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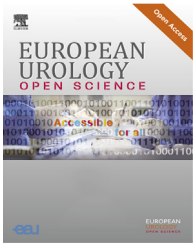

European Association of Urology

Renal Disease

Preoperative Renal Parenchyma Volume as a Predictor of Kidney Function Following Nephrectomy of Complex Renal Masses

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Abstract

Background: The von Hippel-Lindau disease (VHL) is a hereditary cancer syndrome with multifocal, bilateral cysts and solid tumors of the kidney. Surgical management may include multiple extirpative surgeries, which ultimately results in parenchymal volume loss and subsequent renal function decline. Recent studies have utilized parenchyma volume as an estimate of renal function prior to surgery for renal cell carcinoma; however, it is not yet validated for surgically altered kidneys with multifocal masses and complex cysts such as are present in VHL.
Objective: We sought to validate a magnetic resonance imaging (MRI)-based volumetric analysis with mercaptoacetyltriglycine (MAG-3) renogram and postoperative renal function.
Design, setting, and participants: We identified patients undergoing renal surgery at the National Cancer Institute from 2015 to 2020 with preoperative MRI. Renal tumors, cysts, and parenchyma of the operated kidney were segmented manually using ITK-SNAP software.
Outcome measurements and statistical analysis: Serum creatinine and urinalysis were assessed preoperatively, and at 3- and 12-mo follow-up time points. Estimated glomerular filtration rate (eGFR) was calculated using serum creatinine-based CKD-EPI 2021 equation. A statistical analysis was conducted on R Studio version 4.1.1.
Results and limitations: Preoperative MRI scans of 113 VHL patients (56% male, median age 48 yr) were evaluated between 2015 and 2021. Twelve (10.6%) patients had a solitary kidney at the time of surgery; 59 (52%) patients had at least one previous partial nephrectomy on the renal unit. Patients had a median of three (interquartile range [IQR]: 2–5) tumors and five (IQR: 0–13) cysts per kidney on imaging. The

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median preoperative GFR was 70 ml/min/1.73 m^2 (IQR: 58–89). Preoperative split renal function derived from MAG-3 studies and MRI split renal volume were significantly correlated ($r = 0.848$, $p < 0.001$). On the multivariable analysis, total preoperative parenchymal volume, solitary kidney, and preoperative eGFR were significant independent predictors of 12-mo eGFR. When only considering patients with two kidneys undergoing partial nephrectomy, preoperative parenchymal volume and eGFR remained significant predictors of 12-mo eGFR.

Conclusions: A parenchyma volume analysis on preoperative MRI correlates well with renogram split function and can predict long-term renal function with added benefit of anatomic detail and ease of application.

Patient summary: Prior to kidney surgery, it is important to understand the contribution of each kidney to overall kidney function. Nuclear medicine scans are currently used to measure split kidney function. We demonstrated that kidney volumes on preoperative magnetic resonance imaging can also be used to estimate split kidney function before surgery, while also providing essential details of tumor and kidney anatomy.

1. Introduction

Patients with von Hippel-Lindau disease (VHL) have a strong hereditary predisposition for recurrent multifocal renal tumors and cysts [1–3]. Judicious use of active surveillance, early detection, and surgical resection of renal tumors is critical to reduce the risk of renal impairment, surgical complications, and metastasis [4–6] In recent years, advances in nephron-sparing surgery and imaging techniques have greatly improved renal cell carcinoma (RCC) management strategies for VHL [7,8].

Initial diagnosis and subsequent surveillance are accomplished with routine cross-sectional imaging, utilizing either computed tomography (CT) or magnetic resonance imaging (MRI) [1,9]. Given that patients require frequent cross-sectional imaging for central nervous system, pancreatic, and renal tumors, MRI allows for reduced exposure of ionizing radiation. Additionally, MRI allows for added visualization of vascular involvement and improved sensitivity of extrarenal manifestation of VHL [4–6,9]. In patients with VHL, MRI-based studies of growth kinetics have also been established to monitor the size and trajectory of existing tumors prior to resection [10–12]. Nephron-sparing surgery is preferred when technically feasible to preserve renal parenchyma and delay the need for renal replacement therapy in hereditary kidney cancer [1,13]. Therefore, assessment of renal functional status and parenchymal reserve is particularly imperative in patients with VHL due to the high degree of disease recurrence and the anticipated need for reoperation. Mercaptoacetyltriglycine (MAG-3) renal nuclear scan has been used to estimate differential renal function, with ramifications for surgical decision-making. Specifically, its reporting of split renal function (SRF) may inform the surgeon about the function of residual nephron volume [14]. However, there are several limitations of MAG-3 scans. For example, there are inherent challenges related to cost and logistic planning prior to nephrectomy [15]. Additionally, there is some degree of operator-dependent variation with both scan acquisition and region-of-interest (ROI) segmentation, which can hinder the reproducibility of such scans for serial testing of recurrent masses [15–17]. Lastly, MAG-3 relies on radiotracer uptake and subsequent clearance, as opposed to anatomic detail to assess functional reserve prior to nephrectomy [16]. Any quantity of nonspecific radiotracer uptake can lead to false reporting of higher SRF readings in anatomically altered kidneys. Radiotracer uptake may also be impaired in renal insufficiency, leading to inaccurate reporting of SRF. Given these limitations, use of parenchymal volume assessment with preoperative MRI may offer more precision and accuracy than nuclear renal scans (NRSs) [18,19].

Several studies in the sporadic renal cancer population have demonstrated that direct parenchyma volume measurement using cross-sectional imaging with a CT scan offer high-quality anatomic detail that correlates well with renal function [18–22]. To our knowledge, there is no currently available validated measure of renal volume with MRI in patients with multifocal tumors and cysts, such as in VHL. MAG-3 inadequately provides anatomic detail and possesses limitations for the interpretation of renal function. Parenchymal volume segmentation with MRI offers an opportunity to assess functional risk prior to nephrectomy. Owing to the anticipated need for recurrent surgery on the same renal unit, the application of this MRI-based segmentation has considerable clinical utility for serial monitoring of renal reserve. Similar to the general population, these patients also have medical comorbidities that can interplay with renal function. This study seeks to address the oncologic, anatomic, and medical considerations that influence renal outcomes.

2. Patients and methods

2.1. Patient selection

We identified adult (≥18 yr) patients with VHL who underwent renal surgery at the National Cancer Institute from 2015 to 2020 with preoperative MRI with T2-weighted imaging, diffusion-weighted imaging, and T1 images in unenhanced and enhanced phases (ie, arterial, venous, and delayed).

The patient population for this study initially consisted of 116 individuals with manually segmented kidneys. Of them, three were excluded from the analysis due to missing data on both 3- and 12-mo postoperative estimated glomerular filtration rate (eGFR) follow-up, resulting in 113 patients with 3- or 12-mo follow-up. A single patient had 12-mo, but not 3-mo, postoperative eGFR follow-up. Thus, 112 patients with available eGFR postoperative follow-up data for both 3 and 12 mo were included in the final analysis. Out of these 113 patients, 89 had complete data for a multianalysis of surgical characteristics.

All patients had germline pathogenic variations in the *VHL* gene confirmed using Clinical Laboratory Improvement Amendments–approved assays. All patients provided written, informed consent and were prospectively enrolled in a screening, treatment, and genetic analysis clinical protocol approved by the National Cancer Institute Institutional Review Board.

2.2. Imaging and segmentation methods

MAG-3 nuclear scan ROIs were segmented for each kidney and corresponding background, positioned just outside the kidney lower pole or between the kidneys. Differential renal function was derived from time activity curves with subtracted background activity for both kidneys. SRF was estimated as relative MAG-3 uptake activity in the interval of 60–120 s after injection.

All MRI examinations were conducted on either a Philips MRI scanner (Philips Medical Systems International B.V., Best, The Netherlands) or a Siemens MRI scanner (Aera; Siemens Healthcare, Erlangen, Germany) with 1.5 or 3 tesla magnetic field strength, as described previously [10]. Kidneys were segmented manually on delayed phase of contrast-enhanced T1 scans and coregistered on precontrast, corticomedullary, and nephrographic phases using ITK-SNAP segmentation software (Fig. 1). Kidney parenchyma was defined as renal tissue not affected by tumors or cysts. Precontrast, corticomedullary, and nephrogenic phases were automatically coregistered to the excretory phase. Segmentations were reviewed and modified by an experienced fellowship-trained abdominal radiologist (A.A.M., 14 yr of experience). Volumetric data were extracted using segmented voxel dimension. Split renal volume (SRV) was calculated as follows:

$$Split\ \ renal\ \ volume_{Left} = 100 \times \frac{Parenchyma\ \ volume\ \ left\ \ (cc)}{Total\ \ parenchyma\ \ volume\ \ (cc)}$$

$$Split\ \ renal\ \ volume_{Right} = 100 \times \frac{Parenchyma\ \ volume\ \ right\ \ (cc)}{Total\ \ parenchyma\ \ volume\ \ (cc)}$$

Serum creatinine and protein dipstick were assessed 1 wk before surgery, and once again at 3- and 12-mo postoperative time points; eGFR was calculated using the creatinine-based, race-neutral CKD-EPI 2021 equation [23].

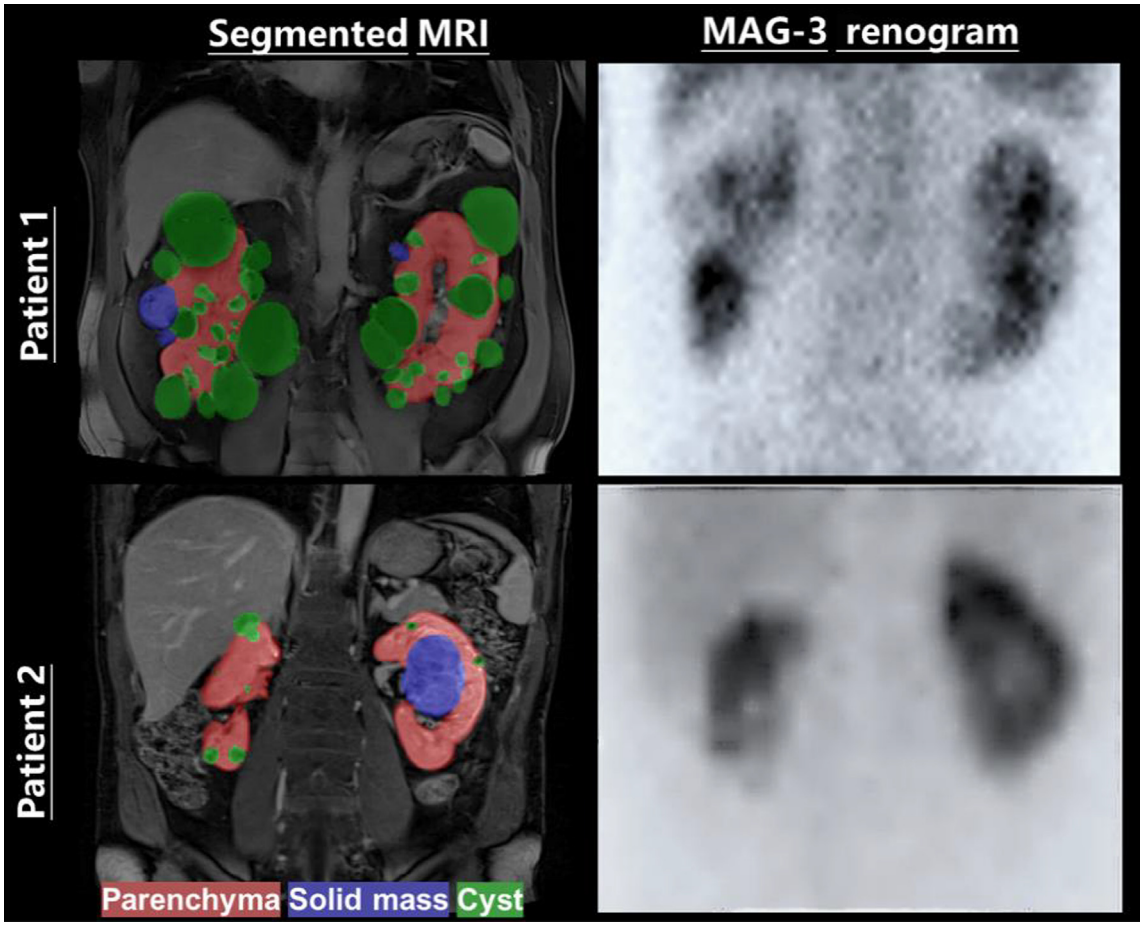


Fig. 1 – Example segmentation via ITK-SNAP on MRI and MAG-3 nuclear renal scan. MAG-3 = mercaptoacetyltriglycine; MRI = magnetic resonance imaging.

2.3. Statistical analysis

A statistical analysis was conducted using R Studio version 4.1.1 (R Foundation for Statistical Computing, Vienna, Austria). Counts and percentages were used to demonstrate all categorical variables, while median and interquartile range (IQR) were used to represent all numerical variables.

To determine the effect of patient and MRI characteristics on postoperative renal function, generalized linear models were utilized, with outcome defined as eGFR at 3 and 12 mo after nephrectomy. Based on these results, a subanalysis of postoperative renal function of patients without a solitary kidney was explored. Multivariable model coefficients were based on standardization of estimates, which were rescaled by dividing them by their standard deviation to reduce the effects of collinearity and compare effect magnitude [24,25]. A linear mixed-effect model was utilized to evaluate the 3- and 12-mo eGFR using repeated-measure analysis of variance to evaluate the time-dependent interaction of eGFR with total parenchyma volume [26,27]. This model was used to examine factors associated with postoperative renal function using postoperative eGFR as the outcome, and controlling for eGFR time point (3 vs 12 mo), total parenchyma volume, ipsilateral cyst and volume, ipsilateral mass count and volume, solitary kidney, hypertension, and diabetes as fixed effects, and patient as a random effect. The interaction between total parenchyma volume and solitary kidney was also evaluated using postoperative eGFR as the outcome, controlling for eGFR time point, total parenchyma volume, ipsilateral cyst and volume, ipsilateral mass count and volume, solitary kidney, hypertension, and diabetes as fixed effects, and patient as a random effect. Regression diagnostics were performed for all models, and significance was determined at $p < 0.05$.

Pearson correlations (R^2) were evaluated between split preoperative renal volume and preoperative split function from MAG-3 renal scans. Additionally, Welch's two-sample *T* test was used to determine statistical differences in parenchyma volume with respect to surgical and medical history.

Table 1 – Baseline patient and tumor characteristics

	N = 113
Age at surgery (yr)	48 (36, 58)
[1]Race, *n* (%)	
Asian	7 (6.2)
Black/African American	5 (4.4)
Multiracial	3 (2.7)
Native Hawaiian or Pacific Islander	2 (1.8)
White	91 (81)
Unknown race	5 (4.4)
[1]Gender, *n* (%)	
Male	65 (58)
Female	48 (42)
[1]BMI	29 (25, 34)
[1]Comorbidities, *n* (%)	
Hypertension (primary)	66 (58)
Diabetes (T1/T2)	20 (18)
Renal function	
[2]Preoperative GFR	70 (58, 89)
[1]Preoperative proteinuria (≥30 mg/dl), *n* (%)	17 (15)
[2]GFR at 3 mo	65 (52, 81)
[2]GFR at 12 mo	66 (53, 84)
[3]Ipsilateral MAG–3 split renal function	51 (46, 60)
[3]Ipsilateral MRI volumetric split renal function	54 (50, 67)
[1]Number of previous partial nephrectomies, *n* (%)	
0	51 (48)
1	34 (32)
2	18 (17)
3	3 (2.8)
[1]Solitary kidney, *n* (%)	12 (11)
No. of tumors identified on MRI	3 (2, 5)
Volume of tumors identified on MRI (cc)	44 (24, 105)
No. of cysts identified on MRI	5 (0, 13)
Volume of cysts identified on MRI (cc)	28 (5, 65)
Bilateral parenchyma volume (cc)	328 (259, 379)
Solitary kidney, *n* (%)	12 (11)
Largest tumor (cm)	3.5 (3.00, 4.50)
Highest Fuhrman grade, *n* (%)	
Grade 1	1 (1.3)
Grade 2	63 (84)
Grade 3	11 (15)
Grade 4	–
Grade 5	–

BMI = body mass index; GFR = glomerular filtration rate; MAG–3 = mercaptoacetyltriglycine; MRI = magnetic resonance imaging.

3. Results

A total of 113 VHL patients, comprising 56% males with a median age of 48 yr, were included in the analysis. Among the cohort, 12 (10.6%) patients had a solitary kidney at the time of surgery. Fifty-nine (52%) patients had a previous partial nephrectomy on the renal unit undergoing surgery (Table 1).

Within our cohort, 110 (97%) patients were treated by partial nephrectomy, and the remaining three patients underwent radical nephrectomy. On preoperative MRI, patients had a median of three (IQR: 2–5) tumors and five (IQR: 0–13) cysts per kidney (Table 1). SRF in MAG-3 studies before surgery and SRV on MRI were correlated with each other ($r = 0.848$, $p < 0.001$; Fig. 2).

Of our total patient population, 58% of patients had a history of hypertension and 18% had a history of type 2 diabetes prior to surgery (Table 1). The median body mass index at the time of surgery was 29 (25–34). The median preoperative eGFR was 70 (IQR: 58–89). The median 3- and 12-mo postoperative GFR were 65 (IQR: 52–81) and 66 (IQR: 53–84), respectively (Table 1). Of patients with previous radical nephrectomy, parenchymal volume was lower and trended toward significance ($p = 0.064$; Supplementary Fig. 1). Parenchymal volumes did not differ significantly by the number of previous partial nephrectomies on the renal unit undergoing surgery ($p = 0.6$; Supplementary Fig. 1). In the multivariable analysis of intraoperative characteristics of partial nephrectomies on postoperative renal function, a significant negative association was found between the number of tumors removed and 3-mo eGFR (β = –0.34, 95% confidence interval [CI]: –0.59, –0.09, $p = 0.01$), but this significance did not persist in the 12-mo analysis (Table 2). The remaining variables, including the surgical approach (open vs robotic), number of cysts removed, largest tumor size, clamp time, estimated blood loss, or surgical duration, were not significant for both 3- and 12-mo eGFR outcomes (Supplementary Table 1).

In the multivariable analysis of 3-mo eGFR, total parenchyma volume was not found to be a significant predictor of renal function (Table 3). However, the only significant predictor was preoperative eGFR ($\beta = 0.74$, 95% CI: 0.60, 0.88, $p < 0.001$). For the 12-mo eGFR, while adjusting for the same covariates, parenchyma volume demonstrated a significant association with renal function ($\beta = 0.19$, 95% CI: 0.02, 0.35, $p = 0.027$). Notably, preoperative eGFR remained a significant predictor of 12-mo eGFR ($\beta = 0.47$, 95% CI: 0.28, 0.66, $p < 0.001$; Table 3). In a subanalysis, when examining the predictors of 3- and 12-mo GFR, specifically

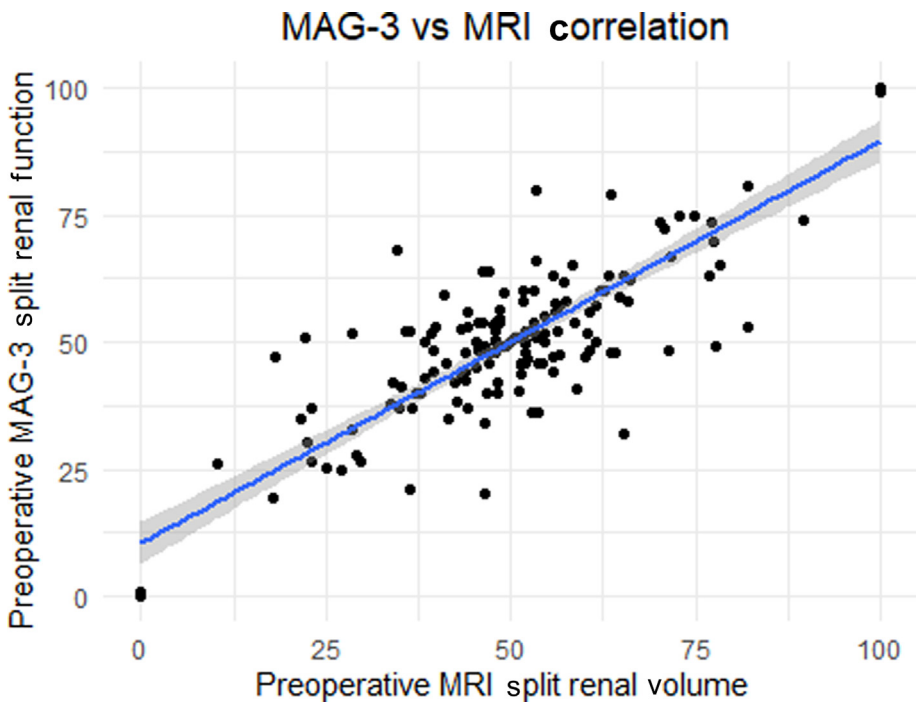


Fig. 2 – Correlation of split renal volume (SRV) using MRI-based renal parenchyma volume and split renal function (SRF) MAG-3 renal nuclear scan (Pearson coefficient: 0.85, R^2: 0.72, $p < 0.001$). MRI = magnetic resonance imaging.

Table 2 – Partial nephrectomy surgical characteristics

N = 95	
No. of tumors removed	4 (2, 8)
No. of cysts removed	0 (0, 3)
Clamp use	19 (20)
Clamp time (min)	22.5 (14, 35)
Estimated blood loss (ml)	1600 (525, 3000)
Surgery duration (min)	401 (307, 456)
Largest tumor (cm)	3.50 (3.00, 4.45)
Approach	
Robotic	77 (81)
Open	18 (19)

in patients who underwent partial nephrectomy and excluding those with a solitary kidney, the multivariable analysis showed that none of the variables, including parenchyma volume, ipsilateral cyst volume, ipsilateral mass volume, number of cysts, number of masses, hypertension, and diabetes mellitus, were significantly associated with renal function. However, preoperative eGFR remained a significant predictor of both 3- and 12-mo GFR (3 mo: $\beta = 0.82$, 95% CI: 0.68, 1.0, $p < 0.001$; 12 mo: $\beta = 0.47$, 95% CI: 0.26, 0.69, $p < 0.001$; Table 3).

On mixed-effect model examining preoperative predictors of postnephrectomy eGFR, total parenchyma volume had a significant positive association with postoperative eGFR ($\beta = 0.048$, 95% CI: 0.01–0.08, $p < 0.001$) when controlling for covariates (Supplementary Table 2). No significant interaction effect was observed between total parenchyma volume and the postoperative evaluation of eGFR at 3 versus 12 mo ($\beta = 0.01$, 95% CI: −0.03 to 0.05, $p = 0.6$). It was also demonstrated that solitary kidney ($\beta = -22.37$, 95% CI: −32.57, −12.17, $p < 0.0001$) and hypertension ($\beta = -7.71$, 95% CI: −14.34, −1.08, $p = 0.029$) were negatively associated with postoperative eGFR. There were no significant associations between eGFR and ipsilateral cyst volume, ipsilateral mass volume, number of tumors identified on MRI, number of cysts identified on MRI, or diabetes mellitus.

When evaluating the interaction between total parenchyma volume and solitary kidney in the context of the same covariates, no interaction effect was observed ($\beta = -0.028$, 95% CI: −0.19, 0.14, $p = 0.74$) when adjusting for covariates (Supplementary Table 2). Still, just as in the prior analysis, total preoperative parenchyma volume ($\beta = 0.054$, 95% CI: 0.022–0.085, $p = 0.0017$) and hypertension ($\beta = -7.71$, 95% CI: −14.28, 0.99, $p = 0.032$) were significant predictors of postoperative eGFR (Supplementary Table 2).

4. Discussion

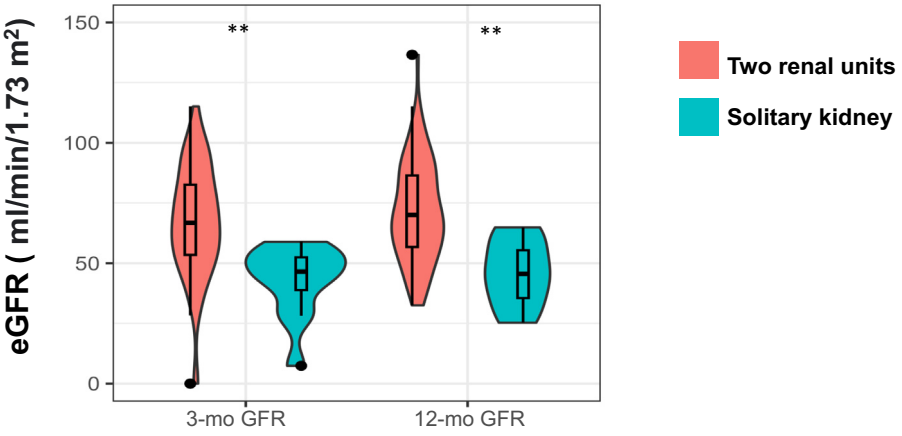
Patients with VHL undergo routine cross-sectional imaging across their lifetimes for tumor surveillance and surgical planning [1,2]. They are at a high risk of surgical chronic kidney disease due to tumor recurrence and the accompanying need for repeat extirpative surgery [1,21,28]. Previous studies have demonstrated the utility of imaging-based parenchymal volume estimation in surgical planning [19,21]. In the sporadic renal cancer population, studies have utilized parenchymal volume derived primarily from CT to assess renal functional reserve and predict new baseline GFR [10,12].

Findings from our study demonstrate that kidney volume prior to renal surgery is an independent predictor of postoperative renal reserve in the context of complex,

Table 3 – Multivariable analysis of preoperative characteristics associated with 3- versus 12-mo eGFR with subanalysis of excluding those with solitary kidney

	3-mo eGFR following partial nephrectomy (*N* = 112)			12-mo eGFR following partial nephrectomy (*N* = 113)			Subanalysis excluding solitary kidney: 3-mo eGFR following partial nephrectomy (*N* = 92)[a]			Subanalysis excluding solitary kidney: 12-mo eGFR following partial nephrectomy (*N* = 93)[a]		
	Beta	95% CI	*p* value	Beta	95% CI	*p* value	Beta	95% CI	*p* value	Beta	95% CI	*p* value
Total parenchyma volume (cc)	0.03	−0.09, 0.15	0.6	0.19	0.02, 0.35	0.027	0	−0.13, 0.13	–	0.21	0.02, 0.39	–
Ipsilateral cyst volume (cc)	−0.07	−0.19, 0.04	0.2	−0.03	−0.19, 0.12	0.7	−0.08	−0.20, 0.05	–	−0.09	−0.27, 0.09	–
Ipsilateral mass volume (cc)	−0.01	−0.13, 0.11	0.9	−0.03	−0.19, 0.13	0.7	0.03	−0.10, 0.17	–	−0.03	−0.22, 0.16	–
Number of cysts (cc)	−0.06	−0.17, 0.06	0.3	−0.09	−0.25, 0.06	0.2	−0.07	−0.19, 0.05	–	−0.12	−0.30, 0.05	–
Number of masses (cc)	0.05	−0.07, 0.18	0.4	0.16	−0.01, 0.32	0.064	0	−0.13, 0.13	–	0.16	−0.03, 0.35	–
Hypertension	−0.15	−0.39, 0.09	0.2	−0.24	−0.56, 0.08	0.14	−0.12	−0.38, 0.14	–	−0.23	−0.61, 0.15	–
Diabetes mellitus	−0.08	−0.37, 0.21	0.6	0.07	−0.32, 0.46	0.7	−0.19	−0.50, 0.12	–	−0.06	−0.52, 0.39	–
Preoperative eGFR	0.74	0.60, 0.88	<0.001	0.47	0.28, 0.66	<0.001	0.82	0.68, 1.0	–	0.47	0.26, 0.69	–
Solitary kidney	−0.5	−0.87, −0.13	0.0091	−0.66	−1.2, −0.16	0.01	–	–	–	–	–	–

CI = confidence interval; eGFR = estimated glomerular filtration rate.
[a] Please refer Supplementary tables to evaluate interaction effects of solitary kidney on parenchyma volume.



	Sum Sq	Mean Sq	F value	Pr(>F)
Solitary kidney	4298	4298	19.68	<0.0001
GFR time point	246	246	1.1265	0.3
Solitary kidney:GFR time point	3.3	3.3	0.015	0.9

Type III analysis of variance table with Satterthwaite's method

Fig. 3 – The eGFR compensation at 3 and 12 mo after nephrectomy. eGFR = estimated glomerular filtration rate; GFR = glomerular filtration rate; Sq = square.

multifocal tumor syndromes, even after controlling for previous surgery and medical history. This relationship persisted in our subanalysis of patients with two intact renal units undergoing partial nephrectomy. Previous radical nephrectomy was an independent factor at both 3- and 12-mo GFR time points, but did not demonstrate a significant interaction with total parenchyma volume (Fig. 3). This relationship is clinically expected, as a solitary kidney contributes to renal dysfunction and changes in parenchyma volume may represent compensatory hypertrophy that is corroborated in the sporadic RCC population [21].

MRI-based parenchyma volume assessment can offer several advantages, with minimal changes to the existing surgical decision-making workflow. At our institution, MRI is the preferred imaging modality for patients with hereditary kidney cancer, given its lack of ionizing radiation and excellent anatomic detail of local structures. Therefore, MRI-based parenchyma volume estimates may obviate the need for an additional testing in the form of an NRS and identify patients with imperative need for partial nephrectomy. Additionally, the performance of an NRS can be diminished in patients with renal insufficiency and its interpretation impaired in patients with altered renal anatomy. VHL patients, given their multiple tumors, cyst and defects from prior surgeries particularly benefit the increased anatomic detail gleaned from MRI and the lack of decreased performance in patients with chronic renal insufficiency. Preoperative ipsilateral SRF from NRSs and SRV from MRI-based segmentation were nearly identical (median 51% and 54%, respectively). An estimation of ipsilateral pre- or postoperative eGFR levels based on SRF from parenchyma volume correlated very strongly with those based on NRSs, as confirmed by high correlation coefficients (both $r \geq 0.85$, $p < 0.001$).

Our present study has limitations, including retrospective design and analysis limited to patients who had the required MRI and associated sequences for lesion detection. The study population is derived from a single, tertiary care institution with extensive experience with VHL and partial nephrectomy. Surgeon preference at this institution includes the frequent use of off-clamp nephrectomy and tumor enucleation with minimal margin. Additionally, there are operator-dependent variations that can be introduced during free-hand scripted segmentation. Although segmentations were confirmed by a single radiologist, user-dependent variation is still possible. Future directions include automation of parenchyma volume assessment, as well as renal cyst and mass volumes for surgical decision-making. Further investigation and validation of our study is necessary to optimize generalizability to other hereditary kidney cancers and cyst-predominant kidney disease.

5. Conclusions

Parenchyma volume analysis on preoperative MRI correlates well with renogram split function and can predict long-term renal function with added benefit of anatomic detail and ease of application.

Author contributions: Mark W. Ball had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Antony, Anari, Gopal, Ball, Malayeri.
Acquisition of data: Antony, Anari, Chaurasia, Firouzabadi, Homayounieh, Gautam.
Analysis and interpretation of data: Antony, Gopal, Turkbey, Gurram, Malayeri, Ball.
Drafting of the manuscript: Antony, Gopal, Anari.
Critical revision of the manuscript for important intellectual content: Chaurasia, Gopal, Kozel, Turkbey, Ball, Malayeri.
Statistical analysis: Antony, Anari.
Obtaining funding: Linehan, Ball, Malayeri.
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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.euros.2023.08.010.

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