

### Preliminary experience with cryoablation of renal lesions smaller than 4 centimeters

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**Nephron-sparing surgical techniques represent an attractive treatment approach for small renal lesions that are limited only by potential operative morbidity. This study tests the hypothesis that an alternative strategy of in situ cryoablation of these lesions may further reduce the incidence of complications with similar efficacy. Beginning August 1996, 17 patients were enrolled in an institutional review board–approved protocol for open renal cryoablation for lesions smaller than 4 cm in diameter. The median age was 62 years (range, 35-75 years). The median preoperative lesion size was 2.0 cm (range, 1.1-4.2 cm) determined with either computed tomography or magnetic resonance imaging. A double freeze-thaw technique to  $-180^{\circ}\text{C}$  was used under direct intraoperative ultrasound monitoring.**

**The median length of follow-up was 30 months (range, 10-60 months), with 8 patients followed up for more than 20 months. The procedure was accomplished in 3 hours (range, 2.25-4.25 hours) through a 5-cm to 7-cm subcostal incision. The median blood loss was 100 mL, and the median hospital stay was 2 days (range, 2-8 days). The median intraoperative lesion size was 2.4 cm, which was not statistically different from preoperative measurements. Postoperative serum creatinine levels were unchanged except for a transient increase from 5.5 mg/dL to 7.0 mg/dL in one patient. Follow-up magnetic resonance imaging scans have demonstrated infarction and a reduction of lesion size in 15 of 16 cases. The size of one patient's mass was unchanged after 3 months.**

**Renal cryoablation via an open approach is associated with few complications and represents a viable alternative to extirpative surgical techniques. The open exposure provides an accurate assessment of the renal unit with definitive ultrasound visualization.**

**(Key words: renal cancer, cryoablation, open technique)**

Cancers of the kidney account for approximately 28,000 cancer diagnoses each year in the United States, and of these, 24,000 are renal cell carcinomas resulting in approximately 10,000 deaths annually.<sup>1</sup> Although radical nephrectomy remains the preferred treatment for localized disease, nephron-sparing surgery has also had much success. The reported 5-year cancer-specific survival rate was 100% with no postoperative recurrences in patients with unilateral stage I tumors smaller than 4 cm in diameter who were treated with nephron-sparing surgery.<sup>2</sup> Studies have also shown that radical nephrectomy and nephron-sparing surgery provide equally effective curative treatment for patients who present with a single, small (<4 cm), and clearly localized renal cell carcinoma.<sup>3</sup>

Because these procedures are associated with significant morbidities, newer modalities are needed to provide local tumor eradication while preserving maximal renal function. Cryoablation, or the in situ destruction of tissue by the application of freezing temperatures, has been used with success in the treatment of other visceral malignancies such as hepatic and prostate cancers. Experience with renal cryoablation has been limited to date and most of the data are obtained from animal models. Because the liver and kidney are similar in relative amount of blood flow and tissue density, experience with hepatic cryoablation may provide insight into potential benefits of renal cryoablation. Based on experimental evidence and clinical experience, we believe that cryoablation of renal tumors with use of intraoperative ultrasound monitoring may be a safe and effective means of providing local tumor eradication while preserving maximal functional renal parenchyma. We present our preliminary data for a phase I/II clinical trial for cryoablation of renal lesions smaller than 4 cm.

#### Materials and methods

A total of 17 patients (11 men, 6 women) were enrolled in the study beginning August 1996. Median age was 62 years (range, 35-75 years). One patient was withdrawn from the study because he was found to have extensive disease intraoperatively and subsequently underwent a radical nephrectomy. Institutional review board (IRB) approval for a phase I/II clinical trial was obtained after the initial experience with four patients. Written informed consent was also obtained on all patients. Patient demographics and lesion characteristics are

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Table 1  
Demographics of Patients Treated With Cryoablation (N = 17)

Patient	Sex	Age, y	Preop* mass	Size, cm		Serum creatinine level, mg/dL		No. of cryo- probes	Location (pole)	Side
				Preop	Intraop	Preop	Postop			
1	M	52	Solid	3.0 × 4.0	2.3 × 3.1	2.5	2.3	2	Mid†	Right
2	M	62	Solid	2.5 × 2.5	2.5 × 3.0	1.0	1.0	2	Mid	Right
3	M	62	Cystic	2.0 × 1.8	2.4 × 1.8	0.7	0.8	1	Mid	Right
4	F	64	Solid	3.5 × 3.6	3.8 × 3.2	1.0	1.0	3	Lower†	Left
5	M	70	Solid	2.2 × 2.2	1.2 × 1.0	4.2	4.8	3	Lower†	Right
6‡	M	64	Solid	2.0 × 2.0	2.2 × 2.1					
7	M	75	Solid	4.2	4.3 × 4.7	0.9	0.9	4	Upper	Left
8	M	47	Solid	2.0	1.8 × 1.7	1.2	1.2	1	Lower	Right
9	M	35	Cystic	2.0 × 2.0	3.0 × 3.0	0.8	0.9	1	Mid§	Right
10	F	46	Solid	2.2	2.3 × 3.3	0.7	0.5	1	Upper§	Left
11	M	69	Solid	1.5	2.1 × 1.6	0.8	0.8	1	Upper§	Right
12	F	56	Cystic	2.0 × 2.1	2.0 × 1.5	0.6	0.5	1	Lower	Right
13	M	39	Solid	3.0	3.0 × 3.0	1.5	1.0	1	Lower§	Left
14	F	70	Solid	1.9	1.8 × 1.9	0.5	0.6	1	Lower§	Right
15	M	67	Cystic	1.5 × 2.0	1.5 × 2.4	0.8	0.7	1	Lower	Left
16	M	37	Solid	2.0	3.0 × 2.0	5.5	7.0¶	1	Mid§	Right
17	F	69	Solid	1.0 × 1.0	1.0 × 1.0	1.5	1.6	1	Lower	Right

\*Preop indicates preoperatively; Intraop, intraoperatively; Postop, postoperatively.

†Solitary kidney.

‡Treated with radical nephrectomy because of appearance of extracapsular extension of disease.

§Contralateral lesion.

¶Serum creatinine level within 1 week postoperatively. No long-term deterioration of renal function has been observed.

listed in *Table 1*. Median preoperative lesion size as measured by magnetic resonance imaging (MRI) or computed tomography (CT) scan was 2.0 cm.

The surgical protocol involved a 5-cm to 7-cm subcostal transperitoneal incision to enter the retroperitoneum. All patients underwent excision of Gerota's fascia and the perirenal tissue surrounding the lesion and all had excised samples sent for histopathologic examination. A regional lymphadenectomy was done in two patients because of concern for nodal enlargement. Beginning with patient 5, a 22-mm Microvasive biopsy gun (Boston Scientific Corp, Natick, Mass) was used to obtain three biopsy specimens or a needle aspiration was done if the lesion was a mass or a complex cyst, respectively, under continual sonographic monitoring. The kidney was then completely mobilized such that a cryoprobe could safely be placed

into the lesion. Once the kidney was mobilized, intraoperative renal ultrasound examination was done by use of a 7.5-MHz sterile, linear-array, T-shaped ultrasound probe to isolate the lesion. One to four cryoprobes, either 3 mm or 8 mm in diameter, were then placed perpendicularly into the lesion, and the position of the probe was verified sonographically. The stick temperature was  $-100^{\circ}\text{C}$  in cases involving multiple probes. For those with single probes, the freezing course was immediately to  $-180^{\circ}\text{C}$ . The lesion was then frozen to  $-180^{\circ}\text{C}$ , underwent a thaw phase to  $0^{\circ}\text{C}$ , and was then refrozen to  $-180^{\circ}\text{C}$ . Lesions were frozen for 3 to 10 minutes. Careful attention was given via ultrasound monitoring to be sure the "ice-ball" encapsulated the entire lesion. A 2-mm to 3-mm margin extended beyond the border of the lesion. In two patients in whom a single probe was used, it was necessary to readjust the

probe after the first freeze cycle to fully encompass the lesion. After the thaw phase, the cryoprobe was removed and the tract was packed with thrombin soaked in absorbable gelatin film. Surgicel (Ethicon, Somerville, NJ) was then sutured into the capsule directly over the probe insertion site. Intercede (Johnson & Johnson, New Brunswick, NJ) was placed over the kidney to prevent adhesions should a repeated operation at a later date be necessary. Next, the wound was irrigated with saline solution and closed in the usual fashion. No drains were used in any patient.

Patients who underwent cryoablation before IRB approval received follow-up MRI imaging in 3 months. Patients who underwent cryoablation after IRB approval received MRI imaging on postoperative day 2, before discharge to home. Follow-up studies were scheduled at 3 months, 6 months, 1 year, and yearly thereafter.

## Results

The median intraoperative lesion measured via ultrasound was 2.4 cm in diameter, which was not statistically different from preoperative measurements. Median operative time was 3 hours (range, 2.25-4.25 hours), with a median blood loss of 100 mL (range, 25-1000 mL). Fourteen patients had 3-mm-diameter cryoprobes, and two patients required 8-mm-diameter cryoprobes because of the larger-sized lesion. Serum chemistry tests were done both preoperatively and postoperatively (Table 1). Two patients were noted to have preoperative renal insufficiency without further deterioration after the cryoablative procedure (Table 1).

Median length of hospital stay was 2 days (range, 2-8 days). Patients were given patient-controlled analgesia for 24 to 72 hours, then switched to oral pain medications. All patients were started on an oral diet postoperative day 1 and advanced as tolerated.

Follow-up data are available for 17 patients, with a median follow-up of 30 months (range, 10-60 months). One patient died 8 months later secondarily to other multiple comorbidities, and one patient was switched to an open radical nephrectomy secondarily to extensive disease. Magnetic resonance imaging done on nine patients 2 days postoperatively revealed changes consistent with infarction in the region of the cryoablated tissue. Two of these patients were found to have some contrast enhancement within the cryoablated region, but outpatient follow-up imaging studies revealed resolution of the contrast enhancement; these regions had changes consistent with hemorrhagic necrosis. The hemorrhagic regions correspond to the previously ultrasound-identified mass intraoperatively. Patients in whom MRI was done for more than 6 months had continual reduction of the lesion and scar formation. There was no evidence of disease recurrence in the kidney. Histopathologic examination of samples revealed renal cancer in 7 (54%) of 13 patients. Aspiration cytology of complex cysts revealed malignancy in 2 (50%) of 4 patients. The remaining patients had benign lesions of the kidney. It should be noted,

Table 2  
Complications of Cryoablation of Renal Cell Carcinoma (N = 17)

Complication	No. of patients
<b>Intraoperative</b>	
Capsular fracture	2
<b>Immediate postoperative</b>	
Diarrhea	1
Congestive heart failure	1
Fever	3
Intravenous infiltration	1
Ileus	1
<b>Late postoperative</b>	
Wound separation	2
Syncope	1

however, that all patients had radiologic evidence of either a solid renal mass or a complex renal cyst (Bosniak class III or IV), which would classically be treated with either a radical nephrectomy or partial nephrectomy.

Complications are depicted in Table 2. Most important, intraoperative complications included two patients in whom capsular fractures developed during the freeze cycle, which resulted in significant bleeding that was controlled with thrombin soaked in absorbable gelatin film packing. In addition, these fractures were associated with the use of multiple probes; bleeding was not clinically significant when single probes were used. Postoperatively, three patients had fevers that spontaneously resolved after evaluation with negative cultures. No source for infection was identified, and no further sequelae resulted. Throughout the series, no patient required any blood products or transfusions.

## Discussion

The widespread use of imaging studies including MRI, CT scan, and ultrasound for unrelated symptoms has caused an increase in the number of small renal lesions being detected. The incidence appears to be increasing at a rate of 1.5% to 2% each year. Of all renal tumors smaller than 3 cm in diameter, 96.7% were discovered incidentally and 77.4% were initially detected by CT scan or ultrasound. Santiago<sup>4</sup> has also shown that the incidence of renal cancer in indeterminate cysts is 14.3% (5 of 35).

Radical nephrectomy is the preferred treatment modality in patients with localized renal cell carcinoma and a normal contralateral kidney. However, nephron-sparing procedures have also been done with good long-term results in patients in whom the lesion is small (<4 cm in diameter). Nephron-sparing surgery or partial nephrectomy is the preferred treatment when localized renal cell carcinoma is present bilaterally or in a patient with an anatomic or functional solitary kidney.

## BRIEF REPORT

In such patients, this procedure allows complete surgical excision of the primary tumor, while preserving the maximal amount of renal parenchyma to obviate the need for immediate dialysis. Local recurrence rates are approximately 7% to 10%, and disease-specific 5-year survival rates are 96% to 100%. Although renal parenchyma is preserved with this type of surgery, the morbidity from nephron-sparing surgery can be significant and includes hemorrhage, formation of urinary fistula, ureteral obstruction, acute renal failure, perirenal abscess, and splenic injury.<sup>5</sup>

Renal cryoablation represents an advancement in nephron-sparing surgery that has further decreased the morbidity of this procedure and is therefore a viable alternative for the management of small renal lesions suspected to be cancer. It has been extensively used for years in treating gastrointestinal metastatic lesions to the liver with satisfactory results. It is based on the principle of rapid freezing, slow thawing, and repetition of the freeze/thaw cycle to disrupt cellular membranes and cause cellular death. Several studies have shown that a freeze temperature to at least  $-20^{\circ}\text{C}$ , followed by a thaw phase, results in cellular death.<sup>6,7</sup> In a 10-year randomized, prospective study comparing cryogenic and conventional surgery for hepatic metastases, patients who had undergone cryosurgery had higher survival rates.<sup>8</sup> In addition, data on single freeze cycles have shown necrosis of intralesional hepatic parenchyma without added benefit of repeated freezing. Finally, Riley et al<sup>9</sup> have shown that cryoablation of the liver has not been related to an increased risk of infection.

Because the results of hepatic cryosurgery have been encouraging, this new technology has been applied to prostatic lesions and, more recently, to small renal lesions suspected to be cancer. Preliminary data for renal lesions in both human and animal studies are encouraging. Cozzi et al,<sup>10</sup> using a sheep model, have concluded that cryosurgery is safe and can achieve focal renal necrosis with preservation of renal tubules. Studies have also shown that at  $-20^{\circ}\text{C}$ , only 2 mm to 3 mm internal to the "iceball" is affected. Finally, Delworth et al<sup>11</sup> have shown that selected renal lesions can be treated safely and with minimal loss of renal function.

Although we encountered minor complications during our study, the only attributable complication directly related to the use of the cryoprobe was bleeding from two fractures within the renal capsule during the freeze cycles. The bleeding was controlled with topical absorbable gelatin film and thrombin. However, it should be noted that both of these fractures resulted while we were using more than one cryoprobe during our initial experience. After refinement of our technique, which included using only a single probe, we no longer encountered significant capsular fractures. There was no mortality due to the cryoablation, and no patients required a blood transfusion.

Our approach to renal cryoablation specifically included the open technique rather than a laparoscopic approach pri-

marily for technical reasons. Mobilization and exposure of the kidney is vital to the freezing process. Lesions that are peripherally or posteriorly located would be difficult to treat laparoscopically because of the potential technical difficulty of probe placement. In addition to location, size is also a factor because larger lesions would be more difficult to monitor sonographically. Because accurate visualization of the freezing process is paramount to the success of the procedure, the cryoprobe itself could potentially risk not treating the entire lesion or not fully encapsulating the treated lesions. With the open approach, complete mobilization and access to any part of the kidney can be obtained along with continual ultrasound monitoring, leaving minimal risk for residual disease.

We arbitrarily elected to treat lesions that were only 4 cm or smaller because we thought that these lesions could be adequately treated with little fear of undertreating the lesion. Larger lesions are more technically difficult to treat because the "iceball" will not encompass the entire lesion, necessitating the need for multiple probes and multiple freeze cycles or the use of a single probe with adjustment of the probe during each subsequent freeze. The cryoprobe not only increases the risk for capsular fractures and subsequent bleeding, but also increases the risk of not treating all of the cancer and leaving residual disease within the kidney.

Follow-up MRI studies have demonstrated infarction and a reduction of lesion size in 15 of 16 cases. Initially, two patients had contrast-enhancing areas at the cryosurgical site on postoperative day 2. These areas, however, were found to be without contrast enhancement on repeated scans 3 months later. One patient with a preoperative complex cystic mass, negative for malignancy, continues to have a persistent mass on follow-up MRI at 3 months. The remainder of patients, with longer follow-up, showed resolution of the lesion with scar tissue formation. A more complete representation of local recurrence should become available with longer follow-up.

### Comments

Cryosurgery has been used successfully in treating liver lesions for several years, and the encouraging results have led to its recent use in renal lesions. To our knowledge, our series represents the largest number of patients and the longest follow-up data available for human renal cryosurgery. This procedure is well tolerated and associated with minimal morbidity. For lesions that are 4 cm or less, the short-term data appear promising, with no evidence of recurrence spanning 60 months of follow-up. The minimal morbidity associated with its use makes cryoablation a viable alternative to nephron-sparing surgery for small lesions; however, long-term data are necessary to evaluate its efficacy.

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