

Cryosurgery

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1. INTRODUCTION

Cryoablation (CA) and its application in medicine began with the collaborative work of Dr. Irving Cooper, a neurosurgeon, and Arnold Lee, an engineer though cryotherapy for medical applications dates back to ancient Egyptian times.¹ The first use of CA consisted of surface treatment in dermatology with liquid nitrogen delivery. Topical application of liquid nitrogen resulted in the destruction of targeted tissue with limited damage to adjacent structures. It was in the mid-20th century that Dr. Cooper used liquid nitrogen to perform stereotactic cryoablation of the basal ganglion in Parkinson's disease patients with tremors and involuntary movements. Later in 1995, Uchida and colleagues first reported successful application of probe-based percutaneous cryoablation (PCA) in 2 patients with advanced renal cell carcinoma (RCC). In 1998, Gill and colleagues were the first to describe laparoscopic cryoablation (LCA). The first clinical application of open cryoablation was successfully performed by Rukstalis and colleagues in 2001. Since these early applications, CA has emerged as a minimally invasive alternative to standard extirpative strategies in the management of kidney and prostate cancer.

2. PHYSICS

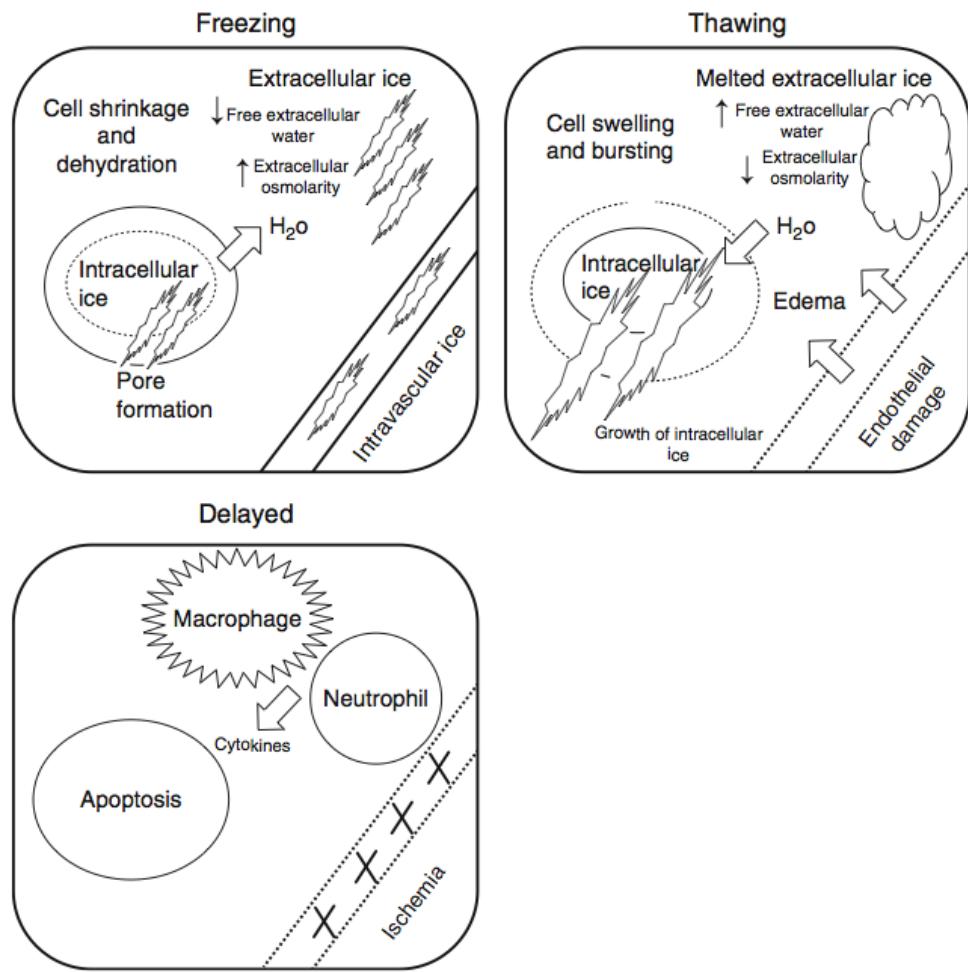


Figure 1: Mechanisms of cryoablation induced tissue injury (The image is obtained from the chapter titled 'Overview of Thermal Ablation Devices: Cryoablation' from Interventional Radiology Techniques in Ablation).

Cryoablation describes a process by which tissue is destroyed through freezing. Destructive mechanisms of CA are due to several factors which can be divided into two major mechanisms: (1) immediate injury and (2) delayed injury with microcirculatory failure.

Contemporary CA technologies use the Joule-Thomson principle to achieve very low temperatures whose tissue effects result in ablation. The Joule-Thomson principle describes the change in temperature of a non-ideal gas undergoing adiabatic (transfer of energy as work, occurring without transfer of heat between a system and its surroundings) expansion. Adiabatic cooling occurs when the pressure of a substance is decreased as it does work on its surroundings. The Joule-Thomson inversion temperature determines whether or not a specific gas or liquid will exhibit heating or cooling upon expansion. Above the Joule-Thomson inversion temperature, heating will occur; below the Joule-Thomson inversion temperature, cooling will occur.

Prime examples of this effect can be seen through the behavior of argon and helium gas in a closed and insulated system. When pressurized and sent through a narrow nozzle or porous barrier, into a larger and lower-pressure chamber, these gases rapidly expand. As the distance between each

argon molecule increases, the intermolecular Van der Waals forces (those working to keep the molecules close together) slow the argon molecules down. This results in a decrease in kinetic energy with a corresponding increase in potential energy in the closed and insulated system. The reduced kinetic energy yields a drop in temperature. Furthermore, it has been shown that higher initial argon pressures give lower temperatures via the Joule-Thomson effect. Thus, during this decompression process, the temperature of argon gas will decrease. Contemporary CA probes utilize Argon gas in this manner.

However, in the case of helium, the rapid expansion will result in Joule-Thomson heating. This heating phenomenon can be attributed to helium's extremely low Joule-Thomson inversion temperature (40 K). Intermolecular repulsion forces between helium atoms overshadow the Van Der Waals forces under higher pressures, thereby giving a high potential energy to the system. So, when helium is allowed to expand under lower pressures, the potential energy decreases, yielding an increase in kinetic energy. Thus, the decompression of helium ultimately results in heat.

In the case of CA, the heat and cold produced by the expansion of helium and argon, respectively, is transferred via conduction and convection to the metallic walls of the cryoprobe. The cryoprobe is subsequently used to freeze or thaw cancerous tissue.

During freezing, the argon-cooled cryoprobe causes both intracellular and extracellular ice -ball formation (**Figure 1**). With rapid cooling, intracellular ice crystal formation occurs in the direct vicinity of the probe, while extracellular ice crystal formation occurs in the outermost regions of the cryoablation region. The intracellular ice formation hastily occurs before water is able to diffuse out of the cells. These intracellular ice crystals are believed to cause cellular damage by physically damaging intracellular organelles and the plasma membrane, thereby resulting in cell death. The peripheral cryoablation regions that undergo extracellular ice crystal formation face cellular damage by different mechanisms. Extracellular ice formation decreases the free water content, thereby creating a hypertonic extracellular environment. Consequently, intracellular water is osmotically extracted as it diffuses into the extracellular environment, thereby causing cell dehydration.

The thaw rate of the frozen tissue is essential for maximizing the efficacy of cryoablation. Although this reversal process shrinks the extracellular ice crystals, the helium-heated cryoprobe contributes to cellular destruction by warming and thawing the frozen tissues. As the extracellular ice crystals melt, the extracellular environment becomes increasingly hypotonic in comparison to the intracellular environment. The osmotic pressure drives water back into the cell, causing swelling and eventual lysis. Furthermore, this intracellular flow contributes to intracellular ice crystal formation, thereby compounding the destructiveness of the thawing process. Hence, increasing the thaw time results in greater cellular damage.

The destructive effects of freezing and thawing represent the immediate effects of cryosurgery, while delayed cellular destruction is manifested through apoptotic and vascular cascades. Damage to the vasculature during intracellular ice formation along with the subsequent perfusion of thrombolytic agents during thawing leads to ischemia and further contributes to cell death. Temperatures between

-40°C and -50°C are needed to bring direct cell death via intracellular ice crystallization. Thus, delayed apoptosis occurs in cells bordering the cryoablation zone, where immediate cell death does not occur because temperatures range from 0°C to -40°C. Furthermore, these apoptotic events in cryosurgery have been associated with the disruption of mitochondrial function.

3. MECHANISM OF DELIVERY

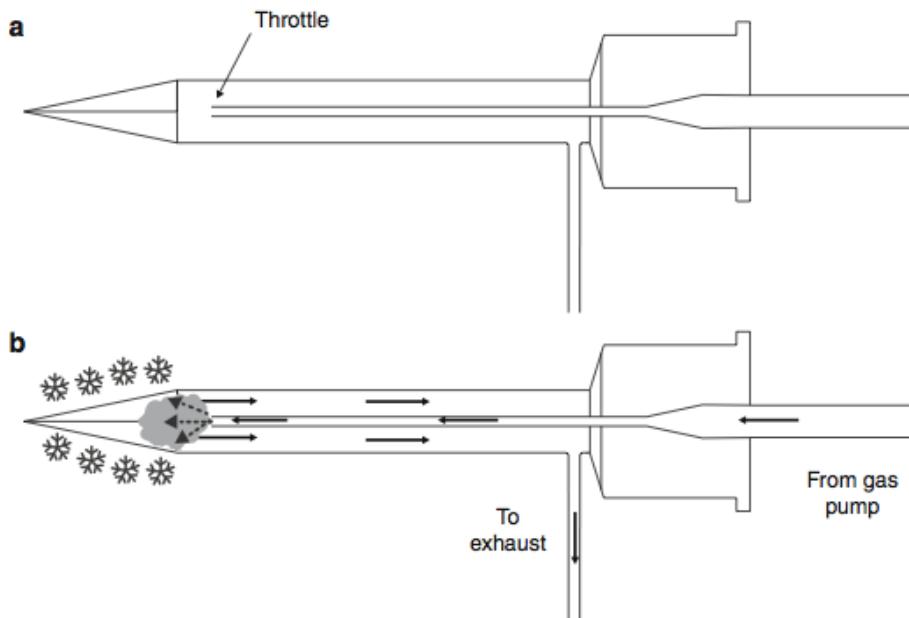


Figure 2: Mechanisms of cryoablation-induced tissue injury (The image is obtained from the chapter titled 'Overview of Thermal Ablation Devices: Cryoablation' from Interventional Radiology Techniques in Ablation).

Pressurized argon gas is pumped into a cryoprobe and sent through a narrow nozzle or throttling device. After the throttling process, the argon gas is allowed to rapidly expand in a larger chamber at the tip of the cryoprobe. The insulation of the cryoprobe allows the expanding argon gas to cool through the Joule-Thomson process without losing any heat to the environment. Sub-zero temperatures achieved by the expanding argon gas is then transferred through conduction and convection to the metal that encases the cryoprobe. The cooled cryoprobe is subsequently used to freeze the tissue. Meanwhile, the argon gas escapes (after cooling the cryoprobe) the cryogenic system through an exhaust system on the proximal end of the cryoprobe (**Figure 2**). Since the rapid expansion of pressurized Helium gas results in heating rather than cooling, helium gas is pumped through the cryogenic probe system to allow the thawing of tissues.

4. SAFETY

Cryoablation is a complex procedure using high pressure argon gas and helium. Although the authors are not aware of any specific technical complications reported with the use of cryoablation machines and cryoneedles, inappropriate technical application may lead to serious adverse events.

Training on appropriate use of cryoablation systems is required prior to conduction of any cryosurgery procedure.

Prior to any CA procedure, the surgical team must assure the availability of sufficient gas (argon and helium) and number and type of needles must be confirmed to conduct and complete the planned procedure. Continuous monitoring of the ice ball is recommended using imaging modalities such ultrasound, CT or MRI. For patient safety, continuous temperature monitoring is provided by thermocouples, which currently consist of small diameter needles which are inserted in the same way as CA needles. These thermocouples or thermal sensors (TS) (**Figure 8**) may be used for real-time temperature monitoring for enhanced safety. The temperature sensors are usually used to confirm that the boundaries of the tumor have been frozen and that adjacent healthy tissue has not been damaged. Studies done by Young and colleagues have shown that using a 14-gauge angiocatheter as a form of cryoprobe insulation may prevent ice burn along the flank. Abraham and colleagues described a novel technique of PCA that was devised to facilitate renal biopsy, cryoprobe placement, and instillation of adjunctive hemostatics while protecting surrounding tissues from thermal injury. Percutaneous access needle has been placed under fluoroscopic guidance to abut the surface of renal tumor, followed by Amplatz super-stiff guidewire and a customized coaxial catheter system, which was used as a conduit for renal biopsy, cryoneedles insertion and instillation of hemostatic agents. This technique was successfully used clinically, and no patients reported pain or paresthesia after a PCA procedure.

During prostate cryoablation, a urethral warming kit must be used. The other aspect of safety is related to its clinical goal of complete destruction of the target lesion. Clinical safety in this context is principally oncological safety and prevention of tumor recurrence.

5. DEVICES

Two major manufacturers of cryoablation systems and probes are Galil Medical Inc., (Yokneam, Israel) and Endocare (Irvine, California, USA). Both systems use the Joule-Thompson principle to cool tissue.

5.1 Galil Medical Inc.

5.1.1 Cryoablation Systems

(manufactured by Galil Medical Inc.)

SeedNet Gold System: Cryoablation System (**Figure 3**).

MRI SeedNet System: This is a modified SeedNet system made compatible with MRI for real time visualization. Additionally, the cryoneedles used for this system are in different sizes, shapes and made of different material to be compatible with magnetic resonance imaging (**Figure 4**).

The Precise Cryoablation System (**Figure 5**).

The Visual-ICE Cryoablation System (**Figure 6**) is a mobile console system intended for cryosurgery. The latest model of cryoablation system includes i-Thaw technology and in addition,

offers several advantages to its predecessors. Built-in gas regulators enable consistent operating pressures. Real time indicators provide estimated remaining gas time. The system allows the surgeon to mix needle types for the same procedure and potential to operate up to 20 needles at the same time.

5.1.2 Cryoablation Probes

Usually, 17-gauge cryoneedles that are 1.47 mm in diameter are considered safe and used in conjunction with cryoablation systems when performing cryosurgery. Commonly used cryoneedles are: IceSeed (1.47 mm, 17G), IceSphere (1.47 mm, 17G), IceRod (1.47 mm, 17G), IceRod CX (1.47 mm, 17G), IceRod Plus (1.47 mm, 17G), IceEDGE (2.4 mm, 13G). **Figure 7** and **Figure 8** demonstrate different characteristics of the needles and the ice balls created by different types of cryoneedles. Ice ball dimensions are described to assist surgeons in selecting the appropriate quantity and type of cryoablation needle(s) to completely ablate the target area. Differences in ice ball dimensions and resulting cryoablation zones are determined by tumor characteristics, the cryoablation needle type, number of needles placed to the target, thermal heat sink from surrounding vasculature, as well as duration and number of freeze-thaw cycles. Intraoperative monitoring of ice ball formation provides direct control throughout the procedure and is essential to safe and successful completion of the procedure.

5.1.3 Multi-point thermal sensors

Temperature sensors are used to aid in monitoring tissue temperature near the target site and adjacent critical structures. Temperature sensors can provide quantitative data to supplement the qualitative information provided by the imaging modality (**Figure 9**).

5.2 Endocare Inc.

5.2.1 Cryoablation system

(manufactured by Endocare Inc.)

Cryocare system: Similar to other cryosurgical systems the Cryocare system (**Figure 10**) utilizes Argon and Helium gas. The Cryocare system combines the latest technology and offers exclusive features such as an on-board training module, integrated ultrasound designed specifically for the needs of cryosurgical procedures, and a CryoGuide intraoperative treatment planning module and AutoFreeze treatment software that simplifies system operation.

AutoFreeze software allows operators to pre-program endpoint treatment parameters that translate into a freeze sequence using a proven treatment algorithm. The freeze is then initiated with the touch of a button and controlled with real time adjustments if needed. Protective endpoints control the temperatures in critical structures.

Direct Access eliminates the need for access kits or dilators, allowing direct entry of the streamlined 2 mm cryoprobes. It also offers a grid system that resembles that used for brachytherapy which enables easy identification of precise entry points provided by the CryoGuide planning software.

Urethral Warmer delivers a continual, closed loop flow of heated water through a uniquely designed urethral catheter. This easy to use warmer provides critical protection against lethal freezing temperatures in the surrounding prostate, protecting delicate urethral tissues from freezing.

5.2.2 Cryoablation Probes

Cryocare cryoablation system uses a wide range of probes of different sizes to produce varying sizes of ice balls. Cryoprobes have shaft lengths that range from 13 cm to 29 cm, diameters that range from 1.7 mm to 8 mm, and are offered in straight or right angle configurations (**Figure 11** and **Figure 12**).



Figure 3: SeedNet Gold System (Used with permission. © 2013 Galil Medical)



Figure 4: MRI SeedNet System (Used with permission. © 2013 Galil Medical)



Figure 5: The Precise Cryoablation System (Used with permission.
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Figure 6: The Visual-ICE® Cryoablation System (Used with permission. © 2013 Galil Medical)



Figure 7: Straight and 90° needles for cryosurgery (Used with permission. © 2013 Galil Medical)

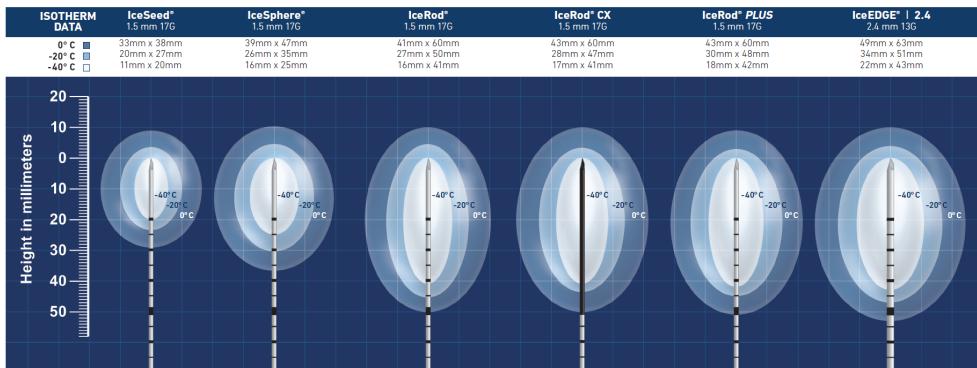


Figure 8: Comparison of different specifications of cryoablation needles.



Figure 9: Thermal Sensors (Used with permission. © 2013 Galil Medical)



Figure 10

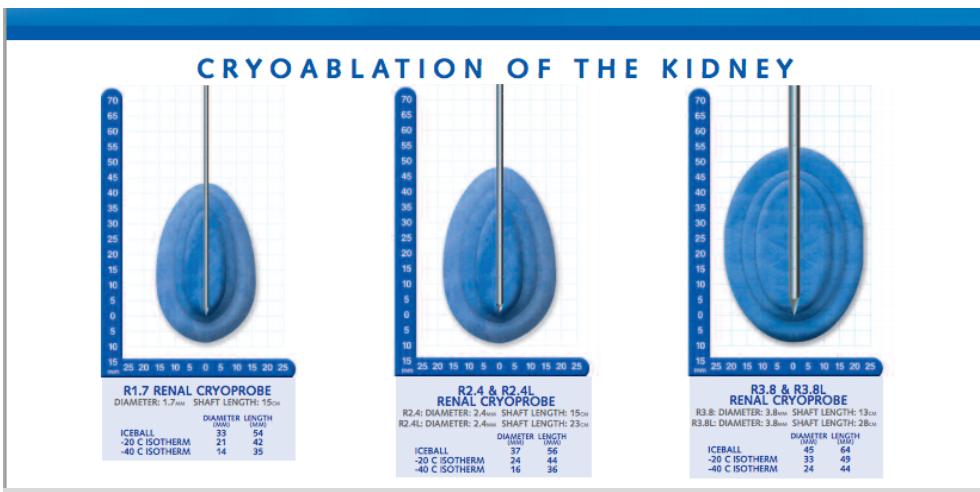


Figure 11: HealthTronics cryoablation probes for kidney cryoablation.

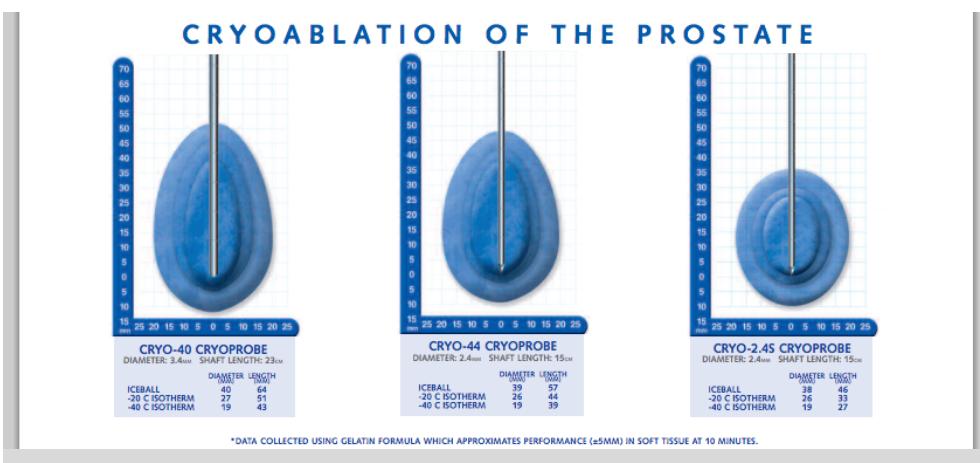


Figure 12: HealthTronics cryoablation probes for prostate cryoablation.

6. CLINICAL INDICATIONS AND PROCEDURES

Cryoablation is a safe and efficient minimally invasive treatment method for kidney and prostate cancers. CA technologies can be deployed via any surgical approach. That said, while open renal cryoablation has been shown as a safe method for ablating renal masses, this method is more historical and rarely performed in contemporary urologic practice. Currently, CA is predominantly performed by either laparoscopic (LCA) or percutaneous (PCA) approaches with image guidance (CT, MRI, US), allowing for precise location of the renal mass and accurate positioning of the cryoprobe(s). CA provides a minimally invasive treatment alternative for patients with significant comorbidities who are poor surgical candidates.

There have been several studies comparing outcomes of PCA to LCA. It has been shown that both CT-guided PCA and LCA yield comparable oncologic and renal functional outcomes. PCA under image-guidance is associated with lower complication rates and shorter hospital stays than the LCA. However, re-treatment rates are also higher when employing the percutaneous method. While the

particular approach is at the discretion of the operating surgeon and patient's preference, in general, tumors located anteriorly or medially with close proximity to bowel or adjacent organs are typically managed laparoscopically. Tumors located more posteriorly and laterally are amenable to PCA, but can also be treated with LCA.

Several factors have been shown to impact surgical and oncologic outcomes of CA. Lehman and colleagues (2008) were the first to document that tumor size was a significant determinate of outcomes during laparoscopic cryoablation procedures, demonstrating a clear association of tumor size and increased morbidity. In their study of 51 patients undergoing LCA, 21 patients had a tumor size > 3 cm. In this group, 62% of patients encountered complications, including two mortalities and a recurrence. In contrast, there were no complications in the group of patients who had tumors < 3 cm. These findings were confirmed by Laguna and colleagues (2009) in a multi-institutional study. Blute and colleagues (2013) demonstrated that greater tumor size is associated with increased rate of immediate failure, as well as local recurrence. Similarly, Klatte and colleagues demonstrated an 85% increase in risk of recurrences for each additional 1 cm in tumor size in the range of 0.5-3 cm. Therefore, tumor size should be strongly considered in preoperative patient counseling and surgical planning. Additionally, patient age, BMI, tumor location, and tumor depth have also been shown to be important factors to consider.

Similarly, recent studies have suggested that CA of localized prostate cancer is an effective treatment option with good short and long-term results. The morbidity associated with treating the whole prostate gland has further pushed urologists to further pursue focal treatment since Onik and colleagues reported on this. Selection criteria are multifactorial and vary widely depending on clinical, histopathological and imaging characteristics of the patients. Focal cryoablation is predominantly indicated for patients with low-risk, early, low-volume cancer and have their disease confined to one side of the prostate gland. However, accurate identification and diagnosis of these patients is essential to avoid undertreatment of the cancer. A variety of advanced biopsy and imaging techniques have been aggressively pursued and evaluated to meet this challenge. Accurate needle positioning during prostate CA is crucial to freeze as much tumor tissue as possible while avoiding thermal injury to adjacent organs. Modern **prostate cryoablation** methods utilize image-guided transperineal approaches. Using a template similar to that used for brachytherapy, cryoprobes are percutaneously inserted through the perineum and into the prostate. Most urologists use biplanar (transverse and longitudinal) transrectal ultrasonography (TRUS) to guide cryoprobe placement and monitor the growing ice ball formation. During the cryoablation process, the progressing boundary of the ice ball is represented on TRUS by a bright hyperechoic line. However, acoustic shadowing can prevent visualization of the anterior boundary of the prostate cryolesion. Prostate CA can also be performed under MRI guidance. To date very limited data on MRI-guided prostate CA is available. Initial experiments in a canine model have shown that this method is feasible. Subsequent clinical studies have demonstrated the viability and safety of using MRI for prostate CA.

Please refer to the ablation section of the **Renal Neoplasms Core Curriculum** chapter for additional clinical information.

Additional indications for cryosurgery have recently been explored. A study from Calixte, et al, in 2019, explored the use of ultrasound-guided cryoablation of the perispermatic cord in men with chronic scrotal content pain refractory to microsurgical denervation of the spermatic cord.² This procedure is performed with the patient under sedation and in the supine position. After local anesthetic, the ultrasound probe is placed lateral and then medial to the spermatic cord percutaneously using ultrasound guidance in order to target branches of the ilioinguinal, genitofemoral and inferior hypogastric nerves. Two freeze-thaw cycles are then performed and a 1.5cm ice ball is created on either side of the spermatic cord. Color Doppler is utilized to ensure testicular arterial supply has not been compromised. In this retrospective study of 221 patients, 75% of men had a significant reduction in pain at a median follow up of 36 months. Further investigation is needed to assess the long-term safety and efficacy of this and other novel applications of cryosurgery.

7. COMPLICATIONS

Access related complications are rare, but can occur during both PCA and LCA. Although PCA can avoid visceral injuries, it is rarely associated with flank pain and neuromuscular paresthesia due to local trauma during needle placement. Needle placement during PCA may result in thermal injury to paraspinal musculature, nerves in retroperitoneum, particularly genitofemoral and ilioinguinal nerves. Most of these neuromuscular symptoms resolve with conservative therapy within 6 to 8 weeks of surgery. While these events are rare with proper application of CA, great care should be taken to prevent these complications and patients should be made aware of them in the informed consent process.

While rare, ice ball fracture and bleeding occur during CA procedures with a reported incidence of 5-8%. Ice ball fracture tends to be less frequent with image-guided PCA. It is theorized that this is due to the tamponade effect of surrounding tissues. Alternatively, the authors believe that the surrounding tissues may stabilize the ice ball preventing fracture. Both of these beliefs remain theoretical, but the diminished risk of ice ball fracture with PCA is well documented. In order to avoid potential complications during the procedure and to improve safety profile, several studies have evaluated and established preoperative risk factors for bleeding complications. Increased risk of tumor fracture, bleeding, and hematoma formation is correlated with an increasing number of cryoprobes, larger tumor size, and centrality of the tumor. Lehman and colleagues were the first to document that tumor size was critical for CA outcomes and larger renal masses were associated with increased morbidity. Earlier generations of cryoneedles were larger in diameter and commonly caused tumor fracture leading to bleeding. However, modern cryoprobes are significantly thinner with temperature sensors which, along with meticulous control with imaging modality during the procedure, help to avoid fracture and bleeding complications. Surgical adhesive and hemostatic agents have been shown to control bleeding during ablation. Additionally, preoperative selective angioembolization can be performed in patients with larger tumor sizes.

Other reported complications of renal CA include thermal injury to adjacent organs, ureteral injury,

pneumothorax, and postoperative fistulas. Critical structures such as the colon and small intestine serve as potential sites for collateral damage due to their proximity to the kidneys. The hydrodisplacement technique, which entails fluid instillation into the surrounding tissue, has been developed and used successfully during PCA. Sterile saline is injected into the different locations of the renal anatomy to increase the distance between the tumor and the surrounding organs. This technique is particularly effective for tumors located on the anterior surface or inferior pole of the kidney.

The incidence of pneumothorax during PCA has been reported as 2-4%. However, most of these pneumothoraxes are asymptomatic and clinically insignificant, and can be managed conservatively.

Complications following prostate cryoablation include thermal injury, urethral mucosal sloughing, perineal pain, urinary retention, urinary tract infections/sepsis, urethral stricture, fistula, urinary incontinence, and erectile dysfunction. Complication rates are significantly higher in patients undergoing salvage cryotherapy.

Overall, complications related to CA technology are rare compared to other energy-based instruments in minimally invasive surgery. Although it is certain that cryoablation technology has great potential for evolution, to date the current systems have been shown to be safe and efficient with encouraging intermediate term follow up in the treatment of renal cortical neoplasms and prostate cancer. Further investigation into other applications of this technology is warranted.

Videos

Core Curriculum Cryoablation 2021 Powerpoint

Presentations

Cryosurgery Presentation 1

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