Percutaneous cryoablation for recurrent low grade renal cell carcinoma after failed nephron-sparing surgery

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Introduction: *Partial nephrectomy has a 3%-4% incidence of local treatment failure. This study is to present a series of percutaneous cryoablation for locally recurrent renal cell carcinoma after partial nephrectomy.*
Materials and methods: *Five consecutive patients were referred to our quarternary center's multidisciplinary Small Renal Mass (SRM) Center for assessment after failure of partial nephrectomy. Tumor size and location was noted. CT-guided cryoablation was performed using an argon/helium-based system (Healthtronics, Austin, Texas, USA). Patients were admitted overnight for observation. Patients were followed with serial imaging, laboratory tests and examination at our SRM Center. Tumor size, location, and nephrometry scores were documented for each patient.*
Results: *Four tumors were endophytic and one was exophytic. The median tumor size was 2.2 cm (1.8 cm -4.0 cm). Nephrometry scores were 8a, 7x, 4p, 6x, 7p, and 6p prior to cryoablation. Median follow up after cryoablation was 32 months (20-39 months). One patient with a 4.0 cm endophytic tumor developed a second recurrence measuring 2.9 cm 13 months following ablation, which was managed successfully with repeat cryoablation with no evidence of disease after an additional 19 months of follow up. Two patients developed self-limited hematuria which was conservatively managed. There were no other complications, and all patients remained at their pretreatment performance status.*
Conclusions: *Percutaneous cryoablation appears to be a safe and effective nephron-sparing modality for control of locally recurrent disease following partial nephrectomy. Most recurrent tumors are endophytic. One patient suffered a second local recurrence, which was managed successfully with repeat cryoablation.*

Key Words: renal cell carcinoma, cryoablation, nephrectomy, nephron-sparing surgery

Introduction

Approximately 65,150 new kidney tumors will be diagnosed in the United States in 2013.[1] The majority of these are stage IA (< 4 cm) with very high potential for cure.[1,2] Nephron-sparing surgery is the gold standard treatment with partial nephrectomy providing limited loss of renal function with disease-free survival similar to radical nephrectomy.[3-6] Techniques have evolved to include laparoscopic or robotic-assisted partial nephrectomy (LPN/RALPN), which will be labeled minimally invasive (MIS) in this manuscript. MIS is associated with a 1%-4% incidence of local treatment failure.[7] These results are similar to open partial techniques.[8] Renal cell carcinoma recurrence presents a dilemma for the treating medical team with no clear guidelines or recommendations.[8,9] Surgical options are limited: repeat partial nephrectomy has significant morbidity,[10,11] with a high probability of conversion to radical nephrectomy. Extirpation of the residual

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kidney (completion nephrectomy) increases long term cardiovascular risks compared to nephron-sparing surgery and increases the risk of renal failure.[6,12]

Percutaneous cryoablation is a nephron-sparing technique that has demonstrated excellent short term efficacy in the treatment of small renal masses, particularly exophytic masses with retroperitoneal fat serving as a thermal insulator.[2,13] The ability to generate a uniform ablation zone in a previously manipulated field containing adhesions and granulation tissue remains unknown. The purpose of this article is to report the technique and outcomes of percutaneous cryoablation in treatment of postoperative locally recurrent renal cell carcinoma.

Materials and methods

Institutional review board approval was obtained for this review. We reviewed our prospectively maintained renal cryoablation database at our NCI Designated Kimmel Cancer Center's multidisciplinary Small Renal Mass (SRM) Center which is a cooperative effort staffed by urologic oncology and interventional radiology. Of the 79 patients treated since July 2008, five were referred for local recurrence after partial nephrectomy. Three were female and two were male with a median age of 69.5 (range 59 yrs-85 yrs). All patients had either possible residual disease or recurrence in the surgical bed based on follow up imaging. Two patients had positive margins from their original surgery. Four tumors had an intra-parenchymal location and one was exophytic. Nephrometry scores prior to cryoablation are found in Table 2. Table 1 shows further patient disease details and their initial surgical interventions. Patient 3 had undergone an open radical nephrectomy on the right side for an 11 cm tumor at the same time as the partial nephrectomy on the left for a 4 cm tumor.

Percutaneous cryoablation was performed with conscious sedation under computed tomography (CT) and CT fluoroscopic guidance using an argon/helium-based system (Healthtronics, Austin, Texas, USA) in all patients. Endocare 2.4 Cryocare Probes were used in all procedures. The number of cryoprobes used was based on maximal tumor diameter: two needles were used for masses < 2 cm diameter and an additional needle for each additional cm diameter. Median number of needles was 2.7 (range 2-4). Two 10-minute freeze cycles were performed separated by a 5-minute active thaw with helium. Following the second freeze cycle, a 7-minute active thaw was performed followed by 2 minutes of passive thawing. Needles were removed when the needle thermistors were above 20 degrees Celsius.

TABLE 1. **Baseline characteristics of the five patients**

Patient #	Age @ cryo	Sex	BMI kg/m^2	NSS surgical technique	Tumor location	Stage	Nephrometry score	Tumor size	Tumor histopathology	Operative margins
1	57	F	37	Open PN	Lower pole (solitary kidney)	T1a	8a	2.2 cm	Clear cell Fuhrman Grade 2	Deep margin positive
2	85	F	30	RALPN (transperitoneal)	Interpolar	T1a	7x	2.2 cm	Clear cell Furhman Grade 2	Deep margin positive
3	67	M	33	Open LPN	Interpolar (solitary kidney)	T1a	4p	2.3 cm	Clear cell Grade na	Negative
4	64	F	39	HALPN (transperitoneal)	Upper pole	-	6x	1.8 cm	Benign cortical cyst	Negative
5	71/ 73	M	45	RALPN (transperitoneal)	Interpolar/ upper pole	T1a	7p	4.0 cm	Mixed CC and chromophobe	Negative

NSS = nephron-sparing surgery; BMI = body mass index; PN = partial nephrectomy; RALPN = robotic-assisted laparoscopic partial nephrectomy; HALPN = hand-assisted laparoscopic partial nephrectomy; CC = clear cell; na = not available

TABLE 2. **Tracked outcomes for the patient group**

Patient #	Charlson Comorbidity index	Disease-free interval from surgery	Tumor recurrence location	Iceball size (cm)	Complications (Clavien Grade)	Progression free follow up (months)
1	2	9 months	Endophytic	4.2 x 3.8	None	20
2	3	26 months	Endophytic	4.3 x 4.4	Hematuria (I)	20
3	2	38 months	Exophytic	3.8 x 3.3	None	39
4	5	61 months	Endophytic	4.4 x 3.8	None	37
5	3	9 months	Endophytic	5.0 x 4.4	Hematuria (I)	13
5	3	13 months from ablation	Exophytic	5.7 x 5.7	None	19 (32 total)

Patient 5 is listed twice as he underwent two cryoablation sessions separated by 13 months. Nephrometry score based on imaging prior to cryoablation

Patients were admitted for observation overnight to the urology service, with serial hemoglobin measurements and pain assessment. All the patients were discharged the following morning. All patients were followed in the SRM Center by Urology and Interventional Radiology jointly with repeat CT or magnetic resonance (MR) imaging and laboratory testing every 3-4 months for the first year, increasing to every 6 months for the second year and annually thereafter. Chest imaging with chest x-ray or CT were followed less frequently and individualized based on initial imaging and risk factors. Demographic, procedural and follow up data were tabulated prospectively in an IRB approved database.

Results

Percutaneous cryoablation demographics are in Table 2. Four tumors were endophytic and one was exophytic with a median size of 2.2 cm (range 1.8 cm-4.0 cm). Two to four needles were used for the ablations, based on tumor size and location at the discretion of the interventional radiologist. The five patients underwent six ablation procedures. Patient 5 had apparent successful ablation of a 4.0 cm endophytic tumor, Figure 1. The resulting iceball encompassed the mass with a 5 mm margin and control at initial follow up. However,

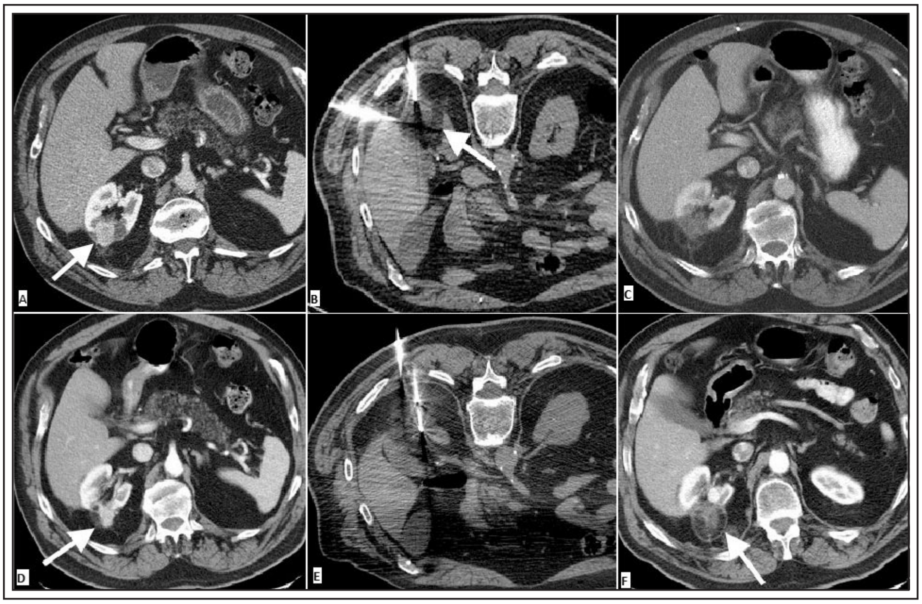

Figure 1. 70-year old male with recurrent renal cell carcinoma following laparoscopic partial nephrectomy.
(A). Contrast-enhanced CT scan in April, 2009 demonstrates a right 4.0 cm parenchymal renal cell carcinoma (Arrow). **(B).** CT-guided cryoablation was performed and the maximal ice ball appeared to cover the mass with a reasonable margin (Arrow). **(C).** Contrast-enhanced CT scan 4 months after ablation without evidence of residual tumor. **(D).** Contrast-enhanced CT scan 13 months after treatment demonstrated local progression (Arrow). **(E).** Maximal ice ball at repeat ablation with 4 cryoprobes encompassed the mass with a margin. **(F).** Contrast-enhanced CT scan at 19 months following the second ablation demonstrates complete tumor necrosis (Arrow).

13 months after ablation, the patient developed a 2.9 cm exophytic area of local progression at the inferior margin of the ablation zone. This recurrent mass was diagnosed as clear cell renal cell carcinoma, Fuhrman grade 2 on biopsy and successfully retreated by a second percutaneous cryoablation procedure. He was disease free 19 months following the second ablation and has no evidence of intra- or extra-renal disease 32 months from the initial ablation. The other four patients remain free of disease after a single cryoablation procedure. All patients have no evidence of local or distant disease at last follow up. The median follow up for the entire cohort is 32 months (19 to 39 months).

All patients were discharged on post-procedure day 1. Two minor complications occurred (both Clavien grade 1): two patients developed hematuria that stopped spontaneously prior to discharge the morning after treatment without transfusion. Hemoglobin levels for all patients remained stable following intervention. Renal function as measured by calculated glomerular filtration rate (Modification of Diet in Renal Disease, MDRD, equation) also remained stable in all patients, not changing in four, and declining by just 10% in one.

Discussion

Percutaneous cryoablation of small renal masses has demonstrated promising short term oncologic and functional outcomes and has become an accepted treatment option for incidental small renal masses, especially in suboptimal surgical candidates.[2,13,14] Cryoablation zones vary widely between tissues and organs due to local tissue interactions and local perfusion.[15] These heterogeneities are minimized in treatment of exophytic renal tumors as perfusion is limited and perinephric fat functions as a thermal insulator, resulting in a greater zone of tissue necrosis.[15] A number of studies have reported the utility of ablation for second primary pulmonary or hepatic malignancies developing separately from successfully resected primary tumors with clean surgical margins.[16-18] However, thermal ablation outcomes within true postoperative fields are not well described, nor is there a significant published experience in renal repeat cryoablation procedures. Given the variable outcomes of cryoablation in different organs, the more complex scenario of locally recurrent tumor surrounded by granulation tissue and postoperative adhesions may pose additional challenges in developing a confluent zone of thermal necrosis due to either altered conductivity or an increase in perfusion-mediated changes.[15,19] It should be noted that the authors understand that the gold standard for recurrent renal cell carcinoma is surgical extirpation. However, given the solitary kidney status in two of our patients, the elderly age in another two, and the high comorbidity index in the final; and given the known complexity of re-resection of locally recurrent renal cell carcinoma in a prior operated field, coupled with our experience in percutaneous renal cryoablation, we believed this approach to be ideal in these particular patients. Many times re-extirpation becomes radical nephrectomy. All of these patients had adequate short term treatment of the recurrence with retention of renal function.

Our needle placement algorithm is slightly more aggressive than other reports,[14] in which two needles were used for tumors up to 3 cm in size and three needles for tumors up to 4 cm. In this study, we used one needle/cm tumor diameter with a minimum of two needles. This approach may have been beneficial regarding the challenging location of four of the five tumors in our group. Endophytic and central renal tumors are more challenging to ablate than exophytic masses secondary to cold-sink effects from local perfusion.[2] The need to perform a second ablation in one of our patients with our needle placement algorithm argues that recurrent tumors after surgery may pose a greater challenge for thermal ablation than those in treatment naïve fields. However, after six ablation sessions in our five patients, complete disease control was obtained at a median follow up of 32 months. Patient 4 deserves some clarification. Although his final pathology after NSS was a benign cortical cyst, his initial imaging prior to this surgery demonstrated a cystic renal mass with enhancing mural nodularity (a Bosniak 3 cyst). Although the pathology from NSS revealed negative surgical margins, the local recurrence of a heterogeneous solid mass at the site of partial nephrectomy must have been related to the enhancing component of the initial imaging.

Recurrent disease after partial nephrectomy is a challenging problem with no clear treatment paradigm. Open partial nephrectomy is the gold standard for nephron-sparing surgery but has a longer recovery time than minimally invasive alternatives.[20,21] As technology improves there has been a push towards more MIS techniques. RALPN is a newer technology which may lower the conversion rate of LPN to radical nephrectomy.[20] Oncologic efficacy with RALPN appears similar to LPN with local recurrence ranging from 1%-4%.[7,20,21] LPN and RALPN, although minimally-invasive, still often involve complete mobilization of the kidney with isolation of the renal hilum, making repeat surgery more complicated. Repeat open nephron-sparing surgery, in one series, has a 19.6% major complication rate and a 1.9% mortality rate.[10] While radical nephrectomy for a small renal mass ensures local tumor control, the glomerular loss significantly increases the risk of morbidity from cardiovascular disease.[12] In our case series, cryoablation was chosen most commonly due to coexistent medical comorbidities, as well as to maximize nephron sparing. Two of our patients had solitary kidneys, but none of our patients have required hemodialysis. All patients had a recurrence adjacent to the NSS procedure. The calculated GFR remained essentially stable in all patients.

Conclusions

In summary, percutaneous cryoablation appears to be an effective minimally invasive alternative to treat locally recurrent or residual disease after partial nephrectomy with good oncologic results and an excellent safety profile in our initial series of patients. There is no accepted treatment algorithm for local recurrence of renal masses within the surgical bed of a partial nephrectomy. The ultimate decision for treatment should be individualized based on tumor characteristics and assessment of medical comorbidities and surgical risk, with close collaboration between the urologist and the interventional radiologist. These results are promising, but more studies are needed to evaluate the efficacy and role of cryoablation in patients with recurrence after nephron-sparing surgery. ☐

References

1. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2013. *CA Cancer J Clin* 2013;63(1):11-30.
2. Thumar AB, Trabulsi EJ, Lallas CD, Brown DB. Thermal ablation of renal cell carcinoma: triage, treatment, and follow-up. *J Vasc Interv Radiol* 2010;21(8):S233-S241.
3. Fergany AF, Hafez KS, Novick AC. Long-term results of nephron sparing surgery for localized renal cell carcinoma: 10-year followup. *J Urol* 2000;163(2):442-445.
4. Lee CT, Katz J, Shi W, Thaler HT, Reuter VE, Russo P. Surgical management of renal tumors 4 cm. or less in a contemporary cohort. *J Urol* 2000;163(3):730-736.
5. Patard JJ, Shvarts O, Lam JS et al. Safety and efficacy of partial nephrectomy for all T1 tumors based on an international multicenter experience. *J Urol* 2004;171(6):2181-2185.
6. Huang WC, Levey AS, Serto AM et al. Chronic kidney disease after nephrectomy in patients with renal cortical tumours: a retrospective cohort study. *Lancet Oncol* 2006;7(9):735-740.
7. Allaf ME, Bhayani SB, Rogers C et al. Laparoscopic partial nephrectomy: evaluation of long-term oncological outcome. *J Urol* 2004;172(3):871-873.
8. Campbell SC, Novick AC, Belldegrun A et al. Guidelines for management of the clinical stage 1 renal mass. *J Urol* 2009;182(4): 1271-1279.
9. Ljungber B, Cowan NC, Hanbury DC et al. EAU guidelines on renal cell carcinoma: the 2010 update. *Eur Urol* 2010;58(3):398-406.
10. Johnson A, Sudarshan S, Liu J, Linehan WM, Pinto PA, Bratslavsky G. Feasibility and outcomes of repeat partial nephrectomy. *J Urol* 2008;180(1):89-93.
11. Liu NW, Khurana K, Sudarshan S, Pinto PA, Linehan WM, Bratslavsky G. Repeat partial nephrectomy on the solitary kidney: surgical, functional, and oncological outcomes. *J Urol* 2009;183(1): 1719-1724.
12. Kates M, Badalato GM, Pitman M, McKiernan JM. Increased risk of overall and cardiovascular mortality after radical nephrectomy for renal cell carcinoma 2 cm or less. *J Urol* 2011;186(4):1247-1253.
13. Atwell TD, Callstrom MR, Farrell MA et al. Percutaneous renal cryoablation: local control at mean 26 months of followup. *J Urol* 2010;184(4):1291-1295.
14. Littrup PJ, Ahmed A, Aoun HD et al. CT-guided percutaneous cryotherapy of renal masses. *J Vasc Interv Radiol* 2007;18(3):383-392.
15. Permpongkosol S, Nicol TL, Link RE et al. Differences in ablation size in porcine kidney, liver, and lung after cryoablation using the same ablation protocol. *AJR Am J Roentgenol* 2007;188(4): 1028-1032.
16. Choi D, Lim HK, Rhim H et al. Percutaneous radiofrequency ablation for recurrent hepatocellular carcinoma after hepatectomy: long-term results and prognostic factors. *Ann Surg Oncol* 2007; 14(8):2319-2329.
17. Kodama H, Yamakado K, Takaki H et al. Lung radiofrequency ablation for the treatment of unresectable recurrent non-small-cell lung cancer after surgical intervention. *Cardiovasc Intervent Radiol* 2012;35(3):563-569.
18. Yang W, Chen MH, Yin SS et al. Radiofrequency ablation of recurrent hepatocellular carcinoma after hepatectomy: therapeutic efficacy on early- and late-phase recurrence. *AJR Am J Roentgenol* 2006;186(5):S275-S283.
19. Chang MI, Mikityansky I, Wray-Cahen D, Pritchard WF, Karanian JW, Wood BJ. Effects of perfusion on radiofrequency ablation in swine kidneys. *Radiology* 2004;231(2):500-505.
20. Long JA, Yakoubi R, Lee B et al. Robotic versus laparoscopic partial nephrectomy for complex tumors: comparison of perioperative outcomes. *Eur Urol* 2012;61(6):1257-1262.
21. Mullins JK, Feng T, Pierorazio PM, Patel HD, Hyams ES, Allaf ME. Comparative analysis of minimally invasive partial nephrectomy techniques in the treatment of localized renal tumors. *Urology* 2012;80(2):316-322.