Published in final edited form as:

J Urol. 2011 January ; 185(1): 49–53. doi:10.1016/j.juro.2010.09.032.

Feasibility and outcomes of partial nephrectomy for resection of at least 20 tumors from a single renal unit

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Abstract

Purpose—Patients with hereditary renal cancer are at increased risk for formation of recurrent, bilateral, multifocal tumors and may require aggressive nephron sparing surgery to prevent renal replacement therapy. Here, we evaluate the feasibility and outcomes of patients who underwent partial nephrectomy with removal of at least 20 tumors from a single renal unit in one setting.

Materials and Methods—We retrospectively reviewed the records of 30 patients who underwent 34 partial nephrectomies with removal of at least 20 tumors at our institution from 1993 to 2008. Operative reports and hospital records were reviewed for perioperative data, renal function and oncologic outcomes. Comparison of preoperative and postoperative renal function was performed using the 2-tailed T test.

Results—There were no mortalities and only one renal unit was lost. The median number of tumors removed was 26.5. The median EBL was 3,500ml, and the median operative time was 9 hours. Perioperative complications occurred in greater than 50% the of cases. There was a statistically significant decrease in postoperative eGFR (67 vs 59 ml/min/1.73m², $p < 0.001$) at 3 months. Only one patient developed metastatic disease, and 8 of the 34 operated kidneys required subsequent intervention during the median follow up of 52 months (4-187).

Conclusions—Aggressive partial nephrectomy for resection of multiple tumors is technically feasible. Although there was a significant decrease in postoperative renal function, more than 80% of the starting renal function was preserved in this cohort, except for one patient. In addition, oncologic outcomes are encouraging at intermediate term follow up.

Keywords

hereditary RCC; partial nephrectomy; outcomes; complications; multifocal RCC

Partial nephrectomy has become a well established alternative to radical nephrectomy especially in patients with a genetic predisposition to bilateral, multifocal renal tumors such as patients with von Hippel Lindau (VHL), hereditary papillary renal cell carcinoma (HPRCC) and Birt-Hogg-Dube.¹ A delicate balance between sound oncologic surgeries and preservation of functional renal parenchyma is necessary to prevent metastatic disease and avoid the need for renal replacement therapy, as these patients tend to develop de novo and recurrent kidney tumors.²

A tumor size of 3cm has been used as a threshold for intervention in patients with some familial multifocal RCC. This 3cm threshold has been shown to be safe for active

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surveillance in these hereditary renal cancer syndromes, with no patients developing metastatic disease while on active surveillance.^{3, 4} Once the largest solid lesion reaches 3 cm, patients are recommended to undergo surgery for the removal of the 3cm lesion and any other lesions detected intraoperatively.

While a number of reports document outcomes of patients with hereditary kidney cancer who have undergone nephron sparing surgeries,^{5- 8} the question of how aggressive these interventions should be remains unanswered. In order to address this question we evaluated the feasibility and outcomes of one of the most challenging cohorts of patients; those who underwent partial nephrectomy for the resection of at least 20 tumors from a single renal unit in a single setting.

Materials and Methods

We queried the database of patients treated at the Urologic Oncology Branch of the National Cancer Institute from 1993 – 2008 and identified 30 patients that underwent a total of 34 partial nephrectomies for resection of at least 20 tumors removed from a single renal unit in a single setting. The surgical treatment of multifocal RCC utilized enuclear resections by removing tumors with their pseudocapsule and leaving functional renal parenchyma preserved, as previously described.² In most cases, solid and cystic lesions are removed with enuclear resection, although cyst stripping is occasionally performed with coagulation of the base. This technique allows for a maximal preservation of parenchymal volume as well as functioning renal tissue. In all cases, intraoperative renal ultrasound was performed during the procedure, and all identifiable renal lesions are resected. The rationale for this technique is based on the principle of maximally delaying the need for any subsequent intervention for recurrent tumors.

The pathology reports of these patients were reviewed for the number of tumors resected, size, type (solid versus cystic) and grade of renal cell cancer. Baseline demographic data was collected on all patients. Operative reports, history and physical examination on admission, anesthesia records, and discharge summaries were reviewed for perioperative and postoperative data. Patients were followed at regular intervals with history and physical examination, renal functional tests, and abdominal and chest imaging starting at 3 months postoperatively.

Functional outcomes were assessed using preoperative and postoperative serum creatinine, estimated glomerular filtration rate (eGFR) calculated using the MDRD equation, and differential renal function obtained with a nuclear renogram (DTPA or MAG3) if both renal units were present. Preoperative and postoperative renal studies were obtained before and at least 3 months after the procedure, respectively.

Oncological outcomes were determined by assessing the development of metastatic disease and the need for subsequent ipsilateral renal interventions for recurrent or *de novo* tumor formation. Statistical analysis was completed using the 2-tailed T test and statistical significance was considered with $p < 0.05$.

Results

Clinical characteristics are shown in Table 1. All 30 patients, who underwent a total of 34 partial nephrectomies on 34 renal units, had an open surgical approach. A third of the patients had had a prior ipsilateral partial nephrectomy, and another third had a solitary kidney at the time of the surgical procedure. Some surgeries resulted in the removal of as many as 70 tumors and lasted as long as 18 hours.

Perioperative outcomes are outlined in Table 2. The majority of patients (88%) required blood transfusions with a median of 6.5 units of blood transfused (range 0 to 32). The most common intraoperative complication was pleural injury and the most common postoperative complication was urine leak (defined as a need for a drain for more than 7 days postoperatively). Urine leaks resolved in the majority of patients without a need for further intervention. One patient required ureteral stenting with eventual resolution of the leak. While postoperative complications occurred in greater than 50% of cases, there were no mortalities in this cohort and patients were discharged from the hospital at a median of 9 days postoperatively. Cardiovascular complications included a postoperative myocardial infarction in one patient and cardiac arrhythmias in 2 others. Loss of a renal unit occurred in 1 patient. In this patient, intraoperatively, a renal vein thrombus was identified, and the decision was made to perform a radical nephrectomy. Because this patient had a poorly functioning contralateral kidney after prior contralateral partial nephrectomy, he required permanent hemodialysis.

Renal functional outcomes are listed in Table 3. Excluding one patient requiring dialysis, the postoperative serum creatinine of the cohort was significantly higher than the preoperative serum creatinine (1.3 vs. 1.1 mg/dl, $p < 0.001$) and the postoperative eGFR was significantly decreased in comparison to the preoperative values (66.5 vs. 59.4ml/min/1.73m², $p < 0.001$). Of the patients with both kidneys remaining, the postoperative renal split function of the operated renal unit was significantly decreased compared to its preoperative contribution (51% vs. 59%, $p = 0.001$).

Oncological outcomes are listed in Table 4. At a median time of 52 months (4-187) all patients are alive. Only one patient (3%) developed metastatic disease at 5 months postoperatively. This patient underwent a successful thoracotomy and metastatectomy for 1 clear cell metastasis to the lung and is presently without evidence of metastatic disease 69 months after his metastatectomy. Additionally, eight (24%) patients required subsequent interventions for tumor recurrence or *de novo* tumor formation, at a median time to subsequent intervention of 33 months (mean of 44 months). Three patients underwent subsequent repeat partial nephrectomy, 2 had a radical nephrectomy, and 2 patients had percutaneous renal radiofrequency ablation. One of the patients treated with RFA underwent another partial nephrectomy 53 months after the RFA. The remaining patient was enrolled in a therapeutic clinical trial; he has not required surgical intervention approximately 3 years after initiation of therapy.

Discussion

Most patients with hereditary renal cancer differ from patients with sporadic disease as their tumors are not only multifocal and bilateral, but they occur at a younger age with a propensity for recurrence and growth.¹⁰ Multiple surgical interventions on the same renal unit are sometimes required to preserve renal function and avoid renal replacement therapy.⁵⁻⁸ In fact, with the frequency of multifocal RCC ranging from 4.3-25%,¹⁰ a significant proportion of RCC patients will present with multiple renal lesions detected radiographically, and many will be counseled to undergo nephrectomy because of technical complexities or oncologic considerations.

Our patient population provides the opportunity to examine the outcomes of surgeries performed for this challenging group of patients. In our series, a third of patients had a partial nephrectomy performed for imperative indications due to the presence of a solitary renal unit. Another third of patients had reoperative renal surgery which has already been shown to be technically complex with a high rate of perioperative complications.⁷⁻⁹ Despite these challenges, there were no mortalities and only one renal unit was lost.

The most common postoperative complication in this series was prolonged urinary leak which was seen in 32% of patients. While this is a higher rate when compared to other reported series,^{9, 16} most of these urinary leaks resolved with conservative management, with only one patient requiring ureteral stenting. Not surprisingly, the major perioperative complication rate in our series was 24%, a number higher than the major complication rates reported in recent partial nephrectomy series by Pasticier (12.6%)¹⁷ and Ray (11%).¹⁸ It is likely that the number of tumors resected as well as the high proportion of repeat partial nephrectomies in our series led to these higher complication rates.

Of note, there was considerable intraoperative blood loss, with 88% of patients in our series receiving a blood transfusion intraoperatively and 12% requiring additional transfusions in the postoperative period. The extensive requirements for transfusions (as many as 32 units) seen in this series is likely a result of our attempt to preserve renal functional parenchyma by reducing ischemic times and performing most of the procedure without clamping the renal hilum. Subjecting patients to prolonged ischemia times may result in loss of renal function, and repeated clamping for select lesions may not be desirable because of the deleterious effects of reperfusion injury.²² While blood loss and transfusions are not inconsequential, the profound effect of prolonged ischemia on renal function has been well recognized. In fact, the duration of renal ischemia has been found to be the strongest modifiable risk factor for the preservation of renal function after partial nephrectomy.^{14,15} We typically perform our tumor resections without renal clamping until absolutely needed. In our series, 59% of surgeries were performed without clamping the renal hilum. Of the patients in which the renal hilum was clamped, more than 80% of these were done with cold ischemia, and the median ischemic time was 42 minutes. When compared to the median preoperative and postoperative serum creatinine values, there was an increase of 0.15mg/dl in the clamped group and 0.20mg/dl in the unclamped group. This did not represent a significant change.

Preservation of renal function with adequate oncological control is the goal in patients with hereditary and multifocal renal cell carcinoma. In our cohort, mean postoperative serum creatinine increased by 0.2mg/dl, similar to the increase of 0.19mg/dl reported by Johnson et al for repeat partial nephrectomy in patients with hereditary renal cell carcinoma.⁹ Although the increase in serum creatinine was statistically significant, and the decrease in creatinine clearance and split function was also statistically significant, these patients retained more than 80% of their preoperative renal function.

While there are several options for renal replacement therapy, dialysis and transplantation are associated with considerable morbidity and mortality. Some studies have shown that renal insufficiency is associated with an increased risk of cardiovascular events and mortality, with the risk being especially prominent in elderly patients.^{23,24} Despite advancements in dialysis technology, the mortality risk for patients requiring dialysis remains high. For instance, a 49 year old patient with ESRD on hemodialysis is expected to live 7 years, compared to 30 years for a person of the same age in the general population.²⁵ While renal transplantation after bilateral nephrectomy could be an approach for management of patients with hereditary RCC, significant shortage of organ availability, complications associated with transplantation, and variable graft survival make this option suboptimal at the present time.²⁵

An additional challenge in patients with hereditary RCC is assessment of cancer control, as these patients are at increased risk for *de novo* tumor formation. It is often difficult to distinguish *de novo* lesions from recurrences. Therefore, the most optimal assessments of oncologic control comes from evaluation of metastatic rates and the need for subsequent renal intervention.

The low rate of metastatic disease in this cohort of patients (3%), is similar to that reported by Johnson et al (5.8%), Steinbach et al (8%), and Roupret et al (0%) for patients with hereditary RCC.^{6, 9, 19} In our cohort, at the median follow of 52 months, only 1 patient developed metastatic disease. This patient's metastasis was detected 5 months after the surgery. Of importance, however, 8 months prior to the diagnosis of his metastatic disease he underwent a partial nephrectomy in the contralateral renal unit for 17 renal masses with the largest solid tumor measuring 5.5cm, thus making the attribution of the cause for his metastatic event difficult. Nonetheless, this patient is without evidence of metastatic disease at this time 5.5 years after his metastatectomy.

It appears that even with the resection of numerous tumors in our cohort, the presence of multifocality and the large number of tumors does not define the metastatic potential. Rather, the size of the largest lesion appears to be the main factor that drives the oncologic outcomes. Duffey et al studied the relationship between tumor size and metastasis in VHL patients, and demonstrated that as many as 21% of patients with tumors 4.1-5.5cm, and as many as 50% of patients with tumors 6-10cm developed metastatic disease.³ The metastatic potential of these hereditary tumors may be best determined by the careful radiological follow up of these patients and timely interventions once a tumor size reaches 3 cm. Similar to patients with inherited forms of kidney cancer, increased rates of metastasis are also seen with larger tumors in sporadic renal cell tumors as well.^{3, 20}

Eight of these patients (24%) developed recurrent or de novo tumors requiring subsequent renal intervention with a median time to intervention of 33 months. Our rate of repeat intervention is comparable to a 27% rate of tumor recurrence in VHL patients reported by Roupret et al.¹⁹ Notably, of these patients that underwent repeat intervention, only 2 required a radical nephrectomy, while the remaining patients kept their native renal units. Of the 2 patients treated with radiofrequency ablation 18 and 82 months after surgery, one has not required any additional intervention at 69 months. The other underwent another partial nephrectomy 53 months after ablation (71months after original ipsilateral surgery). While less invasive techniques such as RFA and cryosurgery are becoming more prevalent for the management of small, asymptomatic tumors in patients with sporadic disease,^{11, 12} we continue to advocate caution in utilizing ablation in patients with multifocal RCC. Additionally, recent studies indicate that renal surgery after ablative therapies is quite challenging and can carry high complication rates.^{13, 21}

Although aggressive partial nephrectomy is technically challenging and is associated with considerable morbidity, this report demonstrates that it is not only feasible, but safe. While it is difficult to weigh high transfusion rates and perioperative complications against preservation of a native kidney, we feel that delaying the need for dialysis or transplantation justifies the morbidity of these interventions. In our series, most patients avoided renal replacement therapy and had adequate oncological outcomes at intermediate follow up.

The limitations of the current study include the retrospective nature of this series and absence of longer follow up of some of the patients in this cohort. Additionally, the cohort of these patients may not be representative of the majority of RCC patients seen in the typical urologic practice. Nevertheless, these data may be useful for physicians that encounter patients with multifocal RCC, and will hopefully encourage consideration of a nephron sparing approach.

Conclusion

Aggressive partial nephrectomy with the removal of at least 20 tumors is feasible. Most patients maintain the majority of preoperative renal function and avoid the need for renal

replacement therapy. The resection of large number of tumors has not been found to increase the risk of metastatic disease, and achieves reasonable cancer control at intermediate follow up.

Acknowledgments

This research was supported by the Intramural Research Program of the NIH, National Cancer Institute, Center for Cancer Research.

KEY TO ABBREVIATIONS

(VHL)	von Hippel Lindau
(HPRCC)	hereditary papillary renal cell carcinoma
(eGFR)	estimated glomerular filtration rate

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Table 1**Clinical Characteristics**

No. of patients/No. of partial nephrectomies	30/34
Median age, years (range)	36 (25-55)
Median body mass index, kg/m ² (range)	25 (20-40)
Men (%)	25 (74)
Left kidney surgeries (%)	13 (38)
Solitary renal units (%)	12 (35)
Surgeries with renal hilar clamping (%)	14 (41)
No of patients with cold ischemia (%)	12 (86)
Median clamp time in mins (range)	42 (18-87)
No. of patients with prior ipsilateral surgery (%)	12 (35)
No. of patients with prior contralateral renal surgery (%)	25 (74)
Median operative time, hours (range)	9 (6-18)
Median No. of tumors removed (range)	26.5 (20-70)
Median No. of solid tumors removed (range)	16.5 (4-65)
Median size of solid tumors removed, cm (range)	4 (2-7)
Patients with Clear cell RCC (%)	30 (88)
Median Fuhrman nuclear grade (range)	2 (1-3)
Patients with VHL (%)	24 (80)
HPRC (%)	2 (7)
BHD (%)	2 (7)
Unknown genetic mutation (%)	2 (7)
Median days hospitalized (range)	9 (5-20)
Median follow up, months (range)	52 (4-187)

Table 2

Perioperative Outcomes

No. of pts/No. of partial nephrectomies	30/34
Median EBL, mls (range)	3,500 (800-19,500)
No. of transfusions (%)	30 (88.2)
Median units transfused (range)	6.5 (0-32)
Intraop complications	
No. of pleural injuries (%)	16 (47)
No. of bowel injuries (%)	1 (3)
No. of renal units lost (%)	1 (3)
Postop Complications	
No. of transfusions (%)	4 (12)
No. urine leakage (%)	11 (32)
No. long term hemodialysis (%)	1 (3)
No. of CV events (%)	3 (9)
No. of intervention for complications (%)	2 (6)
Rhabdomyolysis (%)	2 (6)

Table 3

Preoperative and postoperative renal function

Parameter	No. renal units	Preop	Postop	% change	p value
Median Serum Creatinine (mg/dl)	33	1.1 (0.54-2.1)	1.3 (0.66-2.1)	+18%	<0.001
Median estimated GFR (ml/min/1.73m ²)	33	66.5 (34-134)	59.4 (32-105)	-11%	<0.001
Median differential function of operated unit (%)	19	59 (45-94)	51 (16-92)	-14%	0.001

Table 4**Oncological Outcomes**

No. of pts with development of metastatic disease (%)	1 (3)
No. pts with need for subsequent ipsilateral renal interventions (%)	8 (24)
Median time to intervention, months (range)	33 (10-82)
Type of Subsequent Intervention in 8 patients	
Repeat partial nephrectomy (%)	3 (43)
Radical nephrectomy (%)	2 (29)
Percutaneous radiofrequency ablation (%)	2 (29)
Enrollment in clinical trial (%)	1 (15)