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REVIEW ARTICLE

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Von Hippel-Lindau syndrome from the urologist and oncologist perspective — literature review

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ABSTRACT

Von Hippel-Lindau (VHL) syndrome is a rare genetic disorder characterized by multiple retinal and cerebellar hemangioblastomas that tend to occur in a familial setting. The pattern of inheritance is autosomal dominant. Patients with VHL syndrome have an increased risk of clear cell renal cell carcinoma (ccRCC) as well as pancreatic and testicular cysts and cystadenomas. Tumors associated with VHL syndrome manifest at a young age. This article presents diagnostic methods and discusses the treatment approaches for this syndrome based on a global literature review.

Keywords: von Hippel-Lindau syndrome, familiar angiomatosis of the retina and cerebellum, clear cell renal cell carcinoma, polycystic kidney disease

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Introduction

Von Hippel-Lindau (VHL) syndrome is a rare genetic disorder characterized by familial cerebellar and retinal angiomatosis. This syndrome is an example of an autosomal dominant disease, with an estimated occurrence rate ranging from 1:36,000 to 1:100,000 [1, 2]. There are two types of this syndrome: type 1 VHL without a pheochromocytoma and type 2 with a pheochromocytoma [3–6]. The clinical manifestations are linked to mutations in the *VHL* gene located on the short arm of the third chromosome (3p25-26) [1]. The tumor suppressor gene *VHL* encodes a protein that, through the action of E3 ubiquitin ligase, leads to the degradation of Hypoxia Inducible Factors (HIFs). Under normal conditions, HIFs, which are activated by hypoxia, induce the expression of genes, including vascular endothelial growth factor (VEGF), erythropoietin (EPO), transforming growth factor (TGF), erythropoietin receptor (EPOR), angiopoietin 1, and transferrin, thereby helping to reduce hypoxia. During normoxia, HIFs are degraded by the VHL protein. In patients with VHL disease, the VHL protein loses its

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function, which leads to uncontrolled activation of HIFs and the expression of the aforementioned genes, causing phenomena such as angiogenesis and erythropoiesis. These processes lead to the development of symptoms of VHL syndrome, including hemangioblastomas in the central nervous system, clear cell renal cell carcinoma, retinal hemangioblastomas, pancreatic neuroendocrine tumors, polycystic kidneys, and cysts in the pancreas and epididymis. About 80% of VHL gene mutations occur as a familial trait, and in 20% of patients, they occur *de novo*. In Denmark, a study of 34 families with a *VHL* gene mutation found that the most common types of mutations are missense mutations, deletions or insertions within the reading frame, and nonsense mutations [7].

The disease is characterized by an increased predisposition to develop hemangioblastomas in the central nervous system (CNS; most commonly in the cerebellum and spinal cord), occurring in 60–80% of cases. Other conditions associated with this syndrome include clear cell renal cell carcinoma, retinal hemangioblastomas, pancreatic neuroendocrine tumors, polycystic kidneys, and cysts in the pancreas and epididymis. The syndrome typically presents multifocally, bilaterally, and at a young age, with anaverage onset at 30 [8–25].

The average life expectancy of patients with VHL disease is 49 years. The most common causes of death are clear-cell renal carcinoma and hemangioblastoma [26]. Cases of VHL syndrome in children have also been described in the literature [8–20]. Diagnosis relies on genetic testing and clinical imaging.

Components of VHL type 1

The first type of disease is characterized by predominant deletion mutations. Moreover, in this type, there is an absence of pheochromocytoma. Typically, patients who do not develop pheochromocytoma in VHL syndrome experience complete remission of tumor lesions, with the tumors exhibiting low malignancy [3–6].

Components of VHL type 2

In the second type of VHL syndrome, there is a significant risk (40–60%) of developing pheochromocytoma and clear-cell renal cell carcinoma (ccRCC) [3–6, 21]. Additionally, in type 2, three subtypes are distinguished: 2A, 2B, and 2C [27] They are categorized based on the occurrence of hemangioblastomas and clear-cell renal cell carcinoma [27].

Hemangioblastoma can be observed in subtypes 2A and 2B. RCC is typically found in patients with subtype 2B [27]. Subtype 2C is rare and involves RCC or papillary cell carcinoma (PCC) [28, 29]. Point mutations, such as transversion type, are specific for type 2 VHL [8–20]. Such mutations are additionally nonsense mutations leading to the formation of an abnormal protein structure. The studied gene is a tumor suppressor gene; therefore, mutations in it contribute to the development of tumors.

Diagnosis

In VHL disease diagnosis, medical history (including detailed family history), physical examination, imaging studies (such as magnetic resonance imaging, computed tomography, and ultrasonography), and genetic testing are utilized. The physical examination may reveal various neurological disturbances, such as problems with motor coordination, balance, vision and hearing impairments, muscle weakness, palpable abdominal mass, and feelings of fatigue and weakness.

Von Hippel-Lindau diagnosis is based on genetic tests to confirm or rule out mutations in the *VHL* gene of potentially affected individuals and the family genetic line. Patients should be referred for *VHL* gene testing if the individual's medical history includes either retinal hemangioblastomas (RH), CNS hemangioblastomas, PCC, endolymphatic sac tumors (ELST), or RCC with atypical features 9 including in relatives aged below 46, bilateral or multifocal tumors, and other family members with RCC [30]. In some patients, VHL diagnosis is made based on clinical symptoms. For individuals with a family history of VHL disease, the presence of one characteristic symptom of VHL disease is sufficient, whereas, in the absence of a family history, two symptoms of the VHL syndrome are necessary for diagnosis, one of which must be a hemangioma. It is recommended that the diagnosis and further treatment be conducted by a multidisciplinary team, which includes a clinical geneticist, neurosurgeon, endocrinologist, urologist, ophthalmologist, and oncologist [7].

Specific diagnostic criteria for VHL were constructed (Tab. 1 [31–35]).

In VHL patients, computed tomography (CT) and ultrasonography (US) typically reveal numerous, often bilateral kidney cysts and kidney tumors corresponding to ccRCC. ccRCCs usually coexist with other changes in the CNS or cysts in the pancreas and epididymis. Magnetic resonance imaging (MRI) allows for visualization of changes in the central nervous system. (Fig. 1–8 present CT scans of changes in patients with von Hippel-Lindau syndrome in fairly common locations).

Treatment

The treatment of patients with VHL syndrome depends on the manifestations and clinical symptoms. However, the cornerstone of management is surgical treatment by a multidisciplinary team of specialists.

Table 1. Danish and international criteria for diagnosing Von Hippel-Lindau (VHL) [30–34]

International criteria		Danish criteria
Confirmation of mutation in the family/VHL mutation	Symptom associated with VHL syndrome	Symptom associated with VHL syndrome
Associated with VHL Symptoms included in the criteria	• Retinal hemangioblastoma • CNS hemangioblastoma • RCC • Primitive neuroectodermal tumor (PNET) • Endolymphatic sac tumor (ELST) • Pancreatic cysts • Epididymal cystadenomas • Pheochromocytoma	• Retinal hemangioblastoma • Hemangioblastoma in the cerebellum, brainstem, or spinal cord • Primitive neuroectodermal tumor (PNET) and/or multiple • Pancreatic cysts • Endolymphatic sac tumor (ELST) • RCC • Pheochromocytoma, paraganglioma, and/or glioma
Exclusion of the disease within the family	Hemangioblastoma (CNS or retina) or at least one hemangioblastoma (retina and/or CNS) and other organ damage	At least 2 symptoms associated with VHL syndrome

CNS — central nervous system; RCC — renal cell carcinoma

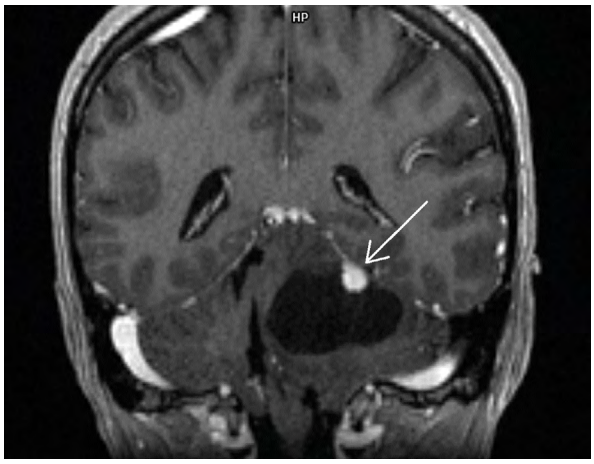

Figure 1. Cystic hemangioblastoma. Enhanced coronal T1-weighted magnetic resonance (MR) image depicts a cystic mass with a strongly enhancing mural nodule (arrow) in the cerebellum

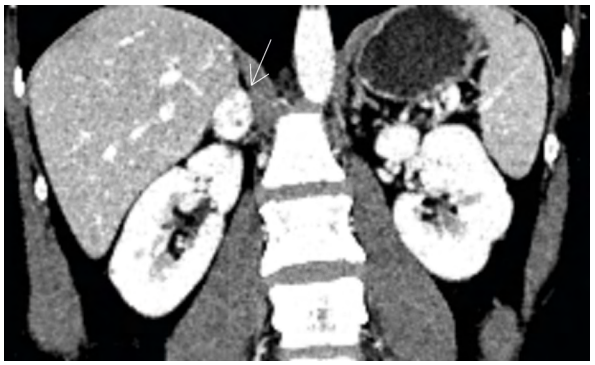

Figure 2. Coronal contrast-enhanced computed tomography (CT) scan shows right adrenal gland pheochromocytoma with homogeneous, vivid enhancement (arrow)

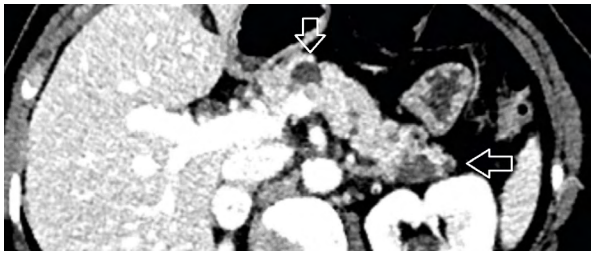

Figure 3. Same patient as in Figure 2. Axial contrast-enhanced computed tomography (CT) image depicts multiple cystic lesions (arrows) scattered within the body and tail of pancreas

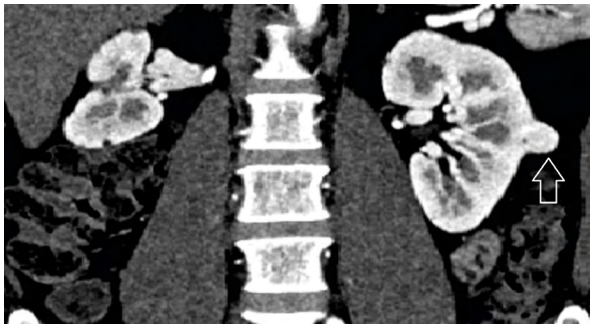

Figure 4. Coronal contrast-enhanced computed tomography (CT) scan shows left renal solid mass (arrow) showing strong arterial enhancement typical for clear cell renal cell carcinoma

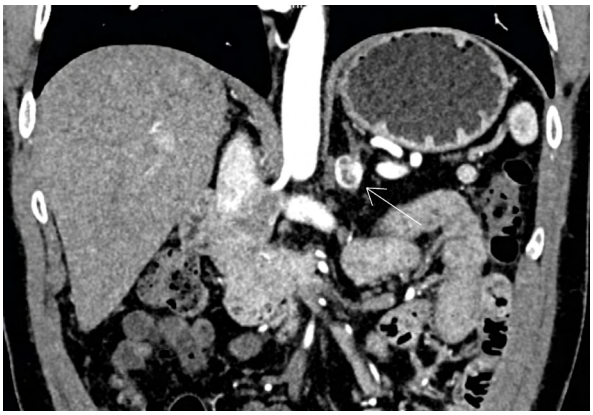

Figure 5. Same patient as in Figure 4. Coronal contrast-enhanced computed tomography (CT) scan depicts left adrenal mass showing heterogeneous enhancement suggestive of pheochromocytoma

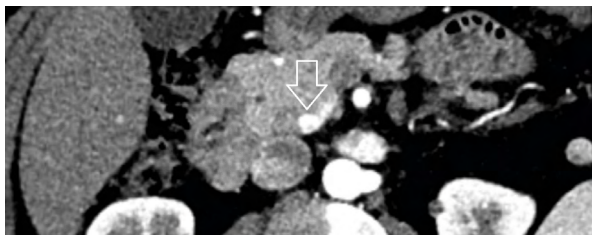

Figure 6. Same patient as in Figures 4 and 5. Axial contrast-enhanced computed tomography (CT) image demonstrates a small well-defined hyperenhancing mass (arrow) located in the pancreatic uncinate process. Computed tomography appearance of the lesion is considered suggestive of neuroendocrine tumor (NET)

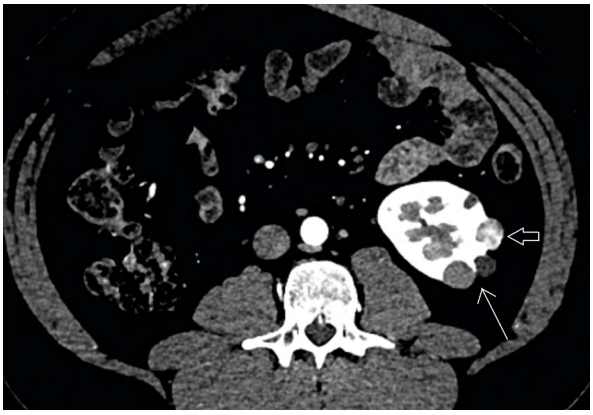

Figure 7. Axial contrast-enhanced computed tomography (CT) image shows complex cystic left renal mass (large arrow) and multiple simple renal cysts (small arrow)

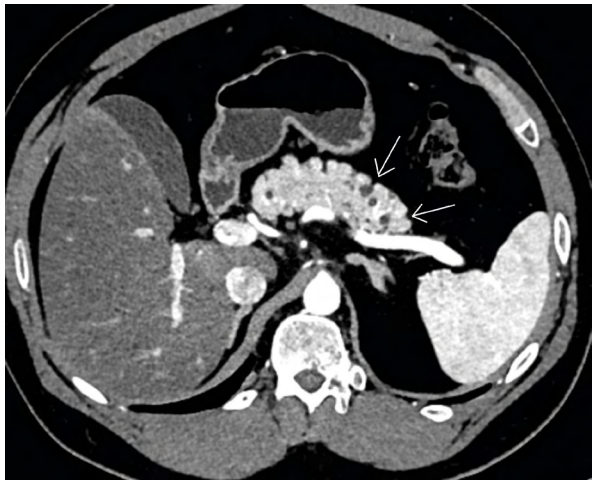

Figure 8. Axial contrast-enhanced computed tomography (CT) image in the same patient as in Figure 7. The arrows show multiple, hypodense cystic lesions within the pancreatic tail

A decision on radical nephrectomy (RN) or sparing surgery nephrectomy (NSS) for patients with kidney tumors depends on the clinical advancement of the tumor. Currently, according to the latest European Association of Urology (EAU) guidelines, if possible, the NSS is the preferred treatment for patients with kidney tumors. However, in the case of VHL syndrome patients, the literature is not unanimous.

Sparing surgery nephrectomy is recommended primarily for patients with ccRCC at stage T1. According to the EAU guidelines, NSS better preserves overall kidney function compared to RN. However, due to incomparable results, the beneficial effect of NSS on overall survival, suggested in some studies, remains unconfirmed. Thus, in the case of VHL syndrome, this method is not preferred because new tumors may rapidly develop from the remaining kidney tissue. Nevertheless, it is recommended to treat tumors smaller than 4 cm with NSS while preserving kidney tissue [36].

Another study states that in patients after NSS, the risk of developing new tumors in the same kidney within five years and the overall risk of reoperation is, respectively, 50% and 25%. However, the treatment strategy adopted by these authors using NSS and strict observation maintained proper kidney function without an increased risk of metastasis [37]. On the other hand, RN usually applies to tumors staged T2 and higher. Currently, the laparoscopic RN is recommended for T2 tumors. Compared to open RN, laparoscopic RN is characterized by decreased blood loss and shorter hospitalization time; patients report less postoperative pain and return to daily activities more quickly.

Open RN is considered the standard procedure for T3 and T4 advanced tumors [38].

An increasing number of medical centers have access to the da Vinci robot. Patients eligible for RN or NSS can also be considered for robot-assisted surgery. However, compared to laparoscopic methods, no significant benefits for patient recovery have been demonstrated with robot-assisted surgery. Moreover, robot-assisted RN (RARN) increases treatment costs [38]. In the treatment of VHL patients, an HIF2a inhibitor (hypoxia-inducible factor) is also used. Under normal conditions, HIF2a, activated by hypoxia, causes the expression of genes, including *VEGF*, *EPO*, *TGF*, *EPOR*, angiopoietin 1, and transferrin, thereby contributing to the reduction of hypoxia. During normoxia, HIF2a is degraded by the VHL protein. In VHL patients, the VHL protein loses its function, leading to uncontrolled activation of HIF2a and the expression of the aforementioned genes, causing such phenomena as angiogenesis and erythropoiesis. These processes lead to the development of symptoms of von Hippel-Lindau syndrome. The HIF2a inhibitor prevents the action of HIF2a, which inhibits the development of VHL syndrome. The HIF2a inhibitor plays a significant role in the treatment of patients with von Hippel-Lindau syndrome and RCC, as the HIF2a factor in this cancer is treated as an oncogene [39]. HIF2a is expressed in various cell types, including endothelial cells of blood vessels, renal glomeruli, cardiomyocytes, and hepatocytes [40]. The second generation of HIF2a inhibitors includes NKT2152, DFF332, and belzutifan. During clinical trials, it was reported that the most common side effects that may occur during treatment are anemia, weakness and fatigue, shortness of breath, and nausea [41]. The LITESPARK-004 study (a phase II clinical trial) evaluated the efficacy of belzutifan treatment in patients with RCC and VHL disease. The drug dosage was 120 mg per day. Treatment was discontinued in the event of disease progression or the occurrence of unacceptable side effects. The study involved 61 patients with a median follow-up of 8.2 months. The objective response rate was assessed at 49% [95% confidence interval (CI) 36–62]. In 30 patients, the disease remained stable after drug application. The following side effects occurred during the study: anemia, weakness, and fatigue, as well as pain and dizziness. To treat anemia, packed red blood cell transfusions and/or erythropoiesis-stimulating agents were used. In August 2021, the Food and Drug Administration (FDA) approved belzutifan for the treatment of adult patients with VHL disease who have RCC, CNS hemangiomas, or pancreatic neuroendocrine tumors that do not require immediate surgical treatment [42].

Phase III clinical trials are also ongoing for the combination of belzutifan with cabozantinib. The results from earlier studies involving this combination of drugs are promising [43].

Necessity of lymphadenectomy and metastasectomy in the case of distant metastasis

Lymphadenectomy in ccRCC patients does not improve long-term survival rates.

In patients with lymph node metastasis, regardless of the disease stage, the 3-year survival rate after nephrectomy is 20–30% [44]. However, in patients with isolated distant metastasis resistant to systemic treatment, performing metastasectomy is recommended. Randomized studies demonstrated that metastasectomy can improve survival rates in patients who respond to systemic treatment, patients with metachronous lung metastasis or metastasis that appeared 2 years after the primary disease diagnosis [45].

Risk of recurrence

The majority of patients with VHL syndrome experience local recurrence (83.7% after 10 years), with an average recurrence-free period of 53 months. Patients treated with NSS should be informed about strict monitoring and the likelihood of future reoperation [37].

Palliative treatment

Currently, significant advancements in the treatment of metastatic ccRCC involve various therapies targeting cellular signaling pathways. The standard approach for metastatic RCC includes agents targeting the VEGF, PD-1, CTLA-4, or mTOR signaling pathways [46].

First-line treatments for patients with ccRCC involve combining programmed cell death protein 1 (PD-1) inhibitors with either vascular endothelial growth factor receptor (VEGFR)-targeted therapy or cytotoxic T-lymphocyte antigen 4 (CTLA-4) inhibition. The primary combinations used are PD-1 inhibitors and VEGFR tyrosine kinase inhibitors (TKIs): axitinib-pembrolizumab, lenvatinib-pembrolizumab, and cabozantinib-nivolumab. Other first-line drugs include ipilimumab-nivolumab (CTLA-4 inhibitor and PD-1 inhibitor) and axitinib-toripalimab (VEGFR TKI and PD-1 inhibitor) [47]. In cases where immune checkpoint inhibitors cannot be used, VEGFR TKIs, such as pazopanib, tivozanib, or sunitinib, may be considered [48, 49]. These drugs can serve as alternatives to the combination of VEGFR with PD-1 inhibitors [47]. The combination of three drugs, ipilimumab-nivolumab-cabozantinib (CTLA-4 inhibitor, PD-1 inhibitor, VEGFR TKI), is currently not recommended because, despite better progression-free survival (PFS) outcomes compared to using two drugs (ipilimumab

Table 2. Follow-up evaluations recommended for patients with Von Hippel-Lindau (VHL) disease [60, 61]

Follow-up evaluation	Initial age	Frequency	Comments
Retinal assessment	< 1 year	Every 6–12 months	Annually, before age 30
Anamnesis and physical examination by a specialist	1 year	Yearly	
Blood pressure and heart rate	2 years	Yearly	
Determination of metanephrine levels	5 years	Yearly	Measurement in plasma preferred, but fractionated metanephrines may be measured in 24-hour urine samples
MRI of the neuraxis (brain and spinal cord)	11 years	Every 2 years	Performed with and without contrast (no contrast during pregnancy); can be coordinated with MRI of the abdomen; thin slices in the posterior fossa and temporal bone; single MRI of the inner ear canal at 15 years of age
Audiometry	11 years	Every 2 years	
MRI of the abdomen	15 years	Every 2 years	Performed with and without contrast (no contrast during pregnancy); assess kidneys, pancreas, and adrenal glands; can be coordinated with MRI of the neuraxis

MRI — magnetic resonanse imaging

and nivolumab), it is associated with higher toxicity [50]. The duration of first-line treatment has not been defined [47].

Second-line drugs include pazopanib, axitinib, sunitinib, cabozantinib (VEGFR-targeted drugs), lenvatinib-pembrolizumab (VEGFR TKI — PD-1 inhibitor), tivozanib (VEGFR TKI), lenvatinib-everolimus (VEGFR TKI — mTOR inhibitor) [47, 51–53]. However, there are no reliable data from studies presenting conclusive evidence of the efficacy of these drugs, so caution is advised in their use. Another second-line therapy is VEGFR-targeted treatment. Immune checkpoint inhibitors are not used in second-line treatment [47].

For third-line therapy, belzutifan (hypoxia-inducible factor 2 alpha) may be used, which has shown more favorable effects compared to everolimus in terms of PFS [54]. VEGFR-targeted therapy can also be considered [47].

Regarding radiotherapy, ccRCC was generally considered resistant to this type of treatment. However, recent studies demonstrate that high-dose stereotactic radiotherapy (SRT) shows some effectiveness in treating metastatic and advanced ccRCC, particularly in cases of oligometastatic disease [55].

Treatment of central nervous system lesions

Microsurgical resection remains the treatment of choice for vascular lesions of the CNS [56].

In cases where patients are not fit enough to meet the requirements for surgical intervention, stereotactic radiation or craniospinal radiation is used. However, long-term studies show that vascular lesions treated with radiation grow similar to their natural history [57]. Prophylactic irradiation is not recommended for patients with VHL-associated vascular lesions as they exhibit unpredictable growth patterns [56].

The primary surgical methods used for treating RH include laser photocoagulation and cryotherapy. They can be used alone or in combination [58]. For small RH lesions near the optic nerve, non-surgical methods include intravitreal injections of anti-VEGF agents [59].

Complete surgical resection is a preferred treatment option for endolymphatic sac tumors [60].

Follow-up protocols

All patients with VHL disease are predisposed to the development of benign or malignant lesions. Even if asymptomatic, such patients should be followed up to detect new lesions and to monitor the progression of known lesions. Follow-up evaluations focus on hemangioblastomas (including retinal hemangioblastomas), endolymphatic sac tumors, pheochromocytomas, clear cell renal carcinomas, and pancreatic cystadenomas, as well as lesions of the epididymis and broad ligament of the uterus, and can be tailored to individual patient needs (Tab. 2 [61, 62])

Summary

Von Hippel-Lindau syndrome is a condition that increases the risk of developing multiple tumors, especially at a young age. It is a rare autosomal recessive genetic disease.

Its symptoms are nonspecific. However, genetic testing is critical in confirming or ruling out the diagnosis. Early detection of VHL syndrome allows planning treatment, which extends and improves the patient's quality of life. Treatment requires specialists from various medical fields, such as urology, oncology, endocrinology, and radiation oncology. Treatment methods depend on the timing and the patient's condition at the time of diagnosis.

Conclusions

1. Early diagnosis of VHL syndrome allows for proper treatment planning, enhancing patient comfort and lifespan.
2. In patients with VHL syndrome and tumors up to 4 cm, NSS is the preferred treatment method.
3. Close monitoring of patients after NSS helps maintain kidney function and does not increase the risk of metastasis.
4. Sparing surgery nephrectomy, compared to RN, leads to better preservation of overall kidney function.
5. Management of VHL syndrome should involve a multidisciplinary team of specialists.
6. Since 2021, belzutifan, which is a HIF2a inhibitor, has been approved for treating patients with VHL disease and RCC.

Article Information and Declarations

Author contributions

K.Kowalik, P.N., K.H., K.Kołaczyk, A.S: Artur Smogór: writing the main part of the manuscript and literature review; K.Kasperowicz, G.D., A.M.: language proofreading of the manuscript; A.G.: corrections to the review. All authors read and approved the final manuscript

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Conflict of interest

The authors declare no conflict of interest.

Supplementary material

None.

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