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# Von Hippel-Lindau disease: strategies in early detection (renal-, adrenal-, pancreatic masses)

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**Abstract.** Von Hippel-Lindau disease (VHL) is a hereditary syndrome characterized by a predisposition for bilateral and multicentric retinal angiomas, hemangioblastomas in the central nervous system (CNS), renal cell carcinomas, pheochromocytomas, islet cell tumors of the pancreas, and endolymphatic sac tumors, as well as cysts in the kidney, pancreas, and epididymis. This review focuses on developments in imaging of renal, adrenal, and pancreatic masses in VHL. Radiology still has a central place in managing of VHL. Radiologists should therefore be aware of the importances of MRI, CT, and US compared with other radiodiagnostic tools for these three organs. Since a conservative approach to the treatment of VHL lesions is now becoming more widely accepted, ongoing follow-up by careful radiological screening with US, and especially with MRI, will play a central role in managing the disease. We also give an overview of recent advances in the molecular biology of VHL, because the combination of imaging with (presymptomatic) DNA analysis has made early detection and screening of lesions possible and led to a reduction in morbidity and mortality.

**Key words:** Von Hippel-Lindau disease – Renal cell carcinoma – Kidney neoplasms – Pheochromocytoma – Pancreatic cyst

## Introduction

Von Hippel-Lindau disease (VHL) is a hereditary syndrome characterized by predisposition for bilateral and multicentric retinal angiomas, hemangioblastomas in the central nervous system, renal cell carcinomas, pheochromocytomas, islet cell tumors of the pancreas, and endolymphatic sac tumors, as well as cysts in the kidney, pancreas, and epididymis. Von Hippel-Lindau disease is a relatively rare disease, with an estimated incidence of between 1/31,000 to 1/53,000 in South Baden (Germany) and East Anglia (Great Britain), respectively [1–3]. The disease is inherited as an autosomal dominant trait with a high penetrance (almost complete by 65 years of age) and variable expression. The basis of familial inheritance of VHL is a germline mutation in a tumor suppressor gene, first identified in 1993 [4].

Most tumors in VHL patients show typical hereditary features. The tumors are often multiple or bilateral, and manifest at a young age. The median life expectancy is reduced to 49 years of age. At present, metastasis from renal cell carcinoma and neurological complications from cerebellar hemangioblastoma are the most common causes of death in VHL [5–8]. However, the life expectancy has strongly improved over past years. Intensive radiological and clinical screening and advanced operation techniques have contributed to the reduction of both morbidity and mortality.

## History

The German ophthalmologist Eugen von Hippel (1867–1938) is usually credited with the first full description of a retinal vascular abnormality [9]. In 1911 he named this abnormality angiomatosis retinae [10]. This condition was already reported in 1879 [11], and the microscopic appearance was described in a brother and sister in 1894 [12]. The pathologist Arvid Lindau published a paper in 1926 describing 40 cases with cystic cerebellar tumors [13]. He associated angiomatosis retinae with cerebellar and spinal hemangioblastomas, and cysts of the kidneys, pancreas, and epididymis. Lindau named this syndrome *central nervous system angiomatosis*. In 1951 Streif noted that in 1864 French physicians had reported the first probable VHL patient who died with brain and retinal tumors [14]. The initial reports on adrenal involvement in VHL appeared in 1953 and 1959 [15, 16]. Melmon and Rosen published the first major

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VHL literature review in 1964 [17]. They stressed the importance of careful screening of the family and gave criteria for the clinical diagnosis of VHL.

Richards et al. diagnosed renal carcinoma with intravenous urography and angiography in two asymptomatic members of a VHL family in 1973 [18], and descriptions of radiographic manifestations in various VHL families appeared [19, 20]. In 1977 Lee et al. advocated selective renal angiography for all VHL patients [21]. The technique of CT was introduced in 1972 as head scanner and revolutionized diagnostic medicine of the whole body. Clinical imaging applications of nuclear magnetic resonance increased in the mid 1980s. Filling-Katz et al. reported in 1989 that gadopentetate dimeglumine (Gd-DTPA)-enhanced MRI gave the best results for assessing central nervous system lesions [22].

A second revolution in the diagnosis of VHL was the identification of the VHL gene in 1993 [4]. Presymptomatic DNA analysis and identification of carriers of VHL germline mutations in families permits the progress of tumor development to be followed from a relatively early age, and optimizes the time in which treatment is carried out.

## Genetics

In 1988 the VHL gene was localized and mapped to chromosome region 3p25–26 using genetic linkage analysis in large VHL families [23]. A positional cloning strategy subsequently led to the isolation and identification of the VHL gene in 1993 [4]. The VHL gene covers approximately 14,500 base pairs (bp) of genomic DNA on chromosome 3. The full-length VHL messenger RNA is a 4,700-bp molecule; an additional mRNA isoform is generated by alternative splicing involving exon 2 [24, 25]. The open reading frame is 852-bp long and contains two intragenic start codons. The protein-coding region translated from the first start codon (nucleotides 214–216) encompasses 639 bp and is divided into three exons of 340, 123, and 179 bp (Fig. 1 a). The promoter of the gene was identified in 1995 [26]. With the isolation of the 3' untranslated region in 1996, together with the known promoter area, exons and introns, the complete sequence of the human VHL gene was identified [27].

The VHL gene is a tumor suppressor gene according to Knudson's "two-hit" hypothesis [28]: Inactivation of both copies of the VHL gene is required for a normal cell to develop into a tumor cell. Different mutational mechanisms may lead to the inactivation of the VHL gene, including small intragenic mutations, loss of heterozygosity (i. e., deletion of a large part of the gene, or even of the entire VHL gene), or hypermethylation [29, 30].

In VHL families germline mutations at the VHL gene are transmitted from affected individuals to their offspring. Von Hippel-Lindau disease has an autosomal dominant pattern of inheritance: Children of a parent who is a carrier of a mutated VHL gene have a 50% chance of inheriting the disease. Patients inherit a mutated germline copy of the VHL gene (the "first hit") from the affected parent: they are heterozygous for the VHL germline defect. The remaining (normal) copy of the VHL gene is affected by an inactivating event (the "second hit") at the somatic level: In such a cell, the complete lack of normal VHL gene product is thought to drive tumorigenesis. The moment of the second hit cannot be predicted and may occur at any age. Generally, tumor development in VHL patients occurs between the age of 20 and 40 years.

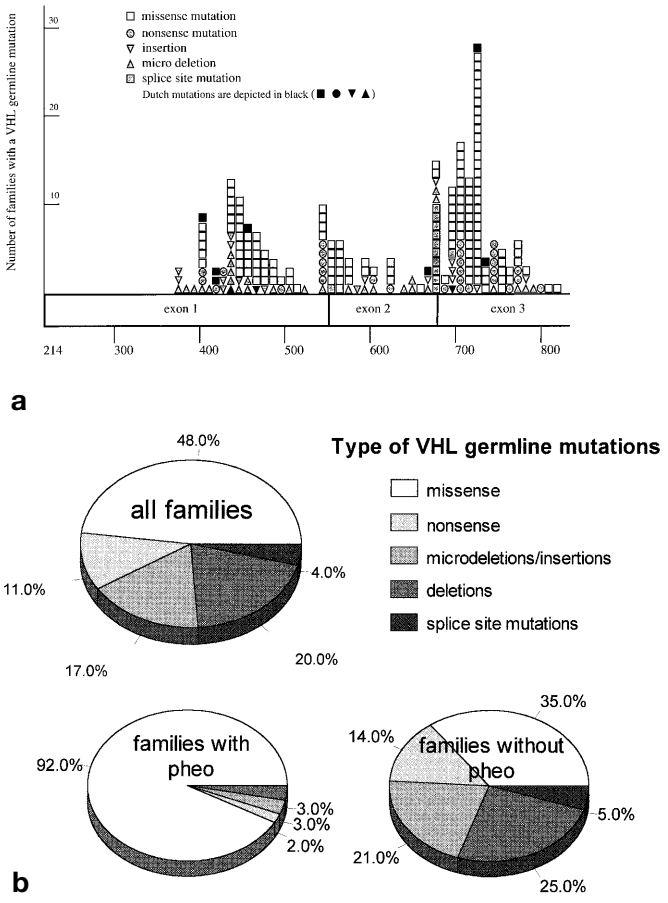



**Fig. 1.** **a** Germline mutations identified in Von Hippel-Landau (VHL) patients from North America, Japan, and Europe (including the Netherlands) are shown. Information was obtained from the World Wide Web page of the National Cancer Institute, Bethesda, Maryland (www.ncifrcf.gov/kidney), and the Clinical Genetics Centre, Utrecht, The Netherlands (unpublished data). The numbers of the nucleotides are shown along the *x*-axis, starting at the first start codon (nucleotide 214) and ending at the stop codon (nucleotide 852). Von Hippel-Landau germline mutations were found between nucleotides 376 and 811. The number of families with a particular VHL germline mutation are shown along the *y*-axis. Each *symbol* represents one family. Mutations found in Dutch VHL families are shown by *black symbols*. **b** Genotype–phenotype correlations in VHL. The pie charts show the total mutational spectrum and the association of mutations with pheochromocytoma. (Based on Zbar et al. [43])

## Structure and possible functions of the VHL protein product

The VHL gene encodes a 213 amino acid protein (pVHL) with a molecular weight of approximately 30 kiloDalton [31], of which the normal function is not precisely known. The observation that inactivation of the VHL gene leads to tumor initiation suggests that pVHL plays a crucial role in the control of cellular proliferation in specific tissues, such as the kidney, retina, and adrenal gland.

In addition to the germline mutations identified in families with VHL syndrome, somatic mutations, and/or loss of the VHL gene are frequently observed in sporadic (i.e., non-familial) tumors, including hemangioblastomas and renal cell carcinomas [25, 32]. Based on its direct role in the intiation of *both* familial and sporadic renal tumors, VHL is considered to be a "gatekeeper" gene in renal cells [33]. According to Kinzler and Vogelstein [33], gatekeepers are genes that directly regulate the growth of tumors by inhibiting growth or inhibiting death. Each cell type has only one (or a few) gatekeepers. Inactivation of a given gatekeeper leads to a very specific tissue distribution of cancer. Several studies have addressed the identification of the normal physiological functions of the VHL gene and its protein product. The VHL protein has been shown to associate with at least five other proteins, namely CUL-2 [34], VBP1 [35, 36], fibronectin (W.G. Kaelin, pers. commun.), and the elongins B and C. The interaction of pVHL with the elongins has provided a possible clue about the normal function of the VHL protein. Based on these in vitro studies, it has been postulated that the VHL protein plays a role in regulating the transcription elongation [37–41]. Transcription (the process of converting DNA sequence into corresponding RNA) elongation is mediated by the initiation factor RNA polymerase II. When normal VHL protein is present in the cell, binding of pVHL to elongins B and C causes RNA polymerase to pause during transcription at several sites along a gene. Mutations of the VHL gene lead to absence of normal pVHL. Failure by pVHL to sequester elongins B and C may result in an ongoing transcription activity. When genes involved in cell-cycle control are regulated at the transcription level by this mechanism, the absence of functional pVHL may lead to abnormal cell proliferation.

Interestingly, the region of the VHL gene that encodes the elongin binding domain (nucleotide 682–781) [39, 42] is a hot spot for missense mutations: Approximately 70% of VHL families have mutations predicted to disrupt VHL binding to elongin (Fig. 1a) [43]. This suggests that this region is critical for the normal functioning of the VHL protein. However, mutations leading to VHL disease are also found outside the elongin binding domain, indicating that other regions of the VHL gene encode proteins that have another function.

The VHL protein is widely expressed in normal human tissues [17, 44]. The pVHL is even expressed in organs not at risk for the disease, suggesting a role for VHL that goes beyond the organs involved in the disease. In human embryos pVHL was expressed in all three germ layers, with strong expression noted in the central nervous system, kidneys, testes, and lung [45]. The intracellular localization of the VHL protein appears to depend on a novel physiological control mechanism: cell density [41, 46]. In sparse cultures VHL is predominantly present in the nucleus, whereas it can be found in the cytoplasm of more confluent cells. The putative role of the VHL protein in transcription elongation (as discussed above) and its ability to localize based on culture conditions suggests an ability to control cellular growth in response to environmental signals [47].

Recently, it was shown that the wild-type (normal) VHL protein inhibits the production of hypoxia-inducible mRNAs, such as the vascular endothelial growth factor (VEGF) mRNA, under normoxic conditions [31, 48]. In renal tumor-derived cell lines which lack normal VHL, VEGF mRNA expression is increased [48]. Thus, the highly vascular nature of VHL-associated neoplasms may be due, at least in part, to dysregulation of hypoxia-inducible mRNAs following loss of function of the VHL protein.

In addition to these biochemical studies, a mouse model has been developed to analyze the function of the VHL gene [49]. Using targeted homologous recombination in murine embryonal stem cells, a so-called "knock-out" mouse model was generated for VHL carrying an inactivating mutation at the *Vhl* gene (the murine homolog of the VHL gene). Heterozygous *Vhl* ( + /-) mice survived beyond 15 months of age without evidence of spontaneous disease. However, homozygosity for the *Vhl* "knock-out" allele leads to embryonic lethality. Apparently, the *Vhl* gene is required for normal embryonic development in the mouse. *Vhl* (-/-) embryos die in utero between 10.5 and 12.5 days of gestation, most likely due to an impairment of placental vasculogenesis [49]. This is in contrast to the observations that the wild-type VHL gene results in decreased VEGF levels and that mutations in the VHL gene are associated with richly vascularized VHL lesions.

## VHL mutations

Germline mutations in the VHL gene are found in up to 80% of the VHL families [50]. In families with an identified VHL germline mutation, almost 60% have a missense mutation, i.e., a mutation that leads to an amino acid subsitution in the VHL protein product. Large deletions account for 20%, and microdeletions, insertions, and nonsense mutations are found in another 20% [43, 51]. (Updated summaries of VHL germline mutations can be found on the World Wide Web at http// www.ncifcrf.gov/kidney and at http://www.uwcm.ac.uk/ uwcm/mg/search/120488.html).

Many different intragenic (i.e., missense and nonsense mutations, splice defects, microdeletions, and insertions) VHL germline mutations have been detected. Most VHL germline mutations are unique to a small number (one or two) of families, suggesting that most of these mutations are of recent origin [43]. However, several recurrent VHL mutations, which occur in multi-

ple, unrelated families, have also been observed (Fig. 1 a).

## Genotype–phenotype correlations in VHL

As illustrated previously, VHL disease is heterogeneous at the molecular level: mutations of all types are found, and they are scattered throughout the VHL gene. From a clinical point of view, VHL is also a heterogeneous disorder: inter- as well as intrafamilial variability in the clinical expression of the disease is common. Based on the presence or absence of renal carcinoma and pheochromocytoma in VHL, a classification of three VHL phenotypes has been proposed: (a) renal carcinoma without pheochromocytoma; (b) renal carcinoma with pheochromocytoma; and (c) pheochromocytoma alone [43].

There is evidence that, to a certain extent, a relationship exists between the specific VHL germline mutation (the genotype) and the clinical manifestation of the disease (the phenotype). Such genotype–phenotype correlations may not only indicate important functional domains of the VHL protein but may also have clinical significance. Based on the knowledge of the specific VHL mutation, surveillance and management of patients may be adjusted.

Interfamilial clinical variability in VHL can partly be explained by differences in the family-specific VHL germline mutation. As shown in Fig. 1 b, almost all families (92 %) with pheochromocytoma (types 2 and 3) have missense mutations in the VHL gene [43]. In VHL families without pheochromocytoma (type 1), most mutations (65 %) are predicted to lead to either constitutional deletion of a VHL allele or synthesis of a truncated VHL protein (Fig. 1 b). Zbar et al. [43] identified germline mutations in 300 of 469 VHL families and noted that 96 % of the families with either deletions, microdeletions/insertions, splice site, or nonsense mutations were affected by VHL without pheochromocytoma [43]. A few specific missense mutations lead to VHL phenotype with pheochromocytoma as well as retinal and CNS hemangioblastoma without renal carcinoma [52, 53].

However, patients with identical VHL germline mutations may display different phenotypes, indicating that the issue of genotype–phenotype correlations in VHL is complex. It is likely that other genetic ("modifier" genes) and/or environmental factors (lifestyle, diet, smoking) may play a role in the clinical manifestation of VHL germline mutations.

## Renal masses

In VHL patients renal lesions can be divided into three different forms with cystic, combined cystic-solid, and solid renal cell carcinoma (RCC) lesions [54]. Cystic lesions, which can be single or multiple, can occur unilaterally but are mostly bilateral. They can grow either slowly or rapidly but can also involute. The combined cystic-solid lesion, in which the solid (malignant) component gradually increases, may lead in turn to a solid RCC lesion.

Renal cell carcinoma may present with hematuria or with back pain. However, most renal tumors are detected as an incidental finding in radiological screening performed for other reasons, whereas a growing number of renal lesions in patients is found by periodical screening of VHL families. If not identified by screening, VHL patients with RCC have a shortened life expectancy. At present, RCC is the cause of death in 15–50 % of VHL patients [5–7], and 30–50 % of symptomatic RCCs have already metastasized to lymph nodes, liver, bone, lung, or brain [17, 55–57]. Fortunately, RCC does not occur in every VHL patient (in different VHL families incidence varies between 3 and 63 % of patients) [5, 53] nor in every kidney, and RCC does not always have a fatal outcome. These features may be caused by differences in family-specific germline mutation, the timing of origin, and the nature of the somatic mutation. The somatic mutations may be induced by environmental factors. For example, current opinion is that smoking (particularly in males) is correlated with the development of RCC [58–60]. There is an increased incidence of RCC in certain professions (e. g., among workers exposed to asbestos [61], trichloroethene [62], leather workers [63], fire fighters, and painters [64]), and a correlation has been found with obesity and hypertension [59, 60].

Renal lesions have a typical hereditary character, i. e., the lesions occur multiply, bilaterally, and at a relatively young age. While sporadic RCC occurs predominantly in the seventh and eighth decades of life [65], the mean age of presentation in VHL patients is 30–36 years [66–69]. However, there is a trend toward detection at younger age, probably as a result of intensification of screening. The youngest reported VHL patients with a RCC are 15 and 16 years old [68, 70]. Poston et al. [67] found a mean of 7.8 cystic and 3.0 solid renal lesions in VHL patients, which is in agreement with our own observations (unpublished) and other studies [5, 54].

Most RCC in conjunction with VHL grow slowly. A radiological study demonstrated that the average increase in diameter in cysts was 0.5 cm/year, and that solid lesions grew at an average of 1.6 cm/year [54]. Complex lesions (with cystic and solid parts) appeared to transform to a predominantly solid lesion that continued to grow, while the cystic part of the lesion gradually regressed. More recently, the mean growth rate of RCC in VHL was found to be between 0.3 cm (own unpublished data) and 0.5 cm/year [71]. This is comparable to the mean growth rate of sporadic RCC, which was reported to be 0.36–0.5 cm/year [72, 73].

Pathologically, RCC is a malignant epithelial tumor of the renal parenchyma and is often found in the renal cortex. The tumor tissue is frequently crowded with recent and old hemorrhages, necrosis, and inflammation, and is surrounded by a pseudocapsule [74, 75]. The most common cellular pattern is clear cell carcinoma [76] arising from cells of the proximal tubuli [77].

Renal cysts in VHL can contain lining epithelium exhibiting atypia, and are therefore considered to be pre-

malignant [57, 67, 78–80]. However, transformation into a solid malignant tumor is rare [81]. Kragel et al. demonstrated that simple cysts in VHL arise more commonly from distal tubules, whereas the majority of RCC arise from proximal tubules [81]. Nevertheless, some renal carcinomas do arise from the distal nephron, and comparison of markers of tubular differentiation in atypical cysts and RCC supports the progression of atypical cysts to carcinoma [81].

Furthermore, by microdissecting material from individual lesions it has been demonstrated that loss of the wild-type allele and retention of the inherited, mutated VHL allele occurred both in cystic lesions and in RCC [82]. This clearly demonstrates that cysts are precursors for RCC, and that loss of the VHL gene (the second hit in Knudson's theory [28]) occurs early in their development.

In past years the treatment of renal lesions in VHL has been discussed by many authors [67, 68, 71, 83–87]. Recommendations range from bilateral nephrectomy to follow-up investigations only. If both kidneys are affected with multiple cysts and tumors, a difficult decision has to be made between radical nephrectomy (RN) or nephron-sparing surgery (NSS). If a patient progresses to having many tumors and/or large indvidual tumors, RN followed by renal transplantation may be the first option. Bilateral nephrectomy followed by transplantation shortens life expectancy and diminishes the quality of life, although this quality has been improved over the past decade by the use of immunosuppressive therapy [88, 89]. Graft 5-year survival rates of 80%, and up to 90% for living donors, have been reported [88, 89]. In general, hemodialysis has a less favorable outcome, but this is most likely influenced by selection of patients [88]. Apart from a diminished life expectancy, the quality of life is reduced for dialysis and transplantation patients. Moreover, it has been suggested that immunosuppression accelerates (pre-existing) neoplastic growth [90].

Nephron-sparing surgery is based on maintaining renal function as long as possible, while reducing the risk of metastases [86]. The most serious complication is renal atrophy and this has been reported in 11% of NSS [86]. In VHL operative removal of solid RCC and those RCC larger than 3 cm which are still growing has been advocated by several authors [54, 71, 72, 86]. Smaller tumors are more likely to be low grade and less frequently associated with metastases. Cancer-specific 5- and 10-year survival rates from NSS have been reported to be 100 and 81%, respectively [68]. These results indicate that NSS can provide effective initial and preventive treatment for VHL patients with RCC.

With the advent of US and CT, there has been an increase in detection of small renal masses [91], and screening of VHL patients is likely to yield a correspondingly high number of such masses. Computed tomography is found to be more reliable than US in detecting renal masses. Jamis-Dow et al. concluded that CT was more sensitive than US for the detection of small renal masses (particularly those smaller than 1.5 cm) [92]. However, a substantial proportion of lesions under 1 cm were not detected with either technique. Nevertheless, US is a critical tool in helping to determine whether a lesion is principally cystic or solid [93].

Intraoperative color Doppler US is helpful in characterizing deep parenchymal cystic lesions and evaluating larger deep or hilar tumors [94]. This technique minimizes blood and renal parenchymal loss and allows safe removal of renal lesions. In particular, patients with many renal lesions benefit from a thorough inspection of the kidney with this technique, before closing [94].

Thin-section (3–5 mm), intravenous contrast-enhanced CT is mandatory, and a helical technique is necessary to ensure that small lesions are not missed [95]. The recent introduction and use of helical- or spiral-CT scanners offers volumetric imaging of the kidneys in a single breathhold and can therefore eliminate respiratory misregistration. These scanners can detect and discriminate lesions smaller than 1 cm by using overlapping intervals and thin collimation [96]. Bosniak and Rofsky claim that in the general population a normal contrast CT scan of the kidneys using 5-mm sections rules out a clinically significant renal parenchymal neoplasm [97]. Moreover, CT can localize exactly postoperative defects in patients after NSS [98]. In patients with reduced functioning renal tissue and patients with only one kidney, as often seen in VHL, tumor enhancement may be problematic because tissue enhancement is directly related to the level of contrast material in the blood [97]. In such cases gadolinium-enhanced (Gd-DTPA) MRI can be of great value, because it provides critical information about lesion vascularity without the risks of intravascular iodinated contrast material.

Imaging of renal masses is also possible with radiolabelled octreotide, which binds to somatostatin receptors of a wide variety of tumors including RCC [99]. An in vivo study demonstrated binding of $^{111}$In-octreotide to RCC in 43% (three of seven patients). In these three patients 20 of 23 known tumor localizations, predominantly metastases, were clearly visualized. This method may not only provide valuable information on the secondary spread of the tumor, but it may also be used to select those patients who could benefit from treatment with somatostatin-receptor analogs [99].

Typically, RCC possess a pseudocapsule [100], which may play a critical role in the success of NSS. Various imaging techniques have been described to reveal a pseudocapsule of the RCC. A surrounding radiolucent rim is observed with angiography, a low- or high-density rim with CT, and a low intensity rim with MRI [74, 75]. The sensitivity of CT in detecting pseudocapsules was lower than that of angiography and statistically significant. T2-weighted MRI is superior for visualizing a pseudocapsule of RCC and also for providing reliable selection criteria for tumor enucleation [75, 100]. The appearance on T2-weighted MRI is related to the fibrous element and compressed renal parenchyma. The inner margins of most pseudocapsules are composed of compressed parenchyma, whereas the outer margins contain reactive hyperplasia of the renal capsule as well as compressed parenchyma [74]. The low-intensity

**Table 1.** Von Hippel-Lindau screening recommendations. NIH National Institutes of Health

| Test | NIH | Netherlands |
|---|---|---|
| Ophthalmoscopy | From infancy, yearly | From age 5 years |
| Fluorescein angiography | Not routine | When indicated |
| Physical examination and neurological assessment | From age 2 years, yearly | From age 10 years, yearly |
| Urinary/blood catecholamines | From age 2 years, every 1–2 years | From age 10 years, yearly |
| US abdomen | From age 11 years, yearly | From age 10 years, yearly |
| CT abdomen | From age 20 years, yearly or every other year | |
| MRI abdomen (MIBG) | When indicated | When indicated |
| MRI with gadolinium of cerebellum and myelum | From age 11 years, every 2 years; after age 60 years, every 3–5 years | From age 15 years, every 2 years |
| MRI petrous bones; Audiometry | If hearing loss, tinnitus and/or vertigo[a] | If hearing loss, tinnitus and/or vertigo[a] |

Information was obtained from Choyke et al. [93] and completed with information kindly provided by G. M. Glenn from the National Institutes of Health, Bethesda, Maryland
[a]These symptoms may be caused by an endolymphatic sac tumor which is associated with VHL [142]

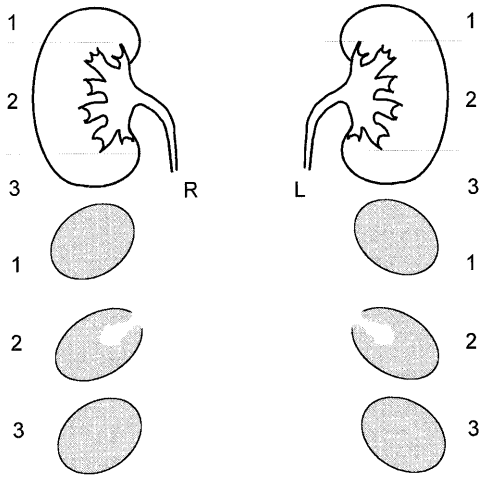



**Fig. 2.** Diagram of the kidney used for monitoring renal lesions

band or rim appears on MRI when the pseudocapsule is thicker than 2 mm. Takahashi et al. mentioned three limitations of the detection of a pseudocapsule by MRI [75]. Firstly, pseudocapsular invasion tends to be observed near the renal hilum, where there are abundant blood vessels. Secondly, if the tumor is small and located at the upper pole, partial volume averaging may obscure the pseudocapsule. A chemical shift artifact, observed at the interface between the tumor and the perinephric fat, forms a third limitation [75, 100].

Some screening protocols recommend yearly alternate CT and US examinations to reduce both costs and radiation (see Table 1) [93]. Other institutes advise that this regime should be complemented by an MRI examination once every 3 years. If renal screening is performed by CT, spiral 3D geometry is preferred. Small masses are less likely to be missed by this method. In our opinion, careful cross-sectional screening with alternate MRI and US gives the best protection for aggressive RCC in most VHL patients. Both US and MRI can distinguish between solid and cystic masses, but the quality and reliability of MRI is equal to or even superior to US in the detection and characterization of renal masses. The best results are obtained by breathhold T2-weighted MR images. Others use T1-weighted gadolinium-enhanced MRI with fat suppression [101], which is useful for the characterization of renal lesions. Angiography is inadequate for detecting renal lesions [102], but was predominantly used as preoperative "road mapping," to identify the renal vascular supply.

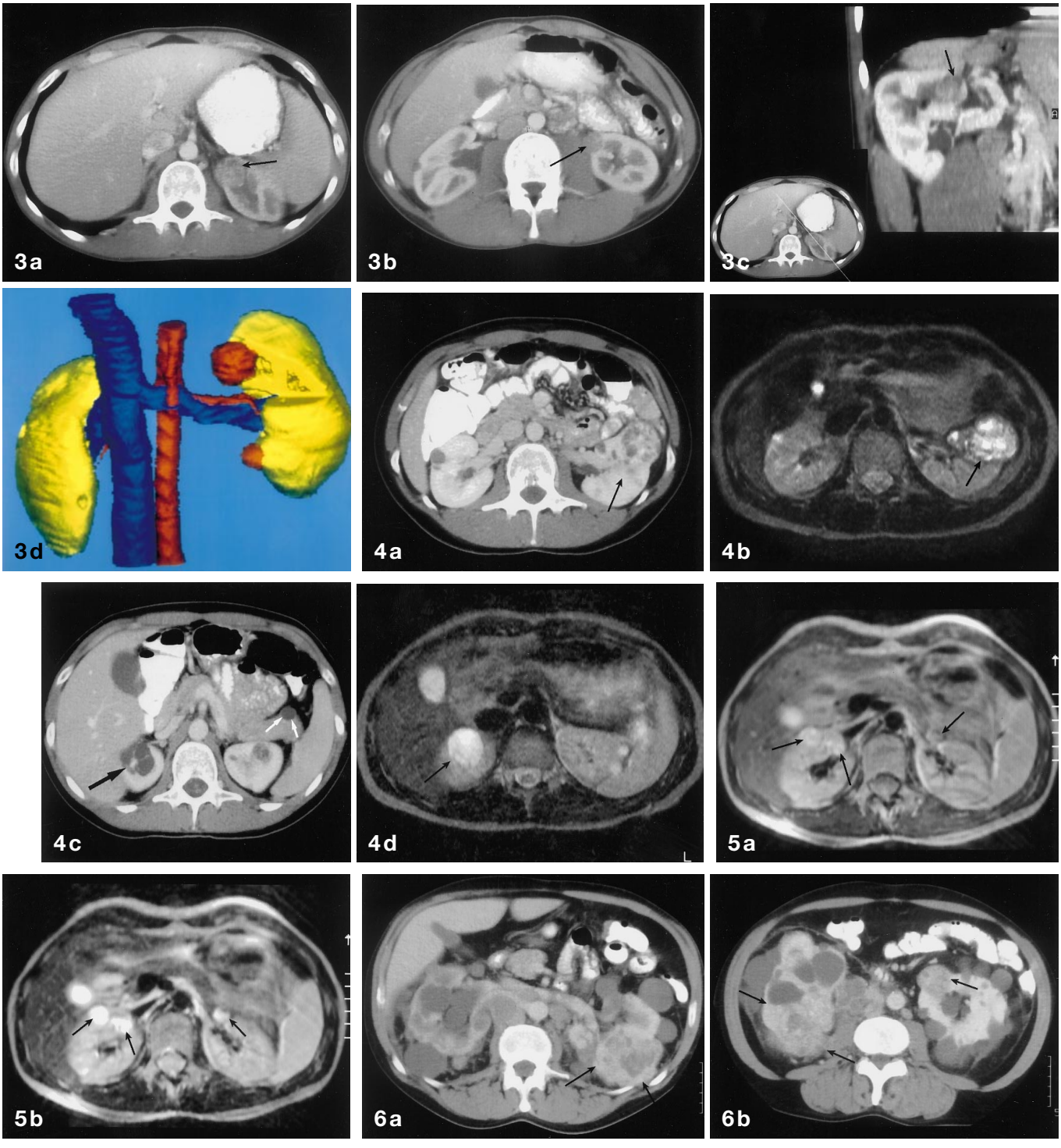
We advise careful radiological screening at least once a year, preferably with MRI. Renal lesions can be adequately monitored by documenting the number, size, and nature of lesions in a schematic figure of the kidneys (Fig. 2). Examples of cases are shown in Figs. 3–6.

## Adrenal masses

Von Hippel-Lindau-associated pheochromocytoma differs from isolated pheochromocytoma in having younger age of onset (19 years earlier), multiple lesions, and a very low proportion of malignant tumors [103]. The mean age at pheochromocytoma diagnosis is 27–29 years [5, 103, 104], with the youngest reported patient 5 years old [104]. Pheochromocytoma may cause palpitations, sweating attacks, hypertension, or paroxysmal unstable blood pressure, and headache. In VHL patients pheochromocytomas often remain quiescent or produce few symptoms, and investigation may show normal biochemical tests. However, the behavior of pheochromocytoma remains unpredictable; biologically inactive lesions may suddenly become dangerous. Benign pheochromocytomas may also become malignant [83]. Approximately 5% of VHL patients die from pheochromocytoma-induced endogenous catecholamine intoxication, which has also caused fatal pregnancy outcome [66, 105, 106].

Pheochromocytoma occur in 0–58% of patients in VHL families [5, 20, 43, 54, 66, 105, 107]. There is strong evidence that the presence or absence of pheochromocytoma is correlated with the type of VHL germline mutations (vide supra genotype–phenotype correlations). In addition to this clear interfamilial difference, intrafamilial differences have been observed.

Von Hippel-Lindau germline mutations are found in approximately 3% of patients with pheochromocytoma without family history; thus, they are sporadic tumors




[108]. A higher percentage of VHL germline mutation was found in familial pheochromocytoma (45 %) and bilateral tumors [109]. This raises the possibility that some VHL mutations might predispose to pheochromocytoma but might be associated with a low risk of other typical VHL lesions [104, 110–115].

Diagnosis is based on biochemical tests and radiology [103]. Laboratory tests may include evaluation of serum and urinary norepinephrine, epinephrine, and vanillylmandelic acid. Measurement of 24-h urinary epinephrine excretion is the most sensitive of the biochemical tests [103].

Radiology testing may include US, CT, MRI and metaiodobenzylguanidine (MIBG) scintigraphy. A low sensitivity for US was reported by Neumann (40 vs 90–95 % in other reports) [103]. In CT scanning pheochromocytomas typically enhance after administration of a contrast medium, and CT is considered useful for evaluating the adrenal glands and organ of Zuckerkandl, but it is less accurate for investigating ectopic sites [93].

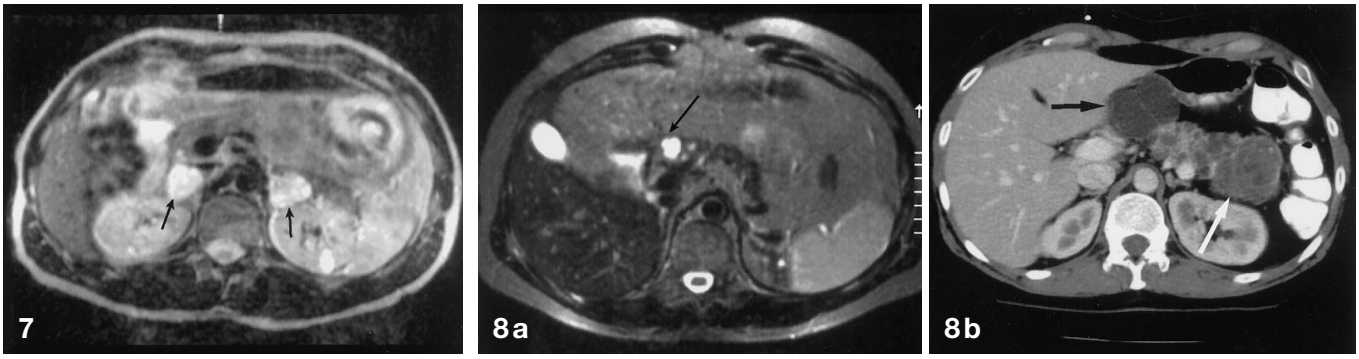



**Fig. 7.** T2-weighted preoperative MRI of asymptomatic bilateral pheochromocytomas *(arrows)* in a 37-year-old male with VHL. Both kidneys are affected with multiple cysts and slow-growing tumors, mostly occurring in places in which surgery is not possible without considerable loss of renal tissue. The largest solid lesion grew from 1.8 cm in 1980 to 2.5 cm in 1996. A difficult decision has to be made between nephrectomy or nephron-sparing surgery. If he progresses to having a larger number of tumors, renal transplantation may be the first option, or one could decide to operate nephron sparingly on qualified tumors

**Fig. 8 a, b.** Pancreatic lesions in VHL. **a** T2-weighted image (TR/TE = 2323/100 ms) shows a small pancreatic cyst *(arrow)* in a 40-year-old male with RCC (not shown). **b** CT in a 31-year-old female with multiple pancreatic cystic lesions in corpus and tail of the pancreas with soft tissue parts, most probably serous cystadenoma *(white arrow)*. On MRI 1 year before, the lesions had high signal intensity on the T2-weighted images. Despite some mass effect, these lesions do not require resection. Moreover, the patient developed a pseudocystic mass *(black arrow)* due to a ventriculoperitoneal catheter in this region, inserted after surgery of a cerebellar hemangioblastoma

Sensitivity of abdominal CT in VHL was reported to be 76 % [103]. T2-weighted MRI demonstrates high signal intensity for pheochromocytoma (Fig. 7) in 95–100 % of cases [103, 116]. Most pheochromocytomas appear markedly hyperintensive to the liver on T2-weighted images, but occasionally pheochromocytomas may be iso- or hypointense to the liver [103]. One of the new techniques for MRI of the adrenal gland is fat suppression, which reduces cardiac and respiratory motion-induced artifacts, accentuates small differences in tissue contrast, and eliminates chemical shift artifacts [117]. MIBG is approximately 75–95 % sensitive for pheochromocytoma and is 100 % specific, but it may not depict very small lesions [93, 103, 116]. Preoperative MIBG scintigraphy is also important in localizing extra-adrenal pheochromocytoma [118]. It has been demonstrated that pheochromocytoma in VHL can also occur in the thorax [118 a].

Operative treatment can be considered if a growing mass in the adrenal gland is established. Recently, satisfactory results have been reported from laparoscopic removal of adrenal tumors [119–121] and in VHL (G. Janetschek, pers. commun.). Enucleation rather than adrenalectomy is recommended by an increasing number of surgeons [106].

◀ **Fig. 3a–d.** Computed tomographic images of the kidneys in the corticomedullary phase after intravenous contrast shows small renal cell carcinomas (RCCs) in the left kidney of a 30-year-old VHL patient. **a** Lesion in the upper pole *(arrow)* measures nearly 3 cm. **b** Smaller lesion *(arrow)* in lower pole of the kidney. Both lesions appear to be encapsulated. Right kidney shows a small cortical cyst. **c** Oblique reconstruction and **d** coronal 3D surface rendering show the exophytic lesions emanating from the medial aspect of the kidney, free from the main renal vessels. In the upper pole the renal parenchyma has been partly cut away. The right kidney shows cortical defects caused by cysts (see **b**). Elective surgery was performed on the left kidney. Encapsulated cystic tumors of 1.8 and 2.6 cm in diameter were removed radically. The larger tumor showed infiltration into the pseudocapsule but did not penetrate it. Radiological follow-up (4 years) showed enlarging cysts in right kidney but no tumor in left kidney

**Fig. 4a–d.** Comparison of CT and MRI of an RCC in a 27-year-old woman with VHL. Screening was started 2 years before these imaging results. Ultrasound showed a left-sided tumor 3 cm in diameter. **a** CT shows a large cystic tumor in the left kidney *(arrow)*. **b** MRI (TR/TE = 2475/100 ms) shows the pseudocapsule *(arrow)* better than CT. Note the cortical cysts in the right kidney. Despite the tumor size of 5 × 5 × 3 cm, nephron-sparing surgery was performed. During operation, major hemorrhage of the wound bed of the left kidney was treated. A small cystic part of the tumor reached the rim of resection, but enucleation was performed radically. The right kidney shows a more central cystic tumor on CT in **c** and MRI in **d** *(arrow)*, which should be removed in the near future. Note the pancreatic cyst in the tail *(small arrows)* in **c**

**Fig. 5 a, b.** Transverse MRI of a 27-year-old VHL patient and bilateral small renal tumors *(arrows)*. T2-weighted images (**a** TR/TE = 2436/50 ms and **b** TR/TE = 2436/100 ms) show two combined solid/cystic lesions *(arrows)* in the right kidney. The one near the hilum is not suited for nephron-sparing surgery. Recently, the lesion in the left kidney *(arrow)* was removed nephron sparingly. Histopathological examination showed a cystic tumor, measuring 2 cm, at closer examination surrounded by an intact pseudocapsule 1–2 mm thick

**Fig. 6 a, b.** A CT scan of extensive disease of the kidneys in a 45-year-old male who was diagnosed in 1966 with retinal angioma in another clinic, but who unfortunately did not receive periodic screening. When he presented with symptoms of back pain in 1996, he already had advanced RCC with metastases in regional lymph nodes, bones, and lungs. The kidneys have a polycystic aspect but contain large solid tumors *(arrows)*. This patient could only be treated by palliative radiotherapy on ossal metastasis in the spine and died 6 months after onset of symptoms

**Pancreatic cystic masses**

The pancreatic manifestations of VHL include simple cysts, diffuse cystosis, cystadenomas, and, rarely, adenocarcinomas [83, 122]. Islet cell tumors are considered separately [93].

The incidence of pancreatic involvement in VHL varied from 0–56% [5, 56, 122–124]. In a review of 275 reported cases [125], 69 (25%) patients had cysts, 4 (1.5%) of which proved to be serous cystadenoma, 14 (5%) cases had islet cell tumor, 2 (0.7%) adenocarcinoma, and 1 patient had an hemangioendothelioma. Pancreatic lesions may be the only abdominal manifestation in VHL (12%) and may precede any other manifestation [122]. The earliest age of discovery reported is 15 years [107].

Cyst formation is found in 70–72% of patients at autopsy studies [56, 126]. The cysts, which are lined with a single layer of epithelial cells, are filled with serous fluid and may be hemorrhagic [127]. They can range from several millimeters to 10 cm in diameter (Figs. 4c, 8a) [93]. Cysts are often multiple and enlarge the pancreas [123], or may eventually replace the entire gland [127]. Complications can arise from space-occupying effects (local pain, bile duct obstruction, pancreatitis), but the cysts are mostly asymptomatic, whereas exocrine and endocrine hormonal insufficiency have been reported in a few cases [17, 93, 123–125, 128–131]. The pancreas may become so replaced with multiple cysts that it becomes nonfunctional, which results in steatorrhea and diarrhea [93]. Insulin-dependent diabetes mellitus has been reported as a complication [129, 130].

Cystadenomas, like cysts, contain serous fluid and are benign in VHL [93, 123]. Serous cystadenoma is a grape-like cluster of multiple microscopic and macroscopic cysts, separated by thickened walls of stroma [93, 122, 129, 132]. Calcification or a central stellate scar may be seen [122].

The differential diagnosis of cystic pancreatic lesions in VHL includes pseudocysts (Fig. 8b) caused by pancreatitis, pancreatic involvement in polycystic kidney disease, and echinococcosis [123, 133]. Metastasis from renal cell carcinoma has been described [134] and has to be considered in the differential diagnosis of solid pancreatic masses. Adenocarcinoma in VHL is rare and was first detected by CT in 1979 [5, 20].

Different imaging techniques, such as US, MRI, and CT, have comparable diagnostic value [132]. Ultrasound is the method of choice for screening programs [123]. However, in finding a small lesion, or identifying a solid lesion, CT scanning or MRI may be superior to US [54, 132]. Serous adenoma may appear solid in US because of the multiple acoustic interfaces caused by multiple microscopic cysts [93]. Also, a cystadenoma may be indistinguishable from a cluster of simple cysts, but this has no clinical implications since both are benign lesions [122] (Fig. 8b).

Pancreatic cystadenoma and the long T2 of the serous contents of cysts both result in high signal intensity on T2-weighted images. Gadolinium enhancement may be helpful because of high signal intensity in serous microcystic neoplasm, but it is absent in cystic lesions. The signal intensity on T1-weighted images is usually low but can vary depending on the presence of hemorrhage [127].

Asymptomatic pancreas lesions may represent an important feature that may be useful in detecting early expression of the disease. Because the disease is usually asymptomatic, conservative measures are considered adequate for cystic lesions [123, 125]. However, aggressive resection is mandatory for a solid pancreatic lesion in VHL [125]. Patients with space-occupying cysts have been treated with percutaneous drainage and hypertonic saline sclerosis [93]. Cholestatic jaundice may be treated by endoscopic implantation of a biliary stent [135], or a biliary bypass [125].

*Pancreatic islet cell tumors*

Familial islet cell tumors in VHL were first reported in 1979 [124]. Solid islet cell tumors may occur in 5–17% of the patients [125, 136] and may be unrelated to pancreatic cystic disease [93]. Many islet cell tumors are slow growing, asymptomatic, and nonfunctional [93, 124, 136]. The functional ones most commonly secrete various peptides such as insulin, glucagon, and somatostatin [137]. The frequency of malignant islet cell tumors is very low; only case reports have been published [5, 122–126, 128, 129, 136, 138], some with metastasis [123, 138].

Pancreatic islet cell tumors occur more frequently in patients with pheochromocytoma and may be considered as an additional form of the multiple endocrine neoplastic syndromes [93, 124, 136]. Islet cell tumors arise either from pancreatic islet cells, which are believed to be derived from the neural crest [139], or from a single neuroendocrine-programmed ectoblast [137]. This might indicate that islet cell tumors share a common origin with pheochromocytomas.

The VHL gene does not play a pathogenetic role in the development of non-VHL (sporadic) pancreatic endocrine tumors [140]. This is in contrast to some other tumors of the VHL spectrum (vide supra: structure and possible functions of the VHL protein product). A locus at chromosome 3p25 centromeric of VHL is frequently lost in these tumors and may harbor a novel pancreatic endocrine tumor suppressor gene. Allelic loss at chromosome 3p25 is thought to be correlated with more clinically advanced disease [140].

With US, benign islet cell tumors are usually observed to be well demarcated, round or oval, and hypoechoic relative to pancreatic parenchyma. Success rates for insulinoma localization range from 25–60%, with those for gastrinomas at approximately 20% [137]. Intraoperative US may be useful in identifying focal masses when pancreas-sparing surgery is being considered, but detection of small lesions is difficult. Most islet cell tumors larger than 2 cm can be visualized by any technique, whereas those smaller than 2 cm are best seen with bolus-enhanced, contrast-medium-enhanced, thin-section dynamic CT [137]. Islet cell tumors show intense

enhancement on CT and may contain calcification [93]. As the tumor enlarges, areas of necrosis may be seen. The characteristic arteriographic feature of islet cell tumors is a dense, homogeneous, circumscribed parenchymal blush. Angiography was useful in the past in localizing pancreatic islet cell tumors [93], but has been replaced by CT and MRI. Fat-suppressed and dynamic gadolinium-enhanced MRI are superior to CT in depicting islet cell tumors [141]. Small insulinomas ( < 1.5 cm in diameter) were revealed well on dynamic gadolinium-enhanced, fast low-angle shot (FLASH) images [141]. However, others believe that CT and US are superior to MRI in detecting small islet cell tumors [137].

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# Book review

European Radiology

**Cittadini G.: Double contrast barium enema: the Genoa approach.** Berlin, Heidelberg, New York: Springer, 1998, 137 pages, 72 figures, DM 108.00, ISBN 88-470-0003-3

This new book deals with important pre-procedural aspects of large bowel radiography and how to take advantage of these to create a barium enema of high quality, called the 'Genoa approach or technique'. In contrast to other books on diagnostic imaging of the colorectum, this one covers radiological aspects of large bowel diseases only in part, and then mainly functional disorders. The 'Genoa approach' in essence describes a pharmacological bowel preparation based on sennosides without any cleansing enema, with magnesium sulphate and hydration. Gravity is utilised for barium inflow and muscle relaxants given intravenously before air insufflation.

The chapters in this book deal in detail with various bowel preparations including cathartics and diet, chemistry and biochemistry of barium suspensions, large bowel anatomy, physiology including motility and secretion, but also psychological aspects related to the double-contrast barium enema, including psychoradiological stimulation. A complete list of references is found at the end of each chapter.

The research work behind the book has been done mainly by the author and published in Italian, which means less accessibility to a non-Italian-speaking reader. The text is easy to read on the whole although the author expatiates upon the topics and sometimes uses non-idiomatic words and phrases. The absence of comments on digital radiography, including the use of a C-arm to unloop tortuous segments, is an oversight, as is the summary dealing with carbon dioxide as a negative contrast medium instead of air. The figures given on morbidity and mortality of colonoscopy are outdated and relate to therapy only.

In eulogistic terms, Professor A.R. Margulis in his foreword emphasises the important task of the radiologist to diagnose premalignant polyps in order to prevent a later carcinoma. Although this is true, I do not think that this aspect is the main reason to buy this book, but rather an earnest endeavour to gain more knowledge about fundamental aspects that directly influence the diagnostic confidence of large bowel barium studies. This monograph is thus primarily intended for the radiologist in charge of gastrointestinal radiology, and possibly residents in GI training and GI technicians, not for students.

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