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Investigating the usefulness of a cluster-based trend analysis to detect visual field progression in patients with open-angle glaucoma

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ABSTRACT

Background/aims To investigate the usefulness of the Octopus (Haag-Streit) EyeSuite's cluster trend analysis in glaucoma.

Methods Ten visual fields (VFs) with the Humphrey Field Analyzer (Carl Zeiss Meditec), spanning 7.7 years on average were obtained from 728 eyes of 475 primary open angle glaucoma patients. Mean total deviation (mTD) trend analysis and EyeSuite's cluster trend analysis were performed on various series of VFs (from 1st to 10th: VF1-10 to 6th to 10th: VF6-10). The results of the cluster-based trend analysis, based on different lengths of VF series, were compared against mTD trend analysis.

Result Cluster-based trend analysis and mTD trend analysis results were significantly associated in all clusters and with all lengths of VF series. Between 21.2% and 45.9% (depending on VF series length and location) of clusters were deemed to progress when the mTD trend analysis suggested no progression. On the other hand, 4.8% of eyes were observed to progress using the mTD trend analysis when cluster trend analysis suggested no progression in any two (or more) clusters.

Conclusion Whole field trend analysis can miss local VF progression. Cluster trend analysis appears as robust as mTD trend analysis and useful to assess both sectorial and whole field progression. Cluster-based trend analyses, in particular the definition of two or more progressing cluster, may help clinicians to detect glaucomatous progression in a timelier manner than using a whole field trend analysis, without significantly compromising specificity.

INTRODUCTION

Glaucoma is a leading cause of blindness in the world.[1] Accurate and early detection of visual field (VF) progression is essential for achieving proper management of the disease. However, aggressive IOP-reduction interventions, such as trabeculectomy, can be associated with serious complications so unnecessary treatment must also be avoided.[2 3] Accurate and timely detection of VF progression are somewhat opposing requirements, determined by the statistical sensitivity and specificity of the detection method. Point-wise trend analysis offers a granular assessment of VF progression and the opportunity to detect change sooner;however, point-wise trend analysis can be unreliable as the variability of point-wise VF sensitivity measurements is large, which can mask genuine damage.[4–6] However, trend analysis of global indices, such as mean total deviation (mTD), mitigates variability, but localised VF defects may be ignored.[7–10] Trend analysis using VF clusters offers a compromise between these two approaches; the VF is divided into small clusters, and a trend analysis is carried out in each sector. Indeed, we already reported on the merits of a cluster-based approach to predict future VF sensitivity.[11 12]

EyeSuite is the software used in Octopus perimetry (Haag-Streit, Switzerland) to give an assessment of VF progression. In this software, 10 anatomy-based VF clusters are drawn (see figure 1), and cluster trend analysis is carried out in each of the sectors. In this study, the usefulness of a cluster trend analysis was investigated and compared with an mTD trend analysis. We have recently developed a multicentral retrospective collection of glaucomatous VFs known as the Japan Archives of Multicentral Database In Glaucoma (JAMDIG),[13] and the current investigation was performed using this data set.

METHOD

The study design was an observational case series. The review board of each institute reviewed and approved all protocols. The studies complied with the tenets of the Declaration of Helsinki. Written consent was given by patients for their information to be stored in the hospital database and used for research, otherwise, based on the regulations of the Japanese Guidelines for Epidemiologic Study 2008, issued by the Japanese Government, the study protocols did not require that each patient provide written informed consent, instead the protocol was posted at the outpatient clinic to notify the study to the participants.

Data used in analysis

All of the data analysed in the current study were drawn from the JAMDIG.[13] JAMDIG is a database collected from eight institutes in Japan, as introduced in the online supplementary appendix. The details of the database are given elsewhere.[13] In short, all VF data satisfying the inclusion criteria below were retrospectively collected from the

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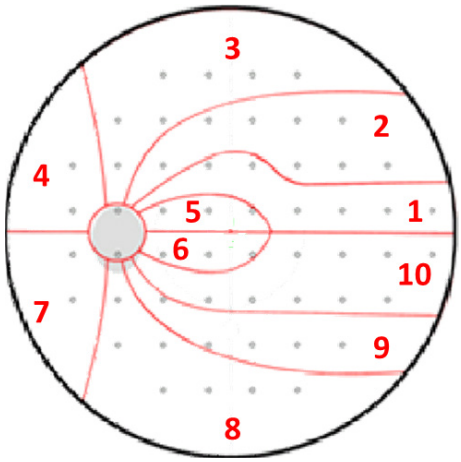

Figure 1 EyeSuite clusters 10 clusters in the EyeSuite software (left eye). The right eye was mirror imaged.

electronic records of each institute: (1) eyes with primary open angle glaucoma (POAG) including normal tension glaucoma (NTG), (2) glaucoma was the only disease causing VF damage, (3) each eye had at least 10 VF measurements with 24–2 or 30–2 Humphrey Field Analyzer using the SITA standard programme (HFA; Carl Zeiss Meditec, Dublin, California, USA), excluding one baseline VF. VF reliability was defined as fixation loss (FL) rate <20% and also false positive (FP) rate <15% following the criteria used by the HFA software.[13] The exclusion criteria were age below 20 years, possible secondary ocular hypertension in either eye, unreliable VFs in any of the 10 VFs and history of surgical treatment or YAG laser capsulotomy during the observation period. In the initial collection, VFs were drawn from 1348 eyes of 805 patients. A total of 436 eyes were excluded because of an unreliable test result in any of the 10 VFs, and 184 eyes were excluded due to a history of surgical treatment or YAG laser capsulotomy during the observation period. As a result, VFs were collected from 728 eyes of 475 patients, and series of 10 reliable VFs were analysed in the current study; when more than 10 VFs were available, the last 10 VFs were collected and used in the analysis.

Statistical analysis

Three trend analyses were implemented: point-wise, cluster-based and an mTD trend analyses, using all 10 VFs ($VF_{1\text{-}10}$). Progression was deemed to have occurred when the progression rate was negative and statistically significant (p value<0.05). Prior studies have defined progression based on a combination of a significance level and a particular progression rate,[7 14 15] such as less than −1.0 dB/year; however, this approach has only been validated for an MD trend analysis. There is no consensus on what progression rate is suitable to define progression for point-wise trend analysis and no research at all to define a suitable rate for cluster trend analysis, hence we defined progression as any negative progression rate for all of the different trend analyses.

Each trend analysis was repeated using a subset of VFs, from the second to tenth VF ($VF_{2\text{-}10}$) through to the sixth to tenth VF ($VF_{6\text{-}10}$), and progression was again deemed to have occurred if the progression rate was negative and statistically significant at the 5% level. Results were compared against the determination of progression of the relevant cluster with all 10 VFs. The following 'consistency measures' were used to measure performance: (1) proportion both progressing (PBP): trend analysis based on the subset of VFs was significant and negative, and trend analysis of the complete VF series ($VF_{1\text{-}10}$) was also significant and negative, (2) proportion both not progressing (PBNP): trend analysis of the subset of VFs was negative and not significant, and trend analysis of $VF_{1\text{-}10}$ was negative and not significant, (3) proportion inconsistent progression (PIP): trend analysis of reduced series suggested progression but trend analysis of $VF_{1\text{-}10}$ did not. In the current analysis, trend analysis of the longest VF series ($VF_{1\text{-}10}$) represents a surrogate for the ground truth; therefore, PBP, PIP and PBNP are proxy metrics for the true positive rate (sensitivity), the false positive rate and the true negative rate (specificity), respectively.[16] The different metrics (PBP, PBNP and PIP) were compared between cluster trend analysis and mTD trend analysis, using a pairwise comparison method.

To investigate the relationship between whole field progression (mTD trend analysis) and sectorial progression, we compared the number and spatial distribution of clusters that were deemed to have progressed according to cluster trend analysis with the progression result from the mTD trend analysis. We looked for at least one cluster progressing, at least two clusters progressing, at least three clusters progressing, and also at least two adjacent clusters progressing, and at least three adjacent clusters progressing for all VF series. Finally, the ability of a cluster-based trend analysis to predict future whole field progression was compared with a point-wise trend analysis using receiver operating characteristic (ROC) curves, drawn for the number of significantly progressing test points and the number of progressing clusters; the area under the ROC curve (AUC) was calculated for each approach.

All of the analyses were performed using the statistical programming language R,[17] which is a free software environment for statistical computing and graphics (R V.3.2.3; Foundation for Statistical Computing, Vienna, Austria). Holm's method was used to correct p values for the problem of multiple testing.

RESULT

Characteristics of the study population are summarised in table 1. The mTD at baseline was −6.6±5.9 dB (mean±SD) and initial patient age was 55.2±12.0 years. Ten VFs were measured over 5.6±1.2 (1.6 to 10.4) years and the progression rate of mTD was −0.3±0.6 (−7.2 to 2.2) dB/year. The mTD values of the first and tenth VFs were −7.0±6.2 (−26.7 to 2.6) and −8.8±6.8 (−27.8 to 3.9) dB, respectively. With the mTD values of the initial VF, 376 eyes (51.6%) had mTD higher than −6.0 dB, 193 eyes (26.5%) had mTD between −6.0 dB and −12.0 dB, 115 eyes (15.8%) had mTD between −12.0 dB and −18.0 dB and 44 eyes (6.0%) had mTD worse than −18.0 dB.

Table 2 shows the level of agreement between the results of mTD trend analysis and cluster trend analysis. Between 21.2% (154 eyes: $VF_{6\text{-}10}$) and 45.9% (334 eyes: $VF_{1\text{-}10}$) had a progression with the mTD trend analysis (negative and statistically significant slope with the p value of <0.05). The results of cluster trend analysis

Table 1 Subject demographics

Demographics	Value
Initial age, year, mean±SD (range)	55.2±12.0 (17 to 82)
Period 10 VFs were measured, year, mean±SD (median; range)	5.6±1.2 (5.4; 1.6 to 10.4)
mTD at first VF, dB, mean±SD (range)	−7.0±6.2 (−26.7 to 2.6)
mTD at tenth VF, dB, mean±SD (range)	−8.8±6.8 (−27.8 to 3.9)
The progression rate of mTD, dB/year, mean±SD (range)	−0.3±0.6 (−7.2 to 2.2)

mTD, mean total deviation; VF, visual field.

Table 2 Relationship between cluster trend analysis and mean total deviation (mTD) trend analysis

	Progressive only with mTD trend analysis	Progressive both with mTD and cluster trend analyses	Progressive only with cluster trend analysis	Not progressive both with mTD and cluster trend analyses	p Value	Progressive only with mTD trend analysis	Progressive both with mTD and cluster trend analyses	Progressive only with cluster trend analysis	Not progressive both with mTD and cluster trend analyses	p Value
	$VF_{6\text{-}10}$					$VF_{5\text{-}10}$				
Cluster 1, % (eye)	14.3 (104)	6.9 (50)	5.2 (38)	73.6 (536)	<0.001	16.2 (118)	10.4 (76)	6.3 (46)	67.0 (488)	<0.001
Cluster 2, % (eye)	12.1 (88)	9.1 (66)	5.2 (38)	73.6 (536)	<0.001	13.9 (101)	12.8 (93)	4.8 (35)	68.5 (499)	<0.001
Cluster 3, % (eye)	12.1 (88)	9.1 (66)	3.8 (28)	75.0 (546)	<0.001	14.4 (105)	12.2 (89)	3.8 (28)	69.5 (506)	<0.001
Cluster 4, % (eye)	16.6 (121)	4.5 (33)	4.7 (34)	74.2 (540)	<0.001	19.9 (145)	6.7 (49)	4.7 (34)	68.7 (500)	<0.001
Cluster 5, % (eye)	14.4 (105)	6.7 (49)	6.0 (44)	72.8 (530)	<0.001	18.0 (131)	8.7 (63)	7.4 (54)	65.9 (480)	<0.001
Cluster 6, % (eye)	15.7 (114)	5.5 (40)	7.1 (52)	71.7 (522)	<0.001	18.8 (137)	7.8 (57)	5.6 (41)	67.7 (493)	<0.001
Cluster 7, % (eye)	17 (124)	4.1 (30)	5.1 (37)	73.8 (537)	<0.001	20.7 (151)	5.9 (43)	3.4 (25)	69.9 (509)	<0.001
Cluster 8, % (eye)	15.5 (113)	5.6 (41)	4.0 (29)	74.9 (545)	<0.001	16.3 (119)	10.3 (75)	5.1 (37)	68.3 (497)	<0.001
Cluster 9, % (eye)	13.3 (97)	7.8 (57)	4.8 (35)	74.0 (539)	<0.001	15.4 (112)	11.3 (82)	6.2 (45)	67.2 (489)	<0.001
Cluster 10, % (eye)	13.2 (96)	8.0 (58)	5.4 (39)	73.4 (535)	<0.05	12.9 (94)	13.7 (100)	6.2 (45)	67.2 (489)	<0.001
≥1 clusters, % (eye)	1.0 (7)	20.2 (147)	33.0 (240)	45.9 (334)	<0.001	1.0 (7)	25.7 (187)	36.4 (265)	37.0 (269)	<0.001
≥2 clusters, % (eye)	4.8 (35)	16.3 (119)	12.6 (92)	66.2 (482)	<0.001	4.3 (31)	22.4 (163)	19.8 (144)	53.6 (390)	<0.001
≥3 clusters, % (eye)	8.8 (64)	12.4 (90)	3.8 (28)	75.0 (546)	<0.001	8.0 (58)	18.7 (136)	9.6 (70)	63.7 (464)	0.33
Adjacent two clusters	9.6 (70)	11.5 (84)	4.8 (35)	74.0 (539)	<0.001	8.4 (61)	18.3 (133)	7.4 (54)	65.9 (480)	0.58
Adjacent three clusters	15.2 (111)	5.9 (43)	0.7 (5)	78.2 (569)	<0.001	15.4 (112)	11.3 (82)	1.4 (10)	72.0 (524)	<0.001
	$VF_{4\text{-}10}$					$VF_{3\text{-}10}$				
Cluster 1, % (eye)	15.8 (115)	16.3 (119)	6.9 (50)	61.0 (444)	<0.001	18.1 (132)	19.6 (143)	5.5 (40)	56.7 (413)	<0.001
Cluster 2, % (eye)	15.7 (114)	16.5 (120)	4.3 (31)	63.6 (463)	<0.001	15.7 (114)	22.1 (161)	4.5 (33)	57.7 (420)	<0.001
Cluster 3, % (eye)	17.6 (128)	14.6 (106)	4.8 (35)	63.0 (459)	<0.001	17.7 (129)	20.1 (146)	4 (29)	58.2 (424)	<0.001
Cluster 4, % (eye)	22.7 (165)	9.5 (69)	3 (22)	64.8 (472)	<0.001	27.5 (200)	10.3 (75)	4.3 (31)	58.0 (422)	<0.001
Cluster 5, % (eye)	19.8 (144)	12.4 (90)	5.8 (42)	62.1 (452)	<0.001	23.5 (171)	14.3 (104)	6.2 (45)	56.0 (408)	<0.001
Cluster 6, % (eye)	21.3 (155)	10.9 (79)	4.4 (32)	63.5 (462)	<0.001	25.1 (183)	12.6 (92)	5.5 (40)	56.7 (413)	<0.001
Cluster 7, % (eye)	24.3 (177)	7.8 (57)	3.3 (24)	64.6 (470)	<0.001	28.6 (208)	9.2 (67)	3.6 (26)	58.7 (427)	<0.001
Cluster 8, % (eye)	20.1 (146)	12.1 (88)	5.2 (38)	62.6 (456)	<0.001	21 (153)	16.8 (122)	4.4 (32)	57.8 (421)	<0.001
Cluster 9, % (eye)	16.9 (123)	15.2 (111)	4.9 (36)	62.9 (458)	<0.001	19.2 (140)	18.5 (135)	4.5 (33)	57.7 (420)	<0.001
Cluster 10, % (eye)	15.5 (113)	16.6 (121)	7.6 (55)	60.3 (439)	<0.001	17 (124)	20.7 (151)	7.6 (55)	54.7 (398)	<0.001
≥1 clusters, % (eye)	0.1 (1)	32 (233)	30.1 (219)	37.8 (275)	<0.001	0.4 (3)	37.4 (272)	29.7 (216)	32.6 (237)	<0.001
≥2 clusters, % (eye)	3.3 (24)	28.8 (210)	13.3 (97)	54.5 (397)	<0.001	2.6 (19)	35.2 (256)	13.2 (96)	49.0 (357)	<0.001
≥3 clusters, % (eye)	8.5 (62)	23.6 (172)	4.7 (34)	63.2 (460)	<0.001	7.7 (56)	30.1 (219)	5.2 (38)	57.0 (415)	0.08
Adjacent two clusters	8 (58)	24.2 (176)	7.1 (52)	60.7 (442)	0.63	6.7 (49)	31 (226)	7.6 (55)	54.7 (398)	0.62
Adjacent three clusters	16.9 (123)	15.2 (111)	1.2 (9)	66.6 (485)	<0.001	18.1 (132)	19.6 (143)	1.4 (10)	60.9 (443)	<0.001
	$VF_{2\text{-}10}$					$VF_{1\text{-}10}$				
Cluster 1, % (eye)	18.1 (132)	22.9 (167)	5.6 (41)	53.3 (388)	<0.001	20.1 (146)	25.8 (188)	5.1 (37)	49.0 (357)	<0.001
Cluster 2, % (eye)	17.3 (126)	23.8 (173)	4.5 (33)	54.4 (396)	<0.001	18.3 (133)	27.6 (201)	5.2 (38)	48.9 (356)	<0.001
Cluster 3, % (eye)	19.5 (142)	21.6 (157)	4.4 (32)	54.5 (397)	<0.001	21.3 (155)	24.6 (179)	4.5 (33)	49.6 (361)	<0.001
Cluster 4, % (eye)	29 (211)	12.1 (88)	3.8 (28)	55.1 (401)	<0.001	33.8 (246)	12.1 (88)	3.6 (26)	50.5 (368)	<0.001
Cluster 5, % (eye)	23.1 (168)	18 (131)	5.8 (42)	53.2 (387)	<0.001	25.7 (187)	20.2 (147)	5.8 (42)	48.4 (352)	<0.001

Continued

Table 2 Continued

	Progressive only with mTD trend analysis	Progressive both with mTD and cluster trend analyses	Progressive only with cluster trend analysis	Not progressive both with mTD and cluster trend analyses	p Value	Progressive only with mTD trend analysis	Progressive both with mTD and cluster trend analyses	Progressive only with cluster trend analysis	Not progressive both with mTD and cluster trend analyses	p Value
Cluster 6, % (eye)	27.6 (201)	13.5 (98)	5.2 (38)	53.7 (391)	<0.001	28 (204)	17.9 (130)	4.3 (31)	49.9 (363)	<0.001
Cluster 7, % (eye)	31.5 (229)	9.6 (70)	2.6 (19)	56.3 (410)	<0.001	35 (255)	10.9 (79)	1.9 (14)	52.2 (380)	<0.001
Cluster 8, % (eye)	22.5 (164)	18.5 (135)	5.1 (37)	53.8 (392)	<0.001	22.8 (166)	23.1 (168)	3.6 (26)	50.5 (368)	<0.001
Cluster 9, % (eye)	20.5 (149)	20.6 (150)	4.7 (34)	54.3 (395)	<0.001	21.7 (158)	24.2 (176)	4.9 (36)	49.2 (358)	<0.001
Cluster 10, % (eye)	18.3 (133)	22.8 (166)	6.6 (48)	52.3 (381)	<0.001	18.5 (135)	27.3 (199)	6.3 (46)	47.8 (348)	<0.001
≥1 clusters, % (eye)	0.3 (2)	40.8 (297)	29.1 (212)	29.8 (217)	<0.001	0 (0)	45.9 (334)	26.5 (193)	27.6 (201)	<0.001
≥2 clusters, % (eye)	2.3 (17)	38.7 (282)	12.5 (91)	46.4 (338)	<0.001	1.4 (10)	44.5 (324)	12 (87)	42.2 (307)	<0.001
≥3 clusters, % (eye)	7.3 (53)	33.8 (246)	5.6 (41)	53.3 (388)	0.26	6.5 (47)	39.4 (287)	4.8 (35)	49.3 (359)	0.22
Adjacent two clusters	7.3 (53)	33.8 (246)	8 (58)	51.0 (371)	0.70	5.9 (43)	40 (291)	6.2 (45)	47.9 (349)	0.91
Adjacent three clusters	18.8 (137)	22.3 (162)	1.2 (9)	57.7 (420)	<0.001	19.2 (140)	26.6 (194)	1.5 (11)	52.6 (383)	<0.001

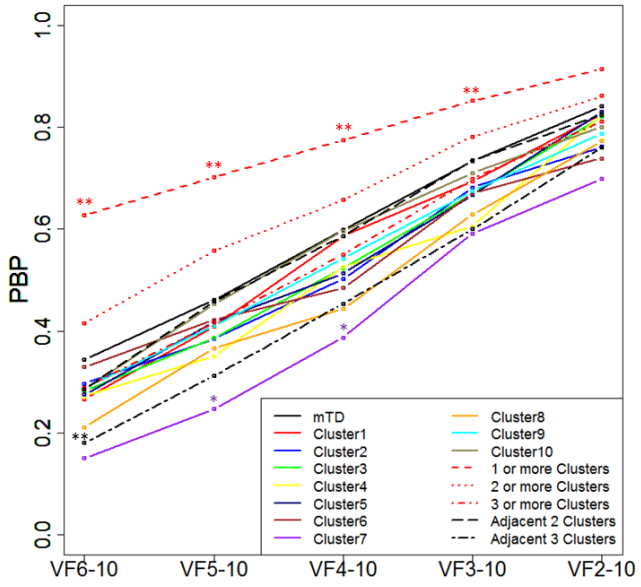

Figure 2 PBP for cluster trend analysis and mean total deviation mTD trend analysis. The PBP rates for cluster trend analysis were significantly lower than those for mTD trend analysis on two occasions: cluster 7 with $VF_{5\text{-}10}$ and cluster 7 with $VF_{4\text{-}10}$. The ≥1 clusters PBP rates were significantly higher than those from mTD trend analysis for four VF series. There was no significant difference in ≥2 clusters and ≥3 clusters PBP rates with mTD trend analysis PBP rates in all VF series. The adjacent three clusters PBP rate was significantly lower than that from mTD trend analysis for $VF_{6\text{-}10}$. * and **: PBP was significantly different ($p<0.05$ and $p<0.01$) with the pairwise χ^2 test after correction of p values for multiple testing using Holm's method. PBP, 'Proportion Both Progressing'; mTD, mean of 52 total deviation values correspond to 24–2 Humphrey visual field, ≥1 clusters: progression in at least one cluster, ≥2 clusters: progression in at least two clusters, ≥3 clusters: progression in at least three clusters, adjacent 2 clusters: progression in at least two adjacent clusters, adjacent 3 clusters: progression in at least three adjacent clusters.

were significantly correlated with those from mTD trend analysis in most of the cases ($p<0.05$, McNemar's test); however, between 1.9% (14 eyes: cluster 7, $VF_{1\text{-}10}$) and 7.6% (55 eyes: cluster 10, $VF_{3\text{-}10}$ and $VF_{4\text{-}10}$) of clusters were progressive with the cluster trend analysis but not with the mTD trend analysis. Up to 36.4% (265 eyes: $VF_{5\text{-}10}$), 19.8% (144 eyes: $VF_{5\text{-}10}$) and 9.6% (70 eyes: $VF_{5\text{-}10}$) of VFs showed progression in clusters that was not reflected in the mTD trend analysis based on one or more, two or more and three or more clusters progressing, respectively. Conversely, up to 1.0% (7 eyes: $VF_{1\text{-}10}$), 4.4% (35 eyes: $VF_{1\text{-}10}$) and 8.8% (64 eyes: $VF_{2\text{-}10}$) of eyes progressed according to the mTD trend analysis but not with cluster-based progression analysis based on one or more clusters, two or more.

Figure 2 illustrates PBP rates for the cluster trend analysis and for the mTD trend analysis. The PBP rate was between 15.1% (cluster 7, VF6-10) and 83.1% (cluster 5, VF2-10) for cluster trend analysis and between 34.4% (VF6-10) and 84.1% (VF2-10) for mTD trend analysis. The PBP rates for cluster trend analysis were significantly lower than those for mTD trend analysis on two occasions: cluster 7 with $VF_{5\text{-}10}$ and cluster 7 with $VF_{4\text{-}10}$ ($p=0.049$ and 0.032, respectively, pairwise test). The PBP rate for progression defined based on one or more progressing clusters was between 62.8% ($VF_{6\text{-}10}$) and 91.5% ($VF_{2\text{-}10}$); PBP rates were significantly higher than those from mTD trend analysis for four VF series: $VF_{6\text{-}10}$, $VF_{5\text{-}10}$, $VF_{4\text{-}10}$ and $VF_{3\text{-}10}$ ($p<0.01$).

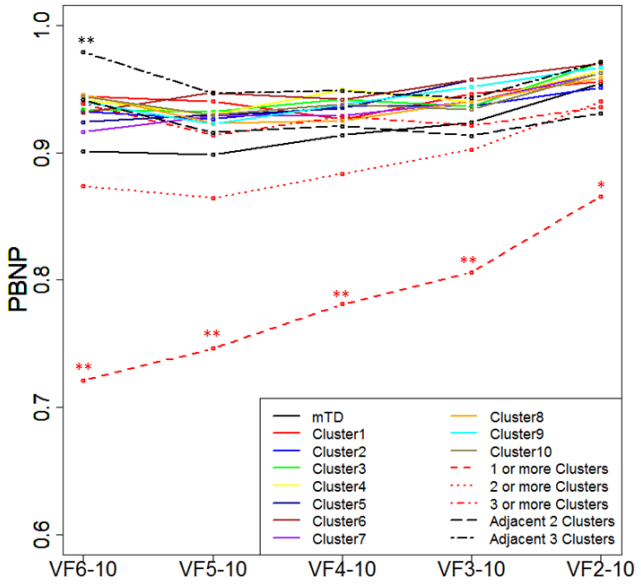

Figure 3 PBNP for cluster trend analysis and mTD trend analysis. There was no significant difference between cluster trend analysis and mTD trend analysis results (pairwise χ^2 test after correction of p values for multiple testing using Holm's method). The PBNP rates for ≥1 clusters were significantly lower than those from mTD trend analysis for all VF series. There was no significant difference in the PBNP rates for ≥2 clusters and ≥3 clusters versus mTD trend analysis PBNP rates in all VF series. The adjacent three clusters PBNP rate was significantly higher than that from mTD trend analysis for $VF_{6\text{-}10}$. * and **: PBNP was significantly different ($p<0.05$ and $p<0.01$) with the pairwise χ^2 test after correction of p values for multiple testing using Holm's method. PBNP, 'Proportion Both Not Progressing'; mTD, mean of 52 total deviation values correspond to 24–2 Humphrey visual field, ≥1 clusters: progression in at least one cluster, ≥2 clusters: progression in at least two clusters, ≥3 clusters: progression in at least three clusters, adjacent 2 clusters: progression in at least two adjacent clusters, adjacent 3 clusters: progression in at least three adjacent clusters.

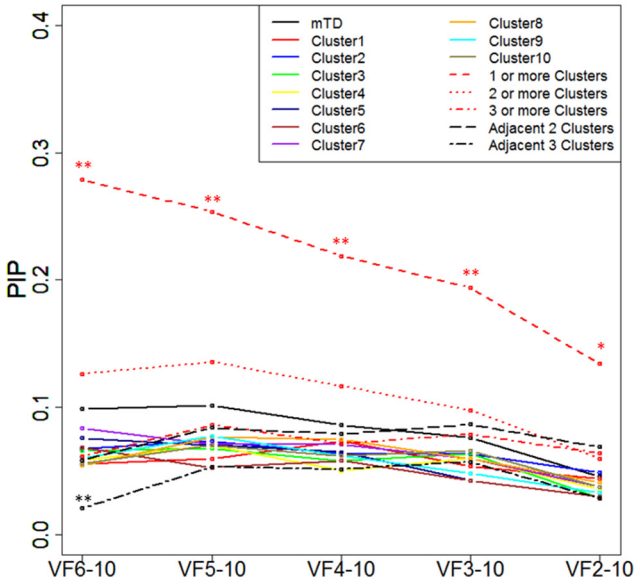

Figure 4 PIP for mTD trend analysis and cluster trend analysis. No significant difference was observed between cluster trend analysis and mTD trend analysis. The PIP rates for ≥1 clusters were significantly higher than those from mTD trend analysis for all VF series. There was no significant difference in the PIP rates for ≥2 clusters and ≥3 clusters versus mTD trend analysis PIP rates in all VF series. The adjacent three clusters PIP rate was significantly lower than that from mTD trend analysis for $VF_{6\text{-}10}$. * and **: PIP was significantly different ($p<0.05$ and $p<0.01$), with the pairwise χ^2 test after correction of p values for multiple testing using Holm's method. PIP, 'Proportion Inconsistent Progression'; mTD, mean of 52 total deviation values correspond to 24–2 Humphrey visual field, ≥1 clusters: progression in at least one cluster, ≥2 clusters: progression in at least two clusters, ≥3 clusters: progression in at least three clusters, adjacent 2 clusters: progression in at least two adjacent clusters, adjacent 3 clusters: progression in at least three adjacent clusters.

The PBP rate for progression defined based on two or more progressing clusters was between 41.6% ($VF_{6\text{-}10}$) and 86.1% ($VF_{2\text{-}10}$). The PBP rate for progression defined based on three or more progressing clusters was between 28.9% ($VF_{6\text{-}10}$) and 81.1% ($VF_{2\text{-}10}$). The PBP rates for progression defined as two and three adjacent clusters were between 28.5% ($VF_{6\text{-}10}$) and 82.4% ($VF_{2\text{-}10}$) and between 18.0% ($VF_{6\text{-}10}$) and 76.1% ($VF_{2\text{-}10}$), respectively. PBP rate from progression definition based on three adjacent progressing clusters was significantly lower than that from mTD trend analysis for $VF_{6\text{-}10}$ ($p<0.01$).

Figure 3 shows the comparison of PBNP rates between cluster trend analysis and mTD trend analysis. PBNP was between 91.7% (cluster 7, VF6-10) and 97.1% (cluster 3, VF2-10) for cluster trend analysis and between 89.8% (VF5-10) and 95.4% (VF2-10) for mTD trend analysis; no significant difference was observed in any comparisons (pairwise test, $p>0.05$). The PBNP rate for progression defined based on one or more progressing clusters was between 72.1% ($VF_{6\text{-}10}$) and 86.6% ($VF_{2\text{-}10}$); these rates were significantly lower than those from mTD trend analysis for all VF series ($p<0.05$ for $VF_{6\text{-}10}$, $VF_{5\text{-}10}$, $VF_{4\text{-}10}$ and $VF_{3\text{-}10}$ and $p<0.01$ for $VF_{2\text{-}10}$). The PBNP rate for progression defined based on two or more progressing clusters was between 86.4% ($VF_{5\text{-}10}$) and 94.0% ($VF_{2\text{-}10}$). The PBNP rate for progression defined based on three or more progressing clusters was between 91.4% ($VF_{5\text{-}10}$) and 93.8% ($VF_{6\text{-}10}$). The PBNP rates for progression defined as two and three adjacent clusters were between 91.3% ($VF_{3\text{-}10}$) and 94.1% ($VF_{6\text{-}10}$) and between 94.3% ($VF_{3\text{-}10}$) and 97.1% ($VF_{2\text{-}10}$), respectively. PBNP rate from progression definition based on three adjacent progressive clusters was significantly higher than that from mTD trend analysis for $VF_{6\text{-}10}$ ($p<0.01$).

Figure 4 shows the comparison of PIP rates between cluster trend analysis and mTD trend analysis. PIP rate was between 3.0% (cluster 5, VF2-10) and 7.8% (cluster 9, VF5-10) for C-TA and between 4.6% (VF2-10) and 10.1% (VF5-10) for mTD trend analysis; no significant difference was observed in any comparisons (pairwise test, $p>0.05$). The PIP rate for progression defined based on one or more progressing clusters was between 13.4% ($VF_{2\text{-}10}$) and 27.9% ($VF_{6\text{-}10}$); these were significantly higher than those from mTD trend analysis for all VF series ($p<0.05$ for $VF_{6\text{-}10}$, $VF_{5\text{-}10}$, $VF_{4\text{-}10}$, $VF_{3\text{-}10}$ and $p<0.01$ for $VF_{2\text{-}10}$). The PIP rates for progression defined based on two or more progressing clusters and three or more progressing clusters were between 6.0% ($VF_{2\text{-}10}$) and 13.6% ($VF_{5\text{-}10}$) and between 6.2% ($VF_{6\text{-}10}$) and 8.6% ($VF_{5\text{-}10}$), respectively. The PIP rates for progression defined as two and three adjacent clusters were between 5.9% ($VF_{6\text{-}10}$) and 8.7% ($VF_{3\text{-}10}$) and between 2.1% ($VF_{6\text{-}10}$) and 5.7% ($VF_{3\text{-}10}$), respectively. PIP rate from progression definition based on three adjacent progressive clusters was significantly lower than that from mTD trend analysis for $VF_{6\text{-}10}$ ($p<0.01$).

The mean number of VF tests and duration needed for the first detection of VF progression with the mTD trend analysis

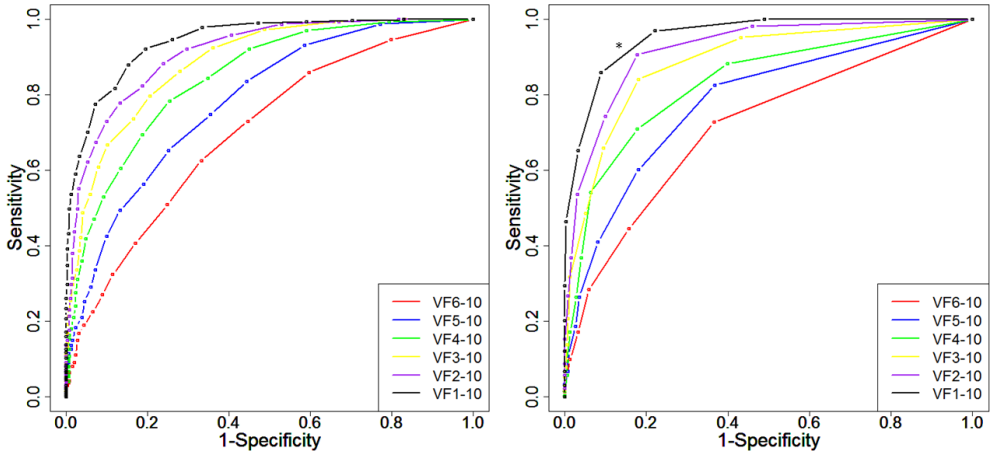

Figure 5 ROC curves for predicting progression in $VF_{1\text{-}10}$. The left and right figures represent those using the number of progressing test points and the number of progressing clusters, respectively. The AUC for $VF_{1\text{-}10}$ was significantly larger using the number of progressing clusters versus the number of progressing points (Delong's test, p<0.05), as shown by '*' in the figure. AUC, area under the ROC curve; mTD, mean of 52 total deviation values correspond to 24–2 Humphrey visual field; ROC, receiver operating characteristic; VF, visual field.

was 6.81±1.72 (mean±SD) VFs and 3.73±1.33 years, respectively. These values were significantly larger and longer than those attained with the definition of one or more progressing clusters: 1.33 VFs and 0.87 years. Similarly, the definition of two or more progressing clusters detected progression earlier than the mTD trend analysis by 0.60 VFs and 0.39 years.

ROC curves to predict significant progression in the mTD trend analysis ($VF_{1\text{-}10}$) using the number of significantly progressing test points (from point-wise trend analysis) or the number of clusters (from cluster trend analysis) are shown in figure 5. The AUCs were between 87.0% (VF6-10) and 94.3% (VF1-10) for point-wise trend analysis and between 88.7% (VF6-10) and 95.6% (VF1-10) for cluster trend analysis. Delong's test for the difference between the AUCs showed a significant difference for $VF_{1\text{-}10}$ (p=0.046).

DISCUSSION

In this study, a cluster-based trend analysis was investigated and contrasted with whole VF and point-wise trend analyses. The results of full field trend analysis (mTD trend analysis) and the cluster-based trend analysis were significantly correlated. A small number of eyes were missed by cluster trend analysis when showing progression with mTD trend analysis (from 0.0% to 1.0%; table 2). However, there were relatively larger proportion of clusters observed to progress when mTD trend analysis suggested no significant progression. In addition, cluster trend analysis was no worse than mTD trend analysis in performance according to the PBP, PBNP and PIP statistics. Finally, measuring the number of clusters progressing appears to be as useful as the number of VF test points progressing in predicting future whole field progression, as suggested by similar AUCs. This implies cluster trend analysis is as robust as mTD trend analysis and, at the same time, cluster trend analysis is more sensitive to focal VF progression than mTD trend analysis.

Assessing the trend of global VF indices (such as mTD or mean deviation (MD)) over time remains one of the most popular methods to measure glaucomatous VF progression. This method is more robust to false positive results than point-wise trend analysis; however, glaucomatous change/progression usually occurs locally so whole field trend analysis is not ideal to achieve early detection of progression. However, point-wise trend analysis can be very unreliable, because of the large variability of measurements,[4–6] particularly when glaucomatous deterioration is predominant.[6] Cluster-based trend analysis offers one approach to overcome this problem. The PBNP rate (a surrogate metric for the true negative rate) and PIP rate (a surrogate measurement for the false positive rate) associated with the cluster trend analysis were not worse than those observed for mTD trend analysis; however, the PBP rate (a surrogate metric for the true positive rate) was significantly lower for cluster trend analysis than it was for mTD trend analysis on two occasions (among 50 comparisons: 10 clusters x 5 VF series): cluster 7 with $VF_{5\text{-}10}$ and cluster 7 with $VF_{4\text{-}10}$. Cluster 7 corresponds to retinal area nasal and superior to the optic disc and tends not to be predominantly affected in glaucoma.[18 19] Sensitivity measurements are more variable in this peripheral area of the VF, and the lower PBP rate was only observed in relatively short series of VFs (six and seven VFs long). Thus, the current results suggest cluster trend analysis is no less robust than mTD trend analysis in clusters where glaucomatous VF damage tends to occur and with long series of VFs.

Clinicians may benefit from observing the results of a cluster trend analysis in addition to trend analyses of the whole field and point-wise VF sensitivity. Interestingly, our results suggest that an mTD trend analysis can mask a considerable proportion of progression observed in EyeSuites clusters. In particular, our results suggest that focusing on one or more and two or more progressing clusters, compared with monitoring whole field progression, clinicians can detect progression with smaller number of VF tests and shorter observation period by 1.33 VF tests/0.87 years and 0.60 VF tests/0.39 years on average. However, the probability that an eye that shows significant progression in an mTD trend analysis is missed by a cluster trend analysis was low but varies according to the definition of cluster-based progression. As we would expect, the probability increased with the number of progressing clusters. For the definition of one or more progressing clusters, just up to 1.0% of global progression was missed, for two or more progressing clusters, the proportion was up to 4.8% and for three or more progressing clusters, the rate was up to 8.8% (see table 2). Although cluster-based progression defined by one or more progressing clusters is sensitive to detect progression, false positives are a concern. However, when progression

was defined by two or more, three or more or two adjacent progressing clusters, PBP, PBNP and PIP rates were not significantly different from those observed for mTD trend analysis. Thus, a cluster-based trend analysis appears to be a clinically useful method to detect progression, especially in longer VF series (since this is associated with an increase in PBP and PBNP rates, and a decrease in the PIP rate). More specifically, the PBP rates for progression defined based on one or more progressing clusters were significantly higher than mTD trend analysis; however, the PBNP rates for progression defined based on one or more progressing clusters were significantly lower than mTD trend analysis, and also the PIP rates for progression defined based on one or more progressing clusters were significantly higher than mTD trend analysis. This is explained by relatively large variability that increases both sensitivity and false positives. The contrary result was obtained in $VF_{6\text{-}10}$ for trend analysis based on three adjacent progressive clusters, and this can be explained by the population characteristics; most subjects stayed at relatively early stage of glaucoma for the observation period, and few proportions of eyes progressive based on mTD trend analysis had three adjacent progressive clusters (figures 2, 3 and 4). Thus, it is advised to use the definition of two or more, three or more or two adjacent progressing clusters. The current study did not specify which of these three definitions is the best because they showed no significant difference in PBP, PBNP and PIP rates for every VF series with pairwise test in our analysis (data not shown).

In an ROC analysis predicting significant progression from an mTD trend analysis of $VF_{1\text{-}10}$, the number of significantly progressing clusters had an AUC similar to that for the number of significantly progressing test points for VF series $VF_{6\text{-}10}$ through to $VF_{2\text{-}10}$ and a significantly larger AUC for $VF_{1\text{-}10}$. This is probably because cluster trend analysis is more robust to VF variability than point-wise trend analysis. This result is important because point-wise trend analysis is already employed in clinics using specialised software such as PROGRESSOR (Medisoft, Leeds, UK).

A limitation of the current study is that relatively stable VF series (−0.3 dB/year) were investigated. Research should be carried out in eyes with faster progression rates to further explore the usefulness of cluster trend analysis. It would also be helpful to contrast cluster trend analysis with other approaches; for example, a new regression model was recently proposed by Zhu *et al*.[20] Indeed, improvements to the standard regression model could be applied to try to improve the cluster trend analysis. A further limitation concerns the judgement of progression, which can be made based on a combination of the magnitude of progression and the significance level[21]; we did not follow this approach; however, the usefulness of including a progression rate should be investigated for cluster trend analysis in future. We recently reported that smaller clusters can be advantageous to predict future VF sensitivity. Although we did not investigate the usefulness of different clusters here, we would expect smaller clusters would be associated with more variable results; however, it would be worthwhile to explore other clustering approaches.[22] Also our proxy estimates of both sensitivity and specificity may be inflated because of the inherent correlation between prior VFs and $VF_{1\text{-}10}$. Also, the studied patients in the study was recruited in Japan where the prevalence of NTG is very high.[23] Another study would be needed to validate the current results in other population.

In conclusion, the results of point-wise, the EyeSuite cluster-based and whole field trend analyses were compared in the current study. As a result, it was suggested that a whole field trend analysis can miss local VF progression. Furthermore, cluster-based trend analysis appears as robust as mTD trend analysis. In particular, it was suggested it was a good compromise to use the definition of two or more progressing clusters.

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Investigating the usefulness of a cluster-based trend analysis to detect visual field progression in patients with open-angle glaucoma

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Notes