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Evaluation, diagnosis and surveillance of renal masses in the setting of VHL disease

Jad Chahoud[1], **Melissa McGettigan**[2], **Nainesh Parikh**[2], **Ronald S. Boris**[3], **Othon Iliopoulos**[4], **W. Kimryn Rathmell**[5], **Anthony B. Daniels**[6], **Eric Jonasch**[7], **Philippe E. Spiess**[1] **on behalf of International VHL Surveillance Guidelines Consortium-Renal Committee**

[1]Department of Genitourinary Oncology, H. Lee Moffitt Cancer Center, 12902 Magnolia Dr., Tampa, FL 33612, USA

[2]Department of Diagnostic Imaging and Interventional Radiology, H. Lee Moffitt Cancer Center, 12902 Magnolia Dr., Tampa, FL 33612, USA

[3]Department of Urology, Indiana University School of Medicine, Indianapolis, IN, USA

[4]Center for Cancer Research, Massachusetts General Hospital Cancer Center, Harvard Medical School, Boston, MA 02139, USA

[5]Department of Medicine, Vanderbilt University Medical Center, Nashville, TN 37232, USA

[6]Division of Ocular Oncology and Pathology, Department of Ophthalmology and Visual Sciences, Vanderbilt-Ingram Cancer Center, Vanderbilt University Medical Center, Nashville, TN, USA

[7]Department of Genitourinary Medical Oncology, UT MD Anderson Cancer Center, 1515 Holcombe Ave, Houston, TX 77030, USA

Abstract

This brief report focuses on the evaluation and diagnosis of clinically localized renal masses in children and adults with Von Hippel–Lindau (VHL) disease. Counseling considerations pertinent to the urologists, medical oncologists, and multidisciplinary teams involved in the care of these patients are addressed. As practice patterns regarding the evaluation and management of VHL tumors can vary considerably, this report aims to provide guidance on some of the controversies associated with the diagnostic evaluation and initial management of localized renal masses in VHL patients.

Keywords

Renal mass; Von Hippel–Lindau; VHL; Renal cell carcinoma; RCC

✉Jad Chahoud, Jad.Chahoud@moffitt.org.

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Background

Von Hippel–Lindau (VHL) disease is a rare syndrome associated with multiple benign and malignant tumors, including renal cell carcinoma (RCC) [1–4]. The evaluation and management of these renal masses is of high importance, as these tumors decrease the life expectancy of VHL patients and impart significant distress to both patients and their families [5]. The impact of these renal masses on patient mortality is driven by end-stage renal failure secondary to surgical resections or the development of metastatic RCC. Therefore, a well-described approach that incorporates timely detection of renal masses and balances the appropriate timing for active surveillance and surgical resection is highly important for treating patients with VHL disease. Renal masses present at an early age as multicentric renal cysts of various complexity. These masses are found in approximately 42–63% of patients; the earliest age at presentation of this disease is noted to be 16 years, with a mean age of 37 years [6, 7]. Although the Bosniak criteria were developed to use radiographic parameters for the risk stratification of incidental cystic renal masses, these criteria should not be solely used to inform the management of renal cysts in patients with VHL Renal cysts in VHL disease are biologically different from incidental renal cysts, with the majority having foci of cellular malignancy in their walls that require active surveillance [8, 9]. RCC is diagnosed in approximately 40–70% of patients with VHL disease, with an estimated median age at the time of diagnosis of 39 years and the earliest reported age of presentation of 13 years [10, 11]. The diagnosis of RCC in VHL disease is predominantly of the clear cell histology, and patients with VHL type 1 and type 2B are at significantly increased risk of developing RCC compared to patients with other types [8, 12, 13]. The incidence and mortality of metastatic RCC have significantly decreased among patients with VHL disease since the implementation of routine abdominal imaging screening guidelines [7, 14]. Over the past two decades, a multitude of recommendations have been supported by different international groups to guide the screening, surveillance, and management of renal masses. When developing our renal mass screening and surveillance recommendations, we considered age-specific RCC risk, the youngest reported ages at presentation of RCC occurrence, the presumed growth rate, the most sensitive and specific imaging, and the potential clinical impact of tumor progression. These guidelines aim to standardize the screening recommendations for and the approach toward evaluating renal masses in VHL disease.

Methodology

Search methods

The International VHL Surveillance Guidelines Consortium-Renal Committee was composed of an inclusive group of experts from leading VHL Alliance Clinical Care Center members with expertise in genitourinary medical oncology, radiology, interventional radiology, and urological oncology. The Renal Committee first met to formulate important clinical questions for the screening, diagnosis, and surveillance of clinically localized renal masses in children and adults with VHL. A systematic literature search was then performed between August 2019 and December 2019, using the PubMed database, and a manual search of additional relevant articles identified from the reference section was conducted. The data

were sequentially abstracted by one investigator (JC), and all investigators then graded the strength of the published literature evidence as a group during multiple group meetings and categorized each of the renal committee recommendations.

Defining the panel recommendation categories based on the level of evidence and panel consensus level

To categorize the strength of evidence, the panel referred to the overall body of evidence available for a particular question, including individual study quality, consideration of study design, consistency of findings across studies, adequacy of sample sizes, and generalizability [15]. The panel categorized the strength of the body of evidence as either "high-level of evidence," in which the panel had a high level of certainty (ie, meta-analysis of randomized control trials, well-conducted and highly-generalizable randomized control trials, or exceptionally strong observational studies with consistent findings), or "low-level of evidence," in which the panel had a moderate or low level of certainty (ie, randomized control trials with weaknesses of procedure, poor generalizability, or extremely small sample sizes or observational studies that are inconsistent or have small sample sizes). Table 1 shows the criteria used to categorize the strength of the committee's recommendation, which was made on the basis of (1) the quality of supporting studies and (2) the panel's consensus on the benefit and risk of the intervention.

Routine screening evaluation

Renal mass screening imaging

The committee aimed to define recommendations to guide the use of appropriate renal mass–directed imaging, including modality type, timing to initiate, and frequency of screening imaging for patients with VHL disease. The committee also assessed this question for patients with VHL disease during pregnancy. We first summarized the previously published or endorsed screening recommendations for renal masses in patients with VHL disease (Table 2). We then summarized and discussed the reported data regarding (1) the earliest and latest age at which a patient receives a de novo RCC diagnosis, (2) renal mass kinetic growth rate, (3) renal mass size associated with metastatic RCC risk, (4) risk of renal mass diagnosis per VHL type, and (5) management of renal masses in patients with VHL disease during pregnancy.

Although the mean age at diagnosis of RCC is 37 years, the earliest reported age of renal tumor diagnosis in VHL is 16 years [6, 7]. The oldest age at which a patients with VHL is diagnosed with de novo RCC is 65 years [16]. There are no recommended guidelines on the screening and surveillance of patients with VHL disease before conception and during pregnancy. Specific imaging modality recommendations are summarized in Table 3 and in the following section on screening and surveillance recommendations. The panel agreed that due to a lack of scientific evidence, these recommendations are not specific to any type of VHL disease.

Screening and surveillance recommendations

- We recommend starting renal mass screening at the age of 15 years using MRI scans of the abdomen with or without contrast. Screening imaging should be continued every 2 years if no tumor is detected. If a tumor is detected, refer to the “Active Surveillance and Initial Management” section (level 2A).
- We recommend dedicated renal sequences be included in MRI screening if this is performed as part of the same study for RCC and pancreatic neuroendocrine tumors (level 2A).
- An MRI of the neuroaxis may be performed at the same time as performing an MRI of the abdomen and may be done under a single, long anesthesia event, especially with children. However, both the neuroaxis protocol and the abdominal protocols should be conducted consecutively. It is not recommended to evaluate the abdominal organs solely using a neuroaxis protocol (level 2A).
- The treating physician can consider alternating with a renal ultrasound if there are no concerning lesions identified on MRI imaging and if the patient has significant concerns or limitations in having an MRI scan of the abdomen with or without contrast (level 2A).
- Based on contraindications (metallic implants, renal failure, etc.), the following order of imaging priority applies: MRI (with and without contrast) > MRI (without contrast) > CT (with contrast) > CT (without contrast) > ultrasound (kidneys, adrenals, and pancreas only) (level 2A).
- Screening imaging should be performed before any planned conception if possible. If required, screening MRI scans performed during pregnancy should be done without contrast (level 2A).

Physical examination

A physical examination is warranted as part of the initial diagnostic workup for every VHL patient with a clinically local renal mass. Although it has a limited role in the diagnosis of clinically localized disease, a physical examination has value in distinguishing the signs and symptoms of advanced disease in patients with paraneoplastic syndromes. In patients with localized disease, a physical examination may also reveal unsuspected adenopathy, varicocele, or stigmata of chronic kidney disease (CKD), which could influence management decisions.

Laboratory evaluation

A laboratory evaluation is warranted as part of the initial diagnostic workup to evaluate kidney function, prognosis, and completeness of metastatic workup. Routine laboratory tests should include serum creatinine, liver enzymes, hemoglobin, leukocyte and platelet counts, lymphocyte-to-neutrophil ratio, lactate dehydrogenase, and serum-corrected calcium.

Active surveillance and initial management

The majority of VHL patients will be diagnosed with a renal mass on screening imaging, and the size, growth kinetics, and patient comorbidities will guide the initial management. A growing body of literature exists regarding active surveillance for VHL patients with clinically localized small renal masses measuring < 3 cm [20–23]. A number of retrospective studies and meta-analyses have evaluated the safety of AS among patients without VHL disease; these studies show that in well-selected patients, the risk of metastatic progression while on AS is < 2% beyond the first 3 years of follow-up [20–23]. Although prospective studies are currently limited by short follow-up durations, their findings appear to be in concordance with those of retrospective studies, [24–27] in which renal masses are evaluated every 3–6 months for 2 years to establish tumor growth kinetics and extended imaging intervals are performed once stability is confirmed. The committee evaluated multiple kinetic studies among VHL patients, [9, 28–32] VHL registry reports and committee expertise devised the following recommendations to guide the active surveillance and initial management of renal masses in patients with VHL.

Active surveillance and initial management recommendations

- For small renal masses defined as renal masses < 3 cm, we recommend active surveillance with MRI, with dedicated renal sequences every 3–6 months for the first year to determine the tumor kinetic growth rate (level 1A).
- If the tumor kinetic growth rate is within the expected rate of 2 to 4 mm per year, we recommend surveillance imaging every 6 months for the first year and every 12 months for the subsequent 2 years (level 2A).
- If a tumor is noted with a concerning kinetic growth rate of ≥ 5 mm per year, we recommend imaging every 3–6 months until the tumor is treated or demonstrates a stable expected growth rate (level 2A).
- If screening imaging demonstrates complete stability of monitored renal masses for 3 years, we would consider performing renal screening imaging every other year (level 2A).
- For renal masses > 3 cm, we recommend evaluation for surgery with nephron-sparing techniques, as they have been shown to preserve renal function (level 2A). Referral to academic center with expertise in VHL is preferred.
- Ablative techniques, including radiofrequency ablation and cryoablation, may be used in patients with smaller tumors who are at high operative risk (level 2A).
- Surveillance imaging should be performed before planned conception. An MRI without contrast should be used during pregnancy. Active surveillance is preferred for renal masses < 4 cm during pregnancy, when surgical intervention can be delayed until after delivery (level 2A).

Renal mass biopsy recommendations

A renal mass biopsy is rarely indicated in patients with confirmed VHL diagnosis, except for the following situations:

- Prior to percutaneous ablation or for suspected post-surgical/post-ablative recurrence
- Atypical radiographic features suggestive of alternate diagnosis to primary renal malignancy (eg, infection/inflammation)
- Patients with prior or concurrent extra-renal primary malignancy that could confound the diagnosis

For cystic lesions, we recommend avoiding a biopsy unless both growth kinetics and radiologic features are indeterminate. If at least 1 lesion is convincing for malignancy, then the need for biopsy is obviated.

If a biopsy is necessary, obtaining core needle sample(s) should be considered to improve diagnostic yield [33]. We recommend performing 18G core biopsies for solid renal masses to increase diagnostic yield and to inform molecular therapy if necessary [34]. Additionally, it is recommended to have a cytotechnologist on site at the time of biopsy to facilitate real-time assessment of the sample adequacy of these renal mass biopsies [35].

Patient counseling recommendations

- A urologist should lead the counseling process (agreed ± nephrology input if needed), consider all management strategies, and review the most common and serious urologic and non-urologic morbidities of each treatment pathway (level 2A).
- A multidisciplinary team should be included (level 2A).
- Provide counseling that includes current perspectives about tumor biology and a patient-specific risk assessment that is inclusive of tumor size and imaging characteristics (level 2A).
- Provide counseling on the importance of renal functional recovery related to renal mass diagnosis and management. Consider referral to nephrology in patients with a high risk of CKD progression or CKD. Such patients may include those with estimated glomerular filtration rate levels < 45 mL/minute/1.73 m^2, patients with diabetes with preexisting CKD, or those in whom estimated glomerular filtration rate levels are expected to be < 30 mL/minute/1.73 m^2 after intervention (level 2A).

Conclusion

We propose a renal tumor screening and surveillance paradigm for individuals with VHL disease based on specific risks. Although these recommendations are derived from existing guidelines, in considering screening onset and intervals, we placed high priority on the earliest ages of tumor onset, kinetic tumor growth rates, and the clinical impact of delayed

detection of RCC. Despite our reliance on available data, these guidelines remain largely based on expert opinion. Another limitation to this manuscript is that we did not conduct a formal Delphi consensus survey, instead we sued voting to categorize consensus between the panel memebers. Future efforts should incorporate a prospective assessment of clinical outcomes of individuals with VHL disease, who are screened according to these proposed guidelines. The main impediments to these avenues of future research are the relatively low prevalence of VHL disease and the prolonged duration over which associated tumors may arise. These characteristics of the condition make accruing enough numbers of affected patients for these studies challenging and success on conducting such studies will rely on collaborative multi-institutional efforts.

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Table 1

Category of evidence and panel consensus

Category	Description	Methodological quality of supporting evidence	Panel consensus
1A	Strong recommendation based on a high level of evidence	Meta-analysis of randomized control trials Randomized control trial Well-designed observational study with consistent findings	Based on a high level of evidence, there is uniform consensus that the intervention is appropriate
2A	Moderate recommendation based on a low level of evidence	Observational study with deficiency in design and without randomization Well-designed quasi-experimental study Case series	Based on a low level of evidence, there is uniform consensus that the intervention is appropriate
2B	Moderate recommendation based on a low level of evidence	Observational study with deficiency in design and without consistent findings Well-designed quasi-experimental study Case series	Based on a low level of evidence, there is consensus that the intervention is appropriate
3	Conditional recommendation	Any level of evidence	Based upon any level of evidence, there is major panel disagreement that the intervention is appropriate

Table 2

Summary table of RCC screening recommendations in VHL disease [7, 11, 14, 17, 18]

Publications on VHL RCC screening	Type of imaging recommended, frequency at which it is performed, and age at which screening begins	Stop routine screening	Pregnancy
Hes et al. [36] (Netherlands)	Annual abdominal ultrasound, age 10 y Every 2 years MRI abdominal, age ≥ 15 years (alternate ultrasound and MRI)	N/A	N/A
Binderup et al. [17] (Denmark)	First MRI abdominal between, age 8–14 years Annual abdominal imaging, age ≥ 15 years (ultrasound or MRI)	N/A	N/A
Kruizinga et al. [18]	Annual abdominal imaging, age ≥ 18 years	Age 34 years	N/A
VHL Alliance 2016 (United States)	Annual abdominal ultrasound, age 8–15 years Annual abdominal imaging, age ≥ 16 years (alternate ultrasound and MRI)	Age 65 years	N/A
Kidney cancer research network of Canada 2016	Annual abdominal ultrasound, age 8 years Every 2 years MRI with or without abdominal, age ≥ 15 years[a]	Age 65 years	N/A
NCI 2016 (adapted from VHL alliance 2016) (United States)	Annual abdominal imaging, age ≥ 16 years (ultrasound alternating with MRI)	N/A	N/A
Rednam et al. [7]	Annual MRI abdominal, age ≥ 10 years[a]	N/A	N/A

MRI magnetic resonance imaging, *N/A* not available

[a]Discrepancy was noted between in-text recommendations and table. In-text recommendation was used, as it included an explanation of the authors' consensus

Table 3

Summary recommendations by modality

Modality	Recommendation
Ultrasound	Abdominal ultrasound to include the kidneys with standard 2D (B-mode) grayscale and color Doppler images in sagittal and transverse planes showing upper/middle/lower poles
	Contrast enhanced ultrasound may have a role in confirming cysts or in improving visualization of the kidneys (not yet determined)
MRI	Abdominal MRI[a] (at least 1.5 T magnet). Standard T1, T2, and fat-suppressed images should be acquired. Pre- and post-contrast gadolinium-enhanced fat-suppressed T1-weighted images should be obtained in the axial plane (preferably including coronal or sagittal post-contrast images). Diffusion- weighted imaging may also be included
	Timing of contrast administration when imaging multiple organ systems together should be as follows: obtain non-contrasted images of the central nervous system and abdomen first, then give contrast using a power injector and perform multi-phase contrast-enhanced imaging of the abdomen, including pancreas and kidneys, during the late arterial phase and delayed venous phases. Finally, a late post-contrast imaging of neuroaxis is to be performed
	Abdominal MRI scans without contrast when gadolinium is contraindicated due to allergy or impaired renal function
	The American College of Radiology recommends following the same precautions with children as with adults for gadolinium contrast administration. Group II agents (Gado- benate dimeglumine, Gadobutrol, Gadoteri- dol) are generally considered safe, with few, if any, unconfounded cases of nephrogenic systemic fibrosis. The risks versus benefits of gadolinium agents should be discussed between the radiologist and clinician for patients with stage IV or V chronic kidney disease (who are not on chronic dialysis) [19].

[a] MRI surveillance for RCC and pancreatic neuroendocrine tumors may be part of the same study