

Natural History of Von Hippel-Lindau Disease-associated and Sporadic Clear Cell Renal Cell Carcinoma: a Comparative Study

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Research Article

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Abstract

Purpose: To compare the tumor growth kinetics between sporadic clear cell renal cell carcinoma (ccRCC) and Von Hippel-Lindau disease-associated renal cell carcinoma (VHL-associated RCC). To analyze predictive markers for the growth rate of these two types of RCC.

Methods: The clinical data of patients with renal tumors who received active surveillance were collected retrospectively. Immunohistochemical staining was utilized to analyze the expression levels of VHL, PBRM1, H3K36me3, and BAP1 in the postoperative specimens.

Results: The age of the VHL group was significantly younger than that of the sporadic group ($P < 0.0001$). The mean linear growth rate (LGR) was significantly faster in the sporadic group ($P = 0.0004$). The tumors of those in the sporadic group tended to have a higher histologic grade ($P = 0.0011$). In the sporadic group, tumor histologic grade was an independent predictor for rapid mean LGR ($P = 0.0022$). In the VHL group, tumor initial MTD was the only independent predictor for rapid mean LGR ($P = 0.0001$). Tumors with low VHL expression and negative PBRM1 expression showed a faster growth rate in the sporadic group ($P = 0.001$ and $P = 0.008$, respectively). The expression levels of the 4 biomarkers showed no impact on the tumor growth rate in the VHL group.

Conclusion: Sporadic ccRCC grew faster than VHL-associated RCC. High histologic grade, low VHL expression and negative PBRM1 expression were predictors of faster growth in sporadic ccRCC. A large initial MTD was a predictor of faster growth for VHL-associated RCC.

Introduction

Renal cell carcinomas (RCCs) represent approximately 3% of all cancers, of which clear cell renal cell carcinoma (ccRCC) is the most common histotype, representing 70–80% of cases (Deng and Melamed, 2012; Ljungberg et al., 2019). Although the vast majority of RCCs are sporadic, approximately 3% of RCCs are hereditary, and Von Hippel-Lindau disease-associated renal cell carcinoma (VHL-associated RCC) is a common hereditary RCC (Maher, 2018). The detection of renal masses (RMs) has increased worldwide over the past several decades due to the widespread use of advanced imaging examinations (Chow et al., 1999; Kümmerlin et al., 2008; Wagstaff et al., 2014). Of all the newly discovered RMs, the proportion of renal masses ≤ 4.0 cm (small RMs) is increasing (Chow and Devesa, 2008; Cooperberg et al., 2008; Hsieh et al., 2017). However, the mortality rate of RMs has not decreased as the operation rate of small RMs has increased, and the specific mortality rate of small RMs has even increased gradually (Hollingsworth et al., 2006; Van Poppel et al., 2007; Campbell et al., 2009; Sun et al., 2011; Scosyrev et al., 2014; Ljungberg et al., 2019). A number of studies have demonstrated that 20–30% of small RMs are confirmed to be benign tumors after surgery (Vasudevan et al., 2006; Crispen et al., 2008). In addition, Campbell et al. reported that in patients aged 75 years or older with small RMs, only patient age and comorbidities were independent predictors of overall survival outcomes, and surgical intervention did not provide significant survival benefits (Lane et al., 2010). Based on the above factors, urologists have paid increasing attention to researching the therapeutic effect of active surveillance (AS) of small RMs. To date, several researchers have assessed the natural history of sporadic ccRCC and VHL-associated RCC, but no consensus has been reached on the tumor growth rate and its predictive markers (Crispen et al., 2009; Zhang et al., 2009; Staehler et al., 2010; Mason et al., 2011; Zhang et al., 2012; Zhang et al., 2015; Peng et al., 2019; Schuhmacher et al., 2019). Few studies have explored the difference in natural history between the two types of RCC. In this study, sporadic ccRCC and VHL-associated RCC were analyzed together to compare the differences in growth rate between the two tumors. In addition, RCC is a highly heterogeneous tumor (2013; Hsieh et al., 2017). The TRACERx renal study showed, for the first time, that ccRCC can be divided into

several evolutionary subtypes, and the main basis for typing is mutations in the VHL, PBRM1, SETD2 and BAP1 genes (Edmunds et al., 2008; Turajlic et al., 2018). Schraml et al. verified that the four subtypes of ccRCC have differences in tumor stage and nuclear grade (Bihl et al., 2019). Therefore, we believe that it may be possible to predict the growth rate of ccRCC by determining whether there are mutations in these four genes. In the present study, the differences in the expression levels of VHL, PBRM1, H3K36me3 and BAP1 between the two groups were measured by immunohistochemical staining, and their relationship with the tumor growth rate was analyzed.

Materials And Methods

Patient selection

We searched the databases of renal tumors at the Institute of Urology, Peking University to identify patients who had renal tumors and received AS from January 1990 to December 2019. A total of 87 patients with 137 tumors were diagnosed with VHL-associated RCC; the mean age of all patients was 33 (range, 18–69) years, and more than half of the patients were men (50/87, 57.3%). The mean period of AS was 19.2 (range, 3–211.4) months. A total of 60 patients had 61 tumors that were considered sporadic ccRCC, and patients with pathologically confirmed non-ccRCC were excluded. The mean age was 55 (range, 26–81) years, and the majority of patients were men (47/60, 78.3%). The mean period of AS was 27 (range, 2–155) months. Delayed intervention, including radical nephrectomy and nephron-sparing surgery, was performed for all sporadic ccRCCs and 28 tumors the VHL-associated RCC group.

Methods

Patient characteristics, clinicopathological features, VHL disease information and natural tumor history were recorded. The linear growth rate (LGR) and volumetric growth rate (VGR) were used to evaluate the growth rate of tumors. The former refers to the growth rate of tumors on a certain diameter line, often expressed by the growth rate (cm/year) of the maximal tumor diameter (MTD) measured on the tumor cross section. The latter can also be described as the volume doubling time (VDT). Immunohistochemical staining was utilized to analyze the expression levels of VHL, PBRM1, H3K36me3, and BAP1 in the postoperative specimens. All results were evaluated with the assistance of urological pathologists blinded to the patients' clinical data. According to the comparison with normal renal tissue staining, the VHL, H3K36me3 and BAP1 staining results were used to divide the tumors into low expression and high expression groups, and PBRM1 staining results were used to divide the tumors into negative and positive groups.

Statistical analysis

The Wilcoxon rank-sum test was used to compare the two groups. Fisher's exact test was used to compare the expression levels of VHL, PBRM1, H3K36me3, and BAP1 between the two groups. Logistic regression and a general linear model were used to analyze the growth rate predictors. All data were recorded using Microsoft Office Excel and processed using SPSS V.22.0 statistical software. A P value < 0.05 was considered statistically significant.

Result

Patient characteristics and tumor features

The patient characteristics, clinicopathologic features and tumor growth rates of the two groups are summarized in Table 1. The VHL disease information of the VHL group is summarized in Table 2. Although male patients were predominant in both of the groups, there was a statistically significant difference in the sex ratio between the two

groups, which means that there were more male patients in the sporadic group ($P = 0.0087$). The median age of tumor onset in patients in the sporadic group was 55 (range, 26–81) years, while that of the patients in the VHL group was lower, at 33 (range, 18–69) years, and the difference between the two groups was statistically significant ($P < 0.0001$). Only one patient in the sporadic group had bilateral disease. The number of patients with bilateral disease in the VHL group was significantly higher than that in the sporadic group ($P < 0.0001$), with a total of 60 bilateral cases (69%). Regardless of whether the initial tumor size was measured by MTD or volume, there was no statistically significant difference between the two groups. The median AS times of the two groups were 27 (range, 2–155) months in the sporadic group and 19.2 (range, 3–221.4) months in the VHL group. The AS time of the sporadic group was significantly longer than that of the VHL group ($P = 0.001$). Regardless of whether tumor size was measured by MTD or tumor volume, the final average size of the tumor in the sporadic group was significantly larger than that in the VHL group (MTD, $P < 0.0001$; volume, $P < 0.0001$). It is worth mentioning that not all VHL-associated RCCs were resected during the study. We found that the AS time in the sporadic group was still longer than that in the VHL group when we included only patients with VHL-associated RCCs who underwent surgery; however, there was no significant difference in the final average tumor size between the sporadic group and the VHL group.

Table 1
Patient characteristics and tumor features

Variables	Over all	Sporadic group	VHL group	P
Sex				0.0087
Male (%)	97 (66.0)	47 (78.3)	50 (57.5)	
Female (%)	50 (34.0)	13 (21.7)	37 (42.5)	
Age, yr Median (range)	40 (18–81)	55 (26–81)	33 (18–69)	<0.0001
Side				<0.0001
Unilateral (%)	86 (58.5)	59 (98.3)	27 (31.0)	
Bilateral (%)	61 (41.5)	1 (1.7)	60 (69.0)	
Initial tumor size				
Median (range)				
MTD, cm	2.0 (0.3–7.8)	1.9 (0.3–6.7)	2.1 (0.4–7.8)	0.8739
Volume, cm ³	4.9 (0.03–252.7)	5.5 (0.58–135.8)	4.9 (0.03–252.7)	0.4715
Duration of AS, mo Median (range)	22.8 (2–221.4)	27(2–155)	19.2(3–221.4)	0.001
Final tumor size				
Median (range)				
MTD, cm	3.0 (0.5–14.1)	4.0 (1.4–11.8)	2.6 (0.5–14.1)	<0.0001
Volume, cm ³	17.4 (0.07–1493.0)	42.9 (1.6–895.4)	9.4 (0.07–1493.0)	<0.0001
LGR, cm/yr				0.0004
Mean ± SD	0.62 ± 0.92	0.91 ± 1.0	0.49 ± 0.84	
Median (range)	0.38 (-2.5–4.7)	0.61 (0–4.7)	0.30 (-2.5–4.7)	
VGR, cm³/yr				<0.0001
Mean ± SD	28.0 ± 68.0	37.2 ± 66.2	23.9 ± 68.6	
Median (range)	3.5 (-149.3–464.0)	9.3 (0.64–303.3)	2.0 (-149.3–464.0)	
VDT, days				0.1176
Mean ± SD	542.0 ± 943.7	673.9 ± 625.9	480.2 ± 1057	
Median (range)	443.2 (-2255.7–7115.7)	560.6 (32.5–3214.3)	425.6 (-2255.7–7115.7)	
Surgery				<0.0001
NSS (%)	41 (46.1)	19 (31.2)	22 (78.6)	

MTD, maximal tumor diameter; LGR, linear growth rate; VGR, volumetric growth rate; VDT, volume doubling time.

Variables	Over all	Sporadic group	VHL group	P
RN (%)	48 (53.9)	42 (68.8)	6 (21.4)	
Pathological stage				0.7913
T1 (%)	74 (83.2)	51 (83.6)	23 (82.1)	
T2 (%)	6 (6.7)	5 (8.2)	1 (3.6)	
T3 (%)	9 (10.1)	5 (8.2)	4 (14.3)	
Histological grade				0.0011
G1 (%)	40 (44.9)	20 (32.8)	20 (71.4)	
G2 (%)	43 (48.3)	36 (59.0)	7 (25.0)	
G3 (%)	6 (6.7)	5 (18.2)	1 (3.6)	
MTD, maximal tumor diameter; LGR, linear growth rate; VGR, volumetric growth rate; VDT, volume doubling time.				

Table 2
VHL disease information of VHL group

Variables	Amount, n (%)
VHL subtypes	
Subtype I	64(73.6)
Subtype II	23(26.4)
Mutations	
Missense mutation	40(46.0)
Truncating mutation	47(54.0)
mutation sites	
Exon 1	34(39.1)
Exon 2	20(23.0)
Exon 3	27(31.0)
Others	6(6.9)
Combined tumors	
Central nervous system hemangioblastoma (CHB)	41(47.1)
Retinal hemangioblastoma (RHB)	13(14.9)
CHB + RHB	13(14.9)
None	20(23.0)
Family history	
Yes	20(23.0)
No	59(67.8)
Not clear	8(9.2)

Table 3
Expression of VHL, PBRM1, H3K36me3, and BAP1 in the two groups

Biomarkers	Over all (n = 73)	Sporadic group (n = 56)	VHL group (n = 17)	P
VHL				0.7829
Low expression (%)	38 (52.1)	30 (53.6)	8 (47.1)	
High expression (%)	35 (47.9)	26 (46.4)	9 (52.9)	
PBRM1				0.4100
Negative (%)	28 (38.4)	20 (35.7)	8 (47.1)	
Positive (%)	45 (61.6)	36 (64.3)	9 (52.9)	
H3K36me3				1.0000
Low expression (%)	15 (20.6)	12 (21.4)	3 (17.6)	
High expression (%)	58 (79.4)	44 (78.6)	14 (82.4)	
BAP1				0.0574
Low expression (%)	17 (23.3)	10 (17.9)	7 (41.2)	
High expression (%)	56 (76.7)	46 (82.1)	10 (58.8)	

For patients who ultimately received surgical treatment, the proportion of nephron-sparing surgery was 31.2% in the sporadic group and 78.6% in the VHL group, and the difference was statistically significant ($P < 0.0001$). There was no difference in the tumor stage of all tumors that were finally removed between the two groups ($P = 0.7913$). The vast majority of tumors in the two groups were T1 stage (sporadic group, 83.6%; VHL group, 82.1%). The most common histological grade of the sporadic group was G2 (59.0%), and that of the VHL group was G1 (71.4%). There was a statistically significant difference in tumor histological grade between the two groups ($P = 0.0011$).

Comparison of tumor growth rate in the two groups

The tumor growth kinetics of the sporadic group and VHL group are presented in Table 1. The growth rate of tumors in the sporadic group was significantly faster than that of the VHL group (LGR, $P = 0.0004$; VGR, $P < 0.0001$). However, there was no significant difference in VDT between the two groups ($P = 0.1176$). The distribution of LGR, VGR and VDT in the two groups is presented in Fig. 1. The distribution of these three growth rate indicators in the sporadic group presented a “right-side tailing”. In contrast, the three indicators in the VHL group had an obvious central tendency.

Immunohistochemical analysis

The immunohistochemical staining results of the analyzed 4 biomarkers are shown in Fig. 2. The results of VHL, H3K36me3, and BAP1 staining were distinguished by low and high expression because all of the tumors expressed these markers, while PBRM1 staining was distinguished by negative and positive. The comparison of the expression levels of these 4 biomarkers in the two groups is presented in Table 2. Obviously, the expression levels of these 4 biomarkers were not significantly different between the two groups. A further log-linear model analysis showed that there was no correlation between any two of the four biomarkers between the two groups.

Influencing factors of tumor growth rate

In the sporadic group, age, sex, and tumor initial MTD were not correlated with the tumor growth rate, and only tumor histological grade was correlated with the LGR ($P = 0.0022$) and VGR ($P = 0.0043$), which means that the higher the tumor grade was, the faster the tumor growth rate was. However, initial MTD was correlated with VDT ($P = 0.0012$). In the VHL group, age, sex, histological grade, VHL subtypes, mutation types, combined tumors and family history were not associated with the tumor growth rate. However, initial MTD significantly affected the LGR ($P < 0.0001$) and VGR ($P < 0.0001$). In addition, only the combination of central nervous system hemangioblastoma or retinal hemangioblastoma was correlated with VDT ($P = 0.0407$).

The effects of the expression of VHL, PBRM1, H3K36me3, and BAP1 on tumor LGR, VGR and VDT are presented in Table 4. In the VHL group, the expression levels of the 4 biomarkers were not correlated with the tumor growth rate. In the sporadic group, the expression levels of H3K36me3 and BAP1 were not correlated with the tumor growth rate. However, the expression of VHL was correlated with the tumor LGR ($P = 0.001$), VGR ($P = 0.021$) and VDT ($P = 0.002$), and low expression of VHL promoted the tumor growth rate. The expression of PBRM1 was correlated with the tumor LGR ($P = 0.008$) and VDT ($P = 0.047$) and had a weak correlation with VGR ($P = 0.051$). Tumors with negative expression of PBRM1 grew faster. We further performed a subgroup analysis, which classified low VHL expression with negative PBRM1 as group 1, low VHL expression with positive PBRM1 and high VHL expression with negative PBRM1 as group 2, and high VHL expression with positive PBRM1 as group 3. The tumor growth rates of the three groups are shown in Fig. 3. Obviously, for LGR and VGR, the relationship between the three groups was group 1 > group 2 > group 3. For VDT, the relationship between the three groups was group 3 > group 2 > group 1. There was a statistically significant difference between group 1 and group 3 (LGR, $P = 0.000$; VGR, $P = 0.012$; VDT, $P = 0.003$). There was a significant difference between group 2 and group 3 (LGR, $P = 0.004$; VDT, $P = 0.014$; but VGR, $P = 0.058$). However, there was no significant difference between group 1 and group 2. In summary, we conclude that both low expression of VHL and negative PBRM1 expression are predictors of the rapid growth of sporadic ccRCC.

Table 4
The effect of four biomarkers expression on tumor growth rate.

		VHL		PBRM1		H3K36me3		BAP1	
		low	high	negative	positive	low	high	low	high
Sporadic group (n = 56)	LGR (cm/yr)	0.74	0.37	0.77	0.42	0.62	0.58	0.58	0.61
	median (range)	(0.12–4.74)	(0–1.53)	(0.22–3.60)	(0–4.74)	(0.20–2.80)	(0–4.74)	(0.17–4.74)	(0–3.80)
	P	0.001		0.008		0.348		0.381	
	VGR (cm ³ /yr)	61.3	6.43	26.8	7.74	14.5	9.96	5.02	17.5
median (range)	(0.73–303.3)	(0.65–42.9)	(0.79–303.3)	(0.65–245.8)	(0.75–303.3)	(0.65–274.0)	(0.79–205.8)	(0.65–303.3)	
P	0.021		0.051		0.466		0.295		
VDT (days)	322.9	658.0	377.6	587.7	378.3	573.9	362.5	573.3	
median (range)	(32.5–2633.4)	(157.7–1948.1)	(69.0–1518.9)	(32.5–2633.4)	(117.6–1518.9)	(32.5–2633.4)	(32.5–1581.3)	(69.0–2633.4)	
P	0.002		0.047		0.358		0.285		
VHL group (n = 17)	LGR (cm/yr)	0.42	0.72	0.50	0.64	0.29	0.95	0.29	0.68
	median (range)	(-0.41–1.89)	(0.21–2.07)	(-0.41–1.89)	(0.21–2.07)	(-0.41–0.36)	(-0.25–2.07)	(-0.41–2.07)	(0.24–1.89)
	P	0.423		0.481		0.068		0.270	
	VGR (cm ³ /yr)	8.11	10.4	5.32	10.4	6.22	21.5	6.22	10.2
median (range)	(-9.42–159.6)	(2.39–87.6)	(-9.42–159.6)	(2.39–87.6)	(-9.42–10.0)	(-3.41–159.6)	(-9.42–72.6)	(3.35–159.6)	
P	0.963		0.321		0.300		0.364		
VDT (day)	289.0	284.0	240.8	424.6	851.3	280.7	233.9	366.4	
median (range)	(-1015.5–1053.2)	(165.4–1197.6)	(-1015.5–1197.6)	(173.7–1047.9)	(-785.6–1053.2)	(-1015.5–1197.6)	(-1015.5–1053.3)	(165.4–1197.6)	
P	0.815		0.423		0.591		0.364		

LGR, linear growth rate; VGR, volumetric growth rate; VDT, volume doubling time.

Discussion

The gold standard for RM treatment is surgical resection(Campbell et al., 2009; Ljungberg et al., 2015). However, with the advancement of modern medicine, the increase in the detection rate and operation rate of small RMs has not reduced the mortality rate(Hollingsworth et al., 2006; Sun et al., 2011). Therefore, AS was recommended as a strategy

for managing small RMs(Campbell et al., 2009; Ljungberg et al., 2015). However, there have been few studies on the natural history of sporadic ccRCC and VHL-associated RCC reported in the global literature. The present study aimed to compare the natural history of sporadic ccRCC and VHL-associated RCC combined with immunohistochemical analysis. Compared to sporadic ccRCC, we found that patients with VHL-associated RCC were younger, more likely to develop bilateral tumors, and had a lower histological grade at onset, which was consistent with the conclusions of previous studies(Maher et al., 2011; Ben-Skowronek and Kozaczuk, 2015). In addition, our study revealed that the sex ratio in patients with VHL-associated RCC was more equal, while the proportion of males in the sporadic group was higher, which was closer to the sex ratio of sporadic ccRCC shown in a previous large-scale epidemiological study(Siegel et al., 2020). There was no significant difference in the initial tumor size between the two groups, regardless of whether the tumor size was measured by MTD or volume. The sporadic group received AS for a longer period than the VHL group. We believe that this might be due to selection bias, as most sporadic ccRCC patients receiving AS had surgical contraindications. This conjecture is supported by the fact that the final average tumor size of the sporadic group at the last follow-up was larger than that of tumors in the VHL group.

A previous meta-analysis showed that the mean LGR of sporadic small RMs was 0.28 cm/yr, and the growth rate of RCC diagnosed pathologically was approximately 0.4 cm/yr(Chawla et al., 2006). Our study only included patients diagnosed with ccRCC through pathology; the mean LGR was 0.91 cm/yr, and the median was 0.61 cm/yr. This result more accurately reflects the growth rate of ccRCC. In the VHL group in our study, the mean LGR was 0.49 cm/yr, and the median was 0.30 cm/yr, which was similar to that described in previous reports(Jilg et al., 2012; Zhang et al., 2012). We further compared the tumor growth rate of the two groups and found that the mean LGR and mean VGR of the sporadic group were significantly faster than those of the VHL group, which was consistent with previous findings that VHL-associated RCC is more indolent(Neumann et al., 1998; Zhang et al., 2012). We also found that VHL-associated RCC had zero or even negative growth, which was not observed for sporadic ccRCCs. Compared with sporadic ccRCC, the LGR distribution of VHL-associated RCC was more concentrated, which indirectly indicates that the heterogeneity of sporadic ccRCC was greater than that of VHL-associated RCC.

Mutations in VHL, PBRM1, SETD2, and BAP1 cause loss of function of the encoded proteins in ccRCC. A study based on whole-genome sequencing found that PBRM1 and BAP1 mutations are largely mutually exclusive in ccRCC(Peña-Llopis et al., 2012). Schraml et al. reported that there was a significant correlation between the expression levels of PBRM1, H3K36me3 and BAP1 based on the tissue chip technique(Bihr et al., 2019). However, our study used immunohistochemical staining to analyze the expression levels of VHL, PBRM1, H3K36me3, and BAP1 in all tumors of the two groups and revealed that there was no correlation between any of them. We hypothesize that the reason for the different results in our study is that immunohistochemistry cannot accurately reflect gene mutations, and the results of immunohistochemical staining were also affected by the time of tissue fixation and conditions of wax block storage.

Which factors are predictors of the tumor growth rate have always been the focus of research on the natural history of renal tumors, but there are still no widely accepted conclusions. This study revealed that in the sporadic ccRCC group, the patient's age, sex, and initial size of the tumor had no effect on the tumor growth rate, which was consistent with the results of most other studies, including our previous studies(Chawla et al., 2006; Crispen et al., 2008; Zhang et al., 2015). However, histological grade was correlated with the tumor growth rate, and the higher the grade was, the faster the growth rate was. In the VHL group, the initial size of the tumor was an influencing factor for the growth rate, and other VHL disease-related factors, such as subtypes and mutation types, were not correlated with the tumor growth rate. We believe that these differences further prove that VHL-associated RCC and sporadic ccRCC are two different tumors, even though they are both classed as ccRCCs by histology. Loss of VHL protein is

known to contribute to the initiation and progression of VHL disease-associated tumors as well as certain sporadic tumors, including ccRCC. Schraml et al. reported that PBRM1 was the second most frequently mutated gene in RCC after VHL, and loss of PBRM1 was correlated with advanced tumor stage, low differentiation grade and worse patient outcome (Pawłowski et al., 2013). However, Kilic et al. reported that weak PBRM1 and VHL expression was significantly associated with higher Fuhrman grade, but only weak VHL expression was associated with a higher pT stage and with decreased patient overall survival times, but PBRM1 expression did not affect the overall survival outcome (Högner et al., 2018). Our study revealed that the expression of VHL and PBRM1 was correlated with tumor histological grade; lower VHL expression was associated with higher tumor histological grade, but this trend was not observed for PBRM1. Moreover, we found that low VHL expression and negative PBRM1 were both correlated with the tumor growth rate and may have had additive effects in sporadic ccRCC. It is possible that VHL and PBRM1 will become sensitive predictors of the growth rate of sporadic ccRCC.

Due to the limitations of retrospective design and sample size, prospective studies with a larger sample size are required to verify these results. Moreover, this study only qualitatively measured the protein expression level through immunohistochemistry; thus, the results remain to be further verified at the quantitative level.

Conclusions

Sporadic ccRCC grew faster than VHL-associated RCC and showed more variation in growth rate. The expression levels of VHL, PBRM1, H3K36me3, and BAP1 were not different between sporadic ccRCC and VHL-associated RCC. High histologic grade, low VHL expression and negative PBRM1 expression were predictors of faster growth in sporadic ccRCC. A large initial MTD was a predictor of faster growth for VHL-associated RCC.

Declarations

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Conflict of interest:

The authors declare that they have no conflict of interest.

Availability of data and material:

The datasets analysed during the current study are available from the corresponding author on reasonable request.

Code availability:

Not applicable.

Author contributions:

Xuesong Li and Kan Gong contributed to the study conception and design. Material preparation, data collection and analysis were performed by Jie Wang, Lei Zhang, Jianhui Qiu and Ziao Li. The first draft of the manuscript was

written by Jie Wang and Lei Zhang and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Ethics approval:

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Figures

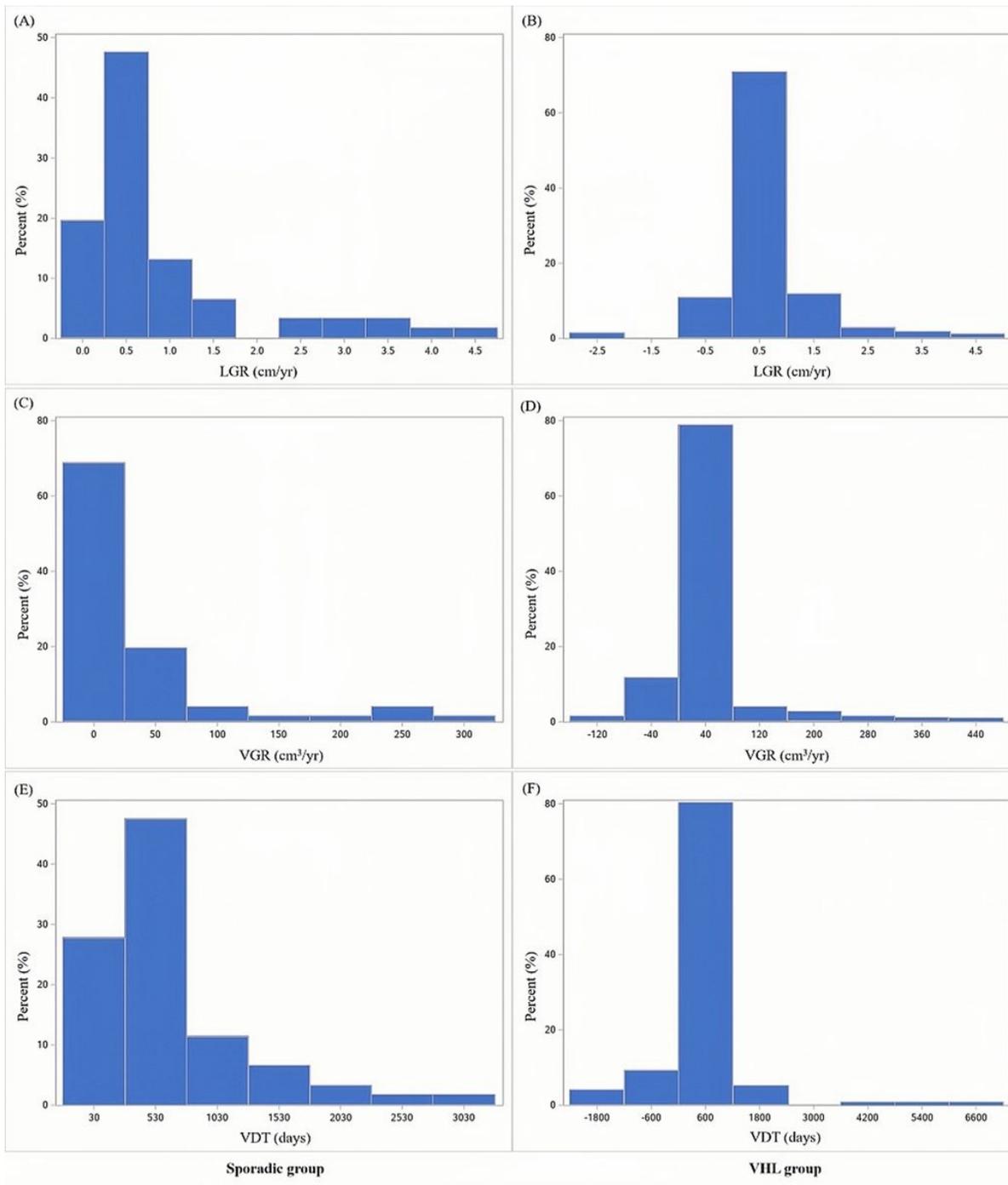


Figure 1

The distribution of tumor growth rate in the two groups: (A) and (B) are the distribution histograms of LGR in the sporadic group and VHL group, respectively; (C) and (D) are distribution histograms of the VGR in the sporadic group and VHL group, respectively; (E) and (F) are the distribution histograms of VDT in the sporadic group and VHL group, respectively.

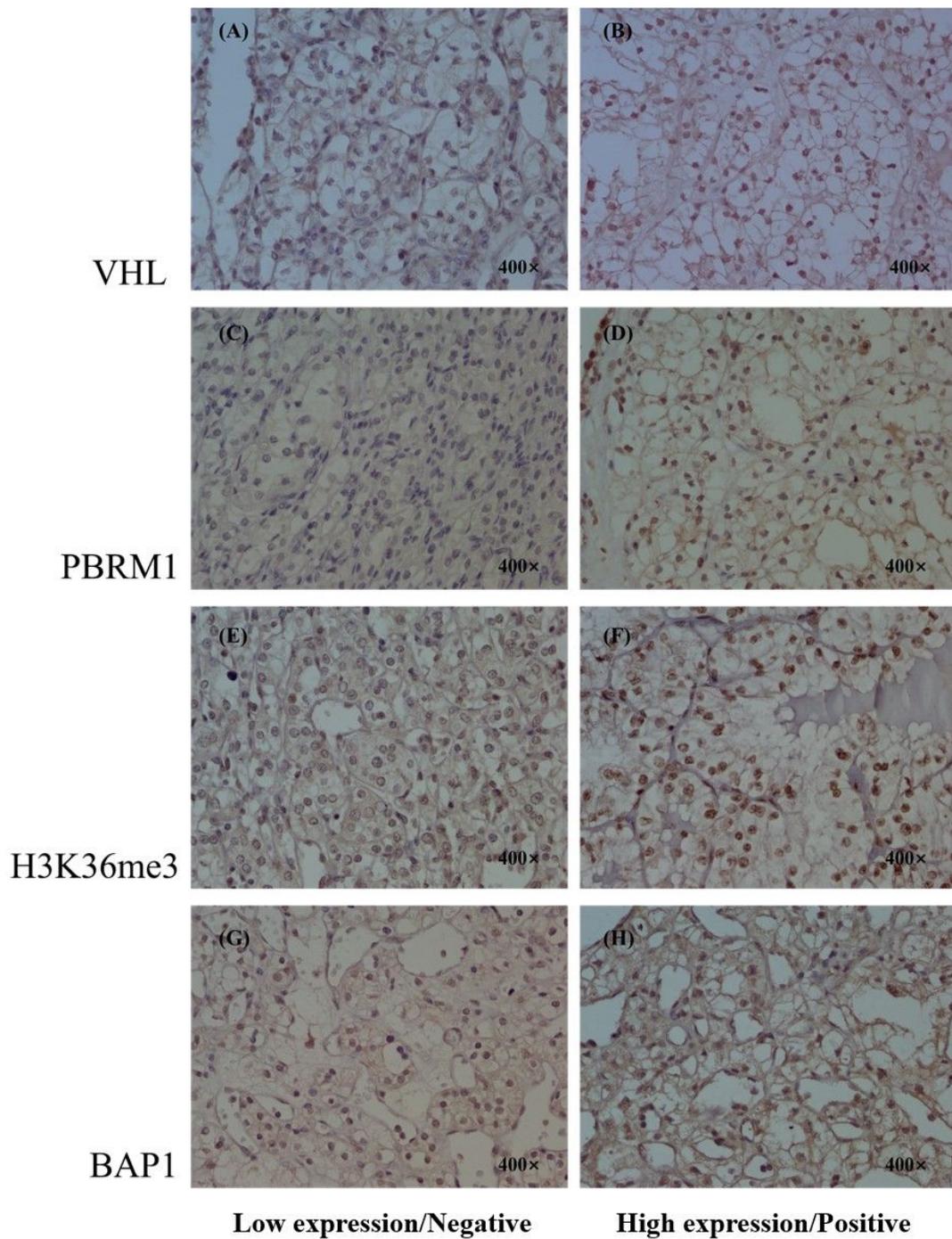


Figure 2

Schematic diagram of the results of VHL, PBRM1, H3K36 me3, and BAP1 staining. (A) The low expression of VHL. (B) The high expression of VHL. (C) The negative of PBRM1. (D) The positive of PBRM1. (E) The low expression of H3K36 me3. (F) The high expression of H3K36 me3. (G) The low expression and of BAP1. (H) The high expression of BAP1.

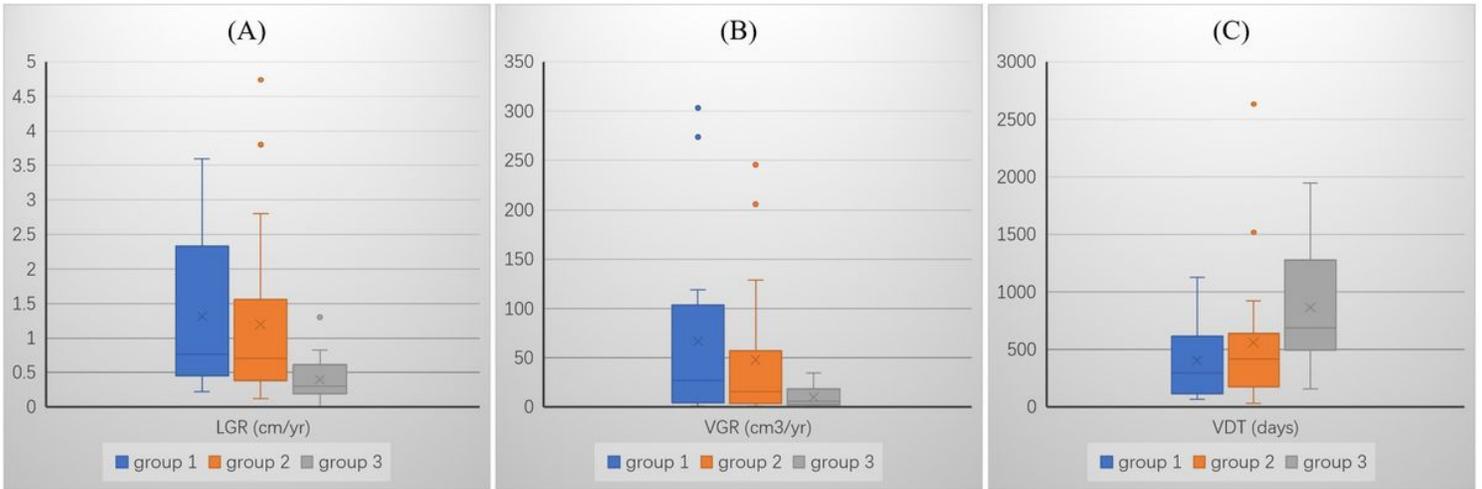


Figure 3

Comparison of the sporadic ccRCC growth rate in the three groups. Group 1 included patients who had low VHL expression and were negative for PBRM1. Group 2 included patients who had low VHL expression with positive PBRM1 and high VHL expression with negative PBRM1. Group 3 included patients who had high VHL expression and were positive for PBRM1. (A) The comparison of the median LGR between the three groups was group 1>group 2>group 3. (B) The comparison of median VGR between the three groups was group 1>group 2>group 3. (C) The comparison of median VDT between the three groups was group 3>group 2>group 1.