Kidney International, Vol. 50 (1996), pp. 944–951

Renal involvement in von Hippel-Lindau disease

DOMINIQUE CHAUVEAU, CHRISTIAN DUVIC, YVES CHRÉTIEN, FRANÇOIS PARAF, DOMINIQUE DROZ, PHILIPPE MELKI, OLIVIER HÉLÉNON, STÉPHANE RICHARD, and JEAN-PIERRE GRÜNFELD

Departments of Nephrology, Urology, Pathology, and Radiology, Ecole Pratique des Hautes Etudes, Hôpital Necker, Assistance Publique-Hôpitaux de Paris, Paris, France

Renal involvement in von Hippel-Lindau disease. Renal involvement in von Hippel-Lindau (VHL) disease has emerged as the most prevalent cause of death in this hereditary disorder. In a group of 43 VHL patients (23 unrelated families) with renal lesions we examined whether severity of renal disease is affected by parental inheritance and VHL subtype (1, without pheochromocytoma; 2, with pheochromocytoma). We also tested whether and how nephron-sparing surgery could be applied. Renal involvement comprised multiple cysts and bilateral and multifocal carcinomas (RCC) which were detected by screening in 38 patients, at 30.5 (14 to 62) years of age. The severity of the renal disease was similar in VHL type 1 (79% of the pedigrees) and 2 (21%). It was not influenced by the sex of the carrier. Twenty-nine patients were operated on at a mean age of 33.6 years: 21 patients (28 kidneys or 61% of all operated kidneys) underwent nephron-sparing surgery, 4 had complete ablation of involved kidneys and thus required dialysis, 3 had uninephrectomy and 1 had cyst fenestration. Vascular thrombosis was the most severe early complication. It occurred in 4 of 9 kidneys treated by *ex vivo* surgery. During a median follow-up of 29 months, local recurrence occurred in 5 of 21 (24%) patients treated by nephron-sparing surgery, whereas 2 developed metastasis. Chronic renal failure (creatinine > 120 μmol/liter) affected 11 patients; in 9 of them, it was due to sequelae of surgery. In conclusion, screening of RCC and nephron-sparing surgery are of value in VHL patients. However, indications of *ex vivo* surgery should be drastically restricted and renal sequelae are not uncommon. Renal followup is required because of the risk of recurrence.

von Hippel-Lindau (VHL) disease is a dominantly inherited disorder characterized by a predisposition to develop hemangioblastomas of the central nervous system and retina, pheochromocytomas, pancreatic cysts and tumors and renal lesions [1–3]. The unique gene responsible for VHL disease has been located and identified on the short arm of chromosome 3 (3p25). In contrast with genetic locus homogeneity, variable expression is customary among families with the disease [4]. Some kindreds are prone to pheochromocytomas (type 2 VHL disease), whereas they never appear in others (type 1 VHL) [5, 6]. Within families, affected members also exhibit phenotypic variability.

Kidney involvement ranges from simple cysts to renal tumors, including atypical cysts with solid components. Multifocal lesions are typical. Solid tumors are invariably renal cell (clear cell) carcinomas (RCC) [7–10]. As most renal carcinomas develop at an older age than any other complication, radiologic screening and early surgical treatment are advocated and presumably improve long-term outcome. To delay end-stage renal failure in otherwise severely affected VHL patients, nephron-sparing surgery has been recommended [10–13].

The current study describes our experience with 43 VHL patients having renal involvement. Our objectives were to delineate the role of parental inheritance and VHL subtype on phenotype variability and to test whether and how nephron-sparing surgery could be applied to this group of patients.

Received for publication January 2, 1996
and in revised form April 17, 1996
Accepted for publication April 17, 1996

Methods

Patient population

From 1986 to July 1995, 43 patients with VHL disease were referred for renal involvement to our Clinic. Diagnosis of VHL was established if the patient presented with one of the above-mentioned lesions and a positive family history. In the absence of family history (sporadic cases) lesions involving two different systems were required [2]. Attention was devoted to renal involvement in at-risk or affected relatives, including patient interview and review of hospital and autopsy records.

Renal and extrarenal investigative workup

We currently screen for renal involvement by yearly abdominal ultrasound from 15 years of age. If a renal lesion is detected, CT scan of the abdomen is performed before and after contrast media, using 5-mm-thick contiguous sections. Renal lesions are classified as solid if their precontrast attenuation is greater than 20 UH and enhances with contrast material, or cystic if their spontaneous attenuation is below 20 UH and does not enhance after contrast media. High density lesions that do not enhance are considered as cystic. Renal masses consisting of cysts with one or few cloisons or a vegetant element, or both solid and cystic components with a prominent cystic part, are classified as complex lesions. Lesions are regarded as undetermined if their dimensions are less than 5 mm. Magnetic resonance imaging (MRI) and renal arteriography are applied in patients who are candidates for renal-sparing surgery. MRI was performed preoperatively, using body coil studying both kidneys in 10 patients, or dual surface coils placed adjacent to the kidney being studied in 7 patients. In addition, 6 kidneys requiring *ex vivo* surgery were studied by intraoperative MRI.

Extrarenal assessment includes MRI of the brain and spinal cord, blood pressure measurement, 24-hour urinary collection for metanephrine and normetanephrine, and direct ophthalmoscopy. In patients with solid renal lesions, chest X-ray is included.

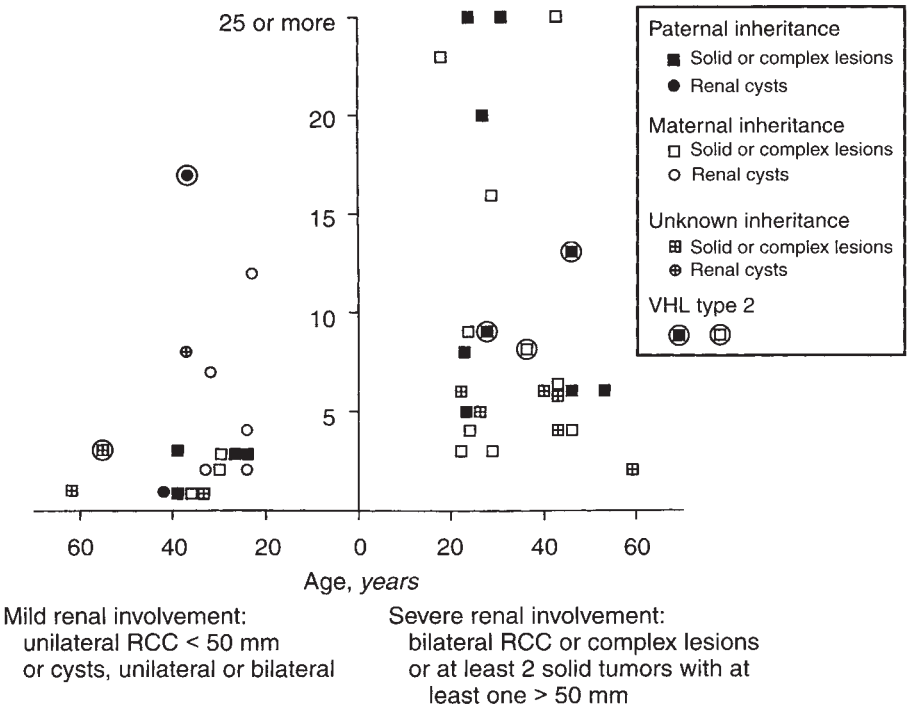

Fig. 1. *Diagram showing the number and the types of renal lesions identified by initial CT-scan, the ages of patients at discovery, and the sex of the carrier in VHL disease.* The left side of the Figure shows patients with "mild" and the right side, patients with "severe" renal involvement. The ordinate shows the number of renal lesions, the abscissa, the ages at discovery. Patients with both cystic and solid lesions were classified as "solid or complex lesions."

Surgical management

It was considered in all patients presenting with at least one solid or complex lesion greater than 25 mm. Nephron-sparing surgery was regarded as the most appropriate approach if the diameter of the renal lesion was less than 50 mm and if less than 5 to 6 solid lesions were identified pre-operatively in the ipsilateral kidney. Solid lesions were excised by either partial nephrectomy or wedge resection with a rim of normal surrounding renal tissue or enucleation. We initially performed *ex vivo* tumor excision using surface hypothermia and peroperative MRI screening for detecting occult deep lesions and optimizing tumor withdrawal. Autotransplantation was performed either at the original site (5 kidneys) or in the iliaca fossa (4 kidneys). Since 1994 all surgical procedures have preferably been performed *in situ*. We have never tried to remove purely cystic lesions. Synchronous resection refers to bilateral surgical treatment within a six-month period, even though bilateral renal-sparing operations were planned at an interval of at least 30 days when indicated. Asynchronous resection refers to bilateral surgery distant by more than six months. If warranted, radical nephrectomy (including adrenalectomy) was performed. Bilateral radical nephrectomy was not performed in patients with evidence of metastatic disease but no urologic symptoms. Enlarged regional lymph nodes were biopsied at operation. Postoperative followup of patients included physical examination, chest radiography, abdominal CT and renal function tests performed at six months and yearly thereafter.

Pathology

For pathology study all surgical specimens were examined and serially sliced. All lesions observed were prepared for routine light microscopy analysis using hematoxylin-eosin, PAS and silver methenamine staining. Simple cysts were defined as a single layer of flat chromophilic or clear cells lining the wall, atypical cysts as a layer 2 or 3 clear cells thick, and cystic carcinomas as cystic formations with at least one focus of multilayer clear cells or papillary projections. All renal cell tumors were classified according to Thoenes criteria, architectural growth and cytonuclear atypias (Furhman's grade) [14].

For statistical analysis, we compared mean values with the Mann-Whitney test. Statistical significance was taken at the 5% level.

Results

Clinical presentation: Renal and extrarenal manifestations

We examined 43 patients (25 females, 18 males) with VHL disease and kidney involvement. Renal lesions were detected through presymptomatic screening in 38 patients, at initial evaluation in 17 patients, and during follow-up in 21. Age distribution at diagnosis of renal involvement is depicted in Figure 1: mean age was 30.5 years (range 14 to 62) for all patients and 30.6 (14 to 62) if only solid lesions are considered. Three patients had widespread metastatic disease when diagnosis of RCC was first considered at 31, 39 and 43 years of age, respectively. Renal tumors were the only manifestation of von Hippel-Lindau disease in two patients, at ages 22 and 62, respectively. Extrarenal manifestations of von Hippel-Lindau disease are summarized in Table 1. Mean age at diagnosis of first VHL manifestation was 28.0 years (range 9 to 62).

Family study: Parental inheritance and VHL subtype

A family history of VHL disease was traced in 37 out of 43 patients belonging to 23 apparently unrelated families. The disease was inherited from the father in 14 patients and from the mother in 19. Inheritance remained unknown in 10 (including 6 sporadic cases). A total of 18 families (32 patients) and five

Table 1. Extrarenal manifestations of von Hippel-Lindau disease in 43 patients with renal involvement

Lesion	*N*	%
Central nervous system		
Retinal hemangioblastoma	22	51
Cerebral or brain-stem hemangioblastoma	28	65
Spinal cord hemangioblastoma	15	35
Abdominal lesions		
Cystic pancreatic disease	26	60
Pancreatic solid tumors	4	9
Pheochromocytoma	5	12
Cystadenoma of broad ligament	1	2
Liver cysts	1	2
Giant liver hemangiomas	1	2
Others		
Endolymphatic sac tumor	1	2

Table 2. Natural history of renal lesions according to parental inheritance and VHL phenotype

	Inheritance		VHL phenotype	
	Paternal (14 patients)	Maternal (19 patients)	Type 1 (38 patients)	Type 2 (5 patients)
Age at diagnosis	30.5 ± 3.0	28.5 ± 1.5	31.6 ± 1.8	38.4 ± 5.4
N	14	19	38	5
Age if diagnosed by screening	30.0 ± 3.4	28.0 ± 1.6		
N	12	17		
Age at 1st operation	35.4 ± 2.8	29.8 ± 3.1	31.8 ± 2.1	42.7 ± 5.8
N	12	10	25	4
Age at 1st operation if diagnosed by screening	35.3 ± 3.4	30.0 ± 3.4		
N	10	9		

Values are expressed as mean age (±SEM) in years
None of the above differences achieves statistical significance

sporadic cases were classified VHL type 1 (79% of all pedigrees), whereas five families (5 patients) and one sporadic cases were VHL type 2 (21%). Mean ages at diagnosis of renal involvement and first operation for RCC were not significantly affected neither by parental inheritance nor by VHL subtype (1 or 2) (Table 2).

Clustering for severe renal involvement was observed in four VHL type 1 families including 15 VHL members. In each of these kindreds, two to four of the affected relatives (12 of 15) developed metastasis or required bilateral renal surgery before 40 years of age. So far we have not been able to characterize the molecular lesions in these families.

Radiological findings

According to CT criteria, 823 lesions were initially characterized into four radiologically distinct patterns (Figs. 2 to 4 and Table 3). Cysts were the most common lesions (34%) and were found in 74% of the patients. Complex and solid patterns lesions made up 35% of CT lesions. Solid lesions were observed in 34 of 43 patients, 19 having bilateral disease. Finally 31% of all lesions remained too small (< 5 mm) during the study period to be appropriately characterized. On follow-up, progressive enlargement of solid or complex renal lesions requiring surgery was observed in 21 patients. Among eight patients initially exhibiting renal cystic disease either isolated or associated with renal lesions of unknown significance, only two developed solid lesions on follow-up (mean 4.5 years).

Preoperative MRI was performed in 17 patients and findings were concordant with CT in 8. MRI missed 37 lesions in 4 patients, 92% of them being less than 5 mm in size on CT-scan. MRI helped to better characterize 15 lesions in 7 patients, only 3 being > 5 mm diameter. A selective renal angiogram was performed in 24 patients and disclosed only 81 hypervascular tumors in 34 kidneys (range 0 to 7 in each kidney), as compared to 139 solid tumors detected by CT. Angiography missed solid lesions demonstrated by CT in 25 kidneys. Subsequently angiography was proven to have missed one or more RCC in 24 out of 38 of the operated kidneys.

Surgical procedures and follow-up

A total of 29 patients required surgical treatment (Table 4). Three patients had previously undergone unilateral nephrectomy before referral to this Renal Unit. First operation was performed at a mean age of 33.6 ± 10.9 years (range 18 to 59). Bilateral disease ($N = 18$) required synchronous resection in 14 and asynchronous surgery in 4 cases. Complete removal of involved kidneys and renal replacement therapy was the only treatment possible in four patients aged 25 to 43 years, having multiple renal cell carcinomas (5 to 32 in each kidney) of moderate size (less than 50 mm) but associated with numerous cysts precluding sparing surgery. Eleven patients presented with unilateral disease requiring surgery.

Our series comprises a total of 21 patients (28 kidneys) who underwent nephron-sparing surgery. In addition, because of a bilateral local recurrence, one patient underwent a repeat partial nephrectomy in one kidney and nephrectomy in the other. Therefore 29 nephron-sparing operations were performed on these 21 patients, enabling *in situ* removal of 53 tumors from 19 kidneys and *ex vivo* resection of 31 tumors from 9 kidneys. Intraoperative MRI detected 9 deeply seated lesions unidentified on preoperative imaging, and reclassified three lesions as solid tumors but missed two small RCC only discovered at examination of one kidney. All but one of these tumors were less than 20 mm in size.

No patient died in the perioperative period. Early complications included vascular thrombosis requiring kidney removal ($N = 4$), ischemic acute renal failure in patients with a solitary kidney ($N = 3$) without requirement for dialytic support, sepsis ($N = 1$) and urinary fistula ($N = 1$). All occurred in patients treated by *ex vivo* surgery. A single minor fistula occurred after *in situ* operation. Nephrectomies were uncomplicated. Regular dialysis was started in four patients who became anephric, including one for whom *ex vivo* operation failed.

On long-term follow-up (median 29 months, range 3 to 117) chronic renal failure related to bilateral parenchymal removal affected five additional patients (serum creatinine 120 to 172 μmol/liter, stable over time). Progression of tumoral disease was detected in 3 patients, either as local recurrence three years after bilateral sparing surgery ($N = 1$) requiring reoperation of both kidneys, or as distant metastasis (2 cases). In 4 additional patients, recurrence of local tumoral disease was suspected on CT, the lesions being still too small for firm identification. Extrarenal manifestations related to VHL developed in 6 patients during the follow-up period, including hemangioblastomas of the central

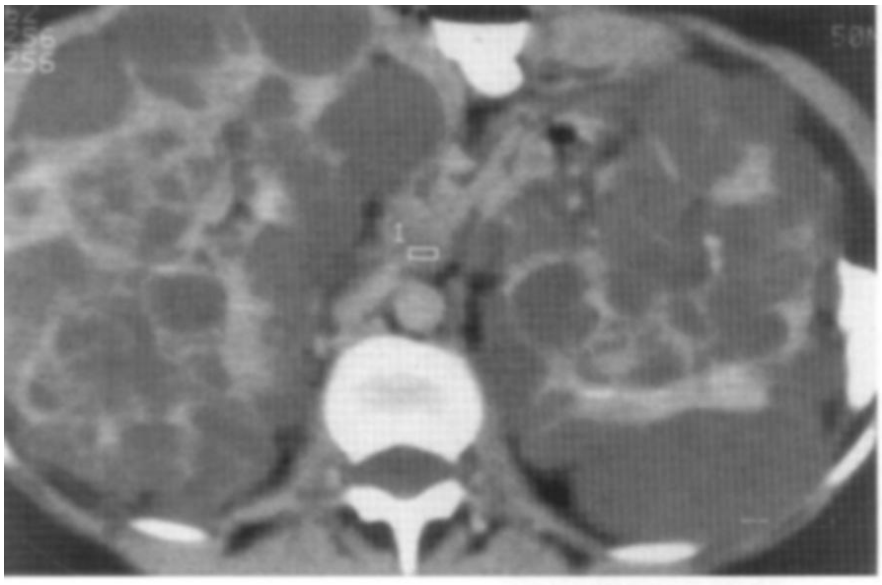

Fig. 2. *Patterns of renal lesions on CT-scan.* Numerous cysts with massively enlarged kidneys mimicking autosomal dominant polycystic kidney disease in a 36-year-old woman.

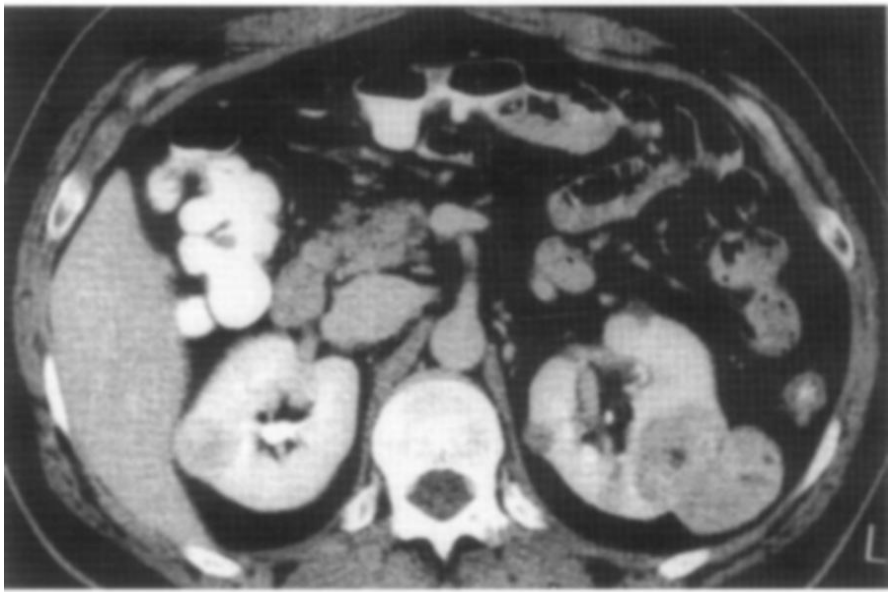

Fig. 3. *Patterns of renal lesions on CT-scan.* Bilateral and multiple solid tumors in a 43-year-old man with type 2 VHL disease.

nervous system ($N = 4$), leading to death in one patient on regular dialysis, hemangioblastoma of the retina ($N = 1$) and pancreatic solid tumor ($N = 1$).

Fifteen patients with renal involvement did not undergo surgery, either because lesions were cystic or indeterminate but small ($N = 12$), or disease was metastatic ($N = 1$) or renal replacement therapy was declined ($N = 2$). On follow-up (mean 43 months, 9 to 144 months), 2 of them died of metastases, local progression of renal solid tumors was demonstrated or suggested by CT in 4 and 2 patients, respectively, and regression of atypical cysts was documented in 2. Two patients developed progressive renal failure, attributed to invading cystic and tumoral disease (VHL type 1, serum creatinine 222 μmol/liter), and to radiation nephritis for malignant pheochromocytoma (VHL type 2), the latter requiring regular dialysis. Two nonoperated patients experienced extrarenal complications related to VHL disease.

Pathology

Three major types of gross lesions were recognized: solid nodular lesions (0.2 to 6 cm in diameter), cystic lesions of variable size (0.2 to 10 cm), most of them containing microscopic solid formations; and white retracted scars at convexity in 6 kidneys.

A total of 219 RCC were removed from 46 kidneys. Detailed study by light microscopy is available for 181 (Table 5). Twelve percent included eosinophilic cell areas. Five kidneys included 10 to 32 carcinomas. Additionally 203 cysts were removed, and 138 of them were examined histologically. The final diagnosis concluded to (a) 16 (11%) cystic carcinomas, all clear cell type grade 1 with

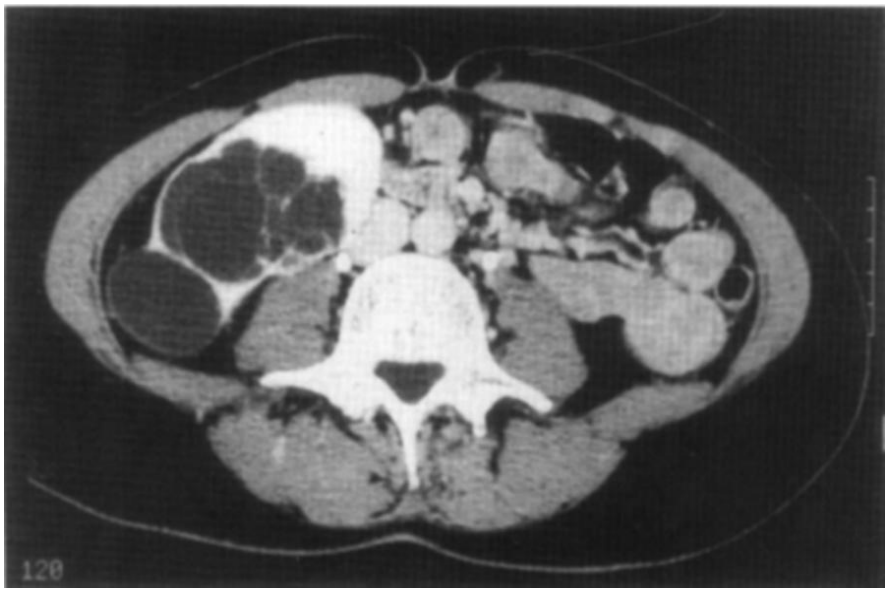

Fig. 4. *Patterns of renal lesions on CT-scan.* Cystic and complex lesions in a 23-year-old type 1 VHL patient.

Table 3. Radiological findings on initial CT-scan in 43 patients with von Hippel-Lindau disease

Lesions[a]				
Type	Number (percent)	Number of patients with Bilateral	Unilateral	No
Cysts	282 (34)	20	12	11
Complex	146 (18)	13	15	15
Solid	136 (17)	19	14	10
Undetermined (size ≤ 4 mm)	259 (31)	18	10	15
All	823 (100)			

[a] The absolute number of lesions do not include findings in two patients (3 kidneys) with massively enlarged kidneys including unnumerable cysts and solid lesions (Fig. 2)

Table 4. Surgical procedures performed in 29 VHL patients

Unilateral disease (N = 11)	
Nephrectomy	3
Nephron sparing surgery (NSS)	7
Obstructive cyst fenestration	1
Bilateral disease (N = 18)	
Bilateral nephrectomy	4[a]
Unilateral nephrectomy and NSS	7[b]
Bilateral NSS	7

[a] Including one patient with a single congenital kidney
[b] Including 3 patients who had undergone uninephrectomy prior to referral to our hospital

Table 5. Histopathology of renal lesions in 46 kidneys from 29 VHL patients

Solid tumors (N = 195)	%	Cystic lesions (N = 138)	%
Renal cell carcinomas (N = 181)		Simple cysts (N = 102)	75
		Clear cells	50
Clear cell type	100	Chromophilic cells	25
Chromophilic cells areas	12		
Fuhrman grade			
1	81		
2	16	Atypical cysts	14
3	3	(N = 20)	
Architecture			
Compact	50	Cystic carcinomas	11
Tubulocystic	50	(N = 16)	
Tubular	<1		
Papillary	0		
Fibrous nodules (N = 14)			

large cystic cavities, (b) 20 atypical cysts (14%), 0.3 to 7 cm, edged with several layers of clear cells and (c) 102 simple cysts.

Widespread metastasis were present in one non-operated VHL type 1 woman with several RCC in both kidneys, the largest being 45 mm in diameter. Conversely, large tumors (50 to 100 mm in diameter) were removed in 5 VHL type 1 or 2 patients without evidence of dissemination. Finally, a non-secreting pheochromocytoma was incidentally found in 3 cases, whereas the adrenal gland was enlarged in four additional cases (2 metastasis, 2 without evidence of tumor).

Discussion

Renal involvement is a frequent and commonly severe manifestation of von Hippel-Lindau (VHL) disease. Its incidence reaches 24% in a retrospective review of the literature including 554 patients [2], 28% in a cohort of 152 patients followed in a single center [3] and 31% in the French National VHL registry [9]. However, cumulative age distribution curves have shown that among patients who survive to 60 to 70 years of age, 90 to 95% develop kidney lesions [3, 15, 16]. Of note, a longitudinal radiological survey documented that at 60 years of age the cumulative probability of diagnosis of renal cyst reached 95%, whereas solid renal masses affected 77% of the population and plateaued thereafter [8]. In the last decade improvement in both screening and treatment of hemangioblastoma and pheochromocytoma, potentially fatal in young VHL patients, has promoted RCC to the leading cause of death [3, 15].

It should be stressed that the 43 patients included in our series were referred to Necker Hospital for kidney involvement over a ten year period. Concurrently extrarenal lesions were treated elsewhere. Therefore our data do not provide insight into prevalence of renal lesions in VHL disease. However, renal involvement was actually the initial manifestation in only 3 (7.2%) patients in this series. Mean age at diagnosis of renal lesions, either solid or not, was 30 years and 88% of them were detected by screening. Such recruitement enables early diagnosis and most likely explains discrepancies with the corresponding figures in the series of Steinbach (36 years; 65 patients, 63% detected by screening) and Maher (44 years; 43 patients, 18% detected by screening) [3, 17]. Among the 34 patients with solid tumors, 19 (56%) had bilateral disease. An in depth review of the literature by Nelson, Oyasu and Dalton also found that 56% of 138 VHL patients with RCC had bilateral disease [12]. The updated experience from 8 medical centers in the United States, including 65 patients with presumably longer follow-up, suggests that this number may even reach 83% [17].

The severity of the renal lesions is well exemplified in our series where 29 of 43 (64%) patients required surgical treatment at a mean age of 33.6 years, two to three decades prior to mean age at surgery for sporadic RCC. Early discovery of RCC in VHL disease has been stressed in the literature, with the diagnosis being made at 15 [17] and at 16 years of age [18]. In addition, bilateral renal surgery was required in 18 of 29 (62%) patients who were operated on. Whether propensity to metastasize differs in the sporadic and the VHL-related forms of RCC has been questioned. In the sporadic form about half of the patients with local recurrence after conservative surgery have concomitant metastatic disease, at variance with the VHL form where the corresponding number is 8% [17]. Possibly smaller tumor size and stage at initial removal partially explain these discrepancies. Nevertheless, we documented metastasis in one patient whose largest solid renal lesion did not exceed 45 mm.

What does promote the severity of the renal involvement? Genetic factors are likely to play a role. In VHL type 2 families with pheochromocytoma, two subtypes have been defined: 2A without RCC, and 2B with RCC. In VHL 2A families a unique 505 T to C mutation has been detected [19], whereas in VHL 2B families a hot-spot mutation was found at nucleotides 712 and 713 [20]. In contrast, no correlation has been found between genotypic and renal phenotypic lesions in VHL type 1 families [6, 21], but the risk of developing renal carcinoma is very high in these cases (see above). Our data suggest a similar severity of kidney lesions in VHL type 1 and 2B patients, albeit our series of type 2B families is short. Interestingly, we showed that in 4 out of 18 (22%) VHL type 1 families, RCC exhibited a very aggressive course. While genomic imprinting has been demonstrated to influence the severity of some inherited disorders, the sex of the carrier determining the profile of the disease in the offspring, this possibility had not so far been explored in VHL disease. With regard to RCC, we could not find evidence for genomic imprinting.

In contrast, other VHL patients have a much less aggressive renal disease. Some have only a single renal carcinoma, often discovered late in life, simulating sporadic RCC. In the series collected by Steinbach et al, 11 patients (17%) belonged to this group [17]. In our group, four patients had a similar presentation, including a 62-year-old man with an unilateral single RCC. The rate of progression of RCC in VHL disease might be influenced by the molecular mechanisms involved in carcinogenesis. The VHL gene encodes a protein that binds to elongins B and C and thus regulates the rate of transcription elongation mediated by RNA polymerase II. Some mutations are located within the elongin binding site of the VHL protein but some others are not [22–25]. Inactivation of the VHL gene, a tumor suppressor gene, may result from various mutations or from abnormal methylation [26, 27]. It is also suggested that other as yet unidentified factors possibly protect against multicentric or aggressive RCC in some patients or families.

In addition, VHL renal involvement may present as only cysts. Eight of our patients had purely cystic disease. This peculiar phenotype may also arise after 60 years of age [28]. Pathogenesis, prognosis and treatment of renal cysts raise unsolved issues. The renal cyst epithelium is often atypical in VHL, with multiple cell layers and foci of cells highly suggestive of RCC in 25% of our specimens as in previous studies [7, 10]. Studies by antigenic markers indicate some similarity between cyst epithelial cells and renal carcinoma cells [29]. However, long-term follow-up by CT-scan of 168 cysts in 28 patients over a five-year period documented only two transformations into solid tumors, whereas 7% of the cysts spontaneously involuted [8]. Despite these results, these authors advocated later extensive excision of all visible cystic lesions when concomitant solid tumours require surgery [28]. We have elected a much more conservative approach.

Surgical management of renal lesions in VHL disease requires an individualized approach. This includes careful evaluation of both central nervous system lesions, whose surgical care may be indicated and then has priority, and functional pheochromocytoma, which should be excised prior to or at the same time as renal surgery [30]. Surgical options for solid renal tumors of significant size (> 25 mm) are nephrectomy, which exposes to renal failure in case of bilateral disease, and nephron-sparing surgery which carries the risks of residual disease or local recurrence in the remnant renal parenchyma and subsequent metastasis [11, 31].

Like others, we opted for sparing surgery when possible and treated accordingly 28 kidneys from 21 patients (61% of all operated kidneys). We agree with the conclusion meanwhile reached by Walther et al that "in VHL patients, solid renal lesions should be removed when they are ≥ 30 mm in diameter," and that "smaller neoplasms centrally located or adjacent to vital structures may also be indications for earlier renal operations." We documented local recurrence in 5 of 21 patients (24%) at 31 months, in keeping with the 36% rate found at 26 months among 19 patients [28]. Both experiences are too short at the moment to confirm that this attitude is well-founded on the long term. The multicenter experience collected by Steinbach in 49 patients in the meantime provides a rationale to support this approach since 5- and 10-year cancer specific survival rates were evaluated at 100 and 81%, respectively. Simultaneously, the corresponding rates of local recurrence were 29 and 85% [17]. Only 2 of 49 patients (4%) developed metastasis in the series mentioned above, but 2 of 21 (9%) in our experience. Close follow-up and repeat surgery are thus the counterpart of nephron sparing surgery.

Intraoperative detection of small lesions may be of value to increase the efficacy of nephron-sparing surgery. Compared with preoperative imaging, we documented that intraoperative MRI enhances both sensitivity and specificity to characterize the small (< 10 mm) renal lesions in VHL disease. Despite caution in

cooling the kidney transiently removed, intraoperative MRI prolonged ischemia time and might have contributed to the high rate of vascular thrombosis we observed. The reliability of intraoperative ultrasound for localization of small lesions is also debated: some had little success in finding nonpalpable solid tumors [31], whereas others concluded that 38% of resected lesions had not been detected on preoperative imaging [32]. Despite this increased excision of small tumors, recurrence reached 36% at two years in this series [28].

Conservative surgery not being possible or not considered, a total of 17 kidneys were initially removed in our patients. Presumably long-term survival should be less in these patients, most of whom had a more aggressive renal disease than in the nephron-sparing group. Five- and 10-year survival rates were 95 and 77% in 16 patients reviewed in the multicenter study [17].

Chronic renal failure affected 11 of our 43 patients (26%). Of note, one patient developed severe renal failure in association with diffuse bilateral cystic and solid tumors. Hauschild also reported a 51-year-old man requiring regular hemodialysis for VHL disease mimicking autosomal dominant polycystic kidney disease who died four months later of widespread metastases of RCC [33]. The mechanism of reduced glomerular filtration rate in our case may be related to cystic compression of renal parenchyma or alternatively to its infiltration by cancer. End-stage renal disease has so far not been reported in the purely cystic form of VHL disease. Sequelae of renal surgery accounted for renal failure in 9 of 11 patients, including four requiring regular dialysis. Steinbach et al recently reported that despite attempted nephron-sparing surgery, 15 of 65 patients (23%) ultimately developed end-stage renal failure [17]. The most serious complication of renal surgery was postoperative vascular thrombosis, which occurred in 4 out of 9 *ex vivo* operations. Owing to these pitfalls we have drastically restricted the indications of *ex vivo* surgery, which together with extensive parenchymal resection are now well identified risk factors for severe complication of sparing surgery [34, 35]. For patients on renal replacement therapy without metastatic malignancy, renal transplantation is advisable if extrarenal features do not preclude it. At least 19 VHL patients have received this form of replacement therapy [17, 36, 37]. The optimal interval (1 or 2 years) between kidney removal and transplantation in order not to miss residual malignancy, as well as long term survival, are not known.

Reprint requests to Dr. D. Chauveau, Department of Nephrology, Hôpital Necker, 161, rue de Sèvres, 75015 Paris, France.

References

1. Horton WA, Wong V, Eldridge R: von Hippel-Lindau disease: Clinical and pathological manifestations in nine families with 50 affected members. *Arch Int Med* 136:796–777, 1976
2. Lamiell JM, Salazar FG, Hsia YE: von Hippel-Lindau disease affecting 43 members of a single kindred. *Medicine* 68:1–29, 1989
3. Maher ER, Yates RW, Harries R, Benjamin R, Benjamin C, Harris R, Moore AT, Ferguson-Smith MA: Clinical features and natural history of von Hippel-Lindau disease. *Quart J Med* 283:1151–1163, 1990
4. Neumann HPH: von Hippel-Lindau disease, in *Inherited Disorders of the Kidney*, edited by Morgan S, Grünfeld JP, Oxford, Oxford University Press (in press)
5. Neumann HP, Wiestler OD: Clustering of features of von Hippel-Lindau syndrome: Evidence for a complex genetic locus. *Lancet* 337:1052–1054, 1991
6. Lineham WM, Lerman MI, Zbar B: Identification of the von Hippel-Lindau (VHL) gene. *JAMA* 273:564–570, 1995
7. Solomon D, Schwartz A: Renal pathology in von Hippel-Lindau disease. *Hum Pathol* 19:1072–1079, 1988
8. Choyke P, Glenn GM, Walther MM, Zbar B, Weiss GH, Alexander RB, Hayes WS, Long JP, Thakore KN, Linehan WM: The natural history of renal lesions in von Hippel-Lindau disease: A serial CT study in 28 patients. *AJR* 159:1229–1234, 1992
9. Richard S, Chauveau D, Chrétien Y, Beigelman C, Denys A, Fendler JP, Fromont G, Paraf F, Hélénon O, Nizard S: Renal lesions and pheochromocytoma in von Hippel-Lindau disease. *Adv Nephrol* 23:1–27, 1994
10. Poston CD, Jaffe GS, Lubensky IA, Solomon D, Zbar B, Linehan WM, Walther WM, Walther MM: 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* 153:22–26, 1995
11. Novick AC, Streem SB: Long-term followup after nephron sparing surgery for renal cell carcinoma in von Hippel-Lindau disease. *J Urol* 147:1488–1490, 1992
12. Nelson JB, Oyasu R, Dalton DP: The clinical and pathological manifestations of renal tumors in von Hippel-Lindau disease. *J Urol* 152:2221–2226, 1994
13. Lund GO, Fallon B, Curtis MA, Williams RD: Conservative surgical therapy of localized renal cell carcinoma in von Hippel-Lindau disease. *Cancer* 74:2541–2545, 1994
14. Gogusev J, Fournet JC, Couturier J, Béroud C, Patey N, Augusti M, Chrétien Y, Paraf F, Adafer E, Droz D: Renal cell carcinoma: Recent progress. *Adv Nephrol* 23:71–90, 1994
15. Neumann HPH, Eggert HR, Scheremet R, Schumacher M, Mohadier M, Wakhloo AK, Volk B, Hettmannsperger U, Riegler P, Schollmeyer P, Wiestler O: Central nervous system lesions in von Hippel-Lindau syndrome. *J Neurol Neurosurg Psychiatry* 55:898–901, 1992
16. Neumann HPH, Lips CJM, Hsia YE, Zbar B: von Hippel-Lindau syndrome. *Brain Pathol* 5:181–193, 1995
17. Steinbach F, Novick AC, Zincke H, Miller DP, Williams RD, Lund G, Skinner DG, Esrig D, Richie JP, de Kernion JB, Marshall F, Marsh CL: Treatment of renal cell carcinoma in von Hippel-Lindau disease: A multicenter study. *J Urol* 153:1812–1816, 1995
18. Keeler LL, Klauberg GT: von Hippel-Lindau disease and renal cell carcinoma in a 16-year-old-boy. *J Urol* 147:1588–1591, 1992
19. Brauch H, Kishida T, Chen GF, Pausch F, Hofler H, Latif F, Lerman MI, Zbar B, Neumann HPH: von Hippel-Lindau (VHL) disease with pheochromocytoma in the Black Forest region of Germany: Evidence for a founder effect. *Hum Genet* 95:551–556, 1995
20. Crossey PA, Richard FM, Foster K, Green JS, Prowse A, Latif F, Lerman MI, Zbar B, Affara NA, Ferguson-Smith MA, Maher ER: Identification of intragenic mutations in the von Hippel-Lindau disease tumour suppressor gene and correlation with disease phenotype. *Hum Molec Genet* 3:1303–1308, 1994
21. Chen F, Kishida T, Yao M, Hustad T, Glavac D, Dean M, Gnarra JR, Orcutt ML, Duh FM, Glenn G, Green J, Hsia YE, Lamiell J, Li H, Wei MH, Schmidt L, Tory K, Kuzmin I, Stackhouse T, Latif F, Linehan WM, Lerman M, Zbar B: Germline mutations in the von Hippel-Lindau disease tumor suppressor gene: Correlations with phenotype. *Hum Mutat* 5:66–75, 1995
22. Duran DR, Pause A, Burgess WH, Aso T, Chen DYT, Garrett KP, Conaway RC, Conavry JW, Linehan WM, Klausner RD: Inhibition of transcription elongation by the VHL tumor suppressor protein. *Science* 269:1402–1406, 1995
23. Aso T, Lane WS, Conaway JW, Conaway RC: Elongin (SIII): A multisubunit regulator of elongation by RNA polymerase II. *Science* 269:1439–1443, 1995
24. Kibel A, Iliopoulos O, de Caprio JA, Kaelin WG: Binding of the von Hippel-Lindau tumor suppressor protein to elongin B and C. *Science* 269:1444–1446, 1995
25. Kishida T, Yao M, Chen F, Orcutt ML, Lerman MI, Zbar B: A novel donor splice site mutation associated with two mRNAs in von Hippel-Lindau disease. *Hum Mol Genet* 3:1191–2, 1994
26. Whaley JM, Naglich J, Gelbert L, Hsia E, Lamiell JM, Green JS, Collins D, Neumann HPH, Laidlaw J, Li FP, Klein-Szanto

AJP, SEIZINGER BR, KLEY N: Germ-line mutations in the von Hippel-Lindau tumor-suppressor gene are similar to somatic von Hippel-Lindau aberrations in sporadic renal celle carcinoma. *Am J Hum Genet* 55:1092–1102, 1994

27. HERMAN JG, LATIF F, WENG Y, LERAN MI, ZBAR B, LIUS, SAMID D, DUAN DR, GNARRA JR, LINEHAN WM, BAYLIN SB: Silencing of the VHL tumor-suppressor gene by DNA methylation in renal carcinoma. *Proc Natl Acad Sci USA* 91:9700–9704, 1994
28. WALTHER MM, CHOYKE PL, WEISS G, MANOLATOS C, LONG J, REITER R, ALEXANDER RB, LINEHAN WM: Parenchymal sparing surgery in patients with hereditary renal cell carcinoma. *J Urol* 153:913–916, 1995
29. KRAGEL PJ, WALTHER MM, PESTANER JP, FILLING-KATZ MR: Simple renal cysts, atypical renal cysts, and renal cell carcinoma in von Hippel-Lindau disease: A lectin and immunohistochemical study in six patients. *Mod Pathol* 4:210–214, 1990
30. NEUMANN HPH, BERGER DP, SIGMUND G, BLUM U, SCHMIDT D, PARMER RJ, VOLK B, KIRSTE G: Pheochromocytomas, multiple endocrine neoplasia type 2, and von Hippel-Lindau disease. *N Engl J Med* 329:1531–1538, 1993
31. FRYDENBERG M, MALEK RS, ZINCKE H: Conservative renal surgery for renal cell carcinoma in von Hippel-Lindau's disease. *J Urol* 149:461–464, 1993
32. WALTER MM, CHOYKE PL, HAYES W, SHWKER TH, ALEXANDER RB, LINEHAN WM: Evaluation of color Doppler intraoperative ultrasound in parenchymal sparing renal surgery. *J Urol* 152:1984–1987, 1994
33. HAUSCHILD S, FEDDERSEN A, FRAHM C, KREFT B, WALLNER SJ, STEINHOFF J: Das v. Hippel-Lindau-syndrom. Differentialdiagnose von Zystennieren im Erwachsenenalter. *Dtsch Med Wschr* 120:790–794, 1995
34. STORMONT TJ, BILHARTZ DL, ZINCKE H: Pitfalls of "bench surgery" andautotransplantation for renal cell carcinoma. *Mayo Clin Proc* 67:621–628, 1992
35. CAMBPELL SC, NOVICK AC, STREEM SB, KLEIN E, LICHT M: Complications of nephron sparing surgery for renal tumors. *J Urol* 151:1177–1180, 1994
36. PETERSON GJ, CODD JE, CUDIHEE RE, NEWTON WT: Renal transplantation in von Hippel-Lindau disease. *Arch Surg* 112:841–842, 1977
37. PENN I: The effect of immunosuppression on pre-existing cancers. *Transplantation* 55:742–747, 1993