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Research Article

von Hippel-Lindau Disease-Associated Pheochromocytoma: Epidemiology, Clinical Characteristics, and Screening and Surveillance Protocols in Japan

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Keywords

- VHL
- von Hippel-Lindau disease
- Pheochromocytoma
- Epidemiology

Abstract

von Hippel-Lindau (VHL) disease is an autosomal dominantly inherited syndrome characterized by a predisposition to various neoplastic lesions. To clarify the epidemiology and clinical characteristics of VHL-associated pheochromocytoma (PHEO) in Japan, we have summarized VHL-PHEO characteristics from a nationwide cross-sectional survey for VHL disease on the basis of the epidemiological study program for incurable disease by the Japanese Ministry of Health, Labour and Welfare. The details of the survey included age of onset, sex, living area, treatment modalities, and patient outcome. The incidence rate of PHEO in VHL disease was 1.5% (62/409). Males and females were equally affected. The mean and median ages of onset were 29.7 and 31.5 years, respectively. The age of onset was distributed between 10 and 75 years and presented two peaks between 15-20 and 35-40 years. Twenty-six (42%) bilateral cases, 8 (13%) extra-adrenal paragangliomas, and 4 (6.4%) malignant cases were observed. Forty-one (65%) patients underwent surgical resection once and 13 (19%) underwent 2 or 3 surgeries, whereas six (10%) were surveyed without surgical treatment. Fourteen of 26 bilateral PHEOs (56%) received steroid replacement therapy following bilateral adrenal surgeries. Four cases died from metastatic PHEOs and one from a severe infection during steroid replacement therapy. None of the patients died of cardiovascular complications due to PHEO crisis. From the current survey results, it is concluded that VHL-PHEO characteristics in Japan are similar to those in Western countries. Based on the above, we propose a screening and surveillance protocol for VHL-PHEO in Japan. Due to its rare incidence and unique characteristics, the continuous survey and registration of VHL-PHEO will remain important to understanding the disease's nature.

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ABBREVIATIONS

VHL: von Hippel-Lindau disease; PHEO: Pheochromocytoma.

INTRODUCTION

Von Hippel-Lindau disease (VHL) (MIM 193300) is an autosomal dominantly inherited disorder characterized by a predisposition to develop multiple tumors and cystic lesions in many organ systems [1,2]. These lesions include retinal angiomas, central nervous system (CNS) (cerebellar, brainstem, and spinal cord) hemangioblastomas, endolymphatic sac tumors, pancreatic neuroendocrine tumors, pheochromocytomas, renal cell carcinomas (RCCs), endolymphatic sac tumors, epididymal cystadenomas in males, and broad ligament cystadenomas in females [1-5]. The disease incidence is estimated at 1 in 36,000-46,000 live births in Western countries, and the disease penetrance is over 90% by 65 years of age [2,6,7].

The gene responsible for VHL is located on the short arm of chromosome 3 (3p25.3); in 1993 the gene was identified as a VHL tumor suppressor by a positional cloning approach [8,9]. The VHL gene is categorized as a classic tumor suppressor. According to Knudson's two-hit mechanisms, germline mutation in one allele is present in all the cells of affected individuals who inherit the genetic trait. The second VHL allele is somatically inactivated in tumors associated with VHL patients [10]. On the other hand, both VHL alleles are found to be inactivated by two independent somatic alterations in tumors with non-inherited sporadic occurrence, including clear cell subtype RCC, CNS hemangioblastoma, and pheochromocytoma [11-15].

VHL disease (or the VHL family) is clinically classified into two major categories, depending on the absence or presence of pheochromocytoma as a tumor manifestation [16-18]. Type 1 patients have almost no risk of developing pheochromocytoma, but present other cardinal manifestations. Approximately 80% of VHL families are type 1, while the remaining 20% of families are categorized as type 2, having a high risk of pheochromocytoma. The frequency of pheochromocytoma is 10-20% among all VHL patients, whereas it rises to as many as 70-80% of affected members in the type 2 family. Type 2 is further classified into three subtypes, labeled 2A, 2B, and 2C. Type 2A patients have a low risk of developing RCC, while type 2B patients have a high risk. Both types of patients develop CNS and retinal hemangiomas. On the other hand, Type 2C patients develop pheochromocytomas exclusively [17,19,20]. Genotype-phenotype correlation analyses demonstrated that VHL type 1 families have a variety of mutational types, including missense, nonsense, and frameshift mutations in the highly conserved region and large genomic deletions. These mutations are likely to result in a gross alteration or complete loss of pVHL functions. In contrast, the majority of type 2 families have missense mutations at specific amino acid positions in the pVHL, affecting particular pVHL functions [17-20].

VHL-associated pheochromocytomas (VHL-PHEOs) have been characterized mainly in the Western population; as such, the epidemiology and clinical features in Japanese Asian population have not previously been elucidated. In this study, we first performed nationwide surveillance of VHL patients in Japan. We summarize the current epidemiology and clinical status of VHL-PHEO herein, and we also propose a screening and surveillance protocol for VHL-PHEO patients in Japan.

MATERIALS AND METHODS

Nationwide surveillance of VHL patient in Japan

We performed nationwide, cross-sectional surveillance of VHL patients in Japan. In the first survey, we asked a total of 4,545 medical doctors with specialties in urology (n=1,200), neurosurgery (1,141), ophthalmology (1,149), and pancreatic diseases (1,055) whether they had treated any VHL patients during the 2 years from April 2009 to March 2011. Subsequently, in a second survey, an inquiry-based investigation was carried out with 240 doctors who replied that they had been treating patients diagnosed with VHL. The final response rate was 70.4% for the 2nd questionnaire. In each VHL patient, investigations of all VHL-related diseases were performed, including the onset age of each VHL-related disease, living prefecture, sex, family history of VHL, with or without genetic testing, information on survival and outcome, and the types of treatment modalities. The status of corticosteroid replacement therapy after surgery was also asked for the VHL-PHEO patients. The study protocol was approved by the institutional ethics committee of the Koch University School of Medicine.

RESULTS AND DISCUSSION

Epidemiology

In total, 409 VHL patients were registered by corresponding doctors. Among them, 62 (15%) were suffering from PHEO and considered to be VHL type 2 patients. The distribution of onset age in VHL-PHEO was from 10 to 75 years (median=31.5, mean=29.7±2.0 years), and 2 major age peaks (15-20 and 35-40 years) were observed (Figure 1-A). There was a tendency for the type 2A (without RCC) patients to belong to the younger age peak and type 2B (with RCC) to the elder peak, respectively (Figure 1-B, C).

The involvement of PHEO in bilateral adrenal glands was observed in 26 out of 62 (42%) patients, and extra-adrenal PHEO (paraganglioma) was observed in 8 (13%). There was no difference between the sex distribution (31 cases each in males and females). Malignant PHEOs with distant metastasis were present in 4 cases (6.5%) with ages of onset of 21, 26, 33, and 50 years, respectively.

Treatments and patient outcomes

The frequency of surgical intervention for PHEO was once in 41 patients, twice in 10, and three times in 1. There was no patient registered who underwent 4 or more PHEO surgeries.

Continuous corticosteroid replacement therapies after surgical intervention were carried out in 14 (56%) of 26 patients with bilateral adrenal PHEOs (Table 1). Steroids were not administered, however, for the remaining 12 cases. Of these 12 patients, adrenal-sparing surgery was done in 8, unilateral adrenal surgery plus watchful surveillance of the contralateral tumor in 3, and observation only in 1.

Regarding patient outcomes, 4 patients with malignant PHEO died of metastases; in addition, another patient died of severe cholecystitis during the steroid replacement therapy after bilateral adrenalectomy. However, no patient was reported to have died of

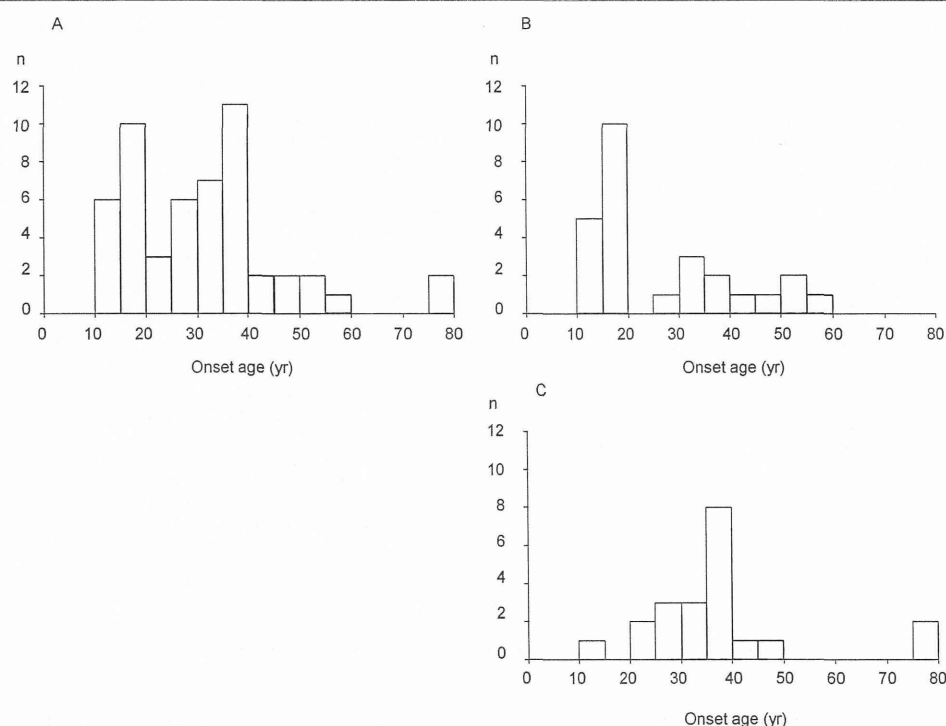


Figure 1 The onset-age distribution of von Hippel-Lindau disease-associated pheochromocytoma in Japan.

Data was available for a total of 52 patients (A), type 2A (without renal cell carcinoma) patients (n=26) (B), and type 2B (with renal cell carcinoma) patients (n=21) (C).

Table 1: Adrenal Surgery and corticosteroid replacement therapy in VHL patient with pheochromocytoma.

Surgery	Number of Patients with/without corticosteroid	
	With	Without
Bilateral adrenalectomy	5	0
Unilateral adrenalectomy +contralateral partial adrenalectomy or tumor enucleation	2	7
Unilateral adrenalectomy	1	27
Bilateral partial adrenalectomy or tumor enucleation	0	1
unilateral partial adrenalectomy or tumor enucleation	0	3

cardiovascular complications due to PHEO crisis. At the patient-registration time, a total of 10 VHL-PHEOs were following up, including 4 with the administration of antihypertensive agents and 6 with watchful observation without any treatment due to asyndromic PHEO.

In this study, we first conducted a nationwide surveillance study of VHL patients in Japan. As a result, a total of 409 VHL patients were registered. We then identified the epidemiological and clinical characteristics of VHL patients with PHEO; i.e. VHL type 2, in the Japanese Asian population. Epidemiological characteristics observed in a Japanese patient cohort seem to be basically the same as those reported previously for Western patients, although some older patients (age of onset: range= 10-75 years) and a somewhat higher incidence of malignant PHEO (6.4%) was seen in the Japanese patient cohort compared to the U.S. and European series (age of onset: range 3-60 years and malignant PHEO: 1.6-3.6%) [21,22]. Another interesting point is

that we observed that the VHL type 2A patients (without RCC) tended to have a relatively younger onset age (10-19 years), while type 2B (with RCC) patients tended to have an older age of onset (30-39 years) in the Japanese population.

Previous work has demonstrated that the subset of VHL-associated PHEO shows relatively low hormonal activity compared with other inherited forms of PHEO, including multiple neuroendocrine neoplasia type II (MEN2), paraganglioma syndromes (PGLs), and neurofibromatosis type I (NF1) as well as to PHEO in sporadic occurrence [23-25]. According to the NIH/NCI in the U.S.A. series, among VHL-PHEO patients newly diagnosed by family screening, 35% were asyndromic and non-functioning with a relatively small tumor size [21]. Our surveillance also demonstrated that a substantial number of Japanese VHL-PHEO patients present an asyndromic non-functioning phenotype, and these patients were subsequently followed by observation. Unfortunately, in the current survey, we

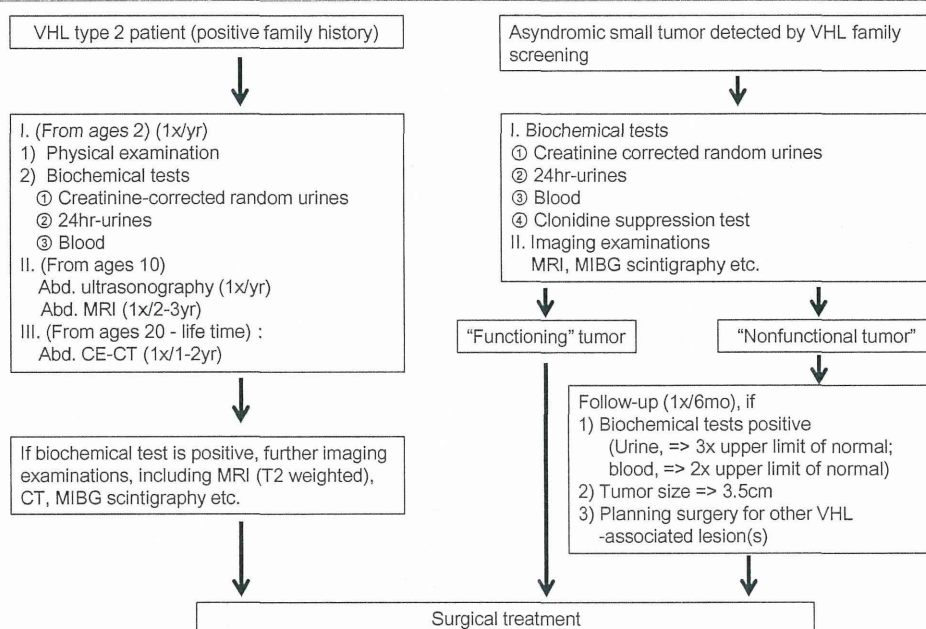


Figure 2 Screening and surveillance algorithm for von Hippel-Lindau disease-associated pheochromocytoma.

did not collect other detailed information such as the PHEO tumor size and location, tumor doubling time, followup period, exact values of catecholamines, and so on. It is our hope that, in the next survey, additional precise data will be collected to further our understanding of this unique and rare disease condition.

Screening and surveillance protocol for VHL-associated PHEO

Based on previous findings together with the current survey results regarding Japanese VHL-PHEO, we propose the following protocol for the screening and surveillance of the disease (Figure 2). In the type 2 VHL family, annual i) physical examination, ii) biochemical tests, including adrenaline, noradrenaline, dopamine, metanephrine, and normetanephrine, for ①blood and ②urine (24-hr urines or alternatively, creatinine corrected random urine specimens), from age 2. Abdominal ultrasonography (yearly) or plain magnetic resonance imaging (MRI) (1x/2-3yr) should start from age 10. MRI is preferred to computed tomography (CT) in children to avoid radiation exposure during development. From age 20, Abdominal CT with contrast enhancement (CE) (1x/1-2yr) is begun. CT-CE can allow for the screening of other VHL abdominal lesions, including simultaneous screening of the pancreas and kidneys. MIBG scintigraphy is not recommended for screening due to radiation exposure and cost. It should be done to provide a definitive diagnosis for PHEO localization. For a patient who is planning surgery for other VHL lesion(s) or a female patient planning a pregnancy, the absence of a biochemically "functioning" tumor within the 6 month should be confirmed.

Diagnosis and treatment

Diagnosis and treatment for VHL-PHEO is basically the same as that for PHEO in the sporadic form. Surgical resection remains the mainstay of treatment for VHL-PHEO. Due to the relatively early onset age, frequent bilateral occurrences, and

a lifetime multiple surgical operations not only for PHEOs but other organ lesions, adrenal-preserving and minimally invasive surgery such as laparoscopic partial adrenalectomy, should be considered whenever possible [26,27]. Additionally, in cases with asyndromic non-functioning PHEO with relatively small size detected by family screening, watchful observation can be selected with both biochemical and imaging evaluations at 6-month intervals. Surgical treatment is then recommended when i) urine or blood biochemical tests become positive (urine, =>3x upper limit of normal; blood, =>2x upper limit of normal), ii) tumor size becomes =>3.5cm, or iii) planning surgery for other VHL-associated lesion(s).

In conclusion, we conducted a first nationwide survey of VHL-PHEO in Japan. We collected a total of 62 VHL-PHEO patients. The epidemiology in Japanese patients seems to be basically the same as that previously reported in Western patients. In addition, some unique characteristics are also emerging from the current survey. Since the relatively rare incidence and unique nature of disease, prospective continuous registrations as well as a phenotype-genotype correlation study in Japanese VHL will be quite important. We have also for the first time proposed a screening and surveillance protocol for Japanese VHL-PHEO patients. We hope that the protocol will be prospectively validated and updated continuously according to the new diagnostic and therapeutic procedures.

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Special Issue on von Hippel Lindau Disease

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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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Special Issue on

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Keywords

- RCC
- VHL
- Prognosis
- Clinicopathological features

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 al 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

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

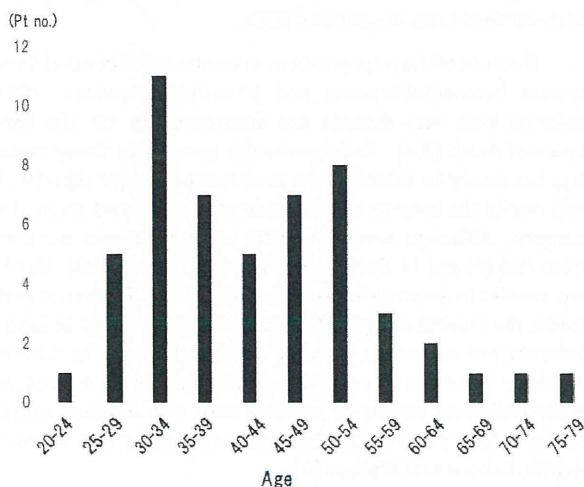


Figure 1 Distribution of age at initial diagnosis of RCC in the 52 vHL patients.

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

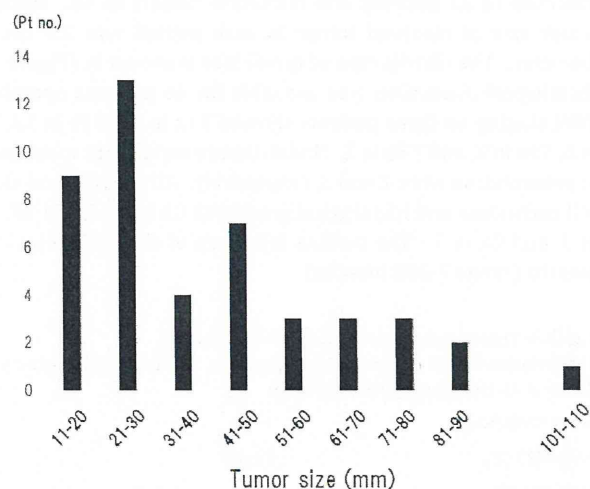


Figure 2 Distribution of largest tumor size of RCC in the 52 vHL patients.

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.

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

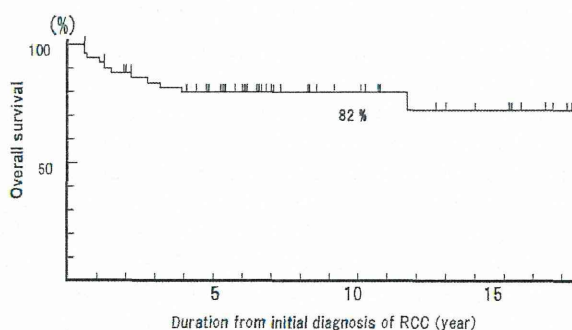


Figure 3 Kaplan-Meier estimates of overall survival in all vHL patients with RCC.

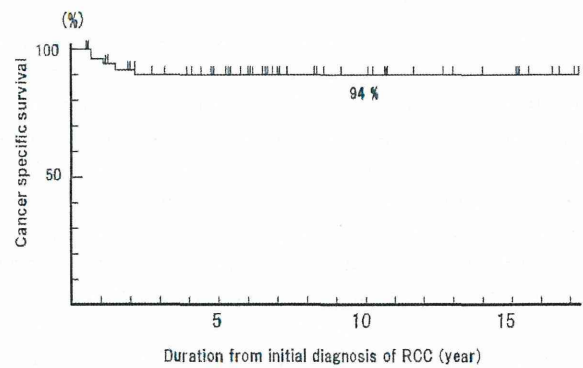


Figure 4 Kaplan-Meier estimates of cancer specific survival in all vHL patients with RCC.

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 radiofrequency 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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