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Ten-Year Experience with Percutaneous Cryoablation of Renal Tumors: Tumor Size Predicts Disease Progression

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Abstract

Introduction: Percutaneous cryoablation (PCA) has emerged as an alternative to extirpative management of small renal masses (SRMs) in select patients, with a reduced risk of perioperative complications. Although disease recurrence is thought to occur in the early postoperative period, limited data on long-term oncologic outcomes have been published. We reviewed our 10-year experience with PCA for SRMs and assessed predictors of disease progression.

Materials and Methods: We reviewed our prospectively maintained database of patients who underwent renal PCA from March 2005 to December 2015 ($n=308$). Baseline patient and tumor variables were recorded, and postoperative cross-sectional imaging was examined for evidence of disease recurrence. Disease progression was defined as the presence of local recurrence or new lymphadenopathy/metastasis.

Results: Mean patient age was 67.2 ± 11 years, mean tumor size was 2.7 ± 1.3 cm, and mean nephrometry score was 6.8 ± 1.7 . At mean follow-up of 38 months, local recurrence and new lymphadenopathy/metastasis occurred in 10.1% (31/308) and 6.2% (19/308) of patients, respectively. Excluding patients with a solitary kidney and/or von Hippel–Lindau, local recurrence and new lymphadenopathy/metastasis occurred in 8.6% (23/268) and 1.9% (5/268) of cases, respectively. Kaplan–Meier estimated disease-free survival was 92.5% at 1 year, 89.3% at 2 years, and 86.7% at 3 years post-PCA. Increasing tumor size was a significant predictor of disease progression (hazard ratio 1.32 per 1-cm increase in size, $p=0.001$).

Conclusions: PCA is a viable treatment option for patients with SRMs. Increasing tumor size is a significant predictor of disease progression following PCA.

Keywords: kidney, carcinoma, renal cell, cryosurgery, disease progression, forecasting

Introduction

THE INCIDENCE OF RENAL-cell carcinoma (RCC) has risen steadily over the past few decades as widespread utilization of diagnostic abdominal imaging has increased incidental discovery of small renal masses (SRMs).^{1,2} In the United States, the estimated number of newly diagnosed RCC cases in 2018 has reached >65,000 and continues to rise.³ Historically, SRMs have been treated aggressively, with radical nephrectomy being the standard of care. Over the past two decades, however, nephron-sparing surgery has

become the preferred treatment option due to the benefits of preserved renal function, along with favorable oncologic outcomes.^{4–6}

While partial nephrectomy has emerged as the most popular treatment option for SRMs, thermal ablation modalities such as cryoablation and radiofrequency ablation remain viable alternatives.⁷ In previous studies, cryoablation has demonstrated reduced morbidity with comparable intermediate-term oncologic profiles to partial nephrectomy.^{8–10} Furthermore, when compared with radiofrequency ablation, cryoablation results in improved local control, fewer retreatments, and decreased risk

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of metastatic progression, making it arguably the most efficacious, thermal ablative modality available.¹¹ Despite its increasing use, however, there remains a lack of long-term oncological and functional data. In this study, we present perioperative, functional, and oncologic outcomes of percutaneous cryoablation (PCA) based on our single-institution experience over a 10-year period.

Materials and Methods

With Institutional Review Board approval, we retrospectively reviewed our prospectively maintained database of patients who underwent PCA for SRMs at our institution between March 2005 and December 2015. All included patients underwent preoperative imaging (CT or MRI) that demonstrated one or more contrast-enhancing renal masses with features concerning for RCC. Indications for PCA included patient comorbidity and surgical risk, history of nephrectomy or otherwise impaired baseline renal function, multiple tumors, tumor size and location, and patient and surgeon preference. Postoperatively, patients underwent surveillance contrast-enhanced imaging (CT or MRI) at 3, 6, and 12 months and annually thereafter.

PCA technique

Our technique for PCA has previously been described.¹² Briefly, PCA was performed by interventional radiology with real-time CT guidance under general anesthesia. Patients were treated with either 3.4-mm cryoprobes (Oncura, Inc., Plymouth Meeting, PA) or 1.7- and 2.4-mm cryoprobes (Endocare, Inc., Irvine, CA), with an average of four probes per tumor. Algorithm-based freezing times were employed based on intraoperative radiographic monitoring and tumor-specific factors, typically with two freeze cycles and an active thaw cycle.

Data collection and analysis

Patient demographics, tumor characteristics, perioperative outcomes, postoperative follow-up imaging, and pre-/postoperative serum creatinine were recorded and assessed. Baseline comorbidities were assessed using the Charlson comorbidity index (CCI).¹³ Tumors were classified according to the nephrometry score.¹⁴ The estimated glomerular filtration rate (eGFR) was calculated preoperatively, at the time of discharge, and at the most recent follow-up using the Modification of Diet in Renal Disease Study equation.¹⁵ Postoperative complications were classified according to the Clavien–Dindo grade.¹⁶ Disease progression was defined as local recurrence (a new enhancing or growing lesion within the margin of the ablated zone) or presence of new lymphadenopathy or metastasis postoperatively. Overall survival (OS) was defined as absence of death from any cause. Disease-free survival (DFS) was defined as survival in the absence of disease progression on follow-up imaging. Additional analysis was performed excluding patients with a solitary kidney due to employment of a less aggressive ablation technique and consequent increased risk of recurrence in this population.

Statistical analysis was performed using R, version 3.2.2. Univariate analysis was performed using the Mann–Whitney *U* test for continuous variables and the chi-squared test for

categorical variables. Multivariate Cox proportional hazards regression analysis was performed to identify variables predictive of disease progression. Kaplan–Meier estimated survival curves were generated for OS and DFS. Statistical significance was defined by a *p* value of <0.05.

Results

PCA was performed on a total of 328 tumors in 308 patients. Patient characteristics are summarized in Table 1. Mean age was 67.2 ± 11 years, mean body mass index (BMI) was 32.3 ± 8.7 , and mean preoperative eGFR was 70.6 ± 27.6 mL/min/1.73 m². There were 34 (11.0%) patients with a solitary kidney and six (1.9%) with von Hippel–Lindau (VHL). Tumor characteristics are summarized in Table 2. The mean tumor size was 2.7 ± 1.3 cm and mean nephrometry score was 6.8 ± 1.7 . Biopsy was performed on 203 (61.9%) tumors, of which 141 received a histopathological diagnosis of RCC. Biopsy was performed preoperatively in 51 (16.5%) patients and intraoperatively in 143 (46.4%) patients.

Perioperative and renal functional outcomes are summarized in Table 3. Mean length of hospital stay was 1.4 ± 2.4 days. At the time of discharge, mean eGFR was 66.9 ± 28.2 mL/min/1.73 m². Intraoperative and postoperative complication rates were 1.0% and 7.1%, respectively. Intraoperative complications consisted of renal parenchymal fracture requiring nephrostomy tube placement (*n* = 1), partial splenic infarction (*n* = 1), and oxygen requirement due to desaturation (*n* = 1). Postoperative complications within 90 days of PCA included blood transfusion in the setting of hematoma or hematuria (*n* = 8), lower extremity deep venous thrombosis (*n* = 2),

TABLE 1. PATIENT CHARACTERISTICS

Characteristic	Value
Age (years), mean (SD)	67.2 (11.0)
BMI (kg/m ²), mean (SD)	32.3 (8.7)
Ethnicity, <i>n</i> (%)	
Caucasian	260/308 (84.4)
African American	45/308 (14.6)
Other	3/308 (1.0)
Sex, <i>n</i> (%)	
Male	192/308 (62.3)
Female	116/308 (37.7)
CCI, <i>n</i> (%)	
0	55/308 (17.9)
1	58/308 (18.8)
2	76/308 (24.7)
≥3	119/308 (38.6)
Preoperative eGFR (mL/min/1.73 m ²), mean (SD)	70.6 (27.6)
History of renal procedure, <i>n</i> (%)	
Prior partial nephrectomy	34/308 (11.0)
Prior radical nephrectomy	33/308 (10.7)
Prior cryoablation	15/308 (4.9)
Solitary kidney, <i>n</i> (%)	34/308 (11)
VHL syndrome, <i>n</i> (%)	6/308 (1.9)
COPD, <i>n</i> (%)	52/308 (16.9)

BMI=body mass index; CCI=Charlson comorbidity index; COPD=chronic obstructive pulmonary disease; eGFR=estimated glomerular filtration rate; SD=standard deviation; VHL= von Hippel–Lindau.

TABLE 2. TUMOR CHARACTERISTICS

Characteristic	Value
Nephrometry score, mean (SD)	6.7 (1.7)
Tumor size (cm), mean (SD)	2.7 (1.3)
Clinical T stage, <i>n</i> (%)	
T1a (≤ 4 cm)	296 (90.2)
T1b (>4 but ≤ 7 cm)	32 (9.8)
Laterality, <i>n</i> (%)	
Left	167 (50.9)
Right	161 (49.1)
Exophytic property, <i>n</i> (%)	
$\geq 50\%$ exophytic	165 (50.3)
$<50\%$ exophytic	116 (35.4)
Completely endophytic	47 (14.3)
Nearness to collecting system, <i>n</i> (%)	
≥ 7 mm	104 (31.7)
>4 but <7 mm	93 (28.4)
≤ 4 mm	129 (39.3)
Missing	2 (0.6)
Anterior–posterior location, <i>n</i> (%)	
Anterior	62 (18.9)
Posterior	182 (55.5)
Lateral	84 (25.6)
Polar location, <i>n</i> (%)	
Upper pole	101 (30.8)
Central zone	118 (36.0)
Lower pole	109 (33.2)
Hilar, <i>n</i> (%)	25 (7.6)
Biopsy status, <i>n</i> (%)	
Not performed	125 (38.1)
Renal-cell carcinoma	141 (43.0)
Clear cell	100 (30.5)
Papillary	25 (7.6)
Chromophobe	1 (0.3)
Unspecified	15 (4.6)
Oncocytoma	21 (6.4)
Angiomyolipoma	3 (0.9)
Other benign biopsies	19 (5.8)
Epithelioid sarcoma (metastasis)	1 (0.3)
Insufficient for diagnosis	18 (5.8)

pulmonary embolism ($n=2$), urinary tract infection ($n=2$), pericardial effusion requiring pericardiocentesis ($n=2$), colonic microperforation ($n=1$), duodenal and ureteral injury resulting in a persistent retroperitoneal abscess and duodenal-ureteral fistula ($n=1$), colonic pneumatosis ($n=1$), chronic obstructive pulmonary disease (COPD) exacerbation ($n=1$), metabolic encephalopathy secondary to acute renal failure ($n=1$), and seizure ($n=1$).

The colonic microperforation occurred in a patient with a 4.3 cm left lower pole tumor, nephrometry score 5a. This presumed intraoperative injury was diagnosed approximately 4 weeks postoperatively, when the patient presented with hematochezia and abdominal pain, and a CT scan was performed. The perforation was managed conservatively, and the patient made a complete recovery. The duodenal and ureteral injury occurred in a patient with a 4.3 cm right lower pole tumor, nephrometry score 8a. This presumed intraoperative injury was diagnosed 2 weeks postoperatively when the patient presented with abdominal pain, and a CT scan was performed. An abscess drain and nephrostomy tube

TABLE 3. PERIOPERATIVE, RENAL FUNCTIONAL, AND ONCOLOGICAL OUTCOMES

Outcome	Value
Length of stay (days), mean (SD)	1.4 (2.4)
Intraoperative complications, <i>n</i> (%)	3/308 (1.0)
Postoperative complications (Clavien II or greater), <i>n</i> (%)	22/308 (7.1)
eGFR at discharge (mL/min/1.73 m ²), mean (SD)	66.9 (28.2)
Creatinine follow-up (months), mean (SD)	39.4 (27.2)
eGFR at latest follow-up, (mL/min/1.73 m ²), mean (SD)	58.9 (27.3)
Change in eGFR (mL/min/1.73 m ²), mean (SD)	−11.7 (38.8)
Surveillance follow-up (months), mean (SD)	37.8 (23.6)
Disease progression, <i>n</i> (%)	44/308 (14.3)
Local recurrence	31/308 (10.1)
New lymphadenopathy or metastasis	19/308 (6.2)
Disease progression (excluding solitary kidney and VHL), <i>n</i> (%)	27/268 (10.1)
Local recurrence	23/268 (8.6)
New lymphadenopathy or metastasis	5/268 (1.9)

were placed, and the complication was managed non-operatively. At present, all drains have been removed.

Univariate analysis comparing mean tumor size, nephrometry score, and age-adjusted CCI of patients with and without postoperative complications requiring intervention (Clavien-Dindo grade ≥ 2) is summarized in Table 4. Patients with postoperative complications had significantly higher mean tumor size (3.7 vs 2.6 cm, $p<0.001$) and baseline comorbidity (59.5% vs 35.8% with CCI ≥ 3 , $p=0.04$) than those without complications.

At a mean creatinine follow-up of 39.4 ± 27.2 months, mean postoperative eGFR was 58.9 ± 27.3 mL/min/1.73 m², representing a mean decline in eGFR of 11.7 ± 38.8 mL/min/1.73 m² (15%, $p<0.001$).

Disease progression was observed in 14.3% (44/308) of patients at a mean follow-up of 37.8 ± 23.6 months. New lymphadenopathy or metastasis was observed in 6.2% (19/308) of patients. Local tumor recurrence occurred in 10.1% (31/308) of patients. Six patients had both local and distant disease progression. Of the entire cohort, a significantly

TABLE 4. UNIVARIATE ANALYSES OF CLINICAL FACTORS PREDICTIVE OF POSTOPERATIVE COMPLICATIONS (CLAVIEN II OR GREATER)

Variable	With postoperative complications	Without postoperative complications	<i>p</i>
Nephrometry score, mean (SD)	7.2 (1.5)	6.7 (1.7)	0.119
Tumor size (cm), mean (SD)	3.4 (1.3)	2.6 (1.3)	<0.001
CCI			
0	18.5%	13.5%	0.040
1	19.2%	16.2%	
2	26.6%	10.8%	
≥ 3	35.8%	59.5%	

Bold values represent statistical significance ($p<0.05$).

higher rate of local recurrence was observed in T1b tumors (34.5%) than in T1a tumors (7.7%) ($p < 0.001$). Excluding patients with a solitary kidney or VHL, the disease progression rate was 10.1% (27/268); local recurrence and new lymphadenopathy or metastasis occurred in 8.6% (23/268) and 1.9% (5/268), respectively. One patient in this subset had both local and distant disease progression. Of the patients with a histopathological diagnosis of RCC (excluding those

with a solitary kidney and VHL), disease progression occurred in 10.7% (12/112); local recurrence and new lymphadenopathy or metastasis occurred in 8% (9/112) and 3.6% (4/112), respectively. One patient in this subset had both local and distant disease progression.

Mean time to local recurrence was 15.1 ± 16.3 months, with 26% (8/31) occurring ≥ 24 months after PCA. Repeat PCA was performed in 19/31 (61.3%) local recurrences, of

FIG. 1. Kaplan–Meier estimated curves for (A) overall survival and (B) disease-free survival, stratified by clinical tumor stage.

which 9 were treated with one reablation. Two patients underwent 2 or more reablations, both of which had persistent disease at the latest follow-up. Twelve patients opted for active surveillance and did not undergo additional treatment.

Kaplan–Meier estimated OS and DFS curves stratified by clinical tumor stage are displayed in Figure 1. The Kaplan–Meier estimated OS and DFS for T1a tumors, respectively, were 98.0% and 95.6% at 1 year, 94.1% and 93.3% at 2 years, and 87.6% and 90.3% at 3 years post-PCA. OS and DFS for T1b tumors, respectively, were 96.3% and 69.0% at 1 year, 80.4% and 61.3% at 2 years, and 67.8% and 61.3% at 3 years. Cox proportional hazards regression analysis evaluating clinical variables predictive of PCA disease progression is summarized in Table 5. Controlling for age, BMI, and tumor location, significant predictors of disease progression were increasing tumor size (hazard ratio [HR] 1.32 per 1-cm increase in size, $p=0.001$) and comorbidity with COPD (HR 2.85, $p=0.032$).

Discussion

The incidence of RCC continues to rise, with an estimated 65,340 new cases and 14,970 deaths in the United States in 2018.³ In the era of nephron-sparing therapy, the emergence of PCA has provided patients with SRMs an alternative treatment option demonstrating favorable perioperative, functional, and oncologic outcomes.^{8–11} Accordingly, current American Urological Association (AUA) guidelines endorse focal ablative therapy as an approach for management of SRMs <3 cm in patients deemed unfit for extirpative surgery due to age, comorbidity, or tumor characteristics.⁷ The oncological success of PCA has been demonstrated in the short and intermediate term; however, few long-term studies exist.^{8–11} In the present study, disease progression occurred in 10% of patients at a mean follow-up of 38 months. Nearly one-third of local recurrences were treated with a single reablation, providing an overall success rate approaching that of extirpative treatment.

Our disease progression rate is within the range of most other published reports.^{10,12,17} Accordingly, multi-institutional data from the 2009 AUA guidelines meta-analysis demonstrated a similar recurrence-free survival rate of 87.6% at mean follow-up of 26 months following cryoablation.¹⁸ However, several recent studies report higher treatment success rates. In a recent comparison of oncologic outcomes following partial nephrectomy and percutaneous ablation, Andrews et al. reported local

recurrence and distant metastasis rates of 3.3% and 0.9%, respectively, in their series of 187 patients with cT1 masses at a median follow-up of 6.3 years.¹⁰ Bhindi et al. reported a combined local failure and metastasis development rate of 4.9% in their series of 618 tumors in 565 patients at a median follow-up of 34 months.⁶ It is worth noting, however, that this study reported missing data on local recurrence and new metastases in 8.5% and 4.6% of the study cohort, respectively. Among other recent, large ($n>150$) single-center studies of PCA, three have also reported lower rates of disease progression than ours, including 8%⁸ (combined local recurrence and metastasis development), 2.8%,¹⁹ and 3.5% (local recurrence)²⁰. Notably, mean follow-up times in these studies were 18.1, 10.8, and 27.9 months, respectively. Our finding that approximately one-quarter of disease progression occurred beyond 24 months, with roughly 9% occurring after 5 years post-PCA, may suggest that several studies lack sufficient follow-up to diagnose late recurrences. Additionally, institution-specific practices pertaining to patient selection for focal vs extirpative treatment likely also have a substantial effect on oncologic outcomes, which may, in part, account for differences in reported figures among centers.

Differences in PCA technique may also account for the wide range of reported disease progression rates in the literature. While our institution utilized algorithm-based empiric freezing times dependent on tumor-specific factors, others have reported the use of variable freeze times based upon adequate ice ball formation observed through radiographic monitoring.^{6,8,19,20} Vricella et al. report using as many as four freeze–thaw cycles to ensure adequate tumor destruction.²¹ These measures may improve tumor control and therefore increase the likelihood of treatment success with PCA.

An important factor in the analysis of oncologic outcomes is the biopsy result of the cohort. Several series, including our own, include a significant number of patients with unsampled, nondiagnostic, or benign tumors, which tends to skew outcomes to appear more positive. Still, roughly 70% of the 203 tumors biopsied in the present study received a histopathological diagnosis of RCC, suggesting that our outcome results are mostly specific to renal malignancies. In our study, disease progression occurred in 10.7% of patients with biopsy-proven RCC, which is congruent with the overall cohort and validates our results. It is important to note that studies have demonstrated both significant intratumoral heterogeneity²² and imperfect concordance between biopsy and final pathology,²³ which create the potential for false negative biopsy results. With this in mind, we postulate that some patients with a benign biopsy may harbor RCC.

Our results support the known association between increasing tumor size and disease progression following PCA. The rate of local recurrence in T1b tumors was nearly five times greater than that of T1a tumors. Accordingly, the Kaplan–Meier analysis demonstrated lower OS and DFS for T1b tumors. Our multivariate analysis found that each 1-cm increase in tumor size was associated with a 1.3-fold increased risk of disease progression. While significant associations between tumor size and disease progression have previously been demonstrated,^{12,24–26} overall results are conflicting. In a study of 139 patients undergoing PCA, Blute et al. did not find tumor size to be predictive of local recurrence.²⁷ Interestingly, two publications from Mayo Clinic showed similar local failure rates following thermal ablation

TABLE 5. COX PROPORTIONAL HAZARDS REGRESSION ANALYSIS OF DISEASE PROGRESSION (EXCLUDING PATIENTS WITH A SOLITARY KIDNEY AND VON HIPPEL–LINDAU)

Variable	Hazard ratio	95% CI	p
Age	0.97	0.93–1.02	0.195
BMI	1.01	0.96–1.07	0.617
COPD	2.85	1.09–7.44	0.032
Tumor size	1.32	1.11–1.57	0.001
Completely endophytic tumor	0.30	0.04–2.33	0.249
Central zone tumor	1.50	0.61–3.70	0.375
Tumor ≤4 cm from collecting system	1.62	0.69–3.82	0.270
Hilar tumor	0.60	0.12–3.06	0.540

Bold values represent statistical significance ($p<0.05$).

among patients with small (<3 cm) vs large (3–8.3 cm) renal masses (2.8% and 3%, respectively).^{19,28} Both studies report disease progression rates considerably lower than most PCA studies, in addition to short follow-up times (10.8 and 15 months, respectively). As mentioned previously, the contrasting findings of the present study may be attributable to substantial differences in follow-up duration, which significantly impact both functional and oncological outcomes. Additionally, variations in PCA technique between institutions (e.g., freeze times, freeze–thaw cycles, number/types of cryoprobes used, and overlapping ablation zones) may explain differences in success rates for larger tumors.

Interestingly, our multivariate analysis also found comorbidity with COPD to be associated with disease progression. While there is no known common biochemical pathway between the pathogenesis of COPD and RCC to explain this relationship, cigarette smoking has been identified as a highly significant risk factor for both COPD and RCC development.²⁹ Furthermore, a known association exists between increasing cigarette use and the likelihood of advanced RCC at presentation.²⁹ Given this relationship, we hypothesize that a diagnosis of COPD may be a surrogate for smoking burden in this study.

Active surveillance is also a robust management option for SRMs. Ideal candidates for active surveillance are typically older, comorbid high-surgical risk patients and thus are often also considered for ablation. Data from the Trial of Delayed Intervention and Surveillance for Small Renal Masses (DISSRM) showed 5-year cancer-specific survival rates of 100% for active surveillance and 99% for primary intervention, accounting for a 9% crossover from active surveillance to primary intervention.³⁰ PCA represents a favorable option in patients who have failed or do not wish to pursue active surveillance.

There was an overall trend toward increased procedural complication risk with increasing tumor diameter, which has previously been reported.²⁵ We believe this to be the result of an increased number of cryoprobes being used for these procedures. Patients with large tumors should be counseled on increased risk of procedural complications as well as incomplete treatment with a single ablation.

The present study has several limitations. First, due to the retrospective design of the study, there exist selection bias and unmeasured confounding variables. Patients selected to undergo PCA typically have inherently different baseline characteristics than those who undergo extirpative surgery. Second, although the present study features one of the longest follow-up durations, more substantial follow-up is required to validate long-term oncological and functional outcomes. Third, renal functional outcomes are naturally confounded by increasing age and comorbidity, thereby making the effect of PCA treatment, specifically, difficult to determine. Fourth, the present study, like many others of PCA, includes a significant number of tumors without pathologic confirmation of malignancy, allowing for potential positively skewed oncological outcomes. Due to concern for possible treatment complications, our interventional radiologists did not routinely perform biopsies before PCA early in the study period given that results are not used to guide PCA treatment decisions. However, as our experience with PCA has increased substantially, biopsies are now performed routinely at the start of each procedure.

Conclusions

PCA has an important role in management of SRMs in select patients, providing acceptable morbidity, preservation of renal function, and favorable long-term oncological control. Approximately one in four local recurrences occurs beyond 24 months after PCA. Increasing tumor size is a significant predictor of disease progression.

Author Disclosure Statement

No competing financial interests exist.

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Abbreviations Used

AUA = American Urological Association
 BMI = body mass index
 CCI = Charlson comorbidity index
 COPD = chronic obstructive pulmonary disease
 CT = computed tomography
 DFS = disease-free survival
 DISSRM = Delayed Intervention and Surveillance
 for Small Renal Masses
 eGFR = estimated glomerular filtration rate
 HR = hazard ratio
 MRI = magnetic resonance imaging
 OS = overall survival
 PCA = percutaneous cryoablation
 RCC = renal-cell carcinoma
 SD = standard deviation
 SRM = small renal mass
 VHL = von Hippel–Lindau