Recurrence of Choroidal Neovascularization Lesion Activity after Aflibercept Treatment for Age-Related Macular Degeneration

Short title: CNV Activity Recurrence after Treatment

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Summary: After successful 1-year aflibercept fixed-regimen treatment for age-related macular degeneration, 43.7% of eyes showed activity recurrence during the second year. Recurrence within 6 months was significantly associated with remnant polypoidal lesions detected by angiography and pigment epithelial detachment morphology observed by optical coherence tomography in eyes with polypoidal choroidal vasculopathy. (50 words)

Abstract

Purpose: To examine the recurrence rate of choroidal neovascularization (CNV) lesion activity in age-related macular degeneration (AMD) and associated factors after 1-year aflibercept treatment.

Methods: AMD eyes with 1-year aflibercept fixed-regimen treatment and a follow-up period of at least 18 months from the initial aflibercept injection for treatment-naïve exudative AMD were retrospectively evaluated. The recurrence rate was examined. Age, gender, visual acuity, AMD subtype, greatest linear dimension, and retinal and choroidal thicknesses at the 12th month examination were compared between eyes with and without recurrence. Presence of remnant polyps and pigment epithelial detachment (PED) morphology were also compared in polypoidal choroidal vasculopathy (PCV) eyes.

Results: Of the 98 eyes studied, 69 displayed a dry macula at the 12th month examination; 43.7% exhibited recurrence during the subsequent 12-month period in Kaplan-Meier analysis. Although no factors associated with recurrence were detected in AMD, remnant polyps and PED morphology at the 12th month examination were significantly associated with recurrence in PCV (P = 0.018 and 0.048, respectively).

Conclusion: Continuous, proactive treatment would be considered overtreatment for more than half of the AMD eyes that achieved a dry macula. Angiography and optical coherence tomography analyses may be useful for predicting recurrence in PCV eyes. (200 words)

Introduction

Age-related macular degeneration (AMD) is a disease that causes severe visual impairment and is of global concern including Asia.[1,2] Exudative AMD is currently treated with intravitreal injections of anti-vascular endothelial growth factor (VEGF).[3–5] However, anti-VEGF drugs have been implicated in the development of cerebral infarction, endophthalmitis, and noninfectious inflammation.[6-10] Therefore, treatment regimens such as pro re nata (PRN)[11,12] and treat-and-extend [13,14] have been compared with fixed-regimen treatments[15,16] with regard to outcomes and the number of injections.

The fixed regimen and treat-and-extend regimen are both designed to be continued proactively for years. However, some patients receiving the PRN regimen can maintain a dry macula for several months without treatment. In our previous study evaluating ranibizumab treatment for the management of AMD, 34% of eyes with complete resolution of retinal exudative change after administration of 3 loading injections did not exhibit recurrence of choroidal neovascularization (CNV) lesion activity during the first year, and 25% showed no recurrence within 2 years.[17] For these patients, both a fixed-regimen and a treat-and-extend regimen would result in overtreatment; hence, discontinuation of proactive treatment at an appropriate time point should be considered. To the best of our knowledge, recurrence of CNV lesion activity following aflibercept treatment has not been thoroughly investigated. This study addresses the need to understand the incidence of CNV lesion activity recurrence after a defined period of treatment with aflibercept.

After a dry macula is achieved, it is difficult to predict which patients will require ongoing treatment in order to prevent recurrence of CNV lesion activity. Fluorescein angiography (FA), indocyanine green angiography (ICGA), and optical coherence tomography (OCT) provide a considerable amount of information relating to AMD;[18,19] therefore, these examinations may help predict which patients will experience recurrence within a short period. We have previously reported the outcomes following 1-year aflibercept fixed-regimen treatment for AMD patients.[16] Treatment was discontinued after 1 year and patients were followed until CNV lesion activity recurred. In the present study, we

examined the recurrence rate of CNV lesion activity after the yearlong treatment with aflibercept and evaluated the factors associated with recurrence.

Methods

This study was conducted in an institutional setting. The Ethics Committee at Kyoto University Graduate School of Medicine approved the study, which was conducted in accordance with the tenets of the Declaration of Helsinki. Each patient provided written informed consent for the study.

To study the recurrence rate of CNV lesion activity after 1-year treatment with aflibercept, we retrospectively evaluated AMD patients with a follow-up period of 18 months or more after the initial injection, who were chosen from the treatment-naïve AMD cohort at Kyoto University Hospital (Kyoto, Japan) for our prospective study of 1-year fixed regimen treatment with aflibercept, some of which were previously reported.[16] All of the patients were older than 50 years of age at the time of the initial injection. They received 3 courses of monthly injections of aflibercept (2.0 mg) followed by 4 bimonthly injections. Eyes with insufficient or additional treatments [i.e. fewer than 7 injections of aflibercept, additional photodynamic therapy (PDT), or vitrectomy for AMD] during the 1-year treatment period were excluded from the present study.

Before treatment, patients underwent comprehensive examinations, including visual acuity (VA) measurement, axial length measurement (IOLMaster, Carl Zeiss Meditec, Dublin, CA, USA), fundus photography, spectral-domain OCT (SD-OCT; Spectralis; Heidelberg Engineering, Heidelberg, Germany), and FA/ICGA (HRA2; Heidelberg Engineering). Cases with polypoidal lesions were diagnosed as polypoidal choroidal vasculopathy (PCV) and cases with intraretinal neovascularization were diagnosed as retinal angiomatous proliferation (RAP). The remaining eyes were categorized as having typical AMD (tAMD), and were divided into 2 groups: eyes with type 1 CNV only were classified as having subretinal pigment epithelial CNVs and eyes with type 2 CNV were classified as having subretinal CNVs.

After the 7th injection at the 10th month, treatment was discontinued. Examinations of VA, SD-OCT (Spectralis), and FA/ICGA were performed at the 12th month examination. Eyes with a dry macula, defined as the absence of

intra- or sub-retinal fluid on raster scan, were included for subsequent recurrence analysis. We regarded eyes with pigment epithelial detachment (PED) and without intra- or sub-retinal fluid as having a dry macula. After the 12th month examination, for eyes with a dry macula, examinations of VA and SD-OCT (Spectralis, or RS-3000; Nidek, Tokyo, Japan) were performed at monthly scheduled visits. No additional treatment was provided until recurrence of CNV lesion activity was noted. This was defined as the development of any of sub-retinal fluid, retinal edema, or new sub-retinal hemorrhage. We did not regard the occurrence of PED alone as recurrence.

The greatest linear dimension (GLD) was measured according to the TAP study protocol.[20] The presence of remnant polypoidal lesions, assessed by angiography at the 12th month examination, was regarded as a candidate factor associated with recurrence. To examine the association between recurrence and SD-OCT findings at the 12th month examination, we measured the central retinal thickness, which was defined as the distance between the vitreoretinal surface and the inner surface of the retinal pigment epithelium (RPE). We also measured the central choroidal thickness, which was defined as the length between the outer border of the Bruch's membrane and the chorio-scleral interface. These measurements were obtained using SD-OCT images of 30º horizontal and vertical scans through the fovea in normal and enhanced depth imaging modes (averaged from 100 scans). The average central retinal and choroidal thicknesses were calculated from horizontal and vertical scans. To examine the morphology of polypoidal lesions in SD-OCT, as described previously,[16] the highest point of PED was determined from 13 raster scans covering a 30º x 10º oblong rectangle (averaged from 50 scans) at the 12th month examination, and from this point, two lines were drawn to connect the RPE line within the PED (Figure 1). The distance between the points of intersection of the 2 lines and Bruch's membrane was measured and was defined as the apical-PED base-length.

The Kaplan-Meier method was used to examine the recurrence rate of CNV lesion activity. Age, logarithm of the minimal angle of resolution (logMAR) VA, GLD, retinal thickness, and choroidal thickness at the 12th month examination were compared between eyes with and without recurrence using

the t-test. Decimal VA was converted to logMAR VA for statistical analysis, and results were shown together with Snellen-equivalent VA. Gender was compared using Fisher's exact test and AMD subtypes were compared using the chi-square test. When eyes with and without recurrence in PCV eyes alone were compared, a significant difference in the presence of remnant polyps was examined using Fisher's exact test. The apical-PED base-length in PCV eyes was compared using the t-test. For comparison of GLD and remnant polyps, eyes without an adequate FA/ICGA examination were excluded. These analyses were performed using the Statistical Package for the Social Sciences (SPSS; v 23.0, IBM, NY, USA). All values are presented as mean ± standard deviation, with *P*-values of ≤ 0.05 considered statistically significant.

Results

Ninety-eight AMD eyes of 98 patients were included in this study. Sixty-nine of these eyes (70.4%) achieved a dry macula at the 12th month examination. The 69 eyes with dry macula consisted of 20 tAMD eyes, including 9 eyes with type 1 CNV only and 11 eyes having type 2 CNV, 40 PCV eyes, and 9 RAP eyes (Table 1). The 29 eyes with wet macula consisted of 19 tAMD eyes, including 12 eyes with type 1 CNV only and 7 eyes having type 2 CNV, 9 PCV eyes, and 1 RAP eye. Among all eyes with a dry macula, 7 eyes continued to receive maintenance injections of aflibercept upon patient demand. For the remaining 62 eyes with a dry macula at the 12th month examination that did not receive maintenance injections of aflibercept during year 2, we used the Kaplan-Meier method to examine CNV lesion activity recurrence. The 62 eyes consisted of 19 tAMD eyes, 37 PCV eyes, and 6 RAP eyes. The mean follow-up period after the initial aflibercept injection was 26.5 ± 4.4 months. Our analyses indicated that the recurrence rate of CNV lesion activity was 52.4% during the observation period following the 12th month examination; 58.4% of the recurrence occurred within 6 months and 46.2% within 3 months following the 12th month examination (Figure 2).

Excluding the eyes that continued to receive aflibercept injections, we compared the 19 eyes that exhibited CNV lesion activity recurrence within 6 months following the 12th month examination and the 43 eyes without recurrence

(Table 2). For comparison of GLD, 4 eyes without an adequate angiography examination were excluded from analysis. Age, gender, logMAR VA, AMD subtype, GLD, retinal thickness, and choroidal thickness at the 12th month examination were not significantly different between eyes with recurrence and eyes without ($P \geq 0.054$). However, when we examined PCV eyes alone, remnant polyps at the 12th month examination were observed significantly more often ($P = 0.018$) in eyes that showed recurrence within 6 months after the 12th month examination [4 of 8 eyes (50.0%)] than in eyes without recurrence within that time frame [2 of 26 eyes (7.7%)]. Furthermore, the apical-PED base-length was significantly shorter in eyes with recurrence of CNV lesion activity than in eyes without recurrence ($P = 0.048$, Figure 3).

Discussion

In the present study, we examined the recurrence of CNV lesion activity after 1-year fixed-regimen treatment with aflibercept. Aflibercept was administered for 1 year including 3 monthly loading doses and 4 subsequent bimonthly maintenance doses. The fixed-regimen treatment achieved a dry macula in 70.4% of eyes at the 12th month examination. This value was consistent with the rate of 67.7% reported in a previous study investigating a Caucasian population.[15] Following a successful aflibercept fixed-regimen treatment for 1 year, the rate of recurrence was 43.7% during the subsequent 12 months and 52.4% during the entire observation period. Among the eyes with CNV lesion activity recurrence, 46.2% was observed within 3 months and 58.4% was observed within 6 months.

The Kaplan-Meier curve suggests that 56.3% of patients with AMD may not experience recurrence after a successful 1-year fixed-regimen treatment with aflibercept despite the discontinuation of treatment. Based on this data, and together with the achieved rates of dry macula by aflibercept treatment (70.4% in the present study), we predict that 39.6% of patients with AMD would not require continuous treatment to maintain a dry macula for 1 year post aflibercept treatment. We therefore suggest that proactive treatment with a fixed-regimen or a treat-and-extend regimen is not suitable for this group of patients with AMD after a 1-year fixed-regimen treatment with aflibercept. Recent treat-and-extend

regimens recommend observation without treatment for eyes maintaining a dry macula at a certain interval after injections so as to prevent overtreatment.[21] Although our findings in the 1-year fixed regimen cannot be directly applied to the treat-and-extend regimen, we suggest that continued injections of aflibercept might result in overtreatment for a significant number of AMD eyes.

Our results also suggest that the 29.6% of the patients with AMD whose eyes did not achieve a dry macula after a 1-year fixed-regimen treatment with aflibercept may need to continue treatment at intervals of 2 months or less. Therefore, these patients cannot attain treatment intervals of greater than 2 months in a treat-and-extend regimen with aflibercept. Considering together that significant number of AMD patients should not receive continuous treatment to avoid overtreatment, limited AMD patients would be appropriate for continuous treatment with an extended treatment interval of more than 2 months in a treat-and-extend regimen. In this group, the appropriate interval is estimated to be between 3 and 5 months for 55.4% of patients, based on our finding that 55.4% of the recurrence during the 12-month follow-up period was observed within 3 months after the 2-month treatment-free period (i.e. between the 10^{th} and 12^{th} months). The appropriate interval would be greater than 5 months in 44.6% of patients. However, as in most treat-and-extend regimens, these patients will actually receive treatment at intervals of less than 5 months because the treat-and-extend regimen usually limits the maximum interval to 3 or 4 months. The maximum interval in treat-and-extend regimens requires further consideration.

The recurrence rate of 43.7% noted during the 12-month period following a 1-year fixed-regimen treatment with aflibercept is an acceptable treatment result for AMD. According to our previous study, in which we reported outcomes following ranibizumab treatment for AMD, 66% of eyes that exhibited complete resolution of retinal exudative change after 3 loading injections experienced recurrence during the 1^{st} year and 75% experienced recurrence within 2 years.[17] The difference in recurrence rates following treatment with ranibizumab and aflibercept may reflect differences between the drugs. However, the difference in the treatment regimens may also have influenced the rate of recurrence. A comparison of the recurrence rates of CNV lesion activity between

aflibercept and ranibizumab using the same treatment regimen is therefore required. Furthermore, these 2 drugs should be compared in the context of a possible exit regimen.[22]

Although we were unable to identify factors associated with CNV lesion activity recurrence in the collective analysis of AMD subtypes, PCV eyes experiencing recurrence did have a characteristic feature of remnant polyps despite the dry macula after aflibercept treatment. Although treatment with aflibercept was effective in achieving regression of polypoidal lesions at the 12th month examination (28/34, 82.4%) in eyes with a dry macula, 4 out of 6 eyes with remnant polyps had CNV lesion activity recurrence. Considering that PCV eyes with remnant polyps exhibited a dry macula during the OCT examination, polyps may represent sub-clinical activity, which precedes CNV activity recurrence within 6 months.

Although the presence of remnant polyps was associated with recurrence, angiography is an invasive examination, so it is not practical to perform this procedure on patients with AMD at every visit.[23,24] Therefore, the ability to predict recurrence by OCT examination would be valuable. When we evaluated PED morphology by measuring its baseline length in OCT, the apical-PED base-length was significantly shorter in eyes with recurrence. This indicates that eyes with longer apical-PED base-length may not experience recurrence of CNV lesion activity shortly after the discontinuation of treatment the way that eyes with shorter apical-PED base-length seem to.

Since the use of aflibercept have been implicated in the development of side effects,[6-10] it is important to avoid redundant treatment. The present study suggests that over 55% of AMD eyes that achieved a dry macula after 1-year of treatment with aflibercept are able to maintain a dry macula in the absence of further treatment during the following 12 months. Discontinuation of treatment after several aflibercept injections should be considered in these cases. In PCV eyes in particular, detection of remnant polypoidal lesions through angiography and PED morphology evaluation with OCT would be useful to determine whether treatment should be continued.

A limitation of this study is its relatively small sample size. Although age, gender, logMAR VA, AMD subtype, GLD, retinal thickness, and choroidal

thickness were not associated with CNV lesion activity recurrence, the evaluation of a larger sample size may enable identification of the factors associated with recurrence. Follow-up period is another potential limitation. However, even when we examined CNV lesion activity recurrence in 42 eyes with a follow-up period of 12 months or longer following the 1-year treatment, results (Figure S1) were similar to the data gathered from observing eyes with a follow-up period of 6 months or longer (Figure 2). Furthermore, cataract surgery may affect the recurrence in AMD.[25] The Kaplan-Meier curve of recurrence regarding the timing of cataract surgery as an observation limit is shown (Figure S2).

In conclusion, a 1-year fixed regimen treatment with aflibercept achieved a dry macula in 70% of AMD eyes, and 56% of these eyes maintained a dry macula without further treatment for 1 year. For these eyes, ongoing proactive treatment with a fixed- or treat-and-extend regimen would not be appropriate. In regards to PCV eyes, treatment for eyes with remnant polyps or shorter apical-PED base-length should be continued to prevent recurrence of CNV lesion activity. Further research is required to determine the optimal treatment regimen for individual patients with AMD.

Appendix

Abbreviations:

AMD = age-related macular degeneration; **CNV** = choroidal neovascularization; **FA** = fluorescein angiography; **GLD** = greatest linear dimension; **ICGA** = indocyanine green angiography; **logMAR** = logarithm of the minimal angle of resolution; **OCT** = optical coherence tomography; **PCV** = polypoidal choroidal vasculopathy; **PDT** = photodynamic therapy; **PED** = pigment epithelial detachment; **PRN** = pro re nata; **RAP** = retinal angiomatous proliferation; **RPE** = retinal pigment epithelium; **SD-OCT** = spectral-domain optical coherence tomography; **tAMD** = typical age-related macular degeneration; **VA** = visual acuity; **VEGF** = vascular endothelial growth factor.

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Figure legends

Fig. 1. Two lines (red lines) were drawn from the highest point (yellow point) to connect with the retinal pigment epithelium (RPE) line (orange line) within the pigment epithelial detachment (PED). The apical-PED base-length (the distance indicated by the blue line) was defined as the distance between the intersection points of the 2 lines and the Bruch's membrane (horizontal black line). Maximum PED height (vertical black arrow) was defined as the height of the highest point of PED in raster scans. PED base-length (horizontal black arrow) was defined as the base length of PED with the highest point of PED in raster scans. Three images have the same maximum PED heights and PED base-lengths, but apical-PED base-lengths are different.

Fig. 2. Kaplan-Meier survival analysis for recurrence of choroidal neovascularization (CNV) lesion activity in age-related macular degeneration after 1-year aflibercept fixed-regimen treatment followed by an observation period of 6 months or longer.

Fig. 3. The apical pigment epithelial detachment (PED) base-lengths in polypoidal choroidal vasculopathy (PCV) eyes with recurrence (n = 9, 416.8 ± 282.0 μm) and those without (n = 28, 686.0 ± 358.7 μm).

Fig. S1 (Supplemental Figure 1. tif). Kaplan-Meier survival analysis for recurrence of choroidal neovascularization (CNV) lesion activity in age-related macular degeneration after treatment with aflibercept for 1 year followed by an observation period of 12 months or longer.

Fig. S2 (Supplemental Figure 2. tif). Kaplan-Meier survival analysis for recurrence of choroidal neovascularization (CNV) lesion activity in age-related macular degeneration with an observation period of 6 months or longer following 1-year treatment with aflibercept. Eyes that underwent cataract surgery during the treatment period were excluded and the timing of the surgery was regarded as the observation limit in the eyes that underwent cataract surgery during the observation period after the 12^{th} month examination.

Fig. S1 (Supplemental Figure 1. tif).

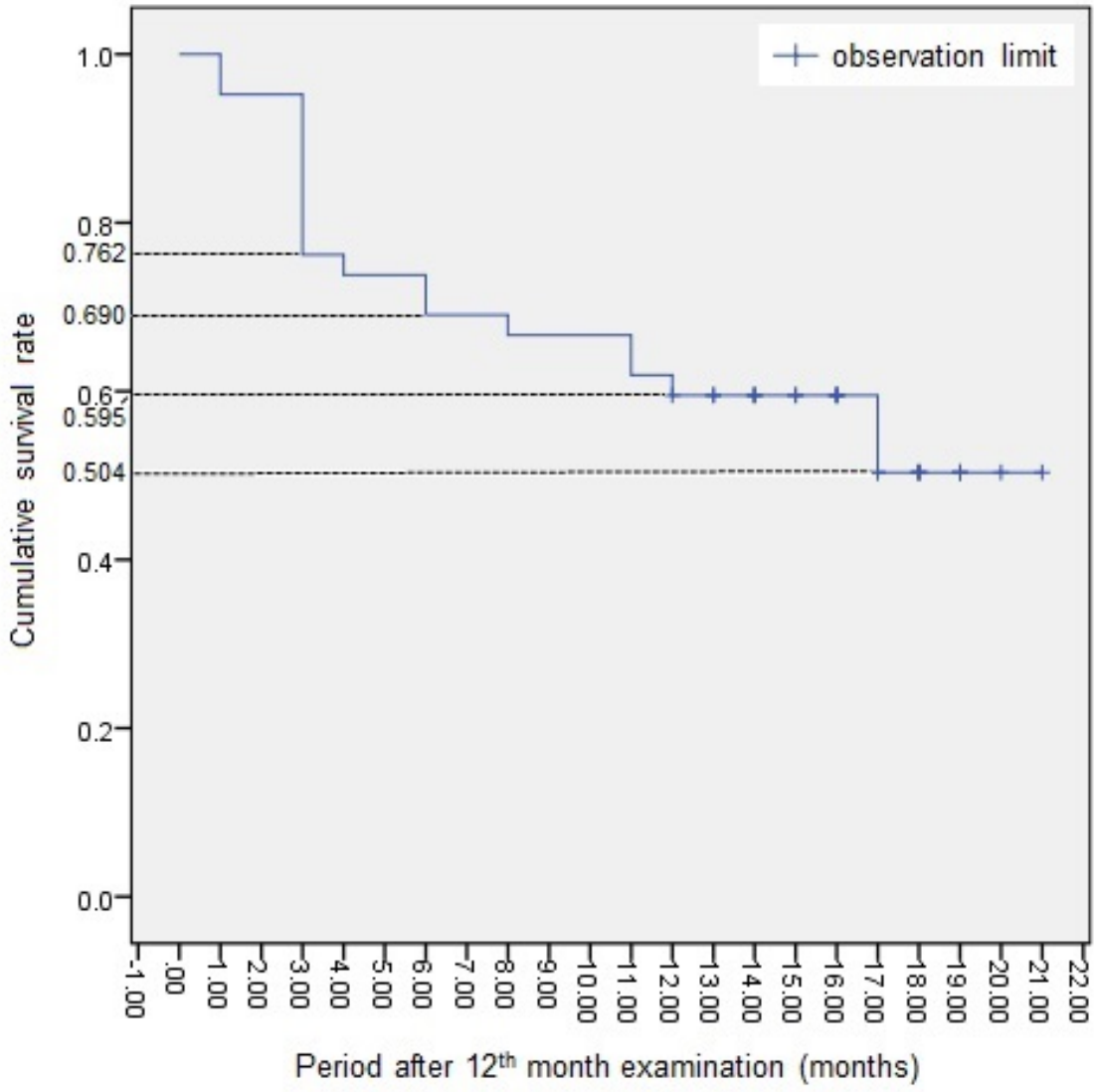


Fig. S2 (Supplemental Figure 2. tif).

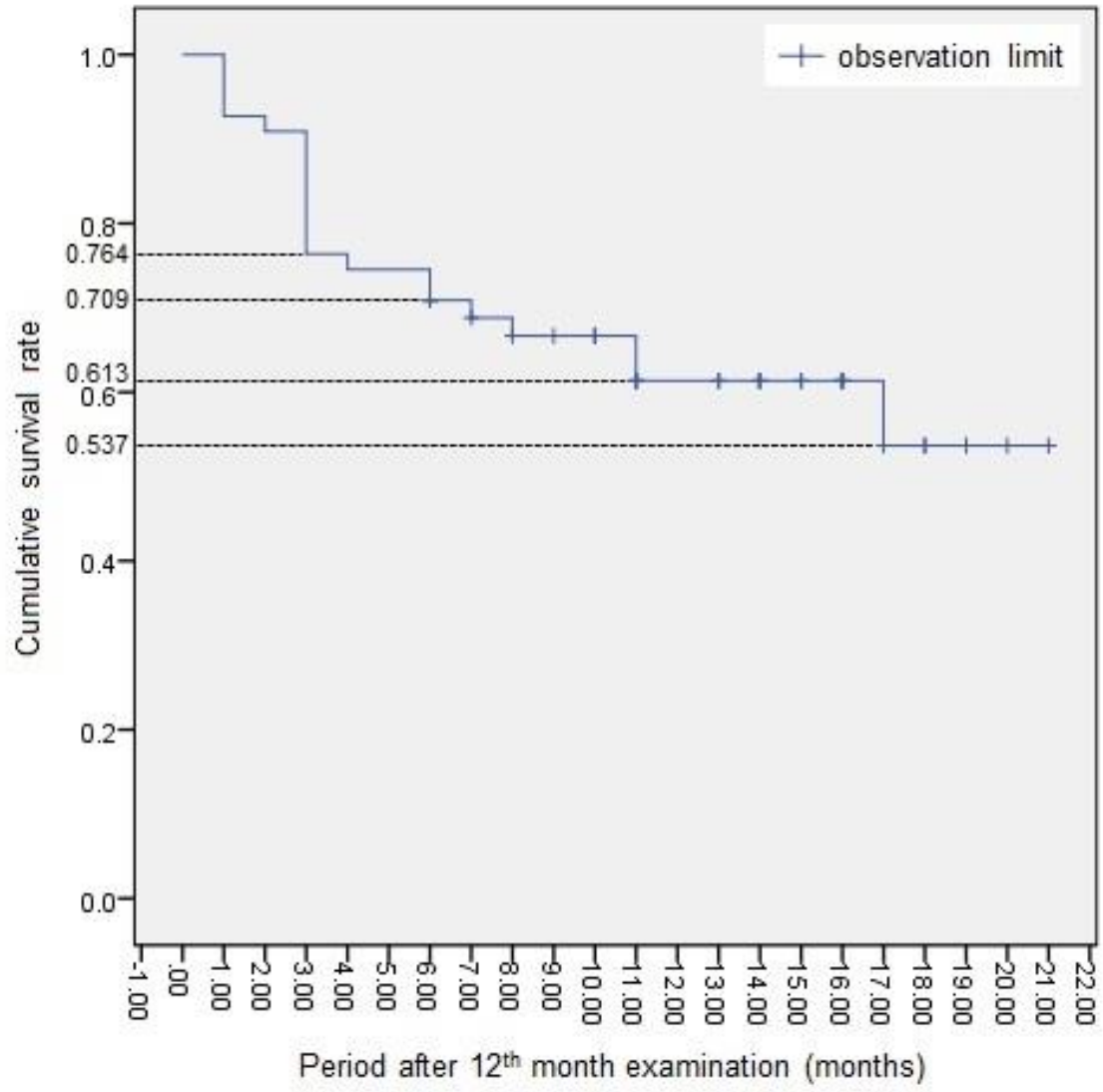


Fig 1

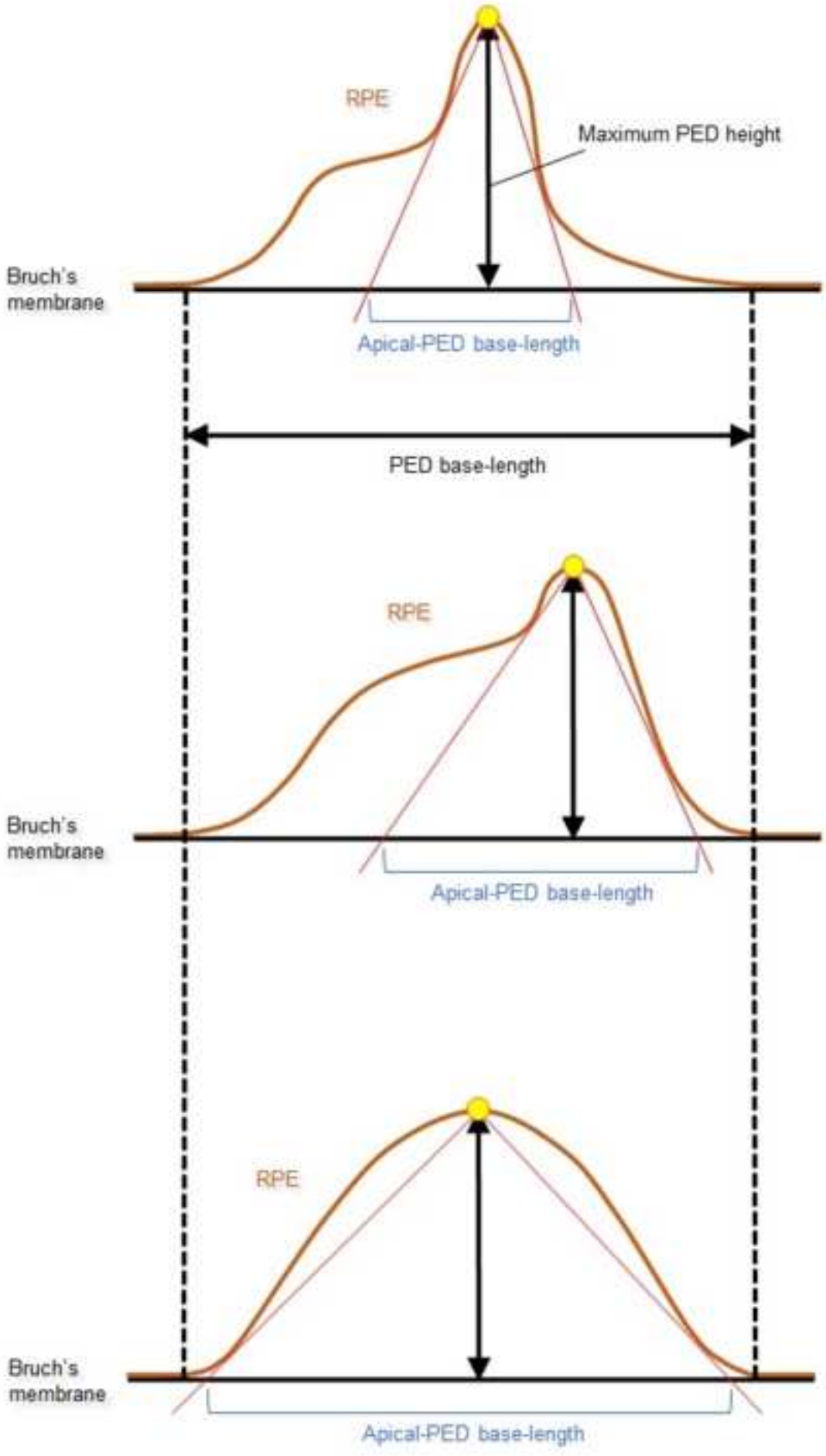
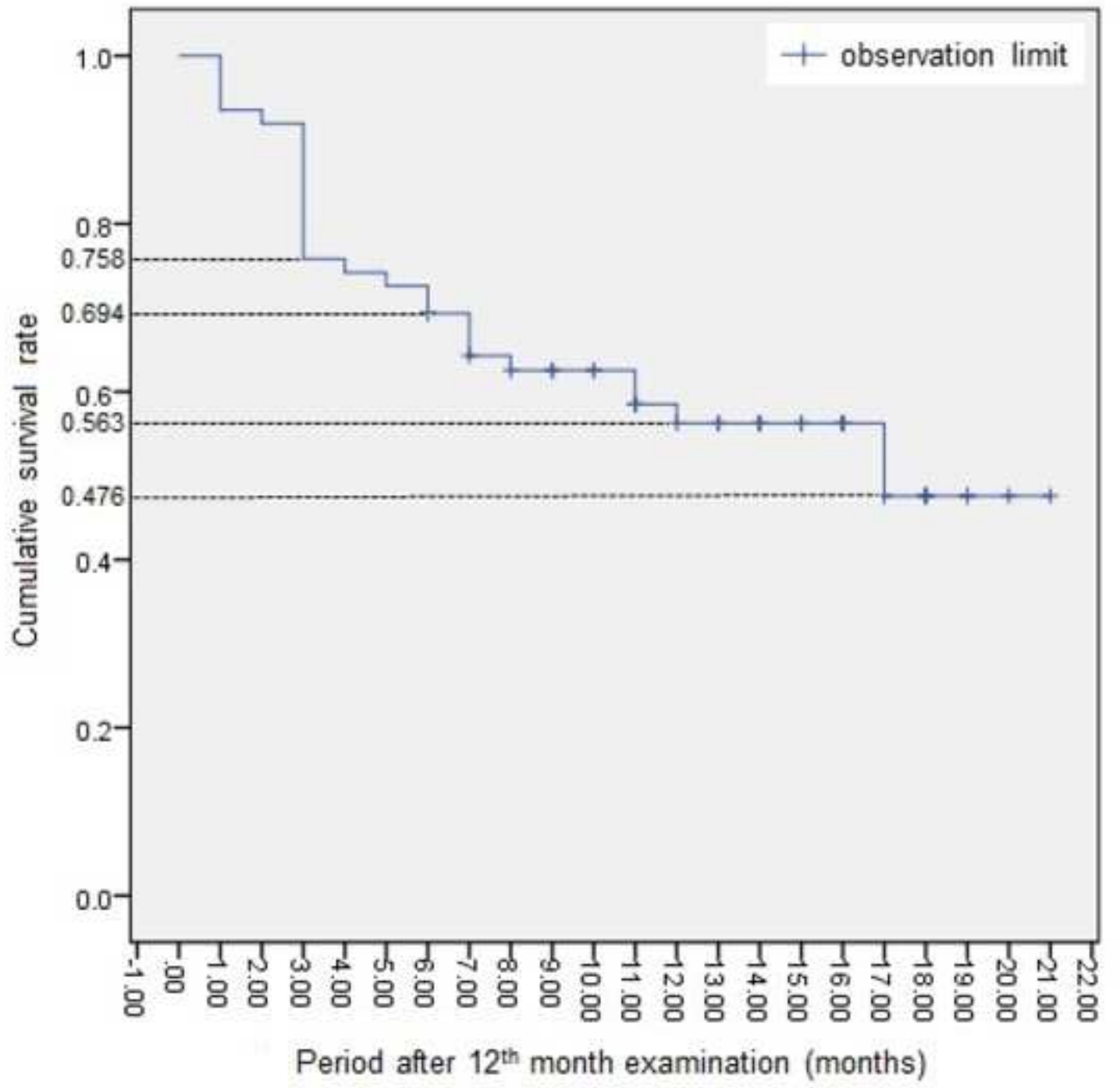

RPE
Maximum PED height
Bruch's membrane
Apical-PED base-length
PED base-length
RPE
Bruch's membrane
Apical-PED base-length
RPE
Bruch's membrane
Apical-PED base-length

Fig 2


observation limit
Cumulative survival rate
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0.6
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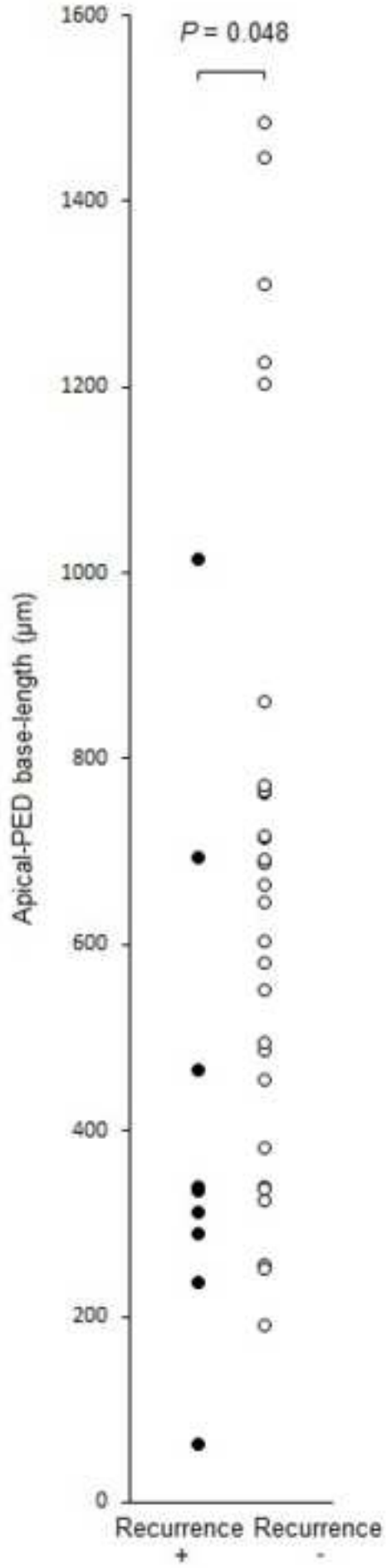
Period after 12th month examination (months)

Fig 3


P = 0.048
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1200
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200
0
Apical-PED base-length (μm)
Recurrence +
Recurrence -

Table 1. Characteristics of the study population at the 12th month examination

	All (n = 98)	tAMD (n = 39)	PCV (n = 49)	RAP (n = 10)
Age (years)	75.9 ± 8.0	76.1 ± 7.8	74.1 ± 7.4	84.3 ± 6.4
Gender (men:women)	61 : 37	28 : 11	30 : 19	3 : 7
Dry macula (eyes)	69	20	40	9
Wet macula (eyes)	29	19	9	1

PCV = polypoidal choroidal vasculopathy; RAP = retinal angiomatous proliferation; tAMD = typical age-related macular degeneration

Table 2. Association between characteristics of eyes with age-related macular degeneration and recurrence of CNV lesion activity

	Recurrence (+)	Recurrence (–)	*P*-value
Age (years)	79.3 ± 7.3	76.2 ± 8.1	0.166
Gender (men:women)	9 : 10	25 : 18	0.581
LogMAR (Snellen-equivalent) VA	0.06 ± 0.20 (20/23)	0.21 ± 0.38 (20/32)	0.054
Subtype (tAMD:PCV:RAP)	8 : 9 : 2	11 : 28 : 4	0.389
GLD (μm)	3059.6 ± 1316.1	3216.7 ± 1243.4	0.664
Retinal thickness (μm)	151.6 ± 36.1	149.6 ± 46.0	0.872
Choroidal thickness (μm)	199.4 ± 92.3	231.1 ± 102.8	0.253

CNV = choroidal neovascularization; GLD = greatest linear dimension; LogMAR VA = logarithm of the minimal angle of resolution visual acuity; PCV = polypoidal choroidal vasculopathy; RAP = retinal angiomatous proliferation; tAMD = typical age-related macular degeneration

GLD was measured according to the TAP study protocol.[20]