

**The area and number of intraretinal cystoid spaces predict the visual outcome after intravitreal ranibizumab monotherapy in diabetic macular edema**

**Evaluation of cystoid spaces in OCT images in DME**

**St. Luke's International University and Hospital**

**Professor and Director**

**Keio University School of Medicine**

**Associate Professor**

**Yoko Ozawa**

## **Disclosure**

Wakasa Seikatsu Co., Ltd. - Funding - Primary Investigator (CI)

Santen Pharmaceutical., Ltd. (C)

Santen Pharmaceutical., Ltd. - Lecture Fees - Lecturer (CI)

Novartis Pharma- (C)

Novartis Pharma- Lecture Fees - Lecturer (CI)

Bayer Yakuhin (C)

Bayer Yakuhin - Lecture Fees - Lecturer (CI)

Senju Pharmaceutical., Ltd. - Funding - Primary Investigator (CI)

Senju Pharmaceutical., Ltd. - Lecture Fees - Lecturer (CI)

This study was approved by the Ethics Committee of the Keio University School of Medicine (20100003), and is registered under the number UMIN000012221.



I, Yoko Ozawa, have just moved from Keio University to **St. Luke's International University and Hospital**, established in 1901.

It is located in Tsukiji, close to Ginza, the central part of Tokyo.

The study that I will talk today was performed in Keio University Hospital where I still have an affiliation.



### Summary of the study

We found that BCVA at 12 months was positively correlated with **the area ratio and number of the intraretinal cystoid spaces evaluated in the OCT images at baseline**, irrespective of age and BCVA at baseline.

These baseline findings were associated with greater extent of ELM and EZ disruptions at 12 months, and final photoreceptor damages after treatments.

The factors help obtain proper informed consent before treatment



Article

## The Area and Number of Intraretinal Cystoid Spaces Predict the Visual Outcome after Ranibizumab Monotherapy in Diabetic Macular Edema

Norihito Nagai <sup>1,2</sup>, Misa Suzuki <sup>1,2</sup>, Atsuro Uchida <sup>2</sup>, Toshihide Kurihara <sup>2</sup> , Norimitsu Ban <sup>2</sup>, Sakiko Minami <sup>2</sup>, Hajime Shinoda <sup>2</sup>, Kazuo Tsubota <sup>2</sup>  and Yoko Ozawa <sup>1,2,3,4,\*</sup> 

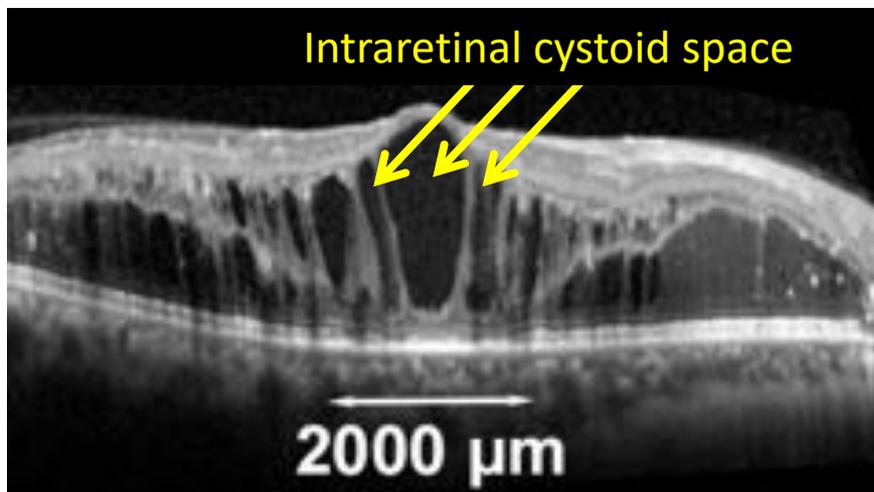
**Purpose:** To determine predictive factors for visual outcome in diabetic macular edema (DME) after anti-vascular endothelial growth factor therapy, which varies across individuals.

**Methods:** We retrospectively reviewed the clinical records of 46 treatment-naive eyes of 46 patients with DME who underwent intravitreal ranibizumab (IVR) monotherapy with a pro re nata (PRN) regimen for 12 months. Best-corrected visual acuity (BCVA) and eye examination data including optical coherence tomography (OCT) images were analyzed.

### ***Optical Coherence Tomography***

Horizontal sections OCT images passing through the fovea were obtained with a Heidelberg Spectralis OCT instrument in OCT Section mode (30, average of a maximum of 100 frames acquired using a retinal tracking system). **Repeat mode** was applied at the time of the follow-up visits to obtain OCT images at the exact same location.

- 1. Number of the intraretinal cystoid spaces**
- 2. Area ratio of the total intraretinal cystoid spaces to the retina**



\*OCT images within a 2000 μm diameter around the foveal center were analyzed.

\*SRF was NOT involved either in the intraretinal cystoid space or retinal areas.

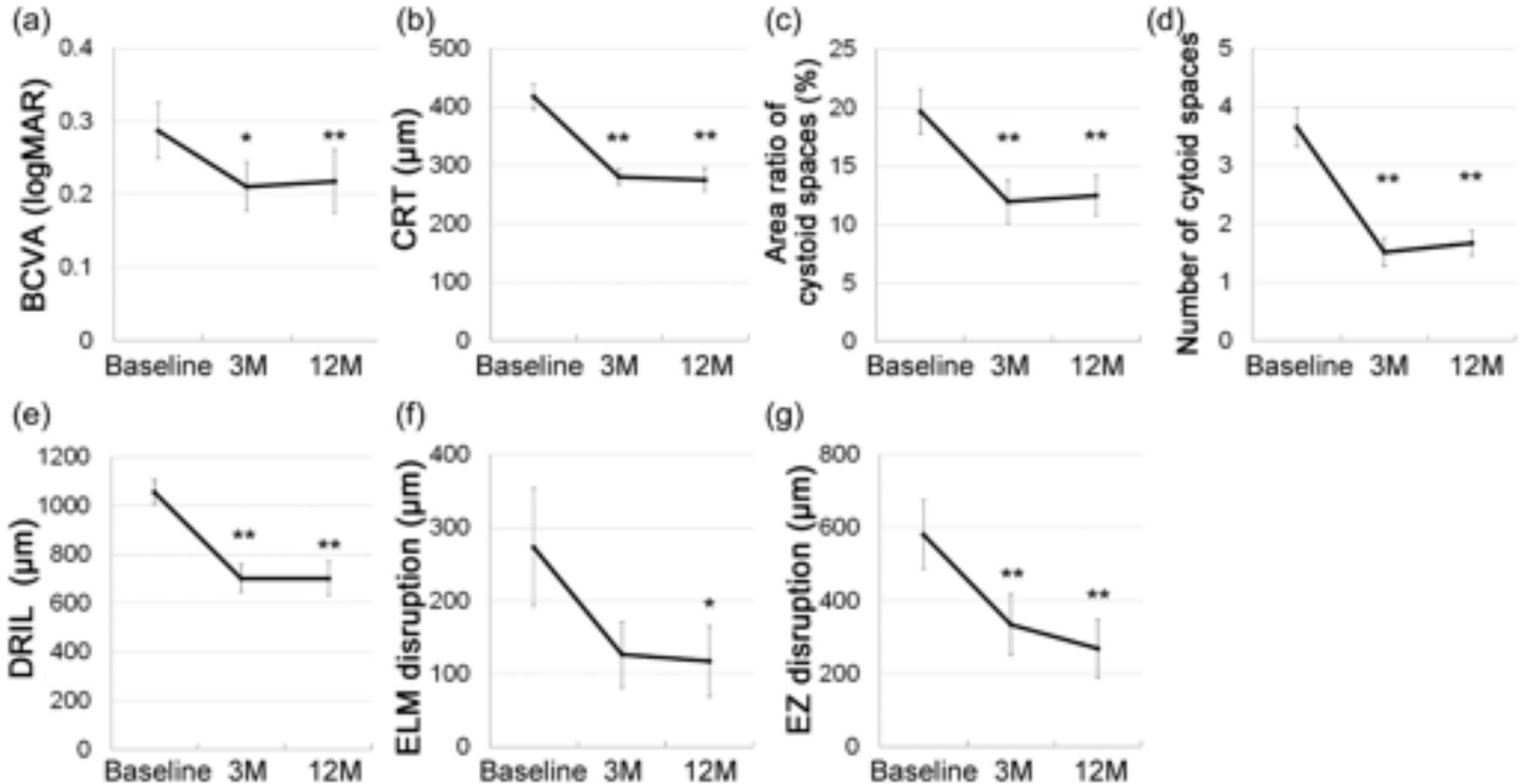


**Table 1. Baseline characteristics.**

|  |                                |
|--|--------------------------------|
| Age (y/o, mean, [range])                                     | 65.5 ± 1.6 [40 - 80]           |
| Sex (male; eyes [%])   | 29 (63.0)                      |
| HbA1c (%; mean, [range])                                     | 7.2 ± 0.1 [5.4 - 10.0]         |
| Hypertension (%)   | 28 (60.9)                      |
| BCVA (logMAR, mean, [range])                                 | 0.285 ± 0.038 [-0.079 – 1.000] |
| Fundus findings  |                                |
| Mild to moderate non-proliferative DR (eyes [%])             | 13 (28.26)                     |
| Severe non-proliferative DR (eyes [%])                       | 20 (43.48)                     |
| Proliferative DR (eyes [%])                                  | 13 (28.26)                     |
| OCT findings   |                                |
| CRT (µm, mean, [range])                                      | 418 ± 21 [167 – 800]           |
| Area ratio of intraretinal cystoid spaces (%; mean, [range]) | 19.7 ± 1.9 [2.9 – 61.7]        |
| Number of intraretinal cystoid spaces (mean, [range])        | 3.7 ± 0.3 [1 – 9]              |
| Extent of DRIL (µm, mean, [range])                           | 1056 ± 51 [280 – 1815]         |
| Extent of ELM disruption (µm, mean, [range])                 | 273 ± 80 [0 – 2000]            |
| Extent of EZ disruption (µm, mean, [range])                  | 580 ± 95 [0 – 2000]            |
| Presence of Hyperreflective Foci (eyes [%])                  | 16 (34.8)                      |
| Presence of SRF (eyes [%])                                   | 9 (19.6)                       |

Data are shown in mean ± SE. HbA1c, Hemoglobin A1c; BCVA, best-corrected visual acuity; DR, diabetic retinopathy; OCT, optical coherence tomography; CRT, central retinal thickness; DRIL, disorganization of retinal inner layers; ELM, external limiting membrane; EZ, ellipsoid zone, SRF, subretinal fluid.

**Figure 1.** Overall, values were improved by ranibizumab treatments.



Repeated measure ANOVA



**Table 2.** Association between BCVA at 12 months and baseline findings.

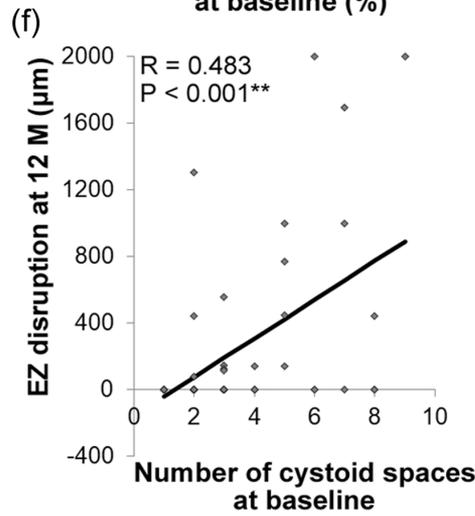
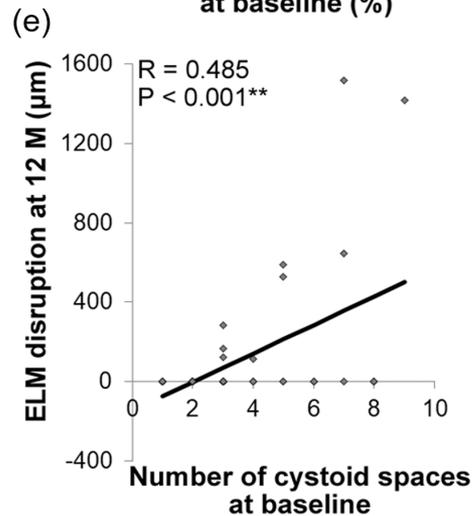
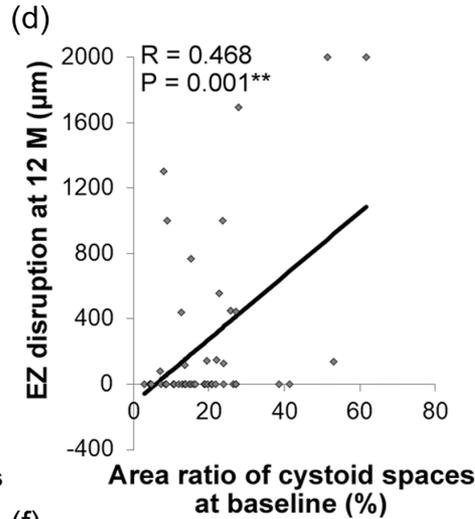
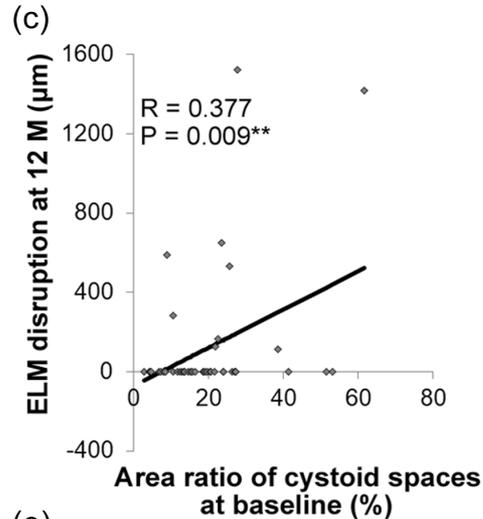
**BCVA at 12 months** was positively correlated with **the area ratio and number of the cystoid spaces at baseline** after adjusting for age and baseline BCVA.

|  | Crude  |         |                 | Multi-adjusted |                    |                       |
|--|--------|---------|-----------------|----------------|--------------------|-----------------------|
|  | R      | p       | 95%CI           | R              | p                  | 95%CI                 |
| Age  | -0.015 | 0.919   | -0.304 to 0.276 | -              | -                  | -                     |
| Sex (male)                                       | 0.030  | 0.843   | -0.263 to 0.318 | 0.046          | 0.604              | -0.082 to 0.139       |
| HbA1c  | -0.136 | 0.368   | -0.410 to 0.161 | -0.070         | 0.431              | -0.079 to 0.035       |
| Hypertension                                     | -0.220 | 0.141   | -0.480 to 0.075 | -0.058         | 0.524              | -0.148 to 0.075       |
| BCVA   | 0.830  | <0.001  | 0.711 to 0.903  | -              | -                  | -                     |
| Proliferative DR                                 | 0.162  | 0.284   | -0.135 to 0.432 | 0.090          | 0.327              | -0.061 to 0.179       |
| CRT  | 0.311  | 0.036   | 0.023 to 0.572  | 0.049          | 0.608              | -0.001 to 0.001       |
| <b>Area ratio of intraretinal cystoid spaces</b> | 0.688  | < 0.001 | 0.488 to 0.811  | <b>0.407</b>   | <b>&lt; 0.001*</b> | <b>0.006 to 0.013</b> |
| <b>Number of intraretinal cystoid spaces</b>     | 0.557  | < 0.001 | 0.319 to 0.730  | <b>0.241</b>   | <b>0.012*</b>      | <b>0.008 to 0.059</b> |
| Extent of DRIL                                   | 0.593  | < 0.001 | 0.365 to 0.753  | 0.168          | 0.119              | -0.001 to 0.001       |
| Extent of ELM disruption                         | 0.405  | 0.005   | 0.130 to 0.622  | 0.029          | 0.778              | -0.001 to 0.001       |
| Extent of EZ disruption                          | 0.157  | 0.296   | -0.139 to 0.428 | -0.088         | 0.346              | -0.001 to 0.001       |
| Presence of Hyperreflective Foci                 | -0.014 | 0.926   | -0.303 to 0.277 | 0.024          | 0.785              | -0.010 to 0.126       |
| Presence of SRF                                  | -0.016 | 0.915   | -0.305 to 0.275 | 0.037          | 0.681              | -0.106 to 0.160       |

Stepwise multiple linear regression models adjusted for age and BCVA at baseline. HbA1c, Hemoglobin A1c; BCVA, best corrected visual acuity; DR, diabetic retinopathy; CRT, central retinal thickness; DRIL, disorganization of retinal inner layers; ELM, external limiting membrane; EZ, ellipsoid zone, SRF, subretinal fluid. \*p < 0.05.

**Figure 2. Area ratio and number of the cystoid spaces at baseline were positively correlated with ELM and EZ disruptions at 12 months.**

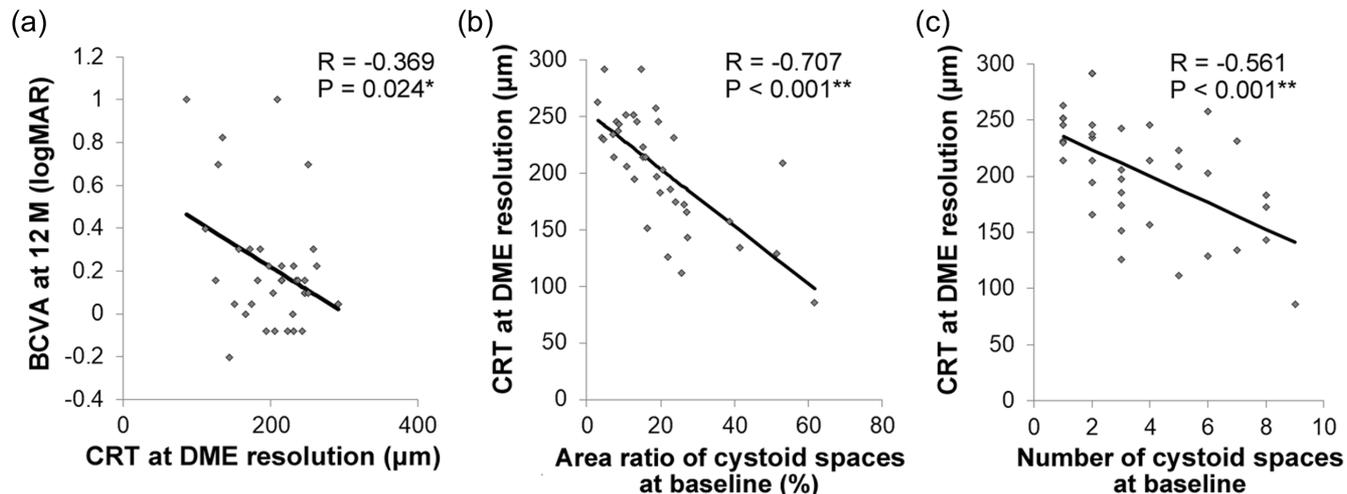
**Area ratio and number of the cystoid spaces at baseline were related to photoreceptor damage after treatments.**



### Figure 3. The values at the time of diabetic macular edema (DME) resolution.

(a) BCVA at 12 months was negatively correlated with central retinal thickness (CRT) at the time of DME resolution; **if the retina was thin at the time of DME resolution, final BCVA was worse.**

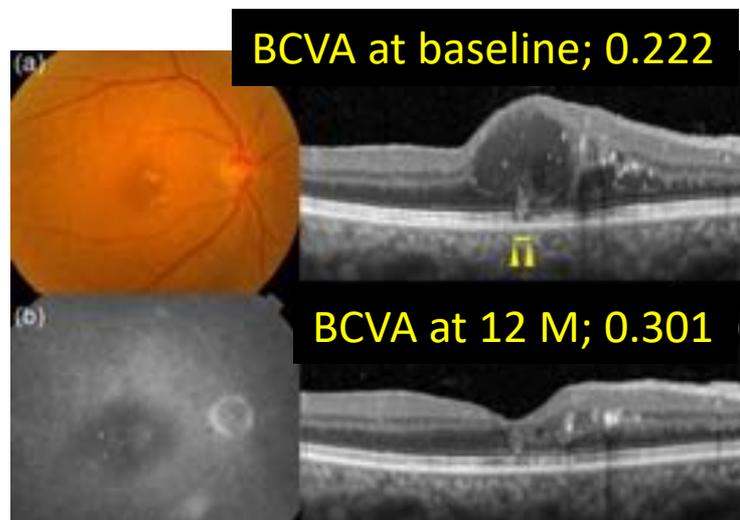
(b, c) CRT at the time of DME resolution was negatively correlated with area ratio and number of the cystoid spaces; **if the cystoid spaces were greater at baseline, CRT at the time of DME resolution was thin, and the retina was atrophic.**



## Figure 4. Representative cases

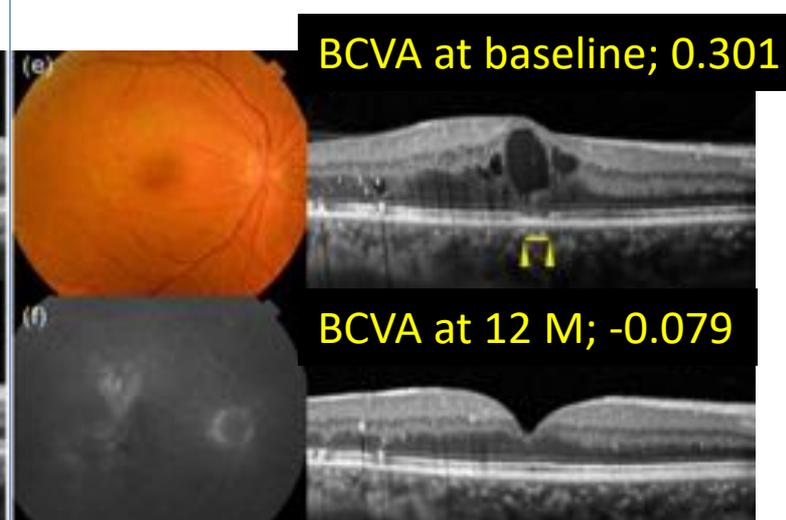
High area ratio and large number of intraretinal cystoid spaces

Note that the extents of ELM (0  $\mu\text{m}$ ) and EZ (271  $\mu\text{m}$ ) disruptions were relatively small at baseline.



Low area ratio and small number of intraretinal cystoid spaces

Note that the extents of ELM (60  $\mu\text{m}$ ) and EZ (220  $\mu\text{m}$ ) disruptions were also relatively large at baseline.



BCVA are shown in LogMAR.

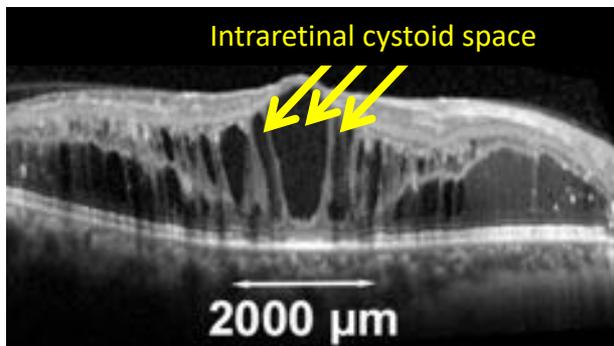
Even if DME was resolved by the treatments, if the patient had a greater area ratio and number of intraretinal cystoid spaces at baseline, the final BCVA was worse.



# Conclusions

The area ratio and number of intraretinal cystoid spaces on initial OCT images were predictors of visual outcome after IVR therapy in DME irrespective of baseline age and BCVA.

The factors were related to retinal degeneration in DME and can help obtain proper informed consent before treatment.



Thank you for your kind attention.

