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Renal Tumors in Patients with von Hippel-Lindau Disease: “State of Art Review”

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1. Introduction

The disease that has perpetuated the names of two prestigious European physicians, **Eugen von Hippel and Arvid Lindau**, is a familial syndrome characterised by the occurrence of highly vascular tumours in different organs¹. Von Hippel-Lindau (VHL) disease is a rare, autosomal dominant genetic disease (Online Mendelian Inheritance in Man 193300) that is estimated to occur in 1/36,000 live births and with clinical manifestations usually becoming apparent between 18 and 30 years. VHL germline mutation predisposes patients to renal cysts and carcinoma, central nervous system and retina hemangioblastoma, pancreatic cysts and neuroendocrine tumors, pheochromocytoma, endolymphatic sac tumors and epididymal or adnexal cystadenoma². Clinical diagnosis requires one major manifestation of von Hippel-Lindau disease in patients with a familial history, and at least two major manifestations including one haemangioblastoma in isolated cases. Patients are at high risk for early multiple and recurrent clear cell Renal Cell Carcinoma (RCC)³. Total nephrectomy was systematically done in the past to prevent the risk of metastatic progression, which led to end stage renal disease requiring dialysis. Preserving normal renal parenchyma emerged as a major therapeutic goal in VHL cases. Since several groups reported that most RCC in VHL cases has low pathological grade, grows slowly and never becomes metastatic at less than 3 cm, in the early 1990s Nephron Sparing Surgery (NSS) was developed. The standard therapeutic procedure for RCC in VHL cases was to monitor small lesions by imaging and perform partial nephrectomy for any RCC that became 2.5 to 3 cm. During the last decade percutaneous ablative therapies, such as RFA and cryotherapy that were developed to treat localized RCC in select patients emerged as a novel nephron sparing therapy applicable to patients with VHL.

The worldwide von Hippel-Lindau Family Alliance greatly contributes to such dissemination by organising International Symposia once every 2 years which are an excellent opportunity for doctors, scientists, and affected individuals to meet and exchange information on fundamental and clinical issues ([http:// www.vhl.org](http://www.vhl.org))².

2. Historical aspects

Although the contributions of von Hippel and Lindau were decisive, many others played an important part in the description of clinical manifestations, but not all can be cited (a complete history of von Hippel-Lindau disease is detailed in the articles from Melmon and

Rosen, Lamiell and colleagues, and Resche and colleagues)^{4,6}. In 1872, Jackson first described a cerebellar haemangioblastoma, and retinal haemangioblastoma was described by Panas and Rémy in 1879¹.

The first recorded case of a probable patient with von Hippel-Lindau disease was a 35-year-old woman who died in 1864 with eye and brain tumours⁷. In 1895 von Hippel described the fundoscopic findings in the eye of a 23-year-old man, Otto Mayer, who had presented 2 years earlier with visual loss. Both the superior temporal artery and vein were dilated and supplied a prominent rounded mass located at the periphery of retina⁸. In 1904, von Hippel presented further details of the same patient, who had developed three similar lesions, as well as another similar case, of a 28-year-old man⁹. Von Hippel studied the histological characteristics of the right eye of Otto Mayer and concluded in 1911 that the retinal lesion was a congenital cystic capillary angiomas, which he named angiomas retinae¹⁰. However, it was Arvid Lindau who linked the retinal, cerebral, and visceral components of the disease into a single coherent entity in 1926. In his dissertation, he added 16 of his own patients to 24 previously reported patients with cystic cerebellar tumours¹¹. He noted that cerebellar tumours were frequently associated with retinal lesions but also with renal cysts, hypernephroma (renal cell carcinoma), and pancreatic and epididymal cysts. The term von Hippel-Lindau disease was first used by Davison and colleagues¹² in 1936 and has been in common use since the 1970s. In 1964, Melmon and Rosen summarized these data and coined the term “von Hippel-Lindau disease”⁴.

The most recent developments have followed the identification of the VHL gene, first located on 3p25–26 in 1988 by Seizinger and colleagues, and fully described in 1993 by Latif and coworkers^{1,3}.

3. Genetic disorders and renal cell carcinoma

RCC represents 2-3% of all cancers, 7000 people are diagnosed with RCC each year in the UK, and 3600 annually succumb to the disease. It is estimated that 54,390 men and women in the United States will be diagnosed with kidney cancer, while 13,010 will die of their disease in next year. This number can also be expressed as 1 in 72 men and women will be diagnosed with cancer of the kidney during their lifetime and this incidence continues to rise¹³.

There is an apparent increase in the incidence of RCC of 2.5% per year. This may in part be attributed to improved imaging techniques and an increased detection rate of incidental lesions.

Approximately 4% of RCCs are of hereditary origin and VHL is the commonest cause. Furthermore, approximately 75% of RCCs are of clear cell histology (cRCC), and VHL is the hereditary cause of cRCC¹⁴. There are at least six other histological subtypes, each associated with a hereditary syndrome¹⁵ (table 1). Hereditary cancer syndromes can be difficult to identify and early recognition is important, as it facilitates correct management of the patient, as well as screening of relatives. Principally, mutations can be “loss-of-function mutations” in tumor suppressor genes and “gain-of-function-mutations” in protooncogenes, which are then called oncogenes. Research regarding hereditary clear cell RCC has led to the identification of a relevant gene locus on the short arm of chromosome 3. This loss-of-function mutation led to the assumption of the existence of a tumor suppressor gene, and subsequently, further research led to the identification of the VHL gene.

Syndrome	Gene locations	Relative frequency	Histology	Other renal abnormalities	Systemic associations
VHL	3p26	28- 45%	Clear cell	Cysts	CNS haemangioblastoma Retinal angiomas Pancreatic cysts and neoplasm Phaeochromocytoma
Tuberous sclerosis	9q34, 16p13	1-2%	Clear cell	Cysts, papillary, oncocytoma	CNS tubers Cutaneous angiofibromas
Hereditary papillary RCC	7q34	19%	Papillary type 1	None	None known
Birt-Hogg- Dube	17p11	8-15%	Chromophobe	Clear cell, papillary, oncocytoma	Lung cysts Pneumothorax
Lynch type 2	2p16, 3p31	2-9%	Transitional cell carcinoma	None	Carcinoma of colon, ovary, endometrium, stomach
Medullary carcinoma of the kidney	11p	Unknown	Medullary carcinoma	None	Sickle cell trait
Hyperparathyroidism Jaw tumour	1q25	Unknown	Papillary	Cysts	Parathyroid tumours Fibro-osseous mandibular/ maxillary tumours
Familial papillary thyroid cancer	1q21	Unknown	Papillary	Oncocytoma	Papillary thyroid cancer Nodular thyroid disease

Table 1. The hereditary renal cancer syndromes

In the early 1980s, the search to identify a loss of heterozygosity in one of the alleles of a cancer gene was initiated, with the hope that loss of heterozygosity would indicate the presence of a cancer gene at that location. A tumor suppressor gene requires loss of function or inactivation of one or both of the genes, often by mutation of 1 allele combined with deletion, or loss, of the second allele, whereas, an oncogene is activated by 1 change in the gene. In the initial studies, loss of segments at chromosome 3 in tumor tissue suggested that a cancer gene for kidney cancer was present at this location¹⁶. Dr Knudson’s “two hit” theory postulates that most tumor suppressor genes encode proteins responsible for the negative regulation of cellular growth. A mutation that causes a loss of the function in one these proteins will lead to tumorigenesis or uninhibited cell growth. As the gene of interest for clear cell kidney cancer was too large to localize with the technology that was available at the time, an approach focusing on a hereditary form of kidney cancer, von Hippel-

Lindau, was used as the model of investigation. The hope was that the gene involved in hereditary kidney cancer may involve the same gene as in the sporadic form of kidney cancer¹⁷. Lubensky and colleague performed a study that supported the two-hit theory of inheritance in VHL disease. The makeup of 26 renal cysts was studied with microdissection techniques. They found that each cyst was lined with a single layer of clear epithelial cells. Twenty-five of the 26 cysts had a mutation of the wild-type allele; in only one case was the usual heterozygosity of the disease maintained. This finding supports two-hit theory: once the heterozygosity for VHL is lost in a specific organ, in this case the kidney, the cyst can progress into a tumor¹⁸.

4. Genetics in von Hippel-Lindau

Consistent loss of the short arm of chromosome 3 in VHL associated kidney tumors was identified¹⁹. Genetic linkage analysis was utilized to help identify the VHL gene, which was identified on the short arm of chromosome 3p²⁰. The loss of the single normal allele of the VHL gene in the kidney cancer cell samples was critical and suggested that there was an inherited gene at this location, which was associated with the development of VHL-associated clear cell kidney cancer. Germline mutations on the VHL gene are identified in nearly 100% of VHL families²¹. The disease is caused by germline mutations in the VHL tumour-suppressor gene; the same gene is inactivated in most cases of sporadic renal-cell carcinoma and Central Nervous System (CNS) haemangioblastomas. The VHL gene seems to be pivotal in the processes of angiogenesis, an oxygensensing pathway involving the hypoxia-inducible factor (HIF), a heterodimeric transcription factor. The VHL gene product targets the subunit of HIF for polyubiquitylation and proteasomal degradation. This is the rationale for development of specific inhibitors of hypoxia-inducible factors and their downstream targets, which lead to potential new treatments. The development of a second mutation causing deletion of the normal VHL allele leads to tumor formation in affected individuals. More than 300 different types of mutations have been described that involve the three exons of the VHL gene.

The different clinical manifestations of VHL can be associated with the location and type of the VHL gene mutation^{22, 23}. Penetrance of the traits is far from complete, and for some such as pheochromocytomas, they tend to be clustered in certain families but do not occur in others²⁴. Maranchie et al.²⁵ identified a significantly higher incidence of renal cell carcinoma in patients with partial germline VHL mutations vs. those with complete VHL gene mutations. It is now known that with mutation analysis (e.g., insertion, deletion, missense, or nonsense) and the location (e.g., codon position) of the mutation, correlations can be made to the phenotype, i.e., the extent of involvement of the various organ systems affected by VHL.

Germline mutations in VHL have been identified in almost all patients with von Hippel-Lindau disease and correlations between the genotype and the phenotype are emerging, confirming clinical distinction based on the presence or absence of phaeochromocytoma. Such mutations have been identified in several patients without classic clinical criteria and a diagnosis of von Hippel-Lindau disease must now be considered in patients with an apparently sporadic tumour, especially in the case of phaeochromocytomas. Specific germline mutations in VHL have been associated with a rare recessive haematological condition (Chuvash polycythaemia) and might also be implicated in some sporadic apparently congenital polycythaemias²⁶.

The function of the VHL gene has been evaluated extensively. It is a small gene that encodes 854 nucleotides on 3 exons and is responsible for encoding the VHL protein²⁰. The VHL protein forms a complex with proteins including elongin C, elongin B, and Cul-2²⁷⁻²⁹ and targets the α subunits of the hypoxia inducible factors, such as HIF- α and HIF-2 α , which are instrumental to ubiquitin mediated degradation³⁰. There are multiple downstream genes, such as Glut 1 (glucose transport), vascular endothelial growth factor (VEGF, blood vessel growth), epidermal growth factor (EGF), transforming growth factor (TGF- α), for which HIF regulates. The expression of these genes increases in clear cell carcinoma when the VHL gene is inactivated (figure 1). Many of the receptors for HIF regulated genes are the targets for the new targeted therapeutic approaches for clear cell carcinoma³¹. Studies have shown that if the VHL complex is unable to bind to the HIF proteins, tumorigenesis results. Mutations in the oxygen-dependent domain or the VHL binding site of HIF-2- α , but not of HIF-1- α , result in tumorigenesis in xenograft models. Kondo and colleagues³³ showed that inhibition of only HIF-2- α suppresses pVHL deficient tumor growth. This finding established that HIF-2- α is a critical component to tumorigenesis in clear cell RCC. As previously discussed, HIF proteins are key regulators of oxygen homeostasis, and tight regulation of HIF allows cell survival and growth at the time of hypoxic stress. HIF acts via transcriptional regulation of VEGF, PDGF, EGFR, GLUT1, erythropoietin, and TGF- α . Loss of VHL is thought to result in a pseudohypoxic state, so that cellular response pathways mediated by HIF are activated despite normal oxygen conditions.

Understanding the VHL pathway and these pseudohypoxic pathways has provided the opportunity to develop therapies that target the downstream HIF pathway genes VEGF and PDGF with agents such as sunitinib that have a high affinity for the VEGF and PDGF receptors.

Other strategies, such as targeting HIF transcription and HIF stability, also are being evaluated in clinical trials.

5. Clinical diagnosis

VHL disease is among the group of disorders known as “phakomatoses” in which lesions arise from a single germ layer. The lesions of VHL disease are primarily mesodermal in origin. The clinical manifestations of VHL disease span a spectrum of phenotypic variability. It has virtually complete penetrance but variable expressivity. The syndrome is characterized by multiple tumor types, including kidney tumors, pheochromocytomas, epididymal cystadenomas, retinal angiomas, hemangiomas of the CNS, and pancreatic islet cell tumors.

Diagnosis of von Hippel-Lindau disease is often based on clinical criteria. Patients with a family history, and a CNS haemangioblastoma (including retinal haemangioblastomas), phaeochromocytoma, or clear cell renal carcinoma are diagnosed with the disease. Those with no relevant family history must have two or more CNS haemangioblastomas, or one CNS haemangioblastoma and a visceral tumour (with the exception of epididymal and renal cysts, which are frequent in the general population) to meet the diagnostic criteria^{4, 34}. Specific correlations of genotype and phenotype have emerged in affected families. Several familial phenotypes of von Hippel-Lindau disease are now recognised, providing useful information to screen and counsel affected individuals. Type 1 families have a greatly reduced risk of phaeochromocytomas, but can develop all the other tumour types generally associated with the disease. Type 2 families have phaeochromocytomas, but have either a

low-risk (type 2A) or high-risk (type 2B) for renal cell carcinomas. Type 2C families have phaeochromocytomas only, with no other neoplastic findings of VHL (table 2)³⁵.

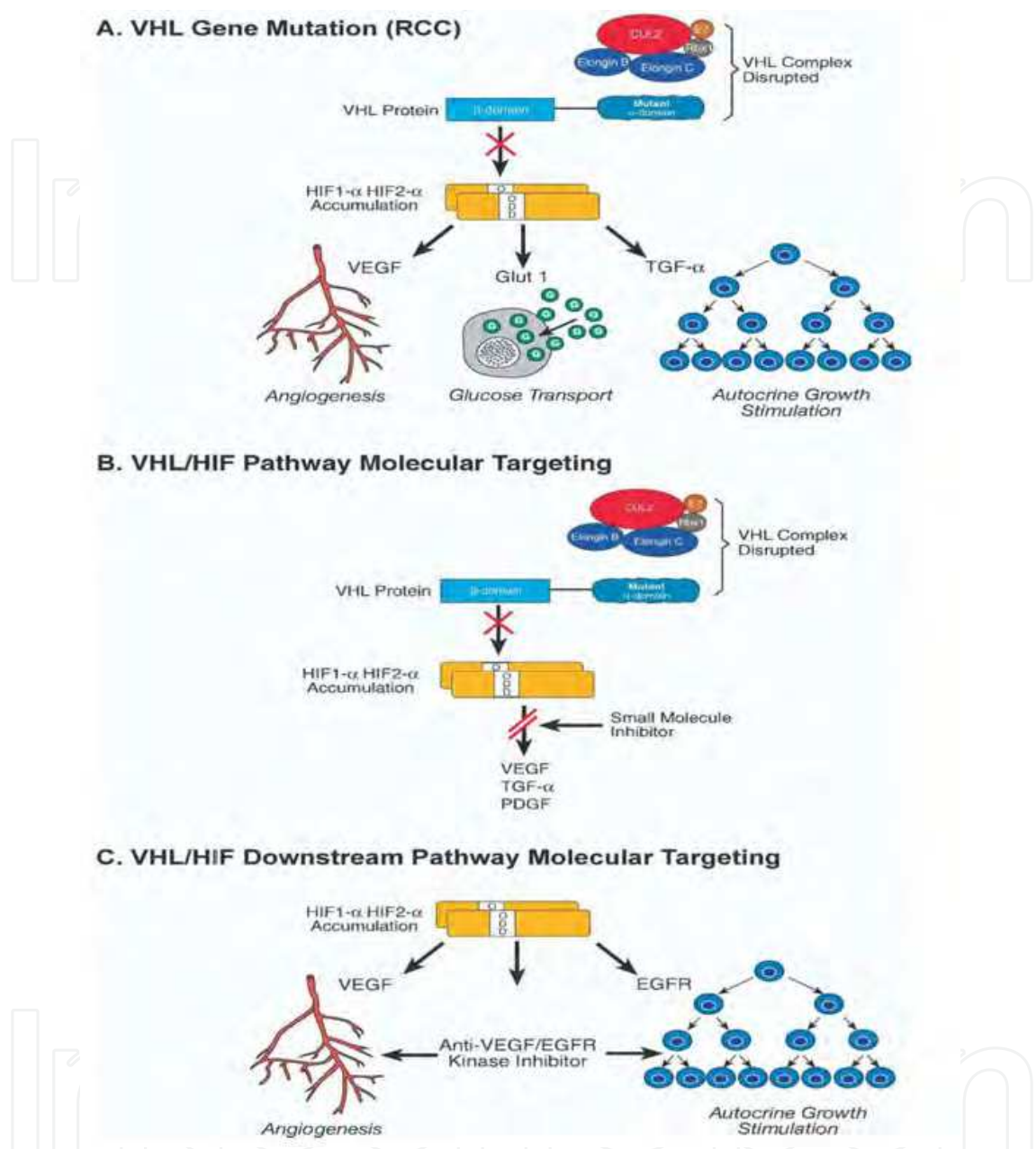


Fig. 1. ⁷⁰ The *VHL* gene complex targets hypoxia-inducible factors (HIF) for ubiquitin-mediated degradation. When there is a mutation in the *VHL* gene in clear cell kidney cancer, in either the elongin binding or the HIF binding domain (A), HIF is not degraded and this protein over-accumulates. Increased HIF levels lead to increased transcription of a number of downstream pathway genes that are thought to be important in kidney cancer, such as vascular endothelial growth factor (VEGF), the glucose transporter, GLUT1, and transforming growth factor α (TGF- α) (B). Targeted approaches to therapy currently include tyrosine kinase inhibitors that target the downstream gene receptors (C). Other approaches being developed to target the VHL-HIF pathway in clear cell kidney cancer include the development of small molecules or other agents which block HIF transcription. Reprinted from Linehan et al³².

	Clinical characteristics
Type 1	Retinal haemangioblastomas CNS haemangioblastomas Renal cell carcinoma Pancreatic neoplasms and cysts
Type 2A	Phaeochromocytomas Retinal haemangioblastomas CNS haemangioblastomas
Type 2B	Phaeochromocytomas Retinal haemangioblastomas CNS haemangioblastomas Renal cell carcinomas Pancreatic neoplasms and cysts
Type 2C	Phaeochromocytoma only

*Endolymphatic sac tumours and cystadenomas of the epididymis and broad ligament have not been assigned to specific von Hippel-Lindau types.

Table 2. Genotype-phenotype classifications in families with von Hippel-Lindau disease*

The age of onset of VHL disease is variable and depends both on the expression of the disease within the individual and within the family and on the screening protocol used to detect asymptomatic lesions. More intensive screening regimens can increase greatly the number of affected individuals discovered in a family. Retinal lesions generally are the first lesions to be diagnosed.

Of the non-urologic stigmata, the most common in patients who survive to age 60 years are retinal angiomas, which affect 70% of patients, and CNS hemangiomas, which affect 84% of patients. The urologic manifestations include renal clear cell carcinoma (RCC), pheochromocytoma, and epididymal cystadenomas, which affect approximately 40%, 18%, and 10% of patients, respectively. Approximately a third of the patients who have VHL disease (13%–42%) die of metastatic disease.

The median age of death from VHL disease is 49 years, and the most common causes of death are neurologic complications of cerebellar haemangioblastoma and metastatic renal carcinoma. Approximately 53% of patients who have VHL disease die of complications of cerebellar hemangioblastoma, and 32% die of metastatic RCC³⁶.

6. Screening and surveillance for von Hippel-Lindau disease

Genetic testing for VHL is widely available and involves a simple blood test with an accuracy approaching 100% if the mutation is known³⁷. However, the test is only available in select laboratories. Antenatal diagnosis is also feasible. In the past 15 years there have been major changes in the management of VHL. Better surveillance and genetic testing have improved detection rates of presymptomatic RCCs and these can now be treated with nephron-sparing procedures (NSS) before metastatic disease develops, preserving renal function as far as possible, but as yet there are no standardized screening protocols for VHL and guidelines vary between institutions.

The screening process for patients who have hereditary renal tumor syndromes developed at the Clinical Center of the National Institutes of Health (NIH) (table 3) includes karyotyping for the germline mutations of the VHL gene; abdominal CT with and without intravenous contrast material injection; renal ultrasound; ophthalmologic examination; brain, spinal, and internal auditory canal MRI; scrotal ultrasound for male patients; chest radiograph; and 24-hour urine and plasma catecholamines³⁸.

	PROTOCOL
Urinary catecholamines	From age 2 years: every 1-2 years
Ophthalmoscopy	From infancy: yearly
Enhanced magnetic resonance imaging of brain and spine	From age 11: every 2 years From age 60: every 3-5 years
Abdominal computed tomography or ultrasound	From age 11: ultrasound yearly From age 20: computed tomography every 1-2 years

This is the protocol used at the National Institute of Health, USA.

Table 3. Screening of patients with Von Hippel- Lindau disease

The primary goals of preoperative evaluation for RCC are to define renal anatomy and to identify tumors in the brain, eye, pancreas, and adrenal glands that may present an intraoperative risk if undiagnosed. Such lesions include pheochromocytomas, which would require catecholamine blockade and probably resection at the time of renal surgery, and hemangioblastomas, which carry the risk of hemorrhage at the time of induction of anesthesia. Pancreatic neuroendocrine tumors also might be excised at a single surgical setting. MRI can demonstrate CNS abnormalities most clearly while adequately imaging the abdominal viscera. CT, however, is the most accurate method of screening and follow-up for RCC. In addition to CT or MRI, an angiogram may be obtained preoperatively to define patient renal arterial anatomy before the first surgery. One study showed that angiogram identified only 16% of the multiple small renal tumors that were present ³⁹, making it of limited utility beyond providing a vascular map for the first resection (but few hospitals perform this technique). After surgical treatment for renal tumors, patients should be screened regularly to monitor for recurrence, metastasis, and loss of renal function. Periodic history and physical examination, routine laboratory screening tests, abdominal CT, renal ultrasound, chest CT or radiograph, and renal scans can be performed in addition to monitoring for new manifestations of VHL disease with periodic brain and spine MRIs, urinary catecholamines, and ophthalmologic evaluation⁴⁰. Family members who carry a germline mutation but have not developed a tumour, and those with a mild phenotype can safely be imaged every 2-3 years. However, patients with mutations predisposing them to RCC should be assessed more frequently at 6-12 monthly intervals, depending on tumour growth rates⁴¹. Genetic testing can help predict the risk of developing RCC (as discussed above). Recent studies⁴² have linked specific mutations to more aggressive forms of RCC and poorer survival rates. Such genetic stratification may allow more specific or patient focused surveillance in the future.

7. Renal cell carcinomas and renal cysts in von Hippel Lindau general features

Renal cell carcinomas are the major malignant neoplasm in von Hippel-Lindau disease and the primary cause of inherited renal cancer. These tumours are seen in 24–45% of patients, and adding renal cysts increases the finding of renal lesions to 60%. Renal disease is multicentric and bilateral in at least 75% of patients who have VHL disease. The mean age at presentation is 39 +/- 10 years, which is 10 to 20 years earlier than that reported for sporadic renal disease.

In addition to the young age of presentation, RCC associated with VHL disease also recurs frequently years. Although small renal tumours in this disease tend to be low grade and minimally invasive, their rate of growth varies widely⁴³. Renal lesions are often multiple and bilateral. Walther and colleagues⁴⁴ estimated that 600 microscopic tumours and 1100 microscopic clear-cell-lined cysts might be present in the kidneys of some 37-year-old patients. Results of an investigation of 228 renal lesions in 28 patients, followed for at least 1 year, showed that transition from a cyst to a solid lesion was rare. Solid tumors in VHL disease have been observed to grow at rates of 0.2 to 2.2 cm/year (mean, 1.6 cm/year), which is somewhat faster than rates observed in sporadic RCC. The change that occurs in renal lesions over time in patients who have VHL disease is generally slow and constant, but it has been followed in only a small number of cases ⁴⁵.

However, complex cystic and solid lesions can contain neoplastic tissue that frequently enlarges. Renal cell carcinomas often remain asymptomatic for long intervals. Thus, serial imaging of the kidneys is useful for early diagnosis. Occasionally, the more advanced cases with these neoplasms can present with haematuria, flank pain, or a flank mass. Renal cysts in von Hippel-Lindau disease are typically asymptomatic and seldom need treatment. Renal cysts are present in 59% to 63% of patients who have VHL disease, and some studies believe the number may be as high as 85% Cysts generally preceded the detection of solid tumors by about 3 to 7 years. Studies have shown that at least 21% of cystic renal lesions contain foci of RCC and RCC is reported to develop in 24% to 45% of patients who have VHL disease. Therefore, complex cysts need monitoring, as they often harbour solid components of renal cell carcinoma. Because of the frequent absence of early clinical symptoms and the importance of early detection, diagnosis during presymptomatic screening has the potential to enhance overall outcome.

Contrast-enhanced abdominal CT is the standard for detection of renal involvement in the disease. CT allows detection and quantification by size and number of renal cell carcinomas and cysts, allowing serial monitoring of individual lesions. Imaging is usually recommended in 3–5 mm sections, and before and after intravenous injection of contrast media. Precontrast and postcontrast MRI is an alternative method of detection for patients who have reduced renal function. These carcinomas are yellow or orange and are encapsulated. They can be solid or a mixture of solid and cystic in appearance. Histologically, they are always of the clear-cell subtype, and small carcinomas tend to be low grade. In addition, microscopic examination of small VHL renal lesions consistently demonstrated a pseudo-capsule surrounding these low-grade renal lesions. This pseudo-capsule has since proven to facilitate tumor resection by forming a natural tissue plane for dissection⁴⁶. The recurrence rate of renal tumors is high in patients who have VHL disease. Examination of normal renal tissue of patients who have RCC and VHL disease has shown multiple microscopic renal tumors ⁴³. Treatment recommendations depend on tumour size.

8. Radiology of renal masses in VHL

RCC in VHL usually manifests as a complex cystic mass, which is also the most difficult type of renal lesion to accurately assess, especially when detected incidentally. The Bosniak classification was first described in 1986 and determines the management approach to the sporadic cystic renal mass⁴⁷. The system was devised for CT but can also be applied to MRI. As some patients with VHL require long-term follow-up of renal manifestations with cross-sectional imaging, there are clear advantages of MRI, such as the absence of radiation. CNS manifestations are almost exclusively imaged with MRI in most institutions. MRI has also proved more accurate at assessing cystic pancreatic lesions and distinguishing pheochromocytoma from adenoma on chemical shift imaging. It is also more sensitive than CT in detecting neuroendocrine tumours of the pancreas. For these reasons, several authors advocate annual surveillance of abdominal manifestations with MRI. These advantages must be weighed against potential risks of nephrogenic systemic fibrosis (NSF) with gadolinium compounds when used in renal impairment, as well as logistical factors, such as cost and limited access of MRI at some institutions. However, patients undergoing a lifetime of screening may accumulate relatively large doses of radiation to the kidneys as a consequence of annual screening with CT. Thus, there is no clear-cut answer which is the best imaging modality⁴⁸.

Before CT was widely available 13-42% of patients with VHL died of metastatic RCC⁴³. The discovery of the VHL gene in 1993 unlocked a better understanding of the pathways involved in tumorigenesis. Surgery is still the only curative treatment of RCC. Bilateral nephrectomy with renal-replacement therapy would eradicate all tissue at risk for developing RCC and is a theoretical, but radical, option in a patient with VHL. However, patients with VHL do worse on renal-replacement therapy. A large study⁴⁹ showed a 5-year survival rate of 65% in VHL patients on dialysis compared with 71-86% for the non-VHL group. But renal impairment in the absence of renal surgery is rare among VHL patients. As patients with VHL do worse with renal-replacement therapy, the aim of successful management is to preserve renal function balanced against the risk of developing renal metastatic disease. The secondary aim is to minimize the number of procedures performed to accomplish this. To accomplish these aims accurate imaging-guided diagnosis and nephron-sparing procedures are important.

9. Nephron-sparing surgery and other treatments in von Hippel-Lindau disease

RCC in von Hippel-Lindau disease differs from its sporadic counterpart in that the diagnosis is made at a young age, and there are usually multiple bilateral renal tumors. Although these are generally low-stage tumors, they are capable of progression with metastasis and represent a frequent cause of death in patients with von Hippel-Lindau disease. RCC in these patients is characterized histopathologically by both solid tumors and renal cysts that contain either frank carcinoma or a lining of hyperplastic clear cells representing incipient carcinoma.

Therefore, adequate surgical treatment of localized RCC in von Hippel-Lindau disease requires excision of all solid and cystic renal lesions. Choyke et al.⁵⁰ have shown that intraoperative ultrasonography may be a valuable adjunct for this population of patients. In their series, this study identified additional tumors in 25% of patients with hereditary renal cancer undergoing renal exploration.

The surgical options in patients with bilateral RCC and von Hippel-Lindau disease are bilateral nephrectomy and renal replacement therapy or partial nephrectomy to avoid end-stage renal failure. The general philosophy has been to pursue nephron-sparing surgery if possible, given the multifocal nature of the disease, even for centrally located tumors. The treatment options for patients who have renal involvement in VHL disease have evolved during the last 3 decades. Staged bilateral nephrectomy and hemodialysis have progressed to partial nephrectomy and NSS. The best management approach for VHL disease balances the goals of minimizing the risk of RCC metastasis and preserving renal function and attempts to minimize the total number of surgeries a patient will require over a lifetime⁵¹. There are no specific guidelines regarding the type or timing of surgery in patients who have VHL disease. The treatment strategy of total nephrectomy and Renal Replacement Therapy (RRT) removes all the tissue at risk for RCC and, with it, the risk of metastases. Goldfarb and colleagues⁵² noted a 5-year survival rate of 65% in patients who had VHL disease and who were treated with bilateral nephrectomy and RRT. Some transplant centers consider the presence or potential for VHL-related tumors, including renal and extrarenal tumors, a contraindication for renal transplantation.

The indications for NSS are localized malignancy in a solitary kidney, bilateral synchronous renal lesions, and renal tumors in patients whose contralateral kidney is threatened by local, systemic, or genetic risk factors⁵³.

Although early results of partial nephrectomy were promising, subsequent studies suggested a high incidence of postoperative tumour recurrence in the remaining portion of the kidney. It is likely that most of these local recurrences were a manifestation of residual microscopic RCC that was not removed at the time of the original partial nephrectomy. Walther and colleagues⁵⁴ have reported extensively on their approach of enucleation of small renal tumors associated with VHL disease (figure 2). Preservation of the perirenal fat and fascia are believed to be important in improving the patient's ability to undergo subsequent renal surgeries. The renal capsule is incised, circumscribing the lesions to be resected. All cystic lesions are excised, if possible, because of the potential for development of RCC⁴⁶. Smaller cystic lesions are unroofed, and the base is fulgurated (however it has not been shown that this is completely safe).

A study from the NIH⁵⁵ showed that renal tumors less than 3 cm in size are not considered an indication for radical surgery. Patients who have VHL disease generally are followed expectantly until solid renal lesions are larger than 3 cm in diameter. In the previously mentioned NIH study, the 3-cm threshold for surgery was evaluated in 52 patients who had VHL disease. None of these patients had metastatic disease, and none required RRT. Forty-six of these patients underwent NSS rather than radical nephrectomy. Forty-four patients who had VHL disease developed renal tumors larger than 3 cm. From this study, the authors concluded that using a 3-cm tumor diameter as a threshold for NSS may help prevent metastatic disease. These authors also noted the importance of intraoperative Doppler ultrasound for locating tumors and verifying that all tumors have been removed⁵⁶. A follow-up of this study³⁸ revealed that metastasis did not develop in any patient who had a solid renal tumor smaller than 3 cm. Of 50 patients who had RCC, metastasis developed in 1 patient who had a primary renal tumor that was 4.5 cm in greatest diameter.

One multicenter study⁵⁷ delineated the long-term outcomes after surgical treatment of localized RCC in 65 patients with von Hippel-Lindau disease managed at eight medical centers in the United States. RCC was present bilaterally and unilaterally in 54 and 11 patients, respectively. Radical nephrectomy and partial nephrectomy were performed in 16

and 49 patients, respectively. The mean postoperative follow-up interval was 68 months. The 5-year and 10-year cancer-specific survival rates for all patients were 95% and 77%, respectively. The corresponding rates for patients treated with partial nephrectomy were 100% and 81%, respectively. In the latter group, 25 patients (51%) developed postoperative local recurrence; however, only two of these patients had concomitant metastatic disease. Survival free of local recurrence was 71% at 5 years but only 15% at 10 years. Only 2 of 25 patients who had local recurrence after NSS had metastatic disease at the time recurrence was detected.

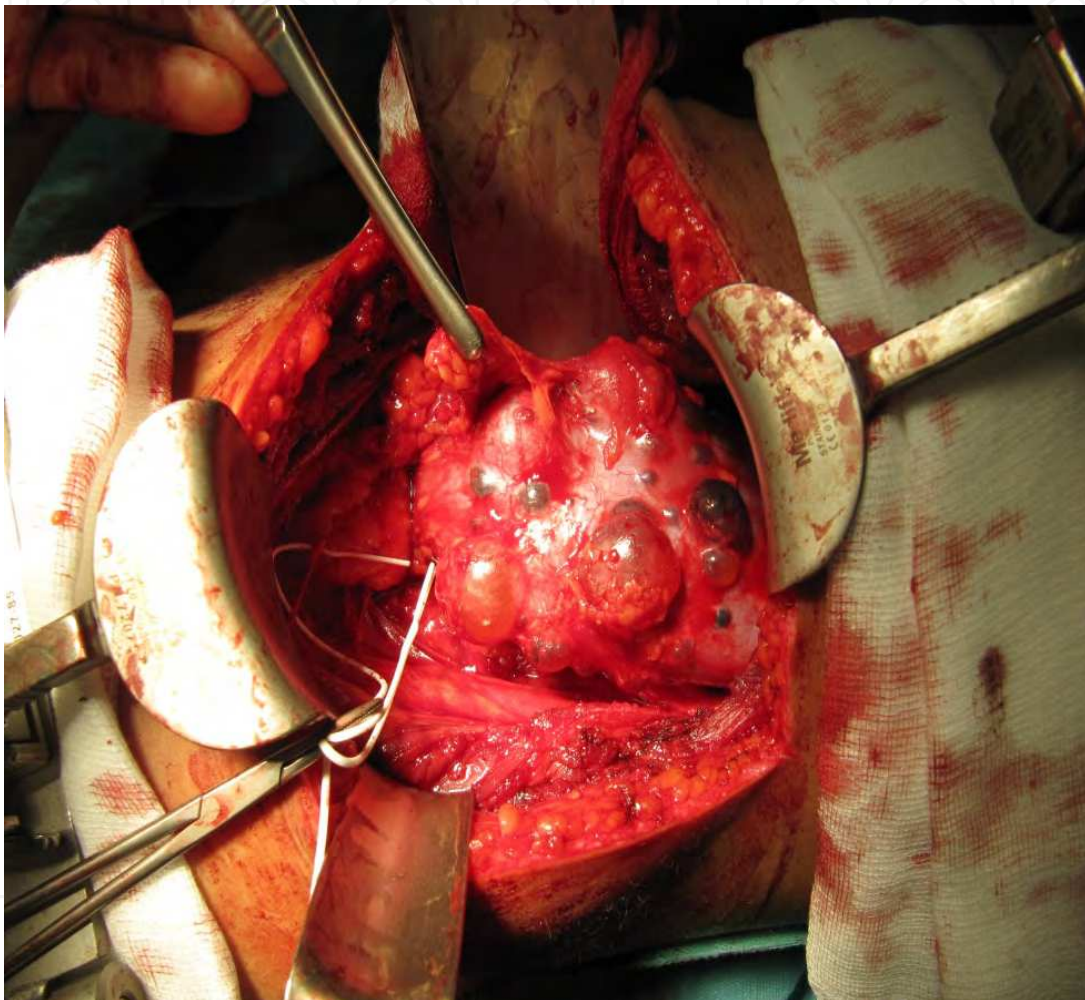


Fig. 2. Intraoperative photograph of multiple tumors and cysts in the kidney in a patient who has VHL disease.

Similarly, Roupret et al.⁵⁸ reported a 27.4% incidence of local recurrence at mean follow-up of 55.9 months after partial nephrectomy for patients with von Hippel-Lindau disease, confirming that these patients are at much higher risk for local recurrence than are patients with sporadic RCC. Ploussard and colleagues⁵⁹ published a series to evaluate the risks of local recurrence after NSS in patients who have VHL disease. Seventeen of 21 patients underwent surgery for RCC when tumors reached 3 cm. Eight patients developed a recurrence, and the mean time to local recurrence was 53+/- 38.8 months (range, 10-115 months). The disease-specific survival rate was 93.8% at 10 years. No metastasis or chronic renal insufficiency was observed in patients undergoing NSS only.

Taken together, these studies suggest that partial nephrectomy can provide effective initial treatment of patients with RCC and von Hippel-Lindau disease but should be withheld until tumor size reaches or eclipses 3.0 cm. Studies show that up to 85% of patients who have VHL disease experience de novo renal tumor recurrence at 10 years⁵⁷.

After nephron-sparing surgery, patients with von Hippel-Lindau disease must be observed closely because most will eventually develop locally recurrent RCC with the concomitant need for repeated renal surgery. In this setting, repeated partial nephrectomy can be challenging because of postoperative fibrosis, and some centers are moving toward thermal ablative modalities to reclaim local control and many surgeons are reluctant to perform additional NSS because of complications related to postoperative fibrosis⁶⁰. These salvage surgeries were greatly complicated by severe fibrosis, scarring, and the obliteration of normal anatomic planes. The authors concluded that aggressive surgical intervention in these patients is indicated, because none of the patients developed metastatic disease as long as 7 years after surgery, and there was 100% survival in this cohort⁶¹. NSS has been performed using the laparoscopic approach in select centers, but the inability to achieve reliable hypothermia along with prolonged ischemia times and increased complication rates have limited its widespread application. **At present, open NSS should be considered the standard of care for treating RCC in the setting of VHL disease.**

When removal of all renal tissue is necessary to achieve control of malignant disease, renal transplantation can provide satisfactory replacement therapy for end-stage renal disease and appears to be safe despite the tumor diathesis.

Newer, minimally invasive techniques⁶², such as radiofrequency ablation and cryoablation, have been applied recently as an alternative to excisional NSS in patients who have RCC. Ablative techniques may^{63, 65} be performed by laparoscopic and percutaneous image-guided techniques. Jolly et al.⁶⁴ concluded in a recent published article that renal survival in patients with VHL who are treated for RCC has improved with time. Their renal survival curves actually reflect the decreasing need to remove all renal tissue to achieve local control of malignancy, in parallel with improved NSS and the emergence of renal salvage techniques such as Radio Frequency Ablation (RFA) (figure 3a and 3b). As well as surgery, nephron sparing procedures now include RFA and cryoablation. In their experience since 2004 RFA has become the exclusive salvage technique. Overall a third of RFA sessions were performed in single functioning kidneys, including 8 in a total of 8 patients who had already been operated on twice and were not candidates for additional NSS.

These all have a role in the surgical management of VHL-associated RCC and experience of these newer modalities in VHL is increasing, and good preliminary success rates are being published. A small study by Shingleton and Sewell⁶⁶ reported the successful treatment of five small RCCs in four patients with VHL using MRI-guided cryoablation, but greater evidence is available for imaging-guided RFA treatment of RCCs in the context of VHL, demonstrating good success rates for exophytic tumours of up to 5 cm in size^{67, 68}.

In conclusion⁶⁹, as patients with VHL with RCC are increasingly treated with nephron sparing techniques, especially RFA, it must be remembered that only long-term follow-up can hopefully confirm that no unexpected metastasis develops beyond increased renal survival. In patients who have a single kidney or multiple bilateral lesions, collateral damage to normal renal parenchyma must be considered. For patients who have VHL disease, and all patients who have hereditary cancer syndromes, the goal of treatment is cancer control, not cancer cure, and preservation of functional parenchyma to avoid the morbidity associated with renal or adrenal loss.



Fig. 3a. Renal tumor in a patient with solitary right kidney and VHL disease

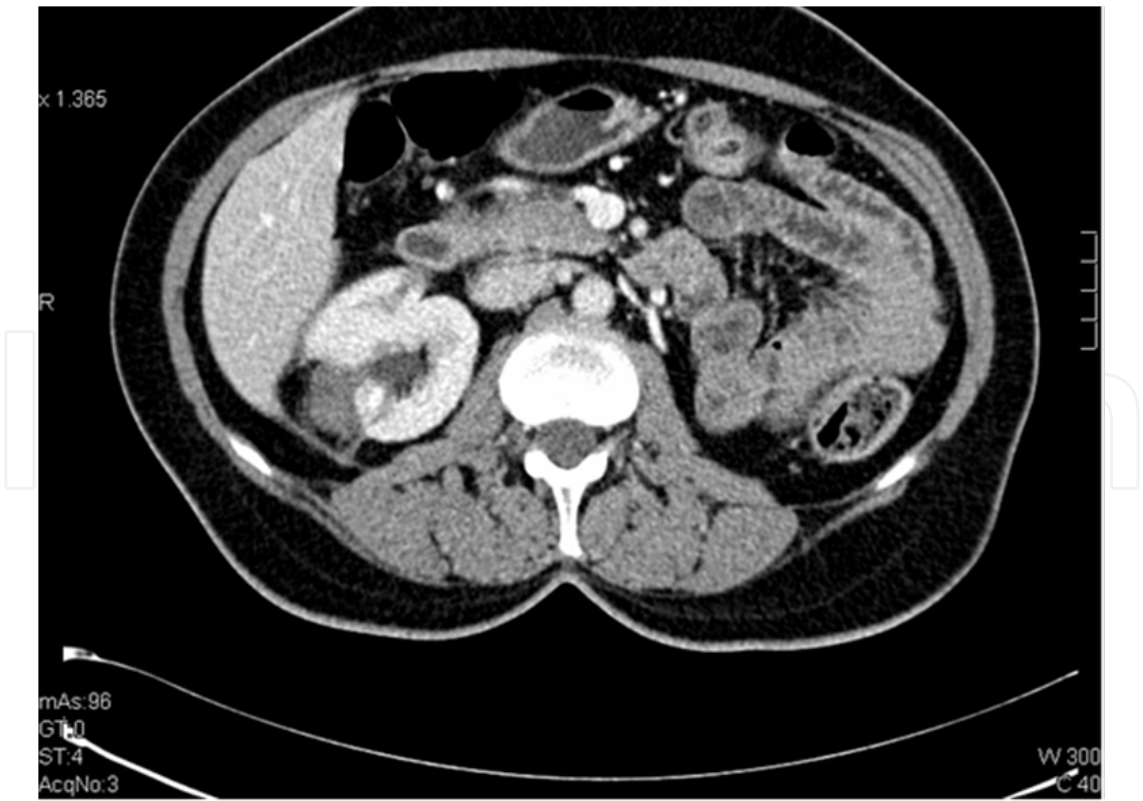


Fig. 3b. Contrast enhanced CT scan after radiofrequency ablation show the absence of contrast enhancement in the ablated area.

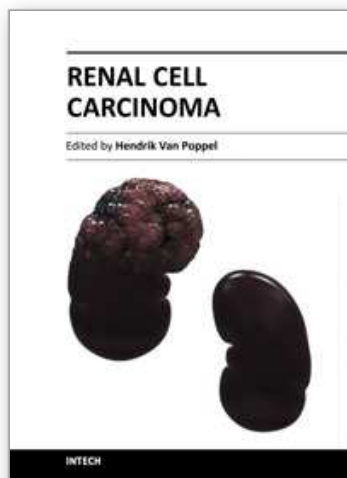
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Surgical and medical oncologists have been unable to decrease renal cell carcinoma mortality for uncertain reasons, although a lot of progress has been made in diagnosis and imaging, recognition of different genetic and pathological entities, management of localized disease and in the research on new drug treatments for advanced stages of the disease, potentially combined with surgery. The purpose of this book, which tackles a number of separate interesting topics, is to provide further insight into the disease and the management of early and advanced renal cell carcinoma. The volume is divided into different parts; the first part covers the characterization of renal masses and the second part covers rare distinct pathological entity. In the management section, active surveillance, partial nephrectomy and radiofrequency ablation are presented. A separate chapter reviews the management of Von Hippel Lindau disease, and finally, conventional and aberrant signaling pathways are explored.

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