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Research Article

Clinicopathological Features and Prognosis of Renal Cell Carcinoma in Japanese Patients with von Hippel-Lindau Disease

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Abstract

Purpose: We analyzed the clinicopathological features and prognosis of renal cell carcinoma (RCC) in Japanese patients with von Hippel Lindau (vHL) disease.

Patients and methods: The subject was 52 vHL patients with kidney tumors. Clinical, pathological, and survival data were collected for each patient. Overall survival was calculated from the date of initial diagnosis of kidney tumor to the date of death as a result of any cause or was censored at the date of the last follow-up. Median follow-up duration of all 52 patients was 79 months.

Results: Of 52 patients, bilateral tumor was observed in 33 patients and multifocal tumors in 40. Median tumor size of largest tumor in each patient was 3.3 cm in diameter. With regard to the treatment, most patients underwent nephron-sparing surgery. All patients had clear cell carcinoma. Although half of patients experienced local recurrences, the 10-year overall survival was 82%. At last follow-up, four patients died of RCC, 5 patients died of central nervous system hemangioblastoma, and 1 died from gastric cancer.

Conclusions: RCC in VHL patients differs from sporadic RCC in clinical features and should be carefully treated and followed closely. Appropriate decisions regarding treatment of RCC in vHL patients should be made from not only oncological outcomes but also long-term renal function outcomes and QOL.

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INTRODUCTION

von Hippel-Lindau (vHL) disease is genetically transmitted in autosomal dominant fashion with high penetrance but variable expression. Manifestations of this disease include retinal angiomas, central nervous system hemangioblastoma, renal cysts, renal cell carcinoma (RCC), pancreatic cysts and pheochromocytoma [1,2]. Renal cell carcinoma is of major importance in vHL disease, and it is a major cause of death [3,4]. The prevalence and clinical features of RCC in vHL patients have been well investigated in Western countries. Neumann et at reported that RCC in patients with vHL disease had a significantly better survival, compared with sporadic RCC [5]. Furthermore, metastases were observed only in tumors larger than 7 cm in diameter. On the other hand, there are few studies on clinical status of RCC in Asian patients with vHL disease [6]. In this study, we analyzed the clinical and pathological features and prognosis of RCC in Japanese patients with vHL disease.

MATERIALS AND METHODS

From 1981 to 2002, 52 patients with vHL disease and kidney tumors on computerized tomography (CT) or MRI were encountered by screening affected kindred or retrospective review of medical record at 29 hospitals in Japan (Table 1). There were 32 male and 20 female and median age at diagnosis of the first kidney tumors in these patients was 42 years (range 20-76). The mostly affected age of the initial diagnosis of RCC was between 30 and 34 years (Figure 1). Of these, 38 patients had a positive family history of vHL disease. Extrarenal manifestations of vHL disease included hemangioblastoma of the central nervous system in 44, retinal angioma in 18, spinal hemangioblastoma in 23, pheochromocytoma in 4, pancreatic cystoadenoma in 32, and epididymal cystoadenoma in 13. Pancreatic neuroendocrine tumor was not clinically diagnosed in all patients evaluated in the present study.The study was performed after approval by Internal Research Board of the participating institutes.

Table 1: Clinical characteristics of 52 vHL patients with RCC.

Median age at diagnosis of RCC (range)	42 years (20-76)
Ratio male: female	32:20:00
Positive family history	38 (73%)
Other vHL organ manifestation	
CNS	44 (85%)
Retina	18 (35%)
Spine	23 (44%)
Pancreas	32 (62%)
Adrenal (pheochromocytoma)	4 (8%)

Abbreviations: CNS: central nervous system

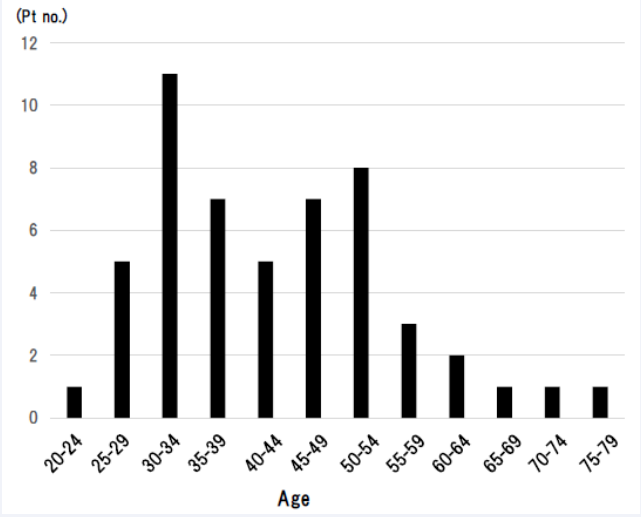

Figure 1 Distribution of age at initial diagnosis of RCC in the 52 vHL patients.

Table 2: Tumor characteristics on initial RCC in 52 vHL patients.

Incidental finding	38 (73%)
Median tumor size (cm)	3.3 (1.1-11)
No. bilateral tumor	33 (63%)
No. multiple tumor	40 (77%)
No. pT1 (a+b)*	37 (80%)
No. G1+2*	36 (78%)
No. Nodal disease	2 (4%)
No. Metastatic lesion:	3 (6%)

*Of 46 patients who were treated with surgery

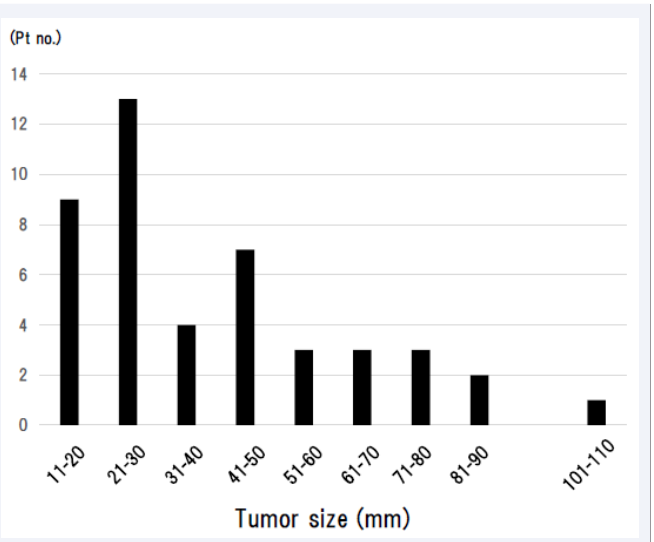

Figure 2 Distribution of largest tumor size of RCC in the 52 vHL patients.

Clinical, pathological, and survival data were collected for each patient. The diagnosis of kidney tumor was initially made by abdominal CT or MRI. For the detection of distant metastasis, chest XP, CT and bone scintigraphy were performed. The stage was assigned according to the 1997 TNM classification of the Union Internationale Contre le Cancer (UICC). The pathological grade and histology were determined according to the General Rules for Clinical and Pathological Studies on Renal Cell Carcinoma in Japan. Follow-up included physical examination, renal function test, chest XP and CT, and, abdominal ultrasonography, CT or MRI to detect any occult recurrence or metastasis.

Patient characteristics were shown as median (range) for continuous variables and number of patients with percentage for

categorical variables. Overall survival (OS) was calculated from the date of initial diagnosis of kidney tumor to the date of death as a result of any cause or was censored at the date of the last follow-up. Cancer-specific survival (CSS) was calculated from the date of initial diagnosis of kidney tumor to the date of death with RCC or was censored at the date of the last follow-up. Survival distributions were estimated using the Kaplan-Meier method. For all statistical analyses, $p<0.05$ was regarded as significant.

RESULTS AND DISCUSSION

At initial diagnosis of kidney tumor, 10 patients had some symptoms including flank pain or hematuria, and the remaining 42 patients had no symptoms (Table 2). Bilateral tumor was observed in 33 patients and multifocal tumors in 40. Median tumor size of maximal tumor in each patient was 3.3 cm in diameter. The distribution of tumor size is shown in (Figure 2). Histological evaluation was available for 46 patients operated. TNM staging on these patients showed T1a in 25, T1b in 12, T2 in 6, T3a in 2, and T3b in 1. Nodal disease and distant metastasis at presentation were 2 and 3, respectively. All patients had clear cell carcinoma and histological grade was G1 in 18, G2 in 18, G3 in 3, and Gx in 7. The median follow up of all patients was 79 months (range 7-208 months)

Table 3: Treatment against RCC in 52 vHL patients.
Abbreviations: NSS: nephron sparing surgery, TN: Total nephrectomy, B: Bilateral, U: Unilateral, F/U: Follow-up

First treatment			
NSS+NSS (B)	12 pts		
NSS+TN (B)		8 pts	
NSS (U)	10 pts		
TN+TN (B)		5 pts	
TN (U)	11 pts		
F/U		6 pts	
Second treatment			
NSS (U)		9 pts	
TN (U)			5 pts
Third treatment			
NSS (U)		2 pts	

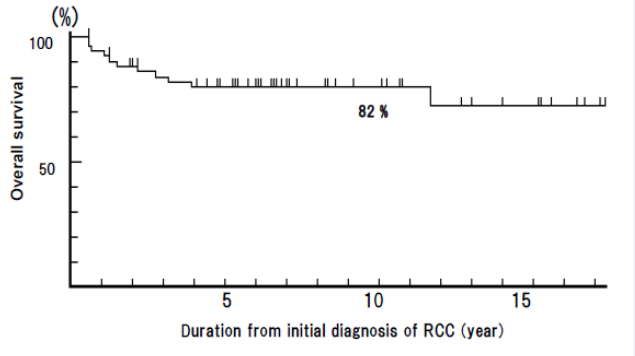

Figure 3 Kaplan-Meier estimates of overall survival in all vHL patients with RCC.

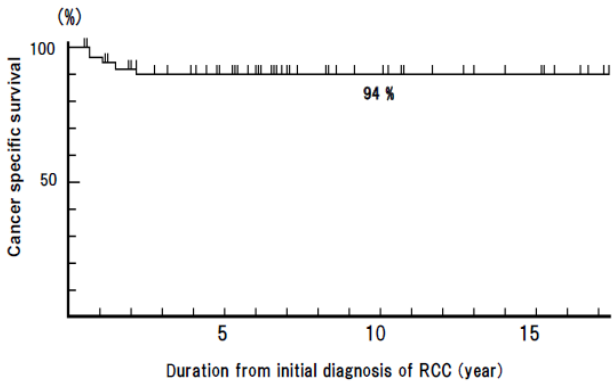

Figure 4 Kaplan-Meier estimates of cancer specific survival in all vHL patients with RCC.

With regard to first treatment for kidney tumors, bilateral nephron sparing surgeries (NSSs) was performed in 12 patients, NSS and total nephrectomy (TN) in 8, bilateral TNs in 5, unilateral NSS in 10, and unilateral TN in 11 (Table 3). Second treatment was performed in 14 of 27 patients who had recurrent tumor in their kidneys, including NSS in 9 and TN in 5. Third treatment was performed in 2 patients. Thus, a total of 87 renal interventions was performed, NSS in 53 (61%) and TN in 34 (39%). In one case, an arterial embolization was done as second treatment.

In all 52 patients, OS and CSS were 82% and 94% at 10 years after initial diagnosis of kidney tumor, respectively (Figure 3 and 4). Furthermore, OS and CSS in 49 patients with no distant metastasis at initial diagnosis were 86% and 100% at 10 years after initial diagnosis of kidney tumor, respectively. At last follow-up, 10 of 52 patients died. Four patients died with RCC, 5 patients died with CNS tumor, and 1 died with gastric cancer.

From the present study, RCCs in Japanese patients with vHL disease were shown to be diagnosed at an early age and there was a high likelihood of multicentricity and bilaterality. With regard to the initial treatment, NSS was performed in most patients. Although about half of patients experienced local recurrences, the 10-years CSS was 94%, which is relatively high compared with survival rates in sporadic RCCs.

Because of the improvement in treatment of central nervous system hemangioblastoma and pheochromocytoma, RCCs in patients with vHL disease are considered to be the leading cause of death [3,4]. To improve the survival in these patients, it is necessary to establish the treatment strategy against RCCs and clarify the long-term outcomes of the patients treated with surgery. Although several reports on these issues were made from the groups in Europe and North America [7,8], there are few studies in Asian patients with vHL disease. From the present study, the clinical and pathological features of RCCs in Japanese patients are shown to be very similar to those in Caucasian patients. Shuin et al reported similar results in a nationwide epidemiological survey of patients with vHL disease using the epidemiology program for incurable disease by the Ministry of Health, Labour and Welfare [9].

As reported by several investigators, NSS has been recommended for the management of kidney tumors in

association with vHL disease due to young patient age, common multicentricity and bilaterality, compared with sporadic RCC. Jilg et al reported on 54 patients who underwent NSS for localized RCC, and had adequate renal function and favorable prognosis [8]. Matin et al also reported similar results [7]. In the present study, most patients except 5 patients with bilateral RNs underwent nephron sparing approach. In fact, local recurrence occurred in 27 of 46 patients who underwent initial management, but these patients had favorable prognosis (10-year OS 82%) by subsequent treatments or close surveillance. Therefore, a conservative approach by NSS would be appropriate from the point of oncological outcomes.

On the other hand, several problems have recently been pointed out on quality of life (QOL) and renal function in these patients. Shuin et al showed that QOL was inversely correlated with the number of operations to the central nervous system and other visceral organs [10]. Furthermore, they reported that repeated operations for kidney tumors resulted in deterioration of the kidney function [9]. Therefore, the indication for surgery should be considered carefully and the total number of surgeries should be kept to a minimum. From this point, Jilg et al proposed a 4.0cm-threshold strategy for NSS by following a strict surveillance protocol [8]. Recently, several modalities including cryosurgery or radiofrequent ablation therapy [11,12], have been introduced in routine clinical practice. These alternative approaches would be helpful in vHL patients with kidney tumors, although the indication should be also considered carefully.

CONCLUSION

In conclusion, RCC in VHL patients differs from sporadic RCC in clinical features and should be carefully treated and followed closely. Appropriate decisions regarding treatment of RCC in VHL patients should be made from not only oncological outcomes but also long-term renal function outcomes and QOL.

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