Safety and Efficacy of Percutaneous Image-guided Cryoablation of Completely Endophytic Renal Masses

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OBJECTIVE To evaluate the safety, efficacy, and oncologic control of percutaneous image-guided cryoablation in the treatment of completely endophytic renal masses. Percutaneous image-guided cryoablation is a minimally invasive and effective treatment for small renal masses. Image-guided cryoablation is an attractive treatment for completely endophytic tumors given the challenge in visualization of such lesions during surgical extirpation.

MATERIALS AND METHODS A retrospective study evaluating percutaneous cryoablation of completely endophytic renal masses with normal overlying renal cortex was performed. From January 2003 to December 2015, 200 endophytic renal masses (RENAL score 3 – endophytic/exophytic) were identified from an internal renal ablation database. After imaging review, 49 tumors with completely intact overlying renal cortex in 47 patients were included in the study. Outcomes, including complications and oncologic efficacy were evaluated according to standard nomenclature.

RESULTS Patients comprised 37 men and 10 women (mean age 64.0 years) who underwent 48 cryoablation procedures to treat 49 renal masses. Mean tumor size was 2.5 ± 0.5 cm. Major complications occurred following 5 of the 48 (10%) procedures. Forty of 46 (87%) tumors with imaging follow-up were recurrence-free at a mean of 56 months. Five of six local recurrences were successfully retreated with cryoablatoin.

CONCLUSION Percutaneous thermal ablation of completely endophytic renal masses is a relatively safe procedure associated with acceptable complication and local tumor control rates. Given the complexities associated with partial nephrectomy, percutaneous cryoablation may be considered an alternative treatment for these select patients. Long-term follow-up studies are necessary to determine the durable efficacy of this treatment. UROLOGY 133: 151–156, 2019. © 2019 Elsevier Inc.

Renal cancer incidence has been gradually rising in the United States (US) over the past decade. However, the death rate has been falling on average approximately 1% per year from 2007 to 2016, with a current 5-year survival of approximately 74.5%.[1,2] In 2019, there will be an estimated 73,820 new cases and 14,770 deaths attributed to renal cancer in the US[1] The frequency of incidentally detected renal masses is increasing secondary to the use of ultrasound, computed tomography (CT), and magnetic resonance imaging (MRI) as part of routine diagnostic workups.[3]

Treatment of localized renal cell carcinoma has evolved from open surgery toward minimally invasive and nephron-sparing procedures, such as partial nephrectomy. Recently, the American Urologic Association consensus guidelines have included percutaneous ablation as an acceptable treatment option for high-risk surgical patients with T1a (≤3 cm) renal tumors.[4] Historically, the ideal renal tumor for percutaneous thermal ablation is small in size (<3 cm), partially exophytic, and posterior in location.[5] However, the treatment of endophytic renal masses has remained problematic due to thermal sink effects from renal hilar blood flow.

Completely endophytic tumors with intact overlying renal cortex present a technical challenge for surgical extirpation due to difficulty with tumor visualization. Therefore, image-guided thermal ablation is a potentially attractive treatment in this cohort of tumors. The purpose of this study was to evaluate the safety, efficacy, and oncologic control of percutaneous image guided cryoablation in the treatment of completely endophytic renal masses.

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MATERIALS AND METHODS

Patients and Tumor Characteristics

Approval for this study was obtained from our Institutional Review Board and the study was compliant with the Health Insurance Portability and Accountability Act. Informed consent was waived by the Institutional Review Board. A retrospective review of patients who underwent cryoablation of a renal mass with RENAL Nephrometry score of 3 in the exophytic/endophytic category from January 2003 to December 2015 was performed yielding a total of 200 tumors.[6] Forty nine (25%) of these tumors had normal overlying renal cortex and constituted our study population. The mean age was 64 years old (range, 27-82). All patients underwent formal consultation with the Urology Department at our institution prior to consideration for cryoablation.

All patients underwent cross-sectional imaging, either CT or MRI, which demonstrated a solid renal mass. Maximum tumor size was determined by the largest measurement using the imaging technique that best depicted the renal mass. The location of the center point of the tumor in the upper, middle, or lower third of the kidney was recorded and lesions were also classified according to their anterior, lateral, or posterior location in the kidney.

Procedure and Follow-up

The cryoablation procedure was performed by 1 of 6 radiologists with 5-14 years of experience performing percutaneous renal ablation. Informed consent was obtained prior to the procedure. Cryoablation procedures were performed under general anesthesia in a hospital CT suite (HiSpeed CT/i system [GE Healthcare, Waukesha, WI] or SOMATOM Sensation Open 40 multidetector CT system [Siemens, Malvern, PA]).

Ablation was performed with either the Endocare cryoablation system with Perc-24 cryoablation probes (Endocare, Austin, TX) or Galil cryoablation system with cryoprobes of 2.1mm or 2.4mm outer diameter (Galil, Arden Hills, MN). The cryoprobes were primarily placed with the use of ultrasound-guidance (ACUSON Sequoia; Siemens). CT fluoroscopic-guidance was used adjunctively or rarely primarily for those tumors difficult to visualize with ultrasound. Probes were placed with 1-2 cm spacing within the tumor in a configuration expected to achieve a confluent ice ball with at least a 0.5 cm lethal margin around the entire tumor. CT was used to verify placement of the cryoprobes. Following confirmation of probe placement, 1 or 2 core biopsy specimens were obtained from the tumor with an 18-gauge × 2-cm biopsy device (Bard Monopty, CR Bard) unless the lesion became obscured by the cryoprobes or at the discretion of the radiologist.

For patients with close proximity of the renal mass to the ureter or central collecting system or those patients with a solitary kidney, an ipsilateral externalized ureteral stent was placed. Specifically, a 5-French temporary externalized ureteral stent and a Foley catheter were placed by a urologist before the ablation procedure. Retrograde pyeloperfusion with room temperature sterile saline was performed during cryoablation for a few selected centrally located lesions with the goal of providing a protective benefit to the urothelium adjacent to the renal mass. Hydrodisplacement of bowel was performed for cases in which adjacent bowel was at risk of being incorporated into the ice ball during the ablation, usually within 1 cm of the tumor. This was performed by infusing sterile saline through a 5 French angio catheter between the at-risk bowel and renal mass using ultrasound or CT guidance.

A freeze—passive thaw—freeze cycle was performed for cryoablation of each tumor. The freeze duration was based on the size of the ice ball needed to completely encompass the mass. Unenhanced CT monitoring of the size and location of the ice ball was performed at approximately 2-minute intervals during each freeze. The CT images were reconstructed in different planes during ablation to ensure that the ice ball completely encompassed the tumor and assess for proximity to adjacent critical structures, such as the bowel and ureter. The total duration of the freeze cycle was dependent on the time required for the ice ball to encompass the index tumor with an additional 0.5 cm lethal margin. After the second freeze, the ice ball was actively thawed for 10-15 minutes and the probes were removed.

Immediately following removal of the cryoprobes with the patient still under general anesthesia, a noncontrast CT scan was performed to assess for complications. Small retroperitoneal hematomas were common and considered a normal postprocedural finding. In those patients without contraindication, contrast-enhanced CT was then performed to assess for technical success of the ablation and further assess for complications that may require intervention, such as embolization. In patients unable to receive iodinated contrast, MRI was performed within 24 hours using a 1.5 T scanner (Signa Excite; GE Healthcare) to ensure technical success. Complications were defined according to the revised Clavien Dindo classification for surgical complications.[7] Any grade 3 or greater complications were recorded. All patients were admitted to the urology service for overnight observation following the procedure.

Follow-up imaging with contrast-enhanced CT or MR was directed at 3, 6, and 12 months after the ablation and annually thereafter. Local tumor recurrence was defined as the presence of enhancement or enlarging soft tissue nodule within or adjacent to the ablation zone on contrast-enhanced CT or MR studies performed 3 months or later after ablation.

Statistical Analysis

Local recurrences were defined by the time period from the date of ablation to the date of the imaging that first documented tumor recurrence. Instances without follow-up imaging ($N = 2$ tumors/patients in $N = 49$ tumors in 47 patients; $N = 1$ tumor/patient in $N = 25$ tumors/patients) were treated as having 0.5 days recurrence-free survival and then censored; in cases where there was no documented recurrence by the study end point, the disease-free interval was censored at the date of the last imaging examination or death. Due to the number of deaths in the cohort, a sensitivity analysis was performed to estimate effect of censoring subjects at last MRI without accounting for death for typical local recurrence-free survival analysis; due to observed inflation in estimation of local recurrence, analysis was instead performed as incidence of local recurrence using the Aalen-Johansen method in a multistate model with competing risk of death. Analysis was performed in R (Vienna, Austria; version 3.4.2).

RESULTS

The 47 study patients included 37 men and 10 women (mean age 64.0 years) who underwent 48 cryoablation procedures for 49 renal tumors. Specifically, 45 patients underwent a single cryoablation procedure for a single renal mass. One patient had 2 tumors treated during the same procedure. One patient underwent 2 cryoablation procedures for unique tumors in 2008 and 2015. Twenty-one patients (45%) had a solitary kidney. Three

Table 1. Patient, tumor, and procedural characteristics

No. Patients	47
• Gender (male/female)	37/10
• # patients with solitary kidney (%)	21 (45%)
• Age, mean (range)	64 y (27-82)
• RENAL score, mean (range)	9 (6-10)
No. tumors ablated	49
• Tumor size, mean (range)	2.5 cm (0.9-4.0)
• RCC	76%
• Oncocytoma	24%
No. procedures	48
• # cryoprobes, mean (range)	(1-5)
• # external ureteral stent	31%)
• # hydrodisplacement	11 (23%)

RCC, renal cell carcinoma.
Table 1 demonstrates patient, tumor and procedural characteristics for the treatment population of completely endophytic renal masses.

(6%) patients had a clinical history of Von-Hippel Lindau syndrome. Mean tumor diameter was 2.5 ± 0.5 cm (range, 0.9-4.0 cm). A mean of 2 cryoprobes (range, 1-5) were used for each ablation procedure. Eleven (21%) patients required hydrodisplacement to move adjacent at-risk structures. Fifteen (31%) procedures were completed with a ureteral stent. The ablation procedure (freeze, thaw, freeze cycles) averaged 10 minutes for the initial freeze (range, 4-16 minutes), 5 minutes for the passive thaw (range, 4-8 minutes), and 10 minutes for the refreeze (range, 4-20 minutes). Data on freeze-thaw-freeze times were not recorded for 2 patients (Tables 1 and 2 and Figs. 1 and 2).

Biopsy was performed on 38 (78%) of the 49 renal tumors. Nondiagnostic biopsies were obtained in 5 (13%) of the 38 tumors. The remaining 33 biopsies yielded renal cell carcinoma in 25 (76%) tumors and oncocytoma in 8 (24%) tumors.

Imaging immediately following the cryoablation procedure showed technical success in all 49 (100%) tumors. Mean change in serum creatinine on the day of discharge following ablation was 0.2 ± 0.2 mg/dL (range, decrease of 0.1 mg/dL to an increase of 2.1 mg/dL). Mean hospitalization was 2 nights (range, 0-17 nights).

Five of 47 (11%) patients experienced 7 major complications related to 5 (10%) procedures, including perinephric hemorrhage requiring angiography and embolization ($n = 2$), obstructing hemorrhage into the renal collecting system requiring

Table 2. Treatment outcomes

Nights of Hospitalization, Mean (range)	2 (0-17)
Major complications, per procedure	5/48 (10%)
• Hemorrhage	2
• Ureteral obstruction due to clot	3*
• Pulmonary embolus	1*
• Death due to sepsis	1*
No. tumors with imaging follow-up >3 months	46
• Months of imaging follow-up, mean, median (range)	56, 54 (3-128)
• # tumors without local recurrence	40 (87%)

Table 2 demonstrates immediate complications and follow-up results for the treatment population of completely endophytic renal masses.
* Denotes complications occurring in the same patient during/after 1 ablation procedure.

ureteral stent placement ($n = 3$), pulmonary embolus ($n = 1$), and death ($n = 1$). The single death was a patient with paralysis and chronic suprapubic catheter, recurrent thromboembolic disease requiring anticoagulation, and chronic decubitus ulcers who developed hematuria and ureteral obstruction following concurrent ablation of bilateral renal masses (including a single completely endophytic tumor). Ureteral stents were placed, but the patient developed pneumonia while in hospital. He was dismissed to home but subsequently was readmitted to his local hospital where he died of presumed sepsis.

Forty-six tumors in 44 patients have imaging follow-up at 3 months or later following ablation. Forty of these 46 (87%) tumors have been successfully treated, without local recurrence, with a mean 56 months of imaging follow-up and median 54 months of imaging follow-up (range, 3-128 months). Local recurrence has developed in 6 tumors (5 RCC, 1 oncocytoma). This includes 5 of the 25 patients treated with biopsy proven RCC (20%). Five of these 6 (4 RCC, 1 oncocytoma) local recurrences have been successfully retreated with cryoablation and are recurrence free at a median follow-up of 55 months and mean follow-up of 53 months.

Death prior to recurrence occurred in 23% (11/47) of patients overall and 25% (5/25) of patients in the biopsy-proven RCC subset. Overall cumulative incidence of local recurrence at 3 and 5 years was 5% (95%CI 1-19) and 10% (95%CI 4-27). Cumulative incidence of local recurrence in the biopsy-proven RCC subset was 10% (95%CI 3-36) at 3 years and 25% (95%CI 10-61) 5 years.

DISCUSSION

The current study shows that percutaneous image-guided cryoablation is effective in treatment of completely endophytic renal masses with intact overlying cortex. Percutaneous cryoablation has been shown to have excellent oncologic efficacy and low complication rates in the treatment of small, exophytic renal masses.[8,9] More recently, the use of percutaneous cryoablation has expanded to include larger and more complex renal lesions, including endophytic and central tumors.[10] Endophytic renal masses often have higher RENAL Nephrometry scores (>9) on cross-sectional imaging, indicating the high complexity of these lesions.[10] However with increasing complexity of renal lesions there are increased complications, particularly bleeding complications when compared with smaller, peripheral lesions.[11,12]

Surgical extirpation of completely endophytic renal tumors presents a unique challenge due to lack of visible landmarks on the kidney surface, often requiring use of advanced techniques for tumor localization.[11] A study by Mullerad et al[13] comparing nephron-sparing surgery in endophytic and peripheral lesions concluded that treatment of endophytic tumors is associated with greater complication rates in comparison with peripheral tumors.

The current study shows durable oncologic efficacy in the treatment of completely endophytic tumors. The favorable outcomes reported reflect lessons learned over more than 10 years of experience. Perhaps more importantly, multidisciplinary coordination between urology, radiology, and anesthesiology allows for optimal patient

Cumulative incidence estimates for local recurrence and death (Overall)

Year	Recurrence (%)	Recurr. 95%CI	Death (%)	Death 95%CI
3	5	1-19	9	4-24
5	10	4-27	12	5-27

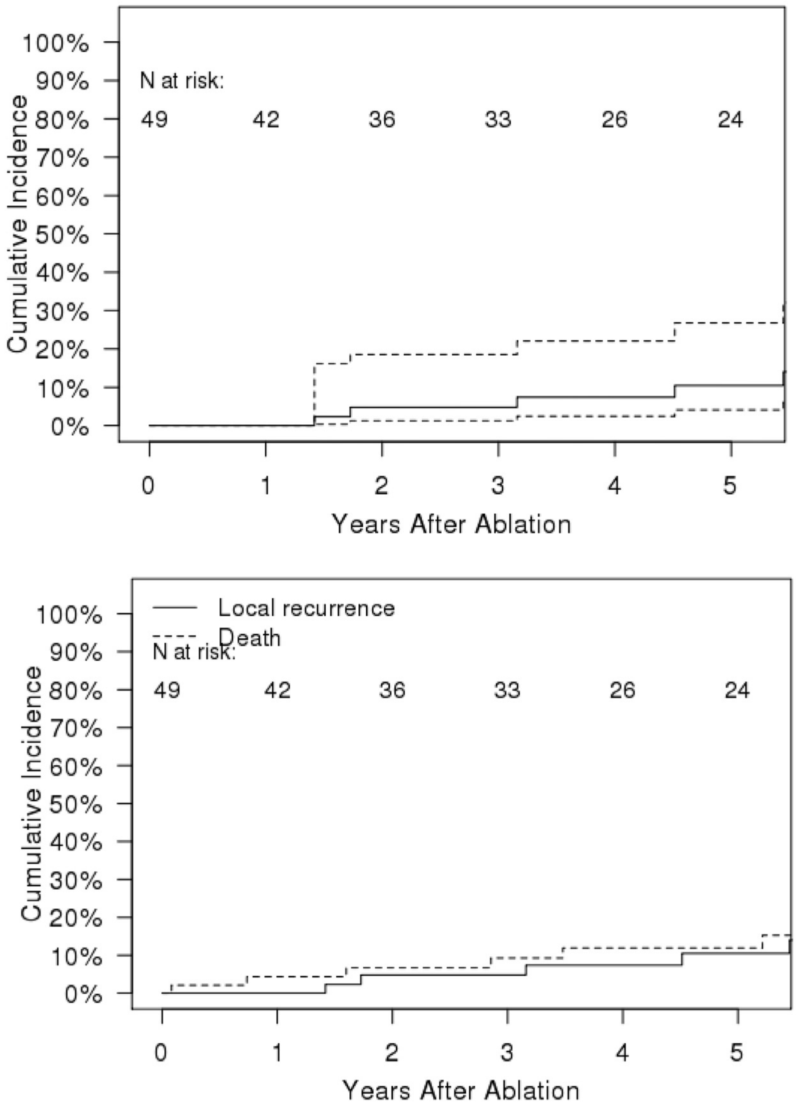


Figure 1. Overall cumulative incidence of local recurrence and death.

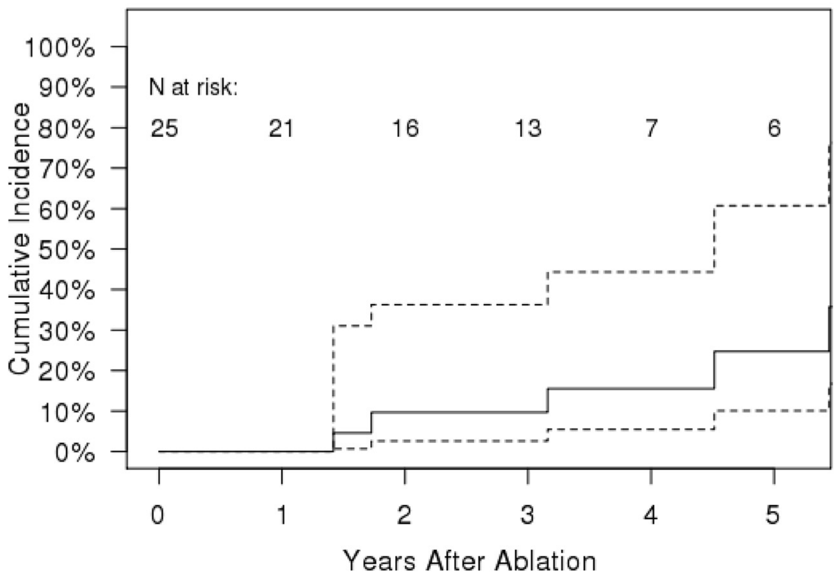
selection and periprocedural management to allow for the complex treatment, as described above. Related to ablation technique, larger caliber cryoprobes are needed to overcome the thermal sink environment inherent to the location of these tumors.[10] In addition, the incorporation of ureteral stents and hydrodisplacement allows aggressive treatment with lesser risk to critical urothelium and bowel. Nevertheless, such treatment was associated with major complications in several patients, again reflecting the need for multidisciplinary care.

There is limited published experience specifically directed to the cryoablation of centrally located renal masses. In their review of centrally located tumors encroaching on the renal sinus, Rosenberg et al found a local tumor control rate of 94% following cryoablation.[14] The results from this and the current study contrasts with the increased rate of local tumor recurrence following radiofrequency ablation of centrally located renal masses, previously reported as high as 18%-33%.[15,16] Iannuccilli et al showed that tumor depth toward the renal sinus was associated with increased incidence of treatment failure compared to exophytic tumors in the treatment of renal masses with radiofrequency ablation.[17]

Interestingly, the rate of local tumor control in this select, completely endophytic cohort is slightly lower than previously published cryoablation and partial nephrectomy analysis from our institution. In this study including all treated

Cumulative incidence estimates for local recurrence and death (Biopsy-proven RCC subset)

Year	Recurrence (%)	Recurr. 95%CI	Death (%)	Death 95%CI
3	10	3-36	14	5-42
5	25	10-61	20	8-49



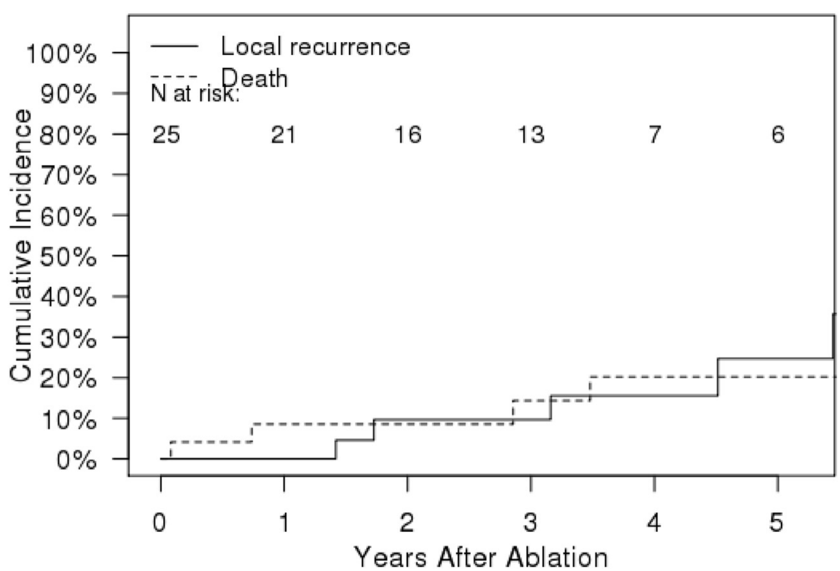


Figure 2. Cumulative incidence of local recurrence and death in the biopsy proven RCC subset. RCC, renal cell carcinoma.

renal masses, reported 3-year local recurrence-free survival was 98% in a study of over 1400 cT1a tumors in patients treated with both partial nephrectomy and thermal ablation.[18] This may be due to more conservative treatment employed in this study cohort where 51% of patients were treated with a solitary kidney or Von-Hippel-Lindau (VHL). In these patients, goals of definitive oncologic control and renal function preservation are often balanced. In many ways, this validates the role of CT monitoring and appreciation for physiological isotherms in varying thermal environments in assuring complete tumor treatment during cryoablation, regardless of tumor location.

Our study is not without limitations. The study is a retrospective review of a single institution experience treating renal tumors with cryoablation. Moreover, some degree of selection bias is present in referral of patients from the Urology department to Interventional Radiology for consideration of thermal ablation. Additionally, the study contains a relatively small number of patients with mean follow-up time of over 4 years. The study also examined patients over a 10-year time period with inherent changes in operator experience and ablation technology during this time.

CONCLUSION

Percutaneous thermal ablation of completely endophytic renal masses is a relatively safe procedure associated with acceptable complication and local tumor control rates. Given the complexities associated with partial nephrectomy, percutaneous cryoablation may be considered an alternative treatment for these select patients. Long-term follow-up studies are necessary to determine the durable efficacy of this treatment.

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