

## RENAL CANCER IN FAMILIES WITH HEREDITARY RENAL CANCER: PROSPECTIVE ANALYSIS OF A TUMOR SIZE THRESHOLD FOR RENAL PARENCHYMAL SPARING SURGERY

McCLELLAN M. WALTHER, PETER L. CHOYKE, GLADYS GLENN, J. CHRIS LYNE,  
WALTER RAYFORD, DAVID VENZON AND W. MARSTON LINEHAN

*From the Urologic Oncology Branch, Department of Radiology, Genetic Epidemiology Branch, and Biostatistics and Data Management Section, National Cancer Institute, National Institutes of Health, Bethesda, Maryland*

### ABSTRACT

**Purpose:** Patients with hereditary forms of renal cancer are at risk for new tumors and metastases. Renal parenchymal sparing surgery has been performed to preserve renal function and quality of life, and prevent metastases. We evaluated a 3 cm. threshold for performing renal parenchymal sparing surgery in patients with von Hippel-Lindau disease and hereditary papillary renal cancer.

**Materials and Methods:** Patients with von Hippel-Lindau disease or hereditary papillary renal cancer and renal cancer were identified by screening affected kindred and by kindred history. Patients with small tumors were followed with serial imaging studies until the largest renal tumor was 3 cm., when renal parenchymal sparing surgery was performed. Renal tumors greater than 3 cm. were resected without delay. Parenchymal sparing techniques were used when possible in each group.

**Results:** The 3 cm. surgical threshold was evaluated in 52 patients with von Hippel-Lindau disease (group 1) at a median followup of 60 months (range 6 to 205). None of these patients had metastatic disease and none has required renal transplantation or dialysis. In 44 patients with von Hippel-Lindau disease (group 2) renal tumors larger than 3 cm. developed. Median followup from the initial radiological diagnosis of renal cancer in this group was 66.5 months (range 0 to 321). Patients in group 1 underwent parenchymal sparing surgery instead of nephrectomy more frequently than those in group 2 (46 of 48 operations or 96% versus 45 of 72 or 63%, Fisher's exact test  $p < 0.0001$ ). In contrast to patients in group 1, metastatic renal cancer developed in 11 of the 44 in group 2 (25%) (Fisher's exact test  $p < 0.0001$ ). A total of 23 patients with hereditary papillary renal cancer were also identified. Median followup in these cases was 44 months (range 0 to 237). Ten patients had tumors less than 3 cm. No patient with tumors less than 3 cm. and 2 of the 13 (15%) with larger tumors had metastases.

**Conclusions:** Using a 3 cm. renal tumor diameter as an indication for renal surgery no patient with renal cancer and von Hippel-Lindau disease or hereditary papillary renal cancer had metastatic disease regardless of the number of tumors. Using a lesion size of 3 cm. as a threshold for performing renal parenchymal sparing surgery may help to prevent metastatic disease, unnecessary renal damage due to frequent surgery and renal dialysis or transplantation.

**KEY WORDS:** kidney; carcinoma, renal cell; Hippel-Lindau disease; neoplasm metastases

von Hippel-Lindau disease and hereditary papillary renal cancer are characterized by multiple bilateral renal tumors<sup>1-5</sup> that may develop and recur throughout a lifetime.<sup>6-9</sup> Currently the treatment options available for hereditary forms of renal cancer are observation with no planned intervention, nephrectomy to remove all tissue at risk for cancer and renal parenchymal sparing surgery to remove renal tumors while sparing normal tissue. Before the widespread use of computerized tomography (CT) von Hippel-Lindau disease renal tumors were not well imaged, and some patients presented with symptoms of advanced renal cell carcinoma. During this era 13 to 42% of the patients with von Hippel-Lindau disease died of metastatic renal cell carcinoma.<sup>10-12</sup> Median age at death was 44 years and the youngest reported patient died at age 23 years. These data represent the best

available estimate of the natural history of untreated von Hippel-Lindau disease.

Hereditary papillary renal cancer is a recently described hereditary cancer syndrome that is inherited in an autosomal dominant fashion and caused by a germline mutation in the met gene. Papillary renal tumors develop in affected patients, and the natural history of this entity is less well documented than that of von Hippel-Lindau disease.<sup>3-5</sup> Median age at death of 41 patients with hereditary papillary renal cancer was 52 years and the youngest reported patient died at age 18 years.<sup>4</sup>

The treatment strategy of nephrectomy and renal replacement removes all tissue at risk for renal cancer and metastases. The 5-year survival in 30 to 40-year-old, white nondiabetic patients with renal failure (these characteristics are similar to those of most patients in whom von Hippel-Lindau disease is detected by screening) is 71% with dialysis and 86% with renal transplantation.<sup>13</sup> Similarly Goldfarb et al noted 65% 5-year survival of patients with von Hippel-Lindau disease who were treated with bilateral nephrectomy

Accepted for publication November 13, 1998.

**Editor's Note:** This article is the second of 5 published in this issue for which category 1 CME credits can be earned. Instructions for obtaining credits are given with the questions on pages 1610 and 1611.

and renal replacement.<sup>14</sup> The potential morbidity and mortality associated with renal replacement therapy make parenchymal sparing surgery attractive to some, including young, often asymptomatic patients with hereditary kidney cancer. Morbidity and mortality must be balanced with the potential benefit of such therapy.

To our knowledge no clear guidelines exist regarding the timing of surgery in patients with hereditary renal cancer. Management strategies, such as nephrectomy, enucleation and watchful waiting, have been used depending on the physician, number, size or location of renal tumors and renal tumor rate of recurrence.<sup>6, 7, 15-18</sup> We evaluated the strategy of following patients with von Hippel-Lindau disease and renal cancer until the largest tumor was 3 cm. in diameter before recommending surgery regardless of the recurrence pattern or number of tumors.<sup>9</sup>

#### MATERIALS AND METHODS

From 1988 to 1998, 96 patients with von Hippel-Lindau disease and 23 with hereditary papillary renal cancer in whom imaging revealed solid renal tumors were identified by screening affected kindred or by historical review of records. Patients at the clinical center of the National Institutes of Health underwent abdominal CT with 5 mm. collimation before and after contrast enhancement with 120 cc ipopamidol at an infusion rate of 1.5 to 2.0 cc per second through a mechanical injector.<sup>19</sup> Renal ultrasound, chest CT or x-ray, physical examination and routine laboratory testing were done during periodic followup every 6 months to 1 year depending on tumor growth rate. In our experience all solid tumors visualized on imaging studies were renal cancer.<sup>2,9</sup>

Of the cases of von Hippel-Lindau disease renal tumors were less than 3 cm. in diameter in 52 (group 1) and larger than 3 cm. in 44 (group 2). We also identified 23 patients with hereditary papillary renal cancer, of whom 10 had tumors of less than 3 cm. in diameter. Patients with small renal tumors were followed with serial imaging studies until the largest renal tumor diameter reached 3 cm., when surgical intervention was recommended. For example, a 28-year-old man was diagnosed with von Hippel-Lindau disease through the screening of affected kindred. Left nephrectomy and right partial nephrectomy were performed. The patient was followed yearly with abdominal CT. On November 22, 1994, 6 years later, CT revealed many cysts in the kidney (fig. 1, A). Two small solid lesions 1.7 × 1.5 and 1.3 cm. in diameter were in the lower half of the kidney, (fig. 1, B and C). Observation was recommended. Imaging of these masses was repeated every 6 months to 1 year to follow their growth. On August 26, 1997 CT revealed many more cysts in the kidney (fig. 1, D). The 2 lesions had grown to 3.0 × 2.2 and 3.0 cm., respectively (fig. 1, E and F). A small cyst adjacent to the tumors remained unchanged during this period (fig. 1, B and E). Surgery was recommended at this 3 cm. cutoff point. The patient underwent renal parenchymal sparing surgery and 32 lesions were removed.

Cystic renal lesions were not used as a criterion for surgery. In patients with larger renal tumors, that is 1 or more renal lesions larger than 3 cm., surgical resection without delay was recommended. Renal parenchymal sparing techniques were used whenever possible in each group. Intraoperative ultrasound was performed to localize small tumors after all visible tumors were resected.<sup>20</sup> Clinical evaluation was performed 2 to 4 months postoperatively. Patients subsequently underwent repeat imaging every 1 to 2 years. Outside records and imaging studies were obtained to complete the followup of patients previously diagnosed and of family members not screened or treated at the National Institutes of Health.

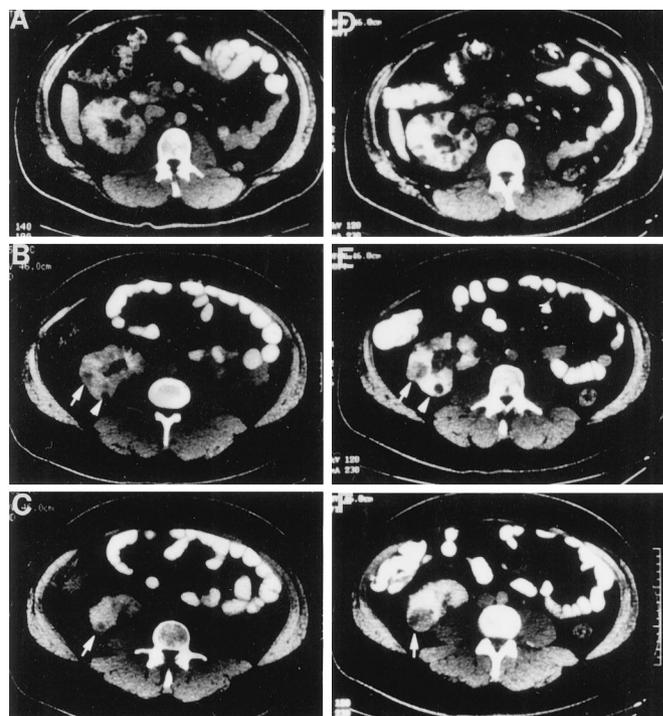


FIG. 1. A, CT reveals many renal cysts 6 years after initial treatment. B and C, 2 small solid lesions (arrows) are visualized in lower half of kidney. D, CT shows many more renal cysts 2.75 years later. E and F, 2 small lesions (arrows) had grown to 3.0 × 2.2 and 3.0 cm., respectively. B and E, small cyst (arrowhead) remains unchanged.

#### RESULTS

**von Hippel-Lindau disease.** We identified 27 men and 25 women 16 to 63 years old (mean age plus or minus standard error of mean  $33.3 \pm 1.5$ ) at the initial diagnosis of renal cancer who had von Hippel-Lindau disease and renal tumors less than 3 cm. (table 1). Two patients refused further followup. Patients in this group were followed until the tumors reached 3 cm., when surgery was recommended. Mean followup from the initial radiological diagnosis of renal cancer was  $59.6 \pm 6.2$  months (median 60, range 6 to 205). In 26 patients a total of 46 partial nephrectomies and 2 nephrectomies were done. An average of  $1.9 \pm 0.2$  renal operations (range 1 to 5) were performed in these patients during followup. Before any surgery mean followup of all 52 cases was  $24.3 \pm 3.9$  months (median 11, range 0 to 90). A total of 26 patients were observed without surgery because the tumors were less than 3 cm. None of these 52 patients had metastatic disease or required renal replacement therapy.

We also identified 32 men and 12 women 16 to 63 years old (mean age  $39. \pm 1.5$ ) at the initial diagnosis of renal cancer who had von Hippel-Lindau disease and renal tumors larger than 3 cm. Patients in group 1 were diagnosed at a younger mean age than those in group 2 (median 31 versus 37.5 years, Wilcoxon rank sum test  $p = 0.003$ ). Median tumor size in group 2 was 4.75 cm. (range 3.2 to 26.0). Mean followup from

TABLE 1. Comparison of groups 1 and 2

	Group 1	Group 2
Tumor size (cm.)	3 or Less	3.2-26.0
No. pts.	52	44
No. renal surgery	26	39
No. operations:		
Nephrectomy	2	27
Partial nephrectomy	46	45
Median mos. followup	60	66.5
No. with metastases (Fisher's exact test $p < 0.0001$ )	0	11

the initial radiological diagnosis of cancer was  $66.0 \pm 9.0$  months (median 66.5, range 0 to 321). Followup of the 2 groups was not significantly different (Wilcoxon rank sum test  $p = 0.85$ ). In 39 patients a total of 45 partial nephrectomies and 27 nephrectomies were done during followup. An average of  $1.9 \pm 0.1$  renal operations (range 1 to 5) were performed in these patients during followup. Parenchymal sparing surgery was done more frequently in group 1 than in group 2 (46 of 48 cases or 96% versus 45 of 72 or 63%, Fisher's exact test  $p < 0.0001$ ). At the time of the initial diagnosis 5 patients who had metastatic cancer, including renal cell carcinoma in 3, and pheochromocytoma and islet cell tumor of the pancreas in 1 each, underwent no renal operation.

Of the 44 group 2 patients 11 (25%) had metastatic renal cancer (fig. 2). Median patient age at the diagnosis of metastases was 50 years (range 33 to 70) and the largest median renal tumor diameter was 9.0 cm. (range 3.5 to 26). The 11 patients with metastases were older at the initial diagnosis of renal cancer than the other 85 with von Hippel-Lindau disease (mean age 34.8 years, Wilcoxon rank sum test  $p = 0.003$ ). There was also a trend toward being older than the 33 other patients in group 2 who had larger tumors (mean age 37.1 years, Wilcoxon rank sum test  $p = 0.052$ ). The frequency of metastases was significantly different in the 2 groups. None of the 52 patients in group 1 versus 11 of 44 in group 2 had metastases (Fisher's exact test  $p < 0.0001$ ). Larger tumors were more frequently associated with metastases (table 2).

**Hereditary papillary renal cancer.** At the initial diagnosis of renal cancer 11 men and 12 women with hereditary papillary renal cancer were 23 to 83 years old (mean age  $47.2 \pm 3.2$ ). In 10 patients tumors were smaller than 3 cm. at the initial evaluation, including 1 each who underwent nephrectomy and partial nephrectomy before evaluation at the National Institutes of Health, and 8 who continue to be followed with tumors smaller than 3 cm. Mean followup of these 10 cases was  $60.9 \pm 21.3$  months (median 49, range 12 to 237).

Mean followup from the initial radiological diagnosis of renal cancer for all patients with hereditary papillary renal cancer was  $59.2 \pm 13.9$  months (median 44, range 0 to 237). In 14 patients a total of 6 partial nephrectomies and 15 nephrectomies were done. An average of  $1.5 \pm 0.1$  renal operations (range 1 to 2) were performed during followup. Of the 23 patients 2 (8.7%) with 7 and 15 cm. tumors had metastases to the local lymph nodes and lung, respectively, at the time of diagnosis. Patients with hereditary papillary renal cancer were older at the initial diagnosis of renal can-

TABLE 2. Comparison of tumor size and metastases

No. Metastases/No. Pts. (%)	Tumor Size (cm.)
0/52	3.0 or Less
1/17 (6)	3.2-4.0
2/10 (20)	4.1-5.5
4/12 (33)	6.0-10.0
4/5 (80)	10.0 or Greater

cer than those with von Hippel-Lindau disease (mean age 47.2 versus 35.9 years, Wilcoxon rank sum test  $p = 0.001$ ). Metastases developed in 11 of the 44 patients (25%) with von Hippel-Lindau disease and renal tumors larger than 3 cm. compared to 2 of 13 (15%) with hereditary papillary renal cancer in the same size group (Fisher's exact test  $p = 0.71$ ).

## DISCUSSION

Renal parenchymal sparing surgery is recommended in a small subset of patients with renal cancer,<sup>21-23</sup> including the subset with hereditary renal cancer, such as von Hippel-Lindau disease or hereditary papillary renal cancer. After renal surgery new cancer may develop throughout a lifetime.<sup>6-9</sup> Multiple operations may be required to remove renal tumors and decrease the risk of metastases. Since each consecutive renal operation is increasingly demanding and patients may have a substantial tumor burden, the decision of when to operate is complex. Presently there are few guidelines on which to base this decision but tumor size may be a prognostic factor.

The most data regarding the association of renal tumor size and prognosis are available on patients with noninherited sporadic renal cancer. Those with small sporadic renal tumors have a high cure rate after radical nephrectomy with greater than 90% 5-year disease specific survival.<sup>22, 24-27</sup> Renal parenchymal sparing surgery performed in similar cases of tumors that are usually less than 3 to 4 cm. is associated with similar 5-year survival.<sup>21, 22, 28</sup>

Disease specific survival of patients with von Hippel-Lindau disease who underwent parenchymal sparing surgeries has been reported to be less than that of those with sporadic renal cancer.<sup>6, 7, 18, 29</sup> However, in these patients with von Hippel-Lindau disease large tumors were associated with higher stage and grade. Latiff et al identified the gene responsible for the development of clear cell renal cancer in von Hippel-Lindau disease, termed the von Hippel-Lindau disease kidney cancer tumor suppressor gene, on chromosome 3p25.5.<sup>30</sup> Gnarr et al believe that this gene is associated with sporadic clear cell renal carcinoma.<sup>31</sup> Thus, there is reason to conclude that the biological behavior of these tumors may be similar. Later age at the initial diagnosis of hereditary papillary renal cancer, relative infrequency of metastases in our hereditary papillary renal cancer cases and larger tumor size associated with metastases also support this strategy in these cases. Based on the low reported occurrence of renal metastases in patients with sporadic renal tumors smaller than 3 cm. in diameter we selected this size threshold and prospectively evaluated this strategy during a median followup of 60 months. To date no patient with renal tumors smaller than 3 cm. has had metastases. All patients retained renal function sufficient to preclude renal replacement.<sup>9</sup>

The high recurrence rate of renal tumors in hereditary renal cancer is not unexpected. Examination of normal renal tissue of patients with renal cancer and von Hippel-Lindau disease has frequently shown microscopic renal tumors. Extrapolations based on these studies predict as many as 600 clear cell renal tumors and 1,100 clear cell cysts per kidney.<sup>32</sup> These cysts develop only in von Hippel-Lindau disease, and they are microscopically and genetically similar to clear cell

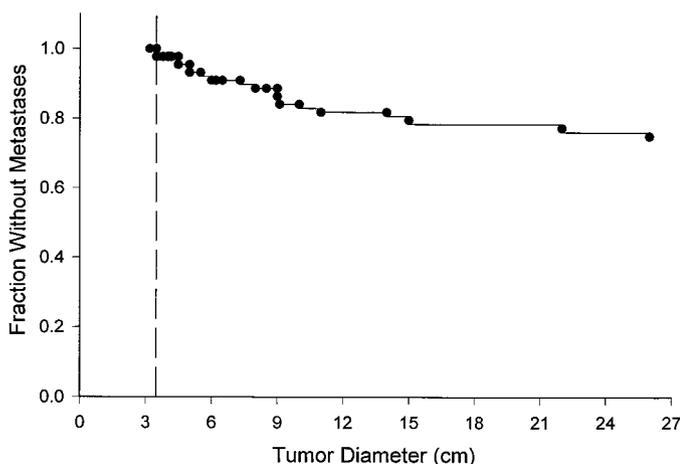


FIG. 2. Tumor diameter versus frequency of metastases in patients with tumor larger than 3 cm. Metastases were found most frequently in patients with largest renal tumors. Dashed line represents smallest renal tumor associated with metastases.

renal cancer.<sup>32,33</sup> Even after resection of all grossly visible disease these patients are not cured of all renal tumors. Rather, "the clock is reset" in each kidney until tumors that are microscopic at renal surgery become clinically evident.

This treatment strategy is associated with an alteration in traditional assumptions about therapy of renal cancer. Small renal tumors are observed until they reach a size associated with a higher risk of metastases rather than being immediately resected. Instead of performing radical surgery renal parenchymal sparing surgery is done when possible to decrease the tumor burden with the knowledge that small microscopic tumors will likely remain after surgery. In our experience a large number of renal tumors are not considered indication for radical surgery as long as tumors are smaller than 3 cm. Patients with von Hippel-Lindau disease who had smaller tumors underwent partial nephrectomy with greater frequency than those with larger tumors (96 versus 63%). These renal parenchymal sparing operations lead to significantly greater preservation of renal tissue. Use of a larger cutoff point for recommending surgery would lead to less renal preservation.<sup>22,34,35</sup>

In our series we removed as many as 53 renal tumors from a single von Hippel-Lindau disease kidney. Patients with this many renal tumors are not amenable to standard techniques of partial nephrectomy, and they may be best served by an enucleation technique.<sup>36</sup> We have found that intraoperative ultrasound is important for locating tumors and verifying that all tumors have been removed.<sup>20</sup> Examination of small von Hippel-Lindau disease renal tumors diagnosed by screening consistently demonstrates a pseudocapsule surrounding these low grade renal lesions,<sup>2</sup> which facilitates resection. This pseudocapsule forms a natural plane for tumor removal. While the pseudocapsule may be invaded, we have not yet observed penetration of this boundary. Thus, we believe that 3 cm. is a conservative size threshold on which to base the decision to perform renal surgery in von Hippel-Lindau disease.

This strategy may decrease the number of surgical interventions a patient will undergo in a lifetime, while potentially providing a margin of safety against renal cancer metastases. A clear discussion of the risks and benefits of surgery in each patient with von Hippel-Lindau disease and hereditary papillary renal cancer is important if that patient is to make an informed decision regarding treatment options. In conclusion, further followup studies are required to determine the role of renal parenchymal sparing surgery versus renal replacement with dialysis or transplantation in the management of renal tumors in von Hippel-Lindau disease, and whether this strategy will successfully decrease the rate of metastases of renal cancer in these patients.

## REFERENCES

- Solomon, D. and Schwartz, A.: Renal pathology in von Hippel-Lindau disease. *Hum Pathol.*, **19**: 1072, 1988.
- Poston, C. D., Jaffe, G. S. and Lubensky, I. A.: Characterization of the renal pathology of a familial form of renal cell carcinoma associated with von Hippel-Lindau disease: clinical and molecular genetic implications. *J. Urol.*, **153**: 22, 1995.
- Zbar, B., Tory, K. and Merino, M.: Hereditary papillary renal cell carcinoma. *J. Urol.*, **151**: 561, 1994.
- Zbar, B., Glenn, G. and Lubensky, I.: Hereditary papillary renal cell carcinoma: clinical studies in 10 families. *J. Urol.*, **153**: 907, 1995.
- Zbar, B., Tory, K. and Merino, M.: Hereditary papillary renal cell carcinoma. *J. Urol.*, **151**: 561, 1994.
- Novick, A. C. and Strem, S. B.: Long-term followup after nephron sparing surgery for renal cell carcinoma in von Hippel-Lindau disease. *J. Urol.*, **147**: 1488, 1992.
- Frydenberg, M., Malek, R. S. and Zincke, H.: Conservative renal surgery for renal cell carcinoma in von Hippel-Lindau's disease. *J. Urol.*, **149**: 461, 1993.
- Choyke, P. L., Glenn, G. M. and Walther, M. M.: The natural history of renal lesions in von Hippel-Lindau disease: a serial CT study in 28 patients. *AJR*, **159**: 1229, 1992.
- Walther, M. M., Choyke, P. L. and Weiss, G.: Parenchymal sparing surgery in patients with hereditary renal cancer. *J. Urol.*, **153**: 913, 1995.
- Lamiell, J. M., Salazar, F. G. and Hsia, Y. E.: von Hippel-Lindau disease affecting 43 members of a single kindred. *Medicine*, **68**: 1, 1989.
- Marshall, M.: von Hippel-Lindau's Disease: Analysis of Age of Onset and Gene Expression in a Human Genetic Disease. Thesis. Honolulu, 1979.
- Neumann, H. P., Eggert, H. R. and Scheremet, R.: Central nervous system lesions in von Hippel-Lindau syndrome. *J. Neurol. Neurosurg. Psychiatry.*, **55**: 898, 1992.
- USRDS 1997 Annual Data Report. Washington, D.C.: United States Department of Health and Human Services, 1997.
- Goldfarb, D. A., Neumann, H. P., Penn, I. and Novick, A. C.: Results of renal transplantation in patients with renal cell carcinoma and von Hippel-Lindau disease. *Transplantation*, **64**: 1726, 1997.
- Levine, E., Weigel, J. W. and Collins, D. L.: Diagnosis and management of asymptomatic renal cell carcinomas in von Hippel-Lindau syndrome. *Urology*, **21**: 146, 1983.
- Spencer, W. F., Novick, A. C., Montie, J. E., Strem, S. B. and Levin, H. S.: Surgical treatment of localized renal cell carcinoma in von Hippel-Lindau's disease. *J. Urol.*, **139**: 507, 1988.
- Loughlin, K. R. and Gittes, R. F.: Urological management of patients with von Hippel-Lindau's disease. *J. Urol.*, **136**: 789, 1986.
- Steinbach, F., Novick, A. C. and Zincke, H.: Treatment of renal cell carcinoma in von Hippel-Lindau disease: a multicenter study. *J. Urol.*, **153**: 1812, 1995.
- Jamis-Dow, C. A., Choyke, P. L., Jennings, S. B., Linehan, W. M., Thakore, K. N. and Walther, M. M.: Small (< or = 3-cm) renal masses: detection with CT versus US and pathologic correlation. *Radiology*, **198**: 785, 1996.
- Walther, M. M., Choyke, P. L., Hayes, W., Shawker, T. H., Alexander, R. B. and Linehan, W. M.: Evaluation of color Doppler intraoperative ultrasound in parenchymal sparing renal surgery. *J. Urol.*, **152**: 1984, 1994.
- Licht, M. R. and Novick, A. C.: Nephron sparing surgery for renal cell carcinoma. *J. Urol.*, **149**: 1, 1993.
- Lerner, S. E., Hawkins, C. A. and Blute, M. L.: Disease outcome in patients with low stage renal cell carcinoma treated with nephron sparing or radical surgery. *J. Urol.*, **155**: 1868, 1996.
- Steinbach, F., Stöckle, M. and Muller, S. C.: Conservative surgery of renal cell tumors in 140 patients: 21 years of experience. *J. Urol.*, **148**: 24, 1992.
- Frank, W., Guinan, P., Stuhldreher, D., Saffrin, R., Ray, P. and Rubenstein, M.: Renal cell carcinoma: the size variable. *J. Surg. Oncol.*, **54**: 163, 1993.
- Bell, E. T.: A classification of renal tumors with observations on the frequency of the various types. *J. Urol.*, **39**: 238, 1938.
- Butler, B. P., Novick, A. C., Miller, D. P., Campbell, S. A. and Licht, M. R.: Management of small unilateral renal cell carcinomas: radical versus nephron-sparing surgery. *Urology*, **45**: 34, 1995.
- Eschwege, P., Saussine, C., Steichen, G., Delepaul, B., Drelon, L. and Jacqmin, D.: Radical nephrectomy for renal cell carcinoma 30 mm. or less: long-term follow results. *J. Urol.*, **155**: 1196, 1996.
- Moll, V., Becht, E. and Ziegler, M.: Kidney preserving surgery in renal cell tumors: indications, techniques and results in 152 patients. *J. Urol.*, **150**: 319, 1993.
- Lund, G. O., Fallon, B., Curtis, M. A. and Williams, R. D.: Conservative surgical therapy of localized renal cell carcinoma in von Hippel-Lindau disease. *Cancer*, **74**: 2541, 1994.
- Latiff, F., Tory, K. and Gnarr, J.: Identification of the von Hippel-Lindau disease tumor suppressor gene. *Science*, **260**: 1317, 1993.
- Gnarr, J. R., Tory, K. and Weng, Y.: VHL tumor suppressor gene mutations in renal carcinoma tumorigenesis. *Nat. Genet.*, **7**: 85, 1994.
- Walther, M. M., Lubensky, I. A., Venzon, D., Zbar, B. and

- Linehan, W. M.: Prevalence of neoplastic lesions in grossly normal renal parenchyma from patients with von Hippel-Lindau disease, sporadic renal cell carcinoma, and no renal disease: clinical implications. *J. Urol.*, **154**: 2010, 1995.
33. Lubensky, I. A., Gnarr, J. R., Bertheau, P., Walther, M. M., Linehan, W. M. and Zhuang, Z.: Allelic deletions of the VHL gene detected in multiple microscopic clear cell renal lesions in von Hippel-Lindau disease patients. *Amer. J. Path.*, **149**: 2089, 1996.
34. Chrétien, Y., Chauveau, D. and Richard, S.: Treatment of von Hippel-Lindau disease with renal involvement. *Prog. Urol.*, **7**: 939, 1997.
35. Di Silverio, F., Sciarra, A., Flammia, G. P., Mariani, M., De Vico, A. and Buscarini, M.: Surgical enucleation for renal cell carcinoma (RCC). Prognostic significance of tumour stage, grade and DNA ploidy. *Scand. J. Urol. Nephrol.*, **31**: 123, 1997.
36. Walther, M. M., Thompson, N. and Linehan, W.: Enucleation procedures in patients with multiple hereditary renal tumors. *World J. Urol.*, **13**: 248, 1995.