Published in final edited form as:
J Urol. 2008 July ; 180(1): 89–93. doi:10.1016/j.juro.2008.03.030.

Feasibility and Outcomes of Repeat Partial Nephrectomy

Aaron Johnson[°], **Sunil Sudarshan**[°], **Jack Liu**, **W. Marston Linehan**, **Peter A. Pinto**, and **Gennady Bratslavsky**[*]
Urologic Oncology Branch, Center for Cancer Research, National Cancer Institute, National Institute of Health, Department of Health and Human Services, Bethesda, MD

Abstract

Purpose—Despite the proven efficacy of nephron sparing surgery, patients with hereditary renal cancer remain at risk for tumor recurrence. Management options for recurrent tumors include completion nephrectomy, ablation, and repeat partial nephrectomy (RPN). We examine the feasibility and outcomes of RPN performed on the same renal unit.

Materials and Methods—We retrospectively reviewed the records of 51 attempted RPN cases on 47 patients from 1992 to 2006. Demographic information as well as intraoperative, perioperative, and renal functional outcome data were collected. Comparison of pre- and postoperative renal function was performed using the two tailed T-test.

Results—Major perioperative complications or reoperations occurred in 10 of 51 (19.6%) cases that included one perioperative mortality (1.9%). In cases of successful RPN, there was a statistically significant increase in postoperative serum creatinine (1.35 vs. 1.16 mg/dL, $p < 0.05$) and a significant decrease in creatinine clearance (84.6 mL/min vs. 95.3mL/min, $p = 0.05$) and renogram split function (52.3% vs. 54.8%, $p < 0.05$). Two patients required long term hemodialysis (3.9%). Ten of the 51 renal units (19.6%) in our study required subsequent operations for additional local recurrence or de novo tumor formations with a median time to subsequent surgery of 50 months. Forty-six of forty-seven patients are alive at median follow up of 56 months.

Conclusions—RPN is technically feasible. Although there is a statistically significant decrease in postoperative renal functional studies, most patients retained sufficient function to avoid hemodialysis. RPN may provide acceptable oncologic control despite the anticipated development of locally recurrent or de novo tumors.

Keywords

partial nephrectomy; complications; outcomes

Partial nephrectomy is undertaken in order to preserve renal function, particularly in patients with a genetic predisposition for bilateral tumors, in an attempt to delay or avoid renal replacement therapy while maintaining oncologic efficacy. Despite the efficacy of nephron sparing surgery (NSS), patients with hereditary forms of kidney cancer such as von Hippel-Lindau (VHL), hereditary papillary renal carcinoma (HPRC) and Birt Hogg Dube (BHD) are

*Correspondence: Gennady Bratslavsky, M.D., Urologic Oncology Branch, National Cancer Institute, Building 10 Room 1-5940, Bethesda, Maryland 20892-1107, Tel: 301 496-6353, Fax: 301 402-0922, Email: bratslag@mail.nih.gov.
[°]Contributed equally to this manuscript

still at significant risk for the development of subsequent *de novo* kidney tumors that may require intervention.[1] In addition, multiple studies have documented locally recurrent kidney tumor formation in patients with prior surgical resection for sporadic renal cell carcinoma (RCC).[2,3]

While repeat partial nephrectomy may maintain the balance between tumor control and renal preservation, the feasibility as well as functional and oncologic outcomes of patients undergoing RPN are not well established. There are a few reports of patients with hereditary kidney cancer that have undergone repeat NSS.[4–6] However, most of these series report limited numbers which may restrict the ability to make conclusions regarding repeat partial nephrectomy. Our ongoing clinical experience in patients with hereditary kidney cancer who are at risk for metachronous tumor formation has provided a unique opportunity to evaluate the feasibility and outcomes of repeat partial nephrectomy.

MATERIALS AND METHODS

Between 1992 and 2006, 51 cases of planned RPN on the same renal unit were performed at our institution on 47 patients with recurrent kidney tumors. All patients were evaluated on a protocol approved by the IRB. Forty-eight (94%) cases were performed on patients with VHL. Data were obtained from a review of operative reports, pathology reports, history and physical examination at time of admission, discharge summaries, and anesthesia records. Patients were followed at regular intervals with history, physical examination, renal functional tests, and abdominal and chest imaging. Functional outcomes were assessed with preoperative and postoperative serum creatinine, 24 hour creatinine clearance, and differential renal function as determined by MAG-3 renogram. Preoperative functional studies were obtained within 3 months before the surgery, while postoperative studies were done at least 3 months after the procedure. Statistical analysis was completed using the two tailed t-test and statistical significance was considered to be $p \leq 0.05$.

RESULTS

Patient characteristics are shown in table 1. A total of 51 RPN were performed in 47 patients. The median age of the patient in our series was 44 years (range 20–70), and 64.7% were men. The majority of cases had previous history of contralateral kidney or non-renal abdominal surgery. One third of the operations were performed on patients with a solitary kidney. Three procedures were performed laparoscopically.

Operative and perioperative outcomes are shown in table 2. Median length of procedure was 7.5 hours (range 4–14). Sixty percent (31/51) of cases utilized renal ischemia with hilar clamping with median time of 31 (range 8–136). The median intraoperative blood loss was 1,800 mL (range 50 – 21,500) and 64.7% (33/51) of patients required intraoperative transfusions with a median of 2 (range 0–31) units transfused. The median number of tumors removed was 7 (range 1–55) with median size of the largest solid lesion resected of 3.5 cm (range 0.9–6.5).

Intraoperative complications occurred in 35.3% of cases (18/51). The majority of intraoperative complications were minor (n=14). The most common intraoperative complication was pleural injury, which occurred in 17.6% (9/51) of the cases. Other minor complications included small renal vein laceration (n=2), small renal artery laceration (n=1), duodenal serosal injury (n=1), and transection of lower pole renal artery (n=1). Major intraoperative complications occurred in 4 of 51 (7.8%) cases and included transection of renal artery leading to loss of the renal unit (n=1), transection of ureter repaired by ureteroureterostomy (n=1), major renal vein laceration

(n=1), and intraoperative myocardial infarction (n=1) with subsequent postoperative expiration of the patient.

Postoperative complications occurred in 43.1% (22/51) of cases. Major postoperative complications occurred in six (11.8%) procedures, including three patients with renal failure requiring hemodialysis, one pulmonary embolism, one pancreatic leak, and one mortality of the aforementioned patient who suffered an intraoperative myocardial infarction. Two of the three patients requiring hemodialysis suffered loss of a solitary renal unit intraoperatively and required long term hemodialysis. The other patient had acute tubular necrosis managed with temporary hemodialysis, and eventually had return of adequate renal function. The minor postoperative complications accounted for 16/51 (31%) cases. The most common postoperative complication was urinary leak, defined as elevated drain creatinine before patient's discharge, which occurred in 8 (15.6%) cases. Urine leaks resolved without intervention in 7 of 8 patients. One patient required temporary ureteral stenting which resulted in eventual resolution of the leak. Other minor postoperative complications included three episodes of ileus, two wound infections, two cardiac arrhythmias with one requiring anticoagulation, and one pleural effusion requiring thoracentesis.

Loss of a renal unit occurred in three patients. One loss was due to intraoperative renal artery injury necessitating nephrectomy of a solitary kidney with resultant dialysis. In the other 2 instances, nephrectomy was performed because NSS was not technically feasible. One of these two patients had a solitary renal unit and required hemodialysis. The other patient had a functioning contralateral kidney and therefore did not require hemodialysis.

Reoperation occurred in two cases. One patient required a ureteral stent placement for persistent urinary leak, which subsequently resolved. The other patient, who had a solitary kidney, suffered a major intraoperative renal vein injury. Following the repair, the patient developed a coagulopathy secondary to extensive bleeding and transfusions. Following repair, the procedure was aborted and the patient transferred to the intensive care unit for correction of the coagulopathy. After correcting the coagulopathy, the patient was taken back to the operating room for successful completion of the partial nephrectomy.

Renal functional outcomes are listed in table 3. In the patients not on dialysis, the postoperative serum creatinine was significantly higher compared to pre-operative serum creatinine (1.35 mg/dL vs. 1.16 mg/dl, $p < 0.05$). Postoperative 24 hour creatinine clearance was significantly decreased compared to preoperative creatinine clearance (84.6 mL/min vs. 95.3 mL/min, $p = 0.05$). Analysis of patients with both kidneys remaining demonstrated that postoperative renal split function of the operated kidney was significantly decreased compared to preoperative split function (52.3% vs. 54.8%, $p < 0.05$).

Ten of the 51 renal units (19.6%) in our study required subsequent operations for additional local recurrence or de novo tumor formations with a median time to subsequent surgery of 50 months. Of the 46 patients who tolerated RPN, all our alive at the median follow up of 56 months.

Three patients in this series had pathologically confirmed metastatic RCC. All 3 underwent successful metastatectomy. None of the patients have required systemic therapy and all are without evidence of metastatic disease at 28, 37, and 47 months, respectively.

DISCUSSION

Hereditary kidney cancer differs from sporadic cases in that tumors are often bilateral, multifocal, and can occur at an earlier age.[7,19] While these tumors are generally low stage, they are capable of progressing and metastasizing once they reach a certain size. The primary

goal of treatment in these patients is prevention of the development of metastatic disease with preservation of renal function. Therefore, patients with hereditary renal cancer syndromes such as VHL are closely monitored with serial imaging until tumors reach 3 cm in size at which point surgical intervention is recommended.[8–10]

The beneficial oncologic outcome of nephron sparing surgery for renal cell carcinoma, both sporadic and hereditary, has been well documented in the literature. However, postoperative local tumor recurrence in patients with hereditary kidney cancer is not an uncommon event. Steinbach *et al*. reported local tumor recurrence in 25 of 49 (51%) VHL patients treated with nephron sparing surgery at a mean follow up of 68 months.[6] Novick *et al*. reported local tumor recurrence in 7 of 9 (77.7%) VHL patients.[5] Although it is difficult to classify recurrent tumors as true local recurrence or *de novo* tumors, the main issue remains the same: the need for repeat intervention.

Management options for recurrent tumors include completion nephrectomy, ablation, and RPN. The presumed oncologic efficacy of completion nephrectomy is countered by the potential deleterious effect of renal function. Early and intermediate outcomes for ablative therapies are encouraging, yet long-term results await.[11,12] Additionally, ablative technologies may not be technically possible, ineffective, or inadvisable for tumors located in close proximity to renal vessels or intimate with the collecting system. Furthermore, experience with ablative therapy in patients with hereditary kidney cancer is limited.[13,14] RPN has been reported in a limited numbers in the literature. Ansari *et al.* reported one case of a patient with VHL that had right radical nephrectomy and left repeat partial nephrectomy 12 years after a primary partial nephrectomy.[4] Novick and colleagues reported on three of seven patients with local tumor recurrence that underwent RPN with complete removal of local recurrences detected at 42, 87, and 92 months postoperatively.[5] In a multicenter study on the treatment of renal cell carcinoma in VHL, Steinbach *et al*. reported that 25 of 49 patients (51 %) treated with nephron sparing surgery had local recurrence with 13 patients undergoing RPN for treatment of the recurrent tumor.[6] The current series is the largest cohort of patients undergoing repeat partial nephrectomy for recurrent renal tumors. As such, it provides an opportunity to comment on the feasibility and outcomes of RPN in relation to previously reported series on primary parenchymal sparing surgery.

In the present series there were forty perioperative complications. Most of these complications were without long-term sequlae. Half of the intraoperative complications were pleural injuries, a complication often not reported in contemporary series of open partial nephrectomies. In addition, urine leak, the most common postoperative complication resolved in all patients. Overall, greater than three quarters of the perioperative complications were self-limited. The major perioperative complication rate in this series was 19.6%. This rate is higher than the major complications rates reported in 2 recent partial nephrectomy series by Pasticier *et al* (12.6%) and Ray *et al* (11%, but it is lower than numbers reported by Bratslavsky, et al for salvage renal surgeries).[15,16,20] Our major complication rates may be higher than complications in first-time, partial nephrectomies, given that RPN may be more technically challenging. Reoperative surgery is complicated by a more difficult dissection due to the presence of scar tissue and obliteration of normal tissue planes. Furthermore, most of our patients had multiple lesions resected (median 7) at the time of RPN.

Preservation of renal function in patients with hereditary kidney cancer is vital for several reasons. While renal replacement options exist, there is significant morbidity and mortality associated with dialysis in addition to significant shortage of organ availability for transplantation. Furthermore, the option for transplantation in VHL patients may be limited and/or delayed in some centers due to the known presence of RCC. In addition, patients with VHL are at risk for multiple renal operations. Over 80% of the patients in this series had prior

surgery on the contralateral kidney, and a third of the patients in this series had a solitary kidney. In our cohort, the mean postoperative serum creatinine increased by 0.19 mg/dL, compared to an increase of 0.5 mg/dL reported by Steinbach and colleagues and an increase of 0.16 mg/dL reported by Walther *et al* for primary nephron sparing surgery in patients with hereditary kidney cancer.[1,6] Although renal functional data in our series showed a statistically significant increase in postoperative serum creatinine as well as a decrease in creatinine clearance and split function, the vast majority of patients retained adequate renal function to prevent renal replacement therapy.

Determination of cancer control rates is complicated by the fact that VHL patients are at continued risk for *de novo* tumor formation. Furthermore, study of a cohort that has required repeat intervention on the same renal unit may select for a VHL phenotype that is particularly prone to RCC formation. Unfortunately, repeat NSS did not preclude the necessity for subsequent intervention on the same renal unit. Ten of 51 (19%) renal units in our cohort required subsequent renal operations for local tumor recurrence emphasizing the continued need for close surveillance. On the other hand, most patients have been managed non-operatively at intermediate follow up from the time of RPN.

Three patients in this series have pathologically confirmed metastatic RCC. The first patient developed metastatic disease in a retrocaval lymph node. The patient had intital radical nephrectomy for a 6.2cm tumor followed by a partial nephrectomy in the remaining solitary kidney for a 6cm solid lesion. This was followed by RPN for a 2.5cm tumor. Two years after successful RPN, a metastatic lymph node was identified and resected. The second patient had evidence of metastatic disease in a retroperitoneal lymph node at the time of repeat partial nephrectomy for an 8 cm mass on his solitary kidney. The third patient developed a metastatic lung lesion. He had a previous contralateral partial nephrectomy for a 4.5cm renal mass. He subsequently underwent resection of the lung lesion. None of the patients have received systemic therapy, and all are alive at 47, 28, and 37 months, respectively, from the time of metastatectomy with out evidence of metastatic disease.

The rate of metastatic disease in our cohort is similar to the 8% reported by Steinbach et al.[6] All of the patients in our study that developed metastatic disease had prior renal surgery for lesions greater than 3 cm. It was previously shown by Walther and colleagues that VHL tumors less than 3 cm have a negligible metastatic potential, while an increasing size of the solid VHL tumors leads to an increased likelihood for metastatic disease.[10] Additionally, in a subsequent study from our institution, 108 patients with tumors smaller than 3 cm were followed for a mean of 58 months without any evidence of metastasis compared to 20 of 73 (27.4%) patients with tumors larger than 3 cm that developed metastases with a mean follow up of 72.9 months.[8] Similarly, larger tumors are clearly associated with metastatic disease in the sporadic population as well.[17,18]

At our institution repeat partial nephrectomy was offered to the overwhelming majority of patients requiring repeat surgery on the same renal unit. Review of our database identified only one patient who underwent a planned radical nephrectomy on a previously operated renal unit. The reason for a decision to proceed with a radical nephrectomy in that case was presence of enlarging renal masses in a kidney with poor residual function after previous surgery. Prior to a decision to offer a repeat partial nephrectomy, we carefully evaluate the size, number and location of lesions, and the relative renal function that each kidney provides.

Some of the patients at our institution have been treated with radiofrequency ablation under a research protocol. We have previously reported our results with ablation of small renal masses with promising outcomes up to 1 year of follow up.[13,14] Unfortunately, due to retrospective nature of this study we cannot reliably comment on factors that determined whether surgery

or ablation was chosen as an intervention. However, the intermediate results of our RFA trial are presently being analyzed and may help us in the future to determine which patients are better suited for ablation and which ones may benefit from surgical extirpation.

Additional note should be made of the importance of intraoperative ultrasound which is routinely used on all cases of partial nephrectomy. It provides an excellent tool for localization of lesions, especially those that are completely endophytic. Given the multitude of tumors on the kidney in our patient population, the additional information gained includes appreciation of proximity of tumors to the collecting system and/ or renal vasculature. At the end of the case, the intraoperative renal ultrasound is also helpful to evaluate for any remaining tumors as well as document adequate perfusion utilizing color Doppler Flow.

The current study has inherent limitations. First, it is a retrospective study. In addition, the feasibility of RPN is certainly prone to selection bias as some patients who required intervention for local recurrence may have undergone ablation. In addition, the VHL population is a very unique patient cohort. Given the low median age of the patient population, patients may be better surgical candidates. In contrast, many of the VHL patients have extrarenal manifestations such as CNS hemangioblastomas, pancreatic neuroendocrine tumors, and adrenal pheochromocytomas that may impact their overall surgical fitness. Nevertheless, the study provides important information about the feasibility and outcomes of this technically challenging procedure.

CONCLUSIONS

RPN results in higher complication rates that primary nephron sparing surgery. The vast majority of patients undergoing RPN on the same renal unit maintained sufficient renal function and avoided renal replacement therapy. Additionally, it provides adequate local cancer control at intermediate follow up. Repeat partial nephrectomy is technically feasible and may assist the urologic surgeon in the management of patients at risk for the development of multiple bilateral synchronous and metachronous renal tumors.

Acknowledgement

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

ABBREVIATIONS

RCC, Renal Cell Carcinoma; RPN, Repeat Partial Nephrectomy; NSS, Nephron Sparing Surgery; IRB, Institutional Review Board; NCI, National Cancer Institute; VHL, von-Hippel Lindau.

References

1. Walther MM, Choyke PL, Weiss G, Manolatos C, Long J, Reiter R, et al. Parenchymal sparing surgery in patients with hereditary renal cell carcinoma. J Urol 1995;153:913. [PubMed: 7853573]
2. Belldegrun A, Tsui KH, deKernion JB, Smith RB. Efficacy of nephron-sparing surgery for renal cell carcinoma: analysis based on the new 1997 tumor-node-metastasis staging system. J Clin Oncol 1999;17:2868. [PubMed: 10561364]
3. Hafez KS, Fergany AF, Novick AC. Nephron sparing surgery for localized renal cell carcinoma: impact of tumor size on patient survival, tumor recurrence and TNM staging. J Urol 1999;162:1930. [PubMed: 10569540]

4. Ansari MS, Gupta NP, Kumar P. von Hippel-Lindau disease with bilateral multiple renal cell carcinoma managed by right radical nephrectomy and left repeat partial nephrectomy. Int Urol Nephrol 2003;35:471. [PubMed: 15198146]
5. Novick AC, Streem SB. Long-term followup after nephron sparing surgery for renal cell carcinoma in von Hippel-Lindau disease. J Urol 1992;147:1488. [PubMed: 1593671]
6. Steinbach F, Novick AC, Zincke H, Miller DP, Williams RD, Lund G, et al. Treatment of renal cell carcinoma in von Hippel-Lindau disease: a multicenter study. J Urol 1995;153:1812. [PubMed: 7752324]
7. Sudarshan S, Linehan WM. Genetic basis of cancer of the kidney. Semin Oncol 2006;33:544. [PubMed: 17045083]
8. Duffey BG, Choyke PL, Glenn G, Grubb RL, Venzon D, Linehan WM, et al. The relationship between renal tumor size and metastases in patients with von Hippel-Lindau disease. J Urol 2004;172:63. [PubMed: 15201738]
9. Linehan WM, Walther MM, Zbar B. The genetic basis of cancer of the kidney. J Urol 2003;170:2163. [PubMed: 14634372]
10. Walther MM, Choyke PL, Glenn G, Lyne JC, Rayford W, Venzon D, et al. Renal cancer in families with hereditary renal cancer: prospective analysis of a tumor size threshold for renal parenchymal sparing surgery. J Urol 1999;161:1475. [PubMed: 10210376]
11. Gervais DA, McGovern FJ, Arellano RS, McDougal WS, Mueller PR. Renal cell carcinoma: clinical experience and technical success with radio-frequency ablation of 42 tumors. Radiology 2003;226:417. [PubMed: 12563135]
12. Park S, Anderson JK, Matsumoto ED, Lotan Y, Josephs S, Cadeddu JA. Radiofrequency ablation of renal tumors: intermediate-term results. J Endourol 2006;20:569. [PubMed: 16903817]
13. Hwang JJ, Walther MM, Pautler SE, Coleman JA, Hvizda J, Peterson J, et al. Radio frequency ablation of small renal tumors:: intermediate results. J Urol 2004;171:1814. [PubMed: 15076283]
14. Pavlovich CP, Walther MM, Choyke PL, Pautler SE, Chang R, Linehan WM, et al. Percutaneous radio frequency ablation of small renal tumors: initial results. J Urol 2002;167:10. [PubMed: 11743264]
15. Pasticier G, Timsit MO, Badet L, De La Torre AL, Halila M, Fassi FH, et al. Nephron-sparing surgery for renal cell carcinoma: detailed analysis of complications over a 15-year period. Eur Urol 2006;49:485. [PubMed: 16443321]
16. Ray ER, Turney BW, Singh R, Chandra A, Cranston DW, O'Brien TS. Open partial nephrectomy: outcomes from two UK centres. BJU Int 2006;97:1211. [PubMed: 16686713]
17. Lau WK, Cheville JC, Blute ML, Weaver AL, Zincke H. Prognostic features of pathologic stage T1 renal cell carcinoma after radical nephrectomy. Urology 2002;59:532. [PubMed: 11927308]
18. Russo P. Renal cell carcinoma: presentation, staging, and surgical treatment. Semin Oncol 2000;27:160. [PubMed: 10768595]
19. Bratslavsky G, Sudarshan S, Neckers L, Linehan WM. Pseudohypoxic Pathways in Renal Cell Carcinoma. Clin Cancer Res 2007;13:4667. [PubMed: 17699843]
20. Bratslavsky G, Liu JJ, Johnson AD, Sudarshan S, Choyke PL, Linehan WM, et al. Salvage Partial Nephrectomy for Hereditary Renal Cancer: Feasibility and Outcomes. J. Urol 2007;179:67. [PubMed: 17997447]

Table 1

Patient characteristics

Characteristics of patients undergoing RPN.

Parameter	Number
Number of repeat partial nephrectomy cases	51
Median age (range)	44 (20–70)
Men (%)	33 (64.7)
Median body mass index (range)	28.8 (17.3–48.0)
Right kidney (%)	31 (60.7)
Solitary kidney (%)	17 (33.3)
Laparoscopic (%)	3 (5.8)
Flank approach (%)	42 (82.3)
Patients with previous contralateral renal surgeries (%)	42 (82.3)
Patients with non-renal abdominal surgery (%)	20 (39.2)
Patients on chronic steroids (%)	5 (9.8)

Table 2

Perioperative Outcomes

Complications of RPN.

Patients with major perioperative complications (%)	10 (19.6%)
Major intraoperative complications (%)	4 (7.8)
Major postoperative complications (%)	6 (11.8)
Minor intraoperative complications (%)	14 (27.5)
Minor postoperative complications (%)	16 (31.4)
Median Length of Procedure in hrs (range)	7.5 (4–14)
Median Intraoperative blood loss in ml (range)	1800 (50–21,500)
Patients receiving intraoperative transfusions (%)	33 (64.7)
Median number of units of PRBC's transfused (range)	2 (0–31)
Patients receiving post-operative transfusions (%)	5 (9.8)
Median number of tumors removed (range)	7 (1–55)
Median size of largest solid tumor in cm (range)	3.5 (0.9–8.0)
Cases with renal ischemia via hilar clamping (%)	31 (60.7)
Median time of ischemia in minutes (range)	31 (8–136)
Prolonged urine leak (%)	8 (15.6)
Renal failure requiring dialysis (%)	3 (5.8)
Loss of renal unit	3 (5.8)
Reoperation (%)	2 (3.9)
Mortality (%)	1 (1.9)

Table 3

Functional Outcomes

Renal functional outcomes following RPN.

	Preoperative (range)	Postoperative (range)	p value
Creatinine (n=44), median (mg/dl)	1.16 (0.80–1.80)	1.35 (0.80–2.90)	<0.05
Creatinine clearance (n=42), median (ml/min)	95.3 (44.6–149.7)	84.6 (23.4–187.0)	0.05
Differential function (n=22), (%)	54.8 (35.0–83.0)	52.3 (31.0–79.0)	<0.05