

Combining optical coherence tomography with visual field data to rapidly detect disease progression in glaucoma: a diagnostic accuracy study

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Scientific summary

Imaging technology to detect glaucoma disease progression

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Scientific summary

Background

Glaucoma is a chronic progressive eye disease that can cause irreversible vision loss. The optic nerve is damaged where it enters the eye, resulting in reduced sensitivity to light in regions of the eye's field of vision. In clinical care and in clinical trials, light sensitivity is measured with the visual field (VF) test. VF measurements are, however, variable and the variability increases as damage worsens, making it difficult to identify glaucoma worsening over time. The damage to the nerve can also be measured with imaging techniques, such as optical coherence tomography (OCT), which measures the thickness of the retinal nerve fibre layer (RNFL); the RNFL contains the retinal ganglion cell axons, which leave the eye through the optic nerve head. OCT RNFL and VF measurements have been shown to correlate over the range of glaucoma damage. Combining VF and OCT RNFL measurements may reduce variability, making it easier to identify glaucoma worsening. To establish the validity of combining VF and OCT RNFL measurements, it should first be demonstrated that treatment slows the rate of RNFL thinning to a similar extent that it slows the rate of VF loss.

Methods

We aimed to compare statistical methods that combine VF and OCT data with the reference standard method [Guided Progression Analysis™ (GPA) software (Carl Zeiss Meditec Inc., Dublin, CA, USA) for the Humphrey Field Analyzer (HFA) instrument™ (Carl Zeiss Meditec Inc., Dublin, CA, USA)], which uses only VF data, to establish whether or not combining OCT and VF allows (1) more rapid identification of glaucoma worsening ('progression') and (2) shorter or smaller clinical trials. We also aimed to explore new statistical methods for combining VF and OCT data.

As there is no 'gold standard' test for glaucoma progression to provide a ground truth, relative measures are required. Instead of criterion sensitivity, the 'hit rate' (proportion of eyes identified as progressing) in eyes at risk of worsening was used as an approximation. Criterion specificity was measured in eyes with a very low probability of worsening (clinically stable patients measured frequently over a space of time too short for clinically relevant deterioration to take place). Time to progression, when specificity was fixed at 95%, was used as another measure of test sensitivity. Other metrics to establish the utility of combining VF and OCT data included the accuracy of the estimated rate of progression. Again, as there is no gold standard measurement, a surrogate outcome was used; the modelled rate of progression over the initial five visits was used to predict the last VF in the series, assuming a linear rate of change, and the prediction error was taken as a measure of the model appropriateness. Finally, the ability of the various models to distinguish the treatment arms in clinical trial data was assessed.

The hit rate, time to progression, prediction accuracy and ability to distinguish treatment status of the various statistical methods was evaluated in the 320 participants, or subsets of them, from the United Kingdom Glaucoma Treatment Study (UKGTS) multicentre randomised placebo-controlled clinical trial who had both VF testing and OCT RNFL imaging. Specificity was evaluated in up to 72 stable glaucoma patients who had between 4 and 14 VF and OCT tests within a 3-month period (the RAPID stable data set). The UKGTS was conducted at 10 teaching and general ophthalmology units. The RAPID data set was collected at a single teaching ophthalmology unit. The UKGTS participants were newly diagnosed patients with mild-to-moderate glaucoma (mean deviation better than -16 dB in the worse eye) randomised to a drop therapy to lower intraocular pressure or placebo. RAPID participants were patients with similar glaucoma severity who were on treatment and who were clinically stable.

Participants underwent VF testing with the HFA 24-2 test pattern and RNFL imaging with time-domain Stratus OCT™ (Carl Zeiss Meditec Inc., Dublin, CA, USA) (TD OCT). The reference test for glaucoma progression was based on the GPA software of the HFA. Index tests were based on previously described methods [Analysis with Non-Stationary Weibull Error Regression and Spatial enhancement (ANSWERS) and permutation analyses of pointwise linear regression (PoPLR); ANSWERS was modified so that the rate of RNFL change could be used as a Bayesian prior for the estimates of the rate of VF change and was termed 'structure-guided ANSWERS' (sANSWERS)]. Other index tests were newly developed methods based on permutation tests, multivariate hierarchical models with multiple imputation for censored values (MaHMIC) and multivariate generalised estimating equations with multiple imputation for censored values (MaGIC).

The main outcome measures were progression criterion specificity, hit rate, time to incident progression, future VF sensitivity prediction error, difference in proportions identified as progressing in the UKGTS treatment groups, hazard ratios (HRs) and study sample size required to measure treatment effects.

Results

The estimated criterion specificity was set at 95% for all tests. The hit rate in the UKGTS cohort for the various statistical methods was 22.2% for GPA, 41.6% for PoPLR, 53.8% for ANSWERS and 61.3% for sANSWERS; all pairs of comparison were significantly different at $p \leq 0.042$. Mean survival time was 93.6 weeks for GPA, 82.5 weeks for PoPLR, 72.0 weeks for ANSWERS and 69.1 weeks for sANSWERS. The trend in VF (\pm OCT RNFL) measurements over the initial 42.4 [standard deviation (SD) 6.2] weeks was used to predict the VF sensitivity values 49.2 (SD 19.8) weeks later; the median prediction errors were 3.8 (5th to 95th percentile 1.7 to 7.6) dB for PoPLR, 3.0 (5th to 95th percentile 1.5 to 5.7) dB for ANSWERS and 2.3 (5th to 95th percentile 1.3 to 4.5) dB for sANSWERS. In distinguishing the UKGTS treatment groups, the HRs were 0.57 [95% confidence interval (CI) 0.34 to 0.90; $p = 0.016$] for GPA, 0.59 (95% CI 0.42 to 0.83; $p = 0.002$) for PoPLR, 0.76 (95% CI 0.56 to 1.02; $p = 0.065$) for ANSWERS and 0.70 (95% CI 0.53 to 0.93; $p = 0.012$) for sANSWERS. Sample size estimates were not reduced by using methods including OCT data.

Permutation test analysis of UKGTS data resulted in hit rates between 8.3% and 17.4%; treatment effects when data were analysed with MaHMIC and MaGIC were non-significant and statistical significance was altered little by incorporating imaging.

Conclusions

The sANSWERS method combining VF and OCT data had a higher hit rate and identified progression more quickly than the reference GPA method and other VF-only methods, and produced more accurate estimates of the rate of progression. However, methods combining VF and OCT data did not improve trial power to identify a treatment effect. The statistical method providing the greatest difference in time to progression and most statistically significant difference was the PoPLR technique using VF data alone. Current OCT imaging technology is already more precise than that evaluated in this work (TD OCT). It is likely, therefore, that current OCT technology would perform better than TD OCT. The size of the RAPID data set limited the precision of the estimates for criterion specificity; however, 'stable' data sets, in which many tests are obtained over a short period of time, are challenging to collect. Future work should evaluate current OCT technology in the context of clinical treatment trials and refine the statistical methods further.

Trial registration

This trial is registered as ISRCTN96423140.

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