Diagnosing Polypoidal Choroidal Vasculopathy using Color Fundus Photography, Optical Coherence Tomography and Optical Coherence Tomography Angiography

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Abstract

Purpose: To compare the diagnostic accuracy of differentiating polypoidal choroidal vasculopathy (PCV) from exudative age-related macular degeneration (AMD), using color fundus photography (CFP), optical coherence tomography (OCT), and swept-source optical coherence tomography angiography (SS-OCTA) without using fluorescein angiography/indocyanine green angiography (FA/ICGA).

Methods: Treatment-naïve eyes with exudative age-related macular degeneration (AMD) that underwent CFP, OCT, SS-OCTA, and FA/ICGA imaging before treatment were identified. Images of each patient were categorized into 2 sets (Set A: CFP+OCT; Set B: CFP+SS-OCTA). In Set B, both the en face and cross-sectional B-scans were analyzed. Each set was reviewed by two graders, and it was determined whether the presumed diagnosis was PCV. Sensitivity, specificity, and area under the curve (AUC) for the diagnosis of PCV were assessed for each set by comparing diagnoses that included ICGA. The number of polypoidal lesions in each set was calculated and compared to ICGA.

Results: A total of 94 study eyes from 94 patients with AMD were included in the study, of which 66.0% were male, and the mean age was 71.8±9.0 years. The PCV diagnosis rate using ICGA was 45.7%. Sensitivity of sets A, B: 0.88, 0.93; specificity: 0.94, 0.96; positive predictive value: 0.93, 0.95; negative predictive value: 0.91, 0.94, AUC: 0.90 (95% confidence interval [CI]:0.83–0.97), 0.96 (95% CI:0.90–1.00). Set A detected polypoidal lesions 1.28±0.91, Set B detected polypoidal lesions 1.47±1.01, ICGA showed 1.51±0.86. In the interclass correlation coefficient analysis, the correlation between Set A and ICGA was ICC=0.76(95% CI:0.60-0.86, p<0.001), and the correlation between Set B and ICGA was ICC=0.84(95% CI:0.72-0.91, p<0.001).

Conclusion: This study highlights that, without using ICGA, both CFP combined with OCT and CFP combined with SS-OCTA demonstrate high sensitivity, specificity, and AUC in diagnosing PCV. It is evident that SS-OCTA contributes to enhancing sensitivity, specificity, and AUC for PCV diagnosis.

Keywords: polypoidal choroidal vasculopathy, swept-source optical coherence tomography angiography, optical coherence tomography, polypoidal lesions
Introduction

Polypoidal choroidal vasculopathy (PCV) is a subtype of exudative age-related macular degeneration (AMD). PCV subtype is about 50% of neovascular AMD cases in Asia, whereas this portion is 10-20% in White population [1,2]. Anti-vascular endothelial growth factor (VEGF) therapy has been effective in PCV [3]. However, compared to outcomes of treatment of other neovascular AMD, eyes with the PCV variant were observed to be poor responders to anti-VEGF therapy [4,5]. For these reasons, it is necessary to differentiate clinically between PCV and typical AMD.

The gold standard of diagnosing PCV is indocyanine green angiography (ICGA) which is characterized by nodular dilatations arising from neovascular networks that branching out mainly in the subretinal pigment epithelial space [6]. Since ICGA is time consuming and invasive, researches have been conducted to replace it. Optical coherence tomography (OCT) images are useful in diagnosing PCV when used alone or in combination with other images. Several OCT features such as sharp peaked PEDs, double layer sign and en face OCT has been helpful for diagnosing PCV and polypoidal lesions [7-9]. In previous study, using color fundus photography (CFP), OCT, and fluorescein angiography (FA) without ICGA, it is possible to diagnose PCV with a sensitivity and specificity of 95% [10].

Recently, swept-source optical coherence tomography angiography (SS-OCTA) image is comparable to ICGA for the diagnosis of treatment-naïve PCV and it may provide enhanced identification of both polypoidal lesions and branched vascular network (BVN) in treatment-naïve PCV than ICGA. Unlike OCT, SS-OCTA might be useful for diagnosing PCV because it shows the blood flow on cross sectional B-scan images and the vascular structure of BVN on en face images [11]. However, the previous study did not report definitive sensitivity and specificity values for diagnosing PCV using multimodal imaging without ICGA. Moreover, other studies that have assessed polypoidal lesions using OCTA have reported varying detection rates ranging from 17% to 92% [11-14]. Therefore, this study aims to identify sensitivity, specificity, predictive accuracy (area under the receiver operating characteristic curve [AUC]) and the detection of polypoidal lesions using CFP, OCT, and SS-OCTA without using ICGA.

Materials and Methods

Patients who visited ________ (_______) March 1, 2017 to February 30, 2021, with treatment naïve exudative AMD including PCV in one or both eyes and underwent four ophthalmologic examinations (CFP, OCT,
SJ Park, et al. Diagnosing PCV using CFP, OCT and SS-OCTA (SS-OCTA, FA/ICGA) were included in this study. This study was approved by the Institutional Review Board of ________ (No. 2023-08-001). Patient with high myopia (≥ 6.0 diopters or greater, axial length of ≥ 26.0 mm or greater), severe media opacity which could not analyze images, or the presence of other retinal vascular disorders (e.g. macroaneurysm, diabetic retinopathy, and retinal vascular occlusion) were excluded. When exudative AMD was diagnosed in both eyes, only the right eye was included. In this study, images and clinical data from 94 eyes of 94 patients with AMD were independently analyzed by two retina specialists. During the analysis, the patients were assessed using two different diagnosing sets. Excluding the use of ICGA, the first set used CFP and OCT images, while the second set used CFP and SS-OCTA images. During the analysis, any disagreement in diagnosis between two retina specialists was reviewed and discussed and consensus was reached with involvement of a senior adjudicator. In this way, we assessed the diagnostic accuracy of PCV among the 94 eyes in the two sets, excluding ICGA. Statistical analysis was then conducted to compare these two groups with the PCV diagnoses made by ICGA.

**Diagnostic criteria of PCV and image analysis**

Each patient has undergone CFP, OCT, SS-OCTA and FA/ICGA at initial visit. CFP images (Visucam524, Carl Zeiss Meditec, Dublin, California, USA or Clarus 500, Carl Zeiss Meditec, Dublin, California, USA) were reviewed for features of extensive subretinal hemorrhage (subretinal and sub-retinal pigment epithelium [RPE] hemorrhage larger than 4 disc diameter) and orange nodule (which shows one or more orange subretinal round elevation) [6,15].

ICGA images (Spectralis; Heidelberg Engineering, Heidelberg, Germany) were analyzed by EVEREST criteria. PCV was diagnosed by focal hyperfluorescent lesions appearing before 6 minutes on ICGA plus at least 1 of the followings: BVN on ICGA, pulsatility on dynamic ICGA, nodular appearance when ICGA viewed steroscopically, hypofluorescent halo on ICGA, orange subretinal nodule on CFP, associated with massive submacular hemorrhage [16,17].

OCT images (Spectralis; Heidelberg Engineering, Heidelberg, Germany) were analyzed for the following features: sharp peaked pigment epithelial detachment (PED), sub-RPE ring-like lesion, complex or multilobular PED, double-layer sign (undulating RPE line that is separated from Bruch’s membrane line underneath), thick choroid with dilated Haller’s layer vessels, predominant subretinal fluid with or without intraretinal fluid, en face OCT complex RPE elevation [6]. The combination of three OCT-based major criteria (Sharp-peaked PED, sub-RPE ring-like lesion, en face OCT complex RPE elevation) were assessed to diagnose PCV (Fig. 1). Detailed OCT
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Criteria of polypoidal lesion were defined according to the recent definition proposed by the Asia-Pacific Ocular Imaging Society PCV Workgroup. [6].

SS-OCTA images (PLEX Elite 9000, Carl Zeiss Meditec, Dublin, California, USA) were analyzed both the en face and cross-sectional B-scans with blood flow images to identify polypoidal lesions using 6mm x 6mm images. The en face slabs were initially automatically created using boundary layers from the RPE to the RPE-fit. RPE-fit layer is corresponded with the Bruch's membrane. These boundary layers were established using the custom segmentation feature and the exact position and thickness of the slab were then manually adjusted to optimize the signal for viewing of the PCV complex. Polypoidal lesions were analyzed by viewing both the en face slabs and cross-sectional B scans. En face slabs with hyper-reflective foci with blood flow signals on cross-sectional B scans were calculated as polypoidal lesions. PCV were diagnosed by at least one polypoidal lesions and combination of dome-shaped, sharp-peaked PEDs and sub-RPE ring-like lesion on the cross-sectional B-scans (Fig. 2) [11,18].

Set analysis and Image Reading

In this study, it was assessed by dividing into two sets, A and B. In Set A, patients were diagnosed PCV by analyzing CFP and OCT. In Set B, CFP and SS-OCTA with en-face and cross-sectional B-scans were analyzed. After analyzing, each set was compared with PCV diagnosed by ICGA. Then, sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and area under the curve were analyzed. Number of polypoidal lesion which can be anatomical marker of PCV were analyzed in each set.

Statistical analysis

Statistical analysis of sensitivity, specificity, PPV, NPV, AUC were analyzed. Cronbach's alpha and interclass correlation coefficient (ICC) were analyzed to evaluate correlation between polypoidal lesions in Set A, Set B and ICGA using single measure, two-way random model. All statistical analysis was performed with IBM SPSS Statistics for Windows (v 24.0; IBM Corp, Armonk, New York, USA).

Results

The mean age was 71.8 ± 9.0, with 66.0% being male. At baseline 45.7% of eyes had diagnosed with PCV, 30.9% with type 1 CNV, 18.1% with type 2 CNV and 5.3% with type 3 CNV, (Table 1). In Set A and Set B,
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40 eyes and 41 eyes were diagnosed with PCV, respectively. However, three eyes in Set A and two eyes in Set B were not diagnosed with PCV on ICGA.

Based on this result, Set A (CFP + OCT) showed a sensitivity of 0.88, specificity of 0.94, PPV of 0.93, NPV of 0.91 and AUC of 0.90 (95% confidence interval [CI]: 0.86–0.97). Set B (CFP+SS-OCTA) had a sensitivity of 0.93, specificity of 0.96, PPV of 0.95, NPV of 0.94 and AUC of 0.96 (95% CI: 0.90–1.00) (Table 2, Fig. 3). Between two image sets, Set B showed better results including the higher sensitivity, specificity, PPV, NPV and AUC. An AUC of 0.8 or greater indicates high prediction accuracy, while an AUC of less than 0.8 indicates relatively low accuracy. Therefore, both sets showed high prediction accuracy but Set B has higher AUC than Set A.

In PCV diagnosed eye, the number of polypoidal lesions were calculated at each set. Set A detected polypoidal lesions 1.28±0.91, Set B detected polypoidal lesions 1.47±1.01, ICGA showed 1.51±0.86. The scatter plots comparing the number of polypoidal lesions in Set A, Set B and ICGA in each patient was analyzed (Fig. 4). In ICC analysis, Cronbach’s α shows 0.86 between Set A and ICGA. In Set B and ICGA, Cronbach’s α was 0.91. In single measure analysis using two-way random model, which showed how much difference is between two groups, showed ICC=0.76 (95% CI: 0.60-0.86), p<0.001 between Set A and ICGA, ICC=0.84 (95% CI: 0.72-0.91), p<0.001 between Set B and ICGA. This showed both Set A and Set B are correlated to ICGA diagnosed group. Set B, which includes SS-OCTA images, shows a stronger correlation in the analysis of the number of polypoidal lesions compared to Set A, and it is comparable to ICGA like previous study [11].

**Discussion**

ICGA is the gold standard for the diagnosis of PCV and it is diagnosed by early subretinal hyperfluorescence and at least one of the criteria (nodular appearance of the polypoidal lesions on stereoscopic viewing, hypofluorescent halo around the nodule, large feeder vessel with a BVN, pulsatile filling of polypoidal lesions, orange subretinal nodules corresponding to the hyperfluorescent area on ICGA, massive submacular hemorrhage) [16,17]. However, its invasive and time-consuming method needs alternative diagnostic technique. This study shows that combining CFP, OCT, SS-OCTA images is possible to diagnose PCV without ICGA in untreated patients with PCV. Previous study showed SS-OCTA only can be accurately diagnose components of PCV lesions such as BVNs and polypoidal lesions [11]. However, in previous study, sensitivity and specificity of PCV diagnosis could not be calculated and PCV cases were diagnosed based on ICGA findings before SS-OCTA.
SJ Park, et al. Diagnosing PCV using CFP, OCT and SS-OCTA images were reviewed. Therefore, graders already knew that polypoidal lesions and BVNs were present in each case. In this study, we evaluated patient with newly diagnosed exudative AMD undergoing image analysis. Therefore, our graders were unaware of the presence of polypoidal lesions and BVNs.

Set A and Set B showed high sensitivity and specificity for diagnosing PCV in this study. Especially, including SS-OCTA images in Set B shows higher sensitivity, specificity, PPV, NPV and AUC and it is superior to OCT images. This result shows that en face images and blood flow signal in cross-sectional B-scan images are helpful in detecting polypoidal lesions and BVN to diagnose PCV. Blood flow signals between the RPE and Bruch's membrane, as well as the sub-RPE ring-like lesion, demonstrate blood flow within the polypoidal lesions. This finding is valuable for diagnosing PCV in few cases (Fig. 2C & Fig 5). Due to these advantages, SS-OCTA resulted in reduced false positive and false negative compared to the OCT-only group (Set A), along with improvement in PPV and NPV.

Compared to ICGA images, Set B showed comparable but lower polypoidal lesion detection rate than ICGA. This may result from manual segmentation and signal attenuation from PED and blood which can give less accuracy in en face images. In addition, lower blood flow rates in polypoidal lesions may also influence the lack of decorrelation signals when using SS-OCTA. [13,19].

There were few studies, which used OCT without ICGA to diagnose PCV. Chang et al. [20] demonstrated high sensitivity of 0.857 and specificity of 0.862 in OCT-based PCV diagnosis for treatment-naïve Korean eyes. Chaikitmongkol V et al [21] also suggested that without ICGA, the combination of CFP and OCT provides high sensitivity and high specificity for diagnose PCV. The image set CFP+OCT demonstrated sensitivity of 0.83 (95% Confidence interval [CI]: 0.69–0.92), specificity of 0.83 (95% CI: 0.72–0.91), AUC of 0.83 (95% CI: 0.76–0.90). However, fundus fluorescein angiography does not improve accuracy. Our study presented comparable outcomes for each parameter, including a sensitivity of 0.88, specificity of 0.94, and an AUC of 0.90 (95% CI: 0.83–0.97) in Set A.

Wang et al. [14] reported that in spectral domain OCTA, polypoidal lesion does not detect as clear as ICGA. However, BVNs showed as clear as ICGA. Kim et al. [11] demonstrated both polypoidal lesions and BVNs were well visualized as ICGA. The number of polypoidal lesions detection (n ± SD) in ICGA group and SS-OCTA group, shows 2.0 ± 1.0 and 2.1 ± 1.2, respectively. In this study, the number of polypoidal lesions were well detected as previous study. This is likely due to the resolution difference between spectral domain OCTA and SS-OCTA in two different study, which SS-OCTA utilizes a longer wavelength of light and penetrates more effectively through the RPE [22,23].
Due to its superior resolution, SS-OCTA exhibited a higher correlation coefficient with ICGA for polypoidal lesion detection in Set B compared to Set A, as observed in the ICC analysis. Although ICGA is considered the gold standard for PCV diagnosis, it may not be able to provide a completely flawless polypoidal lesion detection. For example, there were few cases in which SS-OCTA detected more polypoidal lesions than ICGA. In comparison to ICGA, SS-OCTA may exhibit greater accuracy, and it seems to be proven through subsequent research efforts.

As we know, this is the first study to analyze sensitivity, specificity and AUC for diagnosing PCV in Korean patients using SS-OCTA. However, this study has several limitations. First, this study is retrospective in nature. Second, patients in this study included only Korean patients who have high incidence of PCV. This may cause bias in the analysis process. Therefore, further studies involving other ethnicities, such as White population, among whom PCV is not prevalent, are required to generalize our results. Third, we evaluated en face SS-OCTA images through automatic segmentation of boundary layers extending from RPE to the RPE-fit, which required additional adjustments. To ensure accurate analysis, we optimized the slab thickness and performed custom segmentation. The exact position of the slab was manually adjusted from the boundary layer at the RPE to the RPE-fit. Then, we gradually decreased slab thickness and observed the flow signal on the B-scans from the SS-OCTA to clearly differentiate polypoidal lesion’s signal from surrounding area. It indicates the necessity for future techniques to achieve accurate and rapid analysis of SS-OCTA images. Finally, only treatment-naïve eyes are evaluated in this study. It seems that additional research is needed on how to evaluate PCV during follow-up period after the treatment of patients with PCV.

In conclusion, this study demonstrated that PCV can be accurately diagnosed with high sensitivity and specificity using OCT and SS-OCTA without using ICGA. Additionally, SS-OCTA demonstrates similar polypoidal lesion detection rates to ICGA while enhancing the overall sensitivity and specificity for PCV diagnosis.

Conflicts of Interest: None.

Acknowledgements: None.

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References


Table 1. Demographic and clinical characteristics of patients

<table>
<thead>
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<th>Demographic and Characteristics</th>
<th>Value</th>
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<tbody>
<tr>
<td>Number of eyes</td>
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<tr>
<td>Age (years)</td>
<td>71.8 ± 9.0</td>
</tr>
<tr>
<td>Male (n, %)</td>
<td>62 (66.0)</td>
</tr>
<tr>
<td>Diabetes mellitus (n, %)</td>
<td>17 (18.1)</td>
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<tr>
<td>Hypertension (n, %)</td>
<td>58 (61.7)</td>
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<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Value</th>
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<tbody>
<tr>
<td>PCV (n, %)</td>
<td>43 (45.7)</td>
</tr>
<tr>
<td>Type 1 CNV (n, %)</td>
<td>29 (30.9)</td>
</tr>
<tr>
<td>Type 2 CNV (n, %)</td>
<td>17 (18.1)</td>
</tr>
<tr>
<td>Type 3 CNV (n, %)</td>
<td>5 (5.3)</td>
</tr>
</tbody>
</table>

PCV = polypoidal choroidal vasculopathy; nAMD = neovascular age related macular degeneration; CNV = choroidal neovascularization
Table 2. Sensitivity, specificity, PPV, NPV and AUC of image Set A and Set B.

<table>
<thead>
<tr>
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<th>Set A (CFP + OCT)</th>
<th>Set B (CFP + SS-OCTA)</th>
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<tbody>
<tr>
<td>Sensitivity</td>
<td>0.88</td>
<td>0.93</td>
</tr>
<tr>
<td>Specificity</td>
<td>0.94</td>
<td>0.96</td>
</tr>
<tr>
<td>PPV</td>
<td>0.93</td>
<td>0.95</td>
</tr>
<tr>
<td>NPV</td>
<td>0.91</td>
<td>0.94</td>
</tr>
<tr>
<td>AUC (95% CI)</td>
<td>0.90 (0.83-0.97)</td>
<td>0.96 (0.90-1.00)</td>
</tr>
</tbody>
</table>

PPV = positive predictive value; NPV = negative predictive value; CFP = color fundus photography; OCT = optical coherence tomography; SS-OCTA = swept-source optical coherence tomography angiography; AUC = area under the curve; CI = confidence interval
Fig. 1. Reference images of OCT features in diagnostic criteria. (A-B) 2 features based on cross-sectional OCT, (C) 1 feature based on en face OCT. A, Sharp-peak PED. B, Sub-RPE ring-like lesion. C. En face OCT complex RPE elevation

OCT = optical coherence tomography; PED = pigment epithelial detachment; RPE = retinal pigment epithelium

Fig. 2. Reference images of SS-OCTA features in diagnostic criteria. A, Early phase ICGA image of focal hyperfluorescent lesions. B, En face SS-OCTA image showing hyper-reflective foci in polypoidal lesions. C, Cross-sectional B-scan image shows sub-RPE ring-like lesion with green blood flow signals.

SS-OCTA = swept-source optical coherence tomography; ICGA = indocyanine green angiography; RPE = retinal pigment epithelium

Fig. 3. The ROC curve of Set A (CFP+OCT), Set B (CFP+SS-OCTA). The AUC of Set A (AUC=0.90, 95% confidence interval [CI]: 0.83–0.97) and Set B (AUC=0.96, 95% CI: 0.90–1.00).

ROC = receiver operating characteristic; AUC = area under the curve; CFP = color fundus photography; OCT = optical coherence tomography; SS-OCTA = swept-source optical coherence tomography

Fig. 4. Comparison between the number of polypoidal lesions using Set A (CFP+OCT), Set B (CFP+SS-OCTA) and ICGA images, respectively. A, Scatter plots comparing the number of polypoidal lesions in Set A and ICGA in each patient with PCV. B, Scatter plots comparing the number of polypoidal lesions in Set B and ICGA in each patient with PCV

CFP = color fundus photography; OCT = optical coherence tomography; SS-OCTA = swept-source optical coherence tomography; ICGA = indocyanine green angiography; PCV = polypoidal choroidal vasculopathy

Fig. 5 Case images of a polypoidal lesion found in Set B (CFP + SS-OCTA) but not in Set A (CFP + OCT). A, Early phase ICGA image of focal hyperfluorescent lesions. B, En face OCT image which does not shows definite RPE elevation. C, OCT image shows a PED, which is not sharp-peak PED and there is no definite sub-RPE
like ring lesion. D, En face SS-OCTA image showing hyper-reflective foci in polypoidal lesions. E, Cross-sectional B-scan image shows sub-RPE ring-like lesion with green blood flow signals. F, CFP shows orange subretinal round elevation

CFP = color fundus photography; SS-OCTA = swept-source optical coherence tomography; OCT = optical coherence tomography; ICGA = indocyanine green angiography; PCV = polypoidal choroidal vasculopathy; RPE = retinal pigment epithelium

Fig. 6 Case images of a polypoidal lesion found in SS-OCTA but not in ICGA. A, Early phase ICGA image of no focal hyperfluorescent lesions. (yellow circle) B, En face SS-OCTA image showing hyper-reflective foci in polypoidal lesions. C, Cross-sectional B-scan image shows sub-RPE ring-like lesion with green blood flow signals

SS-OCTA = swept-source optical coherence tomography; ICGA = indocyanine green angiography; RPE = retinal pigment epithelium