

## RENAL CRYOABLATION APPLICATION IN NEPHRON-SPARING TREATMENT

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### ABSTRACT

**Purpose:** Renal cryoablation is an evolving nephron-sparing treatment alternative for select patients with small renal tumors. Initially described via either an open or percutaneous technique, renal cryoablation has been performed by a laparoscopic approach with promising results. We critically review the cumulative evidence available regarding this technique.

**Materials and Methods:** A review of the literature on both experimental and clinical studies was performed and evaluated. Historical aspects, pathophysiology, radiologic evaluation, clinical experience and future horizons of the technique are outlined.

**Results:** Two institutions have reported their clinical experience with laparoscopic renal cryoablation. Despite the lack of long-term follow-up to date, current oncologic adequacy and safety have been encouraging.

**Conclusion:** Experience with renal cryoablation is still evolving. Laparoscopic and percutaneous techniques are promising minimally invasive approaches for this developmental, nephron-sparing treatment modality. Long-term follow-up will determine the precise role of renal cryoablation in the management of selected patients with small renal tumors.

**Key words:** kidney; kidney neoplasms; cryoablation; laparoscopy; nephron-sparing  
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### INTRODUCTION

“Renal mass” is now primarily a radiologic diagnosis. With the increasing use of abdominal ultrasonography and CT scanning, the serendipitous detection of small renal masses has increased 5-fold from 1974 to 1985 (1). This advance has contributed, in part, to a gratifying decrease in the incidence of metastatic renal cell carcinoma from 32% to 17% over the past 2 decades (2).

For the practicing urologist, the term “incidental renal mass” has progressed from being an occasional diagnostic curiosity to being a day-to-day management dilemma. The differential diagnosis of these small, solid or complex cystic, enhancing renal masses includes a variety of benign and malignant conditions. Needle biopsy remains an unreliable tool for making the histologic diagnosis of renal cell cancer, with a reported false-negative rate of 16% and a

non-diagnostic rate of 26% (3). Although small renal cell carcinomas have a slow growth rate (0.35 cm/year) (4), and are at low risk for dissemination, they nevertheless do possess the capability for systemic metastases. Accordingly, although watchful waiting has been a treatment option, current opinion has tended to favor surgical excision, especially for the younger patient. Small (< 4 cm) renal tumors can be treated efficaciously with either partial or radical nephrectomy, with comparable crude and cause-specific survival. Select patients with a localized, unilateral, small (< 4 cm) renal cell carcinoma can be successfully treated with a nephron-sparing partial nephrectomy, even when the contralateral kidney is normal (5,6).

A comprehensive review of renal cryoablation as an emergent nephron-sparing treatment alternative for small renal tumors is presented, including experimental studies and current clinical data.

Historical milestones of renal cryosurgery, the basic pathophysiology of cryotherapy and histologic and radiologic characteristics of a renal cryolesion are outlined.

**HISTORICAL ASPECTS**

Cryosurgery in the treatment of cancer began in the 1850s in London when breast and cervical cancer were treated with iced saline solutions at a temperature of -18° to -22°C (7). The next advance, liquefaction of gases, occurred between 1870 to 1900. Initial investigations involved non-urolologic organs like brain, liver, skin, and rectum (80). Renal cryosurgery began in the mid 1960s when Bush et al. cooled kidneys with liquid nitrogen in an effort to evaluate their functional recovery for purposes of transplantation (9). Subsequent investigations focused on the functional, morphological, histologic, radiologic, and technical (open, laparoscopic, percutaneous, puncture vs. contact) aspects

of renal cryoablation. Uchida et al. were the first to report renal cryoablation in the clinical setting. A chronology of cryosurgery of the kidney is presented in Table-1 (9-23).

**CRYOSURGICAL APPARATUS**

The size and efficacy of the induced cryolesion is determined by the physical characteristics of the cryoprobe employed. Features such as nadir temperature of the cryoprobe, its thermal conductivity and surface area of renal contact directly and proportionately affect the volume and temperature of the ablated tissue. As such, a 3.4 mm probe cooling at the rate of 50° C/min to a nadir probe-tip temperature of -175°C will create a cryolesion 4 cm in diameter in 20 minutes. In contrast, an 8 mm probe cooling at the rate of 100°C/min to a nadir tip temperature of -190°C will result in a cryolesion 7 cm in diameter in 20 minutes (24). Thus, the choice of probe size depends upon the size of the tumor to be cryo-

*Table 1 – Chronology of renal cryoablation*

YEAR	AUTHOR	CONTRIBUTION
<b>Experimental Studies</b>		
1964	Bush (9)	Renal function recovery following rapid cooling with liquid nitrogen.
1974	Breining (10)	Hisotologic and autoradiographic analysis of renal cryoablation.
1979	Helpap (11)	Investigations into the cryoimmunologic response following renal cryoablation.
1981	Sindelar (12)	Ultrastructural changes following renal cryoablation.
1988	Barone (13)	Functional and morphologic effects of renal cryoinjury.
1993	Onik (14)	Ultrasound characteristics of a renal cryolesion.
1996	Stephenson (15)	Open and laparoscopic renal cryoablation in the canine model.
1996	Gill (16)	Laparoscopic and percutaneous renal cryoablation in the porcine model.
1996	Chosy (17)	Thermosensor-monitored renal cryosurgery.
1997	Nakada (18)	Puncture vs. contact renal cryoablation.
1998	Campbell (19)	Impact of renal artery clamping on cryosurgery.
<b>Clinical Studies</b>		
1995	Uchida (20)	Percutaneous renal cryoablation (2 patients)
1996	Delworth (21)	Open renal cryoablation (2 patients)
1998	Gill (22)	Laparoscopic renal cryoablation (10 patients)
1998	Rodriguez (47)	Open & laparoscopic renal cryoablation (7patients)
1999	Gill (46)	Laparoscopic renal cryoablation (32 patients)

*From: Gill IS, Novick AC: Renal cryosurgery. Urology, 54: 215-219, 1999. Reprinted with permission.*

ablated. For tumors larger than 4 cm in diameter, or those with irregular margins, multiple cryoprobes are preferable.

Various cryogens are available for use in cryosurgery. The boiling point of a particular cryogen determines the nadir temperature that the specific cryoprobe can produce. The boiling points of various cryogens at atmospheric pressure are depicted in Table-2. Two commonly used cryosurgical systems

**Table 2 – Available cryogens**

<b>Cryogen</b>	<b>Boiling Point</b>
Freon-22	-41°C
Carbon dioxide	-79°C
Nitrous dioxide	-90°C
Liquid argon	-186°C
Liquid nitrogen	-196°C

employ liquid nitrogen and liquid argon, respectively, as cryogens. In liquid nitrogen-based systems, liquid nitrogen is circulated within the cryoprobe by pressurized nitrogen gas. Liquid nitrogen boils within the cryoprobe tip, and in so doing, extracts latent heat of boiling from its immediate surrounding. For every gram of liquid nitrogen that boils and converts to gas, 209 Joules of heat are extracted. Liquid nitrogen cryoprobes are available in various diameters: 3 mm, 4.8 mm, and 8 mm, with surgical freezing zone lengths varying from 1-5 cm. Liquid argon-based systems rely on the Joule-Thompson effect, in which compressed gas or liquid under high pressure is allowed to expand rapidly through a narrow orifice into the tip cavity of the cryoprobe. Rapid cooling ensues, leading to the creation of an ice ball. The argon-based system is portable and allows for very rapid freezing rates.

### **PATHOPHYSIOLOGY OF THE RENAL CRYOLESION**

During renal cryotherapy, the goal is to ablate the same amount of parenchyma that should be excised during an open surgical nephron-sparing procedure: the tumor itself and a surrounding margin of healthy parenchyma (8). A secondary healing process then occur over time, with sloughing of

the devitalized tissue and replacement of that area by a fibrotic scar. It is clear that certain aspects of cryosurgery are essential, including a rapid freezing, slow thawing, and a repetition of the freeze-thaw cycle (24).

Rapid intracellular ice formation causes irreversible cell death. Tissue interstitium is incorporated by the freezing process in a sequential manner: extracellular matrix freezes initially followed by intracellular freezing. The latter is thought to be the terminal, lethal event. The mechanism underlying tissue cryoinjury is thought to involve a)- immediate cellular damage and, b)- delayed microcirculatory failure. Mazur proposed a two-step theory for cellular damage: ice formation occurs initially in the extracellular space, causing the extracellular fluid to become hyperosmotic (25). Because the cell membrane may be a barrier to the freezing process, the intracellular fluid, although supercooled, remains unfrozen at this stage. To equilibrate chemical osmolality, water permeates out from the cell along the osmotic gradient into the extracellular compartment. This in turn increases the osmolality of the intracellular fluid, resulting in solute concentration and intracellular dehydration. As extracellular ice crystals grow, cells shrink further, sustaining desiccation injury to intracellular structures. This comprises the first step of cellular chemical injury (26). Continued rapid supercooling leads to the second step of cellular damage. Cell membrane dysfunction occurs at temperatures below -10°C, leading to the critical event: intracellular ice formation. Intracellular ice irreversibly disrupts cell organelles and the cell membrane, which is lethal. During thawing, the extracellular compartment becomes briefly hypotonic. Water re-enters the cell causing cell swelling, and possibly cell membrane rupture.

Delayed microcirculatory failure manifests during the thaw phase of the freeze-thaw cycle, leading to circulation arrest and cellular anoxia. Tissue cooling sequentially leads to vasoconstriction, decrease in blood flow, and ultimately, cessation of blood flow. During the 10-20 minute initial thawing period, circulation is restored to the cryoablated area. Experimental hepatic cryoablation has demonstrated the formation of continuous ice crystals along the lumen

of the small blood vessels leading to dilation and destruction of the structural integrity of the microvasculature. Progressive failure of the microcirculation occurs due to a cascade of events: endothelial layer destruction causing vessel walls to become porous, interstitial edema, platelet aggregation, microthrombi, and ultimately vascular congestion and obliteration (24). Although small blood vessel lumens are destroyed within 4 hours after thawing, larger arterioles may remain patent for periods of up to 24 hours (27). Cells that survive freezing's initial assault are destroyed by this secondary impact of ischemia (28). Repetition of the rapid freeze-slow thaw cycle potentiates this damage. The cryoablated area is thus rendered ischemic, leading ultimately to a circumscribed necrosis.

The dimensions of a cryolesion depend upon multiple factors. As already mentioned, the colder the nadir temperature of the cryoprobe tip, the larger the cryolesion. The duration of freezing, the actual area of contact between the cryoprobe and the targeted tissue, and the rate of cooling are important variables. Cell destruction is dramatically enhanced by increasing the cooling rate from 5° C/min to 25° C/min. Tissue vascularity is an important factor, and in general, the more vascular the targeted tissue, the slower is the rate of cryoablation. This phenomenon is termed the "heat sink" effect (29). Flow of warm blood through large adjacent vessels may dissipate the cold temperature of the evolving cryolesion, thereby slowing its rate of growth. Theoretically, this may decrease the efficiency of cryoablation and lead to asymmetric ice ball formation. The "heat sink" effect can, on occasion, be used to therapeutic advantage. To wit, a urethral warming device is employed during prostate cryoablation, in order to protect the urethra from cryodamage. Other biologic characteristics like specific heat, density, and thermal conductivity of the particular tissue or organ also impact on the efficacy with which it undergoes cryodestruction.

Lethal temperature for achieving reliable cell death is approximately -40°C. For normal and cancerous renal cells, a temperature of -20°C causes uniform necrosis. In an elegant study, Chosy, Nakada et al. showed that complete necrosis of in-vivo porcine renal parenchyma occurred uniformly at temperatures

of -19.4°C or lower in all instances (13 of 13 tissue samples). However, when the temperature ranged between -19.4°C and 0°C, tissue necrosis was present in only 80% of renal samples (17).

The temperature within a given cryolesion is not uniform, increasing exponentially as a function of the distance from the cryoprobe. Thus, the temperature at the periphery of the ice-ball is significantly higher than the core temperature at its center (30,31). Accordingly, the visible outer edge of the ice-ball is usually at 0°C, although the temperature at its center (cryoprobe tip temperature) may be -196°C. The temperature begins to decrease incrementally from the periphery towards the center of the ice-ball: it is -20°C at a distance of 4 mm, and -40°C at a distance of 6 mm inside the periphery. In this regard, valuable data were provided by two recent experimental studies wherein a 3.4 mm cryoprobe was used to create renal cryolesions with a diameter of 3.2 cm. Campbell et al. confirmed that the target temperature of -20°C was achieved at a distance of 3.1 mm inside the edge of the ice-ball in all 10 canine kidneys (19). In Chosy's study, all 17 tissue samples taken from within a 3.2-cm diameter area ("within 16 mm of the probe insertion site") were uniformly ablated. However, the directly visible extent of the ice-ball was not an absolute predictor of cellular necrosis: 2 of 18 (11%) of samples obtained from within the area encompassed by the visible ice-ball contained viable tissue. The authors speculated that sampling error as well as the ellipsoid shape of the advancing ice-ball may have contributed to these results (17). Thus, to ensure complete cell kill, the ice-ball must extend well beyond the margins of the targeted tumor. Based on these data and our own laboratory observations, we routinely attempt to extend the ice-ball at least one 1 cm beyond the edge of the tumor, as determined both by laparoscopic visualization and real-time ultrasonographic imaging. This margin should be sufficient to achieve the desired lethal temperature of -40°C within the entire extent of the tumor.

It appears evident that a double freeze-thaw cycle is a primary prerequisite for reliable cryo-induced cell death (24,32). A comparison of single and double freeze-thaw cycles has not been performed as regards the kidney. For prostate adenocarcinoma,

Tatsutani and co-workers showed that the percentage of cells destroyed by freezing to  $-20^{\circ}\text{C}$  (cooling rate  $25^{\circ}\text{C}/\text{min.}$ ) was approximately 80% by the single freeze-thaw cycle compared with 100% by the double freeze-thaw cycle at the same temperature (33). Shinohara and colleagues found that prostate cryoablation induced undetectable PSA levels in 35% of patients following a single freeze-thaw cycle compared with 80% following a double freeze-thaw cycle (34).

## HISTOLOGY

Histologically, the cryoablated tissue reveals progressive changes over time, from typical findings of cell death and tissue non-viability to chronic signs of inflammation, fibrosis and scarring. Initially (1 hour), the renal cryolesion macroscopically demonstrates areas of dark red discoloration consistent with interstitial hemorrhage with an abrupt line of demarcation from the surrounding healthy renal parenchyma. Microscopically, generalized vascular congestion is evident, with only subtle signs of early coagulation necrosis. Hemorrhagic glomeruli, fibrin deposition within capillaries and near complete exfoliation of the urothelium covering the cryoablated papillae is evident (35). The inflammatory response is minimal with only a mild infiltration of polymorphonuclear neutrophils (10). Marked ultrastructural evidence of irreversible cell death is also shown on electron microscopy, such as partial fragmentation and cytoplasmic vacuolization of membranes, disruption of outer membranes and internal crystal of mitochondria, chromatin condensation and loss of nuclear membrane, hemorrhage into glomerular spaces and disruption of epithelial podocytes of glomeruli (12).

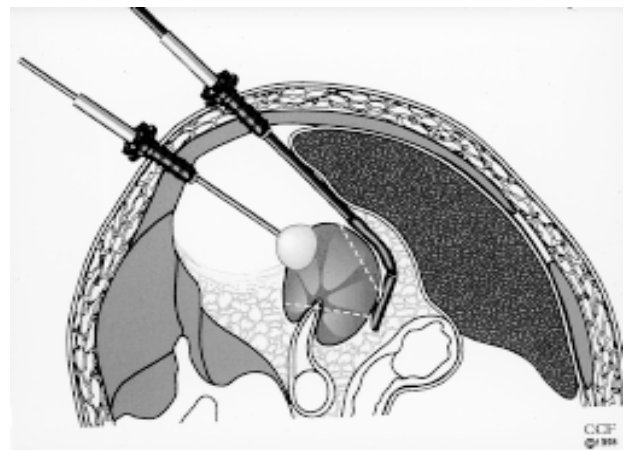
A sharply demarcated, deep-red cryolesion is readily apparent macroscopically after 24 hours. On microscopic examination, complete coagulation necrosis is evident centrally, surrounded by a 0.3 mm-8 mm transitional zone of partial necrosis, which abuts normal renal parenchyma. Loss of cell borders, absence of cytoplasmic organelles, and ghost renal tubules are easily identified in the area of complete necrosis. Hyalinization of glomerular and tubular cellular structure is seen, while nuclear py-

knosis is evident universally in the glomeruli and blood vessels. When examined under electron microscopy, tubular cells appear as proteinaceous aggregates, completely devoid of membranes, while glomeruli are degenerated and glomerular spaces are filled with necrotic cellular debris. Capillary basement membranes remain intact with large intravascular thrombi (12). The zone of partial necrosis contains some viable cells, thus representing an area of sublethal injury. Glomerular architecture is lost and proteinaceous casts are visible in the collecting tubules. Considerable infiltration of polymorphonuclear leucocytes is seen.

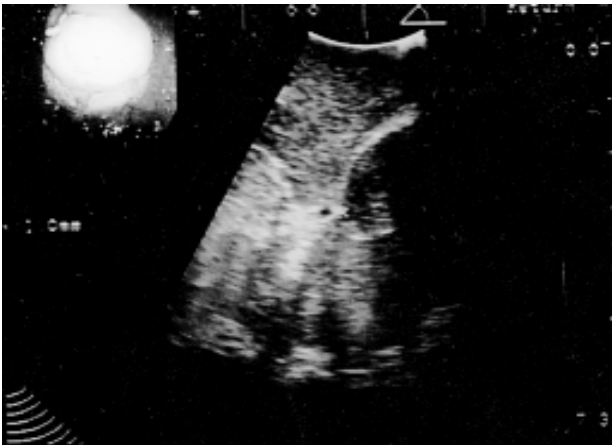
Fibrotic changes and a typical contracted scar are eventually seen after 1 month following renal cryoablation, when chronic inflammation, fibrotic glomeruli and tubules, and no evidence of viable renal parenchyma are observed under microscopic examination.

## RADIOLOGIC EVALUATION

The advances in diagnostic and intraoperative imaging techniques are directly related to the development of cryosurgery. The ultrasound characteristics of a renal cryolesion were initially reported



**Figure 1** – Renal cryoablation under direct intraoperative ultrasound and laparoscopic control. The ice ball must extend 1 cm beyond the margins of the tumor. The ultrasound probe is placed in direct contact with the kidney directly opposite to the tumor. From: Gill IS, Novick AC, Soble JJ: Laparoscopic renal cryoablation: initial clinical series. *Urology*, 52: 543-551, 1998 (Reprinted with permission).



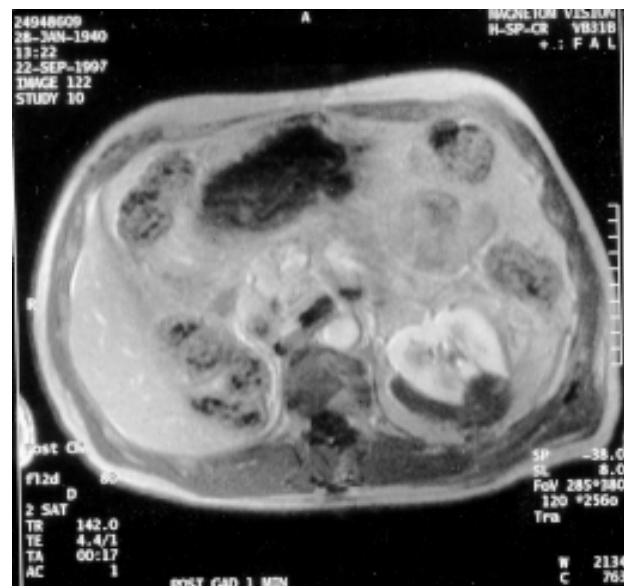
**Figure 2** – Ultrasound monitoring of the evolving cryolesion. Note: 1)- The crescent hyperechoic leading edge and the anechoic body of the iceball under ultrasound control, and 2)- Picture-in-picture laparoscopic view of the iceball.

by Onik et al. in the porcine model, which include an advancing hyperechoic edge with posterior acoustic shadowing (14). As such, intraoperative ultrasonography has been the imaging modality employed by virtually all reported studies of renal cryoablation to date. In our clinical laparoscopic renal cryoablation experience, we position a flexible, steerable, endoscopic, color-Doppler ultrasound probe within Gerota's fascia, in direct contact with the renal surface (Figure-1) for intraoperative monitoring (Panther 2002, Y-Ducer model 8555, Gentofte, Germany) (22). Tumor size, echogenicity, vascularity and distance from the renal sinus are measured. The remainder of the kidney is scanned for any satellite nodules. Ultrasonography is employed to guide the needle biopsy, and the subsequent cryoprobe placement into the center of the tumor such that the probe tip is positioned at, or just beyond, the deep margin of the tumor. The evolving cryolesion is then sonographically monitored real-time until complete ablation of the tumor is confirmed and the ice ball is noted to extend 1 cm beyond the tumor margins circumferentially. Distance of the edge of the cryolesion from the renal sinus is measured, thus minimizing chances of inadvertent cryoinjury to the collecting system (22).

The intraoperative laparoscopic ultrasound characteristics of the renal tumors are heterogeneous echogenicity or mild hyperechogenicity, which con-

trasts with the hyperechoic renal sinus fat. Combined with direct laparoscopic visualization, real-time laparoscopic ultrasound is essential for precise positioning of the cryoprobe tip up to the deep margin of the tumor. Adequate localization of the leading edge of the ice ball as it obliterates the tumor margin, as well as the typical aspect of an enlarging, hyperechoic rim with posterior echo loss of the cryolesion, is easily obtained (Figure-2). Mean tumor size on intraoperative ultrasound (2 cm) was 14% smaller than the mean tumor size on preoperative CT scanning (2.4 cm). This 14% size differential, which for a 2.5-cm renal mass would represent only 3-4 mm, is probably attributable to the angle in which ultrasound measurements were obtained (36).

We selected magnetic resonance imaging as our preferred modality for postoperative follow-up of renal cryolesions, due to its superior soft tissue contrast resolution and multiplanar imaging capability. Successful renal cryoablation is visualized as non-enhancement of the lesion following gadolinium administration (Figure-3). We routinely perform MRI, with and without gadolinium enhancement, on days 1, 30, 60, and 90 postoperatively, in order to assess the kidney and surrounding structures. All cryolesions



**Figure 3** – Successful renal cryoablation is visualized as non-enhancement of the lesion following gadolinium administration, as seen on day 1 MRI.

were isointense to the adjacent normal renal parenchyma on T<sub>1</sub> weighted images and hypointense on T<sub>2</sub> weighted images. A hyperintense peripheral rim at the border between the cryolesion and the kidney on day 1 MRI scans T<sub>1</sub> weighted images was observed in some the cases. After 30 days, an increase in signal intensity on both T<sub>1</sub> and T<sub>2</sub> weighted images was constantly detected, but no gadolinium enhancement of the cryolesion occurred. Radiologist familiarity with these sequential MRI findings allows accurate assessment of spontaneous contraction of the cryolesion over time. We reported a decrease in MRI size of the cryolesion by 14%, 23%, and 40% at 1, 2, and 3 months postoperatively in our 10 initial patients (22). In fact, of the 7 patients who have completed now a 1 year follow-up MRI scan, the cryoablated renal tumor is no longer detected in 3. The other 4 patients observed a decrease in size by 57%.

### **RENAL CRYOABLATION: EXPERIMENTAL DATA**

Many questions needed to be addressed experimentally before embarking on clinical renal cryosurgery. The following experimental data provides the background for the reported clinical experience.

#### **What is the Natural History of a Renal Cryolesion?**

The size of a renal cryolesion contracts over time (17). While on postoperative day 8 a large central area of coagulative necrosis surrounded by a narrow zone of sublethal injury is observed, at 3 months, the area of necrosis is completely absorbed and replaced by fibrosis. In a porcine study involving healthy kidneys, we noted a macroscopic decrease in size of the renal cryolesion by 42% at day 7, 52% at day 30, and complete resorption of the lesion by day 90 (16).

#### **What Happens if the Ice-ball comes in Contact with Adjacent Structures?**

Inadvertent contact of the ice ball or the active cryoprobe with adjacent structures is capable of producing disastrous consequences. Contact of the cryolesion with a loop of small bowel during porcine

laparoscopic renal cryoablation led to complete small bowel obstruction in one animal in our study (16). Also, a significant stricture of the ureteropelvic junction following open renal cryoablation in the canine model has been reported. These reports point to the need of precisely monitoring the intraoperative cryoprobe positioning and cryolesion development. Concern about cryoinjury to the ureter led the authors to recommend adequate mobilization of the kidney away from the ureter prior to cryoablation of the lower renal pole (19).

#### **Is Renal Artery Clamping a Helpful Adjunct During Cryoablation?**

Since constant perfusion of an organ with warm blood could theoretically serve to dissipate the cold temperature during cryosurgery, the effects of renal arterial occlusion on the freezing process were studied. Campbell et al. demonstrated that, based on a canine model of renal cryoablation, renal arterial occlusion during clinical cryoablation was of no practical advantage (19). Occlusion of the main renal artery (5 animals) did not result in increased rate of cooling or differences in the nadir temperature achieved when compared to a control group (5 animals without arterial clamping). The target temperature of -20°C was achieved 1.8 mm inside the edge of the ice-ball in the group with arterial occlusion, and 2.0 mm inside the edge of the ice ball in the group without arterial occlusion. Also, no significant differences were found in terms of mean diameter of the infarcted zone between the 2 groups.

#### **How Accurate is Ultrasonography in Evaluating the Size of the Renal Cryolesion?**

Stephenson et al. created surface contact renal cryolesions in 12 dogs (15). Ultrasound measurements for depth and diameter were determined for each cryolesion. Upon thawing, direct tissue measurements of the easily discernible cryolesion were obtained. The ultrasonic and direct physical measurements were closely concordant for both depth and width, with a correlation coefficient of  $r = 0.9295$  ( $p = 0.0001$ ). In patients undergoing radical nephrectomy, Orihuela et al. performed *in vivo* cryotherapy of the renal cell cancer just before removal of the

kidney (37). A 3-mm cryoprobe (tip temperature -180°C) was employed under ultrasound control. Final tissue temperature at 7.5 mm, 15 mm, and 22.5 mm away from the cryoprobe was noted to be -90°C, -90°C, and -20°C, respectively. Histology showed well demarcated, complete necrosis, resembling hemorrhagic infarct up to 18 mm away from the cryoprobe. The authors found good correlation between ultrasound imaging and the physical dimensions of the cryolesion. Long & Faller described a porcine model of ultrasound-guided percutaneous cryoablation of the kidney (38). They demonstrated the feasibility of the technique regarding tolerability and focal destruction of target areas. However, the consistent difficulty in adequately monitoring the actual intraoperative size of the ice ball with a real-time 2-dimensional ultrasound, due to anatomic interference by the spine and lower ribcage, was a significant limitation of the percutaneous technique employed.

### **What is the Impact of Renal Cryoablation on Overall Kidney Function?**

Functional impact is determined by the amount of renal parenchyma ablated by the ice-ball. The selective destruction of target areas under precise intraoperative monitoring has been essential to preserve normal renal parenchyma. In a solitary kidney canine model (baseline serum creatinine 0.6-0.9 mg/dL), creation of a cryolesion (mean diameter 3.2 cm) resulted in a transient elevation of serum creatinine on postoperative day 2 (1.0-1.9 mg/dL), and a final serum creatinine of 1.0-1.5 mg/dL by day 28 (19). When renal cryoablation was performed bilaterally in the porcine model, mean serum creatinine levels at day 0, 1, 3, and 7 were 1.5, 2.3, 1.8, and 1.4 mg/dL, respectively (16).

### **How do Temperature and Distance from the Cryoprobe Impact upon the Degree of Renal Parenchymal Destruction and Collecting System Damage?**

The ability of tissue destruction and complete necrosis depends directly upon the nadir temperature achieved at that location. Chosy et al. demonstrated that a temperature of -19.4°C or lower is necessary for promoting complete tissue necrosis (17). The tem-

perature at the edge of the ice ball is approximately 0°C, and a temperature of -20°C is routinely achieved 3.1 mm inside the ultrasonographically visualized edge of the ice ball with complete tissue necrosis on histology. Therefore, circumferential extension of the ice ball for at least 3.1-mm beyond the tumor margin ensures adequate intralesional cooling (19).

Regarding the effect of the cryoinjury to the renal collecting system, an experimental study addressing this question has been recently presented by Sung et al. (39). In a porcine model, 18 kidneys were submitted *in vivo* to intentional cryoinjury to the pelvicaliceal system under ultrasound and retrograde ureteropyelogram control, and the acute and long-term (3 months) sequelae were analyzed. After 1 month, regrowth of normal urothelium was noted, with minimal scarring of the lamina propria and smooth muscle, while the adjacent parenchyma was replaced by fibrous scar. Ex-vivo retrograde pyelogram revealed watertight healing of the caliceal system when no physical cryoprobe puncture injury to the renal pelvis was documented.

### **Does Renal Cryoablation Lead to Systemic Hypothermia?**

Renal cryoablation does not alter renal vein or renal arterial temperatures. Perlmutter et al. created renal cryolesions with a probe tip temperature of -147.7°C. Baseline renal artery and renal vein temperatures were 35.3°C and 34.9°C, respectively. Following cryoablation, mean renal artery and vein temperatures were 35.4°C and 34.5°C, respectively (38,40). In our study, systemic (esophageal) temperature during renal cryoablation in a porcine model was noted to decrease only by 1°F to 3°F (16).

## **RENAL CRYOABLATION: CLINICAL STUDIES**

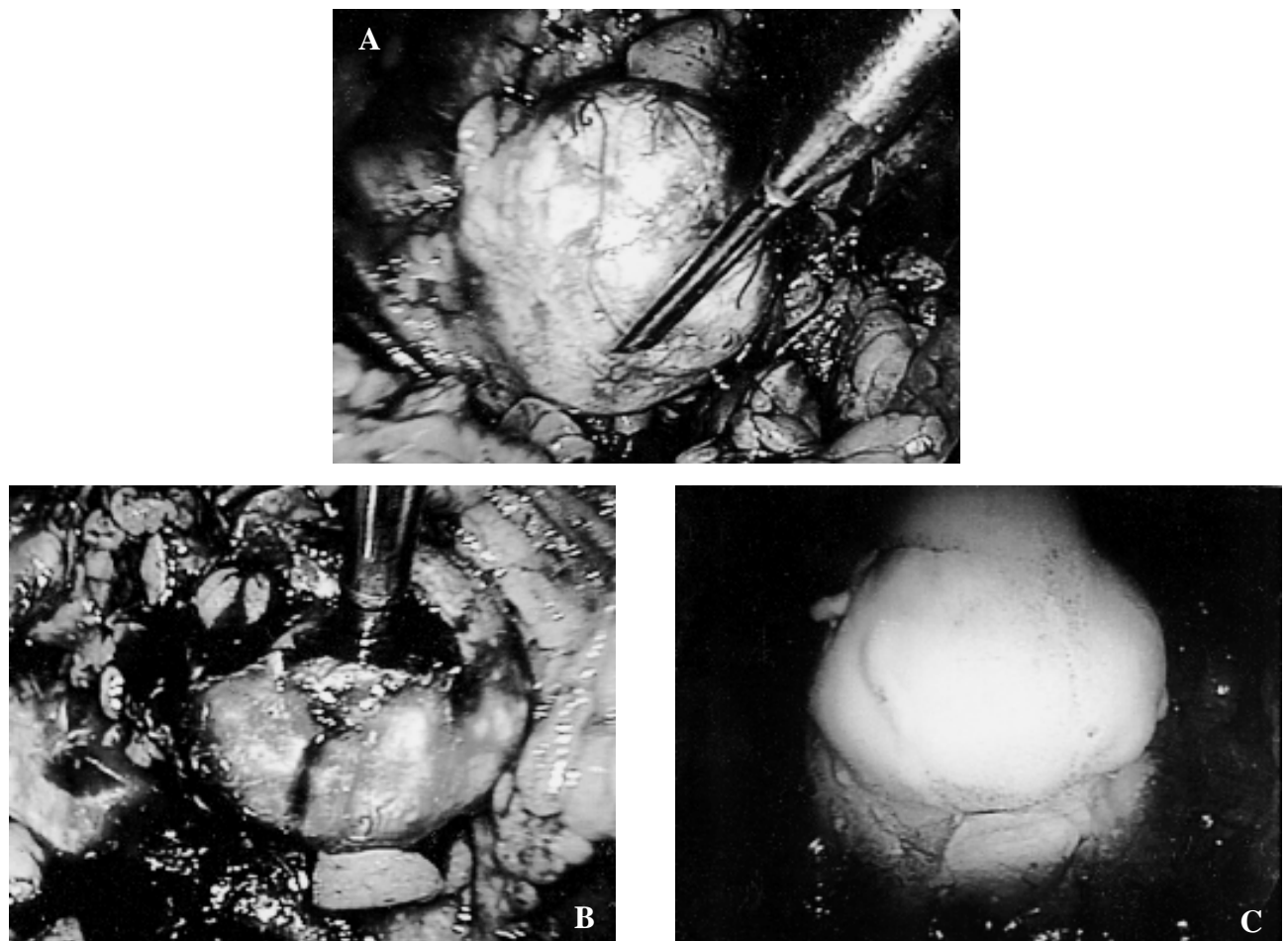
The first reported clinical study of cryoablation as a nephron-sparing procedure was published by Delworth et al., who performed open cryoablation in 2 patients with a solitary kidney (21). The first patient had a 3 cm renal cell cancer and the second had a 10 cm angiomyolipoma. Operative time was 3.5 hours and 4.5 hours, with a blood loss of 200

cc and 700 cc, respectively. Postoperative serum creatinine was 1.3 mg% in both patients and follow-up consisted of a MRI at one month, revealing a significant decrease of the renal carcinoma dimensions and at 3 months, showing a 10% enlargement in size of the angiomyolipoma. Although no pathologic data were included in the study, the authors concluded that renal cryotherapy could be performed safely with minimal loss of renal function.

Two patients with symptomatic, metastatic renal cell carcinoma were treated with percutaneous renal cryoablation by Uchida et al. in 1995 (20). A percutaneous puncture was performed under ultrasound control into the center of the tumor, and tract dilation to 24F was achieved for cryoprobe insertion. Although follow-up was short in these patients and

no pathologic data was available, as they died of metastatic disease at 1 and 10 months postoperatively, follow-up CT scans showed shrinkage of the cryolesion by 20% at 1 month in one patient, and by 81% at 8 months in the second patient (20).

Recently, Shingleton et al. presented their clinical experience of 17 patients treated with percutaneous cryoablation utilizing an interventional MRI unit, under general or local anesthesia with intravenous sedation (41). Patients were discharged home the following day and no complications were reported. Although the authors did not perform control biopsies after the procedure, 94% of tumors were found to have no enhancement on short-term follow-up MRI/CT scan (1-6 mo). Similarly, initial results with other energy sources like the laser or radiofrequency inter-



**Figure 4** – Steps of laparoscopic renal cryoablation: A)- Dissection of the peripheral renal lesion; B)- Puncture of the renal lesion with the cryoprobe, under direct laparoscopic and ultrasound monitoring and C)- Laparoscopic view of the renal cryolesion.

stitial thermoablation under MRI guidance have been reported percutaneously (42-45) and need to be further evaluated.

In our opinion, percutaneous cryoablation may become a potential outpatient nephron-sparing alternative modality in the future. However, the percutaneous approach must not be applied to anterior parenchymal lesions due to the risk of injury to intra-abdominal organs, which limits its applicability to only posteriorly located tumors.

Two centers have provided clinical data on laparoscopic renal cryoablation to date (46,47). We first reported the initial series of 10 patients in the literature in 1998 (22), and have now expanded our experience to 50 carefully selected patients. Our laparoscopic approach is dependent on the anatomic location of the tumor on the kidney. If the lesion is posterior or lateral, we employ a retroperitoneoscopic technique, while the transperitoneal route is selected if the tumors are anterior or anterolateral. During retroperitoneoscopic cryosurgery, a 3-port approach in full flank position is preferred, while a 4-port approach with the patient in a 45-degree oblique position is developed for the transperitoneal procedure. Our technique during laparoscopic renal cryoablation includes complete mobilization of the kidney within Gerota's fascia, excision of the perirenal fat overlying the tumor for histopathologic evaluation, intraoperative imaging of the tumor and remainder of the kidney with a laparoscopic, color-Doppler ultrasound probe, needle biopsy of the tumor and puncture cryoablation (with 4.8 mm cryoprobe) (Figure-4). As postoperative hemorrhage is a concern, careful confirmation of hemostasis after the procedure is undertaken, with observation under reduced CO<sub>2</sub> pressure. If necessary, hemostatic compression with a piece of Surgicel or the use of the argon beam coagulator after gentle relieve of the cryoprobe. Our current practice is to offer laparoscopic renal cryoablation only to carefully selected patients who are candidates for open partial nephrectomy at our center, having a small (< 4 cm), peripheral, exophytic, localized renal tumor located at a distance from the collecting system. In the initial 10 patients (mean age 67.6 years), mean blood loss was 75 cc, cryoablation time was 12.9 minutes and total surgical time was 2.4 hours. Hospi-

tal stay was < 23 hours in 9 of 10 patients. One patient, who was on chronic Coumadin therapy preoperatively, developed an asymptomatic perirenal hematoma due to trauma from a laparoscopic fan retractor, which was treated conservatively. In 32 patients, hospital stay was 1.8 days (22 patients were discharged within 23 hours), mean surgical time was 2.9 hours and mean blood loss was 66.8 cc (range, 10-200 cc) (48). In our expanded experience with 50 patients, no patient required open conversion. By now, 22 patients have undergone a 6-month follow-up CT-directed biopsy of the cryoablated site, with negative results. One patient with previously ablated renal cancer and a negative 6-month CT-directed biopsy was re-biopsied at 9 months for a suspicious nodule on a subsequent follow-up MRI scan. Renal cell carcinoma was demonstrated at biopsy, and laparoscopic radical nephrectomy was performed (49). Twenty-four patients treated by our group were evaluated regarding the impact of cryoablation on renal function and blood pressure for a minimum of 6 months after treatment. No deleterious effect on serum creatinine or blood pressure over a mean follow-up of 20 months was detected, including 5 patients with a solitary kidney (unpublished data).

Rodriguez et al. recently presented their experience with 9 patients with exophytic renal masses with a mean size of 2 cm (23). Mean blood loss was 140 cc and hospital stay was 3 days. There were no intraoperative complications and, at a mean follow-up of 5 months, no tumor recurrences were noted as evaluated by follow-up CT scans.

To date, there has been no report in the literature of urinary fistula or cryoinjury to the bowel, ureter or surrounding structures following clinical laparoscopic renal cryoablation (22,23,46,47,50). However, due to the reported experimental evidence regarding adjacent tissue cryoinjury from inadvertent physical contact of the ice ball, extreme care must be taken to maintain the iceball under complete laparoscopic visualization at all times.

## FUTURE HORIZONS

Experience with laparoscopic renal cryoablation is still evolving. Nevertheless, cumulative data

regarding its safety and efficacy has been presented. Comparatively to the prostate, the kidney is an ideal solid organ for cryoablation. It usually harbors unifocal malignancy and can be easily mobilized laparoscopically, enabling a higher degree of precision in completely involving the targeted area. Long-term oncologic adequacy still needs to be documented before its widespread use recommendation, although recent results are promising. Clinical and radiologic follow-up of these patients will be critical for determining local recurrence and the cancer-specific survival rate following renal cryoablation. Although experimental data suggest adequate healing of the cryodamaged pelvicaliceal system, central tumors still constitute a contraindication for cryoablation. In the other hand, treatment of selected posteriorly located tumors by entirely percutaneous techniques is already possible. Further development of three-dimensional ultrasound and MRI-compatible cryoprobes may allow improved imaging of the acute and chronic renal cryolesion, establishing another minimally invasive alternative for selected cases in an outpatient basis.

Research directed towards the periphery of the cryolesion, the so-called sublethal zone of destruction, is a promising avenue for future investigation. This outer 2-4 cm rim of the cryolesion is the area where some cancer cells may potentially survive lethal injury. Cryoablation causes cells to die by either apoptosis or necrosis. It has been shown that the apoptosis-inhibitor IDN-1529 protects prostate cancer cells (PC-3 cell line) from death even when exposed to temperatures ranging from  $-10^{\circ}\text{C}$  to  $-75^{\circ}\text{C}$  (51). As a corollary, it is plausible that apoptotic-activators may actually promote the death of certain freeze-tolerant cancer cells, such as those located in the peripheral, sublethal zone of a cryolesion. Indeed, Clarke et al. have already shown that canine kidney cell cultures (MDCK) treated with 5-Fluorouracil 2 days prior to freezing lost all cell viability and failed to recover. This degree of cell damage was significantly greater than the loss of cell viability induced by either freezing alone or 5-Fluorouracil alone (52). Such cryosurgical modeling takes advantage of the possible apoptosis-inducing synergistic effects of combination treatments such as radiation and chemo-

therapy regimens already employed in the treatment of certain cancers. Optimal use of such cryoadjuncts may further enhance the lethal effects of cryosurgery.

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