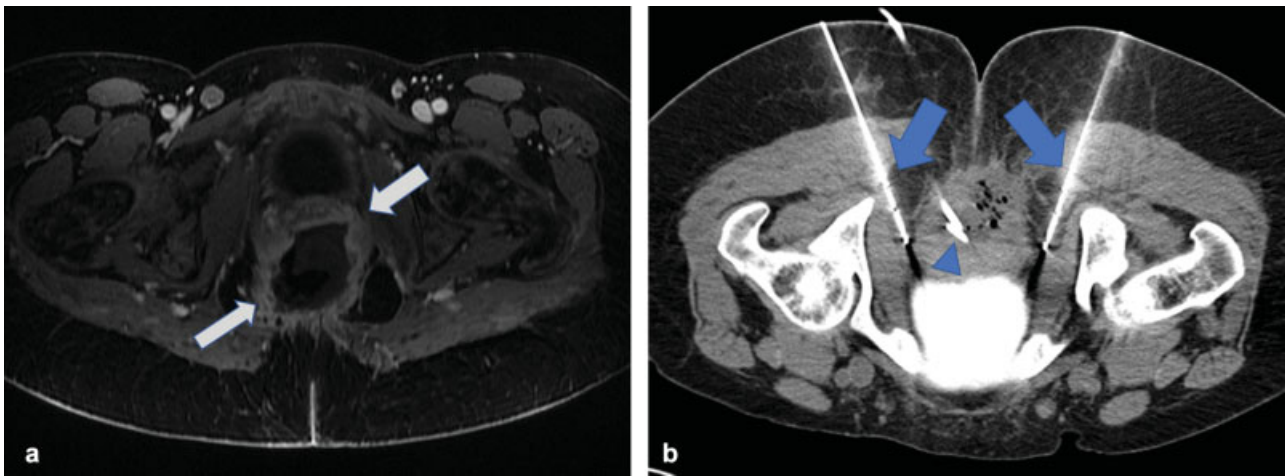


Fig. 3 (a) Axial T1-weighted fat-saturated post-contrast MRI image in the pelvis demonstrates a large pelvic mass (arrows) with a necrotic center in a patient with known advanced cervical carcinoma hospitalized for intractable pain. (b) Axial intraprocedural image demonstrates placement of two cryoablation probes (arrows) adjacent to the proximal pudendal nerves. Incidental note is made of a percutaneously placed drainage catheter (arrowhead).

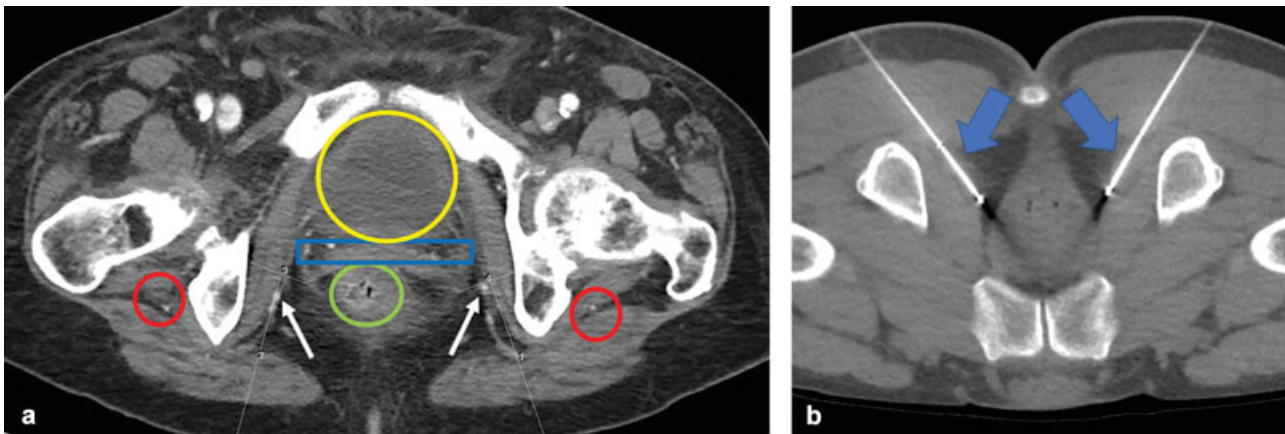


Fig. 4 (a) Single axial contrast-enhanced CT at the level of the pudendal canal, demonstrating anatomy associated with percutaneous access to the pudendal nerve (numbered lines). Without cross-sectional guidance, operators risk damage to the adjacent sciatic nerves (red circles), rectum (green circle), uterus (blue rectangle), pudendal artery and vein (arrows), and/or urinary bladder (yellow oval)—precluding any ablative procedure under landmark or fluoroscopic guidance. (b) Intraprocedural axial CT image at the level of the pudendal canal in a separate patient, demonstrating bilateral cryoablation probes percutaneously placed in the ischioanal fat (arrows).

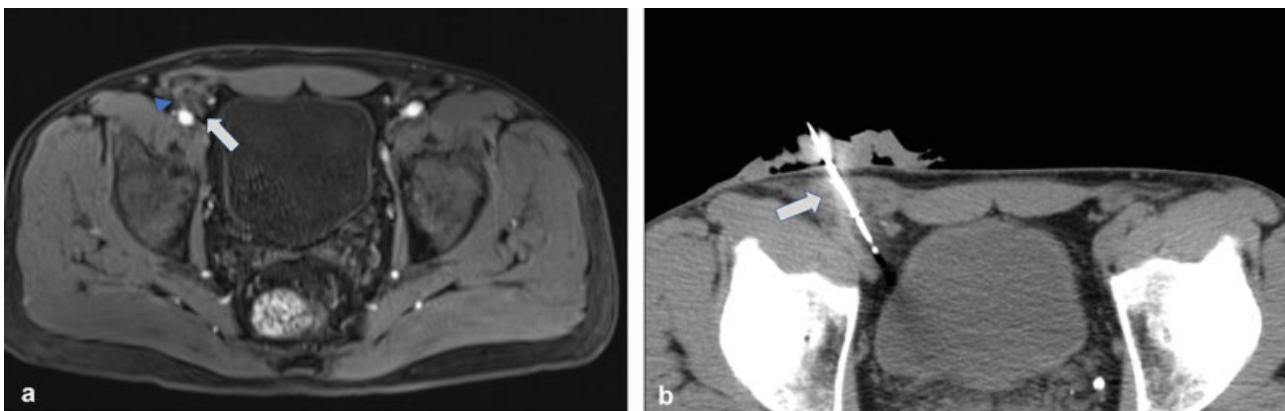


Fig. 5 (a) Single axial T1-weighted fat-saturated post-contrast MRI image at the level of the inguinal ligament demonstrates fibrosis and entrapment (arrow) of the genitofemoral and ilioinguinal nerves between the femoral and inferior epigastric arteries, deep to implanted herniorrhaphy mesh (arrowhead). (b) Corresponding intraprocedural CT image demonstrates ablation of the entrapped nerves and fibrous tissue via safe percutaneous placement of a cryoablation probe (arrow).

image-guided cryoneurolysis for the management of facet syndrome in the cervical and lumbar spines.^{34–38}

Potential complications associated with cryoneurolysis procedures performed in interventional radiology include standard risks associated with percutaneous procedures such as bleeding and infection. In addition, nontarget ablation must be considered and avoided in a similar fashion as undertaken for safe tumor ablation—employing positioning and/or dissection techniques when necessary. Partial ablation may also result in unwanted postprocedure symptoms such as allodynia or acute worsening of pain. Care must be taken to impart a uniform thermal lesion (without mechanically disrupting the nerve) for an adequate amount of time. Lastly, the desired mechanism of injury during cryoneurolysis—as explained later—is separate from the osmotic shift-related mechanism employed for cancer cell destruction, such that associated “active thaws” are not necessary and may result in unwanted damage and/or potential adverse sequela.

What Is New?

The new elements regarding cryoneurolysis that underpin its value and expansion in modern times include the integration of advanced image guidance, and the understanding of neural processes that follow cold exposure. To illustrate, again consider interventions that target the pudendal nerve. The pudendal nerve is derived from the S2–S4 nerve roots and follows a well-described course deep in the pelvis—giving rise to three branches along the way—which supply³⁹ sensation from the external genitalia, perineum, rectum, and skin around the anus. The pudendal nerve is implicated in a well-described, notoriously difficult-to-treat clinical syndrome presenting with pain related to pudendal nerve damage.^{21,22} Without cross-sectional imaging guidance, cryoneurolysis is not an option for these patients, given the morbidity and cost of open surgical approaches, lack of precision and associated risk of landmark or fluoroscopically guided percutaneous access, and inability to monitor the ablation zone. With cross-sectional guidance, a cryoablation probe can be precisely placed in the adjacent ischiorectal fat for safe cryoablation of the pudendal nerve, illustrating how the application of imaging guidance creates novel opportunities for the management of existing, difficult-to-manage clinical conditions (—Fig. 4). Similarly, patients suffering from inguinodynia related to prior surgical intervention represent a population of patients with a well-characterized pain syndrome that has limited treatment options.^{39,40} Using imaging guidance, the confluence of the ilioinguinal and genitofemoral nerves may be targeted safely for the management of pain related to entrapment or postoperative fibrosis (—Fig. 5).

Precise percutaneous access to peripheral nerves may also lend itself to modification of disease states unrelated to pain. Premature ejaculation (PE) is the most common sexual disorder in men worldwide.⁴¹ The application of CT guidance affords safe access to the dorsal penile nerve (a branch of the pudendal nerve) and/or the proximal pudendal nerve for cryoablation—which has been shown to improve symptoms for men diagnosed with PE, potentially providing a large population of

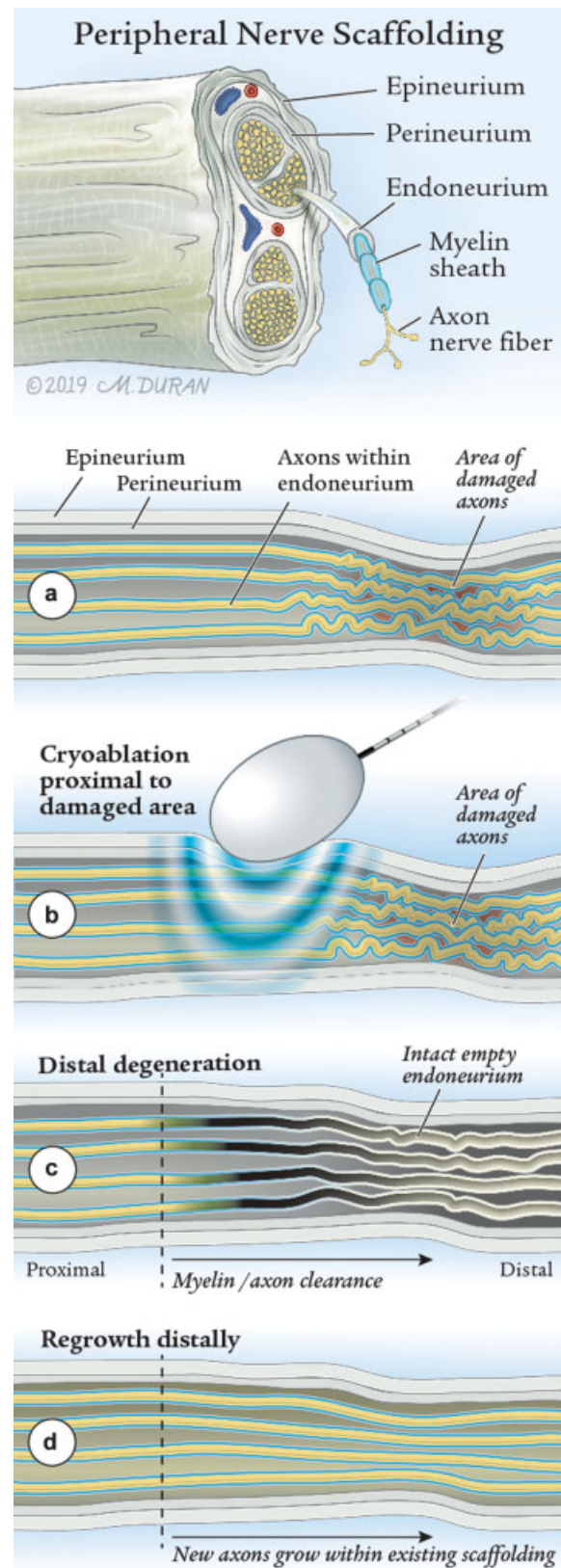


Fig. 6 (a) Illustration of a peripheral nerve demonstrating connective tissue components that serve as an axon scaffold. (b–d) Following cryoablation, a predictable sequence of degeneration with subsequent regeneration can be induced—potentially repairing damaged nerves.

patients with a difficult-to-treat condition a brand new option.⁴² In the same way, our group has targeted the posterior vagal trunk—percutaneously with CT guidance—for purposes of attenuating hunger in patients with Class I or Class II obesity who hope to lose weight with calorie restriction.⁴³

Regarding the mechanism of cryoneurolysis, historically the premise upon which nerve cryoablation procedures have been founded is the induction of a specific, reversible nerve injury.^{2,3,44} Nerve injury classifications are classically described and correlated with clinical course following trauma (crush, stretch, laceration, etc.), the most widely cited of which are the classifications of Seddon and Sunderland.^{45–47} Depending on the diameter and composition of the nerve to be targeted, specific time and temperature combinations can result in a Sunderland 2 injury.

Importantly, this precise neural injury results in several well-described events that may lead to favorable clinical outcomes—cessation of conduction,⁴⁸ induced Wallerian degeneration, and predictable regeneration of axons upon an intact connective tissue scaffold.^{2,44,49} The translation of these events (beyond conduction cessation) has been documented as nerve function recovery in animal studies and in humans^{50–54}—which may have implications for interventional radiologists as neuroregenerative inductive therapies (► **Fig. 6**).

Going forward, interventional radiologists have an extraordinary opportunity to define a new landscape by improving existing techniques and addressing new clinical conditions—pain related or otherwise—using percutaneous image-guided cryoneurolysis. We are uniquely positioned to answer the call for nonopioid procedural alternatives for pain management,^{48,55} as well as to develop solutions for non-pain-related neurogenic clinical conditions.

Conflict of Interest

Dr. Prologo reports grants and personal fees from BTG/Galil Medical, grants from Endocare/Healthtronics, outside the submitted work.

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