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Renal Cryoablation Versus Robot-Assisted Partial Nephrectomy: Washington University Long-Term Experience

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Abstract

Background and Purpose: American Urological Association guidelines endorse partial nephrectomy as the preferred treatment for patients with small renal masses, while considering patients with significant comorbidities potential candidates for ablative therapy. We compared perioperative, renal functional, and oncologic outcomes of renal cryoablation and robot-assisted partial nephrectomy (RAPN) based on our long-term institutional experience.

Patients and Methods: A retrospective review evaluated 267 patients who underwent laparoscopic or percutaneous cryoablation (July 2000–June 2011) and 233 patients who underwent RAPN (June 2007–September 2012) for enhancing renal masses at Washington University.

Results: The perioperative complication rate was 8.6% in the cryoablation group *vs* 9.4% in the RAPN group ($P = 0.75$). There was no significant difference in complication risk between the two treatment modalities on multivariate analysis. Estimated glomerular filtration rate (eGFR) at last follow-up was 6% lower than preoperative eGFR in the cryoablation group and 13% lower in the RAPN group ($P < 0.01$). The advantage of cryoablation in preserving renal function persisted on multivariate analysis ($P = 0.02$). In patients with pathologically proven renal-cell carcinoma, 5-year Kaplan-Meier disease-free survival (DFS), cancer-specific survival (CSS), and overall survival was 83.1%, 96.4%, and 77.1% in the cryoablation cohort *vs* 100%, 100%, and 91.7% in the RAPN group. Mean time to recurrence was 16.2 months (range 0.03–42.0 mos). Cryoablation was associated with increased recurrence risk (hazard ratio [HR] = 11.4, $P = 0.01$) on multivariate analysis.

Conclusions: Cryoablation and RAPN are safe alternatives for managing renal masses amenable to nephron-sparing interventions, offering acceptable morbidity and excellent renal preservation. While RAPN offers improved DFS, for those willing to undergo close postoperative monitoring and accept the potential need for re-treatment of recurrent disease, cryoablation offers excellent long-term CSS.

Introduction

With the widespread use of abdominal imaging, the incidence of newly diagnosed small renal masses (SRM) has increased by approximately 2.5% to 3% per year over the last 30 years.[1] According to the National Cancer Institute, 60,920 new cases of renal-cell carcinoma (RCC) were diagnosed in 2011.[2] Accompanying the increased incidental detection of SRM on abdominal imaging, a downward size and stage migration favoring smaller, stage I tumors has been observed.[3] By 2007, 13.5% of all newly discovered renal masses were < 2 cm, 37% < 3 cm, and 60% < 4 cm.[4] Indeed, incidental, asymptomatic SRM constitute approximately half of all cases of suspected RCC referred to urologists today.[5]

Cumulative data emphasizing the significance of renal preservation,[6–9] in concert with data confirming the equivalency of partial nephrectomy and radical nephrectomy with regard to oncological outcomes,[10] provide the basis for current American Urological Association (AUA) guidelines that recommend partial nephrectomy as the preferred treatment option for managing T_{1a} renal tumors (<4 cm).[11] Nevertheless, cryoablation and percutaneous radiofrequency ablation have been increasingly used as alternatives to partial nephrectomy in the last 10 years. These less invasive thermal ablation modalities have a favorable morbidity profile and are generally associated with rapid convalescence.[12]

Compared with radiofrequency ablation, cryoablation appears to be associated with a decreased incidence of local cancer recurrence, metastatic progression, and re-treatment and is, arguably, the most efficacious alternative to partial nephrectomy when considering ablative treatment options.[13,14] Unfortunately, reports on the long-term oncologic

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and renal functional outcomes of cryoablation are limited.[15] Moreover, a head to head comparison of partial nephrectomy and cryoablation that appropriately controls for prognostically significant baseline tumor and patient characteristics is as scarce in the literature as it is crucial.[16] In the current study, we compared perioperative, renal functional, and oncologic outcomes of renal cryoablation and robot-assisted partial nephrectomy (RAPN) based on our long-term experience with these alternative treatments at Washington University, while controlling for baseline tumor and patient characteristics.

Patients and Methods

The study design was approved by the Human Studies Committee of Washington University. A retrospective review evaluated 267 patients who underwent laparoscopic ($n = 149$) or percutaneous ($n = 118$) cryoablation from July 2000 to June 2011 and 233 patients who underwent RAPN from June 2007 to September 2012 for contrast-enhancing renal masses that were concerning for RCC on preoperative imaging (either CT or MRI) at Washington University. Patient comorbidity and surgical risk, tumor location and size, and the preference of the patient and treating surgeon all contributed to the choice of treatment. In addition to tumor excision and ablation, patients were offered tumor surveillance as a management option for their renal tumor.

Surgical technique

We have previously described our techniques for laparoscopic cryoablation,[15] percutaneous cryoablation,[17] and RAPN.[18]

Postoperative follow-up

For our cryoablation group, cross-sectional imaging with and without contrast was obtained at the following postprocedure intervals: 1 day, 1 month, 3 months, 6 months, 12 months, and then annually. More recently, our follow-up protocol was reduced to CT or MRI at 3 months postprocedure and then yearly up to 5 years. For the RAPN group, abdominal CT or MRI and chest radiography, along with physical examination, were performed at 3 to 6 months postoperatively and yearly thereafter. At each follow-up interval, serum chemistry, including serum creatinine, was evaluated.

Data collection and analysis

Data managers and staff physicians compiled data on patient demographics and tumor characteristics, as well as perioperative, renal functional, and oncologic outcomes after cryoablation or RAPN (Table 1).

Postoperative complications were classified using the Clavien classification system.[19] Multiple logistic regression analysis was performed to assess factors predicting increased risk of perioperative complications (Table 2).

Using the Chronic Kidney Disease Epidemiology Collaboration formula,[20] we evaluated postoperative changes in estimated glomerular filtration rate (eGFR) after cryoablation and RAPN to assess the renal functional outcomes of these procedures. The paired t test was used to compare preoperative eGFR with eGFR at last follow-up in each treatment group, and the independent sample t test was used to compare the mean percent decline in postprocedure eGFR in the two groups. Multiple linear regression analysis identified variables that predicted improved preservation of eGFR posttreatment (Table 3).

For the subset of patients with pathologically confirmed, localized RCC, Kaplan-Meier analysis of disease-free survival (DFS), cancer-specific survival (CSS), and overall survival (OS) was performed in each treatment group. The log-rank test was used to compare DFS, CSS, and OS between the two groups (Fig. 1). A multivariate Cox proportional hazards model identified variables that predicted cancer recurrence in the same patient subset (Table 4).

Statistical analysis was conducted using MedCalc-11.6 and SPSS 20 software. Statistical significance was defined by a two-tailed P value of < 0.05.

Results

A comparison of baseline patient and tumor characteristics and the perioperative, renal functional, and oncologic outcomes of cryoablation *vs* RAPN is provided in Table 1. The perioperative complication rate was 8.6% in the cryoablation group *vs* 9.4% in the RAPN group ($P = 0.75$). Increasing Charlson Comorbidity Index (CCI) (odds ratio [OR] = 1.4, $P = 0.01$) predicted increased perioperative complication risk on multiple logistic regression analysis (Table 2). Individual complications in the cryoablation and RAPN groups are outlined in Table 5.

In the cryoablation group, mean preoperative eGFR was 66.3 mL/min/1.73 m^2 (standard deviation [SD] = 24.7), compared with 61.3 mL/min/1.73 m^2 (SD = 27.0) at last follow-up ($P < 0.01$). Mean preoperative eGFR in the RAPN group was 84.5 mL/min/1.73 m^2 (SD = 20.9) *vs* 73.4 mL/min/1.73 m^2 (SD = 22.4) at last follow-up ($P < 0.01$). Thus, eGFR decreased by a mean of 6.0% (SD = 29.2) in the cryoablation group *vs* 13% (SD = 19.7) in the RAPN group ($P < 0.01$). On multiple linear regression analysis, cryoablation ($P = 0.02$), smaller tumor size ($P = 0.03$), and hilar tumor location ($P = 0.01$) predicted improved renal functional outcomes (Table 3).

In the subset of patients with biopsy-proven, localized RCC, the 5-year Kaplan-Meier-estimated DFS in the cryoablation cohort was 83.1%; CSS was 96.4%; OS was 77.1%; respective 5-year survival for pathologically confirmed RCC in the RAPN group was 100%, 100%, and 91.7%. (Fig. 1) Mean time to treatment failure in the cryoablation group was 16.2 months (SD = 17.9; range 0.03–42.0 mos). Cryoablation (hazard ratio [HR] = 11.4, $P = 0.01$) and endophytic tumor location (HR = 46.9, $P = 0.01$) were the only predictors of cancer recurrence in a multivariate cox proportional hazards model (Table 4).

Discussion

Evidence accumulated over the last decade has shown that partial nephrectomy is not only technically feasible, but also oncologically equivalent to radical nephrectomy.[10] Moreover, overutilization of radical nephrectomy has been linked to chronic renal insufficiency,[7] which, in turn, has been linked to increased risk of cardiovascular disease and premature death.[6–9] Accordingly, current AUA guidelines endorse partial nephrectomy as the primary treatment modality for patients with T_{1a} tumors (< 4 cm) and as an acceptable treatment

Table 1. Comparison of Patient and Tumor Characteristics as Well as Perioperative, Renal Functional, and Oncologic Outcomes in Patients Who Underwent Cryoablation Versus Those Who Underwent Robot-Assisted Partial Nephrectomy

	Cryoablation	*RAPN*	P *value*
Patient characteristics			
Mean age, years (SD)	69.3 (11.0)	57.4 (11.9)	<0.01
BMI (SD)	30.4 (7.8)	30.1 (6.0)	0.57
Sex			
No. male (%)	163/267 (61.0)	127/233 (54.5)	0.14
No. female (%)	104/267 (39.0)	106/233 (45.5)	
Mean age-adjusted CCI (SD)	6.5 (2.2)	2.1 (1.8)	<0.01
Tumor characteristics			
Mean tumor size, cm (SD)	2.5 (1.0)	2.9 (1.5)	<0.01
Mean nephrometry score (SD)	6.4 (1.7)	7.3 (1.9)	≤0.01
Tumor laterality			
Left (%)	127/267 (47.6)	116/232 (51.7)	0.38
Right (%)	138/267 (51.7)	116/232 (48.3)	
Bilateral (%)	2/267 (0.7)	0/116 (0)	
Tumor polarity			
No. upper pole (%)	80/267 (30.0)	50/211 (23.7)	≤0.01
No. midpolar (%)	91/267 (34.0)	102/211 (48.3)	
No. lower pole (%)	96/267 (36.0)	59/211 (28.0)	
Tumor location			
No. anterior (%)	84/267 (31.5)	37/112 (33.0)	≤0.01
No. lateral (%)	49/267 (18.4)	41/112 (36.6)	
No. posterior (%)	134/267 (50.2)	34/112 (30.4)	
Tumor location			
No. exophytic (%)	133/267 (49.8)	80/222 (36.0)	≤0.01
No. mesophytic (%)	93/267 (34.8)	-	
No. endophytic (%)	41/267 (15.4)	142/222 (64.0)	
No. hilar (%)	36/267 (13.5)	26/195 (13.3)	0.96
No. multifocal (%)	23/267 (8.6)	4/233 (1.7)	≤0.01
Tumor pathology			
No. RCC (%)	80/153 (52.3)	185/233 (79.4)	≤0.01
No. other (%)	73/153 (47.7)	48/233 (20.6)	
Perioperative outcomes			
Surgical approach (excluding PCA)			
Transperitoneal (%)	111/146 (76.0)	232/233 (99.6)	≤0.01
Retroperitoneal (%)	35/146 (24.0)	1/233 (0.4)	
Mean operative time, minutes (SD)	164.8 (60.2)	140.6 (41.6)	≤0.01
No. with hilar clamping (%)	0/267 (0)	215/233 (92.3)	≤0.01
Mean WIT, minutes (SD)	0 (0)	17.2 (8.6)	≤0.01
Mean EBL, mL (SD)	74.2 (100.1)	136.3 (112.2)	≤0.01
No. intraoperative complications (%)	18/249 (7.2)	3/230 (1.3)	≤0.01
No. postoperative complications (%)	6/267 (2.2)	18/233 (7.7)	≤0.01
No. perioperative complications (%)	23/267 (8.6)	22/233 (9.4)	0.75
No. perioperative blood transfusion (%)	4/267 (0.4)	9/233 (3.9)	0.10
Renal functional outcomes			
No. with solitary kidney (%)	27/267 (10.1)	3/231 (1.3)	≤0.01
Mean preoperative sCr, mg/dL (SD)	1.2 (0.9)	0.9 (0.3)	≤0.01
Mean sCr on POD #1 (SD)	1.3 (1.1)	1.1 (0.4)	0.03
Mean sCr at last f/u, mg/dL (SD)	1.4 (1.1)	1.1 (0.5)	≤0.01
Mean preoperative eGFR, mL/min/1.73m^2 (SD)	66.3 (24.7)	84.5 (20.9)	≤0.01
Mean eGFR at last f/u, mL/min/1.73m^2 (SD)	61.3 (27.0)	73.4 (22.4)	≤0.01
Mean % change in eGFR at last f/u (SD)	−6.0 (29.2)	−13.0 (19.7)	≤0.01
Mean creatinine follow-up, months (SD)	35.8 (31.1)	11.8 (16.4)	≤0.01
Oncological outcomes in the subset of patients with pathologically proven RCC			
No. positive surgical margins (%)	NA	5/233 (2.1)	-
No. with cancer recurrence (%)	10/79 (12.7)	0/185 (0)	≤0.01
No. necessitating re-treatment (%)	9/79 (11.4)	0/185 (0)	≤0.01
Mean radiographic follow-up, months (SD)	39.8 (34.3)	21.9 (18.8)	≤0.01

RAPN = robot-assisted partial nephrectomy; SD = standard deviation; BMI = body mass index; CCI = Charlson Comorbidity Index; RCC = renal-cell carcinoma; PCA = percutaneous cryoablation; WIT = warm ischemia time; EBL = estimated blood loss; sCr = serum creatinine; POD = postoperative day; f/u = follow-up; eGFR = estimated glomerular filtration rate.

Table 2. Multiple Logistic Regression Analysis Evaluating Factors Associated with Increased Risk of Perioperative Morbidity After Cryoablation or Robot–Assisted Partial Nephrectomy

	OR	*95% CI*	P *value*
Patient characteristics			
Sex	1.00	0.35–2.92	0.99
Male (Referent)			
Female			
Body mass index	1.45	0.50–4.16	0.49
≤30 (Referent)			
≥30			
Age–adjusted CCI (increments of 1)	1.44	1.09–1.91	0.01
Preoperative eGFR, mL/min/1.73m^2	2.01	0.53–7.65	0.31
<60 (Referent)			
≥60			
Solitary kidney	–	–	1.00
No (Referent)			
Yes			
Tumor characteristics			
Tumor size, cm	1.58	0.51–4.94	0.43
<3 (Referent)			
≥3			
Tumor laterality	1.39	0.51–3.83	0.52
Left (Referent)			
Right			
Location relative to renal hilum	1.95	0.49–7.78	0.35
Nonhilar (Referent)			
Hilar			
Exophytic *vs* mesophytic *vs* endophytic (Referent)	1.75	0.49–6.23	0.39
Upper pole *vs* midpolar *vs* lower pole (Referent)	0.76	0.19–3.03	0.70
Anterior *vs* lateral *vs* posterior (Referent)	0.63	0.18–2.26	0.48
Pathology	0.69	0.18–2.70	0.60
Other (Referent)			
Renal-cell carcinoma			
Multifocality	0.28	0.20–3.95	0.35
Unifocal (Referent)			
Multifocal			
Perioperative			
Treatment modality	3.00	0.58–15.69	0.19
Cryoablation (Referent)			
Robot–assisted partial nephrectomy			
Surgical approach	0.29	0.03–3.22	0.31
Transperitoneal (Referent)			
Retroperitoneal			
Operative time, minutes	1.15	0.39–3.43	0.80
<150 (Referent)			
≥150			

OR = odds ratio; CI = confidence interval; CCI = Charlson Comorbidity Index; eGFR = estimated glomerular filtration rate.

alternative for patients with T_{1b} tumors (4–7 cm).[11] Consistent with AUA guidelines, utilization rates of partial nephrectomy now approach 90% at many centers of excellence.[21]

The emergence of minimally invasive thermal ablation therapies over the past decade has provided patients with a diagnosis of renal tumors with a nephron-sparing alternative to partial nephrectomy, which is typically associated with a favorable morbidity profile and a precipitous postoperative recovery.[12] According to current AUA guidelines, thermal ablation is an appropriate treatment alternative to partial nephrectomy in patients who are poor surgical candidates but desire active treatment and are willing to undergo extended radiographic surveillance.[11]

Comparing available thermal ablation modalities, a meta-analysis by Kunkle and associates[13] concluded that cryoablation is associated with superior local and distant cancer control relative to radiofrequency ablation.[14] Notwithstanding the widespread use of cryoablation as an alternative to extirpative surgery for suspected renal malignancy, data on the long-term outcomes of this procedure are limited.[15] Even more pronounced is the paucity of direct head to head comparisons of the perioperative, renal functional, and oncologic outcomes of partial nephrectomy and cryoablation, which appropriately control for prognostically significant baseline patient and tumor characteristics.[16]

In a contemporary meta-analysis evaluating previously published series on outcomes of partial nephrectomy and laparoscopic renal cryoablation, Klatte and colleagues[16] note that while there appears to be an increased risk of perioperative complications (especially "major complications")

Table 3. Multiple Linear Regression Analysis Evaluating Factors Associated with Greater Preservation of Renal Function (Estimated Glomerular Filtration Rate) After Cryoablation or Robot-Assisted Partial Nephrectomy

	Beta-coefficient	*95% CI*	P *value*
Patient characteristics			
Sex	0.13	−2.60 to17.31	0.15
Male (Referent)			
Female			
Age, years	−0.07	−0.63 to 0.31	0.50
Body mass index	0.12	−0.25 to 1.50	0.16
Age-adjusted CCI	−0.24	−5.04 to 0.26	0.08
Preoperative sCr, mg/dL	0.16	−1.85 to 20.19	0.10
Tumor characteristics			
Tumor size, cm	−0.19	−8.44 to −0.35	0.03
Tumor laterality	−0.08	−13.63 to 4.31	0.31
Left (Referent)			
Right			
Location relative to renal hilum	0.23	5.51 to 30.96	0.01
Nonhilar (Referent)			
Hilar			
Exophytic *vs* mesophytic *vs* endophytic (Referent)	0.02	−9.72 to 12.62	0.80
Upper pole *vs* middle pole *vs* lower pole (Referent)	0.03	−9.64 to 13.55	0.74
Anterior *vs* lateral *vs* posterior (Referent)	−0.07	−16.06 to 6.66	0.42
Pathology	0.06	−7.62 to 14.58	0.54
Other (Referent)			
Renal-cell carcinoma			
Multifocality	−0.07	−30.67 to 14.48	0.48
Unifocal (Referent)			
Multifocal			
Bilaterality	−0.10	−23.44 to 6.99	0.29
Unilateral (Referent)			
Bilateral			
Perioperative/postoperative			
Treatment modality	−0.33	−36.17 to −2.53	0.02
Cryoablation (Referent)			
Robot-assisted partial nephrectomy			
Surgical approach	−0.13	−31.86 to 5.25	0.16
Transperitoneal (Referent)			
Retroperitoneal			
Operative time, minutes	0.01	−0.10 to 0.10	0.94
Estimated blood loss, mL	0.05	−0.03 to −0.05	0.59
Length of sCr follow-up, months	0.04	−0.15 to 0.22	0.69

The outcome variable—defined as the percent change in estimated glomerular filtration rate (eGFR) after treatment—was measured as follows: (eGFR at last follow-up—preoperative eGFR)/preoperative eGFR.

CI = confidence interval; CCI = Charlson Comorbidity Index; sCr = serum creatinine.

with partial nephrectomy, compared with laparoscopic cryoablation, this comparison was subject to significant selection bias. For example, differences in tumor size and location between the two treatment groups could not be accounted for in their meta-analysis.[16] In a critique of the meta-analysis of Klatte and coworkers,[16] Novara and colleagues[22] suggest that insofar as tumors that were treated with cryoablation were more likely to be exophytic, secluded from the renal sinus and collecting system, and located at the lateral border of the kidney, the lower rate of complications noted in cryoablation series could very possibly be a reflection of selection bias rather than the result of a less invasive procedure.[22] The absence of a standardized system (eg, the Clavien system[19]) for defining complications and classifying their severity among many of the series in the meta-analysis by Klatte and associates[16] further restricts the meaningful comparison of complication rates between cryoablation and partial nephrectomy.

The first aim of the current study was to compare the perioperative complication rates of RAPN and cryoablation, using a standardized classification system for reporting complications—namely, the Clavien classification system[19]—while controlling for baseline tumor and patient characteristics. In contrast to a recent study by Guillotreau and coworkers[23] that demonstrated increased morbidity with RAPN (20%) relative to cryoablation (12%),[23] perioperative complications in the current study were similar between the RAPN and cryoablation groups (9.4% *vs* 8.6%, $P = 0.75$). When evaluating whether the utilization of RAPN *vs* cryoablation predicted perioperative complication risk in a multivariate model that controlled for baseline patient and tumor characteristics, there was no significant difference in complication risk noted between these two treatment modalities. Indeed, the only factor predicting greater risk of perioperative complications on multiple logistic regression was increasing patient CCI ($OR = 1.4$, $P = 0.01$). Based on the Washington University

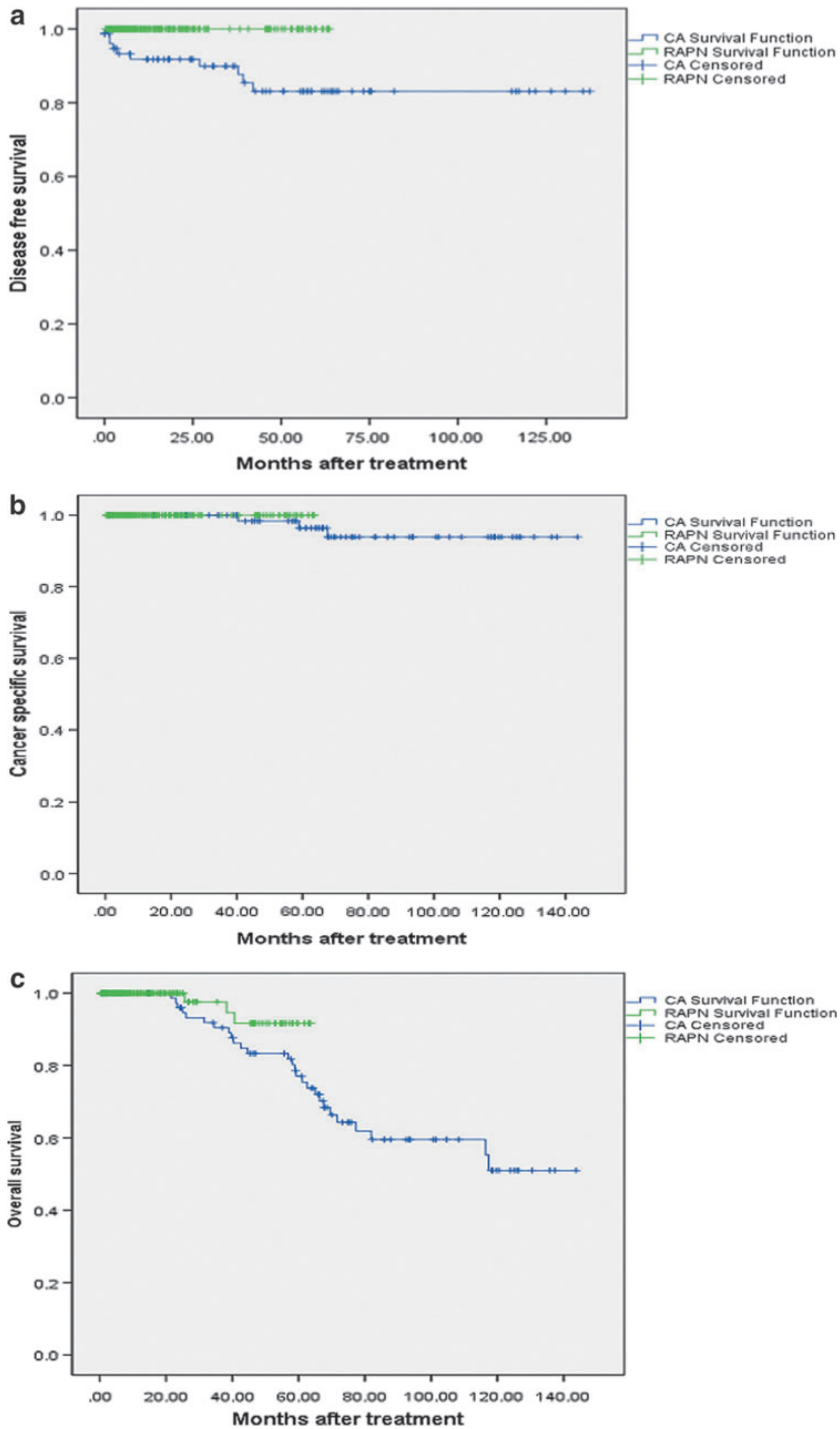

FIG. 1. Kaplan-Meier analysis of disease-free survival **(a),** cancer-specific survival **(b),** and overall survival **(c)** after cryoablation (CA) and robot-assisted partial nephrectomy (RAPN). Respective log-rank: $P<0.01$, $P=0.41$, $P=0.11$.

Table 4. Multivariate Cox Proportional Hazards Model Identifying Variables That Predicted Cancer Recurrence in the Subset of Patients with Pathologically Confirmed Renal-Cell Carcinoma Who Underwent Cryoablation or Robot-Assisted Partial Nephrectomy

	OR	*95% CI*	P *value*
Patient characteristics			
Sex	2.24	0.41–12.3	0.35
Male (Referent)			
Female			
Age, years (increments of 1)	1.03	0.93–1.13	0.56
Body mass index	0.53	0.10–2.84	0.46
<30 (Referent)			
≥30			
Age–adjusted CCI (increments of 1)	0.84	0.54–1.33	0.46
Preoperative eGFR, mL/min/1.73m^2	2.31	0.35–15.48	0.39
<60 (Referent)			
≥60			
Tumor characteristics			
Tumor size, cm	1.63	0.31–8.51	0.56
<3 (Referent)			
≥3			
Tumor laterality	0.83	0.16–4.17	0.82
Left (Referent)			
Right			
Location relative to renal hilum	0.31	0.02–4.05	0.37
Nonhilar (Referent)			
Hilar			
Endophytic *vs* mesophytic *vs* exophytic (Referent)	46.95	3.05–722.34	0.01
Upper pole *vs* midpolar *vs* lower pole (Referent)	0.16	0.01–2.48	0.19
Anterior *vs* lateral *vs* posterior (Referent)	1.12	0.14–8.99	0.92
Multifocality	–	–	0.99
Unifocal (Referent)			
Multifocal			
Perioperative/postoperative			
LCA *vs* PCA *vs* RAPN (Referent)	11.41	1.90–68.67	0.01
Intraoperative complication(s)	6.18	0.36–107.22	0.21
No (Referent)			
Yes			
Length of radiographic follow-up, months (increments of 1)	0.98	0.96–1.01	0.16

OR = odds ratio; CI = confidence interval; CCI = Charlson Comorbidity Index; eGFR = estimated glomerular filtration rate; LCA = laparoscopic cryoablation; PCA = percutaneous cryoablation; RAPN = robot-assisted partial nephrectomy.

experience, one can, therefore, conclude that cryoablation and RAPN are safe treatment alternatives for the management of localized renal masses.

The second aim of this study was to compare the long-term renal functional outcomes of cryoablation and RAPN, controlling for baseline tumor and patient characteristics. It is noteworthy that partial nephrectomy requires the excision of a normal renal parenchymal margin and generally involves clamping of the renal hilum (associated with warm ischemia) during tumor excision, which may, at least in theory, contribute to a greater decline in renal function relative to cryoablation. In the current analysis, cryoablation was, in fact, associated with improved renal functional outcomes compared with RAPN (6% *vs* 13.0% respective drop in eGFR post-treatment, $P < 0.01$). The advantage of cryoablation in preserving renal function persisted after controlling for patient and tumor characteristics on multivariate analysis ($P = 0.02$).

Interestingly, smaller tumor size ($P = 0.03$) and hilar tumor location ($P = 0.01$) also predicted improved renal functional outcomes after cryoablation or RAPN on multivariate analysis. While it is not entirely intuitive that hilar location would be associated with improved renal functional outcomes, one explanation for this finding is that, compared with more peripheral cortical tumors, hilar tumors are more likely to occupy and invade renal sinus fat, and, as such, their ablation or excision may be associated with decreased loss of adjacent functionally active renal parenchyma. Similarly, treatment of smaller tumors would be expected to result in decreased compromise of adjacent normal renal parenchyma.

In comparing the oncologic outcomes of partial nephrectomy *vs* cryoablation, Klatte and coworkers[16] again note significant selection bias, because patients with certain poor prognostic features—for example, larger tumors and centrally positioned tumors with an increased predisposition for vascular invasion—were more likely to be treated with partial nephrectomy than cryoablation. The authors report that their meta-analysis was unable to account for these important confounding differences in baseline patient and tumor characteristics between the two treatment groups, because many of the cryoablation series failed to report these baseline clinical data. Klatte and colleagues[16] also note that the percentage of pathologically proven RCC was lower in the cryoablation

Table 5. Perioperative Complications in the Laparoscopic Cryoablation, Percutaneous Cryoablation, and Robot-Assisted Partial Nephrectomy Treatments Groups

Intraoperative complications	Postoperative complications
LCA	
Conversion to hand-assisted LCA because of difficult visualization	Perinephric hematoma managed conservatively (Clavien I)
2 cases of small liver laceration managed conservatively	Atrial fibrillation with rapid ventricular response medically managed (Clavien II)
4 cases of renal parenchymal fracture—3 managed conservatively and 1 necessitating PRBC transfusion	Lower extremity DVT managed with angiographic administration of tPA (Clavien IIIa)
3 cases of hemorrhage—2 managed conservatively and 1 necessitating PRBC transfusion and subsequent renal artery angioembolization after a prolonged ICU course	Non-ST-elevation myocardial infarction (Clavien IVa)
	Pulmonary embolism (Clavien IVa)
PCA	
Renal parenchymal fracture	2 cases of perinephric hematoma necessitating PRBC transfusion (Clavien II)
5 cases of perinephric hematoma—all managed conservatively	Duodenal-ureteral fistula with retroperitoneal abscess necessitating abscess drainage, percutaneous nephrostomy tube placement, and placement of a duodenal drain and J-tube (Clavien IIIa)
Pneumothorax managed nonoperatively	
Partial splenic infarction	
Oxygen desaturation with supplementary oxygen requirement	
Apnea necessitating abortion of the procedure	
RAPN	
Hemorrhage from a missed renal artery	Readmission for psychiatric issues (Clavien I)
Traumatic nasogastric tube placement necessitating upper gastrointestinal tract endoscopy, which was negative for acute injury	Readmission for pain (Clavien I)
Serosal bowel tear repaired with 8 partial thickness longitudinal sutures	2 cases of ileus managed conservatively (Clavien I)
	Acute renal failure in a patient with CKD managed conservatively (Clavien I)
	6 cases of PRBC transfusion (Clavien II)
	Atrial fibrillation medically managed (Clavien II)
	Hypertensive crisis medically managed (Clavien II)
	Fluid overload medically managed (Clavien II)
	DVT medically managed (Clavien II)
	2 cases of pseudoaneurysm necessitating angioembolization (Clavien IIIa)
	Urinary leakage necessitatng percutaneous drainage (Clavien IIIa)
	2 cases of non-ST-elevation myocardial infarction (Clavien IVa)
	DVT with pulmonary embolism (Clavien IVa)

LCA = laparoscopic cryoablation; DVT = deep vein thrombosis; tPA = tissue plasminogen activator; PRBC = packed red blood cells; ICU = intensive care unit; PCA = percutaneous cryoablation; RAPN = robot-assisted partial nephrectomy; CKD = chronic kidney disease.

series compared with the partial nephrectomy series, which may also bias their comparison of oncologic outcomes between these two groups. This is, in part, because partial nephrectomy series were usually confined to tumors in which RCC was demonstrated on final surgical pathology, while laparoscopic cryoablation series often included tumors in which definitive preablation biopsy was not performed.[16]

The third aim of this study was to compare the long-term oncologic outcomes of cryoablation and RAPN for the management of pathologically proven RCC, while accounting and controlling for differences in baseline patient and tumor characteristics between the two treatment groups. We report a cancer recurrence rate of 12.7% in the cryoablation group, compared with a 0% recurrence rate in the RAPN group ($P < 0.01$) (mean radiographic follow-up 39.8 *vs* 21.9 mos, respectively). Our data are consistent with Cleveland Clinic data that demonstrated a local recurrence rate of 11% after cryoablation *vs* 0% after RAPN ($P < 0.0001$) (mean radiographic follow-up 44.5 *vs* 4.8 mos, respectively).[23] Our comparative Kaplan-Meier evaluation of DFS, CSS, and OS demonstrated a statistically significant long-term advantage in DFS favoring RAPN ($P < 0.01$), but no significant difference in CSS ($P = 0.41$) or OS ($P = 0.11$) between the two groups (Fig. 1). In a multivariate Cox proportional hazards model controlling for baseline patient and tumor characteristics, the risk of cancer recurrence remained higher in the cryoablation group relative to the RAPN group (HR = 11.4, $P = 0.01$). Of note, endophytic tumor growth was also associated with increased risk of cancer recurrence (HR = 46.9, $P = 0.01$) in this multivariate model. This finding may, in part, reflect the greater technical difficulty of visualizing and accessing endophytic tumors, as well as the potentially increased risk of vascular and lymphatic involvement that an endophytic/central tumor location poses.

Several limitations of this study should be addressed. First, this study is a retrospective analysis based largely on review of patient charts. Unavailable data and patient loss to follow-up may potentially impact our overall outcomes. Another limitation of the current study is the longer duration of follow-up in the cryoablation group relative to the RAPN group, which may, in turn, lead to "follow-up bias." Furthermore, because the ascertainment of our study data points predates the creation of standardized scoring systems for evaluation of tumor complexity,[24] appraisal of a tumor complexity score was not feasible in a number of our cryoablation patients. It should be noted, however, that this limitation applies to essentially all previous studies assessing long-term outcomes of cryoablation.[25–28] Despite the inconsistent reporting of a scoring system defining tumor complexity in the current study, individual tumor characteristics (eg, size and location) were appropriately controlled for when comparing outcomes between the cryoablation and RAPN groups.

Another potential limitation of this study is our reliance on radiographic assessment of tumor enhancement, without pathologic tissue corroboration, to define tumor recurrence in the cryoablation treatment group. We acknowledge that the absence of enhancement on cross-sectional imaging does not guarantee the absence of residual tumor cells and, alternatively, that recurrence of enhancement on follow-up imaging may occur without tumor recurrence. Nevertheless, we believe that these diagnostic constraints—inherent to any study of ablative therapy—would not be overcome by performing diagnostic postprocedural biopsies given the incapacity of selective tissue sampling to encompass the tumor bed in its entirety and the heterogeneous nature of the ablated tumor.

The absence of diagnostic pathology in 82% of our percutaneous cryoablation patients, which limited the number of cryoablation patients with confirmed RCC that could be included in our oncologic outcomes assessment, is another study limitation. Because routine diagnostic tumor biopsies may contribute to potentially increased risk of bleeding, as well as reduced visualization, without influencing treatment decisions, we elected not to obtain tissue biopsy during our initial percutaneous cryoablation procedures. With increasing experience performing percutaneous cryoablation, however, we have altered our practice to include diagnostic biopsies when performing this procedure. Consistent gathering of pathologic data will certainly facilitate the evaluation of oncologic outcomes of percutaneous cryoablation in future studies.

Conclusion

Cryoablation and RAPN are safe treatment alternatives for managing renal masses amenable to a nephron-sparing procedure, offering significant preservation of renal function with acceptable morbidity. While RAPN offers improved DFS, for patients who are prepared to undergo close postoperative monitoring and who accept the potential need to undergo salvage treatment in the case of tumor recurrence, cryoablation offers excellent long-term CSS. Patients with compromised health status who desire active treatment but are not medically eligible for major surgery involving renal parenchymal incision are ideal candidates for cryoablation. Additional long-term follow-up and well-designed prospective comparative studies are needed to corroborate these findings.

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Disclosure Statement

Dr. Bhayani is a consultant for Surgiquest. For the remaining authors, no competing financial interests exist.

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Abbreviations Used

AUA = American Urological Association
CCI = Charlson Comorbidity Index
CSS = cancer-specific survival
CT = computed tomography
DFS = disease-free survival
eGFR = estimated glomerular filtration rate
HR = hazard ratio
MRI = magnetic resonance imaging
OR = odds ratio
OS = overall survival
RAPN = robot-assisted partial nephrectomy
RCC = renal-cell carcinoma
SD = standard deviation
SRM = small renal masses