

Percutaneous Renal Cryoablation After Partial Nephrectomy: Technical Feasibility, Complications and Outcomes

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Purpose: Treatment of locally recurrent or de novo tumors in the ipsilateral kidney after partial nephrectomy represents a management dilemma. Percutaneous renal cryoablation offers a minimally invasive treatment option in such cases. We review our single institution experience with percutaneous cryoablation of renal tumors after partial nephrectomy for technical feasibility, complications and outcomes.

Materials and Methods: Between March 2003 and January 2012, 48 patients underwent percutaneous cryoablation for the treatment of 68 ipsilateral renal tumors after previous partial nephrectomy. Oncologic outcomes, complications (Clavien-Dindo classification system) and renal function were evaluated.

Results: Median maximal diameter of the treated renal tumors was 2.5 cm (range 1.2 to 5.4). All cryoablation procedures were considered technically successful. Of the 54 biopsy proven or suspected renal cell carcinomas with 3 or more months of computerized tomography/magnetic resonance imaging followup after cryoablation (median 19, range 3 to 61), 5 cases (9.3%) had local tumor recurrence. Major (grade 3 or greater) complications developed after 3 (5.7%) cryoablation procedures and there were no perioperative deaths. Median change in patient estimated glomerular filtration rate after renal cryoablation was -1.5 ml per minute. No patients required dialysis in the perioperative period, while 2 with stage 4 chronic kidney disease at the time of ablation became dialysis dependent at 5 and 23 months after treatment, respectively.

Conclusions: Percutaneous renal cryoablation after ipsilateral partial nephrectomy is technically feasible, has a low rate of major complications, provides relative preservation of renal function and demonstrates acceptable short-term oncologic outcomes in this challenging population.

Key Words: kidney, ablation techniques, outcome assessment, treatment outcome

PARTIAL nephrectomy represents an excellent treatment option for patients with small renal tumors, with low associated complication rates as well as exceptional oncologic and renal functional outcomes.^{1,2} Although rare, locally recurrent or de novo tumors may arise in

the ipsilateral renal unit. Treatment of these tumors is challenging since repeat renal exposure and partial nephrectomy are technically difficult, and associated with relatively higher perioperative complications, renal loss and local tumor recurrence rates.^{3,4}

Abbreviations and Acronyms

CT = computerized tomography
eGFR = estimated glomerular filtration rate
MRI = magnetic resonance imaging
RCC = renal cell carcinoma

Accepted for publication October 22, 2012.
Study received institutional review board approval.

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Percutaneous cryoablation has been found to be an effective and safe treatment option for select patients with small renal tumors.⁵⁻¹⁰ The long-term efficacy of this technique has yet to be established. However, percutaneous cryotherapy does represent an attractive option for the management of locally recurrent or new ipsilateral renal tumors after partial nephrectomy. With this approach the need for repeat renal exposure and the potential associated complications of surgical dissection in a previously operated field are avoided. To our knowledge, percutaneous cryoablation in such patients has not been previously reported. Therefore, we reviewed our institutional experience with percutaneous cryoablation of renal tumors after partial nephrectomy for technical feasibility, complications and outcomes.

MATERIALS AND METHODS

Study Design and Population

This study was approved by the Mayo Clinic institutional review board. Retrospective review of our renal cryoablation database demonstrated that 378 patients underwent 399 separate cryoablation procedures for the treatment of 430 renal masses between March 2003 and January 2012. Of these patients 48 (12.7%) were treated for 1 or more new or locally recurrent tumors in the same kidney that had been previously treated with partial nephrectomy. Prior excised tumor pathology for these patients is detailed in table 1. Notably 5 of the 77 (6.5%) originally resected RCCs had positive surgical margins. These 48 patients who underwent 53 separate cryoablation procedures for the treatment of 68 renal tumors represented the study population.

Cryoablation Procedure

Percutaneous renal cryoablation was performed as previously described.^{5,9,10} All patients underwent formal consultation at the Department of Urology before treatment. All renal masses were treated in a single cryoablation session by 1 of 5 ablation radiologists with the patient under general anesthesia. No staged ablation treatments were performed. The Endocare cryoablation system (Endocare Inc., Irvine, California) and Perc-24 cryoprobes were used in all cases. A median of 2 (range 1 to 5) cryoprobes were placed in the tumors using ultrasound

and/or CT guidance. A typical freeze-thaw-freeze cryoablation cycle was performed for the treatment of each mass, with a duration of freezing based on coverage of the tumor by the ice ball using CT monitoring every 2 to 4 minutes. Median freeze times were 10 minutes (range 4 to 14) for the first freeze and 8 minutes (range 4 to 12) for the second freeze. An approximately 5-minute passive thaw was performed between the 2 freeze cycles. After the second freeze an approximately 10-minute active thaw was performed before removal of the cryoprobes.

Core biopsies of the masses were obtained from 42 of 68 (61.7%) renal masses at the time of ablation using an 18 gauge × 2 cm biopsy device (Bard Monopty®). The ablation was performed immediately after the biopsy, before biopsy review. The 26 tumors that were not biopsied were assumed to represent malignancy based on imaging appearance and patient history of 1 or more previously resected, biopsy proven RCCs in the ipsilateral kidney.

Hydrodisplacement was required in 17 of 53 (32.1%) procedures to protect the adjacent bowel using the technique described by Bodily et al.¹¹ Externalized ureteral stents were placed and pyeloperfusion was performed during 9 (16.9%) procedures due to proximity of the ureter using a technique similar to that reported by Cantwell et al.¹²

Followup and Outcome Analysis

As adapted from the International Working Group on Image-Guided Tumor Ablation,¹³ technical success was defined as extension of the ice ball at least 0.5 cm beyond the tumor margins on monitoring noncontrast CT performed during the procedure and/or extension of the ablation zone beyond the tumor margins on contrast enhanced CT or MRI performed within 3 months of the ablation. Contrast enhanced CT or MRI of the abdomen was obtained within 24 hours of the ablation after 45 of the 53 (84.9%) ablation procedures. Local tumor recurrence was defined as an enhancing or enlarging soft tissue nodule within or immediately adjacent to the ablation zone on contrast enhanced CT or MRI performed 3 or more months after ablation. Followup CT or MRI beyond 3 months was available for evaluation of 63 of 68 (92.6%) treated renal masses (fig. 1).

Complications were assessed using the revised Clavien-Dindo classification system.¹⁴ Any grade 3 or greater complication was considered a major complication. Renal function outcomes were assessed by glomerular filtration rate estimated from serum creatinine levels using the Modification of Diet in Renal Disease equation.¹⁵ All patients were treated by the Department of Urology after the ablation procedure, including overnight observation.

Statistical Methods

Standard descriptive statistics were used to summarize the sample data. Overall survival was estimated from the date of cryoablation to the date of last clinical followup or date of death, whereas local recurrence-free survival was estimated from the date of ablation to the date of last imaging followup or when followup imaging detected a locally recurrent tumor. The product limit (Kaplan-Meier) estimator was used to estimate each survival function after ablation. Survival curves were displayed with a step-

Table 1. Original excised tumor pathology

	Grade 1	Grade 2	Grade 3	Grade 4	Not Specified	Totals
No. RCC:						77
Clear cell	5	40	8	0	4	57
Papillary	3	12	1	0	0	16
Mixed	1	1	0	0	0	2
Chromophobe	1	1	0	0	0	2
No. oncocytoma						13
No. angiomyolipoma						3

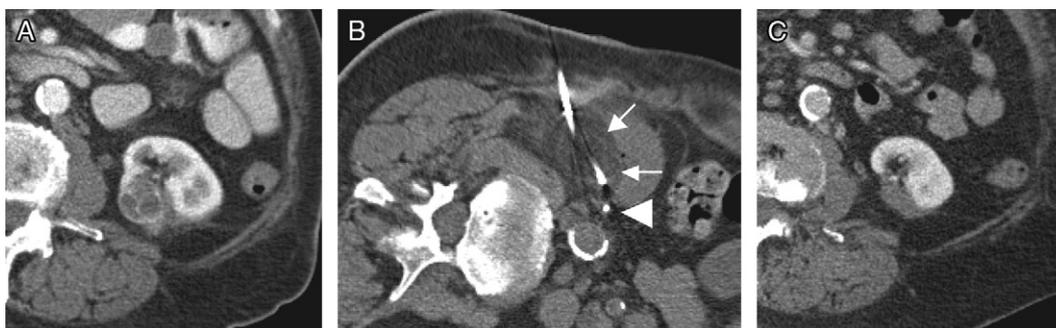


Figure 1. Renal cryoablation imaging findings. *A*, contrast enhanced CT shows 2.5 cm biopsy proven RCC recurrence in left partial nephrectomy bed. *B*, noncontrast CT during cryoablation demonstrates low attenuation ice ball (arrows) surrounding cryoprobes and completely encompassing target mass. Retrograde pyeloperfusion was performed via externalized ureteral stent (arrowhead) during procedure to protect adjacent ureter. *C*, contrast enhanced CT 46 months after cryoablation shows small post-ablation scar but no evidence of recurrent tumor.

wise function and a log normal function with a 95% CI. Survival analysis was performed using JMP® version 9.

RESULTS

Patient Demographics

Of the 48 study patients 33 were male and 15 were female. Median patient age at cryoablation was 67 years (range 29 to 86). Twelve patients (25.0%) had more than 1 tumor treated in a single cryoablation session. von Hippel-Lindau disease was present in 6 patients (12.5%). Eleven patients (22.9%) had a solitary kidney due to contralateral radical nephrectomy. There were 42 patients (79.2%) with a history of RCC, 5 with a history of only prior renal oncocytomas and 1 with a previously resected angiomyolipoma. Of note, 4 patients with previously resected RCCs also had a history of resected oncocytomas. Six patients (12.5%) had a history of previously resected RCC metastases or radiographic evidence of oligometastatic disease at renal cryoablation.

Of the 48 study patients 39 (83.1%) had significant medical comorbidities which contributed to the decision to undergo cryoablation rather than repeat partial nephrectomy. These patients included 13 (27.1%) with cardiac disease and 10 (20.8%) with chronic kidney disease (stage 3 or greater).

There were 47 (97.9%) patients who had undergone a single prior ipsilateral partial nephrectomy, while 1 (2.1%) patient had undergone 2 prior ipsilateral partial nephrectomies. Median time from original ipsilateral partial nephrectomy to renal cryoablation was 58 months (range 2 to 312).

Renal Tumor Characteristics

Median size of the cryoablated renal tumors was 2.5 cm (range 1.2 to 5.4). Core biopsies were performed in 42 of 68 (61.7%) renal masses (table 2). Of these 42 biopsies 12 (28.6%) showed benign tumors and

the remainder were malignant or nondiagnostic. A total of 26 (38.2%) tumors were not biopsied. All 38 tumors with no biopsy performed or nondiagnostic biopsy were presumed to represent recurrent RCC due to imaging appearance and patient history of previously resected RCC in the ipsilateral kidney.

Imaging evaluation was challenging, especially in patients who had undergone prior multifocal partial nephrectomy. However, only 3 of 68 (4.4%) cryoablated renal tumors were considered local tumor recurrence at the site of prior surgery. The remaining cryoablated renal masses were believed to represent de novo tumors in the ipsilateral kidney.

Cryoablation Results and Complications

All cryoablations were considered technically successful with no residual tumor identified on immediate post-ablation imaging. Median length of hospital stay was 1 day (range 0 to 5). Major complications occurred after 3 of 53 (5.7%) cryoablation procedures. A small intraparenchymal renal artery pseudoaneurysm developed in 1 patient, discovered on 3-month CT followup and treated with coil embolization. Ureteral obstruction due to clots developed in another patient with a solitary kidney, requiring ureteral stent placement. The third patient with von Hippel-Lindau disease and prior perioperative strokes had an

Table 2. Ablated tumor pathology based on 42 biopsies

	Grade 1	Grade 2	Grade 3	Grade 4	Not Specified	Totals
No. RCC:						21
Clear cell	3	7	3	—	4	17
Papillary	1	—	—	—	3	4
No. oncocytoma						9
No. angiomyolipoma						1
No. nondiagnostic						11

acute cerebral infarction the day after the procedure. There were no procedure related deaths.

Renal Function Outcomes

Median eGFR before cryoablation was 58.9 ml per minute (range 9.8 to 112.5). eGFR was also obtained within 2 weeks after 48 of the 53 (90.6%) cryoablation procedures. Median change in patient eGFR after renal cryoablation was -1.5 ml per minute (range -52.2 to 9.7). No patients required dialysis in the immediate peri-ablation period. Two patients with stage 4 chronic kidney disease at the time of ablation eventually experienced progression to permanent dialysis dependence at 5 and 23 months after treatment, respectively.

Oncologic Outcomes

Imaging followup of 3 months or longer after cryoablation (median 19, range 3 to 61) was available for 54 of 58 (93.1%) biopsy proven or suspected RCCs (not shown to be benign by biopsy) in 42 patients. There were 5 (9.3%) cases of local tumor recurrence at 5, 6, 8, 19 and 32 months after ablation, respectively, in 5 different patients. Two patients with local tumor recurrence underwent repeat cryoablation for biopsy proven RCC, and neither patient has evidence of repeat tumor recurrence at 3 and 17 months of followup, respectively. The other 3 patients with local tumor recurrence after cryoablation were observed.

Of 42 patients who underwent cryoablation for a biopsy proven or suspected RCC 2 (4.8%) underwent subsequent cryoablation procedures to treat de novo ipsilateral renal tumors. New metastatic disease developed in 2 (4.8%) other patients during followup. Biopsy proven subcutaneous and hepatic metastases

developed in 1 of these patients, first seen on MRI 17 months after ablation. A solitary biopsy proven hepatic metastasis developed in the other patient and was identified on MRI 19 months after cryoablation.

Subgroup analysis of the 21 cryoablated, biopsy proven RCCs in 19 patients demonstrated 2 (9.5%) local tumor recurrences. None of these 19 patients had de novo ipsilateral renal tumors or new metastatic disease.

Survival

Kaplan-Meier curves depict overall survival (fig. 2, A) and local recurrence-free survival (fig. 2, B) in the 42 patients with biopsy proven or suspected recurrent RCC after partial nephrectomy. Of the patients with biopsy proven or suspected recurrent RCC 4 (9.5%) died during the course of followup. Estimated overall survival at 1, 3 and 5 years after cryoablation was 95% (CI 86–99), 89% (CI 75–96) and 84% (CI 66–94), respectively. None of the patients died as a direct result of metastatic RCC, but 1 patient did have known local tumor recurrence and metastatic disease at the time of his death. Estimated local recurrence-free survival at 1, 3 and 5 years after cryoablation in the 42 patients with biopsy proven or suspected recurrent RCC was 93% (CI 83–98), 81% (CI 63–93) and 73% (CI 48–90), respectively.

DISCUSSION

The optimal treatment of patients with recurrent or de novo ipsilateral tumors after partial nephrectomy remains to be established. While an excellent option to achieve oncologic control, radical (completion) ne-

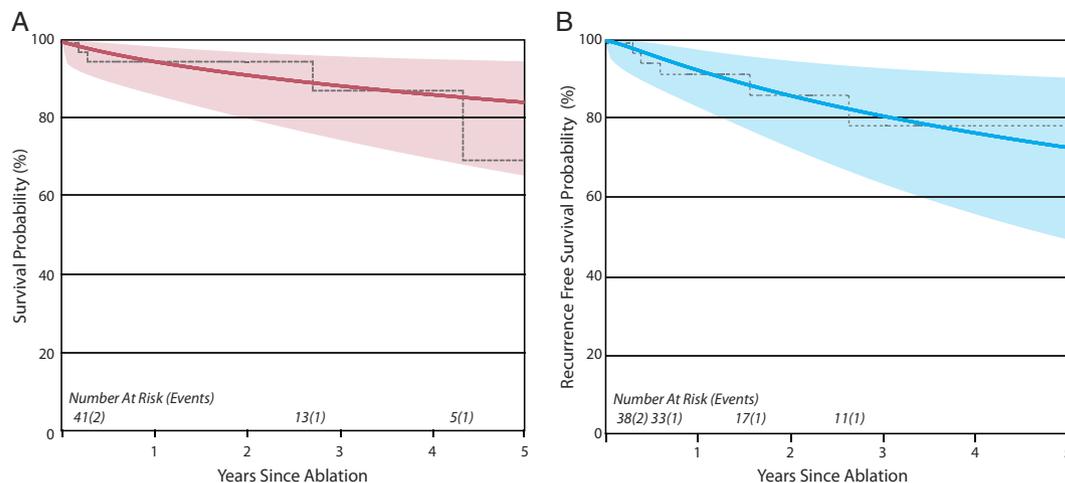


Figure 2. Kaplan-Meier estimates of overall survival (A) and local recurrence-free survival (B) after renal cryoablation in patients with biopsy proven or suspected RCC. Survival curves are displayed as linear step function (broken line) and as log normal approximation (colored line) with 95% CI (shaded region). Number of patients at risk is shown for each point associated with significant event (mortality or local recurrence) in step function.

phrectomy nevertheless puts patients at risk for chronic kidney disease, which in turn has been associated with increased rates of cardiovascular events, hospitalization and death.^{16,17} Repeat partial nephrectomy also represents a treatment option. However, this approach is technically challenging, and has been associated with higher complication and recurrence rates.^{3,4}

The American Urological Association consensus guidelines now include percutaneous ablation as a treatment option for high surgical risk patients with T1a (4 cm or smaller) renal tumors.¹⁸ High risk surgical patients are generally considered to be those with significant medical comorbidities and/or the elderly. Johnson et al reported a major perioperative complication rate of 19.6% in 51 cases of repeat partial nephrectomy, including a mortality rate of 1.9%.³ Liu et al reported a 52% perioperative complication rate, 12% renal loss and 4% mortality in 25 patients treated with repeat partial nephrectomy on a solitary kidney.⁴ Magera et al also reported a major perioperative complication rate of 28% in treatment of 18 patients with repeat nephron sparing surgery.¹⁹ Given these reported results, patients undergoing repeat partial nephrectomy could also be considered high surgical risk. In contrast, percutaneous cryoablation after ipsilateral partial nephrectomy does not pose any specific additional technical challenges compared to renal mass cryoablation in the naïve kidney. This is reflected in the low major complication rate of 5.7% noted in this study. These results are comparable to the 7.7% overall major complication rate reported by Atwell et al in a review of 311 percutaneous renal cryoablations.²⁰

Preservation of renal function is an important consideration in patients with renal neoplasms, particularly after partial nephrectomy. Johnson et al reported a median decrease in creatinine clearance of 10.7 ml per minute after repeat partial nephrectomy, and 3 of 47 (6.4%) patients required dialysis in the perioperative period, 2 of whom required long-term dialysis.³ In the current study we found a median decrease in eGFR of only 1.5 ml per minute. No patients required dialysis in the perioperative setting, although 2 patients, both with preexisting stage 4 chronic kidney disease, eventually had progression to long-term dialysis.

In patients with recurrent or de novo renal tumors after partial nephrectomy, oncologic control remains paramount to assessing treatment efficacy. In a comparable study Johnson et al reported a 6.4% rate of new metastatic disease in their cohort of 47 patients undergoing repeat partial nephrectomy with 19.6% requiring reoperation for local recurrence or de novo renal tumor during a median followup of 56 months.³ Likewise, Liu et al reported a 5% rate of new metastatic disease, and 38% of cases

required reoperation for local recurrence or de novo renal tumors during a median followup of 57 months.⁴ Allowing for differences in the duration of followup, our results are similar to these published studies. That is, in patients with biopsy proven or suspected RCC and at least 3 months of imaging followup after cryoablation, we noted a 9.3% rate of local tumor recurrence and new metastatic disease in 4.8% of patients during a median followup of 19 months. As expected, given the complexity of the patients' tumor history in this study, the oncologic outcomes are inferior to previously reported renal cryoablation results. For example, in a recent study from our institution on cryoablation in 116 cases of solitary sporadic biopsy proven RCC there was 1 (0.9%) technical ablation failure, and of the 80 cases with 3 or more months of imaging followup (median 21 months) only 1 (1.1%) had local tumor recurrence and none had metastatic disease.²¹

Percutaneous renal ablation can be performed with patients under varying levels of anesthesia. We believe that the benefits of general anesthesia outweigh the potential risks. Particularly in a medically complicated patient population, general anesthesia limits hemodynamic and respiratory fluctuations that might occur during these occasionally lengthy procedures. The collaboration with anesthesia allows the proceduralist to focus only on the technical aspects of the procedure, without worrying about patient factors such as pain control and patient movement. A drawback of this practice is that our patients are monitored overnight in the hospital after general anesthesia, while renal cryoablations performed elsewhere with local and/or moderate sedation can often be done in an outpatient setting.

In our practice core renal mass biopsy is performed immediately before ablation, after placement of the cryoprobe. Since we believe it is often difficult to completely exclude malignancy with core biopsy,^{22,23} we perform ablation of any solid renal mass regardless of pathology results. Although the accuracy of renal mass biopsy continues to improve, we still have a relatively high nondiagnostic biopsy rate (26% in this study) and the role of percutaneous biopsy for the treatment of small renal masses remains controversial.²⁴

We acknowledge that there are major limitations of this retrospective study. A matched control group was not possible due to the significant heterogeneity and complexity of patient and tumor characteristics in our study population. In addition, patients in this series were treated based on imaging findings after partial nephrectomy and biopsy was performed inconsistently due to known history of RCC. Only 21 of the treated tumors (in 19 patients) were biopsy confirmed RCC, which considerably confounds the evaluation of oncologic outcomes. However, local tumor recurrences in these 19 patients were almost iden-

tical to those in our larger group of patients with known or suspected RCC. Finally, followup in this study was considerably shorter than in the comparison repeat partial nephrectomy studies, and it is likely that with longer followup, additional local tumor recurrence, de novo RCCs and/or new metastatic disease will develop in our patients treated with cryotherapy.

CONCLUSIONS

Percutaneous renal cryoablation is a viable treatment alternative for patients with ipsilateral recurrent tumors after partial nephrectomy. It is associated with a low complication rate, minimal decrease in renal function and acceptable short-term oncologic outcomes in this otherwise difficult to treat patient cohort.

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