Revalidating the Usefulness of a “Sector-Wise Regression” Approach to Predict Glaucomatous Visual Function Progression

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PURPOSE. We previously developed a method to measure visual function progression using “Progression sectors,” which were derived from a clustering analysis of pointwise rates of glaucomatous visual field (VF) progression; however, only short series of VFs, where pointwise linear regression (PLR) is typically not reliable, were analyzed. The purpose of the current study is to further investigate the usefulness of a sector-wise approach in longer series of VFs where the accuracy of PLR is inherently greater.

METHODS. We analyzed 16 VFs from each of 71 eyes in 45 patients. Sectorial averages of total deviation (TD) values were calculated at each “Progression sector,” consisting of 23 sectors as well as at “Nouri-Mahdavi” (NM) sectors, consisting of 10 sectors. Linear regression then was applied to predict sectorial averages in the 11th to 16th VFs and absolute prediction errors were compared to PLR.

RESULTS. Absolute prediction errors associated with linear regression of the “Progression sectors” were significantly smaller than those from PLR (P < 0.05) when predicting values in the 14th to 16th VFs. Conversely, prediction errors with NM sectors were significantly larger than those from PLR and “Progression sectors” (P < 0.01) when predicting values in the 11th to 16th VFs.

CONCLUSIONS. It is useful to use “Progression sectors” to predict future VF progression in short (1–10 VFs) and long (>10 VFs) VF series, compared to PLR and NM sectors.

Keywords: visual field, glaucoma, static perimetry, clustering

An accurate measurement of glaucomatous visual function progression is extremely important for clinical glaucoma management, not least because unnecessary medical and surgical IOP reduction interventions can be associated with various ocular and general complications.1–3 At the clinical setting, the rate of visual field (VF) progression generally is calculated by applying linear regression to VF measurements. For example, the rate of mean deviation (MD) change can be calculated using the Guided Progression Analysis (GPA) software on the Humphrey Visual Field Analyzer (HFA; Carl Zeiss Meditec AG, Dublin, CA, USA), while changes in pointwise sensitivity can be measured using the PROGRESSOR software (Medisoft, Inc., London, UK).

Earlier detection of focal glaucoma progression can be achieved by using a sectorwise or pointwise linear regression (PLR) analysis1–15 compared to an event analysis,4,6,10 trend analysis with global indices,5,7,8 or pattern deviation.11 However, poor reproducibility of pointwise VF sensitivity measurements16 can hamper early detection17,18 and reduce the accuracy of predictions of future visual function damage.

In our recent study, we reported that accurate predictions of visual function damage can be achieved by measuring progression in 23 small VF sectors (“Progression sectors,” see Fig. 1),19 because the effect of pointwise variability is reduced. The “Progression sectors” were developed based on clustering of progression rates in longitudinal series of VFs (n = 10) from 412 eyes in 412 open-angle glaucoma patients. This approach is in contrast to many other previous methods in which VF sectors were decided according to cross-sectional intertest point relationships.15,20–25 However, Nouri-Mahdavi et al.24 also developed VF sectors consisting of 10 sectors based on pointwise progression speed. Our previous report suggested that the 10 VF sectors from the report of Nouri-Mahdavi et al.24 (“Nouri-Mahdavi” [NM] sectors) were not useful to accurately predict future progression compared to our proposed “Progression sectors.”19 One of the problems with the clustering technique is how to adequately choose the number of clusters.25

Previous research suggests that at least five,26 eight, or even more27–29 VFs are needed to obtain a reliable forecast of future VF progression. Thus, our original study merely validated the usefulness of “Progression sectors” to predict future damage (a patient’s 10th VF) using short series of VFs (3–9 VFs measured approximately every 6 months). The purpose of the current study is to further investigate the usefulness of the “Progression sectors” approach, in comparison with PLR, to predict progression further into the future (11th–16th VFs) using a longer series of VFs (10 VFs) where PLR is inherently more reliable.

METHODS

Study Parameters

The study was approved by the Research Ethics Committee of the Graduate School of Medicine and Faculty of Medicine at the
University of Tokyo. Informed consent was obtained from all subjects. This study was performed according to the tenets of the Declaration of Helsinki.

Visual field data were obtained from 71 eyes in 45 patients with glaucoma who were followed up in the glaucoma clinic at the University of Tokyo Hospital. These subjects are a subset of those in our previous report. Visual field data were obtained retrospectively if a subject had more than 10 VFs when our previous study was conducted, otherwise VF data were obtained prospectively in the period of 2013 to 2015. Table 1 shows the demographic and ocular characteristics of the patients. Measurements of VF were performed using the HFA 24-2 and 30-2 test pattern were used in the analysis. Patients’ first VFs were excluded from the analysis. Other inclusion criteria in this study were best corrected visual acuity better than 6/12, refraction within ±6 diopter ametropia, no previous ocular surgery except for cataract extraction and intraocular lens implantation, and no other posterior segment eye disease. Reliability criteria for VFs were applied: fixation losses less than 20% and false-positive responses less than 15%; the false-negative rate was used not following a previous report. A glaucomatous VF was defined if a VF met any of the following criteria: (1) a cluster of ≥3 points in the pattern deviation plot in a single hemifield (superior/inferior) with P < 0.05, one of which must have been P < 0.01, excluding the outermost test point of Humphrey Field Analyzer 30-2 program; (2) glaucoma hemifield test (GHT) result outside of normal limits; or (3) abnormal PSD with P < 0.05. Patients who underwent intraocular surgical treatments during the observed period were excluded. The VF of a right eye was mirror-imaged to that of a left eye.

Prediction accuracy was investigated in the 11th to 16th VFs of a patient using their initial 10 VFs. This is in contrast to our previous study in which the 10th VF was predicted using a patient’s previous VFs. The calculation of prediction accuracy was performed as follows: first, in each cluster, the average of total deviation (TD) values from all test locations within respective cluster was calculated at each sector (23 “Progression sectors,” see Figs. 1 and 10 “NM sectors”) and a linear regression was fit for each cluster location in the VF using the average TD values at the respective cluster location in the first 10 VF follow-ups. The visual function of 11th to 16th VFs were predicted by extrapolating the linear regression. Then, the absolute value of the difference between the predicted sectoral TD values and the actual pointwise TD values as the absolute prediction error was calculated. Finally, prediction errors from the two sector-wise methods were compared to the prediction error associated with PLR.

**Table 1.** Demographic and Ocular Characteristics of the Patients

<table>
<thead>
<tr>
<th>No. of eyes/patients</th>
<th>71/45</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of glaucoma</td>
<td></td>
</tr>
<tr>
<td>Primary open-angle glaucoma</td>
<td>15</td>
</tr>
<tr>
<td>Normal tension glaucoma</td>
<td>49</td>
</tr>
<tr>
<td>Secondary glaucoma</td>
<td>3</td>
</tr>
<tr>
<td>Angle close glaucoma</td>
<td>0</td>
</tr>
<tr>
<td>Congenital glaucoma</td>
<td>4</td>
</tr>
<tr>
<td>Age, y, mean ± SD</td>
<td>61.4 ± 13.0</td>
</tr>
<tr>
<td>Sex, male/female</td>
<td>36/35</td>
</tr>
<tr>
<td>Eye laterality, right/light</td>
<td>30/41</td>
</tr>
<tr>
<td>Baseline IOP, mm Hg, mean ± SD</td>
<td>16.5 ± 4.0</td>
</tr>
<tr>
<td>No. of visual field</td>
<td>16</td>
</tr>
<tr>
<td>Interval between first and 10th visual field, y, mean ± SD</td>
<td>4.9 ± 10.8</td>
</tr>
<tr>
<td>Interval between 10th and 16th visual field, y, mean ± SD</td>
<td>3.8 ± 1.2</td>
</tr>
<tr>
<td>Initial mean of TD, dB, mean ± SD</td>
<td>-7.5 ± 5.4</td>
</tr>
<tr>
<td>Final mean of TD (dB, mean ± SD)</td>
<td>-11.3 ± 6.3</td>
</tr>
</tbody>
</table>

**Statistical Analysis**

All statistical analyses were done using the statistical programming language R (ver. 2.15.0; The R Foundation for Statistical Computing, Vienna, Austria). Absolute prediction errors were compared using the Wilcoxon test where P values were adjusted using Benjamini-Hochberg procedure for multiple testing.

**RESULTS**

The demographics of the patients in this study are summarized in Table 1. The mean of all TD values in the initial VF was -7.5 ± 5.4 dB (mean ± SD) and -11.3 ± 6.3 dB in the 16th VF. Patients’ initial age was 50.9 ± 12.5 years. The global progression rate of the mean of TD values was -0.41 ± 0.88 dB/y. The interval
between the first and 10th VF was 4.9 ± 0.8 years and the interval between the 10th and 16th VF was 3.8 ± 1.2 years.

Figure 2 and Table 2 summarize the absolute prediction errors associated with PLR and the sector-wise methods. The prediction errors associated with the “Progression sectors” were significantly smaller than those with PLR (P < 0.05, Wilcoxon test adjusted with Benjamini-Hochberg procedure for multiple testing) when predicting the 14th to 16th VFs, although the prediction error of the method was significantly larger than PLR when predicting the 11th VF (P < 0.05, Wilcoxon test adjusted with Benjamini-Hochberg procedure for multiple testing). Absolute prediction errors with NM sectors were significantly larger than those from PLR and “Progression sectors” (P < 0.01, Wilcoxon test adjusted with Benjamini-Hochberg procedure for multiple testing) when predicting all future (11th-16th) VFs.

### DISCUSSION

In our previous study we reported that the prediction of future visual function progression could be improved by dividing the VF into small sectors. Indeed, our previous studies strongly supported this notion. In the current study, the usefulness of these “Progression sectors” was further investigated using this longer series of VF data. As a result, accurate predictions were observed with the PLR and “Progression sectors” approach than the “NM sectors” approach in predicting a patient’s 11th to 13th VFs, and more accurate predictions were observed with the “Progression sectors” approach than with PLR and also “NM sectors” in predicting a patient’s 14th to 16th VFs.

It is widely acknowledged that PLR is relatively unreliable until a considerable number of VFs are accumulated. Indeed, our previous studies strongly supported this notion. In the current study a larger number of VFs (n = 10) was used to predict future visual function damage, and prediction accuracy was once again observed to fall as the interval to the predicted VF lengthened. This could be caused by the unavoidable short- and long-term fluctuation of VF measurements, including poor fixation/mattention or fatigue. Indeed, significant eye movements can occur during an otherwise reliable VF test. In the current study, 10 VF s were acquired over approximately 5 years, yet PLR remained comparatively unreliable when predicting distant future progression. This is clinically very important because treatments are intensified according to estimates of VF progression rates. The current data were obtained from a standard hospital glaucoma clinic where VF tests were conducted in 6-monthly intervals; however, clinicians often are required to make treatment decisions with less frequently measured VFs. As shown in the current study, future visual function progression was more accurately predicted in the 14th to 16th VFs by applying the “Progression sectors” approach compared to PLR. Conversely, prediction accuracy of the “Progression sectors” method was worse for the immediate (11th) VF compared to PLR; however, the average increase in prediction error for the sectors method for the range of VFs predicted (between 11th and 16th VF) was merely 1.0 dB, which was half of that of PLR.

Nouri-Mahdavi et al. also have reported a sector-based method for measuring VF progression. Glaucomatous VF damage follows the structural pattern of retinal nerve fibers, and our “Progression sectors” and “NM sectors” mirror the structure-function relationship; however, in the current study, “NM sectors” led to a significantly worse prediction of future visual function damage compared to PLR. Glaucomatous progression usually starts focally and, hence, the accuracy of progression detection methods is a balance between reducing the variability of pointwise VF sensitivity by averaging test points and not masking focal damage by averaging too many VF points in sectors. Thus, the poor performance of “NM sectors” for prediction, observed in the current study, could be attributed to the difference in the size of the clusters, since the VF is divided into much larger sectors using the approach of Nouri-Mahdavi et al.

As shown in Figure 1, our “Progression sectors” are smaller in the central area, such as sectors 12 and 15; this result is in agreement with previous reports that suggest these areas tend to progress independently from other test locations. This is probably because of the rich retinal nerve fiber layer (RNFL) distribution in this area. Indeed, our group previously suggested that an even finer sector can be identified in this area, which is smaller than the area.

### Table 2. Mean Absolute Prediction Errors Predicting the 11th to 16th VF Using Initial 10 VFs

<table>
<thead>
<tr>
<th></th>
<th>11th VF</th>
<th>12th VF</th>
<th>13th VF</th>
<th>14th VF</th>
<th>15th VF</th>
<th>16th VF</th>
</tr>
</thead>
<tbody>
<tr>
<td>PLR</td>
<td>3.0 ± 1.3</td>
<td>3.3 ± 1.6</td>
<td>3.2 ± 1.8</td>
<td>4.0 ± 2.0</td>
<td>4.6 ± 2.4</td>
<td>5.1 ± 2.8</td>
</tr>
<tr>
<td>NM Sectors</td>
<td>4.4 ± 1.9</td>
<td>4.5 ± 2.1</td>
<td>4.8 ± 2.1</td>
<td>4.9 ± 2.3</td>
<td>5.2 ± 2.5</td>
<td>5.6 ± 2.8</td>
</tr>
<tr>
<td>Progression Sectors</td>
<td>3.2 ± 1.3</td>
<td>3.5 ± 1.5</td>
<td>3.7 ± 1.5</td>
<td>3.8 ± 1.7</td>
<td>3.8 ± 1.5</td>
<td>4.2 ± 1.8</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>PLR vs. NM</th>
<th>PLR vs. Progression Sectors</th>
<th>NM vs. Progression Sectors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Value</td>
<td>&lt;0.001</td>
<td>0.002</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>&lt;0.001</td>
<td>0.08</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>&lt;0.001</td>
<td>0.027</td>
<td>&lt;0.001</td>
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<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
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<tr>
<td></td>
<td>0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
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</tbody>
</table>

Data are given as mean and SD.

In conclusion, predicting future visual function damage is difficult due to the inherent variability of these measurements; however, the accuracy for future visual function damage using our sector-based approach is equal or improving in short and long VF series compared to PLR and NM sectors.

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### References

Predict Glaucomatous Visual Function Progression