Management recommendations for pancreatic manifestations of von Hippel–Lindau disease

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Consensus Statement

Management Recommendations for Pancreatic Manifestations of Von Hippel–Lindau Disease

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Von Hippel–Lindau disease (VHL) is a multineoplasm inherited disease manifesting with hemangioblastoma of the central nervous system and retina, adrenal pheochromocytoma, renal cell carcinoma, pancreatic neuroendocrine tumors and cysts, and neoplasms/cysts of the ear, broad ligament, and testicles. During 2018-2020, the VHL Alliance gathered several committees of experts in the various clinical manifestations of VHL to review the literature, gather the available evidence on VHL, and develop recommendations for patient management. The current report details the results of the discussion of a group of experts in the pancreatic manifestations of VHL along with their proposed recommendations for the clinical surveillance and management of patients with VHL. The recommendations subcommittee performed a comprehensive systematic review of the literature and conducted panel discussions to reach the current recommendations. The level of evidence was defined according to the Shekelle variation of the Grading of Recommendations, Assessment, Development, and Evaluation grading system. The National Comprehensive Cancer Network Categories of Evidence and Consensus defined the committee members' interpretation of the evidence and degree of consensus. The recommendations encompass the main aspects of VHL-related pancreatic manifestations and their clinical management. They are presented in a clinical orientation, including general planning of screening and surveillance for pancreatic neuroendocrine tumors, utility biochemical biomarkers, the optimal choice for imaging modality, indirect risk stratification, indications for tissue sampling of VHL-related pancreatic neuroendocrine tumors, and interventions. These recommendations are designed to serve as the reference for all aspects of the screening, surveillance, and management of VHL-related pancreatic manifestations. ***Cancer* 2022;128:435-446**. © *2021 American Cancer Society*.

KEYWORDS: neuroendocrine tumor, pancreas, recommendations, surveillance, von Hippel–Lindau.

INTRODUCTION

Von Hippel–Lindau disease (VHL) is a multineoplasm inherited disease with an autosomal dominant trait. The annual incidence is approximately 1 in 36,000 live births.[1,2] VHL is caused by pathogenic variants in the *VHL* tumor suppressor gene[3] located at chromosome 3p25, and it manifests with hemangioblastoma of the central nervous system and retina, adrenal pheochromocytoma, renal cell carcinoma (RCC), pancreatic neuroendocrine tumors and cysts, and other neoplasms/cysts of the ear, broad ligament, testicles, and more.[4]

The penetrance of pancreatic neuroendocrine tumors (PNETs) among patients with VHL ranges between 8% and 17%[5-8] and may have a female predominance.[5-9] Other pancreatic abnormalities, including cysts, cystadenomas, and mixed tumors,[6] may also develop in patients with VHL, and this should be considered a possible diagnostic pitfall.

VHL-related pancreatic neuroendocrine neoplasms (PNENs) are clinically distinct from sporadic PNENs in multiple aspects. The European Neuroendocrine Tumor Society guidelines define a PNEN's grade on the basis of cell morphology (well differentiated vs poorly differentiated), and there are 3 grades (G1, G2, and G3) based on proliferative indices such as the mitotic rate and Ki-67 expression.[10] Compared with sporadic PNENs, VHL-related PNENs are much less often high-grade[11,12] or metastatic.[8] The rarity of high-grade VHL-related PNENs has led the committee to use *VHL-related PNET* throughout this article.

A PNEN may be functional; that is, it may secrete hormones that cause clinical syndromes. Such syndromes include recurrent and/or multiple gastroduodenal ulcers (Zollinger-Ellison syndrome) from gastrin oversecretion, recurrent hypoglycemic episodes from insulin oversecretion, and watery diarrhea syndrome from vasoactive intestinal polypeptide

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oversecretion. Although patients with sporadic PNENs have a relatively high rate of functional PNETs, VHL-related PNETs are almost exclusively nonfunctional.[4,13]

The unique clinical course of VHL-related PNETs affects their management, including the diagnosis, the decision to intervene and the type of intervention, and the surveillance plan. The high pretest probability for a PNET allows avoiding a cytopathological diagnosis when there is a typical radiological appearance. Patients with VHL typically have multiple tumors; thus, any unnecessary or extensive surgical resection may lead to an unjustified major parenchymal sacrifice (early pancreaticoduodenectomy or even total pancreatectomy is sometimes wrongly proposed). There may be insufficient consideration by teams of digestive diseases due to life-threatening tumors that affect other organs during VHL, such as pheochromocytoma. Finally, misdiagnosis with other vascularized pancreatic masses may lead to the wrong clinical decision (mainly pseudosolid pancreatic cystadenomas and, more rarely, pancreatic metastases of RCC).

There are several comprehensive guidelines for the diagnosis, surveillance, and management of patients with PNENs.[14,15] However, because of the unique characteristics of VHL-related PNETs, as detailed previously, and the complex context of VHL, in which multiple neoplasms may develop in parallel to PNETs, there was a need for VHL-specific recommendations for the management of these unique neoplasms. During 2018-2020, the VHL Alliance (VHLA) gathered several committees of experts in the various clinical manifestations of VHL to review the literature and gather evidence on VHL.

In the current report, we detail the results of the discussion of a group of experts in the pancreatic manifestations of VHL along with their proposed recommendations for the clinical surveillance and management of patients with VHL. The committee produced 2 sets of guidelines. First, general recommendations are implemented within the main VHLA guidelines for the surveillance and management of VHL-related manifestations. These guidelines are discussed briefly in the first subsection of this article ("General Planning of Screening and Surveillance for PNETs in Patients With VHL"). Second, the committee recommendations for the diagnosis, surveillance, and management of VHL-related pancreatic manifestations are detailed in later subsections of this report.

METHODS

The committee used the best available research evidence to develop the recommendations and conducted panel discussions to reach the current recommendations. The level of evidence was defined according to the Shekelle variation of the Grading of Recommendations, Assessment, Development, and Evaluation grading system.[16] In addition to the level of evidence, the committee used the National Comprehensive Cancer Network's Categories of Evidence and Consensus to define the committee members' interpretation of the evidence and degree of consensus.[17] None of the committee members had any conflict of interest with any topic discussed in this article.

DETAILED RECOMMENDATIONS FOR VHL-RELATED PANCREATIC MANIFESTATIONS

General Planning of Screening and Surveillance for PNETs in Patients With VHL

Recommendation 1.1—Patients with VHL should be followed in a VHL clinical care center (CCC) whenever feasible. (D/2A)

Surveillance of PNETs

Recommendation 1.2—The initiation of screening for PNETs in patients with VHL should be no later than the age of 15 years. (C/2A)

Recommendation 1.3—Screening for pancreatic manifestations of VHL, when no lesions are present yet, should be performed in 2-year intervals. (C/2A)

Recommendation 1.4—In a patient with VHL and no pancreatic manifestations detected by the age of 65 years, no further screening for pancreatic manifestations is required. (C/2A)

Recommendation 1.5—Patients with VHL-related PNETs should be followed in a VHL CCC whenever feasible. (D/2A)

Recommendation 1.6—All patients with VHL and specifically patients with VHL-related PNETs should be in a VHLA-certified CCC. However, when routine surveillance in a VHL CCC is not feasible, the following criteria indicate a referral to a VHLA CCC for consultation: a patient with a solid pancreatic lesion with an imaging appearance typical of a PNET. The following criteria indicate a referral to a VHL CCC: a tumor diameter > 1.5 cm, any tumor grow Consensus Statement th between 2 scans, and/or suspected PNET metastases. (D/2A)

As for the age range for screening and surveillance, the youngest age at diagnosis reported for a patient with VHL and a PNET was 10 years, and the youngest patient with a metastatic VHL-related PNET was 11 years old.[9] The median age at disease onset is in the early to mid-30s, with ages ranging from the early teenage years to the seventh to eighth decades.[7-9] The committee defined

the recommendations so that 95% of PNETs would be detected, as defined in the goals for all committees, and co-assessment of visceral manifestations of VHL with a uniform surveillance protocol would be enabled. Hence, the committee made the recommendation to initiate screening no later than the age of 15 years and to cease screening at the age of 65 years if no pancreatic lesion is detected by that age.[18,19]

The pancreatic manifestations in a patient with VHL are typically a small part of a complex matrix of manifestations. A VHL multidisciplinary team with experts in various relevant specialties should preferably provide medical care for patients with VHL. These specialties include ophthalmology, urology, neurosurgery, gastroenterology, oncology, and neuroendocrinology. The VHLA accredits multidisciplinary teams with sufficient capabilities as CCCs after a thorough review by the VHLA Clinical Council.[20] The recommendation to refer patients with VHL to CCCs stems from the need to be familiar with all the other manifestations and unique characteristics of VHL-related PNETs.

In the rare cases in which a CCC is not accessible for routine surveillance, the patient should be referred for consultation and management planning if the tumor is large (diameter > 15 mm), if there is any tumor growth, or if PNET metastases are suspected. A VHL specialist consult may be obtained in situations of uncertainty through expert networks or the VHLA. Telemedicine may serve to improve patient care when an in-person evaluation is not possible.

Although most patients with VHL harbor germline VHL mutations, a subset of patients may be diagnosed on the basis of disease manifestations and/or their family history. Thus, in addition to patients with genetic testing, the committee suggested using the recommendations for patients diagnosed with VHL on the basis of the international criteria, which require the detection of 2 hemangioblastomas or 1 hemangioblastoma and a visceral neoplasm, or on the basis of the Danish criteria, which require the detection of any 2 VHL-related manifestations.[21]

Recommendation 1.7—In women planning a pregnancy, pancreatic protocol magnetic resonance imaging (MRI) should be performed before the planned conception. (D/2A)

Recommendation 1.8—In a pregnant woman with no known PNETs, no pancreatic imaging is required during pregnancy. (D/2A)

VHL-related PNETs have an indolent course and a low risk for metastasis in comparison with sporadic PNENs. Furthermore, in a series of 52 patients with VHL (26 women), a lower age-adjusted manifestation development rate was found in pregnant patients versus nonpregnant patients, and no appearance or life-threatening progression of PNETs has been reported in pregnant patients with VHL.[22]

On the basis of these data, it will be prudent to perform a pancreatic MRI scan for evaluation when a pregnancy is being planned as close to conception as possible. However, in patients with VHL who are pregnant and are not known to harbor a PNET, the decision to perform abdominal MRI should be based on specific complaints, and the low-risk nature of this manifestation and its typically indolent course should be considered.

Biochemical Biomarkers

Recommendation 2.1—Biochemical biomarkers are not useful for the screening of VHL-related PNETs. (D/2A)

Recommendation 2.2—Plasma pancreatic polypeptide levels may be used for assessing disease burden in patients with VHL-related PNETs. (C/2A)

Recommendation 2.3—Specific biochemical evaluations should be performed for VHL-related PNETs as clinically indicated. (D/2A)

Although a large subset of sporadic PNETs are functional and necessitate screening for functional status with a potential impact on patient management,[23] in a large study of 108 patients with VHL-associated PNETs, none of the patients had biochemically or clinically functional PNETs.[8] Plasma chromogranin A is commonly used as a biomarker for neuroendocrine tumors but has been found to not be useful for assessing the burden of VHL-related PNETs.[24] Chromogranin A can be secreted by other VHL-related neoplasms such as pheochromocytoma, and increased levels may stem from decreased renal function, which is commonly encountered in patients with multiple RCCs.[25,26] Tirosh et al[27] demonstrated a strong correlation between the disease burden of VHL-related PNETs and plasma pancreatic polypeptide levels. The advantage of this marker is its specificity for pancreatic lesions in comparison with chromogranin A. The blood transcriptome–based marker NETest has been validated as a diagnostic and prognostic biomarker for neuroendocrine neoplasms in various scenarios.[28-31] However, in the context of VHL-related PNETs, there are not sufficient data to suggest its use at this time point.

Because nearly all VHL-associated PNETs are nonfunctional, hormonal screening for functional PNETs is generally unnecessary. In the infrequent scenario in which patients with VHL-related PNETs present with symptoms suggesting a functional PNET, the investigation should follow the currently available guidelines for investigating functional PNENs.[14]

Imaging Modality

Anatomical imaging

Recommendation 3.1.1—The anatomic imaging modality of choice for VHL-related PNETs should follow the imaging methods for sporadic PNETs, preferably gadolinium-enhanced pancreatic MRI with an early arterial phase. (C/2A)

Recommendation 3.1.2—In patients with VHL-related PNETs with contraindications for MRI, triple-phase pancreatic computed tomography (CT) is preferable to other imaging modalities. (C/2A)

Recommendation 3.1.3—In light of the low risk of small PNETs in the context of VHL, nonpancreatic abdominal CT/MRI may be considered for the imaging of VHL-related PNETs if it is performed for the surveillance/screening of other VHL-related visceral manifestations. Pancreatic ultrasound has very low sensitivity for PNETs and is not useful for the screening/surveillance of VHL-related PNETs. (D/2A)

Recommendation 3.1.4—Endoscopic ultrasound (EUS) is not recommended as a screening tool and may be used only when both contrast-enhanced MRI and CT are contraindicated, there is an indication for biopsy of a pancreatic lesion (see recommendation 6.1), or there is doubt about lesions seen on MRI/CT and management may be changed. (D/2A)

The considerations for the modality of choice for a PNEN evaluation should follow the currently available guidelines.[32] Contrast-enhanced CT, MRI, or both are the most frequently used modalities for PNET screening in patients with VHL. On both CT and MRI, a PNET typically appears as a hypervascular lesion in early scans (25-30 seconds) after contrast injection and washes out in the late phase.[33] Studies assessing the diagnostic value of MRI and CT in head-to-head comparisons in the VHL population are sparse. A direct comparison between CT and MRI (n = 27) showed no difference in detecting solid pancreatic lesions between the 2 modalities.[34] Another study (n = 40) demonstrated better sensitivity for CT than MRI for pancreatic lesions.[35] However, a follow-up study reported comparable detection rates for VHL-related PNETs.[24] In the sporadic PNET population, small PNETs (<1 cm in diameter) may be missed on CT, with the sensitivity ranging from 29% to 94%,[36,37] whereas MRI is more accurate than CT for the detection of smaller tumors.[36]

Transabdominal ultrasound is a relatively inexpensive and widely available imaging modality. However, the reported sensitivities for PNET detection are low (9%-64%), mainly when tumors are located at the distal pancreas and masked by the gastric air bubble.[37] EUS outperformed CT, MRI, and ^{11}C-5-hydroxytryptophan positron emission tomography (PET) in detecting PNETs in 22 patients with VHL, even when tumors > 1 cm were included.[38] However, EUS is an invasive method. Because of the low risk of small VHL-related PNETs and the potential complications of EUS, its role in screening for VHL-related PNETs has not been determined.[39] Hence, EUS is the least favorable modality among the 3 possible modalities suggested for the screening or surveillance of VHL-related PNETs. Lower radiation exposure is another advantage of MRI over CT, especially when we consider the lifelong cumulative radiation exposure due to pancreatic imaging in patients with VHL.[40]

Choosing the imaging modality for patients with VHL is complex for several reasons. First, patients with VHL have a high incidence of other visceral neoplasms with a unique differential diagnosis for any lesion detected. Second, it is questionable whether missing small tumors increases morbidity because PNETs smaller than 1.2 to 1.5 cm rarely advance to metastatic disease (see the discussion and recommendations in the section entitled "Indirect Risk Stratification of VHL-Related PNETs"). Third, imaging of the pancreas is often supplanted by imaging required for the surveillance/screening of other visceral organs, such as the kidneys and adrenals. In light of the low risk of small VHL-related PNETs, unless there is a clear indication for performing pancreas-specific imaging, compromising on scan sensitivity will be preferred over additional scans.

Functional imaging

Recommendation 3.2.1—In patients with VHL, ^{68}Ga-DOTATATEc PET/CT imaging is highly sensitive for detecting PNETs, but it should be reserved for PNET staging before a planned intervention or for the characterization of a pancreatic mass with radiological characteristics that are not typical for a PNET (nonenhancing or rapidly growing lesions). (C/2A)

Recommendation 3.2.2—^{18}F-2-deoxy-D-glucose (^{18}F-FDG) PET/CT is not helpful for regular characterization of VHL-related PNETs or their risk stratification. (C/2A)

Recommendation 3.2.3—Functional imaging in patients with VHL should be interpreted with consideration of possible pitfalls of VHL by a radiologist or nuclear medicine specialist experienced in VHL. (D/2A)

Recommendation 3.2.4—^{68}Ga-DOTATATE PET/CT can be used to evaluate VHL-related pancreatic lesions when metastatic disease is suspected on the basis of anatomic imaging and/or before a planned intervention, but not for routine screening. (D/2A)

The optimal functional imaging test for patients with VHL-associated PNETs has not been clearly defined. Kitano and colleagues prospectively compared 4 imaging modalities, including 6-^{18}F-fluoro-L-3,4-di hydroxyphenylalanine (^{18}F-DOPA) PET/CT, ^{18}F-FDG PET/CT, CT, and MRI, in a cohort of 40 patients with VHL-associated PNETs. CT imaging had higher sensitivity than ^{18}F-FDG PET/CT and ^{18}F-DOPA PET/CT.[24,35] In VHL-related PNETs, the FDG standardized uptake value was not predictive of metastatic potential but was reported to identify otherwise unknown metastatic disease in 3 patients.[41]

Practically every VHL-related neoplasm has been shown to have avidity for ^{68}Ga-DOTATATE[42-46] and particularly for visceral lesions.[34] Hence, it is not surprising that the somatostatin receptor–based imaging ^{68}Ga-DOTATATE PET/CT had higher detection rates than CT for any VHL-related lesions[34] and a superior detection rate in another study of ^{68}Ga-DOTATOC PET/CT.[47]

The high sensitivity of these scans should be considered during interpretation in the context of VHL. For example, a ^{68}Ga-DOTATATE–avid pancreatic lesion may be an RCC metastasis, and a parapancreatic ^{68}Ga-DOTATATE–avid mass may be pheochromocytoma, a paraganglioma, or a lymph node metastasis of a PNET or RCC.

^{18}F-FDG PET or ^{68}Ga-DOTATATE can clarify cases in which solid microcystic serous adenomas are suspected because this lesion may be difficult to distinguish from PNETs on CT or MRI.[48,49] In light of the high rate of kidney disease in patients with VHL, functional imaging studies may be helpful in PNET surveillance for patients with chronic kidney disease, in whom contrast-enhanced CT and MRI scans are contraindicated. An additional confounder unique to patients with VHL is FDG uptake by brown adipose tissue. This uptake is mediated by norepinephrine, which is typically secreted by VHL-related pheochromocytoma.[50]

Indirect Risk Stratification of VHL-Related PNETs

Recommendation 4.1—In patients with VHL, a PNET whose largest diameter is <1.5 cm confers low risk, and if it is stable in 2 consecutive scans, it may be followed up every 2 years. (C/2A)

Recommendation 4.2—In patients with VHL, a PNET 3 cm in diameter or larger should be resected. (C/2A) PNETs that are 2 to 3 cm in diameter and located at the head of the pancreas should be considered for surgical resection. (D/2A)

The high risk for developing PNETs among patients with VHL enables diagnosing PNETs radiologically with no need for tissue acquisition. Although this approach obviates the need for invasive procedures for diagnosis, the clinician requires an alternative for a tumor grade, derived from a pathological examination, to define the risk for tumor progression or metastases. The diameter of VHL-related PNETs, based on anatomical imaging, is a consistent and reliable measure for risk stratification. Several studies reported a very low risk for metastasis or tumor progression in patients with small PNETs, which were defined as having a diameter smaller than 1.2 to 1.5 cm.[12,51] On the contrary, larger tumors with a diameter greater than 2.8 to 3 cm were associated with an increased risk for metastasis.[8,9,12] Moreover, tumor growth, measured by the short tumor diameter doubling time (<500 days), was associated with an increased risk for metastatic disease,[8] but this was not validated and was questioned by a study demonstrating nonlinear growth of VHL-related PNETs.[24]

The genotype-phenotype association described in the initial reports of VHL led several groups to assess the association between the type of germline *VHL* variant and the phenotype and outcome of patients with VHL-related PNETs. Variants in exon 3 of the *VHL* gene were associated with an increased risk for metastatic diseases in 2 separate studies from the National Institutes of Health.[8,12] A missense variant in codon 167 was found to have a high risk for metastatic disease,[9,52] and a missense variant was found in 1 study to be associated with the risk for metastatic disease with a 100% negative predictive value.[12] An algorithm for the surveillance of VHL-related PNETs, using the germline *VHL* genotype for patients with an intermediate risk based on the lesion diameter, was suggested. However, this algorithm was not validated prospectively.

The management of VHL-related PNETs 2 to 3 cm in diameter depends on multiple factors and should be determined per patient on the basis of the tumor location: pancreatic head lesions should be considered for resection earlier if enucleation is possible to avoid the need for Whipple's procedure. Other VHL-related PNETs may be followed expectantly.

Indirect risk stratification as a whole is unique for VHL-related PNETs. The reason is the noninvasive assessment of the lesions, which is aimed at reducing to a minimum any invasive procedures in patients who undergo multiple surgeries for the various manifestations

of their disease. Similarly to sporadic PNENs, the lesion diameter is the main risk-stratifying parameter, and it can reassure patients with small PNETs. An additional unique aspect of VHL is the lack of utility for ^{18}F-FDG PET/CT for the stratification of VHL-related PNETs. Even indolent VHL-related PNETs show ^{18}F-FDG uptake due to their glycolytic metabolism.

Indications for Tissue Sampling of VHL-Related PNETs

Recommendation 5.1—In patients with VHL, solid pancreatic lesions with a radiological appearance typical of neuroendocrine tumors should not be biopsied. (C/2A)

In patients with VHL-related PNETs, fine-needle aspiration (FNA)/fine-needle biopsy (FNB) will be required only in exceptional scenarios. Such intervention should be performed only after the need for it has been discussed with a clinician experienced in VHL-related PNETs and only after radiologists experienced in neuroendocrine tumor imaging have been consulted. Cases for which sampling should be considered include the following: 1) a rapidly progressing pancreatic mass, 2) a pancreatic mass with radiological characteristics that suggest an exocrine pancreatic tumor (low vascularity and no uptake on somatostatin receptor-based imaging), and 3) suspected metastasis from a different tumor such as RCC. Even in these specific cases, FNA/FNB should be performed only if the result will alter the patient's management.

For patients who are candidates for FNA/FNB of pancreatic tail lesions, documented normal catecholamine and metanephrine profiles are mandatory to ensure that the lesion is not a functional paraganglioma or left adrenal pheochromocytoma. It should be noted that VHL-related pheochromocytomas are characterized by a noradrenergic biochemical profile. Thus, normal epinephrine/metanephrine blood/urine levels do not exclude this diagnosis. If indicated, the modality of choice for the biopsy of a PNET is EUS-guided FNA.

In contrast to the low risk for a PNEN in non-VHL patients with a pancreatic mass (3%), in patients with VHL, the upfront risk for developing a PNET ranges between 8% and 17% and is much higher when a mass is detected. Furthermore, because patients with VHL are prone to develop multiple PNETs throughout their lifetime, the cumulative risk for complications should be considered. Hence, a solid pancreatic lesion detected in patients with VHL should be considered a PNET unless there are strong parameters to suggest otherwise. The rule is that FNA/FNB should not be performed unless otherwise indicated. Additionally, a pancreatic cystadenoma may mimic a PNET in patients with VHL but has a very low malignant potential.[48,53]

Interventions

Interventions for localized high-risk lesions

Surgery.

Recommendation 6.1.1—Enucleation rather than formal resection should be attempted for lesions suitable for parenchyma-sparing procedures. (C/2A)

Recommendation 6.1.2—Total pancreatectomy should be used rarely, only when all other options for limited resection have been considered and only after the presence of distant metastases has been ruled out. (C/2A)

Recommendation 6.1.3—At the time of resection of a high-risk lesion, additional lesions less than 1.5 cm in diameter may not be resected. (C/2A)

Previously, no consensus existed for the type of surgical resection that should be used for high-risk PNETs in patients with VHL. Currently available guidelines exist for the surgical approach in PNETs.[54] The unique approach to VHL-related PNETs is discussed here. Treatment options include enucleation versus resection and laparoscopic approaches versus open approaches.[55] Enucleation of VHL-related PNETs is an attractive surgical approach because of the potential for recurrence and compromised pancreatic function by cystic disease. Enucleation generally requires a lack of involvement of the main pancreatic duct and a low risk of harboring regional metastatic disease. Long-term outcomes of enucleation are similar to those for formal resections.[8,55] It is recommended that enucleation be performed along with regional lymphadenectomy. Certain criteria suggest resection rather than enucleation, such as the diameter (>3 cm), the tumor diameter doubling time (500 days), a mutation in exon 3, and other high-risk genetic characteristics.[12,24,51,56] To spare parenchyma, some have advocated that at the time of resection for high-risk lesions, additional lesions that are less than 1.5 cm in size be left alone without significant changes in survival outcomes.[51]

EUS-guided ablation.

Recommendation 6.1.9—Patients with high-risk lesions who are unable or unwilling to undergo surgical treatment may be considered for EUS ablation by either radiofrequency ablation (RFA) or ethanol injection, preferably in a clinical trial. (D/2A)

Ablation, either by thermal injury or by caustic material, has been used to treat PNETs over the last decade. Theoretical advantages of ablation include its minimally invasive nature when it is applied by EUS or percutaneously.

A few small retrospective and prospective reports have indicated that the local control rates and overall survival are acceptable.[57-60] Limitations of its use are the lack of associated lymph node sampling, the lack of data about long-term results, and the occasional severe complications of pancreatitis and portal vein occlusion.[57,61] Furthermore, the limited series of RFAs has been restricted nearly entirely to a subset of patients with tumors less than 3 cm and a mix of functional and nonfunctional tumors, and there is a lack of evidence for patients with VHL-related PNETs.

Advanced disease

Medical intervention.

Recommendation 6.2.1—Systemic treatment for patients with advanced VHL-related PNETs should follow the guidelines for sporadic PNETs. (C/2A)

Recommendation 6.2.2—For patients with advanced, well-differentiated VHL-related PNETs, pazopanib may be considered. (C/2A)

The vast majority of PNETs in VHL are well-differentiated, low-grade tumors. The management of advanced PNETs in VHL should generally follow therapy paradigms for sporadic PNETs.[15,62] It is important to note that the unique genetic profile of VHL-related neoplasms[63] suggests a distinct response to interventions in comparison with non–VHL related neuroendocrine tumors, including sporadic and MEN1-related tumors, and this should be taken into consideration when one is weighing the optimal regimen.

A multidisciplinary team should guide the treatment selection in the context of the status of other VHL-related manifestations.

Tyrosine kinase inhibitors, including sunitinib, sorafenib, axitinib, and pazopanib, have been evaluated for unresectable and/or progressive VHL-related neoplasms.[64] Among those, sunitinib was evaluated in a prospective randomized controlled trial of sporadic PNETs and prolonged progression-free survival,[65] and it may be effective for the management of PNETs in patients with VHL.[66-69] Jonasch et al[70] reported the efficacy of pazopanib in treating VHL-related neoplasms in a phase 2 study, which included 17 assessed pancreatic lesions, and there was high efficacy in reducing the size of PNETs.

The most promising therapeutic modalities for VHL-related manifestations are the HIF2 inhibitors and specifically belzutifan. VHL deficiency leads to uncontrolled HIF1 activity and pseudohypoxia. In light of the dependence of HIF1 on dimerization with HIF2, HIF2 inhibitors may reverse this effect.[71] HIF2 inhibitors have shown preliminary efficacy in VHL-related renal tumors.[72-74] In August 2021, the US Food and Drug Administration (FDA) approved the use of belzutifan for VHL-related tumors, including VHL-related PNETs. In regard to VHL-related PNETs, 120 mg of belzutifan once a day, administered orally, had an overall response rate of 83% for VHL-related PNETs.[75]

Cystic disease

Recommendation 6.3.1—Patients with pancreatic cysts who experience pain or an enteric/biliary obstruction should be considered for intervention. (C/2A)

Recommendation 6.3.2—Patients with pancreatic cysts in whom the diagnosis of a malignant or premalignant lesion cannot be excluded should be considered for intervention. (C/2A)

Recommendation 6.3.3—When the indication for intervention is a biliary/enteric obstruction, a bypass rather than resection should be preferentially considered to spare pancreatic parenchyma. (C/2A)

Recommendation 6.3.4—Parenchyma-sparing resection with regional lymphadenectomy is suggested for pancreatic cysts of an uncertain malignant status. (D/2A)

Recommendation 6.3.5—In patients with symptomatic cysts, cyst drainage or marsupialization may be considered. (D/2A)

Cystic diseases of the pancreas in patients with VHL are common. According to a systematic review, they are simple cysts in 47% of screened patients and serous cystadenomas in an additional 11% of screened patients. In this review, when cysts were present, they were multiple in up to 86% of patients. Symptomatology related to these cysts appears rare in surveillance series, whereas some studies have suggested up to a 16% likelihood of symptoms.[76] Autopsy series suggest that they may be found in up to 72% of patients with VHL.[77] These are essentially never malignant processes, and intervention should be based only on symptomatology or an inability to discern them from other lesions with malignant potential. Specifically, serous microcystic cystadenomas can mimic intraductal papillary mucinous neoplasms (IPMNs), mucinous cystic neoplasms, cystic adenocarcinomas, cystic PNETs, or solid pseudopapillary carcinomas. When symptoms occur, they are related to the cyst's mass effect and can include early satiety, pain, gastrointestinal obstruction, and jaundice. An institutional review at the Mayo Clinic from 2000 to 2016 identified 48 patients with VHL with cystic lesions of the pancreas.[78] They confirmed that multiple cysts were present in 87.5% of the patients. Simple cysts were found in 71%, serous cystadenomas were found in 29%, IPMNs were found in 10%, and 4% had

cystic PNETs. The presence of IPMNs and cystic PNETs underscores the importance of the appropriate diagnosis of these cysts and the occasional need for surgical intervention in cases of diagnostic uncertainty due to the premalignant nature of some of these lesions. Eight percent of the patients reported symptoms, including abdominal pain and pancreatic insufficiency. One patient required resection for symptoms of abdominal pain.[78]

When the indication for surgery is diagnostic uncertainty, resection is indicated. Parenchyma-sparing procedures such as enucleation should be preferentially used but require distance away from the pancreatic duct.

Lymph node dissection should be added to enucleation in cases of suspected malignancy. When the indication for surgery is biliary or gastrointestinal obstruction, surgical management options include endoscopic stent placement; surgical bypasses such as hepaticojejunostomy, hepaticoduodenostomy, and gastrojejunostomy; and only then resection.[13,79-82] Hammel et al[6] described an alternative treatment for simple cysts including radiological decompression and cyst marsupialization, and it appeared to have success in the 2 patients described. Another case report described a patient who underwent multiple pancreatic cyst fenestrations at the time of enucleation of a PNET, and it was complicated by severe postoperative ascites.[83]

UNSOLVED CLINICAL ISSUES AND FUTURE RESEARCH DIRECTIONS

In recent years, our understanding of the natural course of VHL-related PNETs has advanced pronouncedly since the reports of large, prospective natural history studies. Personalized patient surveillance is closer than ever on account of robust data on the risk for metastatic disease based on the lesion diameter and the germline VHL genotype. However, although follow-up based on these parameters is possible, no prospective validation studies have enabled interventions based on certain criteria because the benefit (or potential harm) has not been assessed yet.

The unique genetic and epigenetic landscape of VHL-related PNETs may explain the different disease course in comparison with sporadic PNETs and suggests a different response to medical interventions. Hence, more data are required on the efficacy of the various interventions for patients with VHL-related advanced PNETs, including tyrosine kinase inhibitors, mTOR inhibitors, and the much anticipated HIF2 inhibitors.

A collaborative approach to large-scale, retrospective studies of patients with VHL and even more—the prospective validation of previously reported data—are needed to improve the care that we can provide to our patients.

EXECUTIVE SUMMARY

Recommendation 1.1—Patients with VHL should be followed in a VHL CCC whenever feasible. (D/2A)

Recommendation 1.2—The initiation of screening for PNETs in patients with VHL should be no later than the age of 15 years. (C/2A)

Recommendation 1.3—Screening for pancreatic manifestations of VHL, when no lesions are present yet, should be performed in 2-year intervals. (C/2A)

Recommendation 1.4—In a patient with VHL and no pancreatic manifestations detected by the age of 65 years, no further screening for pancreatic manifestations is required. (C/2A)

Recommendation 1.5—Patients with VHL-related PNETs should be followed in a VHL CCC whenever feasible. (D/2A)

Recommendation 1.6—All patients with VHL and specifically patients with VHL-related PNETs should be in a VHLA-certified CCC. However, when routine surveillance in a VHL CCC is not feasible, the following criteria indicate a referral to a VHLA CCC for consultation: a patient with a solid pancreatic lesion with an imaging appearance typical of a PNET. The following criteria indicate a referral to a VHL CCC: a tumor diameter > 1.5 cm, any tumor growth between 2 scans, and/or suspected PNET metastases. (D/2A)

Recommendation 1.7—In women planning a pregnancy, pancreatic protocol MRI should be performed before the planned conception. (D/2A)

Recommendation 1.8—In a pregnant woman with no known PNETs, no pancreatic imaging is required during pregnancy. (D/2A)

Biochemical Biomarkers

Recommendation 2.1—Biochemical biomarkers are not useful for the screening of VHL-related PNETs. (D/2A)

Recommendation 2.2—Plasma pancreatic polypeptide levels may be used for assessing disease burden in patients with VHL-related PNETs. (C/2A)

Recommendation 2.3—Specific biochemical evaluations should be performed for VHL-related PNETs as clinically indicated. (D/2A)

Imaging Modality

Anatomical imaging

Recommendation 3.1.1—The anatomic imaging modality of choice for VHL-related PNETs should follow the imaging methods for sporadic PNETs, preferably gadolinium-enhanced pancreatic MRI with an early arterial phase. (C/2A)

Recommendation 3.1.2—In patients with VHL-related PNETs with contraindications for MRI, triple-phase pancreatic CT is preferable to other imaging modalities. (C/2A)

Recommendation 3.1.3—In light of the low risk of small PNETs in the context of VHL, nonpancreatic abdominal CT/MRI may be considered for the imaging of VHL-related PNETs if it is performed for the surveillance/screening of other VHL-related visceral manifestations. Pancreatic ultrasound has very low sensitivity for PNETs and is not useful for the screening/surveillance of VHL-related PNETs. (D/2A)

Recommendation 3.1.4—EUS is not recommended as a screening tool and may be used only when both contrast-enhanced MRI and CT are contraindicated, there is an indication for biopsy of a pancreatic lesion (see recommendation 6.1), or there is doubt about lesions seen on MRI/CT and management may be changed. (D/2A)

Functional imaging

Recommendation 3.2.1—In patients with VHL, ^{68}Ga-DOTATATE PET/CT imaging is highly sensitive for detecting PNETs, but it should be reserved for PNET staging before a planned intervention or for the characterization of a pancreatic mass with radiological characteristics that are not typical for a PNET (nonenhancing or rapidly growing lesions). (C/2A)

Recommendation 3.2.2—^{18}F-FDG PET/CT is not helpful for regular characterization of VHL-related PNETs or their risk stratification. (C/2A)

Recommendation 3.2.3—Functional imaging in patients with VHL should be interpreted with consideration of possible pitfalls of VHL by a radiologist or nuclear medicine specialist experienced in VHL. (D/2A)

Recommendation 3.2.4—^{68}Ga-DOTATATE PET/CT can be used to evaluate VHL-related pancreatic lesions when metastatic disease is suspected on the basis of anatomic imaging and/or before a planned intervention, but not for routine screening. (D/2A)

Indirect Risk Stratification of VHL-Related PNETs

Recommendation 4.1—In patients with VHL, a PNET whose largest diameter is <1.5 cm confers low risk, and if it is stable in 2 consecutive scans, it may be followed up every 2 years. (C/2A)

Recommendation 4.2—In patients with VHL, a PNET 3 cm in diameter or larger should be resected. (C/2A) PNETs that are 2 to 3 cm in diameter and located at the head of the pancreas should be considered for surgical resection. (D/2A)

Indications for Tissue Sampling of VHL-Related PNETs

Recommendation 5.1—In patients with VHL, solid pancreatic lesions with a radiological appearance typical of neuroendocrine tumors should not be biopsied. (C/2A)

Interventions

Interventions for localized high-risk lesions

Recommendation 6.1.1—Enucleation rather than formal resection should be attempted for lesions suitable for parenchyma-sparing procedures. (C/2A)

Recommendation 6.1.2—Total pancreatectomy should be used rarely, only when all other options for limited resection have been considered and only after the presence of distant metastases has been ruled out. (C/2A)

Recommendation 6.1.3—At the time of resection of a high-risk lesion, additional lesions less than 1.5 cm in diameter may not be resected. (C/2A)

Recommendation 6.1.9—Patients with high-risk lesions who are unable or unwilling to undergo surgical treatment may be considered for EUS ablation by either RFA or ethanol injection, preferably in a clinical trial. (D/2A)

Advanced disease

Recommendation 6.2.1—Systemic treatment for patients with advanced VHL-related PNETs should follow the guidelines for sporadic PNETs. (C/2A)

Recommendation 6.2.2—For patients with advanced, well-differentiated VHL-related PNETs, pazopanib may be considered. (C/2A)

Cystic disease

Recommendation 6.3.1—Patients with pancreatic cysts who experience pain or an enteric/biliary obstruction should be considered for intervention. (C/2A)

Recommendation 6.3.2—Patients with pancreatic cysts in whom the diagnosis of a malignant or premalignant lesion cannot be excluded should be considered for intervention. (C/2A)

Recommendation 6.3.3—When the indication for intervention is a biliary/enteric obstruction, a bypass

rather than resection should be preferentially considered to spare pancreatic parenchyma. (C/2A)

Recommendation 6.3.4—Parenchyma-sparing resection with regional lymphadenectomy is suggested for pancreatic cysts of an uncertain malignant status. (D/2A)

Recommendation 6.3.5—In patients with symptomatic cysts, cyst drainage or marsupialization may be considered. (D/2A)

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