Validation of 3D volumetry for a novel anti-angiogenic therapy of neovascular age-related macular degeneration

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Purpose

Morphologic alterations in the retina have been shown to influence the functional response to anti-angiogenic therapies in neovascular age-related macular degeneration (nvAMD) and impact the visual outcomes. We wanted to test and validate a new 3D volumetric tool to quantify some of the critical alterations in a subset of patients enrolled in a prospective Phase 1/2 trial.

Materials and Methods

Study Design

The initial phase was an open-label, single-ascending dose of increasing single intravitreal (IVT) doses of an anti-VEGF agent, ranging from 0.03mg to 0.6mg, in patients with nvAMD (treatment naïve or previously treated with an anti-VEGF therapy). Images of two dose groups at the highest doses (n=5 for each group) were evaluated at 5 visits.

Imaging

OCT volume scans were obtained from the Spectralis instrument (Heidelberg Engineering) and were imported into the novel software (RevAnalyzer, ADCIS) for image analysis.

Grading

Three independent trained graders measured three types of retinal alterations: Pigment Epithelium Detachment (PED), Subretinal Fluid (SRF) and Intraretinal Cysts (IRC) based on previously agreed methodology.

Results

Figure 1.A Interface of the RevAnalyzer software with one graded B-scan . **B** Representative PED, SRF and IRC segmented in the software
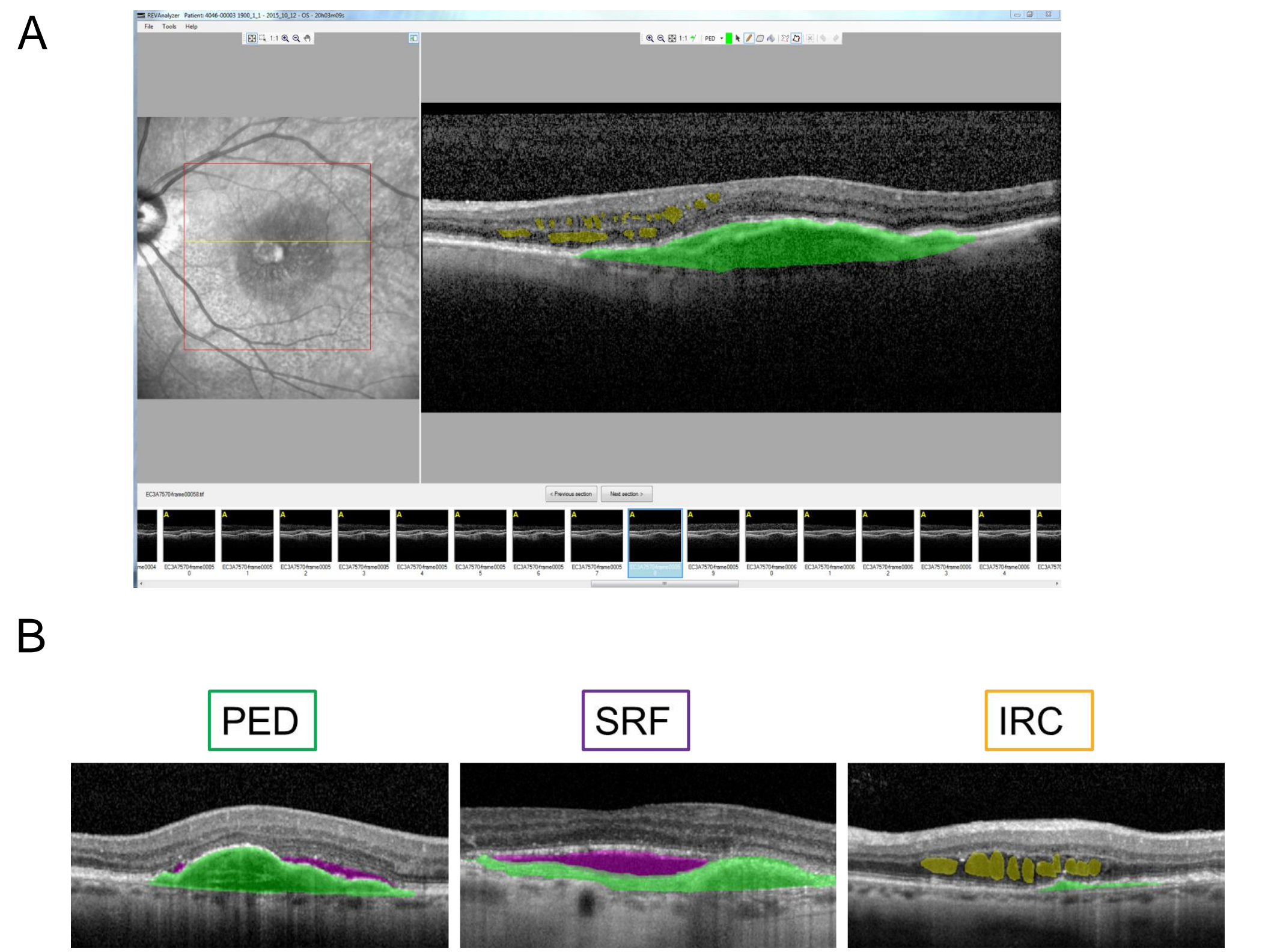

The agreement between graders for PED, SRF and IRC was 97.3%, 94.6% and 96%, respectively.

Table 4. OCT characteristics of nvAMD patients evaluated at baseline based on senior grader

|	n	Percentage
PED	10	
Absent	0	0%
Present	10	100%
SRF	10	
Absent	3	30%
Present	7	70%
IRC	10	
Absent	4	40%
Present	6	60%

For the volume measurements of all PED, SRF, and IRC, the intraclass correlation between graders was 0.90 (95% CI, 085-0.94), 0.98 (95% CI, 0.98-0.99) and 0.95 (95% CI, 0.92-0.97), respectively.

Figure 2. Representative 3D renderings of the same segmented volume scan from three independent graders
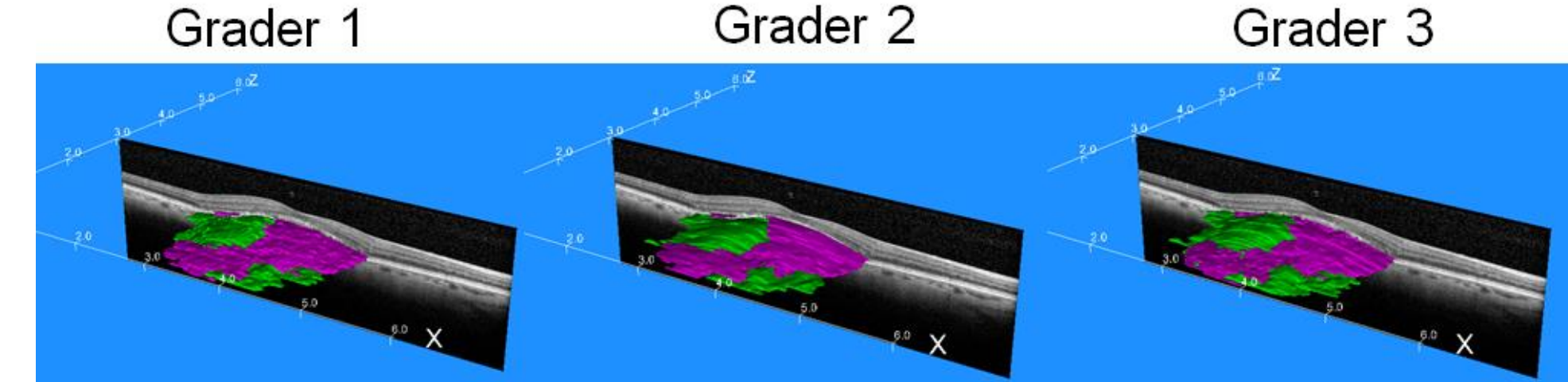
PED volume slowly decreased upon anti-VEGF treatment (average slope of regression line= -2.95) but was responsible for the maximal reduction of the central retinal thickness (CRT; correlation r^2=0.55).
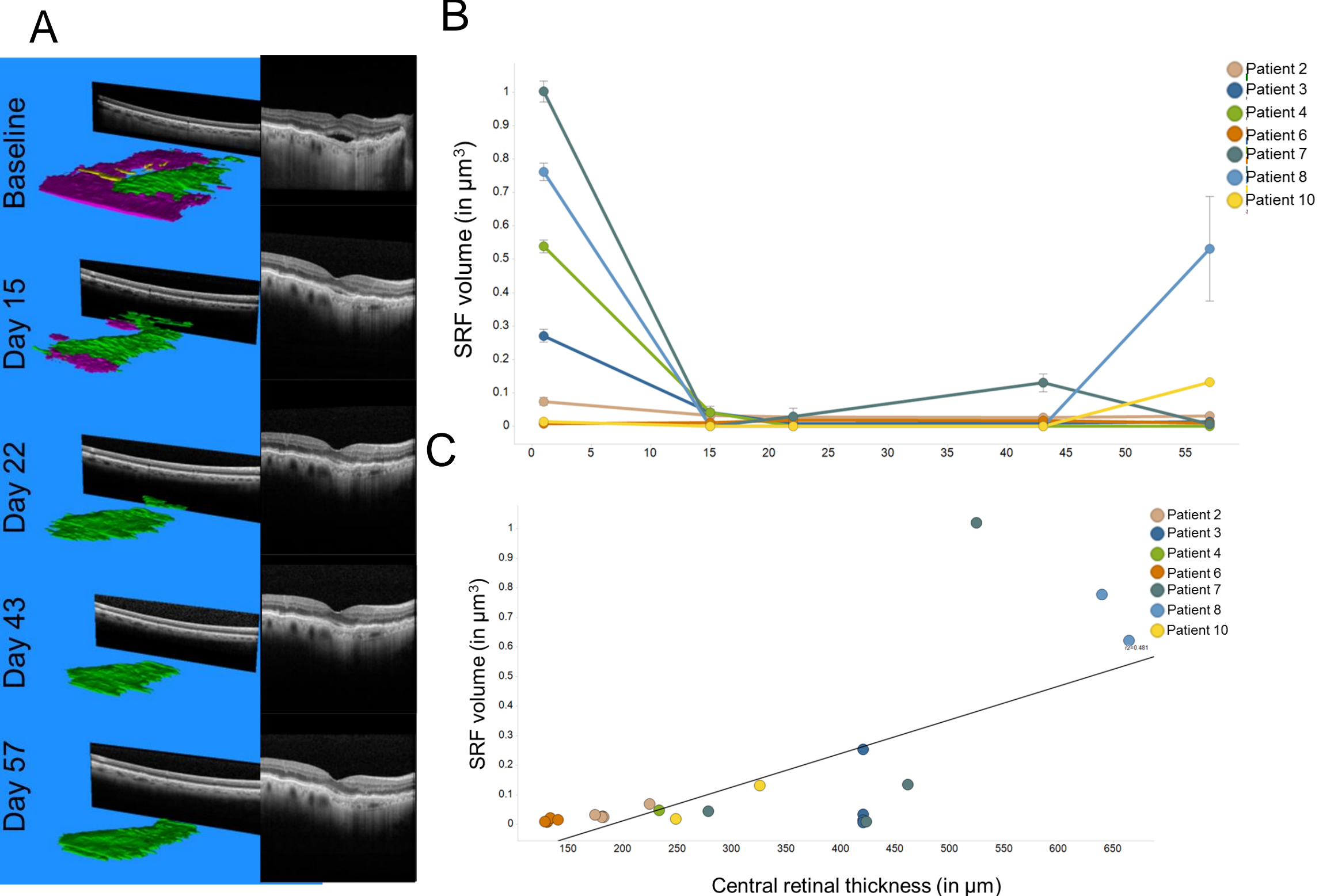
Figure 3. A.3D volumetry to visualize the PED response after anti-VEGF therapy in one patient. **B**. Changes of average PED volume for each patient over time (error bars: SD). **C**. Correlation plot of PED volume and CRT
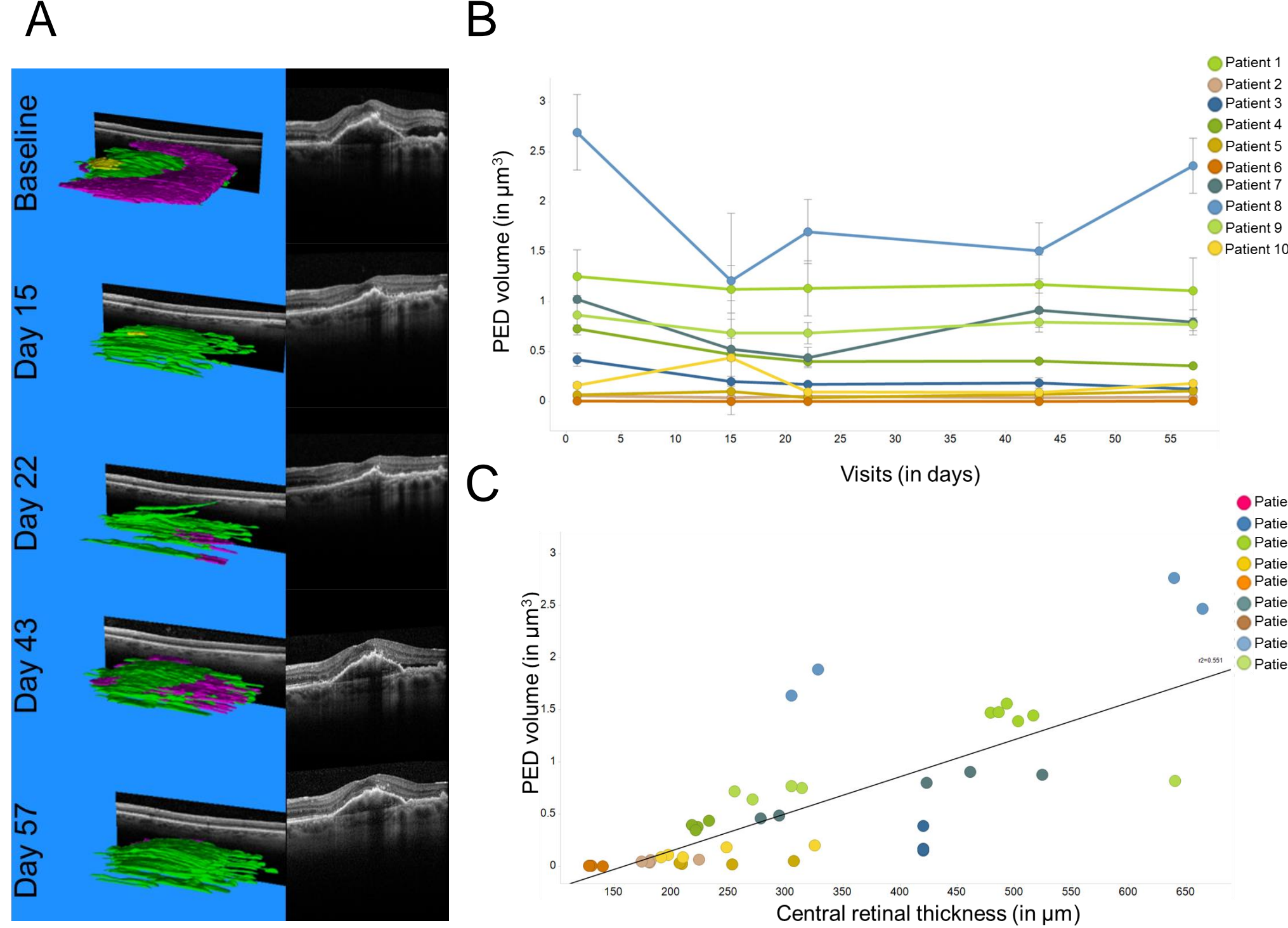

Results

SRF volume seemed to be the most sensitive measurement to our novel anti-VEGF therapy as it rapidly decreased after IVT injection (maximal average reduction at 15 days post-IVT, average slope of regression line = -6.40) and, for some cases, quickly re-appeared before any changes in central retinal thickness.

Figure 4. A. 3D volumetry to visualize the SRF response after anti-VEGF therapy in one patient. **B**. Changes of average SRF volume for each patient over time (error bars: SD). **C**. Correlation plot of SRF volume and CRT


When responsive, the IRC volume also rapidly decreased upon treatment (volume was completely absent at Day 15).

Figure 5. A. 3D volumetry to visualize the IRC response after anti-VEGF therapy in one patient. **B**. Changes of average IRC volume for each patient over time (error bars: SD). **C**. Correlation plot of IRC volume and CRT
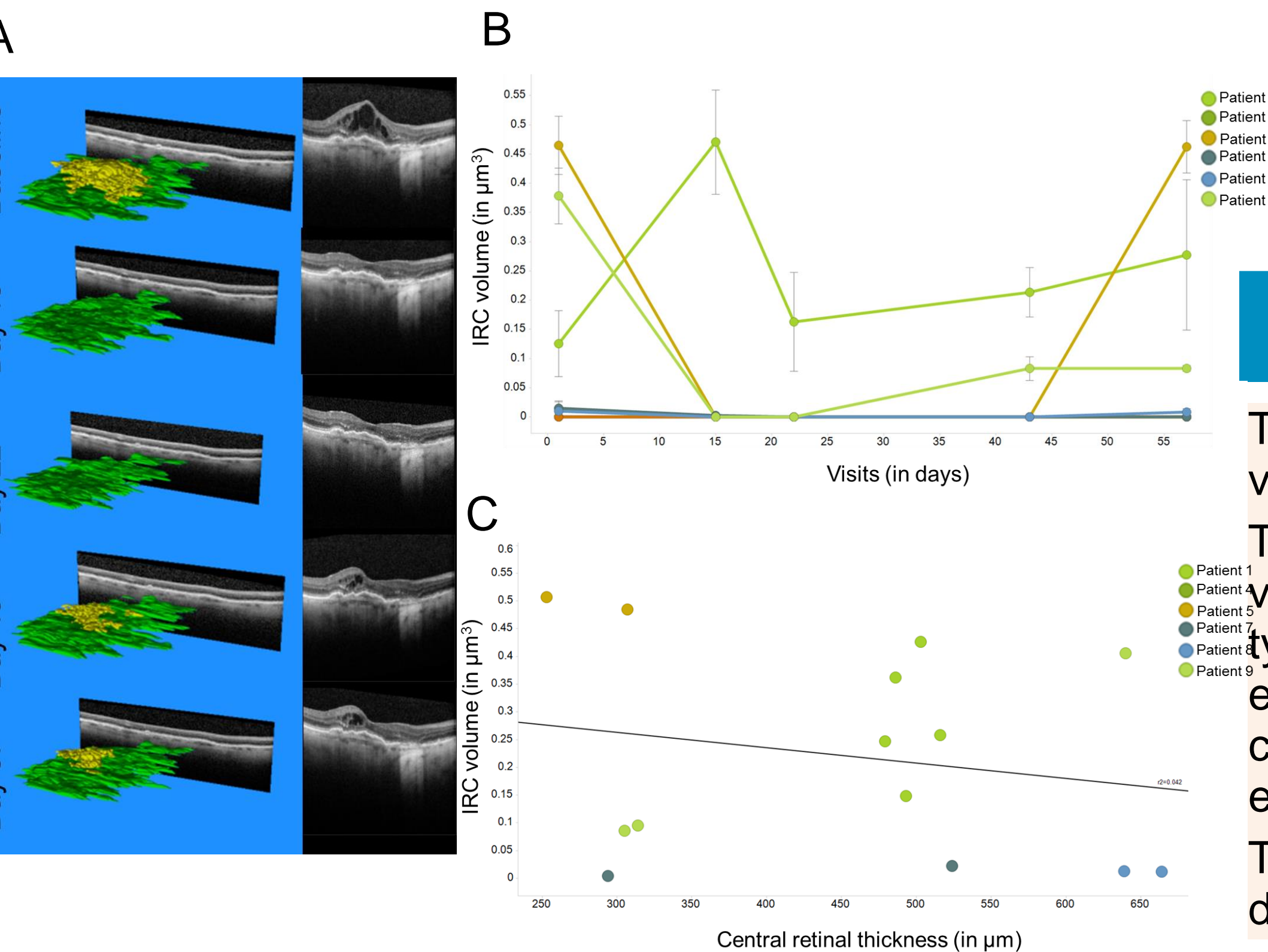
The impact of the changes of volumes upon an anti-VEGF therapy on visual acuity was assessed. The most decrease of PED volume from baseline seemed to mostly correspond to the largest gain in letters. By contrast, the changes of SRF and IRC volume did not seem to correlate with changes of BCVA.

Figure 6. Correlation plots of changes from baseline of PED (**A**), SRF (**B**) and IRC (**C**) volumes with changes from baseline of visual acuity (VA)
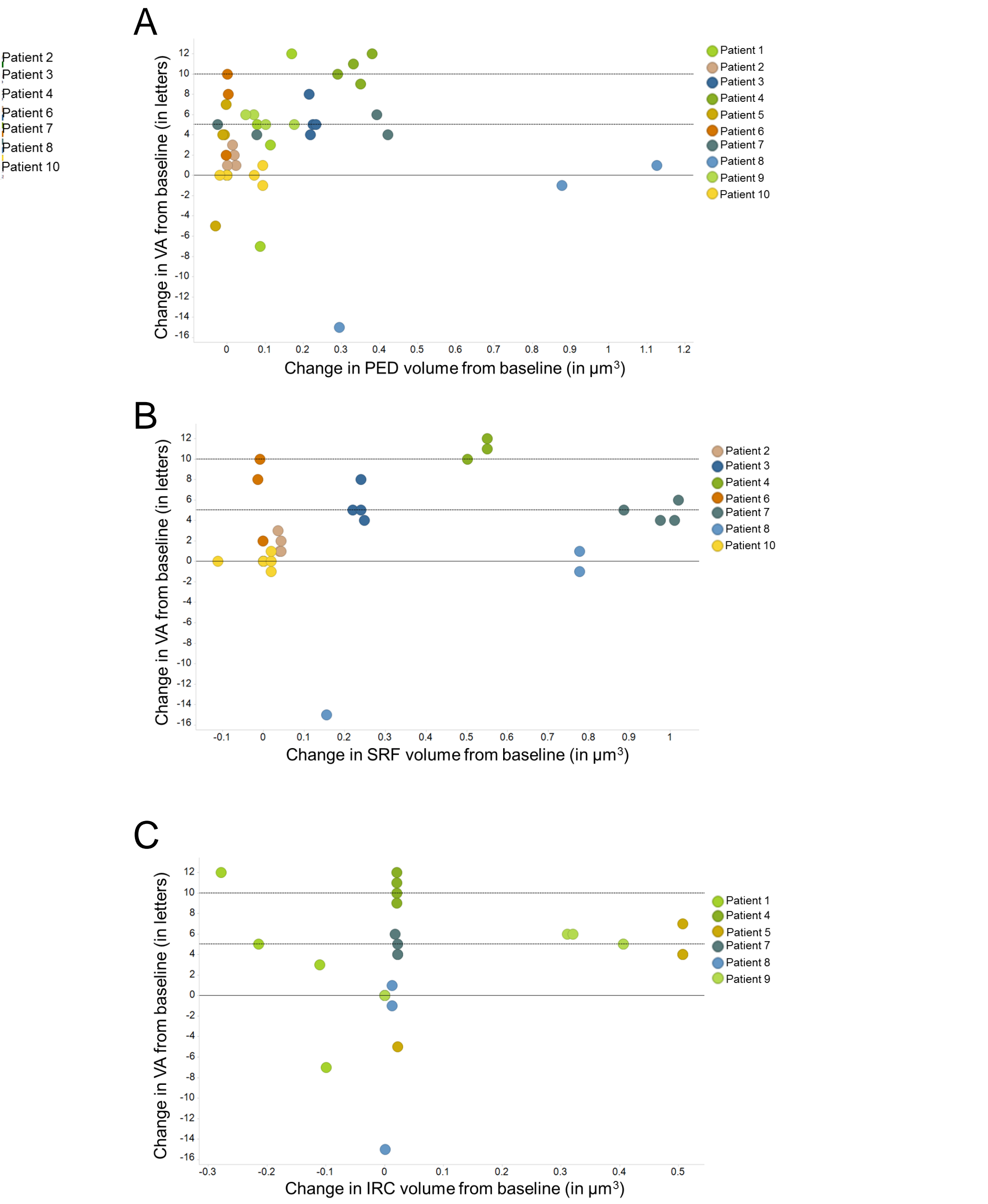
Conclusions

The semi-automated quantification of PED, SRF and IRC volumes was found to be very reproducible between graders.

This innovative software is a valuable tool that allows exquisite visualization of retinal fluid and the refined correlation of sub-types of retinal alterations with retinal thickness and BCVA, as it enables a reproducible measurement of a global volume compared to qualitative assessment or point measurement of each morphologic parameter.

This preliminary work needs to be further investigated in order to determine the relationships between fluids and visual acuity.