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Special Issue on
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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.

Special Issue on
von Hippel Lindau Disease

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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

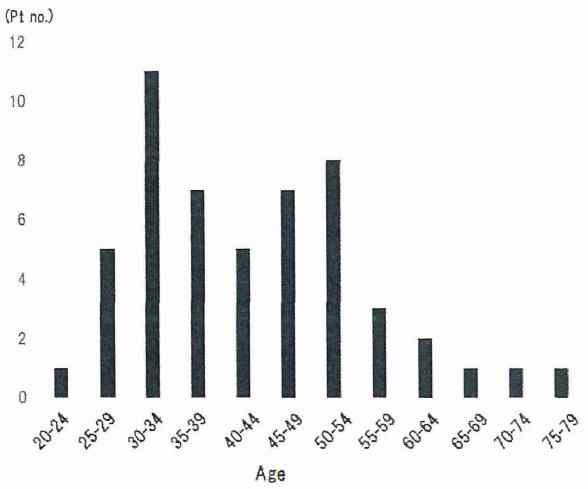

Figure 1 Distribution of age at initial diagnosis of RCC in the 52 vHL patients.

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

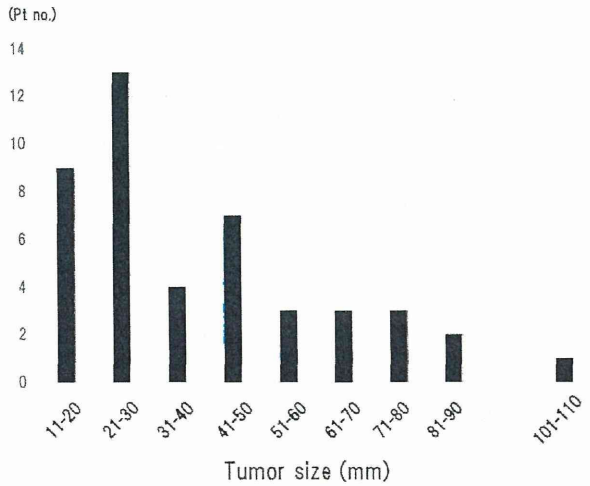

Figure 2 Distribution of largest tumor size of RCC in the 52 vHL patients.

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	

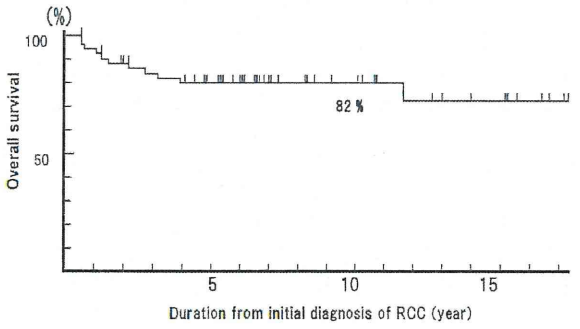

Figure 3 Kaplan-Meier estimates of overall survival in all vHL patients with RCC.

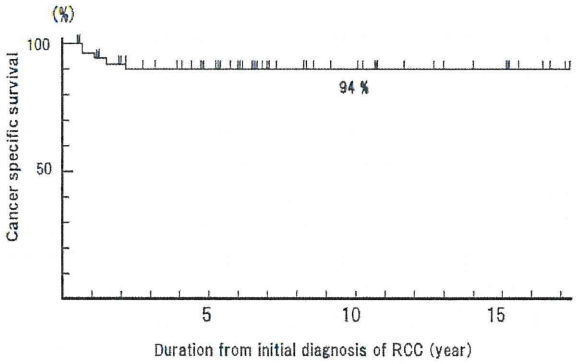

Figure 4 Kaplan-Meier estimates of cancer specific survival in all vHL patients with RCC.

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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Special Issue on
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Research Article

A Proposed Clinical Grading System to Define Impaired Organ Function and Quality Of Life in Patients with von Hippel-Lindau (VHL) Disease in Japan

Taro Shuin[1]*, Ichiro Yamasaki[1], Atsuki Fukushima[2], Isao Nishimori[3], Hiroshi Kanno[4], Masahiro Yao[5], Nobuo Shinohara[6], Ryo Nishikawa[7], Junichi Kuratsu[8], Kiyohiro Houkin[9], Atsushi Natsume[10], Nobuhito Saito[11], Tetsuhide Ito[12], Hisato Igarashi[12], Susumu Ishida[13], Tomonobu Hasegawa[14], Eijiro Nakamura[15], Kazuo Tamura[16] and Shin Yoneya[17]

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Abstract

Patients with von Hippel-Lindau (VHL) disease develop tumors and cysts in the central nervous system (CNS), retina, adrenal gland, kidney and pancreas. These tumors or cysts always require surgical treatment and cause different degrees of impairment in the affected organs. We developed a clinical grading system to evaluate impaired organ function and the quality of life (QOL) of VHL patients. Based on a previous grading system of intractable disease, impaired organ function is divided into five grades (grades 0, 1, 2, 3, and 4 for five affected organs) with QOL taken into consideration. The patient's worst grade was regarded as their final clinical grade. The clinical grading of 46 patients was determined by a questionnaire. Our results showed that proportions of patients with grades 0, 1, 2, 3, 4 were 0% (0), 9% (2), 28% (15), 24% (12), 37% (17), respectively. If patients with two grade 3-affected organs are regarded as finally grade 4, then 46% of patients had grade 4. These results suggest that the organ function of approximately 50% of VHL patients is severely affected. Our study showed that our clinical grading system of VHL disease is relatively easy to use, and reflects the severity and QOL of VHL patients. The use of this system aids the provision of medical care and financial support from the Japanese health care system to VHL patients with severe impairment.

ABBREVIATIONS

VHL: von Hippel-Lindau disease.

INTRODUCTION

von Hippel-Lindau (VHL) disease is an autosomal dominant inherited condition. Patients with VHL develop central nervous system (CNS) and retinal hemangioblastomas, pheochromocytomas, renal cell carcinomas or cysts, pancreatic neuroendocrine tumors or cysts, which may occur from childhood to advanced age. These tumors or cysts result in various clinical problems in the affected organs and may require multiple surgeries, causing organ impairment. Thus, VHL is a serious disease that disturbs the quality of life (QOL) of patients. Our epidemiological survey showed that there are more than 400 affected patients in Japan [1]. The Japanese Health and Welfare Ministry proposed Japanese VHL study group to develop a clinical grading system for evaluating disease severity. Several clinical grading systems for Parkinson's disease exist that assess the severity of motor function impairment and QOL [2]. We therefore developed a new clinical grading system for VHL to assess the impairment of affected organs based on another clinical grading system. We then applied this system in the assessment of Japanese VHL patients. Our results showed that 46% of patients had the worst grade. This grading system may be a good tool to assess impaired organ function and QOL of VHL patients in Japan to support their care by the Japanese health care system.

PATIENTS AND METHODS

The clinical grading system was designed by members of the Japanese VHL study group. The VHL study group consists of three urologists, six neurosurgeons, three ophthalmologists, three gastroenterologists, one pediatric endocrinologist and one geneticist. We asked 46 Japanese VHL patients to answer a questionnaire based on our grading system. The ethics committee of Kochi Medical School approved the present study, which involved clinical questions and a checklist to inquire about the clinical grade.

RESULTS AND DISCUSSION

We designed a clinical grading system that evaluates the function of each affected organ, including the CNS, retina, adrenal

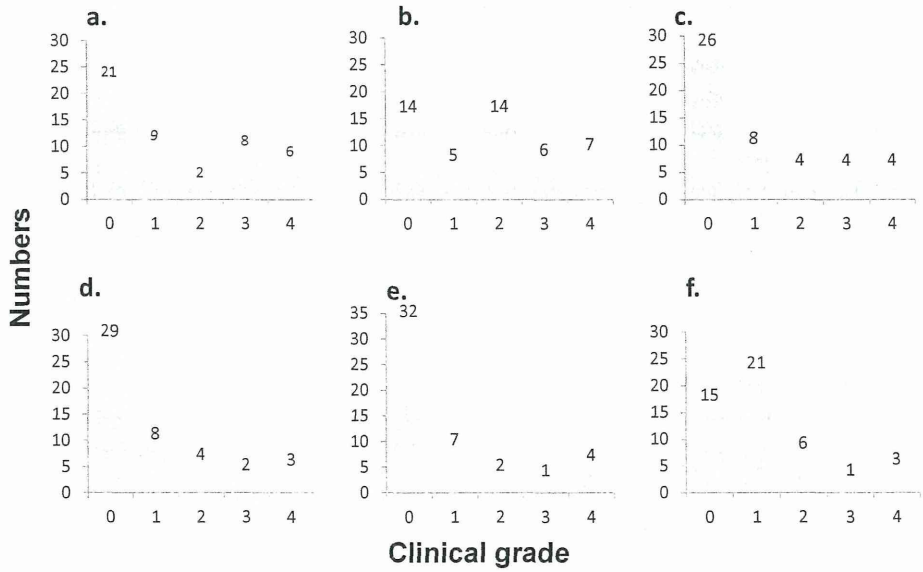

Figure 1 Clinical grade of affected organs in von Hippel-Lindau (VHL) disease. Clinical grades of the affected organs were determined according to our grading system. **A)** Retinal henagioblastoma. **B)** CNS hemangioblastoma. **C)** Renal cell carcinoma. **D)** Adrenal pheochromocytoma. **E)** Pancreatic neuroendocrine tumor. **F)** Pancreatic cyst.

Table 1: Grading system for CNS.

N0:	Hemangioblastomas have not been detected by radiological examinations.
N1:	Hemangioblastomas have been diagnosed by radiological examinations but neurological disability is not observed.
N2:	Hemangioblastomas have been diagnosed by radiological examinations. Neurological disability is very minor. QOL is not disturbed.
N3:	Hemangioblastomas have been diagnosed by radiological examinations. Moderate neurological disability. QOL is moderately disturbed.
N4:	Hemangioblastomas have been diagnosed by radiological examinations. Severe neurological disability. QOL is severely disturbed.

Grade N4 is assigned to severely disabled patients who need help with activities of daily living.
Grade N3 is assigned to moderately disabled patients who require regular, but not daily, assistance with activities.

Table 2: Grading system for retinal hemangioma.

R0:	Retinal hemangiomas have not been detected.
R1:	Retinal hemangiomas have been detected but treatment is not necessary. QOL is not disturbed: retinal exudative changes are not observed and visual acuity is not disturbed.
R2:	Retinal hemangiomas have been detected and treatments are effective. QOL is not disturbed: retinal exudative changes are well controlled by treatments and visual acuity is not disturbed.
R3:	Retinal hemangiomas have been detected and treatments are ineffective. QOL is moderately disturbed: retinal exudative changes are not controlled by treatments and visual acuity is disturbed.
R4:	Retinal hemangiomas have been detected and treatments have minimal effect. QOL is severely disturbed: treatments for retinal exudative changes are not indicated and visual acuity is severely disturbed.

Grade R4 is assigned to visually disabled patients who need help with activities of daily living.
Grade R3 is assigned to moderately disabled patients who require regular, but not daily, assistance with activities.

Table 3: Grading system for pheochromocytoma.

Ph0:	Pheochromocytomas have not been detected by endocrinological examinations and radiological examinations
Ph1:	Pheochromocytomas have been diagnosed by endocrinological examinations. Symptoms of overproduction of catecholamines are absent. QOL is not disturbed
Ph2:	Pheochromocytomas have been diagnosed by endocrinological examinations or radiological examinations. Symptoms of overproduction of catecholamines are absent after medical treatment. QOL are not disturbed after medical treatment.
Ph3:	Pheochromocytomas have been diagnosed by endocrinological examinations and radiological examinations. Symptoms of overproduction catecholamines are not controlled by medical treatments. Symptoms due to shortage of catecholamines or other adrenal hormones after removal of both adrenal glands are also included in this category. QOL is moderately disturbed (Karnofsky Performance Status is between 70 and 90).
Ph4:	(1) Pheochromocytomas have been diagnosed by endocrinological examinations and radiological examinations. Symptoms of overproduction of catecholamines are present even after medical and surgical treatments. Symptoms due to the shortage of catecholamine or other adrenal hormones after the removal of both adrenal glands are also included in this category. QOL is severely disturbed (Karnofsky Performance Status is less than 60.) (2) Malignant pheochromocytomas with distant metastasis are included in this grade.

Table 4: Grading system for renal cell carcinoma.

R0:	Renal cell carcinomas (RCC) have not been detected by radiological examinations.
R1:	RCC have been diagnosed by radiological examinations. Tumors did not require immediate treatment. Renal function (e.g. eGFR) is not impaired. QOL is not disturbed.
R2:	RCC have been diagnosed by radiological examinations. Tumors required immediate medical treatments. Renal function is not impaired even after treatment. QOL is not disturbed.
R3:	RCC have been diagnosed by radiological examinations. Tumors required immediate medical treatment. Renal function is moderately impaired after treatment. QOL is moderately disturbed.
R4:	RCC have been diagnosed by radiological examinations. Tumors required immediate medical treatment. Renal function is severely disturbed after treatments. QOL is severely disturbed.

Table 5: Grading system for pancreatic neuroendocrine tumor.

PNET0:	Pancreatic neuroendocrine tumors have not been detected by radiological and endocrinological examinations.
PNET1:	Pancreatic neuroendocrine tumors have been diagnosed by radiological or endocrinological examinations. Tumors do not require immediate medical treatments. QOL is not disturbed.
PNET2:	Pancreatic neuroendocrine tumors have been diagnosed by radiological or endocrinological examinations. Tumors required immediate medical treatments. QOL is minimally disturbed.
PNET3:	Pancreatic neuroendocrine tumors and distant metastases have been diagnosed by radiological or endocrinological examinations. Tumors required immediate treatments. QOL is moderately disturbed.
PNET4:	Pancreatic neuroendocrine tumors and distant metastases have been diagnosed by radiological or endocrinological examinations. Tumors required immediate treatments. QOL is severely disturbed.

Table 6: Grading system for pancreatic cyst.

PC0:	Pancreatic cysts have not been detected by radiological examinations.
PC1:	Pancreatic cysts have been diagnosed by radiological examinations. Symptoms are absent. QOL is not disturbed.
PC2:	Pancreatic cysts have been diagnosed by radiological examinations but does not requires immediate treatment. QOL is minimally disturbed.
PC3:	Pancreatic cysts have been diagnosed by radiological examinations. Abdominal pain or symptoms due to decreased pancreatic function are present. Immediate medical treatment was required. QOL is moderately disturbed.
PC4:	Pancreatic cysts have been diagnosed by radiological examinations. Abdominal pain or symptoms due to decreased pancreatic function are present. Immediate treatment was required. QOL is severely disturbed.

gland, kidney and pancreas. Grades were defined as follows: grade 0, no apparent tumor or cyst; grade 1, no clinical symptoms and presence of a small tumor or cyst; grade 2, minimal clinical symptoms and presence of a small to medium size tumor or cyst; grade 3, minor clinical symptoms and slightly disturbed QOL with the presence of a moderate size tumor or cyst; grade 4, seriously impaired function in the affected organ and significant disturbance of QOL with the presence of a tumor or cyst (or after surgical treatment). The following six tables show the clinical grading system of the CNS, retina, adrenal gland, kidney, pancreatic neuroendocrine tumor, and pancreatic cyst (Table 1-6).

We analyzed the clinical grade of Japanese VHL patients after asking their clinical history symptom and QOL. The answers of the questionnaires were analyzed and the results are described below. If the clinical grade was regarded as the worst grade of the affected organs, the proportion (number) of patients with grades 0, 1, 2, 3, 4 were 0% (0), 9% (4), 28% (13), 24% (11), 37% (17), respectively. If we regard patients with grades 3 and 4 as those with significant disturbance of organ function, the proportions of patients with either grade 3 or 4 of the retina (Figure 1a), CNS (Figure 1b), kidney (Figure 1c), pheochromocytoma (Figure 1d), pancreatic neuroendocrine tumor (Figure 1e), and pancreatic cyst (Figure 1f) were 30% (14), 28% (13), 18% (8), 11% (5), 11% (5), and 8% (4), respectively. We regarded the patients' highest grades as the final grade. The proportions of patients with grade 4 of one organ, two organs, and three organs were 21% (10), 9% (4), and 7% (3). If patients with two or more grade 3-affected organ functions are regarded as grade 4, then 46% (21) of patients had grade 4 disease.

At present, 56 diseases are regarded as intractable diseases in Japan, and patients suffering from these diseases are fully supported by the Japanese medical insurance system. However, there are many intractable diseases affecting a considerable number of patients. Expansion of the number of diseases with an intractable disease status is being considered to increase financial and medical support to affected patients. The Japanese Welfare Ministry considered expansion of the number of intractable diseases to 300. If the group of intractable diseases is expanded, it would be difficult to provide financial support to all patients with intractable diseases because of financial constraints. A possible solution would be to provide more clinical support to patients with severe disturbance of their QOL, while those with mild disturbance of their QOL would be supported by standard medical insurance. Therefore, we developed this clinical grading system for VHL. The proportion of patients with significant disturbance of QOL was 46% (21 patients). As the QOL of patients is affected for several months after surgical or radiological treatment, the grade should be determined just after these treatments.

Our clinical grading system is still a first step to evaluate QOL of the VHL patients. This grading system especially for renal cell carcinoma and pancreatic neuroendocrine tumor may be still very primitive. It requires improvement with more discussion by our research study group. We would like to improve it with applying it for VHL patients.

CONCLUSION

We developed a clinical grading system to evaluate impaired organ function and QOL of VHL patients. Our results showed that the clinical grading system for VHL disease was relatively easy to use. It reflected the severity and QOL of VHL patients. The use of this system aids the provision of medical care and financial support from the Japanese health care system to severely impaired VHL patients.

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ORIGINAL ARTICLE—LIVER, PANCREAS, AND BILIARY TRACT

Pancreatic involvement in Japanese patients with von Hippel-Lindau disease: results of a nationwide survey

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Abstract
Background The frequency and prognosis of pancreatic endocrine tumors (PNET)/pancreatic cystic tumors (PCT) in Japanese patients with von Hippel-Lindau disease (VHL) are still open to question.
Methods We conducted the first nationwide epidemiological study of VHL disease in Japan to elucidate this question. Data on 377 VHL patients (PNET, 53; PCT, 152) were reported, and then their clinical characteristics were analyzed.
Results PNET was found in 14.1 % and PCT in 40.3 %; 4.5 % had both. The onset of PNET and PCT mostly occurred at 30–39 years of age (median ages, 34 and 33 years, respectively). Metastasis was observed in 7.5 % of PNET patients at diagnosis, and 64.2 % underwent surgery including enucleation, partial and total pancreatectomy, and bypass surgery. Two patients received non-surgical therapies. No PNET-related deaths were observed. In PCT patients, no metastasis was observed at diagnosis, and 9.2 % underwent surgery or drainage. According to the classification system without or with adrenal pheochromocytoma, the VHL patients studied herein were subdivided into 313 (83 %) with VHL type 1 and 64 (17 %) with VHL type 2; 29 (9.3 %) and 24 (37.5 %) patients had PNET with VHL type 1 and 2, suggesting that patients with VHL type 2 were significantly more related to PNET than those with VHL type 1 ($P < 0.01$).
Conclusions This study showed no significant difference in the epidemiology of pancreatic involvement between Japanese and non-Japanese VHL patients. Concerning the prognosis, follow-up study is needed.

Keywords Pancreas · von Hippel-Lindau disease · Neuroendocrine tumor · Pancreatic cystic tumor

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Introduction

The causative gene for von Hippel-Lindau disease (VHL) lies on the short arm of chromosome 3, and VHL is inherited in an autosomal dominant manner [1]. VHL is an intractable disease characterized by various tumors, primarily hemangioblastoma of the central nervous system (CNS), retinal hemangioblastomas, renal cell carcinoma, adrenal pheochromocytoma, pancreatic tumor, endolymphatic sac tumors and epididymal cysts [2]. In Europe and the USA, 1 in 36,000 people [2] and 1 family in 1,000,000 [3] are affected by VHL. Onset occurs in a wide range of age groups from infants/children of <10 years to up to 70 years of age [2]. The most common causes of death in patients with VHL are CNS hemangioblastomas and renal cancer, yielding a reported mean age at death of 40.9 years [4]. Currently, the prevalence of VHL in the Japanese population, the frequencies of individual tumor type and

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