

Baseline polyp size as a potential predictive factor for recurrence of polypoidal choroidal vasculopathy

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Abstract

Purpose To investigate the predictive factors for recurrence of polypoidal choroidal vasculopathy (PCV).

Methods The medical records of 78 consecutive patients (78 eyes) with treatment-naïve PCV who responded to first-line treatment and completed at least a 3-year follow-up after the first remission were retrospectively analyzed. In this comparative cohort study, baseline characteristics were compared between the patients who had at least one recurrence (the recurrence group) and those without recurrence (the non-recurrence group) during at least 3-year follow-up periods. In addition, possible predictive factors for recurrence of PCV were investigated by using Cox regression analysis.

Results Within 3 years of the first remission, 50 eyes (64 %) showed at least one recurrence (mean 1.5; 1 to ~2 times). There were no significant differences in the baseline characteristics between the recurrence group and the non-recurrence group. However, the largest polyp diameter was significantly different: the mean largest polyp diameter ($524 \pm 340 \mu\text{m}$) was significantly larger in the recurrence group compared to that of the non-recurrence group ($352 \pm 173 \mu\text{m}$; $P=0.038$). Cox regression analysis showed that the largest polyp diameter at baseline significantly correlated with recurrence of PCV ($B=1.470$, $P=0.015$).

Conclusions The largest polyp diameter at baseline may be predictive for PCV recurrence, as it was significantly larger in patients who had at least one recurrence.

Keywords Anti-vascular endothelial growth factor therapy · Photodynamic therapy · Polypoidal choroidal vasculopathy · Recurrence

Introduction

Polypoidal choroidal vasculopathy (PCV) is characterized by abnormal branching vascular networks and terminating polypoidal lesions, which are most evident by indocyanine green angiography (ICGA) [1–5]. PCV occurs frequently in Asian populations, accounting for up to 50 % of presumed exudative age-related macular degeneration (AMD) [4–8]. Currently, PCV is generally considered to be a peculiar subset of exudative AMD, especially type 1 choroidal neovascularization, showing abnormal branching vascular networks and terminating polyps beneath the retinal pigment epithelium [2, 9–11].

Although the clinical features and natural course of PCV are distinctively different from those of exudative AMD [1, 2, 4, 5, 7, 12, 13], the treatment strategies for PCV do not significantly differ from those of typical exudative AMD. The representative treatments for PCV include photodynamic therapy (PDT) and intravitreal injections of anti-vascular endothelial growth factor (VEGF). The PDT-based treatments (PDT monotherapy or combination PDT plus anti-VEGF therapy) have shown good long-term visual outcomes and high regression rates for polypoidal lesions [14–18]. Anti-VEGF monotherapy is the mainstay of treatment for exudative AMD, and is also widely used as the first-line treatment for PCV, as several studies have demonstrated favorable visual outcomes

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despite limited polyp regression [19–23]. Recently, evidence-based guidelines for PCV were reported [24]. They suggest that PDT monotherapy or combination therapy (combined PDT with intravitreal ranibizumab injections) as the initial treatment guided by ICGA. If polyp regression is incomplete, re-treatment with PDT monotherapy or combination therapy is again recommended [24]. If there is complete regression of polyps by ICGA, leakage from abnormal branching vascular networks, intravitreal ranibizumab injections are recommended as a re-treatment [24].

Although both PDT-based therapy and anti-VEGF therapy have shown good visual outcomes [16–23], recurrence of PCV is another problem needing to be solved. Long-term follow-up studies with a 3-year minimum follow-up period showed PCV recurrence rates of approximately 69 % to 78 % after PDT-based therapies [14, 16, 25–27] and anti-VEGF monotherapy [28]. Because of the high recurrence rate of PCV, these studies recommend careful follow-up of patients [14, 15, 25–28]. Despite the high rates of long-term recurrence, little is known about the contributing factors. In this study, we investigated risk factors for PCV recurrence after treatment during long-term follow-up periods using ICGA.

Methods

Study subjects

We retrospectively reviewed the medical records of Korean patients with treatment-naïve PCV who fulfilled the inclusion and exclusion criteria. The patients were treated at the Vitreoretinal Service Clinic of Yonsei University Medical Center between October 2006 and October 2013. The first treatment for each patient was performed between October 2006 and September 2010. Written informed consent for each treatment was obtained at the time of each treatment. This comparative cohort study was approved by the Institutional Review Board of Yonsei University College of Medicine and was conducted in accordance with the tenets of the Declaration of Helsinki. Inclusion criteria were: (1) treatment-naïve symptomatic macular PCV with subfoveal leakage documented by fluorescein angiography (FA), (2) the presence of branching vascular networks and polypoidal lesions by ICGA, (3) completion of at least a 3-year follow-up after the first treatment (PDT, combination therapy of PDT with anti-VEGF therapy, or anti-VEGF monotherapy) for PCV, and (4) at least one remission after the first treatment phase (remission defined as the complete resolution of exudative fluid from PCV for at least 6 months after the end of the first treatment period). Exclusion criteria were: (1) PCV with persistent exudative fluid or leakage during the follow-up period, (2) other concomitant ocular diseases, such as diabetic

retinopathy, high myopia, vein or artery occlusion, or epiretinal membrane, and (3) aphakia, absence of posterior capsule, or history of vitrectomy due to reduced anti-VEGF retention.

Examinations

All patients received complete ophthalmologic evaluations including best-corrected visual acuity (BCVA) testing using a decimal visual acuity chart, slit-lamp biomicroscopy, dilated fundus examination with indirect ophthalmoscopy, color fundus photography, digital FA, ICGA, and optical coherence tomography (OCT). OCT images were obtained by time-domain OCT (Stratus®; Carl Zeiss Meditec, Dublin, CA, USA) prior to 2009, and then by spectral domain OCT (SD OCT) subsequently (Spectralis; Heidelberg Engineering, Heidelberg, Germany). FA and ICGA were performed with the Heidelberg Retina Angiograph system (HRA-2; Heidelberg Engineering) and a confocal scanning laser ophthalmoscope.

Polypoidal lesions were classified according to angiographic characteristics [29]. The locations of PCV lesions were subdivided into three categories: subfoveal, juxtafoveal (within 1–199 μm from the foveal center), or extrafoveal (200 μm or more from the foveal center). PCV was classified into two categories according to the number of discrete areas of polypoidal lesions: single or multiple. The representative figures of polypoidal lesions were shown in Fig. 1. The greatest linear dimension included the entire branching vascular network of vessels and polypoidal lesions at the early phase of ICGA; this was assessed with an electronic caliper using HRA-2 software (Heidelberg Engineering). The PCV lesion area was also measured manually with the same procedure. Pigment epithelial detachment (PED) was not considered if there was no underlying vascular component when the greatest linear dimension and PCV lesion area were measured. In addition, the presence of choroidal hyperpermeability was evaluated on late-phase ICGA images.

First-line treatment for PCV

Patients received one of three treatment modalities as the first-line treatment for PCV: a single session of PDT, anti-VEGF monotherapy (three monthly intravitreal injections of anti-VEGF agents), or combination therapy of PDT with anti-VEGF therapy (a single session of PDT and three monthly intravitreal injections of anti-VEGF agents). During the study period, the mainstay of treatments for exudative AMD, including PCV, shifted from PDT-based therapy to anti-VEGF monotherapy in our clinic. Thus, three treatment modalities could be assessed during this period.

For PDT, all patients received a 6-mg/m² infusion of verteporfin (Visudyne; Novartis AG, Bulach, Switzerland) over a period of 10 minutes. Then, 15 minutes after the end

of verteporfin infusion, a diode laser at 689 nm was applied to the PCV lesion. The entire lesion was covered with 50-J/cm² light energy and a light dose rate of 600 mW/cm² for 83 seconds. The laser spot size included an additional 500 µm to cover the borders on each side. If the exudative fluid from the PCV was not completely resolved after PDT, additional PDT was applied at 3-month intervals until the exudative fluid resolved.

Anti-VEGF therapy was administered as three monthly intravitreal injections of ranibizumab (0.5 mg/0.05 mL; Lucentis®; Genentech, Inc, South San Francisco, CA, USA). Topical anesthesia was applied, and 10 % povidone-iodine was used to scrub eyelids and lashes before intravitreal injections. Povidone-iodine eye drops (1.25 %) were applied, and a sterile lid speculum was inserted between the eyelids. The anti-VEGF agent was injected into the vitreous cavity through the superior sclera using a 30-gauge needle at a position 3.5 mm posterior to the corneal limbus in phakic eyes or 3.0 mm posterior in pseudophakic eyes. Pressure was applied to the injection site using a sterile cotton swab for 1 minute to prevent leakage. Patients were instructed to apply antibiotic eye drops for 1 week following the injections.

For combination therapy of PDT with anti-VEGF therapy, patients were treated with one session of PDT and three monthly intravitreal injections of bevacizumab (1.25 g/0.05 mL; Avastin®; Genentech, Inc). PDT was performed as described above. Intravitreal bevacizumab injections were administered immediately after PDT on the same day and in the same manner as previously described.

Follow-up and recurrence of PCV

Follow-up visits were arranged 1 week after each baseline treatment and monthly thereafter. Examinations included BCVA, dilated fundus examination with indirect ophthalmoscopy, and OCT. Three months after the first-line treatments, FA and ICGA were performed to evaluate treatment outcomes. Additional FA and ICGA were performed during monthly follow-up visits when PCV recurrence was suspected due to findings, such as the reappearance of new polyps, subretinal hemorrhage, or subretinal exudation on fundus examination, the reappearance of subretinal fluid on OCT, or decreased vision. Remission was defined as the complete resolution of subretinal exudative fluid and hemorrhages by fundus examination and SD OCT evaluation, regardless of regression of polyps and/or abnormal branching vascular networks. PCV recurrence was defined as the reappearance of active PCV lesions on ICGA with subfoveal leakage on FA and reappearance or development of subretinal exudative fluid on SD OCT examination after at least 6 months after the remission.

We investigated the angiographic data for patients in whom polyp regression occurred after each treatment modality. After evaluating polyp regression, PCV recurrence was also

investigated. If active PCV with leakage was identified prior to 6 months after treatment, the original lesion was considered to be persistent rather than recurrent. The recurrence pattern of PCV was determined using FA and ICGA images that were taken at the time of diagnosis, 3 months after the first treatment, and at the time of recurrence. If polyps regressed after the first treatment, the recurrence pattern was further classified as an exudation from an abnormal branching vascular network without polyps or as the development of new polyps. If polyps did not regress, and recurrent exudation from non-regressing polyps and abnormal branching vascular networks occurred, we defined this type of recurrence as a persistent polyp. After the first treatment period, we treated recurrent PCV with monthly injections of intravitreal anti-VEGF agents, mainly bevacizumab, until the exudative fluid resolved according to OCT.

Statistical analyses

Patient characteristics, including age at initial diagnosis, sex, and BCVA at baseline, were retrieved from medical charts. BCVA results were converted to a logarithm of the minimum angle of resolution (logMAR) value for statistical analysis. In addition to these parameters, the angiographic characteristics of PCV were also retrieved. Data regarding the largest polyp diameter, greatest linear dimension of choroidal vascular networks, area of the entire PCV lesion, presence of PED (larger than the area of one optic disc diameter), polyp location (subfoveal, juxtafoveal, or extrafoveal), and area of discrete polyp lesion (single or multiple) were retrieved and recorded. The first recurrence was defined as our primary outcome measure for statistical analysis.

IBM SPSS 18.0 software for Windows (SPSS/IBM Corporation, Chicago, IL, USA) was used for statistical analyses. We evaluated baseline and clinical factors with respect to the recurrence rates. Hereby the nonparametric analyses were performed with a Mann–Whitney U test and Kruskal–Wallis analysis for the continuous variables and chi-square test for the categorical variables. To minimize the effect of different intervals between the first remission and recurrence, Cox regression analysis was performed. To minimize the possible interaction between the possible risk factors for recurrence of PCV, two-way interactions for possible risk factors were included in Cox regression analysis. Differences with $P < 0.05$ were considered statistically significant.

Results

Overall characteristics of patients

Seventy-eight eyes of seventy-eight patients met the study criteria and were retrospectively analyzed. Among the study

population, 55 patients (71 %) were male, and the mean age at diagnosis was 67 ± 9 years. The mean duration of the first treatment period to achieve the first remission was 6 ± 2 months (3 months to 8 months). At the time of diagnosis, the mean greatest linear diameter was 3 ± 1 mm (0.5 to ~ 7 mm), and the mean largest polyp diameter was 467 ± 380 μm (120 to $\sim 1,650$ μm). The mean area of PCV lesion was 6 ± 5 mm^2 (0.5 to ~ 23 mm^2). The location of PCV was subfoveal (44 patients, 56 %), juxtafoveal (20 patients, 26 %), and extrafoveal (14 patients, 18 %). The discrete area of PCV was 1 in 71 patients (91 %) and multiple in 7 patients (9 %). Choroidal hyperpermeability was present in 24 patients (31 %), and PED was present in 36 patients (46 %). The mean BCVA was 0.64 ± 0.41 logMAR (20/87 Snellen equivalent). During the follow-up period, the mean total number of PDTs was 2 ± 1 times, and the mean total number of anti-VEGF injections was 9 ± 7 times.

Recurrence of PCV

Within 3 years after the first remission of PCV, 50 eyes (64 %) showed at least 1 recurrence. The mean number of recurrence was 1.5 (1 to ~ 2 times) in the eyes with at least one recurrence during follow-up periods. After assessment of recurrence rate, we investigated the regression of polyps and the pattern of recurrence in these patients. Among these 50 eyes, 35 eyes (70 %) showed polyp regression, and 15 eyes (30 %) showed persistent polyps at the time of the first remission. Despite treatment, none of the eyes showed complete regression of abnormal branching vascular networks. In the eyes with recurrence, the recurrence pattern was classified as follows: reactivation of persistent polyps, new development of polyps, and leakage from abnormal branching vascular networks without polyps Fig. 2.

Comparison of patients with recurrent and without recurrent PCV after the first treatment

The baseline characteristics and polyp regression at the first remission were compared between patients with at least one recurrence (the recurrence group) and those without recurrence (the non-recurrence group). There were no significant differences in baseline characteristics, except in the largest polyp diameter. The mean largest polyp diameter was 524 ± 340 μm (170 to $\sim 1,650$) in the recurrence group and 352 ± 173 μm (120 to ~ 570) in the non-recurrence group ($P=0.038$). Distribution map of the largest polyp size at baseline is shown as Fig. 3. Comparisons of the baseline characteristics are described in Table 1.

First-line treatment strategies and recurrence of PCV

Among 78 patients, 12 patients were treated with PDT monotherapy (PDT group). Thirty-four patients received anti-VEGF monotherapy (anti-VEGF group), and 32 patients received combination therapy with PDT plus anti-VEGF therapy (combination group). When we compared baseline characteristics among the three treatment groups, there were no significant differences, including for age at diagnosis ($P=0.135$), sex ($P=0.522$), the baseline mean BCVA ($P=0.275$), and PCV characteristics (location of PCV, $P=0.541$; discrete area of PCV, $P=0.436$; the greatest linear diameter, $P=0.526$, the largest polyp diameter, $P=0.494$; area of PCV lesion, $P=0.311$; choroidal hyperpermeability, $P=0.051$; and presence of PED, $P=0.171$). However, the polyp regression rate at the time of first remission was significantly different among the three treatment groups ($P=0.005$). Significantly higher polyp regression rates were observed in the PDT and combination groups compared to that of the anti-VEGF group. Although the recurrence rates after each treatment were not significantly

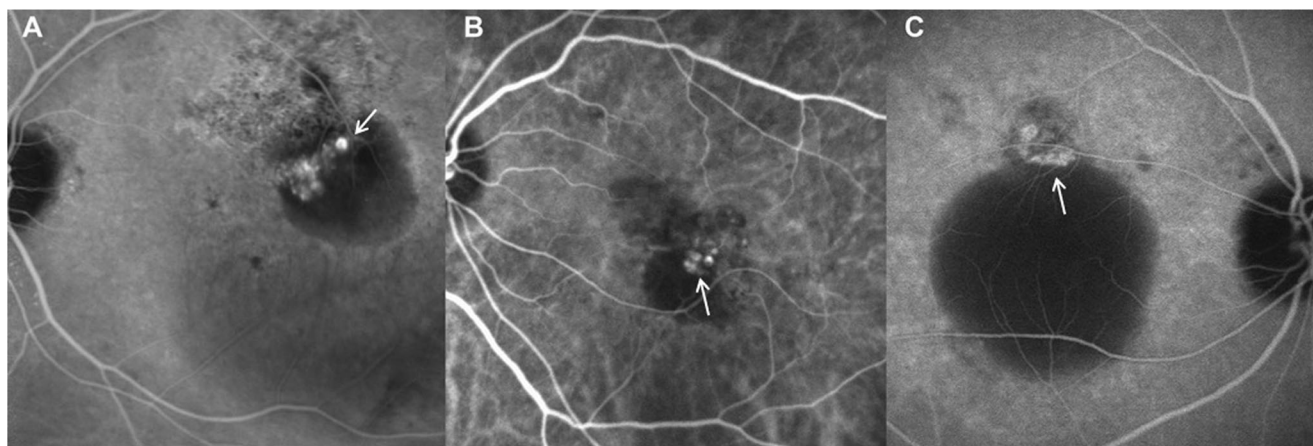
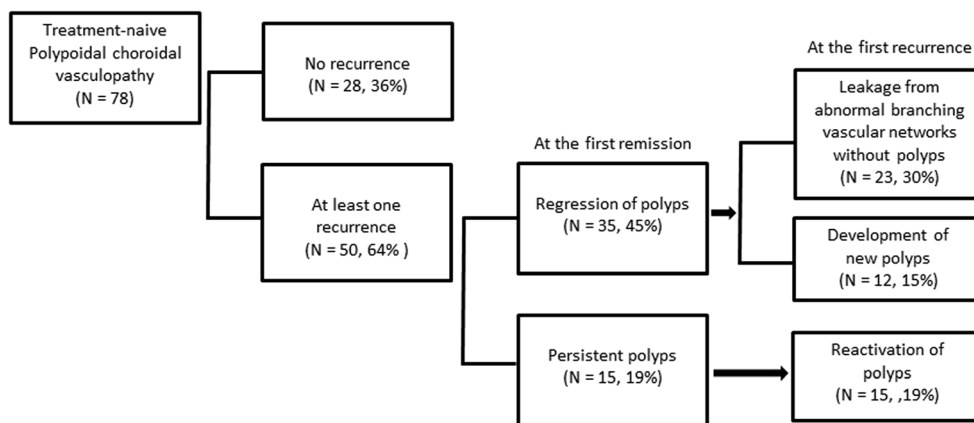


Fig. 1 Representative figures of polyps (a, b, c) in the eyes with polypoidal choroidal vasculopathy. A white arrow in each eye indicates polypoidal lesion

Fig. 2 Classification of the eyes according to the presence of recurrence and its pattern in this study. The recurrence pattern was classified as follows: reactivation of persistent polyps, new development of polyps, and leakage from abnormal branching vascular networks without polyps



different among the three groups ($P=0.758$), the recurrence pattern was significantly different ($P=0.004$).

Predictive factors for recurrence of PCV

We investigated predictive factors for the recurrence of PCV. Baseline characteristics, such as age at the time of diagnosis, sex, and baseline BCVA, were included, as were PCV characteristics, including the largest polyp diameter at baseline, the greatest linear diameter, location, and type of PCV. Treatment strategy (PDT, anti-VEGF therapy, and combination therapy) was also included in the statistical analysis. Because the interval between the first remission and recurrence varied among patients, we performed Cox regression analysis to confirm predictive factors for PCV recurrence (Table 2). Cox regression analysis showed that the largest polyp diameter at baseline was predictive for PCV recurrence ($B=1.470, P=0.015$).

Representative figures are shown in Fig. 4.

Discussion

In this study, we focused on the predictive factor for PCV with at least a 3-year follow-up after the first remission of treatment-naïve PCV. During 3 years after the first remission, 50 patients (64 %) showed at least 1 recurrence. When we compared the baseline characteristics between the recurrence group and non-recurrence group, there were no significant differences except the mean largest polyp diameter at baseline. The mean largest polyp diameter at baseline was significantly larger in the recurrence group when compared to the non-recurrence group. In addition, subsequent Cox regression analysis showed that the largest polyp size at baseline significantly correlated with PCV recurrence.

Baseline lesion sizes, such as the greatest linear diameter and the largest polyp size, have been suggested as possible prognostic factors for visual outcome after treatment of PCV [15, 28, 30–34]. Based on these studies and the current study,

Fig. 3 Distribution map of the largest polyp size at baseline. The mean largest polyp diameter was $524\pm340\ \mu\text{m}$ in the recurrence group and $352\pm173\ \mu\text{m}$ in the non-recurrence group. The mean largest polyp diameter at baseline was significantly larger in the recurrence group than that of the non-recurrence group ($P=0.038$)

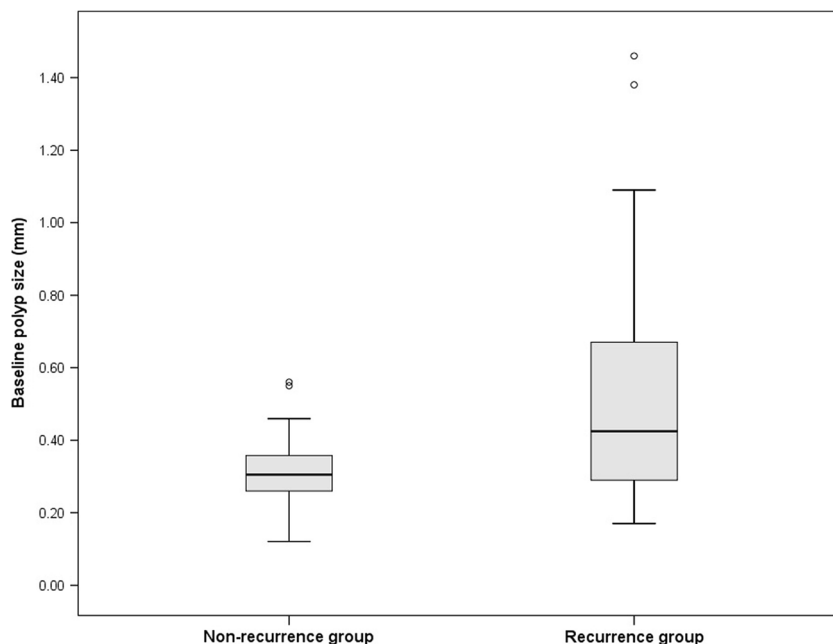


Table 1 Comparison between the patients with recurrence (recurrence group) and without recurrence (non-recurrence group) of polypoidal choroidal vasculopathy (PCV) after treatment with photodynamic therapy (PDT), anti-vascular endothelial growth factor (VEGF) therapy, or combination therapy of PDT with anti-VEGF therapy

	Recurrence group (N=50)	Non-recurrence group (N=28)	P value
Mean age at diagnosis (year, mean±SD)	68±8	65±12	0.126*
Greatest linear diameter (mm, mean±SD)	3±1	3±1	0.542*
Largest polyp diameter (µm, mean±SD)	524±340	352±173	0.038*
Area of PCV lesion (mm ² , mean±SD)	6±6	6±5	0.313*
Baseline BCVA, logMAR (Snellen equivalent; mean±SD)	0.61±0.40 (20/81)	0.76±0.42 (20/115)	0.100*
Location of PCV (number, percent; %)			0.368†
Subfovea	28 (56 %)	16 (57 %)	
Juxtafovea	11 (22 %)	9 (32 %)	
Extrafovea	11 (22 %)	3 (11 %)	
Discrete area of PCV (number, percent; %)			0.509†
One	45 (90 %)	26 (93 %)	
Multiple	5 (10 %)	2 (7 %)	
Choroidal hyperpermeability (number, percent; %)	17 (34 %)	7 (25 %)	0.287†
Pigment epithelial detachment (number, percent; %)	24 (48 %)	12 (43 %)	0.421†
Polyp regression at the first remission	36 (72 %)	23 (82 %)	0.236†
First line treatment (number, percent; %)			0.758†
PDT monotherapy (N=16)	7 (14 %)	5 (18 %)	
Anti-VEGF monotherapy (N=34)	21 (42 %)	13 (46 %)	
Combination therapy (N=32)	22 (44 %)	10 (36 %)	

BCVA, best-corrected visual acuity; LogMAR, logarithm of the minimum angle resolution; SD, standard deviation
*Mann–Whitney U test for continuous variables, and †chi-square test for categorical variables were used for statistical analysis. $P < 0.05$ was set for statistical significance.

the largest polyp size at baseline may represent the disease activity of treatment-naïve PCV, predicting treatment outcome and recurrence. However, the range of the largest polyp size should be further considered. In this study, the results suggest

Table 2 The results of Cox regression analysis for predictive factors associated with recurrence of polypoidal choroidal vasculopathy (PCV)

Possible predictive factors	Coefficient of regression (B)	P
Mean age at diagnosis	0.039	0.127
Sex	-0.707	0.082
Greatest linear diameter	-0.406	0.068
Largest polyp diameter	1.470	0.015*
Area of PCV lesion	0.085	0.145
Baseline best-corrected visual acuity	-0.530	0.468
Baseline central macular thickness	0.002	0.281
Location of PCV	0.545	0.579
Discrete area of PCV	-0.648	0.262
Choroidal hyperpermeability	0.004	0.991
Pigment epithelial detachment	-0.311	0.334
First treatment method	0.149	0.739

$P < 0.05$ was set for statistical significance.

that the mean largest polyp size is significantly large in the recurrence group, and statistical analysis showed the largest polyp size at baseline as a predictive factor for recurrence of PCV. However, there were some patients to be considered. Some patients had recurrence of PCV although the largest polyp size was relatively smaller than the mean largest polyp size of the recurrence group. Some patients also did not show recurrence although the largest polyp size was relatively larger than the mean largest polyp size of the non-recurrence group. These occurrences suggest that there may be other factors affecting the recurrence of PCV. Previous studies have suggested the predictive value of the greatest linear diameter of PCV, although they did not include baseline polyp size [30, 34]. Our results suggest that the largest polyp size represents disease activity and can be used as a predictive factor for PCV recurrence even after the regression of polyps. However, we also think that there may be other factors associated with recurrence of PCV which were not found in our study. Thus, future prospective studies with larger populations may be helpful for confirming the predictive value of the largest polyp size and for further investigation of other predictive factors in patients with PCV.

In addition to predictive factors for PCV recurrence, we investigated the recurrence pattern after three treatment modalities used in this study. PDT-based treatment appears to be

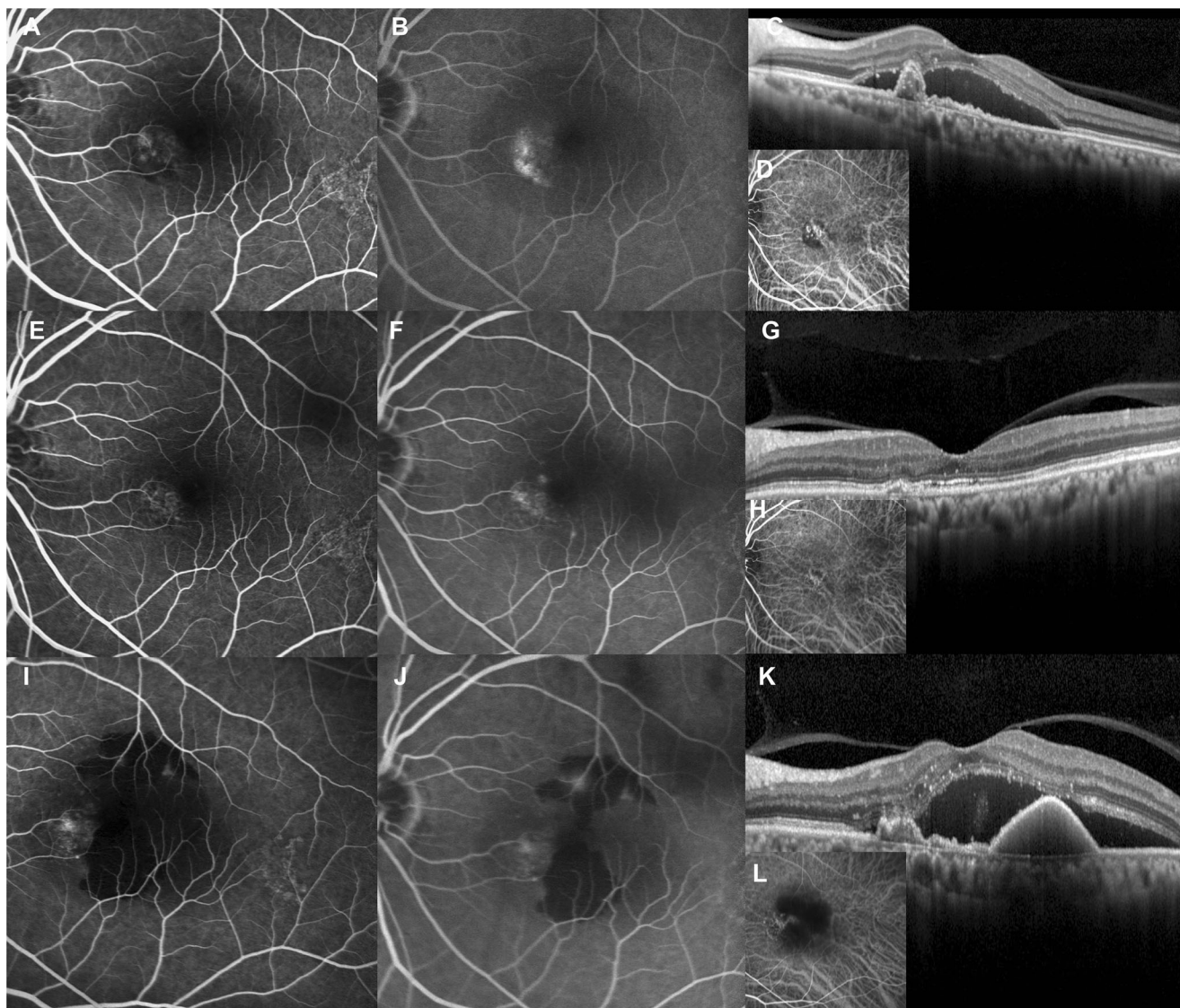


Fig. 4 A 62-year-old male was referred due to decreased vision in his left eye for 1 month. Best-corrected visual acuity (BCVA) of the left eye was 0.7 logMAR (logarithm of the minimum angle resolution; 20/100 Snellen visual acuity). Fluorescein angiography (FA) showed irregular hyperfluorescence at an early phase (a), from which profuse leakage was shown in a late phase (b). Optical coherence tomography (OCT) showed subretinal fluid with vascularized pigment epithelial detachment (c). Indocyanine green angiography (ICGA) showed polyps with abnormal branching vascular networks (d). Combination therapy was performed as for the first-line treatment: a single session of photodynamic therapy (PDT) with three monthly intravitreal injections

of bevacizumab (1.25 mg/0.05 mL; Avastin[®]; Genentech, Inc). After treatment, hyperfluorescence at an early phase (e) did not show profuse leakage at a late phase (f) on FA, and OCT showed resolution of subretinal fluid (g). ICGA showed polyp regression (h), and BCVA improved to 0.3 logMAR (20/39 Snellen visual acuity). After 9 months, BCVA of the left eye decreased to 0.5 logMAR (20/63 Snellen visual acuity); FA showed irregular leakage from the early (i) to late phase (j) on FA. OCT showed subretinal fluid with pigment epithelial detachment (k). Persistent abnormal branching vascular networks were seen on ICGA without definite polyps (l)

more effective for the regression of polypoidal lesions when compared to that of anti-VEGF therapy. The polyp regression rate is 73 % to 99 % after PDT-based therapy [14–18, 35–37], whereas that of anti-VEGF therapy is usually 22 % to 43 % [20, 28, 38, 39]. In this study, polyp regression at the time of the first remission differed significantly among treatment groups. Polyp regression at the time of the first remission was significantly higher in patients who received PDT and combination therapy compared to that of patients who

received anti-VEGF monotherapy; this was consistent with previous studies [14–18, 20, 28, 35–39]. The recurrence pattern was significantly different among treatment groups, possibly in accordance with differences in the polyp regression rates. PDT and combination therapy showed higher rates of polyp regression; the development of new polyps or leakage from abnormal branching vascular networks without new polyps were more dominant in these groups than with anti-VEGF monotherapy. However, the polyp regression rate and

recurrence patterns after each treatment strategy were not significantly associated with recurrence of PCV in this study. The recurrence rates after three treatment modalities were not significantly different in this study, consistent with previous studies [14, 15, 25–27].

This study has several limitations, including the retrospective nature and relatively small study population. The retrospective nature of this study lead to several limitations, including the heterogeneous treatment strategy for treatment-naïve PCV. However, we demonstrated that treatment strategy did not show significant differences in recurrence rates and did not significantly correlate with PCV recurrence. In addition, the baseline characteristics of three treatment modalities were not significantly different, showing fairly random distribution. Another limitation was in the use of anti-VEGF agents, which might affect the outcome. If this study was conducted in a prospective manner, uniform use of anti-VEGF agents could be achieved. However, in our real practice, we should consider various factors, including the Korean National Health Insurance (NHI) system and the patients' economic statuses. Either PDT or ranibizumab is covered by the NHI system; usually, PDT is covered by the NHI system and bevacizumab is used for combined anti-VEGF therapy to reduce patients' economic burden. However, a recent study indicates that there are no significant differences in efficacy or safety for ranibizumab and bevacizumab [40]. Thus, we believe that any potential bias from the difference in anti-VEGF agents was minimal. We believe that a future, long-term study with a prospective design and uniform treatment strategy is needed to strengthen our findings.

In conclusion, the largest polyp size at baseline significantly correlated with PCV recurrence, showing increased risk of recurrence with a larger polyp size at baseline. Thus, patients with larger polyps should be monitored more carefully due to higher risk of recurrence even after successful treatment of PCV.

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Contributions of authors Design and conduct of study (HM Kang and SC Lee); collection of data (HM Kang); management, analysis, and interpretation of data (HM Kang, HJ Koh, and SC Lee); and preparation, review, and approval of the manuscript (HM Kang, HJ Koh, and SC Lee).

Other acknowledgments None.

Compliance with ethical standards All procedures performed in studies involving human participants were in accordance with the ethical

standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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