Acta Med. Okayama, 2011
Vol. 65, No. 2, pp. 135–141

Acta Medica Okayama
http://escholarship.lib.okayama-u.ac.jp/amo/

Case Report

Long-Term Effect of External Beam Radiotherapy of Optic Disc Hemangioma in a Patient with von Hippel-Lindau Disease

Toshihiko Matsuo[a]*, Kengo Himei[b], Kouichi Ichimura[c], Hiroyuki Yanai[c], Soichiro Nose[d], Tetsushige Mimura[e], Yasuyuki Miyoshi[f], and Tomoyasu Tsushima[g]

Departments of [a]Ophthalmology, [b]Radiology, [c]Pathology, [f]Neurological Surgery, and [g]Urology, Okayama University Medical School and Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama 700–8558, Japan, and Departments of [d]Pathology and [e]Surgery, Okayama Saiseikai General Hospital, Okayama 700–8511, Japan

An 18-year-old woman with a 2-year history of hypertension and headache was diagnosed with noradrenalin-secreting bilateral adrenal pheochromocytomas with paragangliomas in the background of von Hippel-Lindau disease with family histories and a missense mutation, 712C to T (Arg167Trp) in the *VHL* gene. She had optic disc hemangioma in the left eye which gradually enlarged and caused serous retinal detachment on the macula in one year. Low-dose external beam radiation (20 Gy) was administered to the left eye using a lens-sparing single lateral technique. She underwent craniotomy for cerebellar hemangioblastoma at the age of 22 years and total pancreatectomy for multiple neuroendocrine tumors at the age of 24 years. In the 6-year follow-up period after the radiotherapy, the optic disc hemangioma gradually reduced in size and its activity remained low, allowing good central vision to be maintained. External beam radiation is recommended as a treatment option for the initial therapy for optic disc hemangioma.

Key words: retinal (papillary, optic disc) hemangioma, von Hippel-Lindau disease, pheochromocytoma, pancreatic neuroendocrine tumor, external beam radiation (radiotherapy)

Von Hippel-Lindau disease is an autosomal dominant disease caused by mutations in the *VHL* gene, a tumor suppressor gene [1–4]. The main manifestations, described initially, are retinal hemangioma and central nervous system hemangioma, the latter of which is frequently cerebellar or spinal cord hemangioblastoma. Later, the syndrome has been known to be complicated with other neoplasms, adrenal pheochromocytoma, paraganglioma, renal cell carcinoma, islet cell tumors, pancreatic cysts and neuroendocrine tumors, epididymal cysts or cystadenoma, and endolymphatic sac tumor of the inner ear [1, 2].

Retinal hemangioma has posed therapeutic problems for ophthalmologists for almost a century [5, 6]. External beam radiation was the first method of treatment introduced for retinal hemangioma [1], but it has not been enthusiastically pursued recently, and is positioned as a salvage therapy to be used only when other modalities of treatment have failed [7]. The other modalities are cryotherapy, direct laser photocoagulation, plaque radiotherapy, transpupillary thermotherapy, photodynamic therapy, and intravitreal injection of anti-vascular endothelial growth fac-

Received September 13, 2010; accepted November 5, 2010.
*Corresponding author. Phone:+81-86-235-7297; Fax:+81-86-222-5059
E-mail:matsuot@cc.okayama-u.ac.jp (T. Matsuo)
Current affiliations: Kengo Himei at Okayama Red Cross Hospital, Okayama 700–8607; Tomoyasu Tsushima at National Hospital Organization Okayama Medical Center, Okayama 701–1192, Japan.

tor (VEGF) antibody drugs [8–12]. The location of hemangioma in the retina is an important factor in determining the treatment options [5, 6]: retinal hemangioma in the midperipheral to peripheral retina can be treated by direct ablation such as laser photocoagulation and cryotherapy [8]. In contrast, optic disc (papillary) hemangioma presents therapeutic challenges to ophthalmologists [10]. In this study, we present the long-term stabilizing effect of external beam radiation to optic disc hemangioma in a patient with von Hippel-Lindau disease who underwent surgeries for bilateral adrenal pheochromocytomas, cerebellar hemangioblastoma, and pancreatic neuroendocrine tumors.

Case Report

At 9 months of the age, the patient was first brought to the Department of Ophthalmology, Okayama University Hospital, due to occasional esotropia noted from birth. Cycloplegic refraction with atropine revealed hyperopia with +5.0 diopters in both eyes, and the patient began wearing glasses to achieve orthophoria upon the diagnosis of accommodative esotropia. At that time, a fundus examination under mydriasis by atropine revealed no abnormalities. She was followed afterwards for several years to develop good visual acuity in both eyes and good stereoacuity.

The patient's paternal grandmother was alive with a history of adrenal pheochromocytoma, breast cancer, and carcinoids, the patient's father died at the age of 34 years of pancreatic cancer associated with bilateral adrenal pheochromocytomas, paragangliomas, and carcinoids, and a younger brother had surgeries for adrenal pheochromocytomas, paragangliomas, and insulinoma.

The patient began to experience headache and palpitation from the age of 16 years. At 18 years old, she was found to have bilateral adrenal tumors (Fig. 1A, B) as well as multiple pancreatic masses (7 in the pancreatic head and one in the tail) by magnetic resonance imaging. The serum noradrenalin was elevated to 6.85 ng/mL (normal: 0.10–0.50 ng/mL) while the serum adrenalin and dopamine were in the normal ranges. Insulinoma was ruled out by insulin secretion tests, and thus non-functioning neuroendocrine tumors were suspected for the pancreatic tumors. She underwent total extirpation of the bilateral adrenal tumors, together with extirpation of 2 paraaortic small masses, which were proven to be pheochromocytomas and paragangliomas, respectively, by pathological examinations (Fig. 2A). She was given oral hydrocortisone at a dose of 25 mg daily. Partial or total pancreatic resection was not chosen by the patient and her mother at the same time as the bilateral adrenal tumors extirpation because they considered it to be too much intervention. Genomic analysis of peripheral leukocytes revealed a heterozygous missense mutation, 712C to T (Arg167Trp), in the *VHL* gene.

At that time at the age of 18 years, she was found to have optic disc hemangioma in the left eye (Fig. 3A). The patient's best-corrected visual acuity was 1.5 with −1.0 diopter correction in the right eye and 1.0 with −1.0 diopter correction in the left eye. The right eye was normal. One year later, at the age of 19 years, she underwent 20 Gy radiation (in 10 fractions using the lens-sparing single lateral technique) to the optic disc hemangioma, since the serous retinal detachment was approaching the fovea. Afterwards, the patient was followed for 6 years until the age of 26 years to observe the diminution of the hemangioma (Fig. 3B–F). She maintained a visual acuity of 1.2 in the left eye.

At the age of 22 years, she began to have dysarthria, numbness and weakness of the upper and lower extremities. She had a mass with enhancement, accompanied by cystic components, in the cerebellar tonsil and dorsal medulla oblongata (Fig. 1C, D) and underwent extirpation by craniotomy and C1 laminectomy to prove hemangioblastoma (Fig. 2C, D). At the age of 23 years, the pancreatic tumors showed gradual enlargement (Fig. 1E), and whole-body 2-[^{18}F] fluoro-2-deoxy-D-glucose positron emission tomography fused with computed tomography (PET/CT) showed abnormal uptake sites in the pancreatic lesions (Fig. 1F) together with abnormal uptake in a regional lymph node. She also showed multiple small nodular lesions in both lungs (Fig. 1G), which were negative on the PET/CT. She underwent endoscopic ultrasound-guided fine-needle aspiration biopsy of the pancreatic tumor to reveal homogeneous round epithelioid cells, positive for CD56 and synaptophysin, suggestive of neuroendocrine tumor.

At the age of 24 years, she abruptly developed cold sweat, nausea, black stool, and dimmed vision,

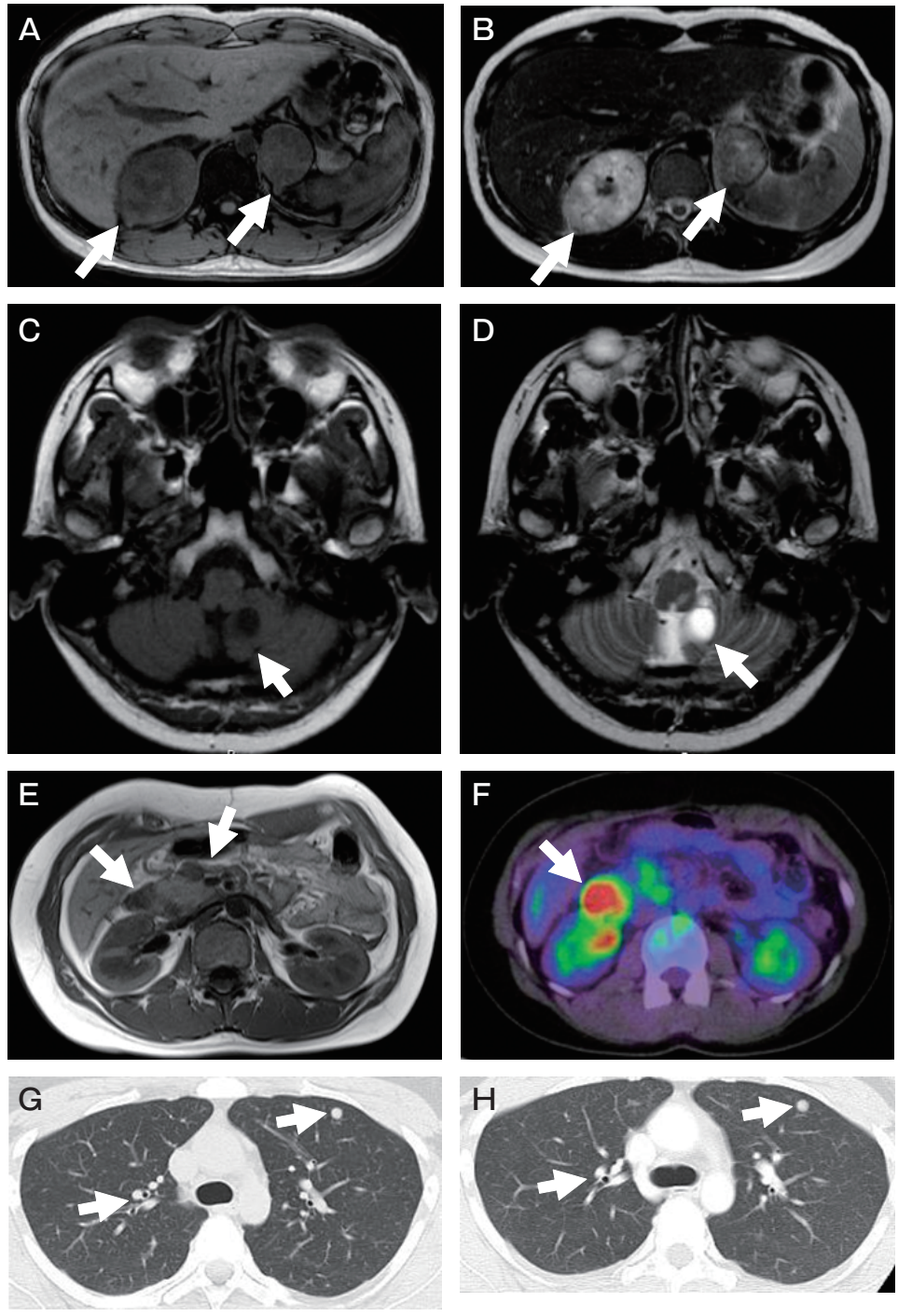

Fig. 1 Bilateral adrenal tumors (arrows) with irregular internal structure on T1-weighted (**A**) and T2-weighted (**B**) magnetic resonance imaging at the age of 18 years; a cerebellar tonsil tumor with a cyst (arrows) on T1-weighted (**C**) and T2-weighted (**D**) magnetic resonance imaging at the age of 22 years; and multiple pancreatic tumors (arrows in **E**) on T1-weighted magnetic resonance imaging and abnormal uptake lesions (arrow in **F**, the maximum standardized uptake value: SUVmax = 13.49) on whole-body 2-[^{18}F]fluoro-2-deoxy-D-glucose positron emission tomography fused with computed tomography (PET/CT) at the age of 23 years. Multiple small nodular lesions in bilateral lungs on computed tomography, metastatic from pancreatic neuroendocrine tumors, observed at the age of 23 years (**G**), remained stationary for one year after total pancreatectomy (**H**).

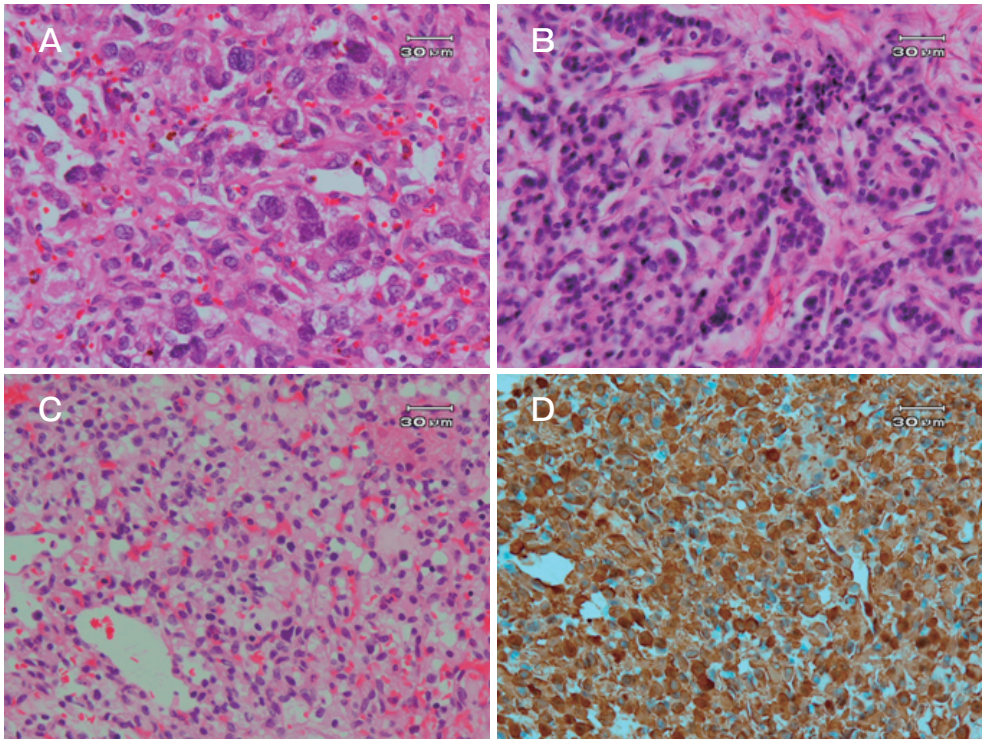

Fig. 2 Hematoxylin-eosin staining of adrenal pheochromocytoma (**A**), pancreatic neuroendocrine tumor (**B**), and cerebellar hemangioblastoma (**C**). Vimentin immunohistochemical staining of cerebellar hemangioblastoma (**D**). Note that hemangioblasts are positive for vimentin. Bar=30 μm.

caused by intestinal bleeding from the pancreatic head. She decided to undergo total pancreatectomy and regional lymph nodes dissection to prove the presence of neuroend rocrine tumors (Fig. 2B). The multiple pulmonary lesions remained stationary for 2 years (Fig. 1H), and apancreatic status was controlled with the combination of insulin aspart and insulin glargine.

Discussion

Von Hippel-Lindau disease is classified into 2 types: type I without pheochromocytoma and type II with pheochromocytoma [2]. Genetic analysis of the *VHL* gene showed that missense mutations, *i.e.*, amino acid-substituting changes, were frequently found in type II while nonsense mutations, *i.e.*, protein-truncating changes, or large deletions were found mainly in type I [3, 4]. The present patient was revealed to have a heterozygous missense mutation, 712C to T (Arg167Trp) [3], which is consistent with the genotypic features of von Hippel-Lindau disease type II.

Bilateral adrenal pheochromocytomas, detected under the guidance of the initial symptoms of hypertension and palpitation, as in this patient, are a key for diagnosing 2 familial diseases, multiple endocrine neoplasia type 2 and von Hippel-Lindau disease [13]. The present patient had a family history of pheochromocytomas, indicative of autosomal dominant inheritance. The detection of retinal hemangioma and the genetic analysis of the *VHL* gene confirmed von Hippel-Lindau disease. It should be noted that retinal hemangioma had been absent at the earlier age when the patient was first seen by ophthalmologists for accommodative esotropia, and that cerebellar hemangioblastoma was detected only later in the course of the follow-up. After successful removal of the cerebellar hemangioblastoma, she was carefully observed for any later development of spinal cord hemangioblastoma [14, 15]. Furthermore, the total pancreatectomy in a case with neuroendocrine tumors, as diagnosed in this patient, is justified from the prognostic point of view, and metastatic lesions of neu-

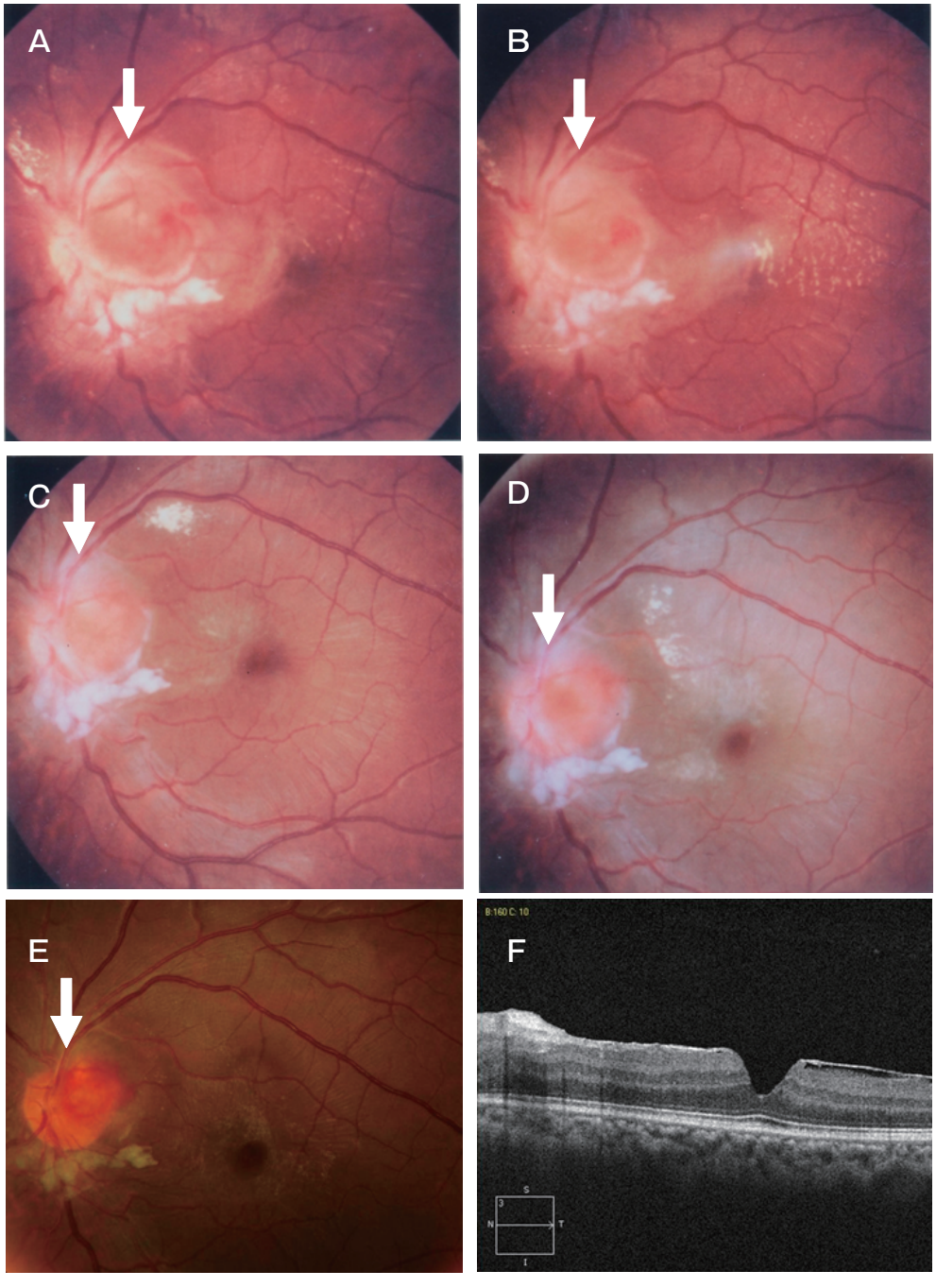

Fig. 3 Optic disc hemangioma (arrows) in the left eye at the age of 19 years before external beam radiation (**A**), 3 months after 20 Gy radiation (**B**), 2 years later (**C**), 3 years later (**D**), and 6 years later (**E**). Horizontal retinal cross-sectional image (**F**) taken at the same time as the fundus photograph (**E**), obtained by optical coherence tomography, shows no subretinal or intraretinal fluid in the macula. Note that serous retinal detachment caused by hemangioma is reaching the fovea in A and B while the subretinal fluid resolves with diminution of the hemangioma in C, D, and E.

roendocrine tumors, even if present, are known to be stable for many years [16, 17]. Therefore, in this patient, no additional treatment was planned, and the metastatic lung lesions were observed during the follow-up.

Hemangioma on the optic disc cannot be directly cryocauterized or coagulated by laser or treated with transpupillary thermotherapy. Photodynamic therapy with verteporfin is successful in inducing degeneration of midperipheral large hemangiomas [11]. However, the use of photodynamic therapy to treat optic disc hemangioma would naturally induce optic disc capillary obstruction, and thus, would lead to optic disc atrophy and a loss of vision [11]. The effect of intravitreal injection of anti-VEGF antibody drugs on retinal hemangioma has been reported recently, but the injection is expected to be repeated several times to control the activity of the tumor [12], based on the experience in age-related macular degeneration in which repeat injections are mandatory to control choroidal neovascularization, as described in a standard regimen. Most recently, the combination of photodynamic therapy with intravitreal injections of anti-VEGF drugs has been described as effective to control serous retinal detachment caused by optic disc hemangioma in a case report [18]. Even in this combined therapy, repeat sessions of both photodynamic therapy and intravitreal anti-VEGF drug injections were required over a period of 5 months.

A decade ago, when intravitreal injection of anti-VEGF antibody drugs was not available, external beam radiation at a low dose (20 Gy) was chosen as an initial main treatment since the leakage from the optic disc hemangioma reached the macula to reduce the vision in the present patient. The external beam radiation was shown to be effective, though at slow speed, in controlling the optic disc hemangioma without causing any adverse effects over a follow-up period as long as 6 years. Furthermore, from the standpoint of requiring no additional treatment, external beam radiotherapy appears to be superior to photodynamic therapy and intravitreal anti-VEGF drug injections, both of which require repeat treatments [11, 12, 18]. In comparison with photodynamic therapy and intravitreal anti-VEGF drug injections, the need for less frequent ophthalmological follow-up visits, required after radiotherapy, is also a merit of the external beam radiation, as in this patient who had systemic manifestations and underwent multiple surgeries.

In conclusion, low-dose external beam radiation was effective in reducing the leakage and diminishing the size of optic disc hemangioma to preserve the central vision over a long follow-up term. External beam radiation is recommended as an initial treatment option for optic disc hemangioma, even in the current situation where other modalities of treatment are available.

References

1. Singh AD, Shields CL and Shields JA: Von Hippel-Lindau disease. Surv Ophthalmol (2001) 46: 117–142.
2. Shuin T, Yamasaki I, Tamura K, Okuda H, Furihata M and Ashida S: Von Hippel-Lindau disease: molecular pathological basis, clinical criteria, genetic testing, clinical features of tumors and treatment. Jpn J Clin Oncol (2006) 36: 337–343.
3. Zbar B, Kishida T, Chen F, Schmidt L, Haher ER, Richards FM, Crossey PA, Webster AR, Affara NA, Ferguson-Smith MA, Brauch H, Glavac D, Neumann HPH, Tisherman S, Mulvihill JJ, Gross DJ, Shuin T, Whaley J, Seizinger B, Kley N, Olschwang S, Boisson C, Richard S, Lips CHM, Linehan WM and Lerman M: Germline mutations in the von Hippel-Lindau disease (VHL) gene in families from North America, Europe, and Japan. Hum Mutat (1996) 8: 348–357.
4. Friedrich CA: Genotype-phenotype correlation in von Hippel-Lindau syndrome. Hum Mol Genet (2001) 10: 763–767.
5. Wong WT, Agron E, Coleman HR, Tran T, Reed GF, Csaky K and Chew EY: Clinical characterization of retinal capillary hemangioblastomas in a large population of patients with von Hippel-Lindau disease. Ophthalmology (2008) 115: 181–188.
6. McCabe CM, Flynn HW Jr, Shields CL, Shields JA, Regillo CD, McDonald HR, Berrocal MH, Gass JDM and Mieler WF: Juxtapapillary capillary hemangiomas. Clinical features and visual acuity outcomes. Ophthalmology (2000) 107: 2240–2249.
7. Raja D, Benz MS, Murray TG, Escalona-Benz EM and Markoe A: Salvage external beam radiotherapy of retinal capillary hemangiomas secondary to von Hippel-Lindau disease. Ophthalmology (2004) 111: 150–153.
8. Singh AD, Nouri M, Shields CL, Shields JA and Perez N: Treatment of retinal capillary hemangioma. Ophthalmology (2002) 109: 1799–1806.
9. Kreusel KM, Bornfeld N, Lommatzsch A, Wessing A and Foerster MH: Ruthenium-106 brachytherapy for peripheral retinal capillary hemangioma. Ophthalmology (1998) 105: 1386–1392.
10. Garcia-Arumi J, Sararols LH, Cavero L, Escalada F and Corcostegui BF: Therapeutic options for capillary papillary hemangiomas. Ophthalmology (2000) 107: 48–54.
11. Schmidt-Erfurth UM, Kusserow C, Barbazetto IA and Laqua H: Benefits and complications of photodynamic therapy of papillary capillary hemangiomas. Ophthalmology (2002) 109: 1256–1266.
12. Wong WT, Liang KJ, Hammel K, Coleman HR and Chew EY: Intravitreal ranibizumab therapy for retinal capillary hemangioblastoma related to von Hippel-Lindau disease. Ophthalmology (2008) 115: 1957–1964.
13. Neumann H, Berger DP, Sigmund G, Blum U, Schmidt D,

Parmer RJ, Volk B and Kirste G: Pheochromocytomas, multiple endocrine neoplasia type 2, and von Hippel-Lindau disease. N Engl J Med (1993) 329: 1531–1538.
14. Wanebo JE, Lonser RR, Glenn GM and Oldfield EH: The natural history of hemangioblastomas of the central nervous system in patients with von Hippel-Lindau disease. J Neurosurg (2003) 98: 82–94.
15. Jagannathan J, Lonser RR, Smith R, DeVroom HL and Oldfield EH: Surgical management of cerebellar hemangioblastomas in patients with von Hippel-Lindau disease. J Neurosurg (2008) 108: 210–222.
16. Kazanjian KK, Reber HA and Hines OJ: Resection of pancreatic neuroendocrine tumors. Results of 70 cases. Arch Surg (2006) 141: 765–770.
17. Teh SH, Deveney C and Sheppard BC: Aggressive pancreatic resection for primary pancreatic neuroendocrine tumor: is it justifiable? Am J Surg (2007) 193: 610–613.
18. Mennel S, Meyer CH and Callizo J: Combined intravitreal antivascular endothelial growth factor (Avastin) and photodynamic therapy to treat retinal juxtapapillary capillary hemangioma. Acta Ophthalmol (2010) 88: 610–613.