Percutaneous renal cryoablation

Abstract  Increased use of cross-sectional imaging has led to an increase in the diagnosis of small renal masses (≤ 4 cm). Percutaneous renal cryoablation allows for a minimally invasive treatment option for select lesions and for the high risk surgical patient. Contemporary series suggest that renal cryoablation maintains good intermediate oncologic outcomes while minimizing patient morbidity. Over time, percutaneous renal cryoablation will play a central role in the management of patients with small renal masses, especially in elderly or comorbid patients.

Introduction  Cryoablation destroys cells by consecutive rapid freeze and thaw cycles, leading to cellular necrosis at temperatures of −20°C or less.1 The therapeutic use of cryoablation dates back to mid-19th century England and James Arnott who used crushed ice and salt solutions to attain temperatures of −20°C.2 The practical ability to clinically apply deeply cryogenic temperatures was realized when liquefied air gases became available just before 1900. Early approaches were limited to superficial application of the cryogen, usually liquid nitrogen, by either spraying or pouring it over the lesion. These techniques limited the clinical applications of cryotherapy.3

In 1961, Cooper and Lee successfully built the first apparatus for cryotherapy. Their liquid nitrogen cryogenic probe would pave the way for modern cryoablating.4 Percutaneous cryoablation for renal tumors was first described by Uchida et al. in 1995 with the first initial case series for laparoscopic renal cryoablation reported by Gill et al. in 1998.5,6 With the increase in the detection of small renal masses due to the widespread use of cross-sectional imaging and the further refinements in cryotherapy technology, percutaneous renal cryoablation has an established role in the treatment of the small renal mass.

Pathophysiology of cryoablation  Freezing provides hypothermic stress to cells as well as severe damage due to ice crystal formation. Although a thermal gradient exists with a freeze zone, there is a distinct transition between unfrozen and frozen tissue which accurately approximates the zone of lethality.7,8 The intensity of the freeze determines the response of the targeted tissue and ranges from an inflammatory response to cellular destruction. An inflammatory response accompanies minor freezing.9,10 If the freezing is severe (less than −20°C), complete destruction of cells results due to intracellular ice crystal formation. Current cryoablation technology generates temperatures much less than −20°C. Pressurized argon gas pumped into the cryoprobes is used for freezing and helium gas used for thawing via the Joule-Thompson effect.11 Cryoablation induces cell death primarily via two mechanisms: a direct cytotoxic effect from intracellular ice crystal formation during a freeze cycle and delayed microcirculatory failure with resultant ischemia during the thaw cycle.7,8 Ice crystal formation removes water from the cells which in turn produces metabolic disturbances related to the freeze concentration of solutes. Ice crystals also cause mechanical damage via cell membrane disruption. The vascular stasis that develops soon after thawing is also a major mechanism of injury as it contributes to endothelial damage, thrombosis and tissue ischemia. Repetition of the rapid freeze-thaw cycles also exacerbates tissue damage.12,13

The cryogenic lesion is histologically characterized by coagulative necrosis in the central portion surrounded by a thin peripheral zone in which cell destruction may be incomplete.7,8 Shortly after thawing, the tissue appears hyperemic along this border and congestion is noted in the central zone. The freeze margin is important with regard to the therapeutic outcome. The temperatures in the freeze margin range from 0°C to
−20°C at which cell survival is possible. Cell death in this region of tissue is generally due to apoptosis and secondary necrosis. Following the thaw phase there is an immediate infiltration of lymphocytes and macrophages into the necrotic tissue. The necrotic tissue is slowly debrided and replaced by a fibrous collagen scar over the following weeks to months.7,8

One advantage of percutaneous renal cryoablation compared to RFA is the ability to visualize the ice ball and thus the zone of ablation on CT during the procedure. A comparison of in vitro, ex vivo and in vivo isotherms for renal cryotherapy using 1.47 and 1.7mm (IceRodsTM, Galil and PERC-17 CryoProbesTM, Endocare) cryoprobes in porcine kidneys with multipoint thermal sensors found that gel and ex vivo isotherms did not predict the in vivo pattern of freezing.9 Furthermore, the cryoprobes should be passed 5mm beyond the tumor border to achieve suitably colder temperatures. Studies evaluating the effect of renal cryoablation on renal arterial structure have shown that ablation injury destroys arteries smaller than 180 μm but that larger arteries remain anatomically intact. It is also important to recognize that larger vessels (especially near the hilum) also serve as a "heat sink" which may increase the iceball temperatures and thus decrease cell kill in the region.10,11 An understanding of the physics of the cryoablation in reference to renal anatomy is thus important in order to maximize the efficacy of the procedure.

Indications and contraindications

Optimal outcomes for renal cryoablation are dependent on appropriate lesion selection as well as careful consideration of surgical indications and contraindications. Currently ablative techniques are used for small, enhancing renal masses (≤ 4 cm) in patients with advanced age and comorbid conditions. Ablation has also been advocated in patients with small renal tumors and baseline renal insufficiency, in patients with multifocal renal tumors attributable to Von Hippel-Lindau disease or in those with an absolute surgical contraindication. Some relative contraindications to ablation include large tumors (>4 cm), hilar tumors, unstable cardiovascular status and poor life expectancy. The only absolute contraindication is an uncorrected coagulopathy.12 The American Urological Association (AUA) Guideline for Management of the Clinical T1 Renal Mass stated that thermal ablation (cryoablation or radiofrequency ablation [RFA]) via either the percutaneous and laparoscopic approach is a treatment option for the patient at high surgical risk who wants active treatment and accepts the need for long term radiographic surveillance.13 The panel states that the standard is for percutaneous renal mass biopsy (specifically core biopsy with or without fine needle aspiration) to be performed prior to treatment to define histology and should also be considered after treatment, particularly if there is a suspicion of recurrence.14 Prior to proceeding with renal cryoablation it is important to counsel patients about available treatment options followed by the risks of the procedure (including the risk of local recurrence and renal functional considerations), the potential need for reintervention, the need for radiographic surveillance, the potential for difficult surgical salvage in cases of tumor progression and the limitations of the current thermal ablation literature.15

Technique

Recent preoperative imaging (CT or MRI) is used in the initial surgical planning. At our institution the radiology staff will perform a planning renal ultrasound with core biopsy of the lesion prior to the day of the procedure so that pathology of the mass is known prior to ablation. Percutaneous renal cryoablation is performed in the radiology suite with both interventional radiology and urology present.16 After administration of general anesthesia a foley catheter is placed and the patient is placed in the flank position and secured to the scanner table. The lesion is localized using both ultrasonography and computed tomography. If adjacent structures (colon, small bowel, pancreas) are in close proximity to the lesion or in the path of cryoprobe placement, hydrodissection is performed in order to displace adjacent organs to allow for safe probe placement and ablation.17 In situations where the tumor cannot be approached safely, the procedure is aborted and plans are made for an alternative management strategy. Generally two cryoablation probes (1.7mm, Endocare) are used depending on the lesion size. After probe placement, a 10-minute double freeze-thaw cycle is commenced. Both CT and US are used to monitor iceball formation. After probe removal a contrast CT is obtained in the radiology suite with delayed images (in cases when the lesion is endophytic or in close proximity to the renal pelvis) to evaluate for hematoma, an acute bleed or collecting system injury. (Fig. 1) Patients are admitted and observed overnight. A hematocrit is drawn post-operatively and the patient is allowed to have a regular diet. Almost all of our patients are discharged home on the first postoperative day. Follow-up imaging consists of an MRI with gadolinium performed 6 months after the procedure.

Outcomes

In a meta-analysis by Kunkle et al. in 2008, cryoablation (19 studies, 372 lesions) was compared to partial nephrectomy, RFA and active surveillance.19 The authors found that patients undergoing cryoablation were significantly older than those undergoing partial nephrectomy (mean age: 65.7 vs 60.1 years old; p=0.001). The mean tumor size was significantly smaller for patients undergoing cryoablation compared to partial nephrectomy (2.56 vs 3.40 cm; p=0.001) but similar when compared to patients undergoing RFA (2.56 vs 2.69 cm; p=0.40). The mean follow-up was significantly shorter for both thermal ablation options when compared to partial nephrectomy (cryoablation, RFA, partial nephrectomy: 18.3
vs 16.4 vs 54.0 months respectively; p<0.001), further highlighting the need for studies with longer follow-up for patients undergoing thermal ablation. When assessing local recurrence, the study found a recurrence rate of 26% following partial nephrectomy compared to 46% for cryoablation and 11.7% for RFA. Progression to metastatic disease was described in 5.6% of patients undergoing partial nephrectomy, 1.2% in patients undergoing cryoablation and 2.3% in patients undergoing RFA.

The panel for the AUA 2009 Guideline for the Management of the Clinical T1 Renal Mass performed a meta-analysis which included 15 studies (644 patients) on cryoablation compared to other treatment options including active surveillance, RFA, open partial nephrectomy (OPN), laparoscopic partial nephrectomy (LPN), open radical nephrectomy (ORN) and laparoscopic radical nephrectomy (LRN). The mean age for patients undergoing cryoablation was 67.0 years compared to 68.5, 59.5, 60.4, 627 and 60.7 years for patients undergoing RFA, OPN, LPN, ORN and LRN respectively. The mean tumor size for patients undergoing cryoablation was 2.6cm compared to 2.7, 3.2, 2.6, 4.9, 48cm for patients undergoing RFA, OPN, LPN, ORN and LRN respectively. The complication rate for patients undergoing cryoablation was 4.9% (95% CI:3.3-7.4%) compared to 6.0%, 6.3%, 9.0%, 1.3% and 3.4% for patients undergoing RFA, OPN, LPN and ORN respectively. ORN complication rates were significantly lower than all other groups. (p<0.05) The complication rates for cryoablation, RFA and OPN were indistinguishable. (p>0.05) The local recurrence free survival rates for cryoablation and RFA (90.6% and 87.0% respectively) were significantly lower than LPN, OPN, LRN and ORN (98.4%, 98.0%, 99.2%, 98.1% respectively). (p<0.05)

Johnson et al. performed a multi-institutional study defining the complications associated with cryoablation (139 cases) and RFA (132 cases) for small renal masses (181 percutaneous, 90 laparoscopic). The rate of major and minor complications for patients undergoing cryoablation were 1.8% (n=2) and 9.2% (n=17) respectively. Reported complications for cryoablation included: Minor: probe site pain or paresthesia (n=10, 7.2%), post-operative urinary tract infection (n=2, 1.4%), post-operative pneumonia (n=1), minor hemorrhage (n=1), elevated serum creatinine (n=1), wound infection (n=1), respiratory difficulty (n=1); Major: significant hemorrhage (n=1), open conversion (n=1) due to inability to access the tumor laparoscopically. There were no deaths in patients undergoing cryoablation and the study showed a decrease in the rate of complications with increased experience. Other potentially significant complications that can occur with percutaneous renal cryoablation include: ureteral stricture—related to the proximity of the ureter to the ablation site, urine leak—as manifest by contrast extravasation outside the collecting system on the delayed phase of post-procedure CT scan imaging, bowel injury and pneumothorax—which can occur when treating upper pole renal tumors (post-procedure CT scans should include the lower lung and viewed with lung windows to exclude pneumothorax). Ice ball fracture is a rare complication associated with renal cryoablation that can be associated with significant hemorrhage requiring prompt intervention. Some risk factors for ice ball fractures
include the use of large-diameter cryoablation probes (those used for laparoscopic cryoablation), use of multiple probes and premature removal of the cryoablation probes before the ice ball has completely thawed.24

Contemporary clinical series have shown that flank pain (cryoprobe site pain or paresthesia) continues to be the most common complication reported for renal cryoablation (9.8%-10.8%).25 In a series of 162 patients by Sidana et al. treated with renal cryoablation, the size of the lesion (p=0.001), the number of cryoablation probes (p<0.001) and chronic anticoagulation (p<0.05) were associated with an increased incidence of significant hematoma. Vricella et al in a retrospective study of 52 patients treated with percutaneous renal cryoablation found that Charlson comorbidity index score (p=0.02) and the number of cryoprobes used (p<0.005) both significantly correlated with an increase in post-operative complications.27

Post-procedure follow-up
The definition of therapeutic success following percutaneous renal cryoablation is based on the radiographic appearance of post-ablation axial imaging. Either contrast CT scan or MRI may be used to radiographically follow patients post-ablation. Post-cryoablation lesions should decrease in size as the resultant inflammatory reaction following the thawing of the ice ball will lead to resorption of the necrotic cellular debris.28 Though contrast enhancement of the lesion and/or growth of the lesion post-procedure can both signal local recurrence it is important to be aware that persistent contrast enhancement can be present up to 9 months post-cryoablation. Stein et al showed that in a series of 30 patients (32 cases) treated with laparoscopic renal cryoablation, 84% of treated renal masses showed no contrast enhancement at the site of treatment at 3 month imaging follow-up.29 However 16% percent of the ablation sites showed enhancement at 3 months with three (9%) persisting by 6 months and only one displayed enhancement at 9 months. The patient with persistent enhancement at nine months underwent a partial nephrectomy which demonstrated no recurrence of cancer. Porter et al. studied the MRI characteristics of patients undergoing renal cryoablation and also found 8 of 23 lesions imaged within 6 to 36 hours after ablation enhanced on MRI.30 Seven of the eight lesions exhibited no enhancement at 6 month follow-up imaging. The authors concluded that it may thus be reasonable to wait 6 months after technically successful renal cryoablation before performing contrast-enhanced MRI. The exact cause of the persistent post-ablation enhancement in treated tumors is not known. Immediately post-ablation, tumor enhancement may be due to delayed coagulative necrosis, persistent enhancement beyond this time may be due to persistent flow in large intratumoral vessels after cryotherapy.31 Bolte et al assessed the MRI appearance of renal ablation sites post-cryoablation and noted peripheral rim enhancement as a common finding (7/18 patients) within 3 months of follow-up.32 Though 4 of the 7 patients had resolution of the rim enhancement on follow-up imaging, patients with peripheral rim enhancement with an increase in lesion size or nodular enhancement were found to have local recurrence. (Fig. 2) Rim enhancement of these lesions may be due to viable tissue at the border of the iceball (since the peripheral edge of the ablation zone only reaches 0°C).33 In cases where there is peripheral rim enhancement with an increase in lesion size or nodular enhancement of the lesion, we recommend a biopsy of the ablation site. Local recurrences post-cryoablation may be treated with repeat cryoablation or surgical management.34

Conclusions
With the advantages of minimal invasiveness, reproducibility and rapid patient recovery, percutaneous renal cryoablation is a promising nephron sparing alternative to partial nephrectomy for the treatment of small renal tumors in select patients. Despite promising short term outcomes, a larger number of studies with > 5 year follow-up is required in order to assess its long term efficacy.
References


29. Stein AJ, Mayes JM, Mouraviev V, Chen VH, Nelson RC, Polascik TJ. Persistent contrast enhancement

