

Different responses to Anti-VEGFs
in AMD: nonresponders,
tachyphylaxis, tolerance, resistance

Gazi University, School of Medicine, Ankara, TURKEY
sengulozdek@gmail.com

Different responses to Anti-VEGFs in AMD

- **GOOD RESPONDERS** (NO FLUID IN OCT, VA↑ after the first 3 injec.)
- **SUBOPTIMAL RESPONSE** (VA=↑ FLUID↓ but +)
- **STABILIZATION** (FLUID IN OCT and VA: SAME after first 3 injec.)
- **NON-RESPONDER** (FLUID IN OCT↑ and VA↓, Hemorrhage (+) after first 3 injec. *Activity score!*)
- **HEMORRHAGIC RESPONSE** (PROGRESSIVE INCREASE IN SUBRETINAL HEMORRHAGE IN SPITE OF INJECTIONS)
- **COMPLICATIONS** (RPE TEAR/ATROPHY)

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LONG TERM RESPONSES TO ANTI-VEGF

- **VERY GOOD RESPONDERS:** May not need additional injections for years after the loading dose! Very few :(
- **FREQUENT TREATMENT NEED**
 - Have some fluid in OCT in spite of monthly injections
 - RAP, Large occult CNV (Type 1)
- **GOOD RESPONSE IN EARLY DOSES** (No fluid after loading dose) →
- **DECREASED RESPONSE WITH TIME:** Tachyphylaxis / Tolerance

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UNFAVORABLE RESPONSE TO ANTI-VEGF

CONTINUING VISUAL LOSS

- Does all continuing visual loss mean non-responderiness?
- How can we define **NON-RESPONDERS**?

TREATMENT RESPONSE TO ANTI-VEGF

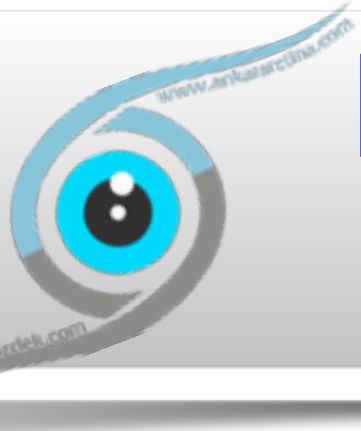
- ANY COURSE WHICH IS BETTER THAN THE NATURAL COURSE OF THE DISEASE IS A GOOD TREATMENT RESPONSE!
- NATURAL COURSE: MARINA & PIER

Holz ,F., et al. IOVS, January 2010, Vol. 51, No. 1- 405-412.

TREATMENT RESPONSE TO ANTI-VEGF

- Mean natural disease progression in VA (model parameter) was estimated as 12.6 letters lost per year (SE 0.5).
- Between patient variability in natural progression was estimated from the MARINA and PIER sham-treated patients: The between patients standard deviation of the natural progression was 20 letters per year.
- Observed, quartile data from sham-treated patients in MARINA and PIER were used to define low (5 letters per year), average (12.6 letters per year), and high (19 letters per year) natural disease progression rates.

Holz ,F., et al. IOVS, January 2010, Vol. 51, No. 1- 405-412.



DEFINITION OF NON-RESPONDER

- DECREASED VISION?
- FLUID IN OCT: SAME or ↑?
- NEW HEMOF **↑ACTIVITY SCORE**
- WIDENING OF THE LESION SIZE?
- FREQUENT TREATMENT NEED???
- SUBFOVEAL FIBROSIS

CLINICAL ACTIVITY SCORING

PARAMETER	GRADING	SCORE
Hemorrhage Amount of hemorrhage associated with the lesion	No hemorrhage	0
	decreased	1
	Same amount	2
	increased	3
OCT Subretinal fluid / retinal thickening / PED	None	0
	Decreased	1
	Any amount at beginning / Stable	2
	Increased	3
FA Staining pattern	No staining/window defect	0
	Staining of scar tissue/PED	1
	Late leakage	2
Size of the lesion Lesion area in FA	Decreased	0
	Beginning size / Stable	1
	Increased	2
Visual assessment Objective		
	Increased	0
	No change	1
	Decreased	2
Visual assessment Subjective		
	Increased	0
	No change	1
	Decreased	2

UNFAVORABLE RESPONSE TO ANTI-VEGF

CONTINUING VISUAL LOSS

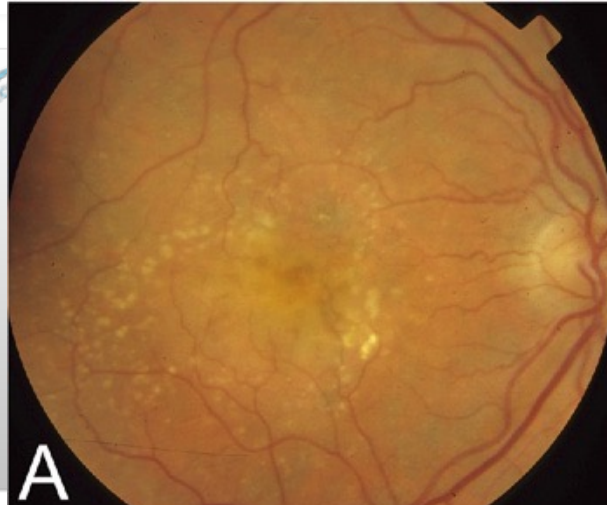
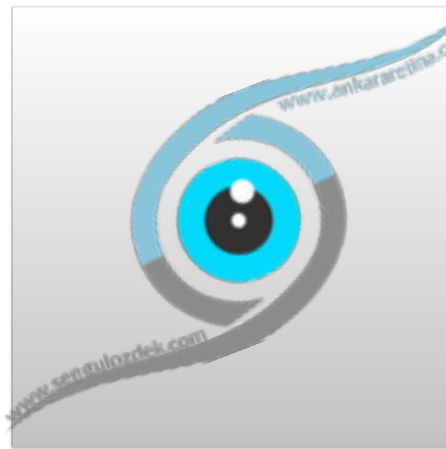


Lesion not active

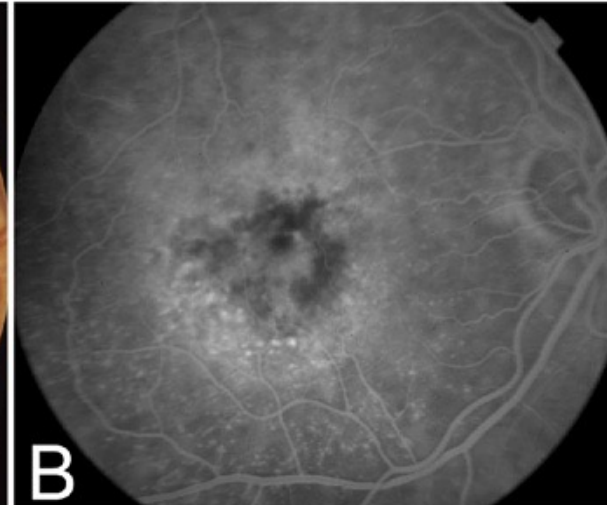
RPE & Photorec. Atrophy/
Subfoveal fibrosis

Lesion active

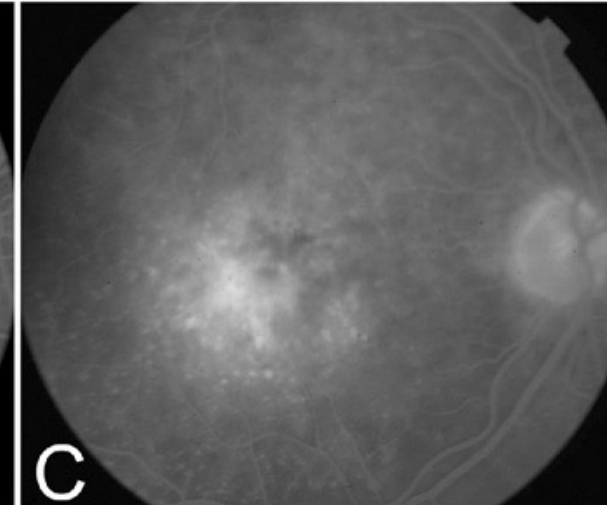
Recurrent, persistent or
progressive exudative dis.
(with Anti-VEGF treatment)



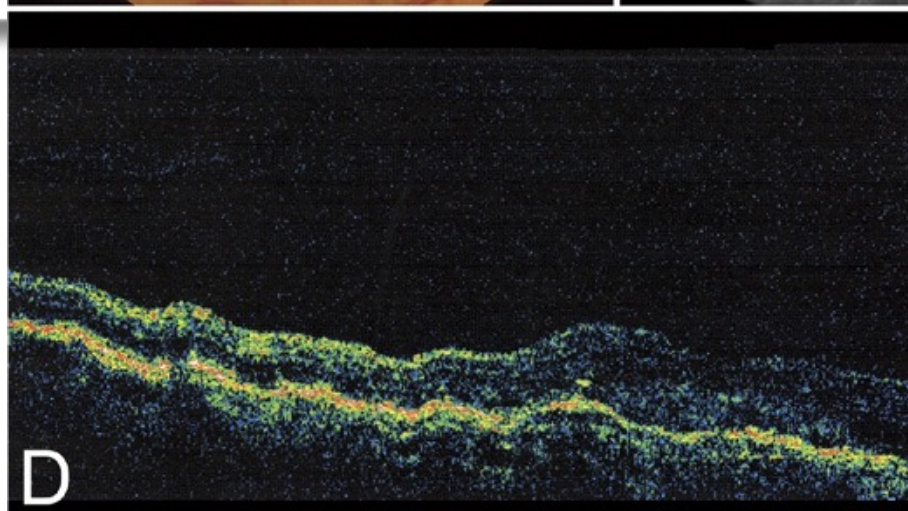
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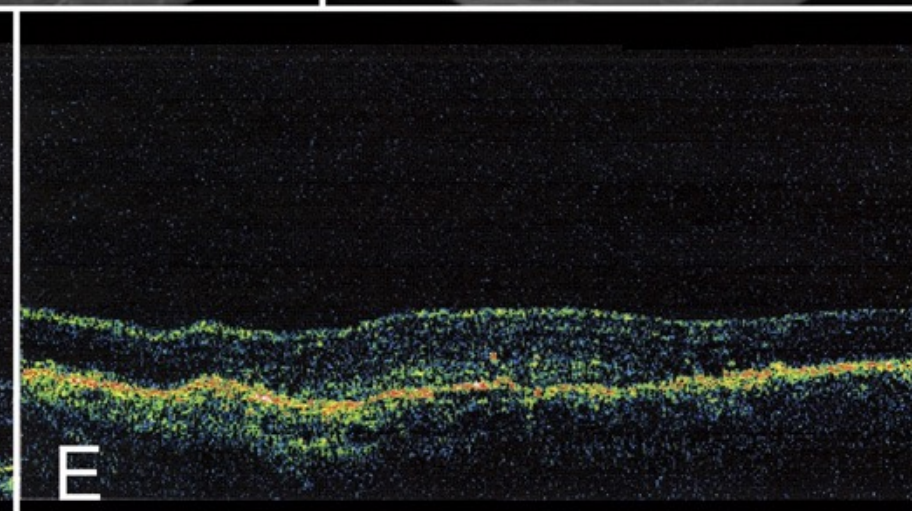
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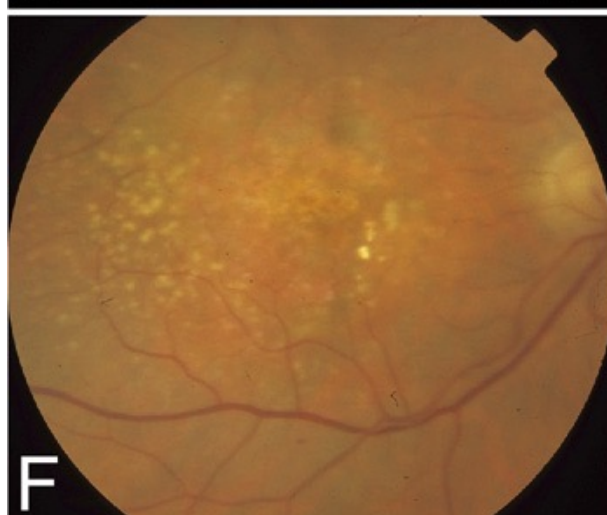
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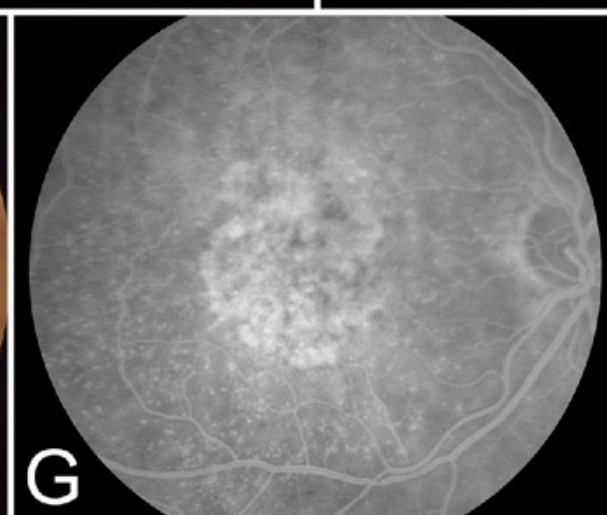
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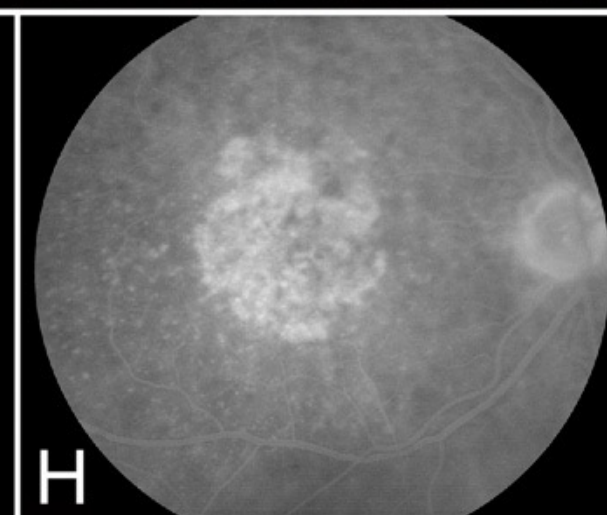
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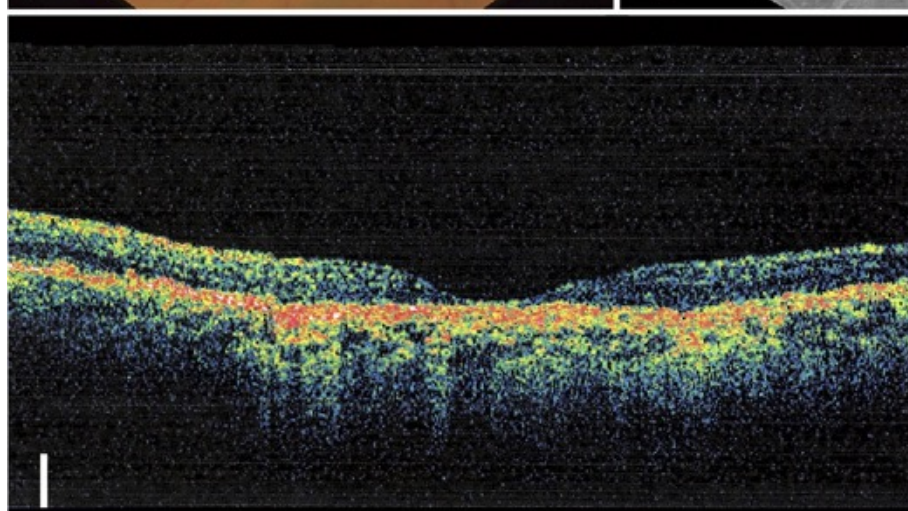
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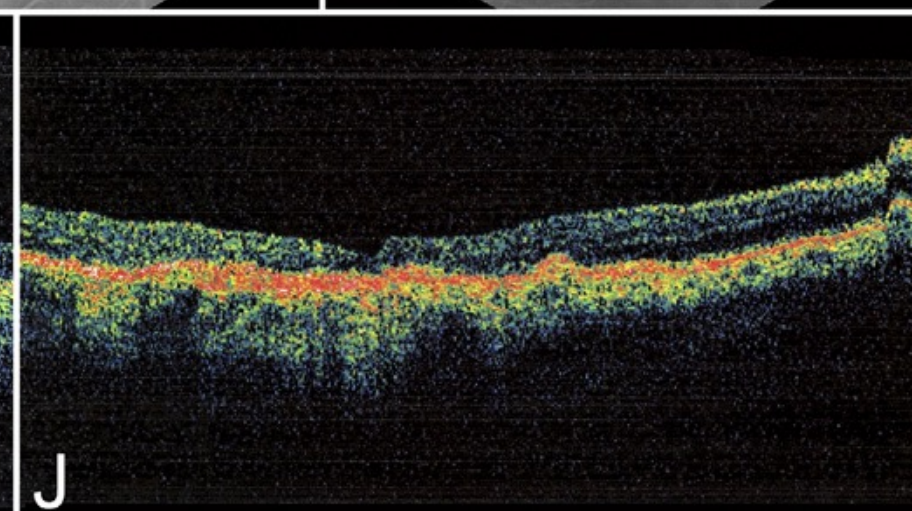
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H



I



J

UNFAVORABLE TREATMENT RESPONSE TO ANTI-VEGF

LESION ACTIVE, VA↓

- Recurrent, persistent or progressive exudative disease
- LESION ACTIVITY SCORE IS HIGH!

UNFAVORABLE RESPONSE TO ANTI-VEGF

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- **NON-RESPONDER** (FLUID IN OCT $\uparrow$ and VA $\downarrow$, Hemorrhage (+) after 3 injec. Activity score!)
- **HEMORRHAGE RESPONSE** (PROGRESSIVE INCREASE IN SUBRETINAL HEMORRHAGE IN SPITE OF INJECTIONS)
- **COMPLICATIONS** (RPE TEAR/ATROPHY)

RESISTANCE???

RESISTANCE TO ANTI-VEGF TREATMENT

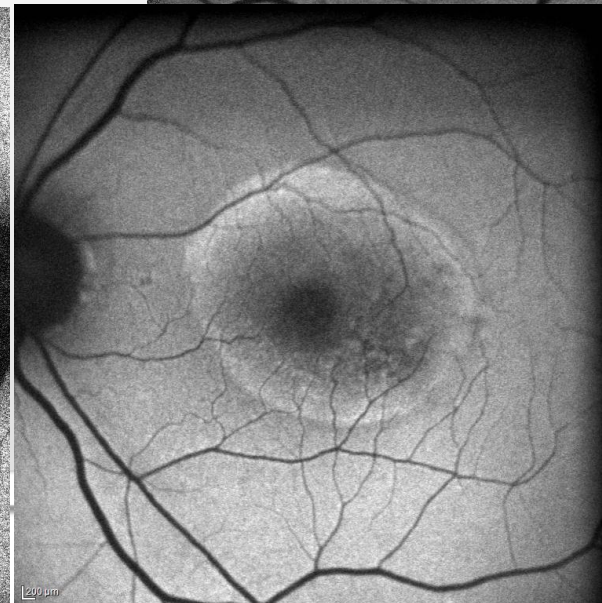
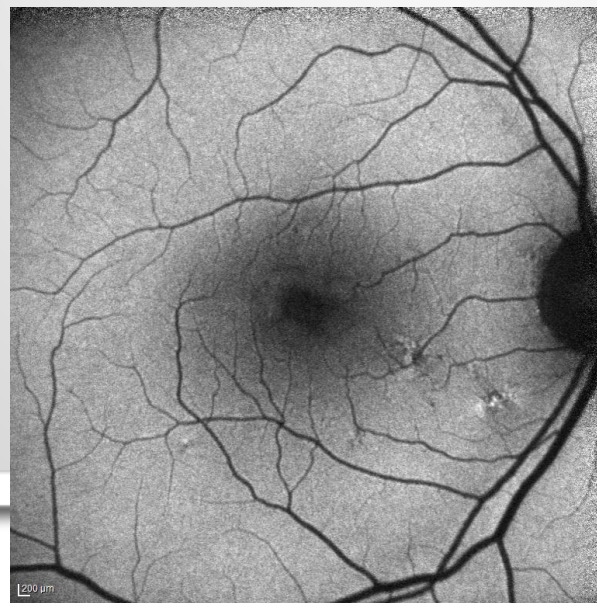
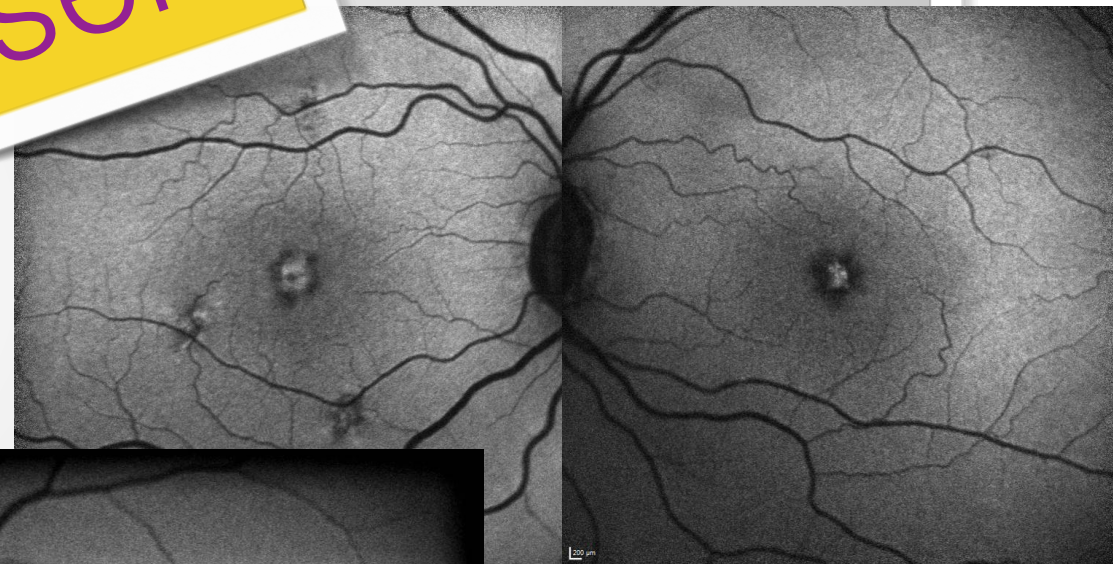
- **WRONG DIAGNOSIS** (46.2%)
 - PCV, RAP, VITELLIFORM (AOVMD), CSCR
- **TACHYPHYLAXIS-TOLERANCE** (22%)
- **NONRESPONDERS** (26.9%)
- **COMPLICATIONS**: RPE tear, atrophy, scarring/fibrosis (11.6%)
- **GENETIC BASIS FOR RESISTANCE**

DIAGNOSTIC MISTAKE



No Drusen!

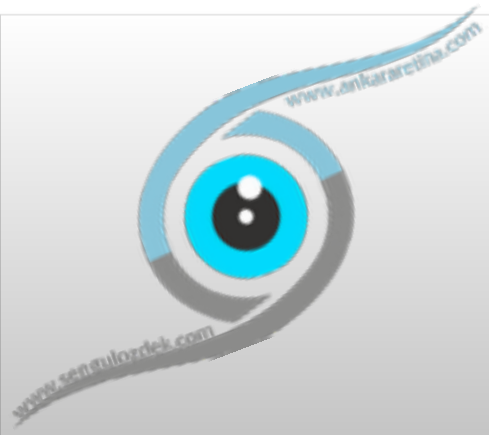
- PCV
- RAP
- VITELLIFORM LESIONS
- CSCR



19.12.2012, OS
HEIDELBERG DAF 30° ART(9)
HEIDELBERG
engineering

14.01.2015, OD

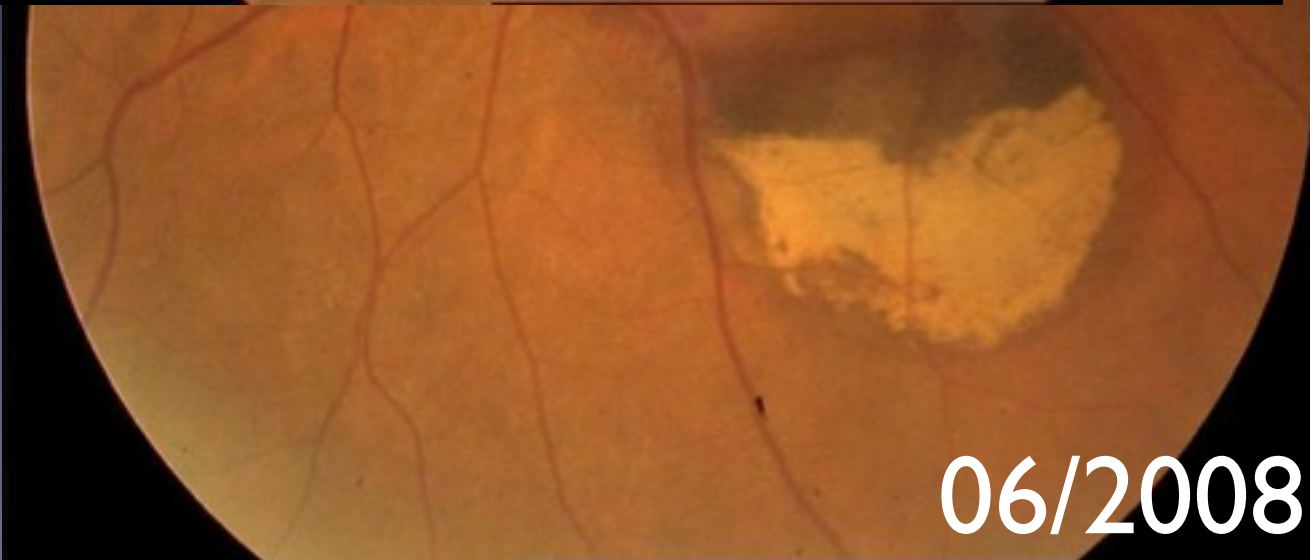
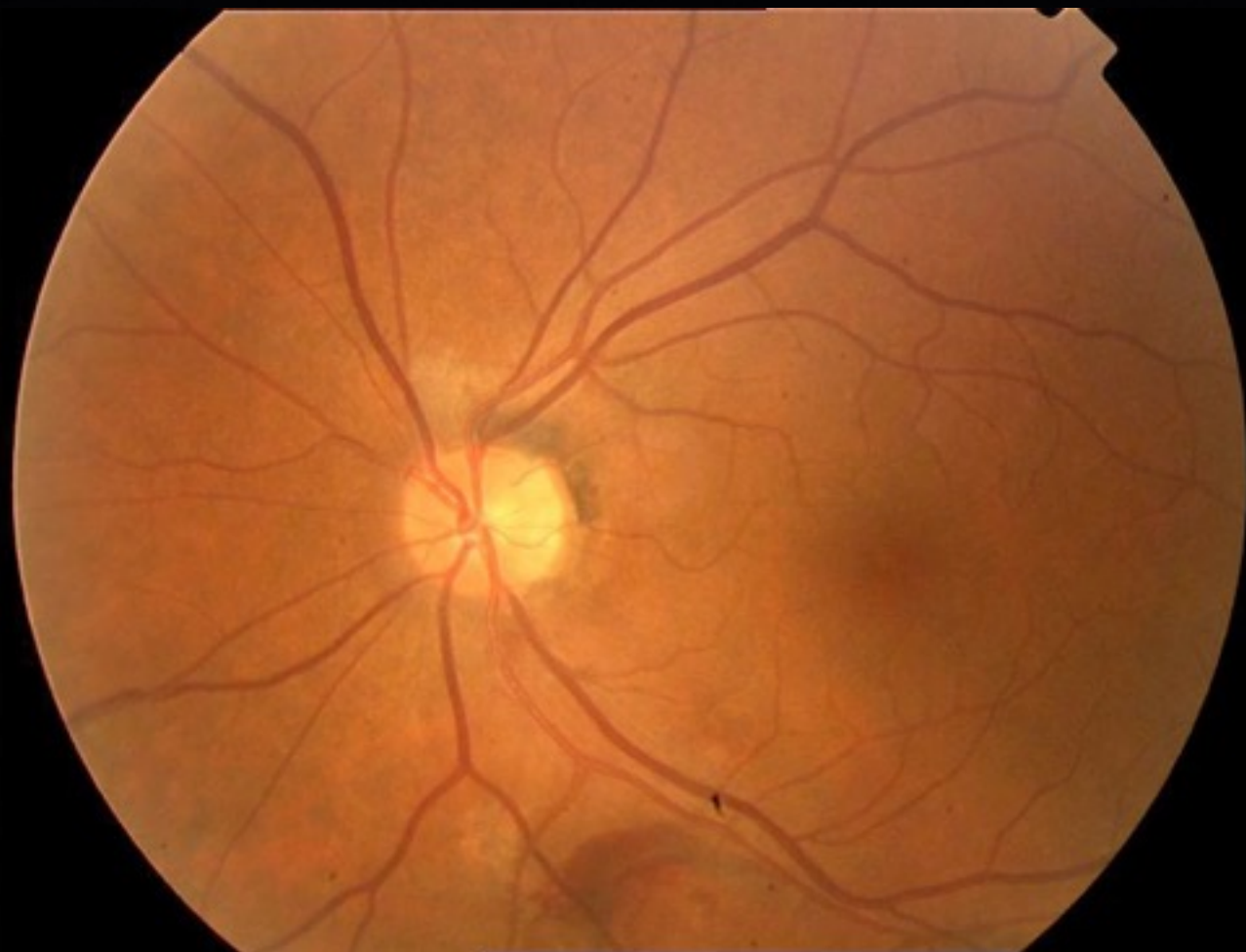
14.01.2015, OS



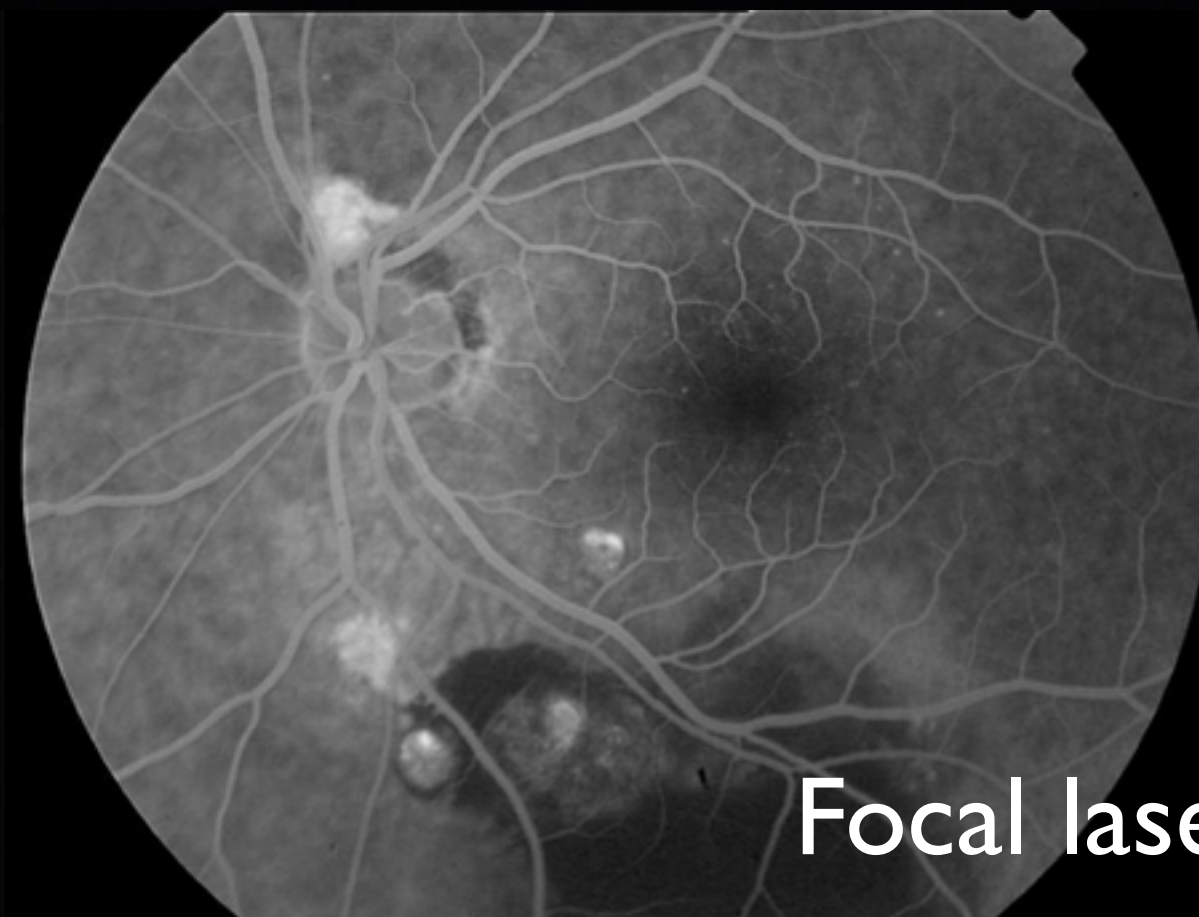
PCV

- A subtype of AMD
- 8–13% (white population), 24–50% (asian)
- No Drusen, slower progression!
- Peripapillary orange-colored subretinal polyps/ arborizing dilated vessels.
- Sub-RPE hemorrhages
- DIAGNOSIS: ICG
- TREATMENT: PDT+Anti-VEGF

64y old M, VA: 20/20



06/2008

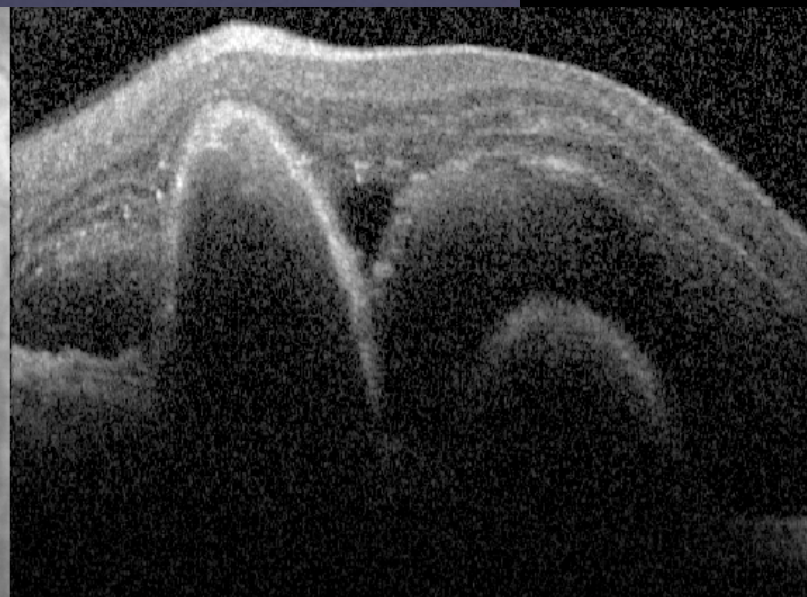
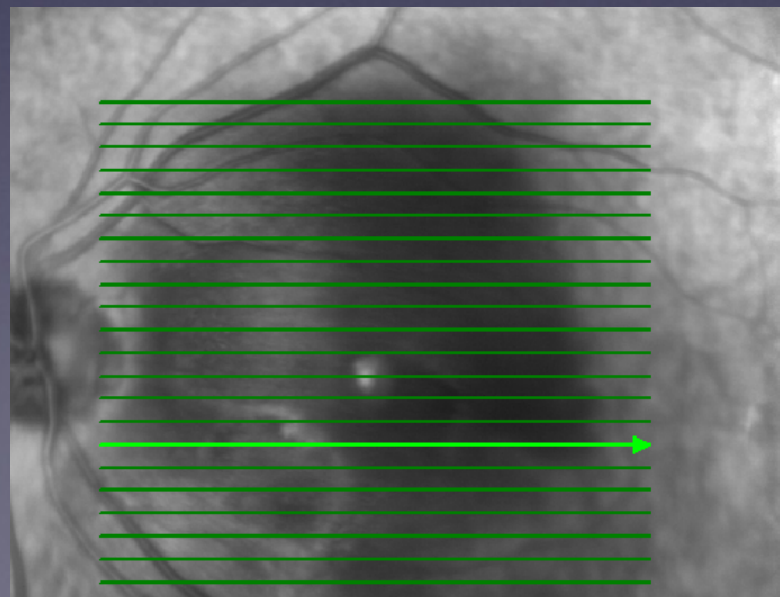
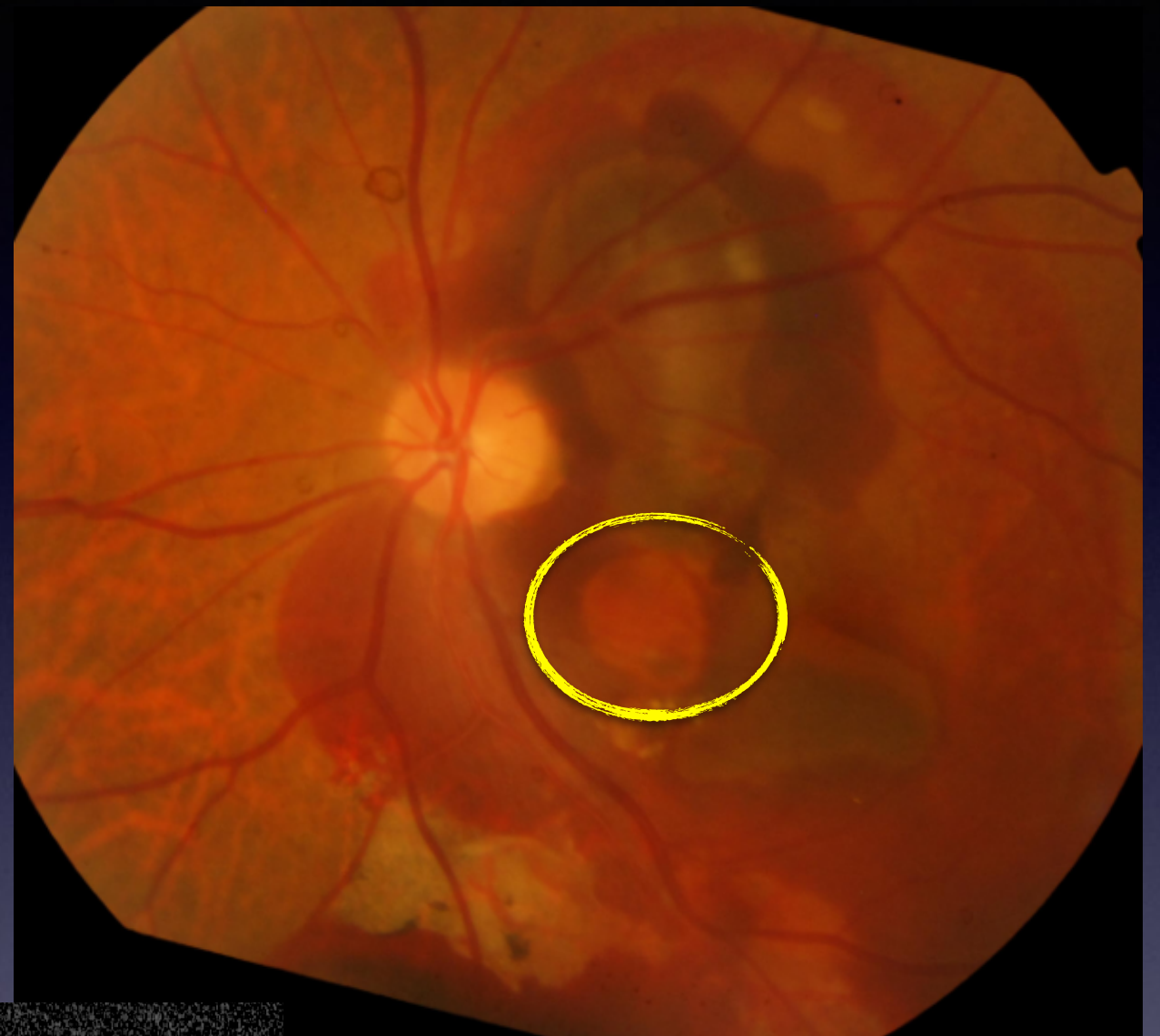


Focal laser



12/2009

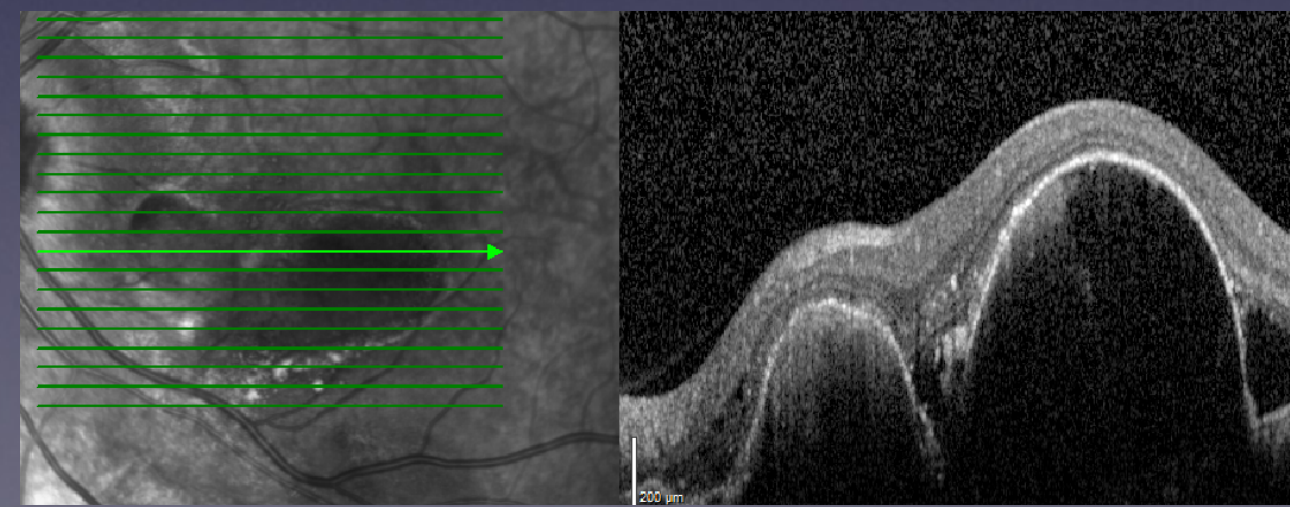
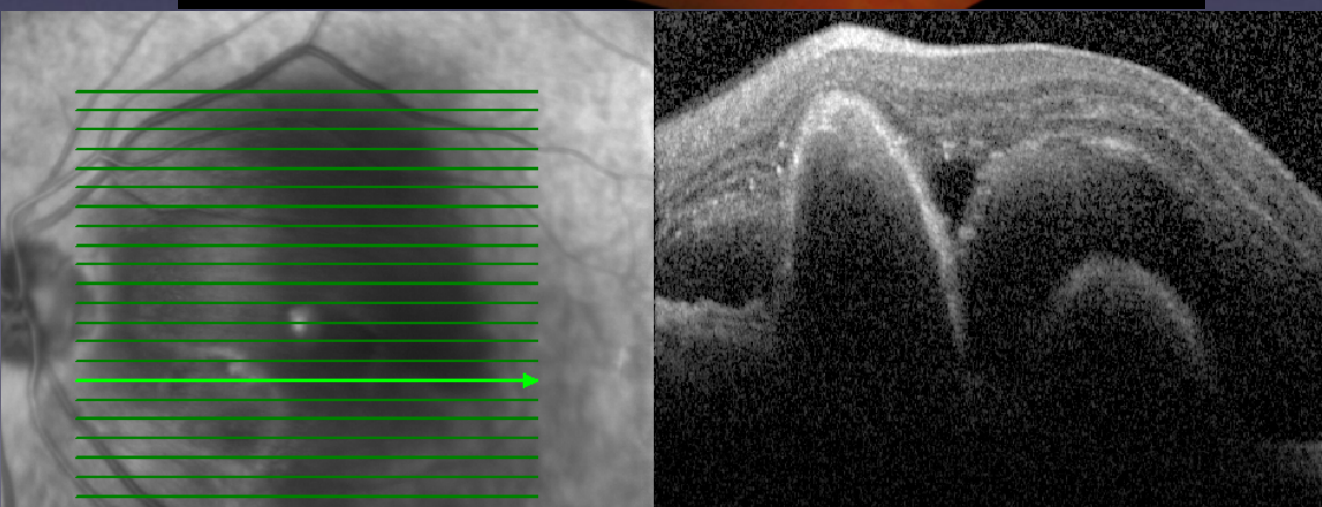
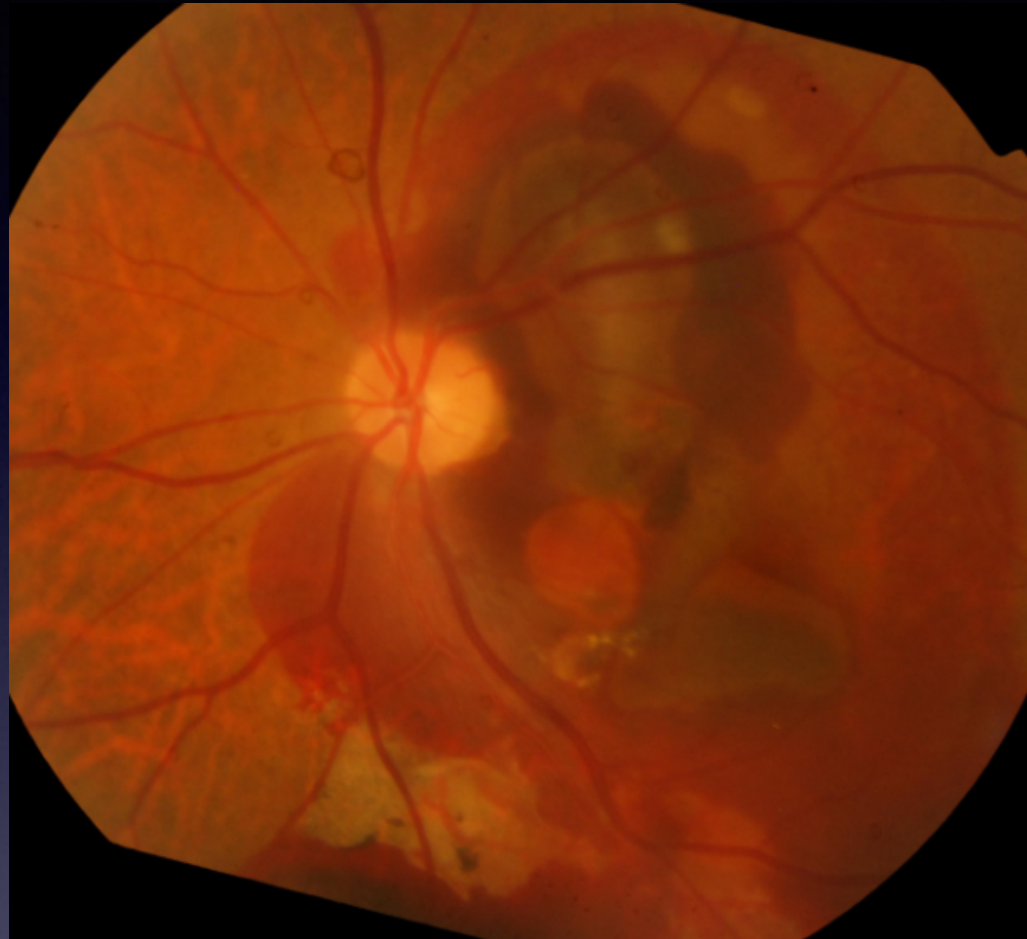
09/2012, VA: CF 2m (L)



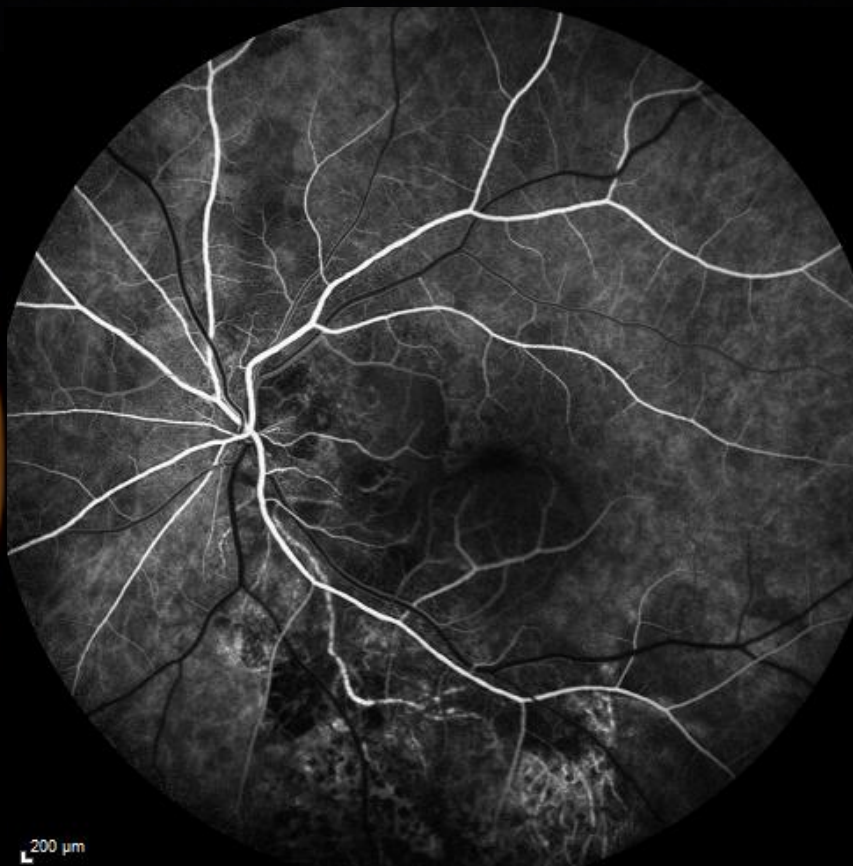
- SF6 Gas + IV tPA (50 μ g/0.05ml) + Anti-VEGF

09/2012, VA: CF

11/2012, VA: 0.4



01/2013: VA:0.2



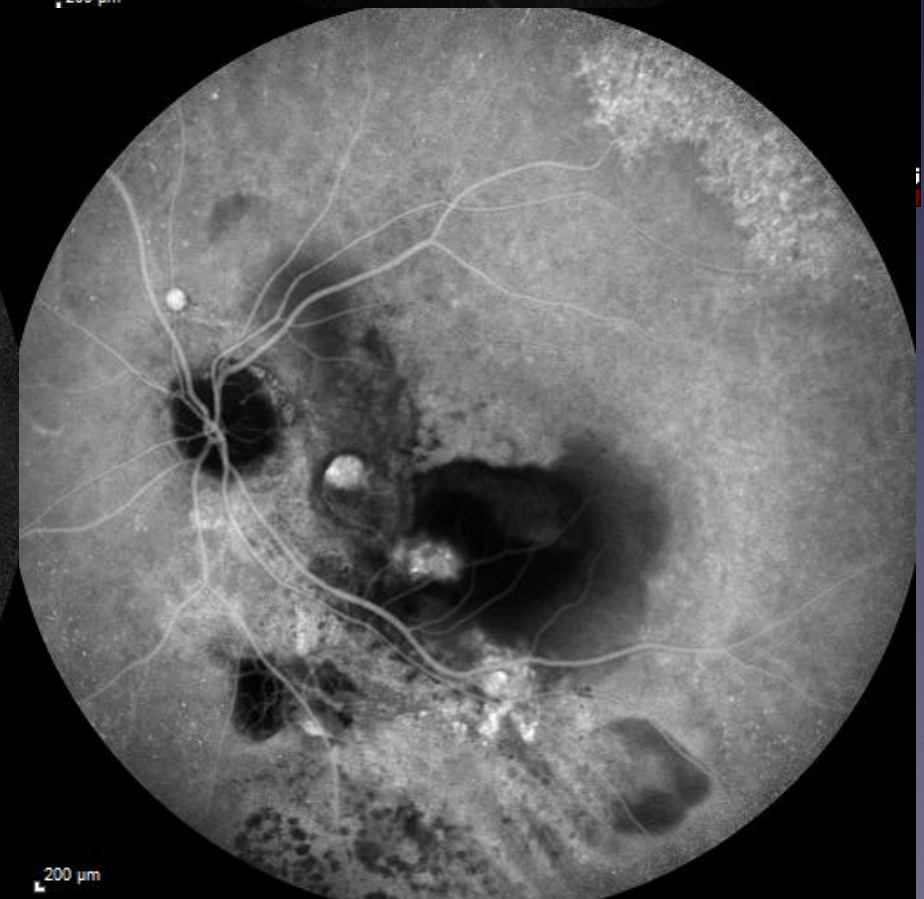
200 μ m



200 μ m



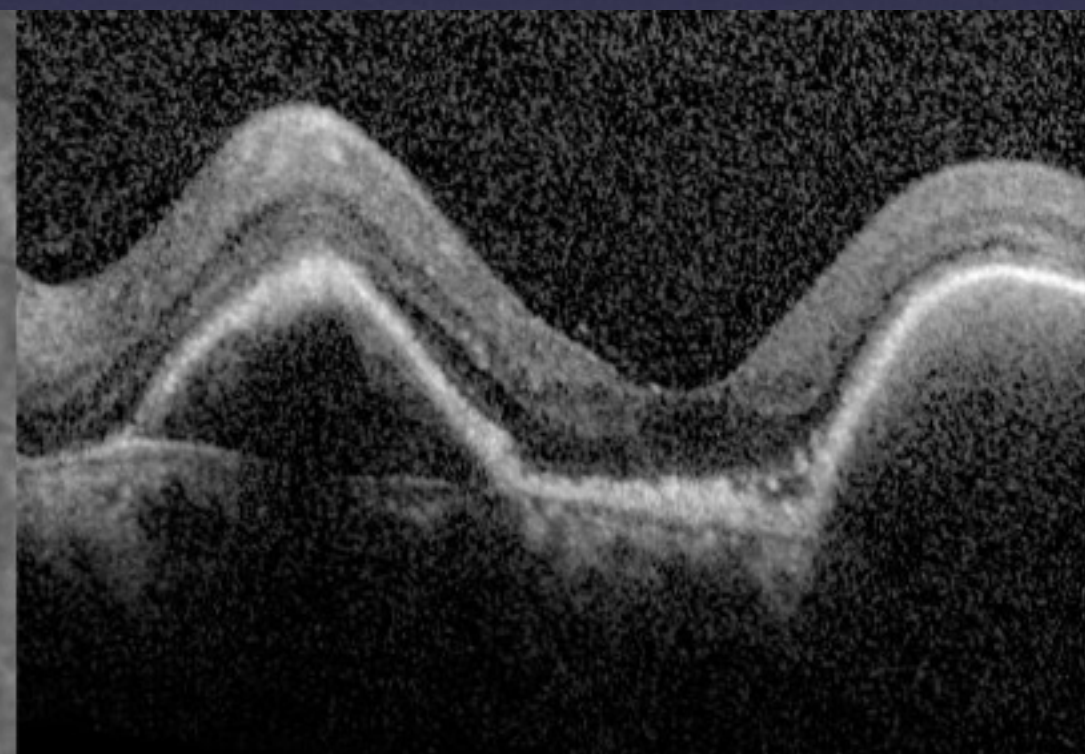
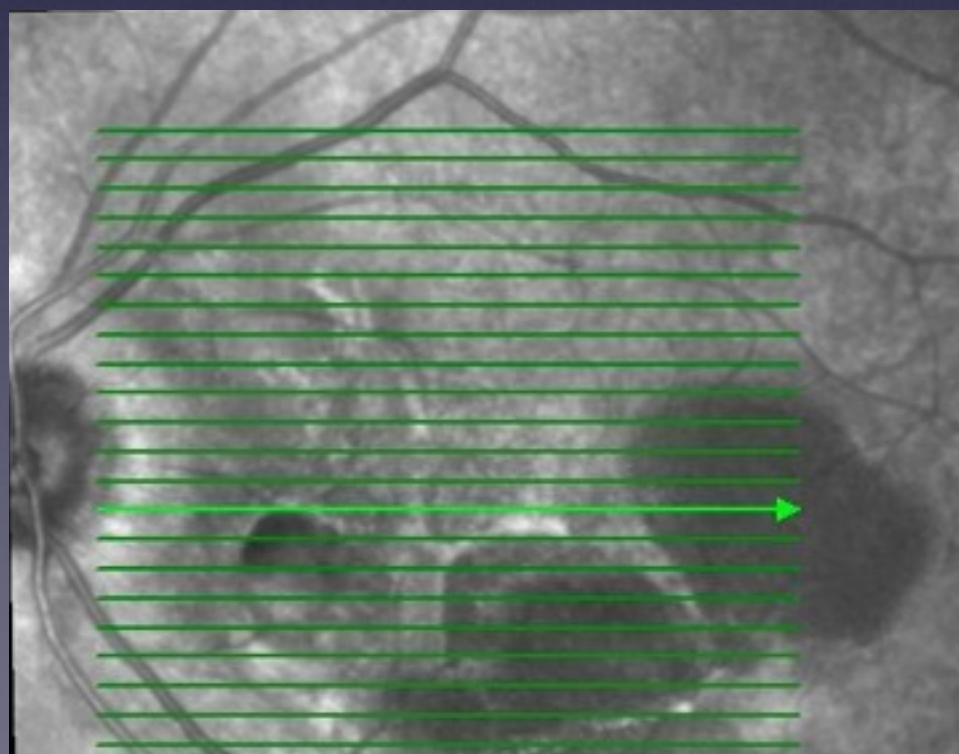
200 μ m



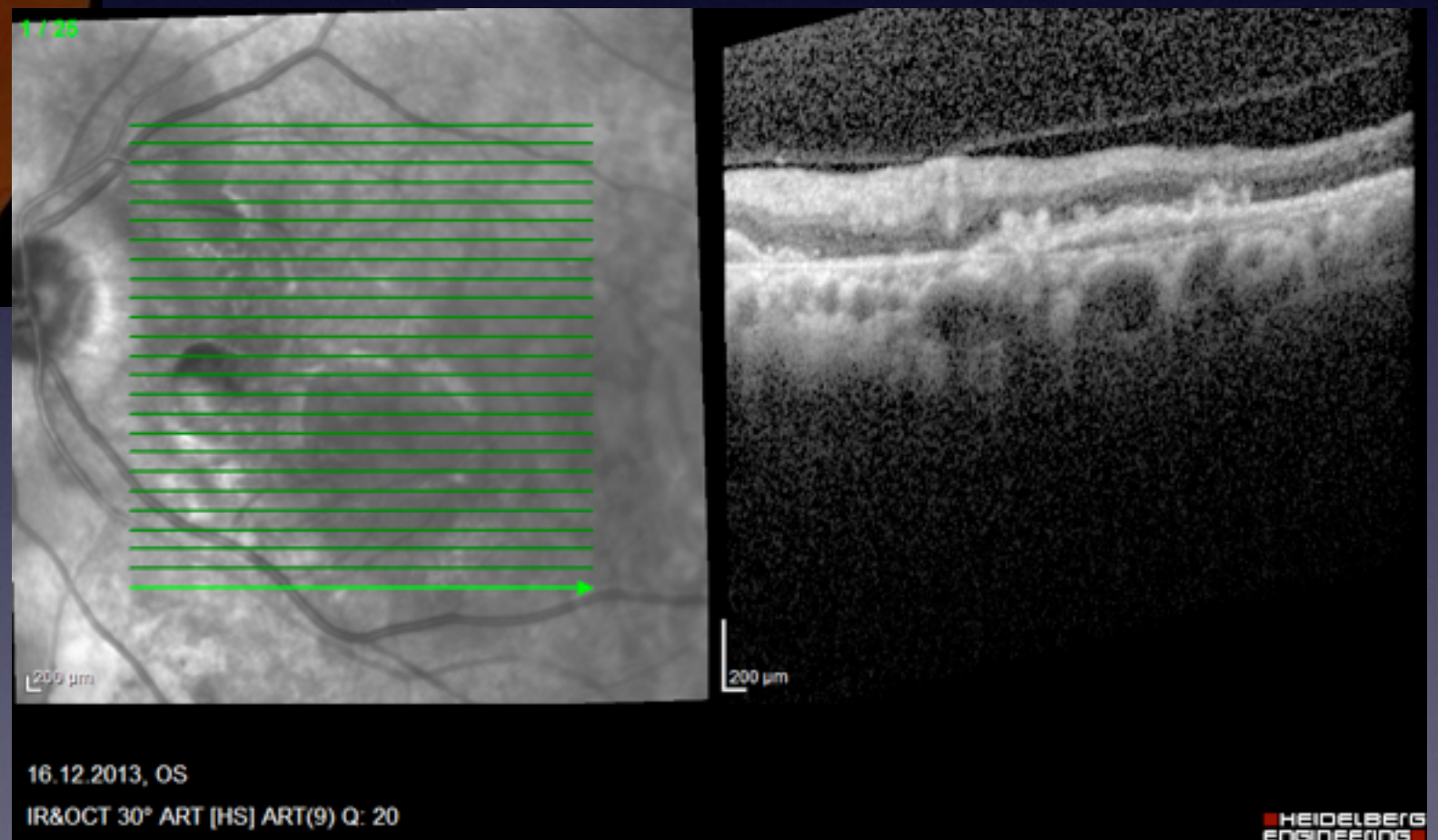
200 μ m

PDT+Anti-VEGF

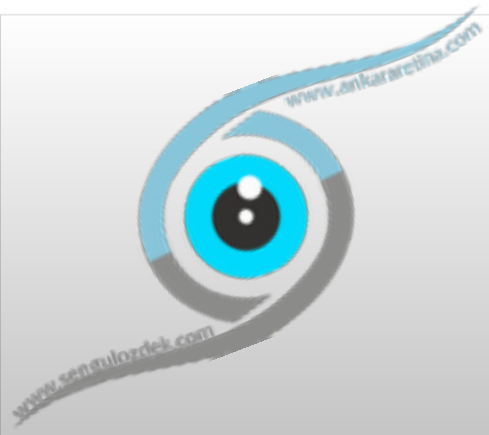
03/2013, VA: 0.3, IV Anti-VEGF



12/2013, VA: 0.2

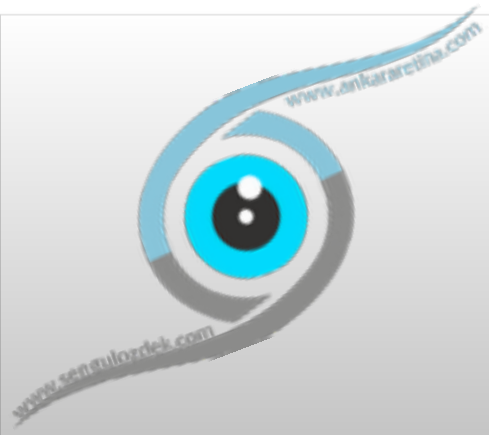


2x PDT + 7 Anti-VEGF



DD: RAP

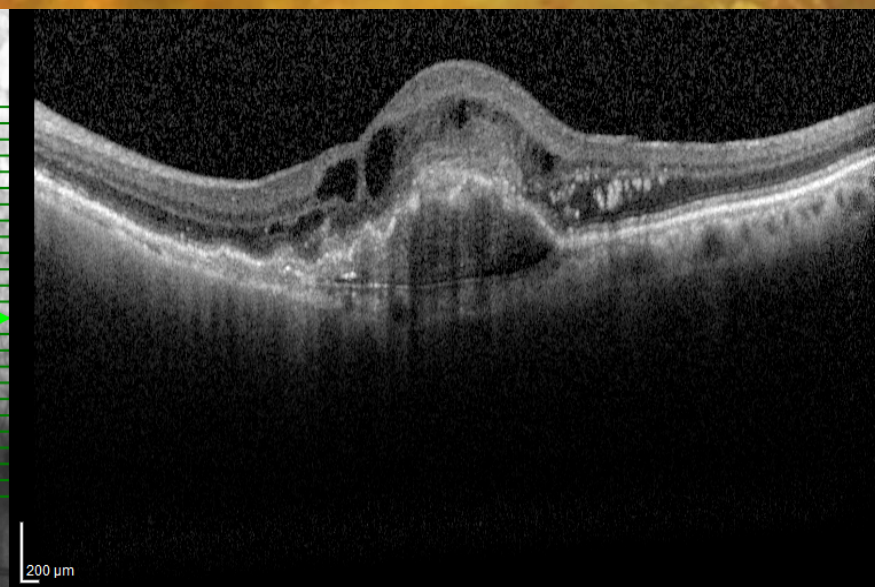
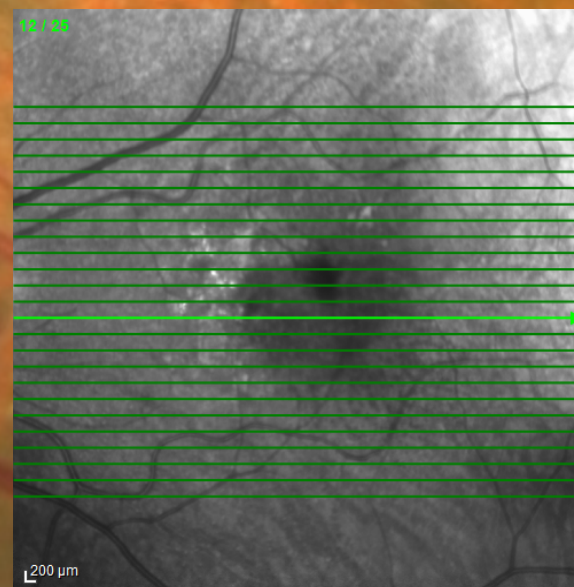
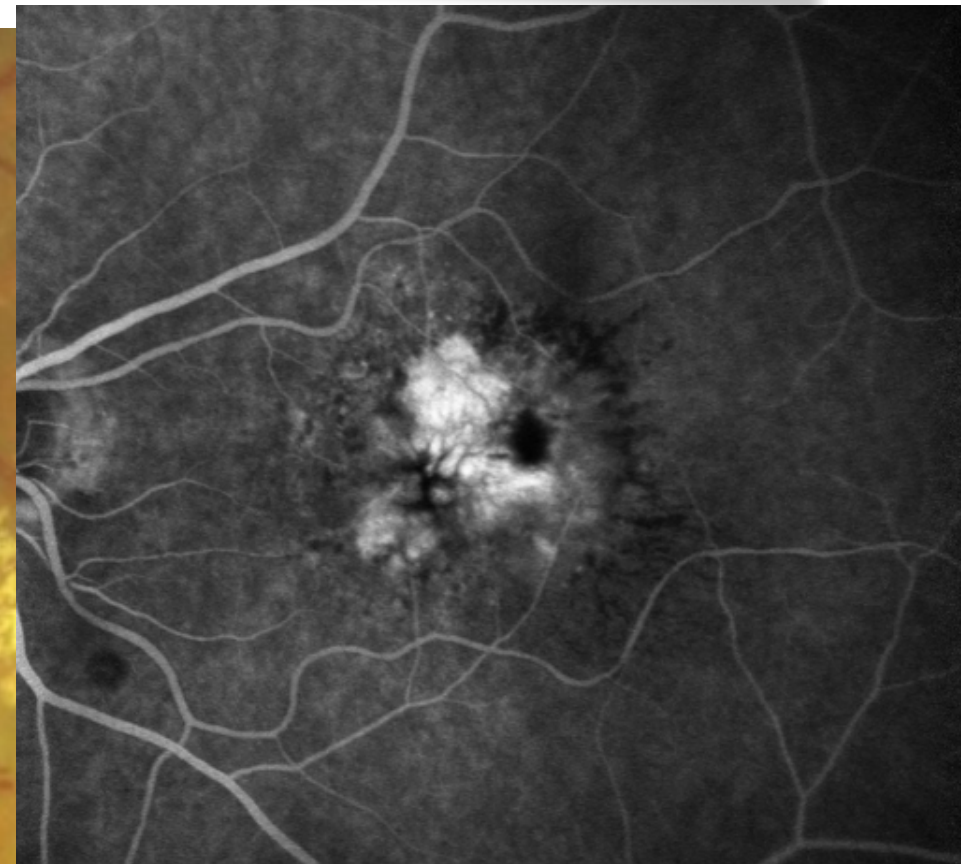
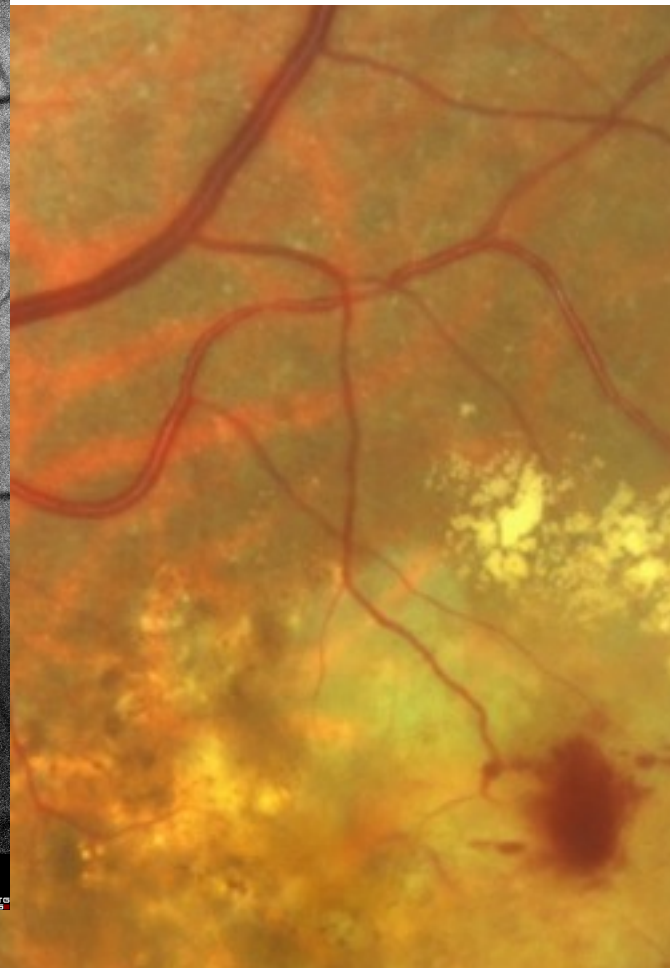
- Yanuzzi 2001: Type 3 CNV
- 15% (white), 4.5% (asian) of all wet AMD
- Stage 1: Intraretinal neovasc.
- Stage 2: Subretinal neovasc.
- Stage 3: Clinically apparent CNVM



RAP

- May be more resistant to treatment
- Combined treatments?
 - PDT
 - PSTT or IVT
 - Anti-VEGF

RAP



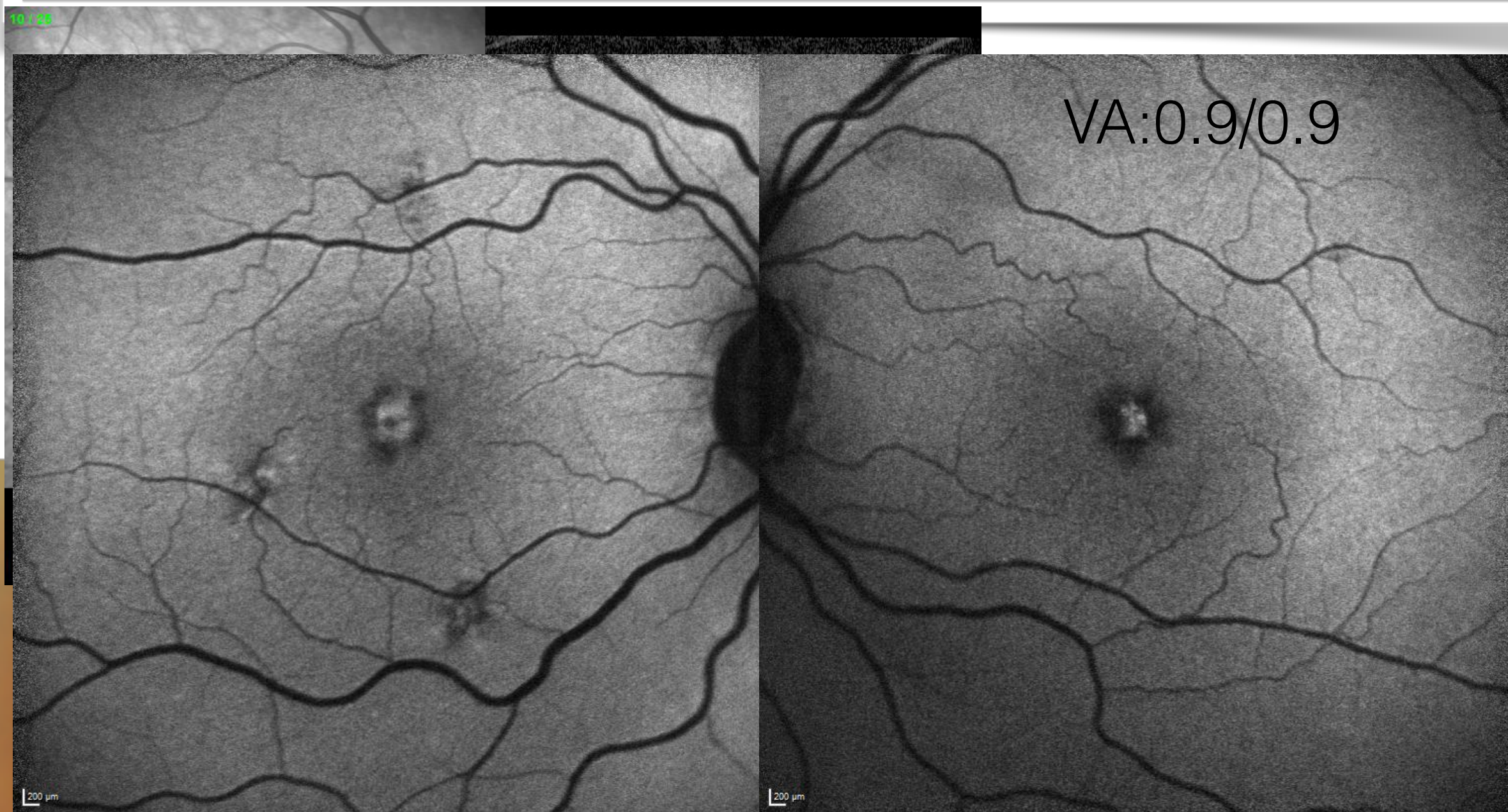
MUTLU, RABIA, 01.01.1936
24.03.2015, OS
IR&OCT 30° ART [HS] ART(9) Q: 24

HEIDELBERG



DD

VITELLIFORM LESION-AOVMD



19.12.2012, OD
BAF 30° ART(11)

19.12.2012, OS
BAF 30° ART(9)

19.12.2012, OS
IR&OCT 30° ART [HS] ART(10) Q: 23

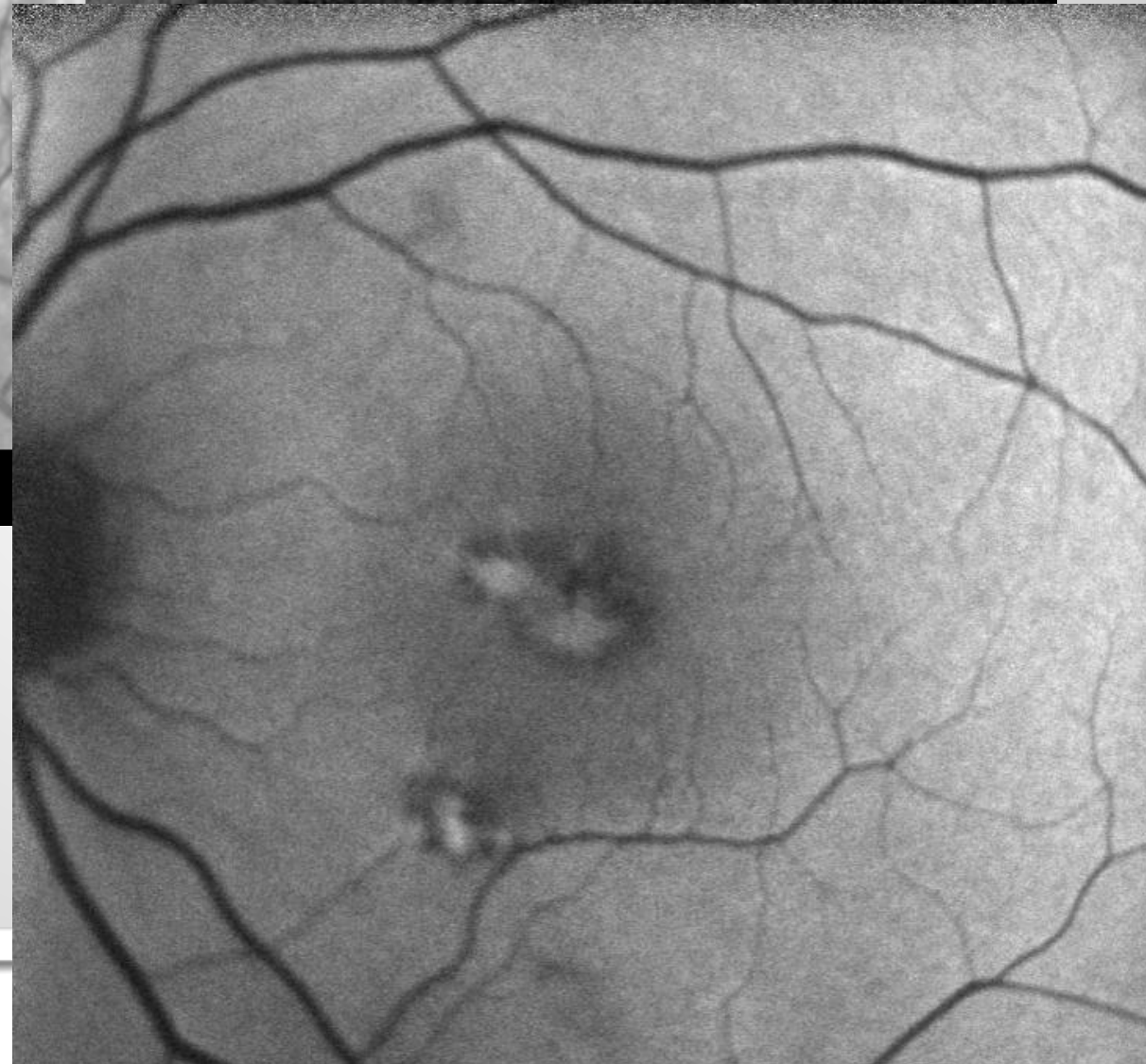
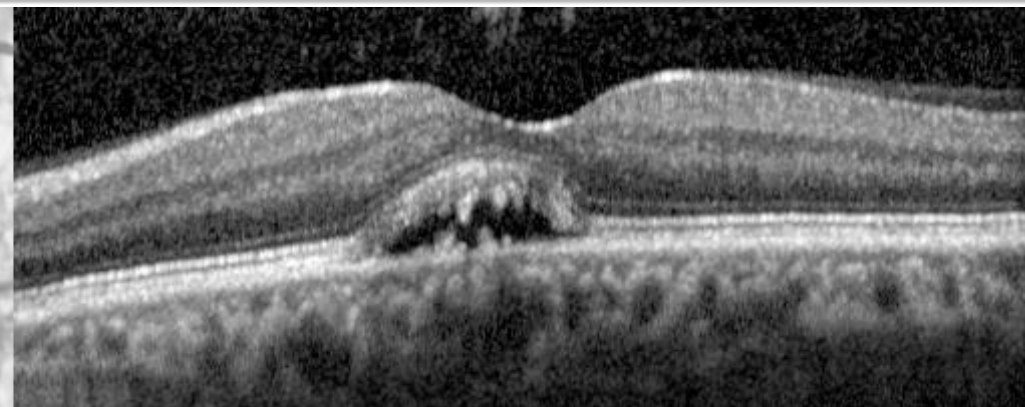
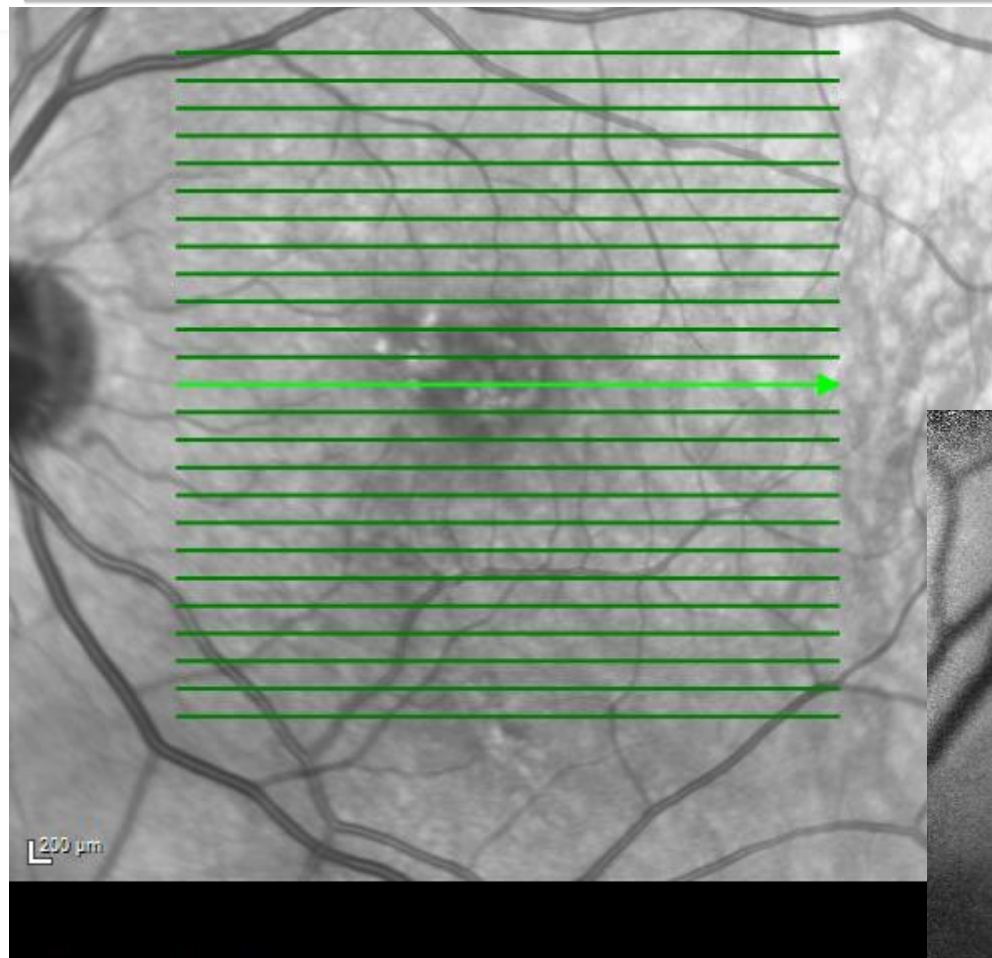
HEIDELBERG
ENGINEERING

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ENGINEERING

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ENGINEERING

DD

VITELLIFORM LESION-AOVMD

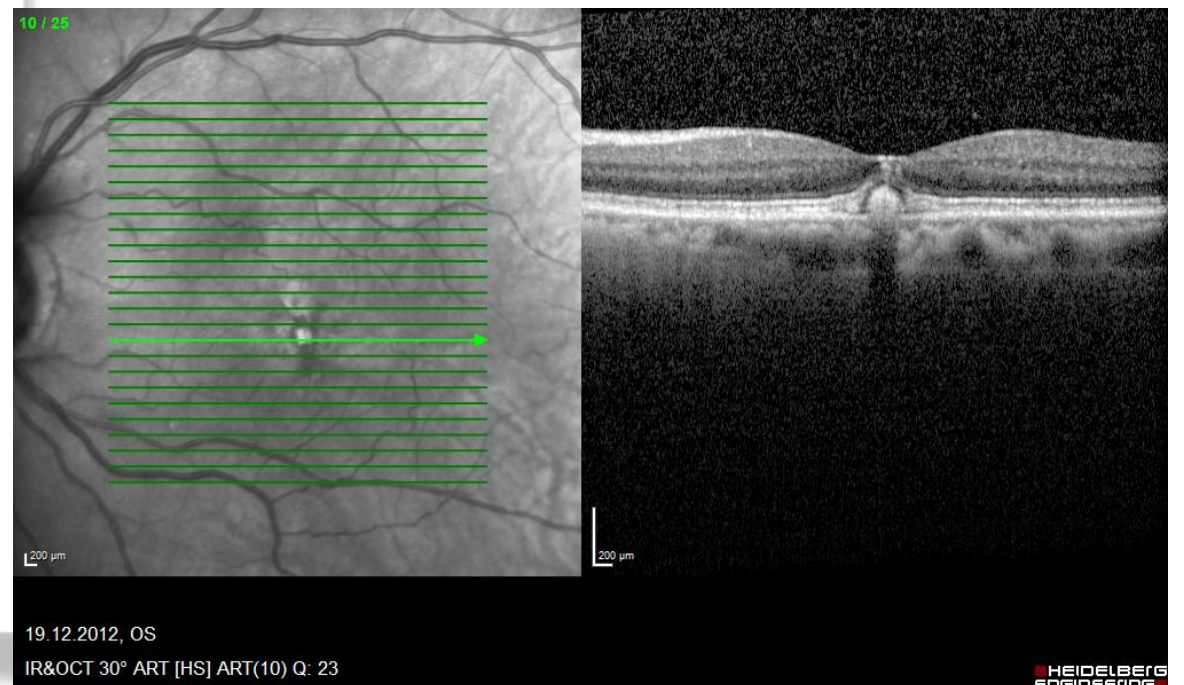
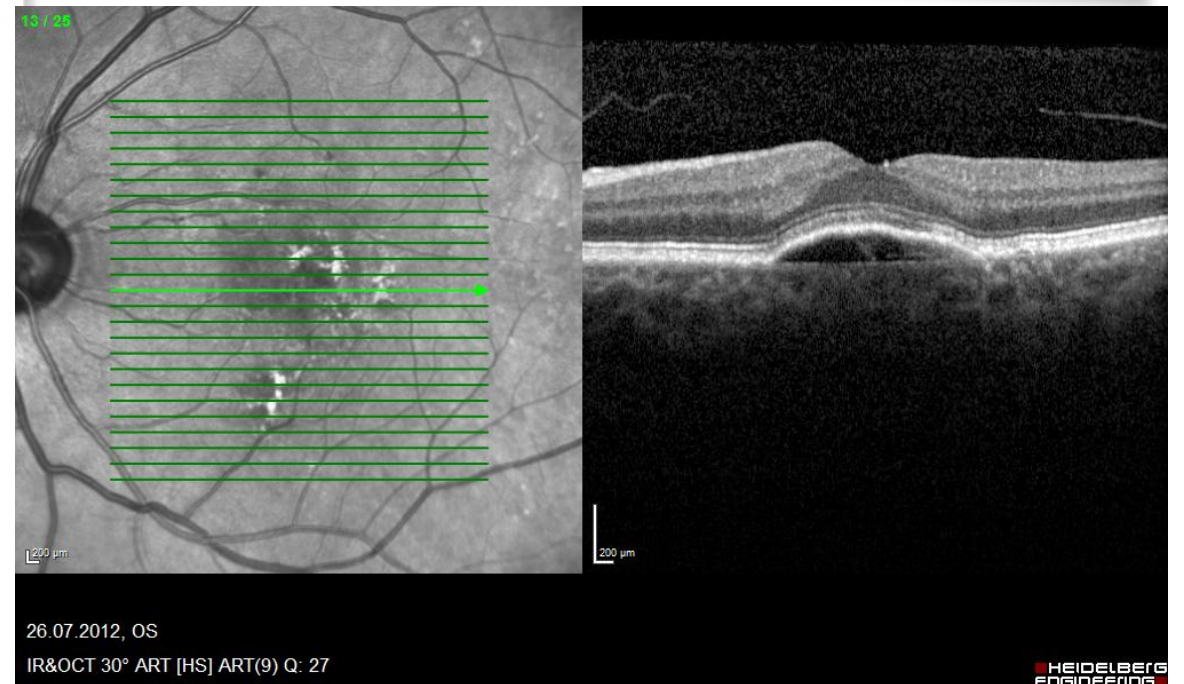


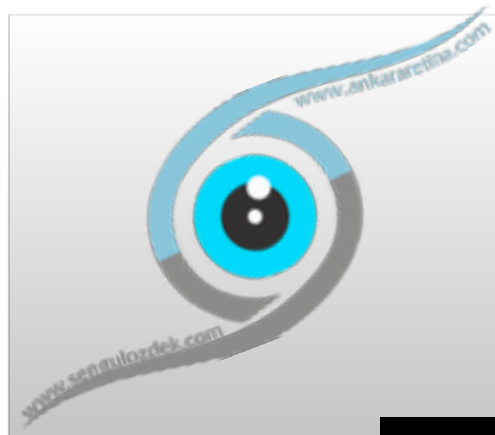


DD

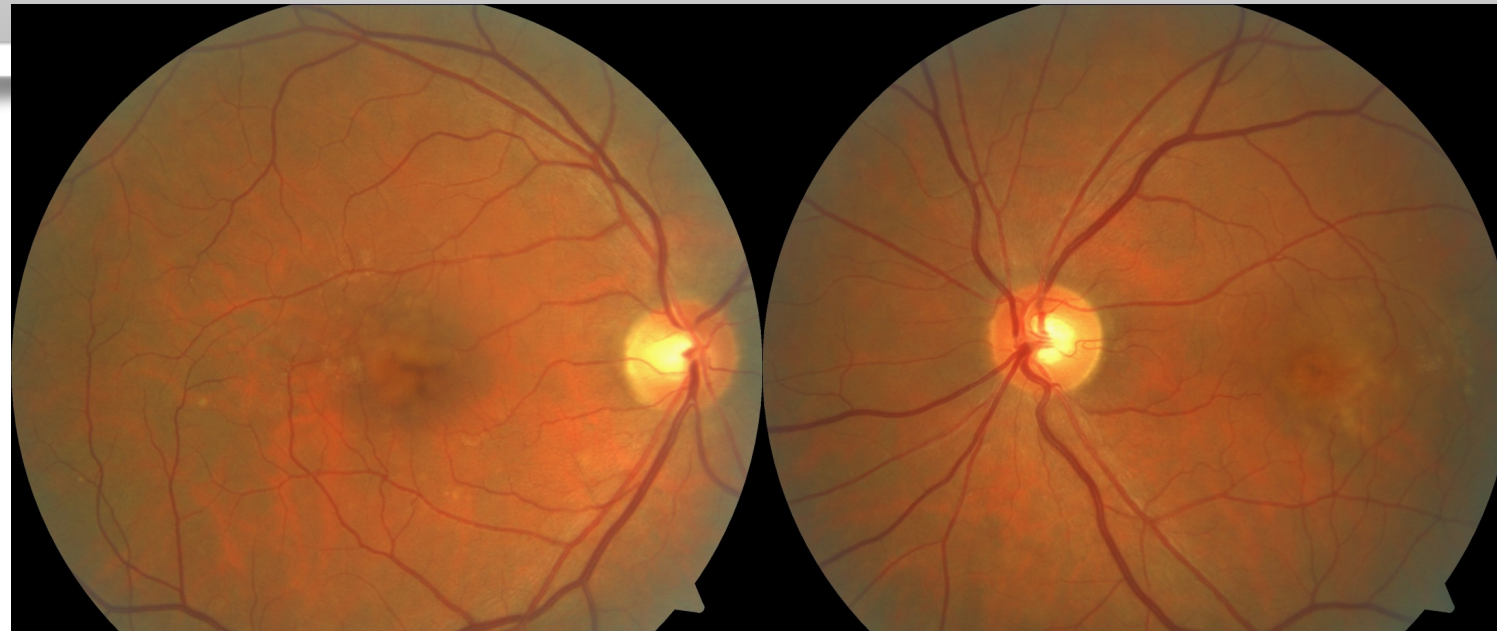
VITELLIFORM LESION-AOVMD

- VA quite well
- No symptom (min metamorphopsia)
- Mostly detected by chance
- No Intraretinal/subretinal fluid
- May have had previous injections.
- Rarely complicated with CNV formation

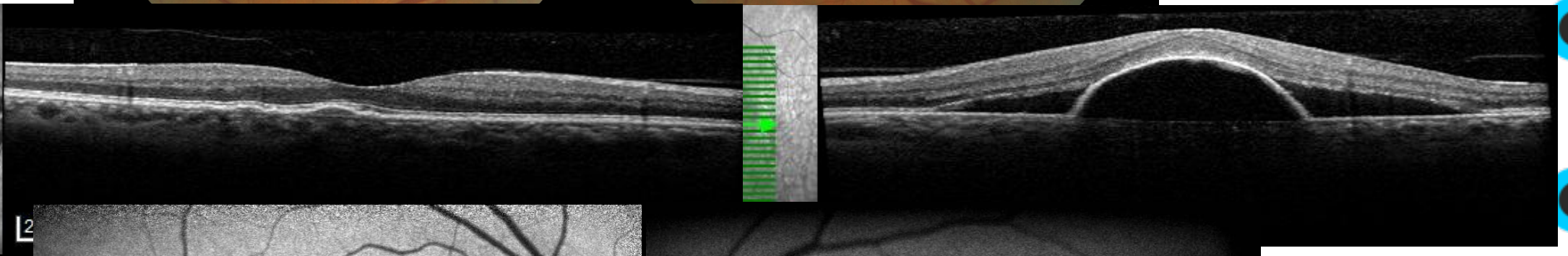
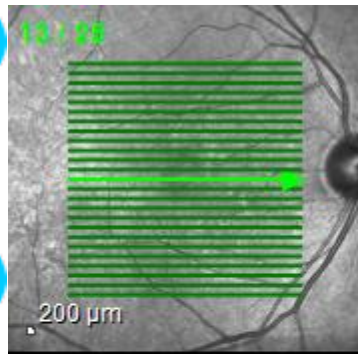




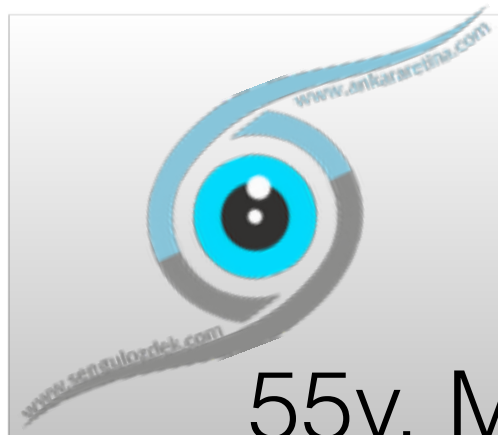
DD: CSCR



62y, F,
VA: 1.0/0.7

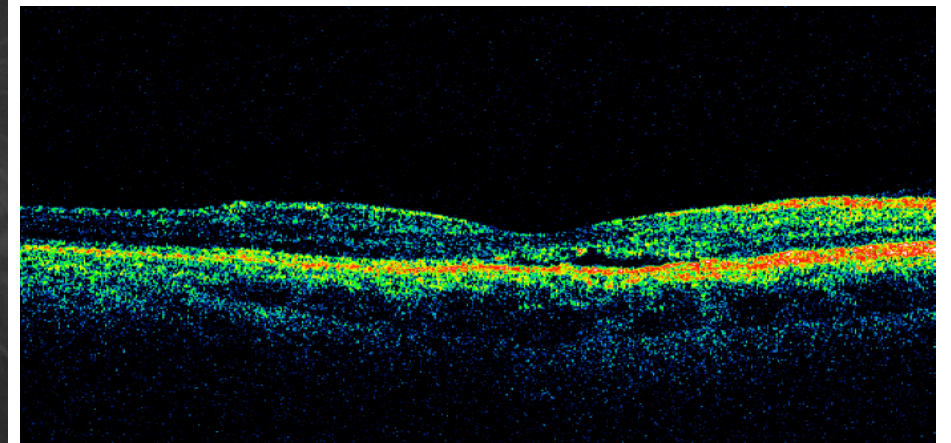
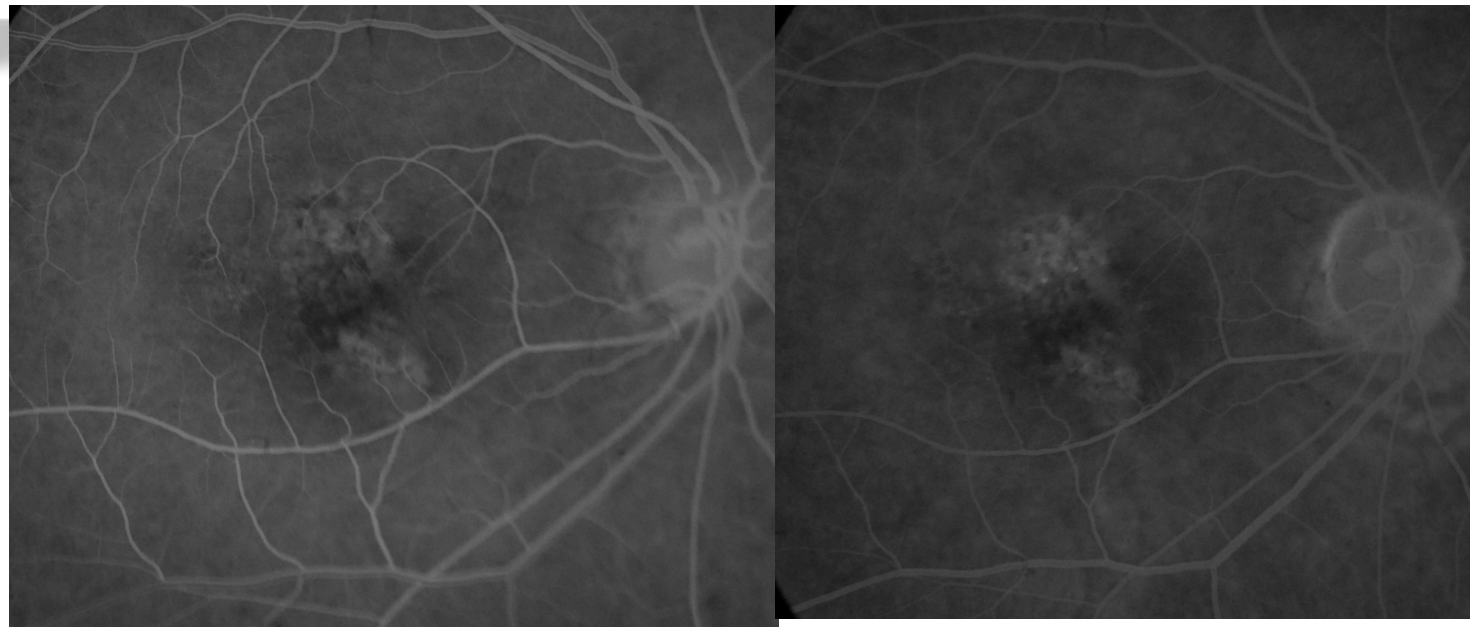


3X INJECTIONS FOR AMD: no response

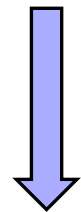


CSCR

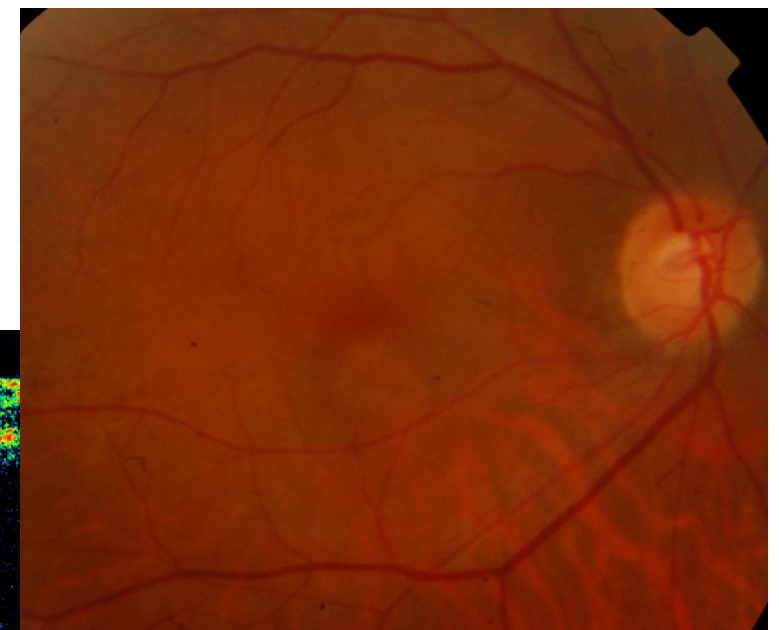
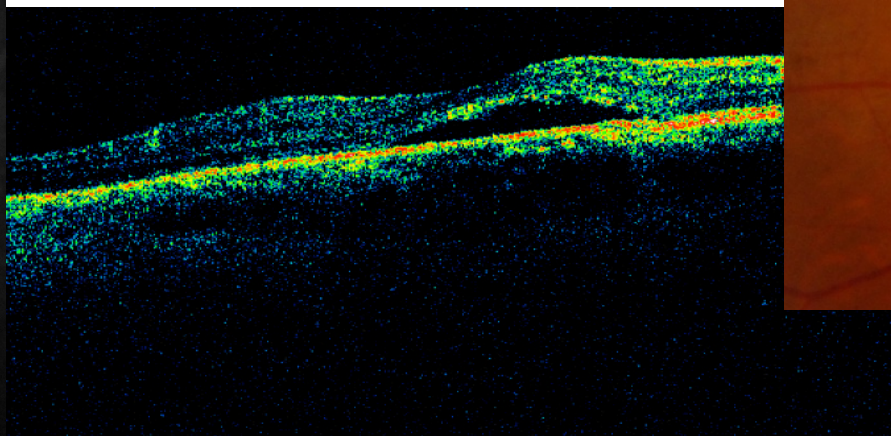
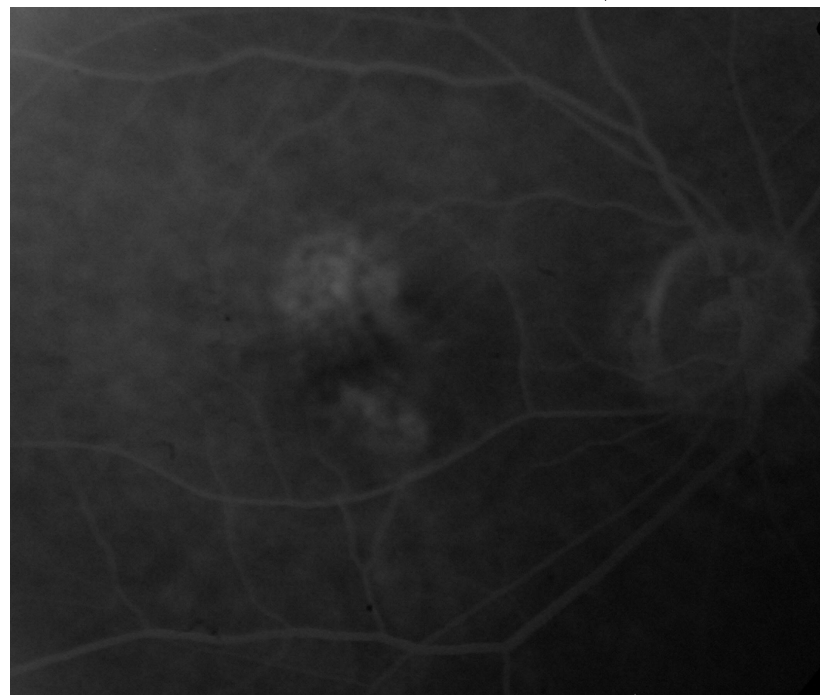
55y, M, VA: 0.5

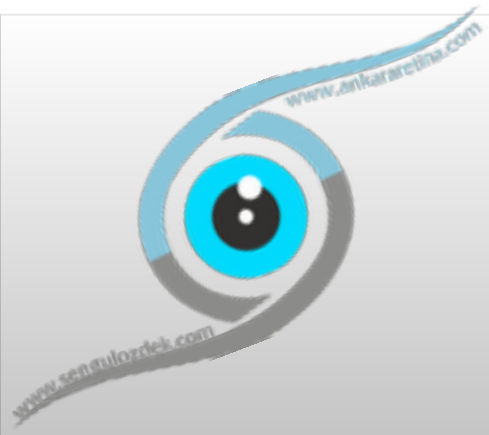


3X Lucentis

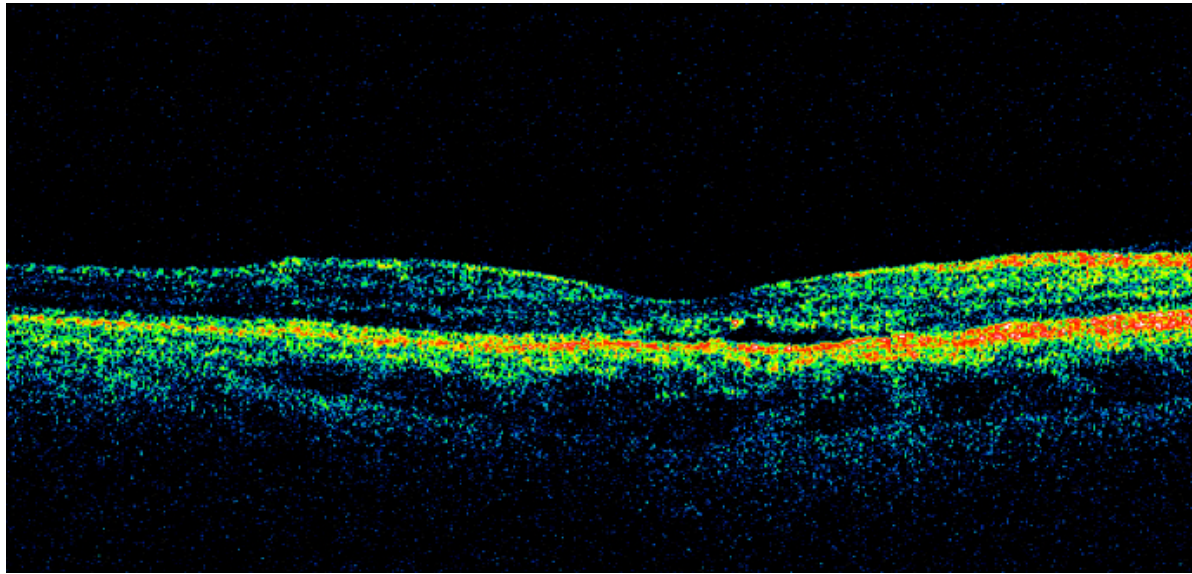


GK: 0,5

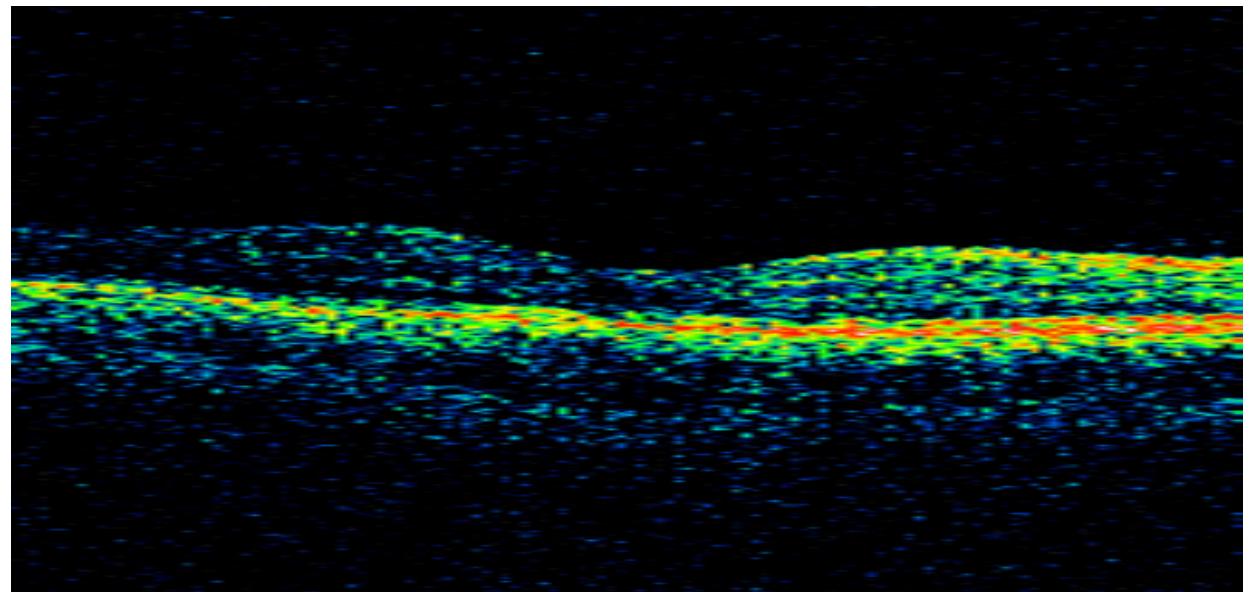




CSCR

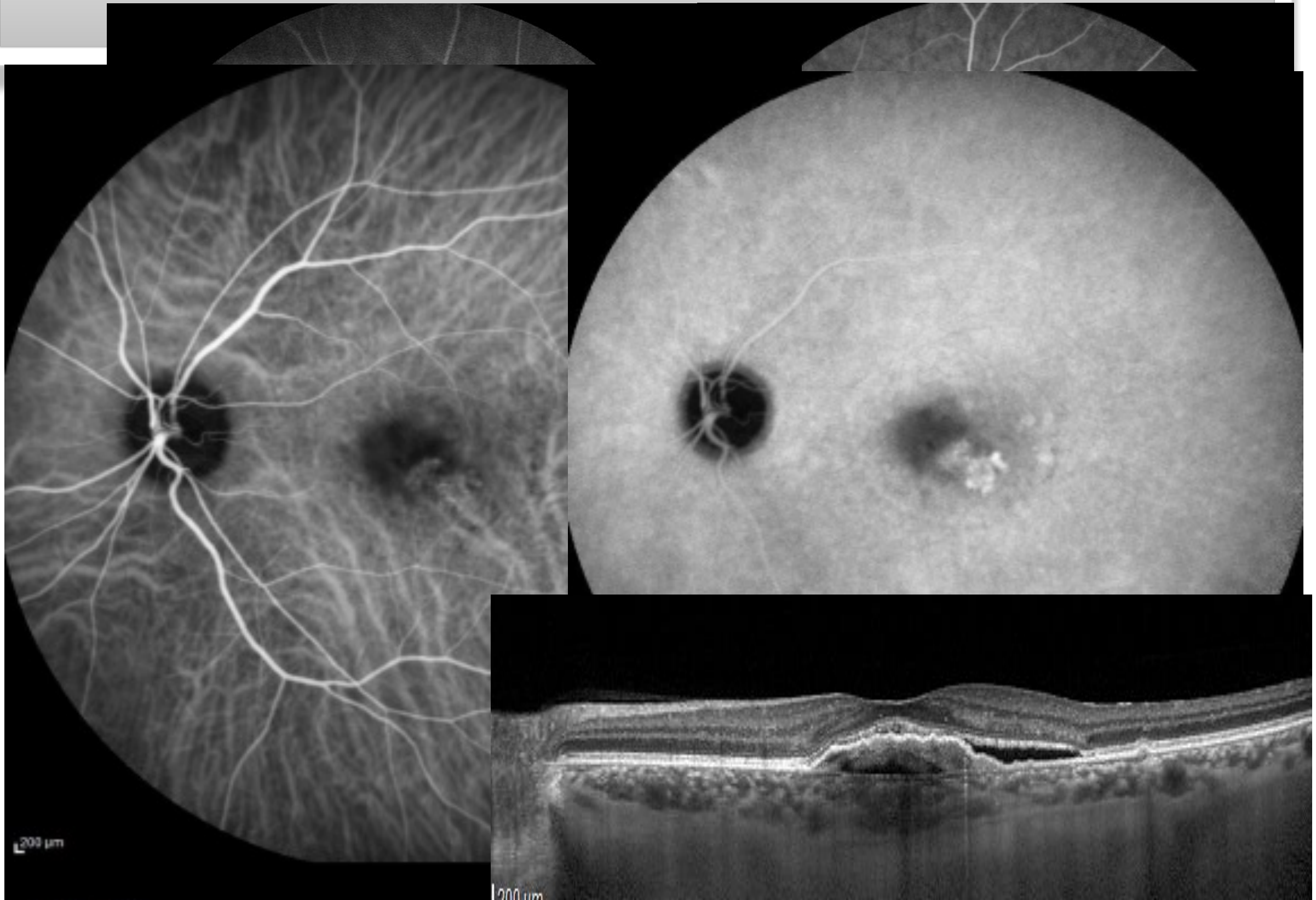


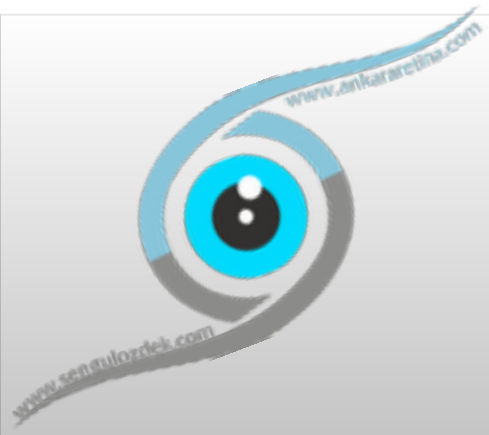
1/2 fluence PDT: 1st mo: VA: 0.7



13rd mo: VA: 0.8

CSCR: Complicated with CNV





CHRONIC CSCR

- No Drusen!
- FA: Mostly bilateral multifocal leakage,
- OCT: Subfoveal fluid and PED (No intraretinal fluid)
- ICG: Choroidal hyperpermeability
- EDI-OCT: Thick choroid
- Treatment: PDT

RESISTANCE TO ANTI-VEGF TREATMENT

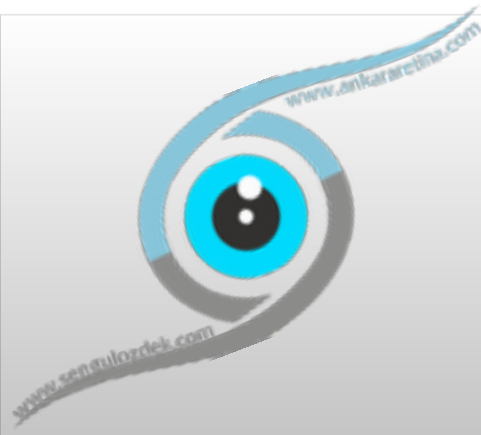
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 - PCV, RAP, VITELLIFORM (AOVMD), CSCR
- TACHYPHYLAXIS-TOLERANCE (22%)
- NONRESPONDERS (26.9%)
- COMPLICATIONS: RPE tear, atrophy, scarring/fibrosis (11.6%)
- GENETIC BASIS FOR RESISTANCE



DECREASED TREATMENT RESPONSE WITH TIME

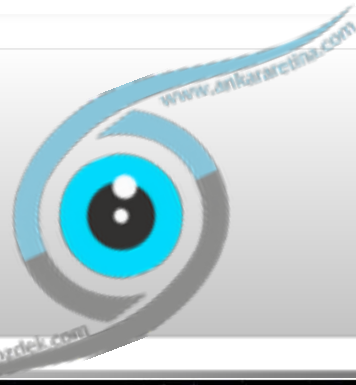
- A reduction in biological effects of long-term medications
- Progressive decrease in therapeutic response after the repeated administration of drugs.

Tachyphylaxis / Tolerance

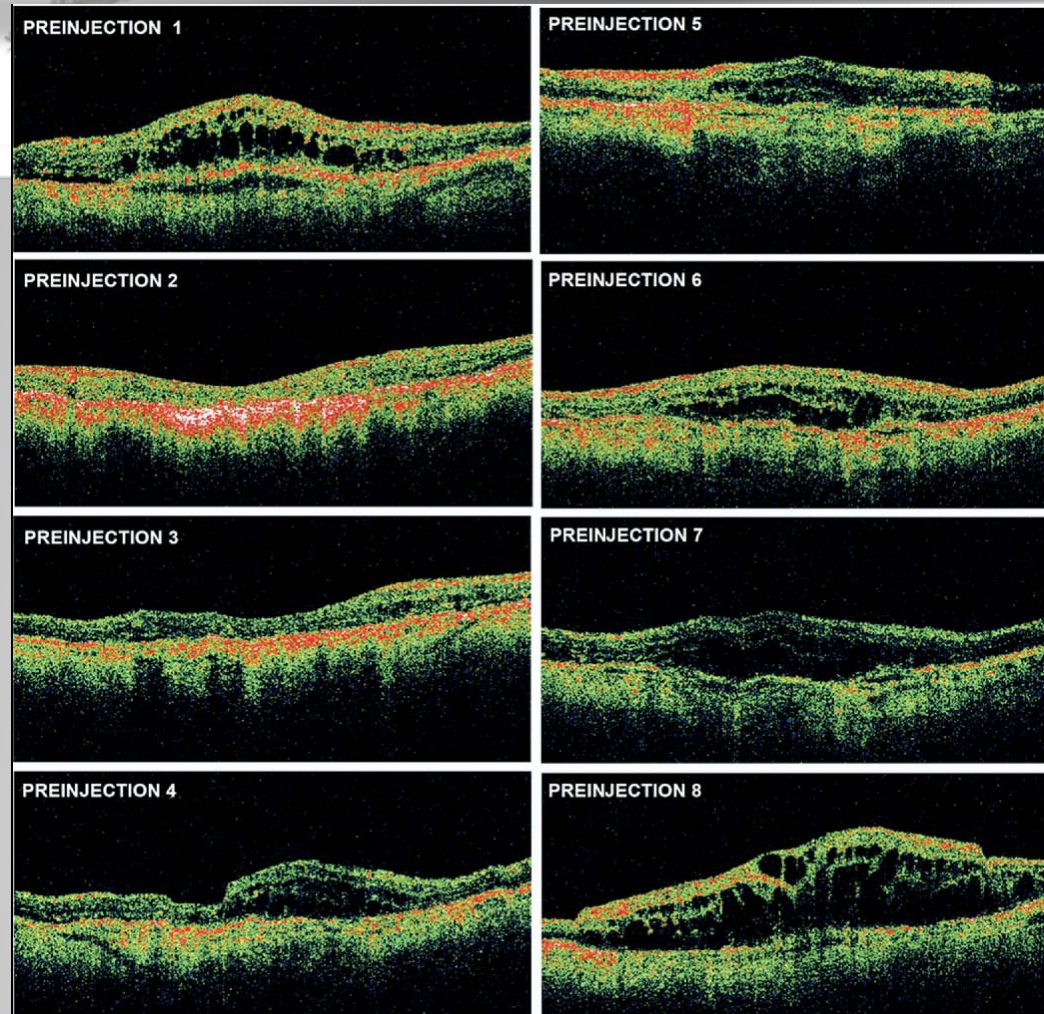


Tachyphylaxis

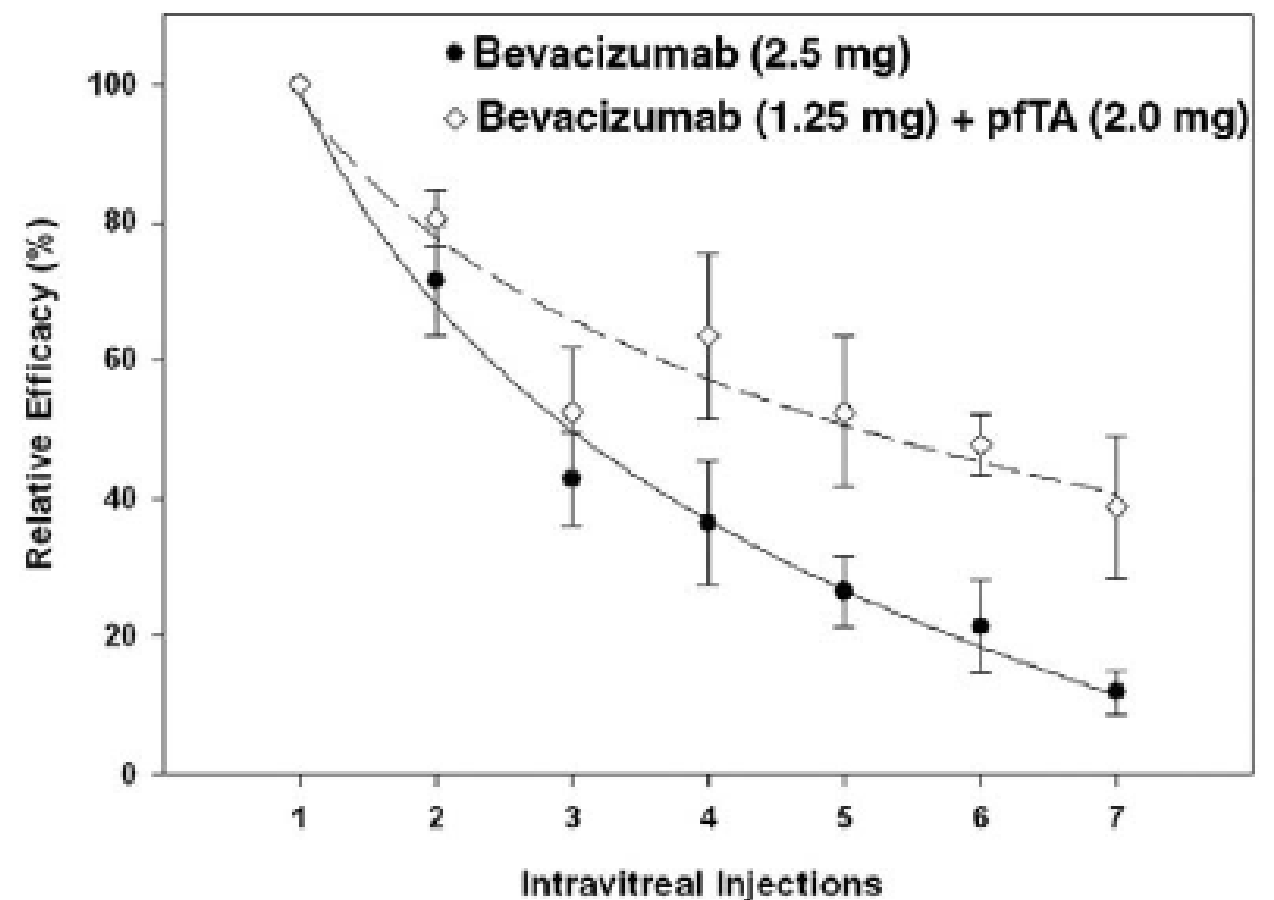
- Keane PA, Liakopoulos S, Ongchin SC, Heussen FM, Msutta S, Chang KT et al. Quantitative subanalysis of optical coherence tomography after treatment with ranibizumab for neovascular age-related macular degeneration. Invest Ophthalmol Vis Sci 2008; 49(7):3115-3120.
- Schaal S, Kaplan HJ, Tezel TH. Is there tachyphylaxis to intravitreal anti-vascular endothelial growth factor pharmacotherapy in age-related macular degeneration? Ophthalmology 2008; 115(12): 2199-2205.
- Forooghian F, Cukras C, Meyerle CB, Chew EY, Wong WT. Tachyphylaxis after intravitreal bevacizumab for exudative age-related macular degeneration. Retina 2009; 29(6):723-731.
- Eghoj MS, Sorensen TL. Tachyphylaxis during treatment of exudative age-related macular degeneration with ranibizumab. Br J Ophthalmol 2012; 96(1):21-23.
- Gasperini JL et al. Bevacizumab and ranibizumab tachyphylaxis in the treatment of choroidal neovascularisation. Br J Ophthalmol. 2012
- Tranos P et al. Resistance to anti-VEGF treatment in AMD. Drug Design, Development and Therapy 2013 (Review)
- Binder S. Loss of reactivity in intravitreal anti-VEGF therapy: tachyphylaxis or tolerance? Br J Ophthalmol 2012; 96(1):1-2. (editorial)



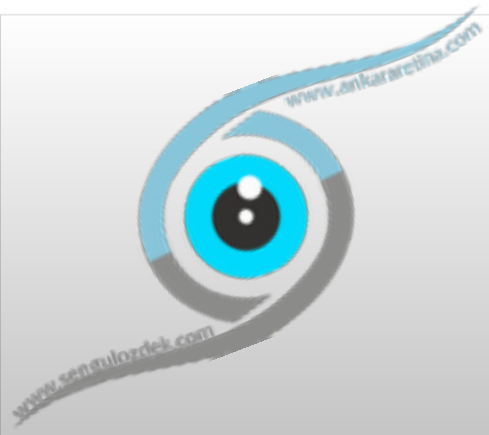
Tachyphylaxis



Decrease in bioefficacy

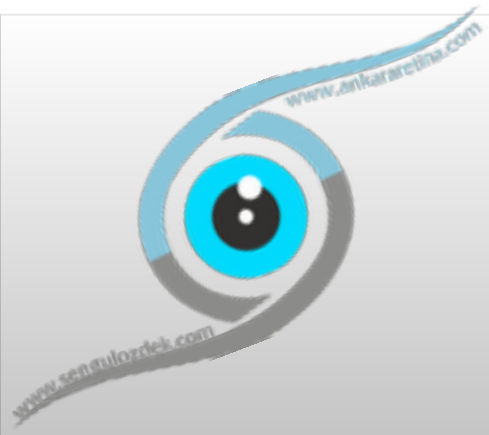


- Schaal S, Kaplan HJ, Tezel TH. Is there tachyphylaxis to intravitreal anti-vascular endothelial growth factor pharmacotherapy in age-related macular degeneration? Ophthalmology 2008; 115(12):2199-2205.



Tachyphylaxis

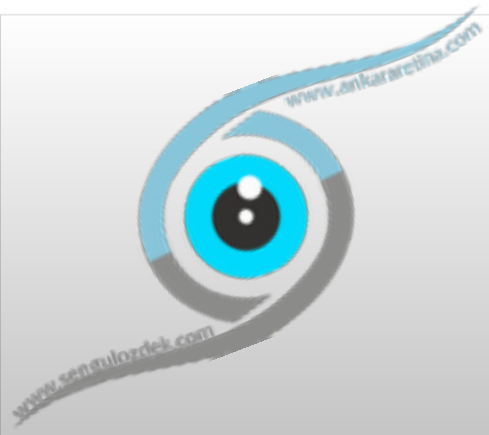
- NIH
- Tachyphylaxis
- 6/59 eye: 10%
- Mean # of injec: 8, mean duration: 100 weeks
- Forooghian F et al. Tachyphylaxis Following Intravitreal Bevacizumab for Exudative ARMD. Retina 2009.



Tachyphylaxis

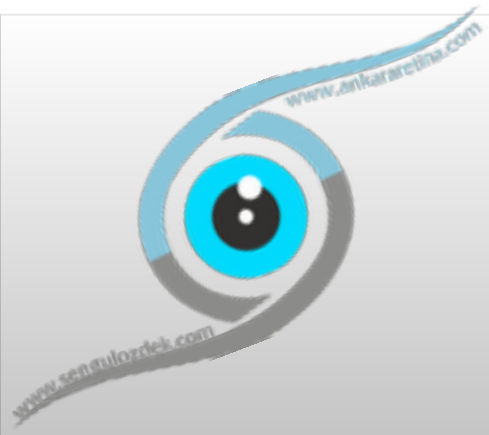
- Tachyphylaxis
- 20/1076 eye: (2%)

- Eghoj MS, Sorensen TL. Tachyphylaxis during treatment of exudative age-related macular degeneration with ranibizumab. Br J Ophthalmol 2012; 96(1):21-23.



Tachyphylaxis

- Doheny Eye Institute
- 26 eye with Tachyphylaxis
- Some after 2-3 injec, some after 10-11 injec.
- 81% had better response when switched to another anti-VEGF
- Gasperini JL et al. Bevacizumab and ranibizumab tachyphylaxis in the treatment of choroidal neovascularisation. Br J Ophthalmol. 2012



Tachyphylaxis

- Early (after 2-3 injec): Tachyphylaxis
 - Late (after 10-15 injec): Tolerance
-
- Binder S. Loss of reactivity in intravitreal anti-VEGF therapy: tachyphylaxis or tolerance? Br J Ophthalmol 2012; 96(1):1-2.
 - Schaal S, Kaplan HJ, Tezel TH. Is there tachyphylaxis to intravitreal anti-vascular endothelial growth factor pharmacotherapy in age-related macular degeneration? Ophthalmology 2008; 115(12):2199-2205.

Purpose

- Rate of tachyphylaxis during treatment with anti-VEGFs for neovascular AMD
- Main characteristics of patients who developed tachyphylaxis after ranibizumab treatment

Tachyphylaxis during ranibizumab treatment of exudative age-related macular degeneration.

Doguizi S, Ozdek S et al.

Int J Ophthalmol. 2015

Patients and Methods

- Retrospectively reviewed records of neovascular ARMD cases treated with anti-VEGFs
- Quantitative analysis of OCT volumes
- Decrease in the ability of repeated injections to reduce retinal volume

Definition

- Evidence of an **initial positive response** (reduction in CRT or PED height) to treatment with IV injections,
- Followed by **an eventual poor response** to treatment (increase in CRT or PED height), despite injections.
- Stabilization of CRT or PED height during treatment was **not** considered tachy/tolerance.

Development of eventual poor response:

<6 injections: Tachyphylaxis

≥6 injection: Tolerance

Results

- Charts of 206 eyes in 201 patients
- Total of 16 eyes found to have a decrease in response (7.7%)
- Mean Follow up: 49.5 months (36-63 mo)
- Tachyphylaxis in 12 eyes (5.8%)
- Tolerance in 4 eyes (1.9%)
- Occult type CNV lesion: in 10 (62.5%)
- Predominantly Classic CNV: in 6 (37.5%)

The median number of injections before developing tachyphylaxis was 3.5 (range 2-5)

The median number of injections before developing tolerance was 11 (range 7-21)

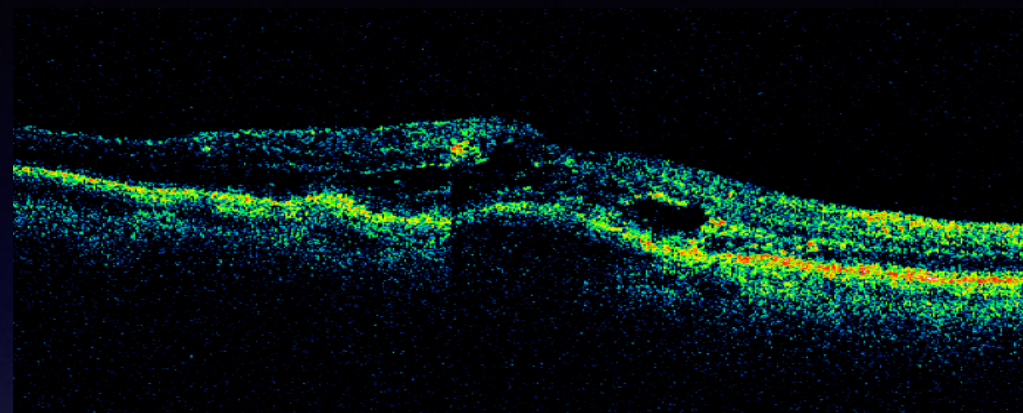
Mean VA in LogMAR

- At baseline: 0.80 logMAR
- At the last visit before developing decrease in response: 0.45 logMAR
- At the time of tachyphylaxis: 0.65 logMAR
- At the last visit: 0.85 logMAR

Mean CRT in OCT

- Baseline CRT: **325** (224-609) μm
- Before decrease in response CRT: **150**
(120-320) μm
- At the time of Tachy/Tol development: CRT
200.5 (130-380)
- At the last visit CRT: **227** (180–325) μm

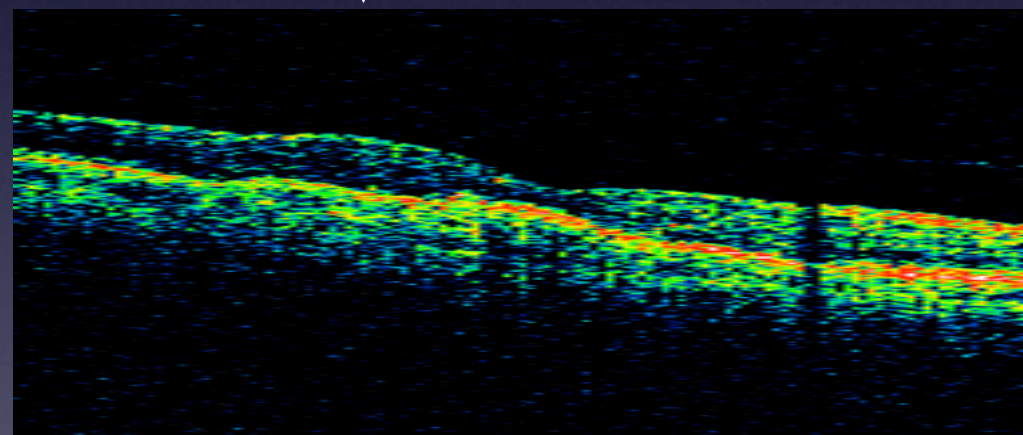
Case I: 64y / K



VA: 0.3



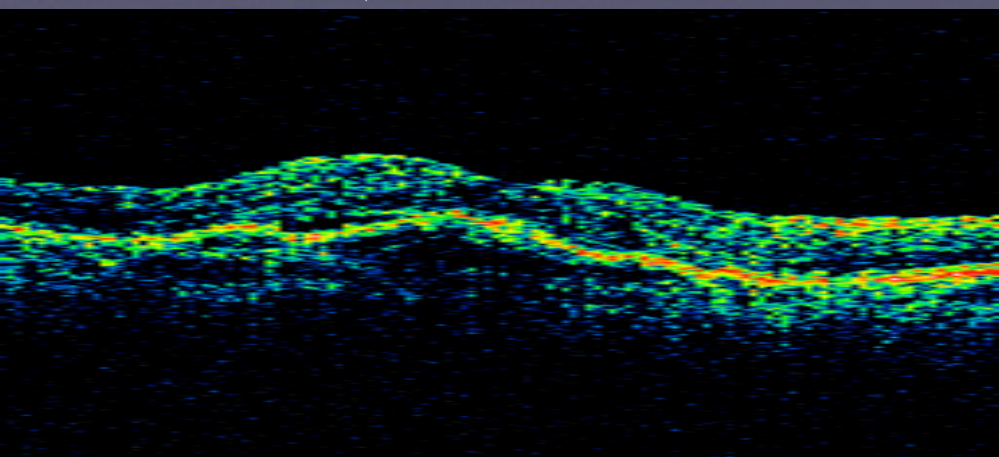
3x Lucentis



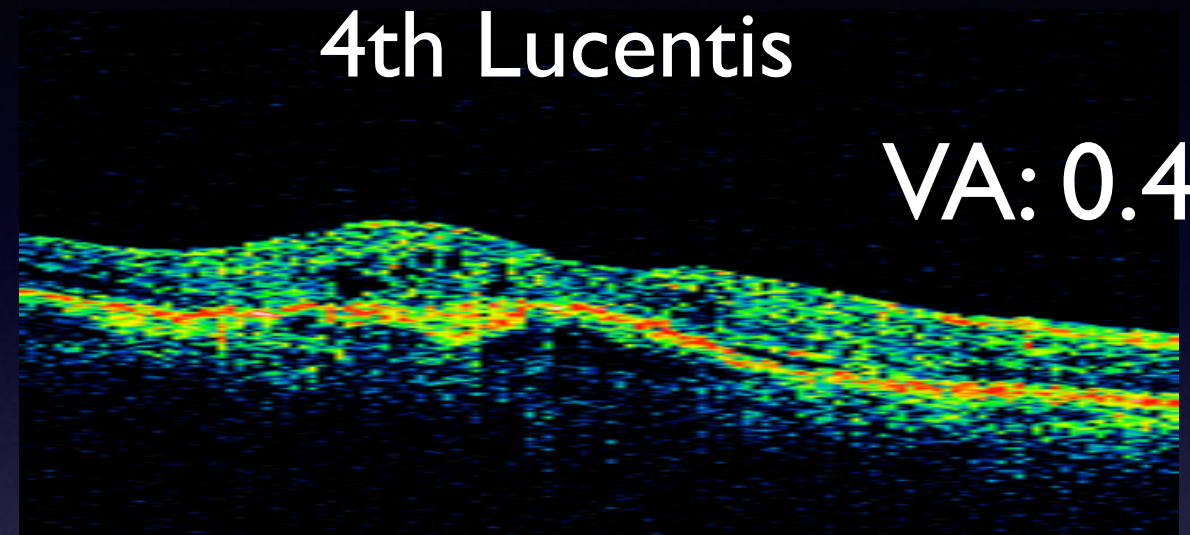
VA: 0.5



2 months



VA: 0.3

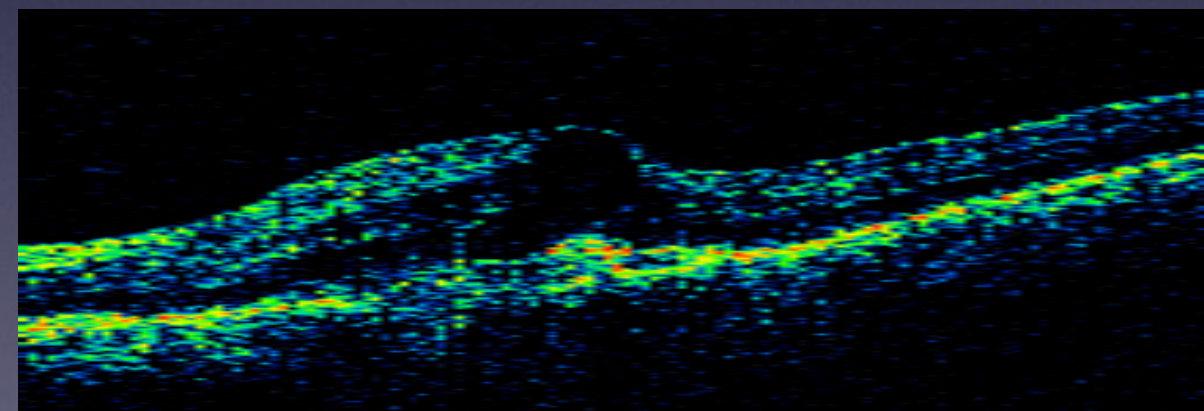


4th Lucentis

VA: 0.4



3x Lucentis



10th month: VA: 0.2

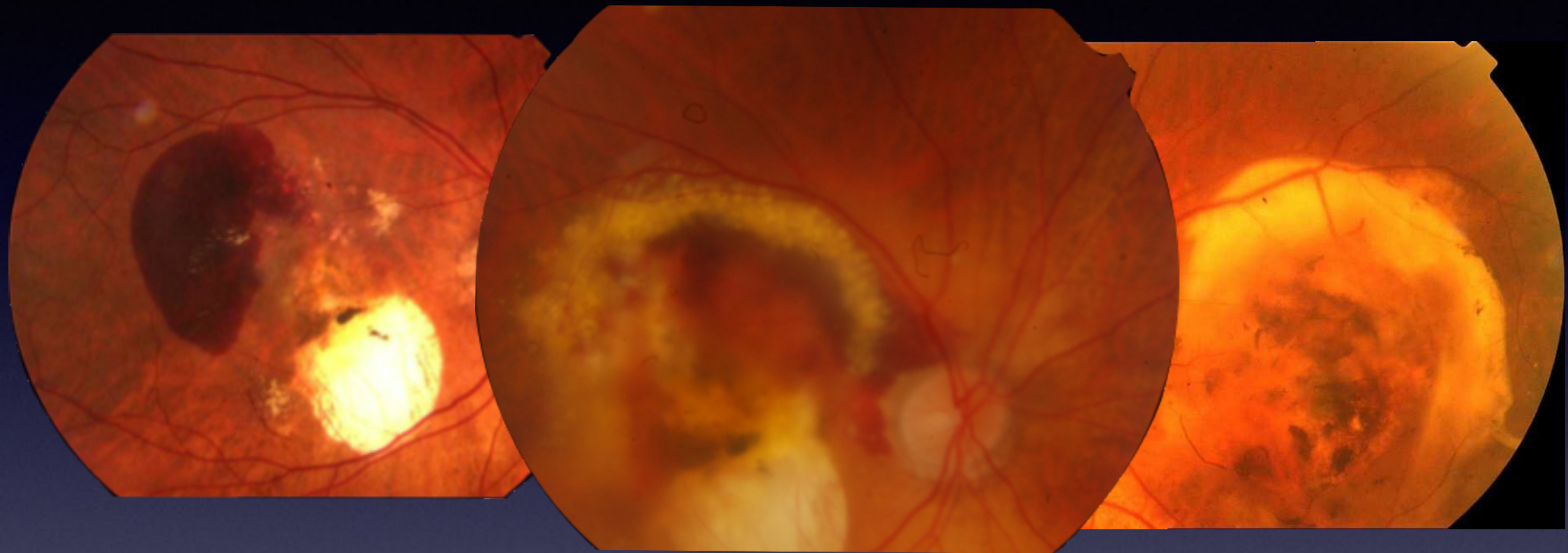
MECHANISMS

- Desensitization of the receptors with long term use!
 - To overcome: More frequent and increased dosing?
 - Forooghian et al: high-dose IVB (2.50 mg) did not restore the therapeutic response (Retina 2009)
- Systemic immune response with neutralizing antibodies:
 - Pharmacokinetic Tolerance*
 - Schaal et al (Ophthalmology 2008): tachyphylaxis can be partially alleviated by the subsequent use of preservative-free triamcinolone
- An increase in other angiogenic factors like fibroblast GF, PlGF, to compensate for the blocked VEGF activity!
 - Aflibercept (VEGF-trap eye): blockage of another pathway “placental growth factor (PlGF)”: dramatic responses in eyes refractory to IVB&IVR (Patel et al Eye, 2013)
- Maturation of the target abnormal vessels

Suggestions to solve the problem

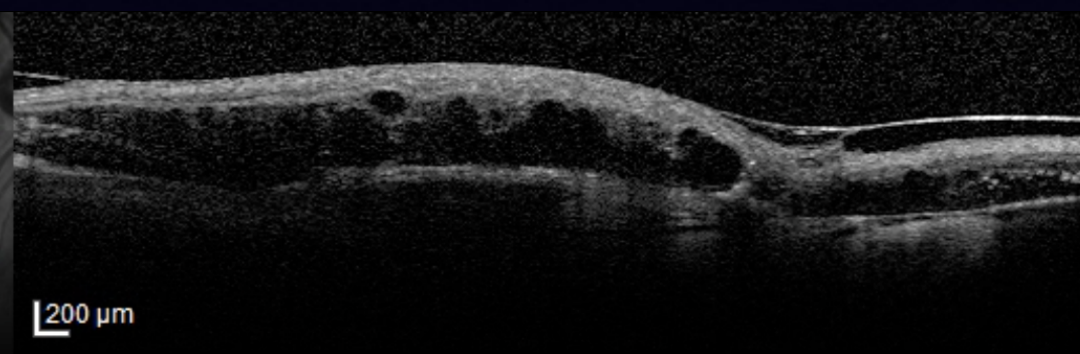
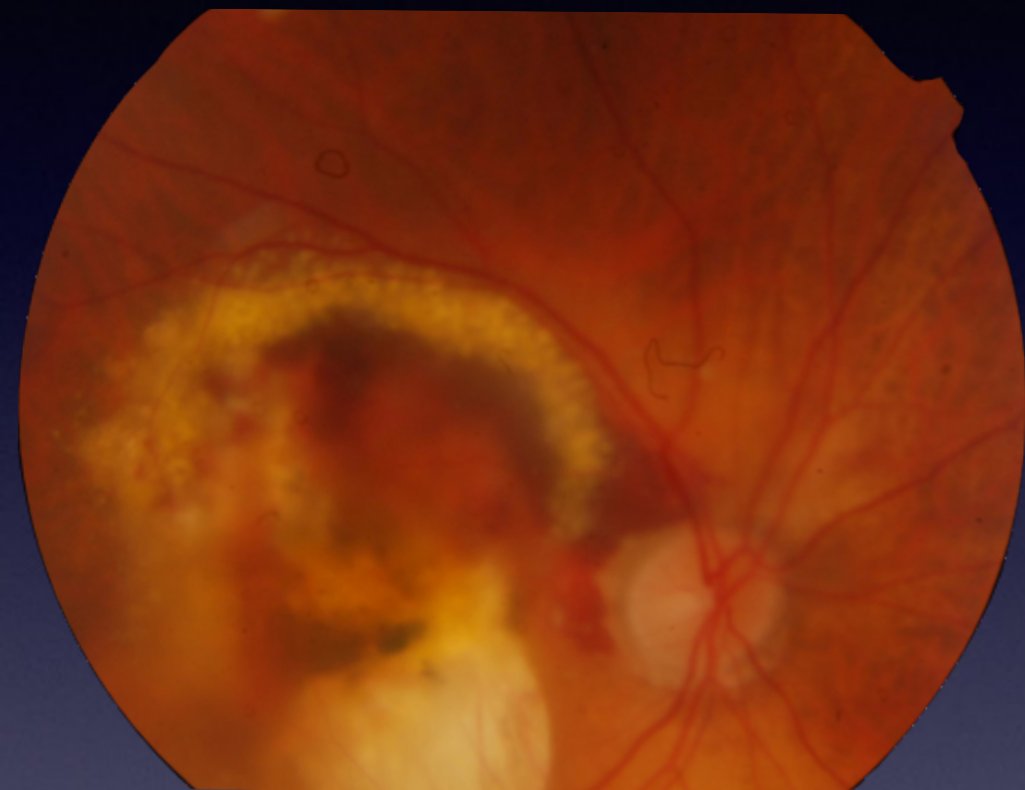
- Tachyphylaxis:
 - interrupt treatment,
 - switch to another anti-VEGF
- Tolerance:
 - increase the dosage,
 - shorten treatment intervals,
 - Use of steroids
 - switch to another anti-VEGF

76y /F VA: 20/400 (R) HM (L)

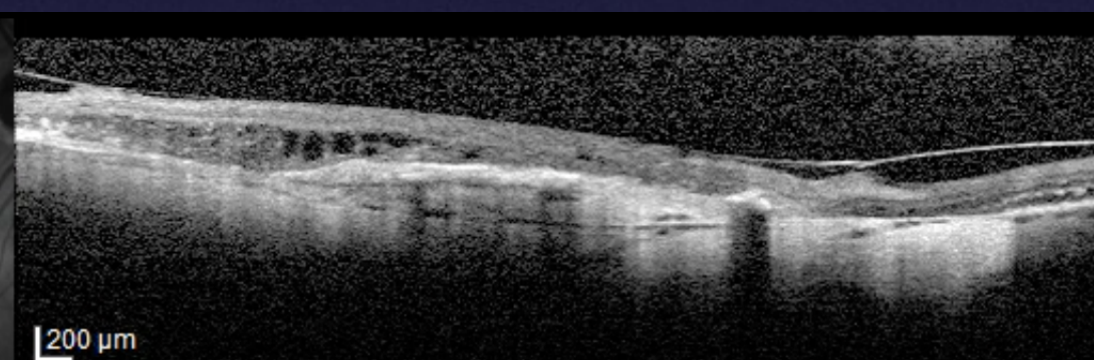


- 2007: 5x Avastin
- 2008: 6x Avastin
- 2009: 6x Lucentis
- 2010: 7x Lucentis
- 2011: 10x Lucentis, 2x IVTA
- 2012: 11x Lucentis
- 2013: 11x Lucentis

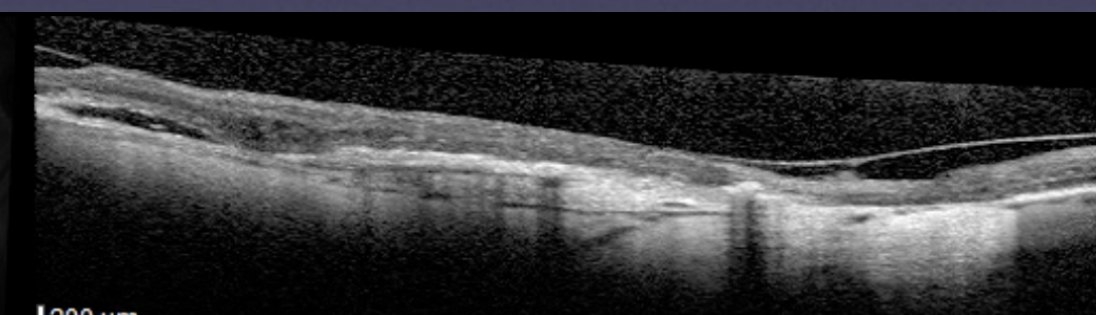
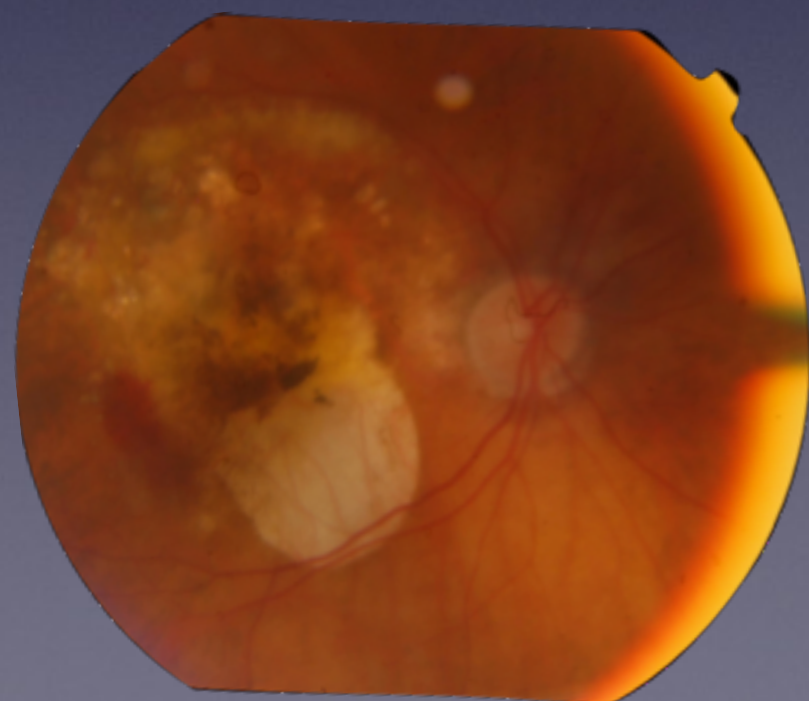
2014-RE



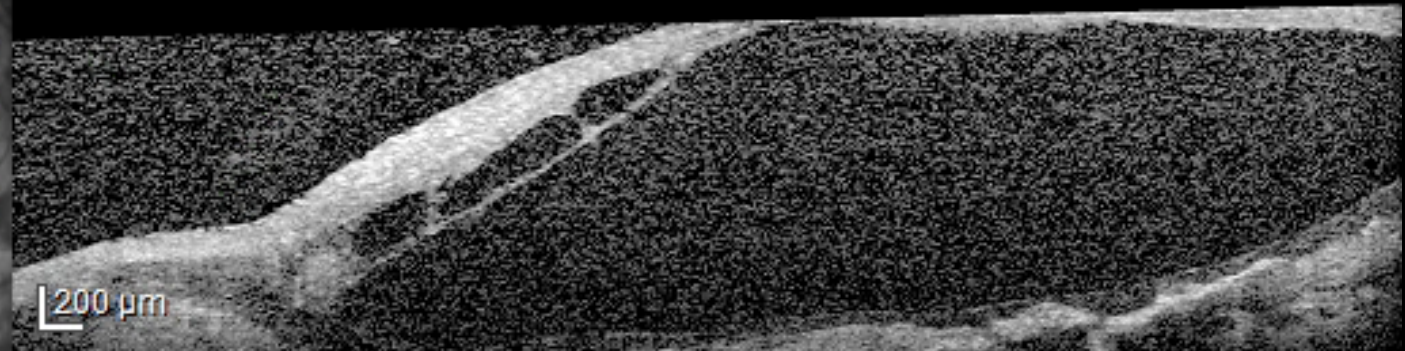
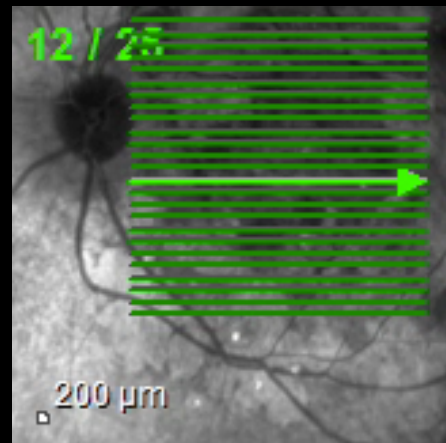
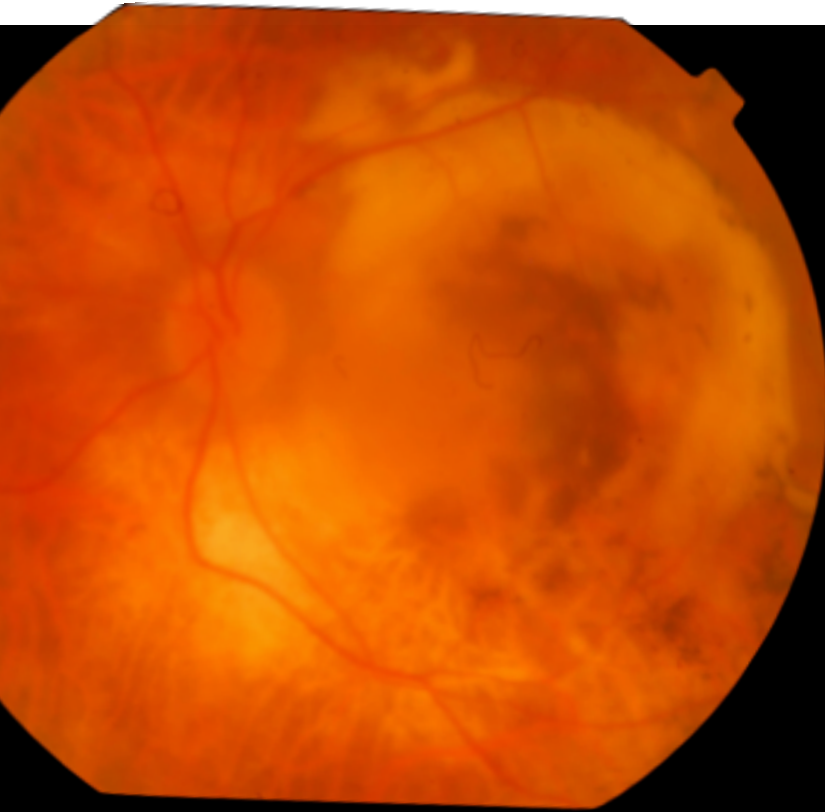
Eylea



Eylea



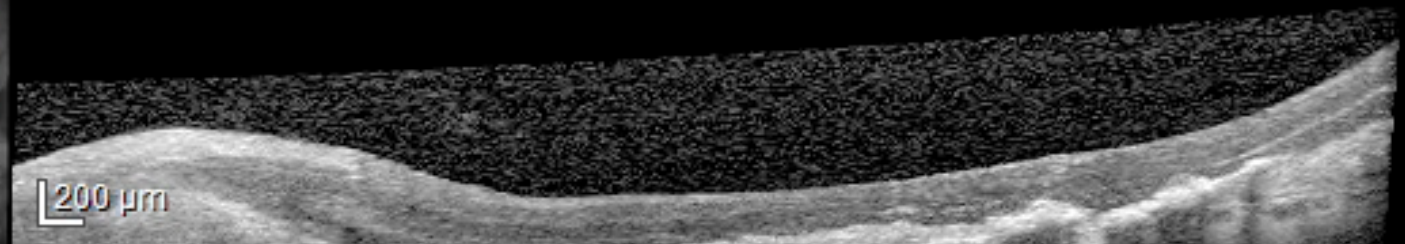
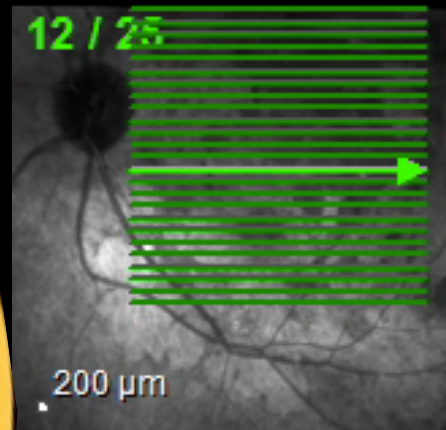
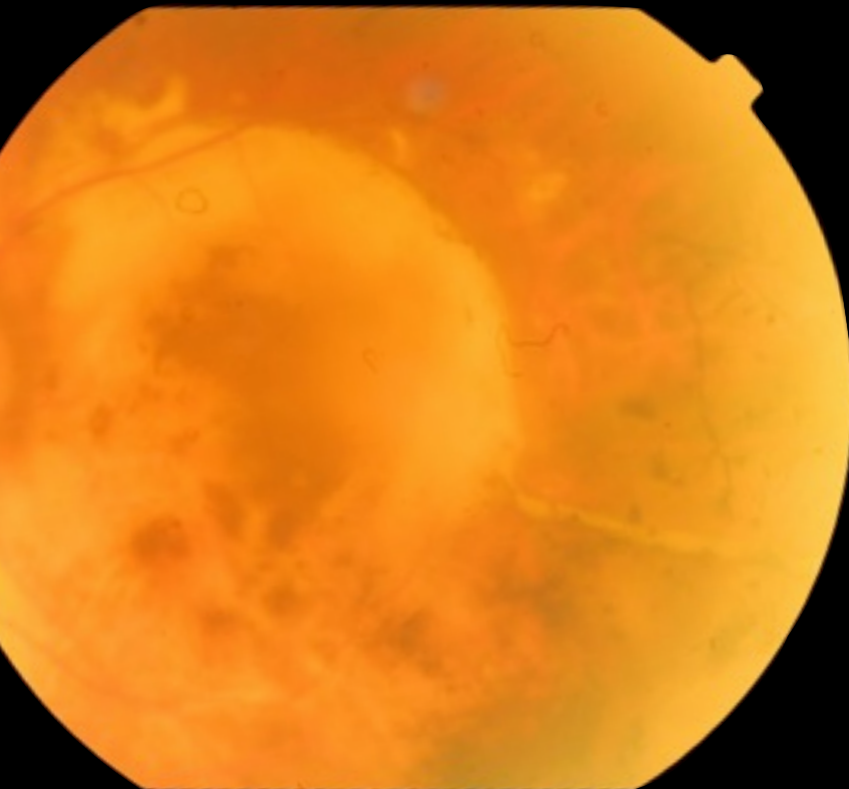
2014- LE



06.01.2014, OS

IR&OCT 30° ART [HS] ART(7) Q: 17

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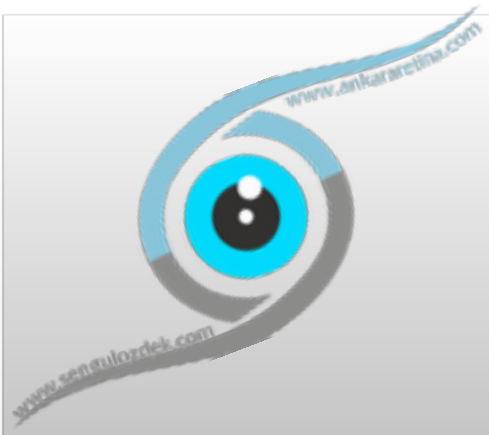
24.02.2014, OS

IR&OCT 30° ART [HS] ART(9) Q: 22

HEIDELBERG
ENGINEERING

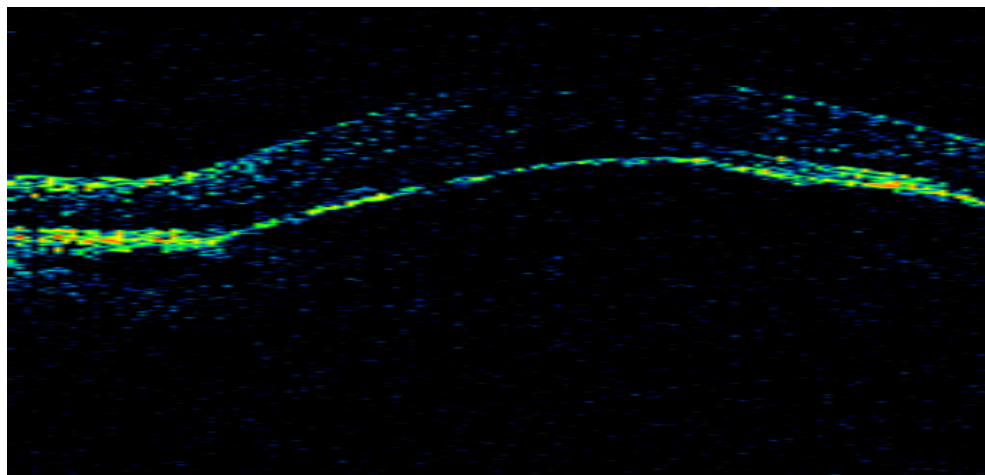
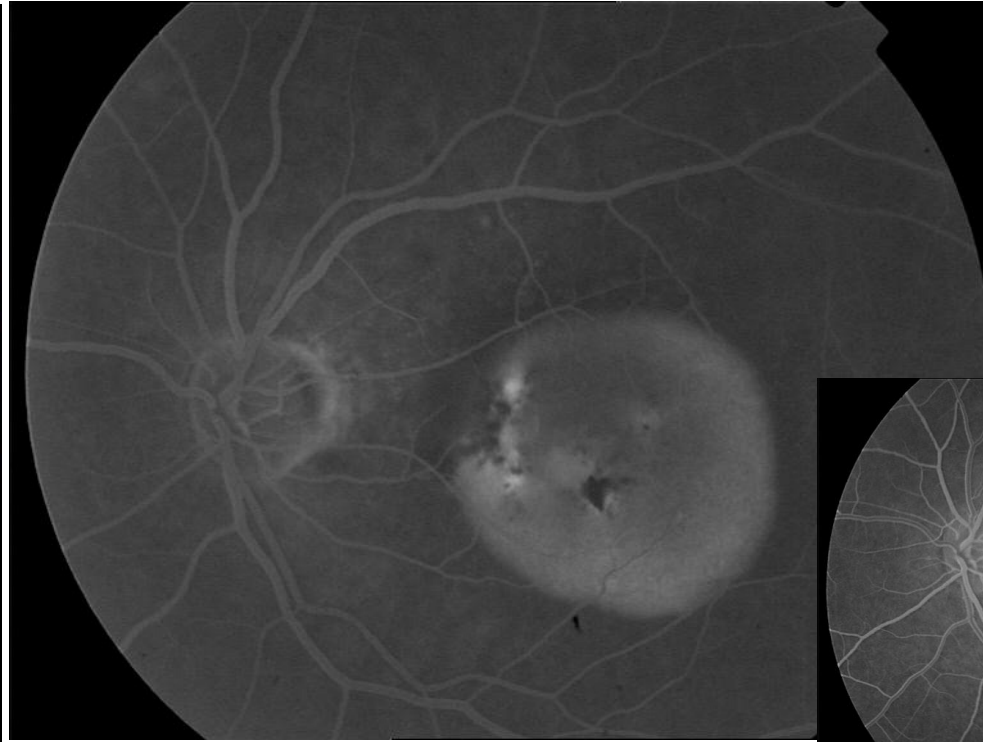
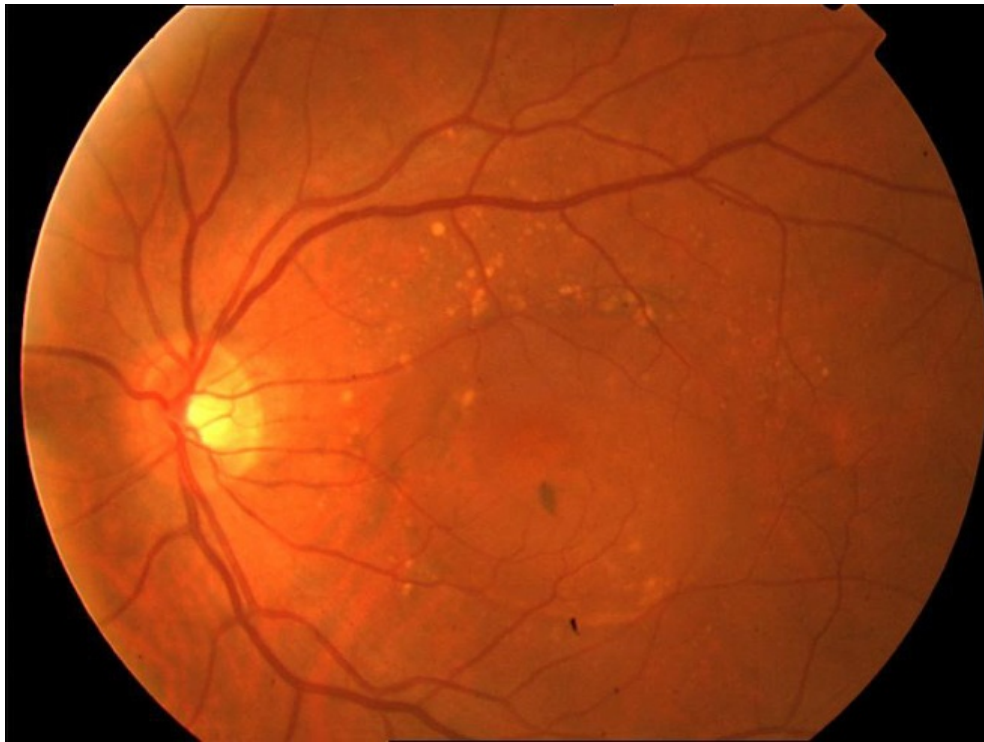
RESISTANCE TO ANTI-VEGF TREATMENT

- WRONG DIAGNOSIS (46.2%)
 - PCV, RAP, VITELLIFORM (AOVMD), CSCR
- TACHYPHYLAXIS-TOLERANCE (22%)
- **NONRESPONDERS** (26.9%) (VA↓ Fluid↑ during loading period, **AS↑**)
- COMPLICATIONS: RPE tear, atrophy, scarring/fibrosis (11.6%)
- GENETIC BASIS FOR RESISTANCE

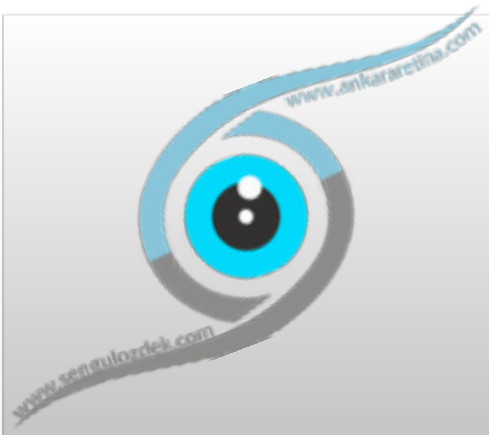


NON-RESPONDER

69y, F, VA: 0.4

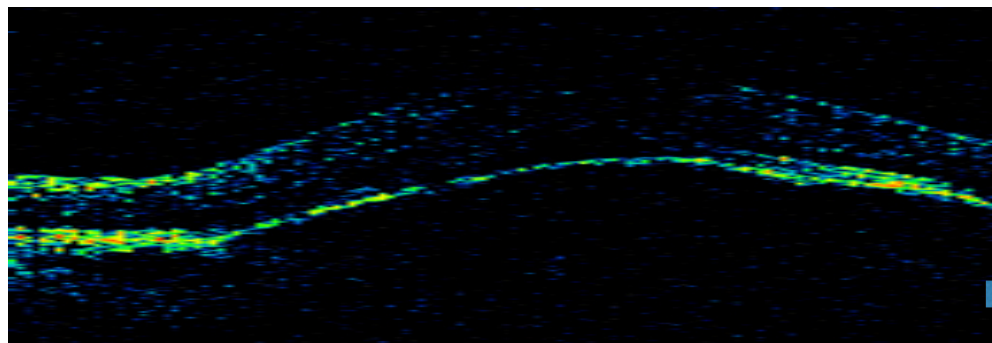


3X Avastin

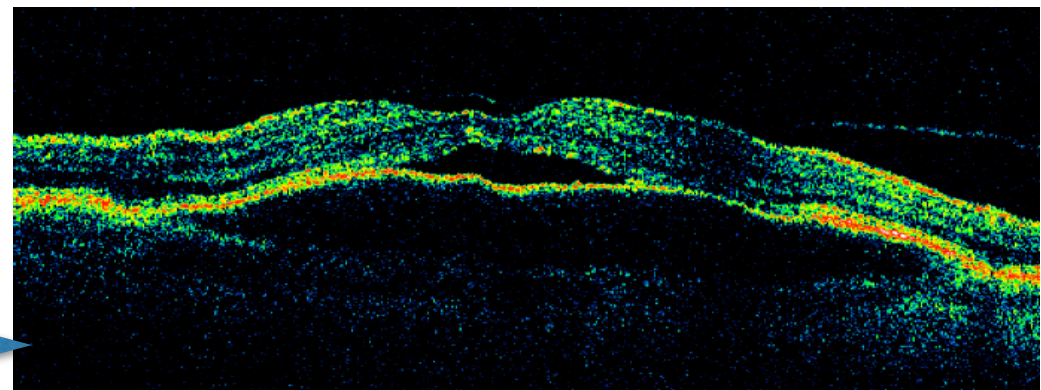


NON-RESPONDER

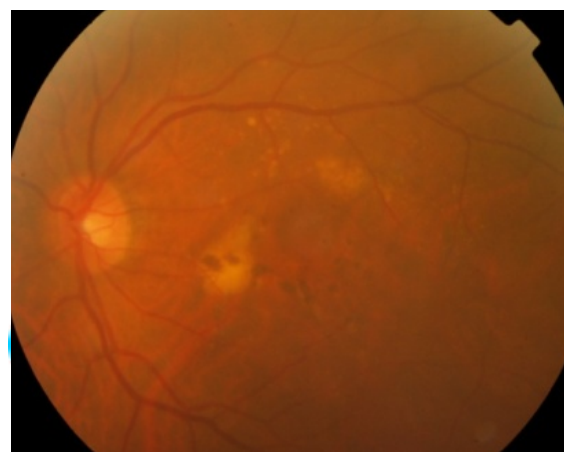
69y, F, VA: 0.4



After 3X Avastin... VA: 0.3



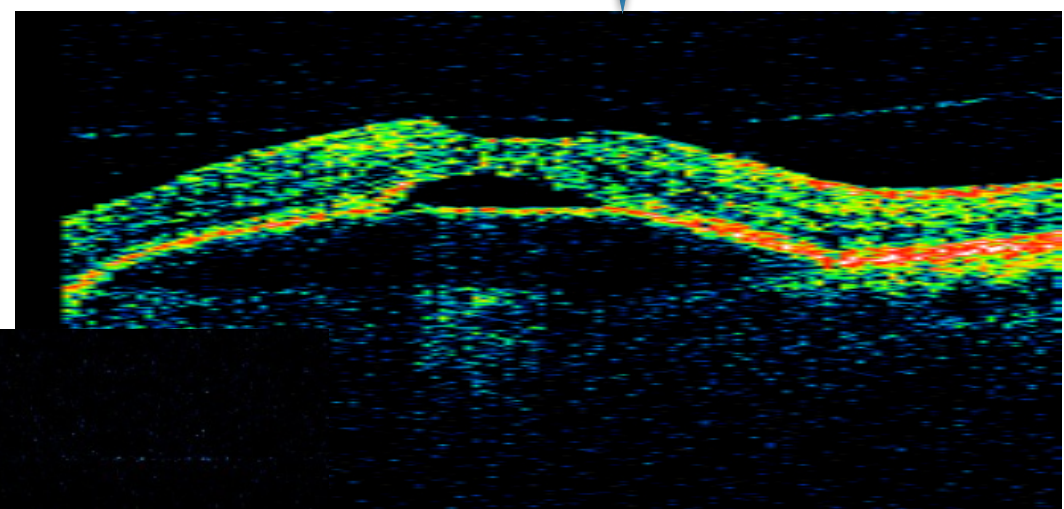
After 3x Lucentis VA: 0.5



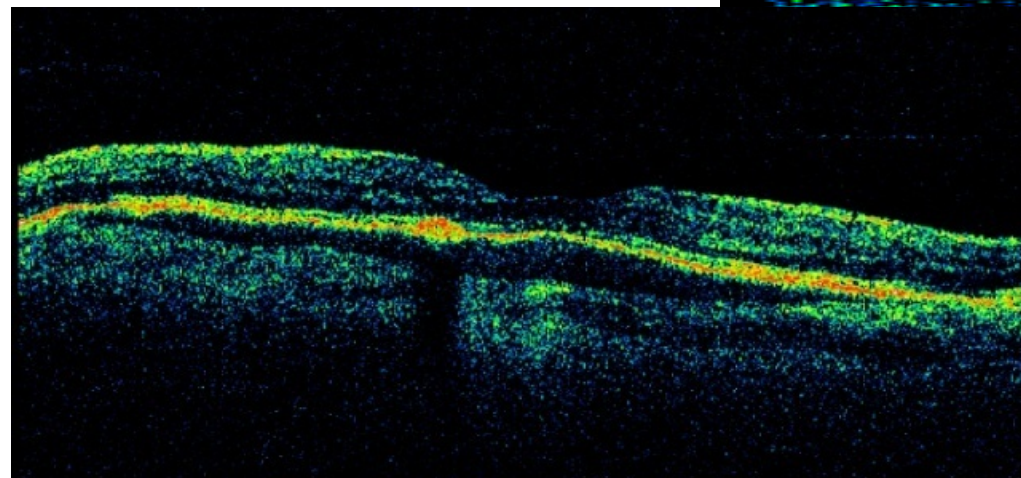
7th mo

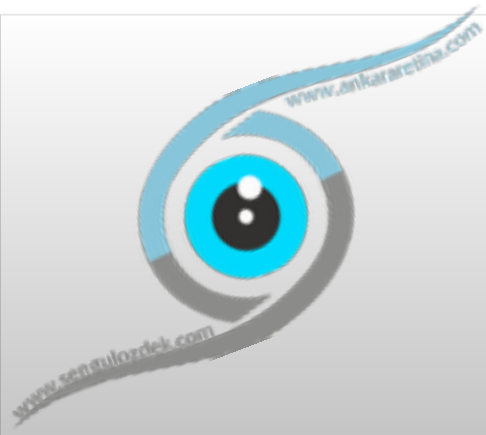
VA: 0.7

1st mo



PDT

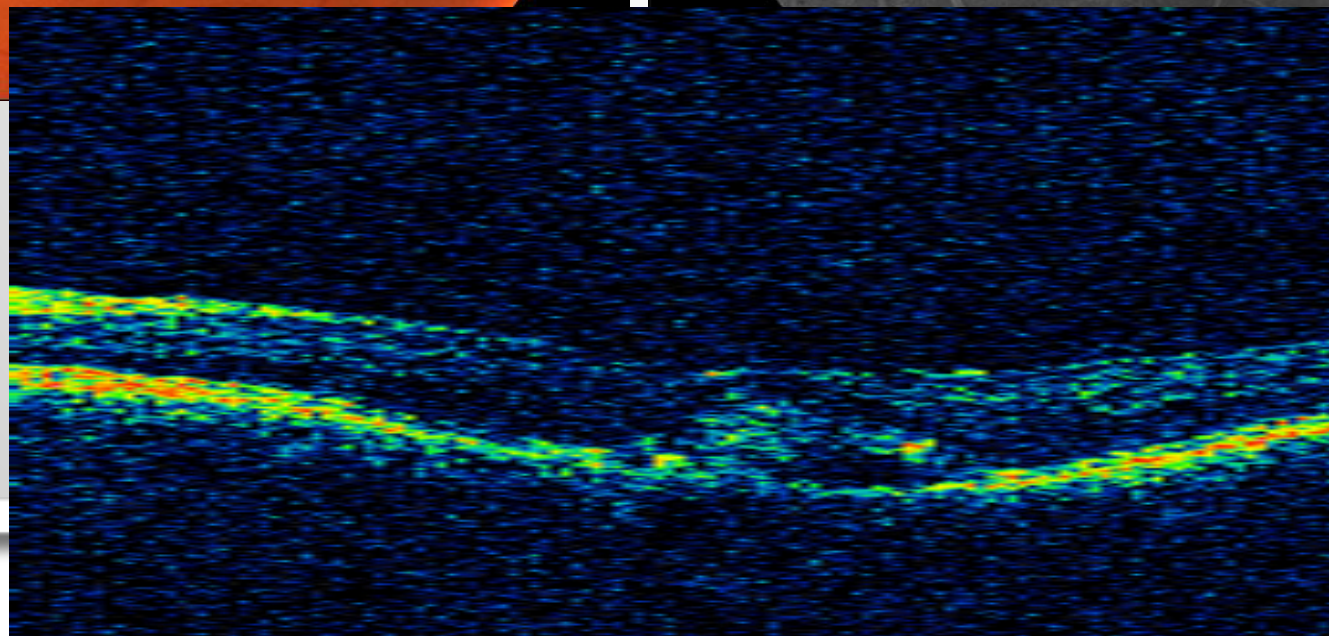
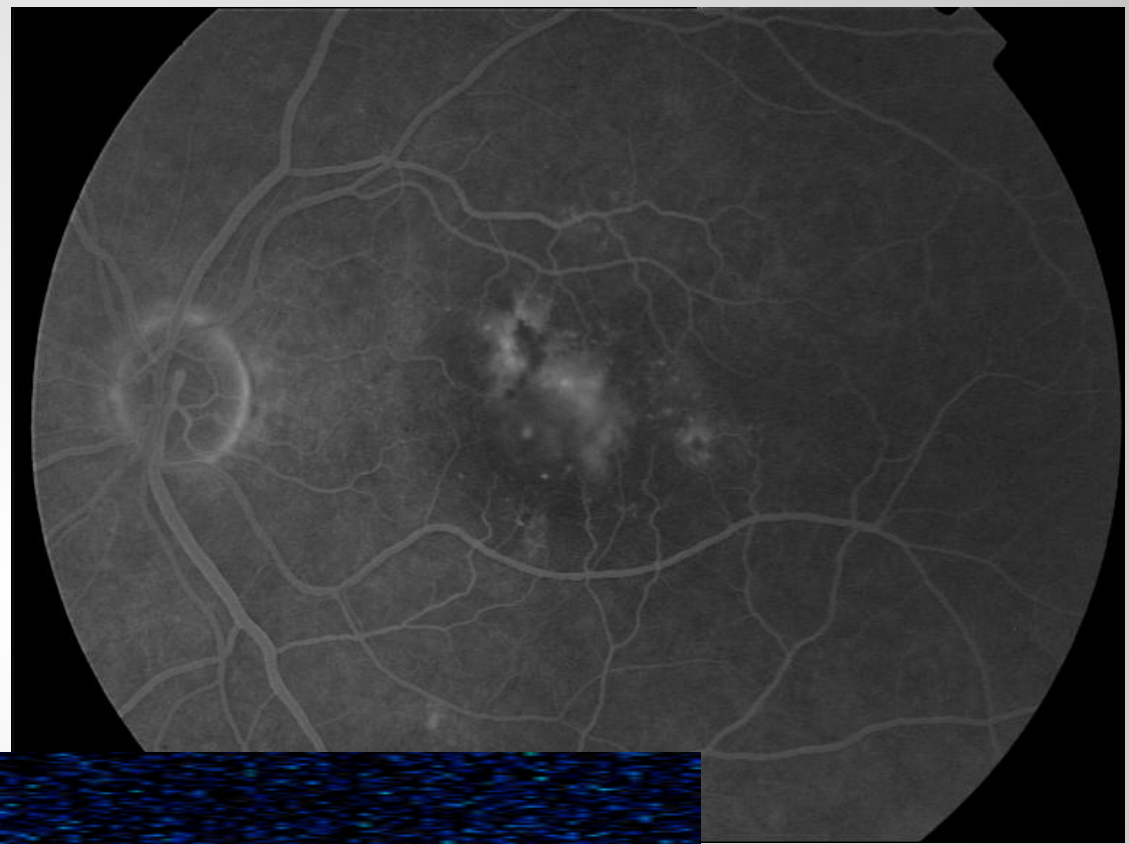




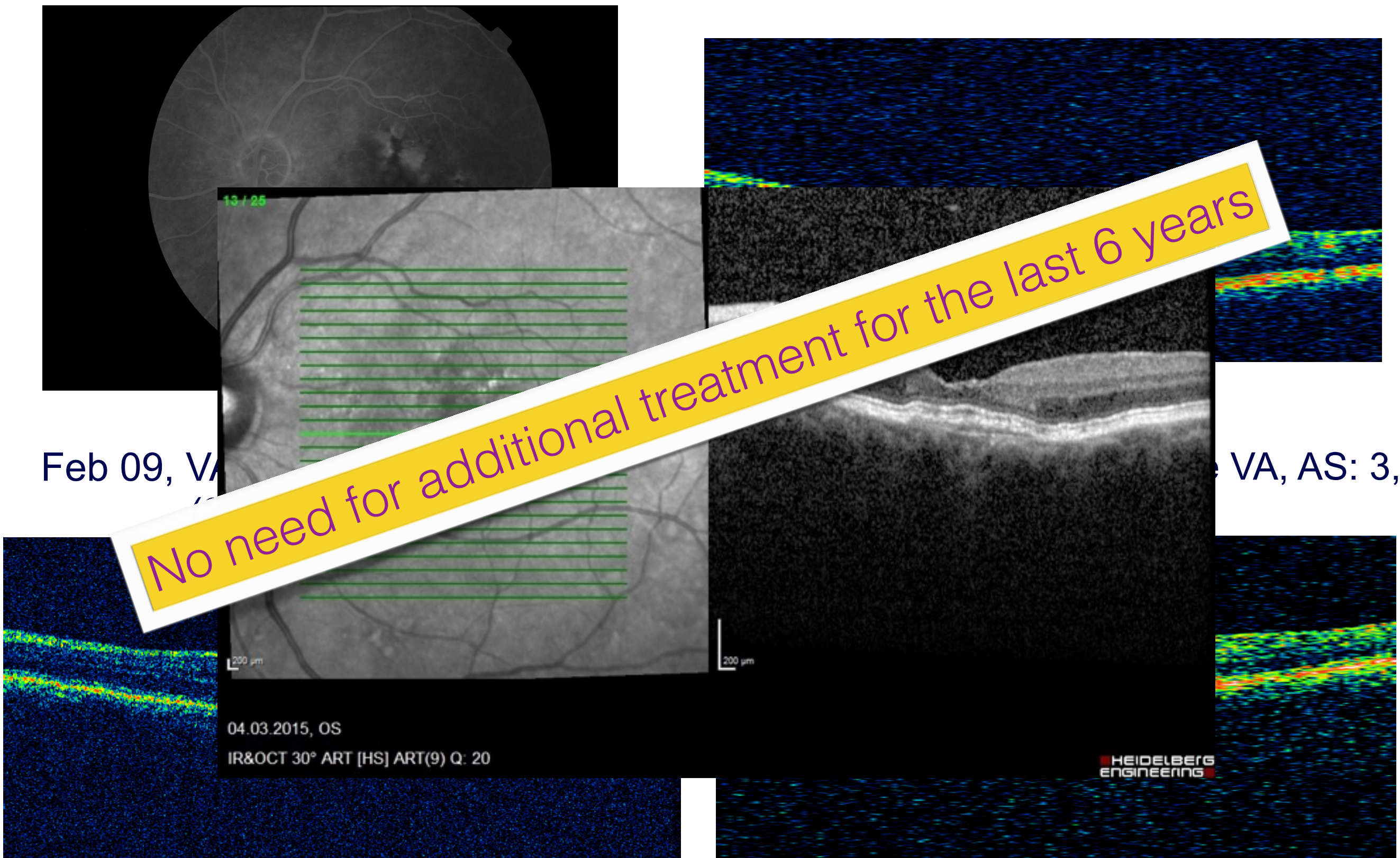
NON-RESPONDER

Switch

64y, F, VA: 0.7, **AS: 7**, IV Avastin (Nov 2009)

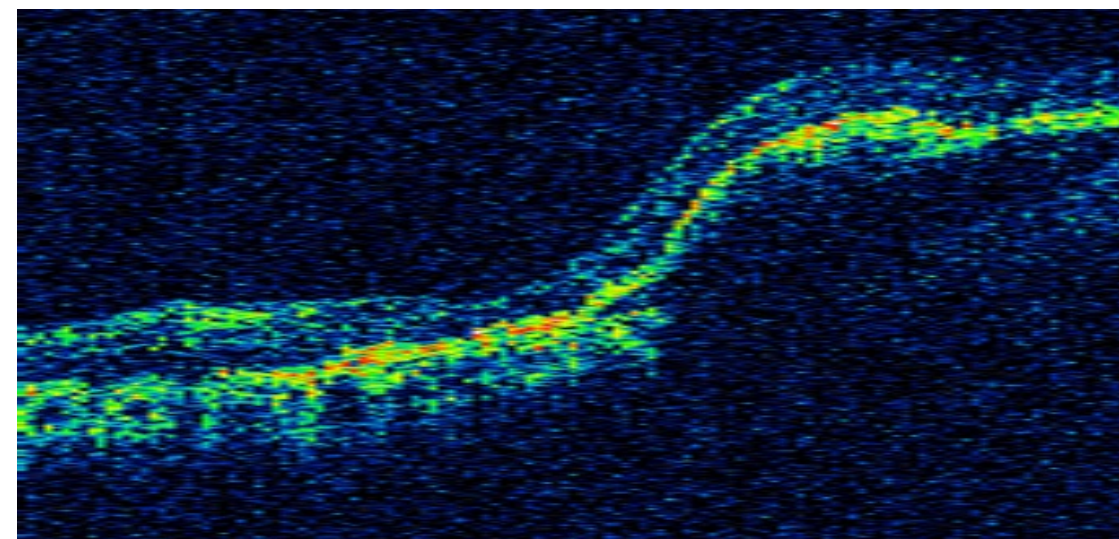
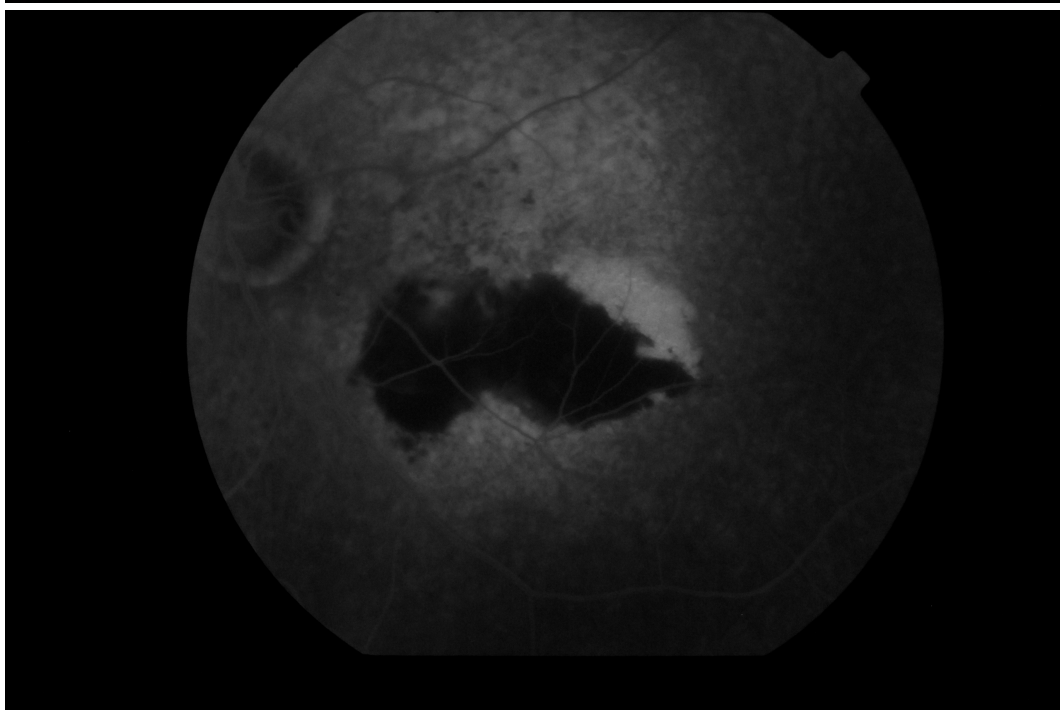
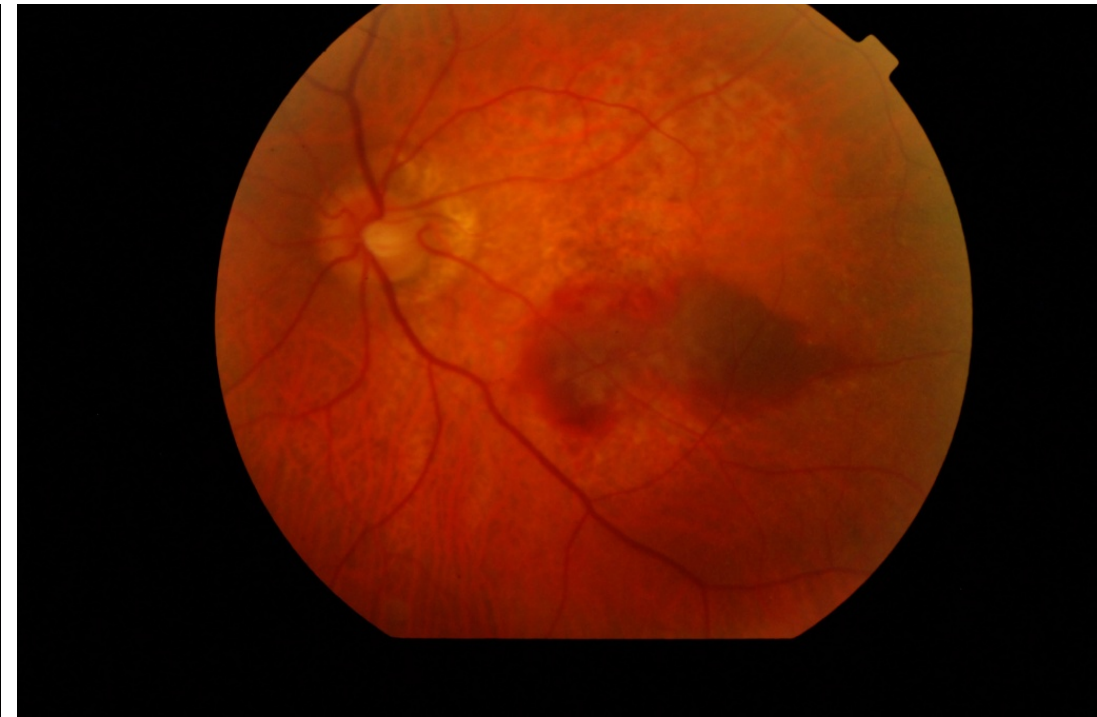
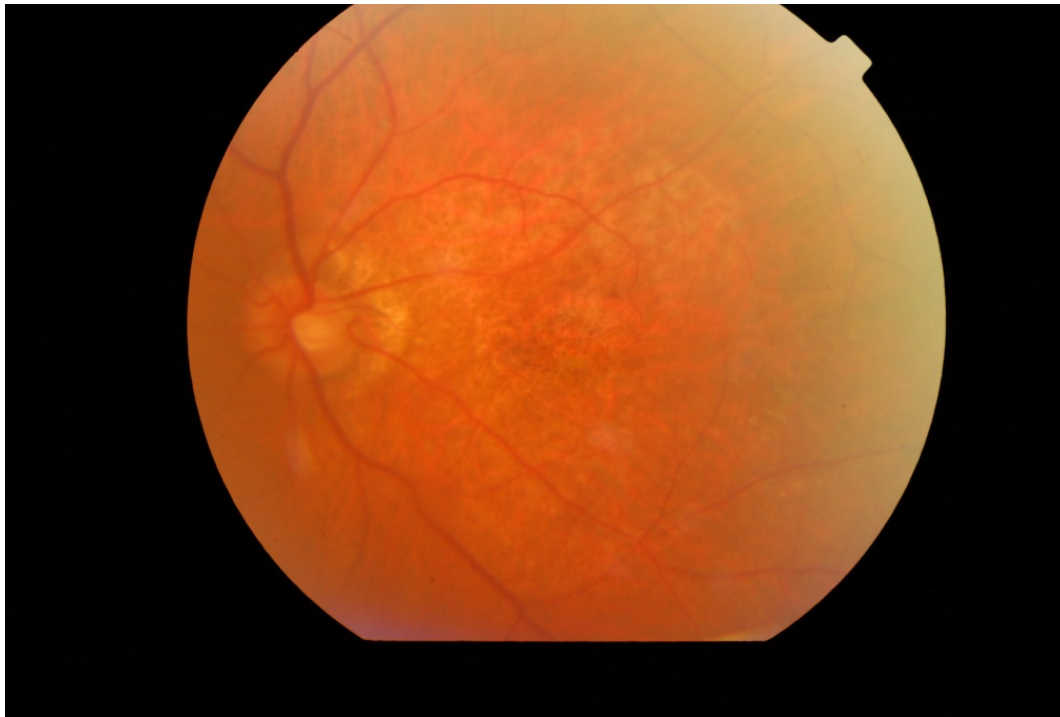


Jan 2009, 2x Avastin, **VA: 0.32**, Subjective Vision↓, AS: 9 (1st Lucentis)



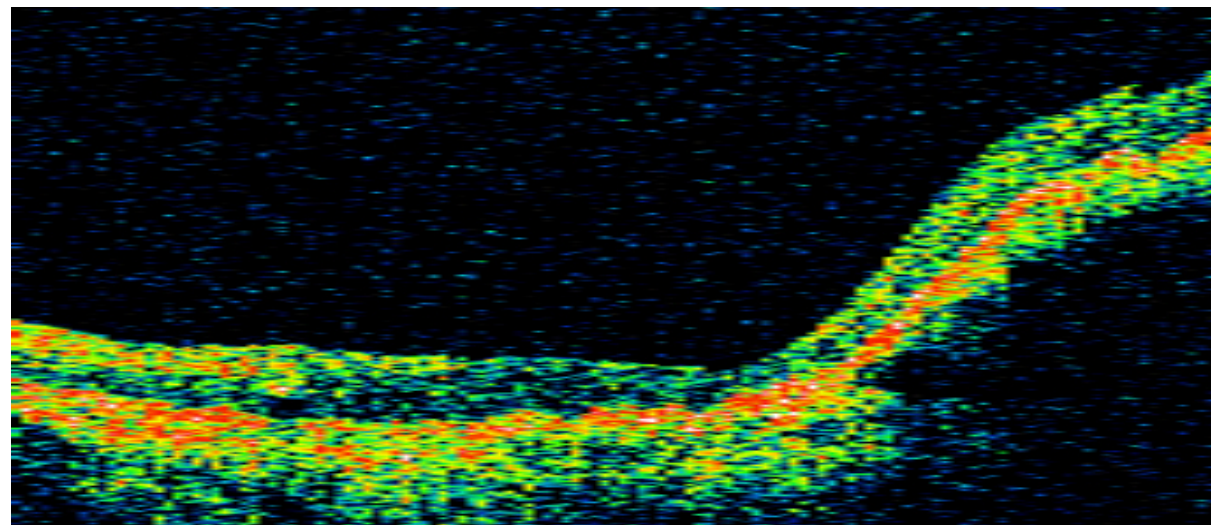
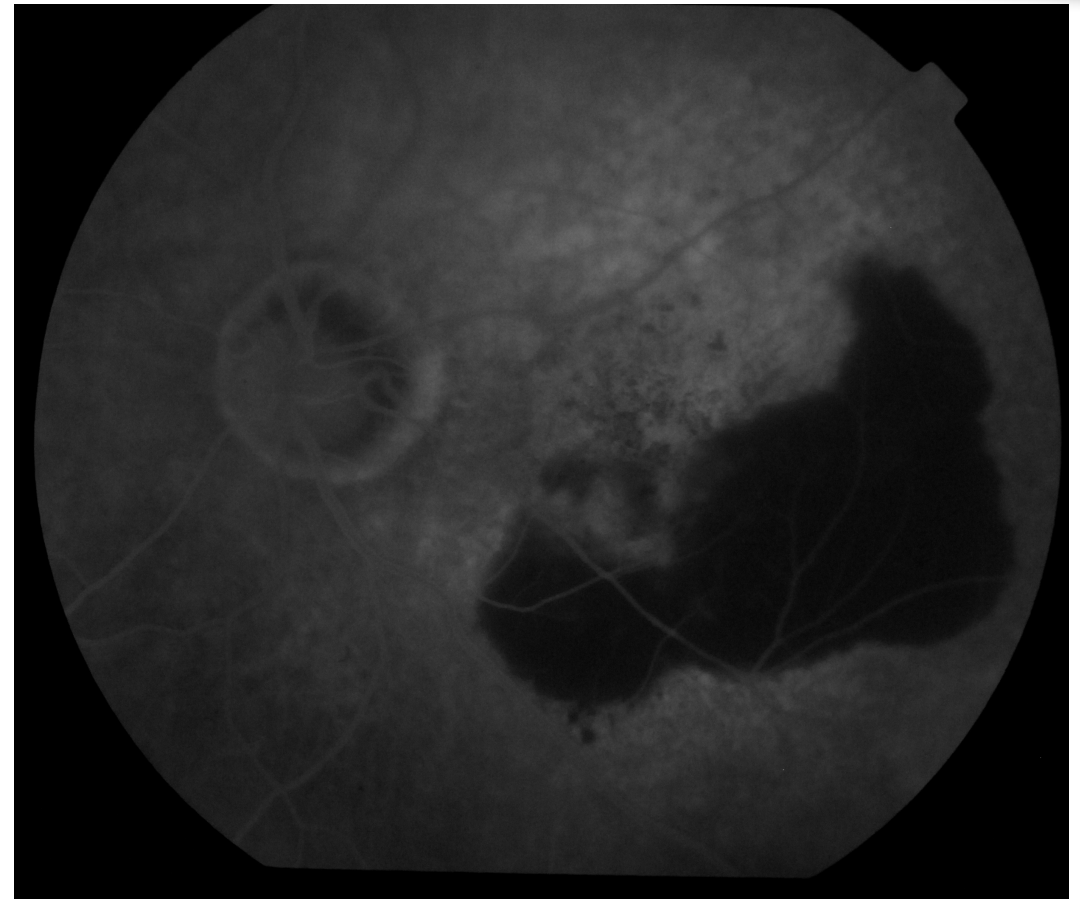
HEMORRHAGIC RESPONSE

72y, VA: 0.1, Jan 2009, IV Lucentis



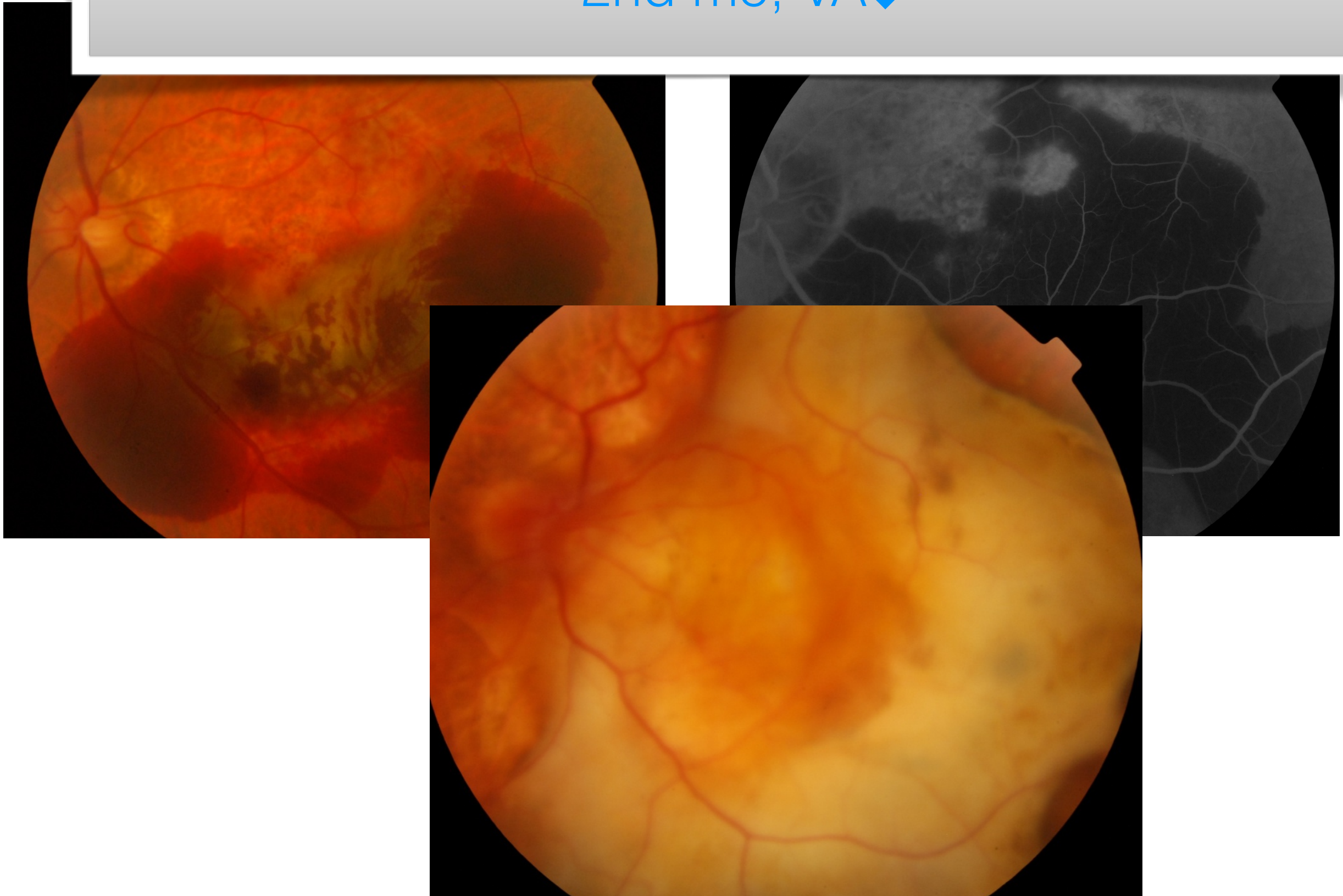
HEMORRHAGIC RESPONSE

1 mo. VA: CF 4m, 2nd Lucentis



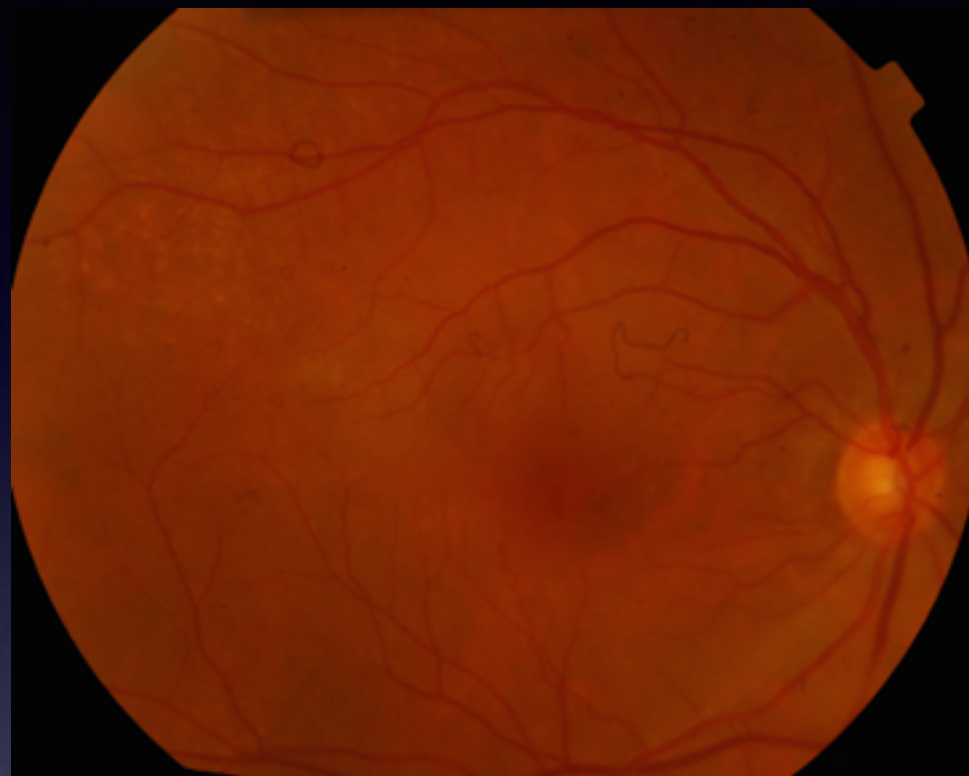
HEMORRHAGIC RESPONSE

2nd mo, VA↓

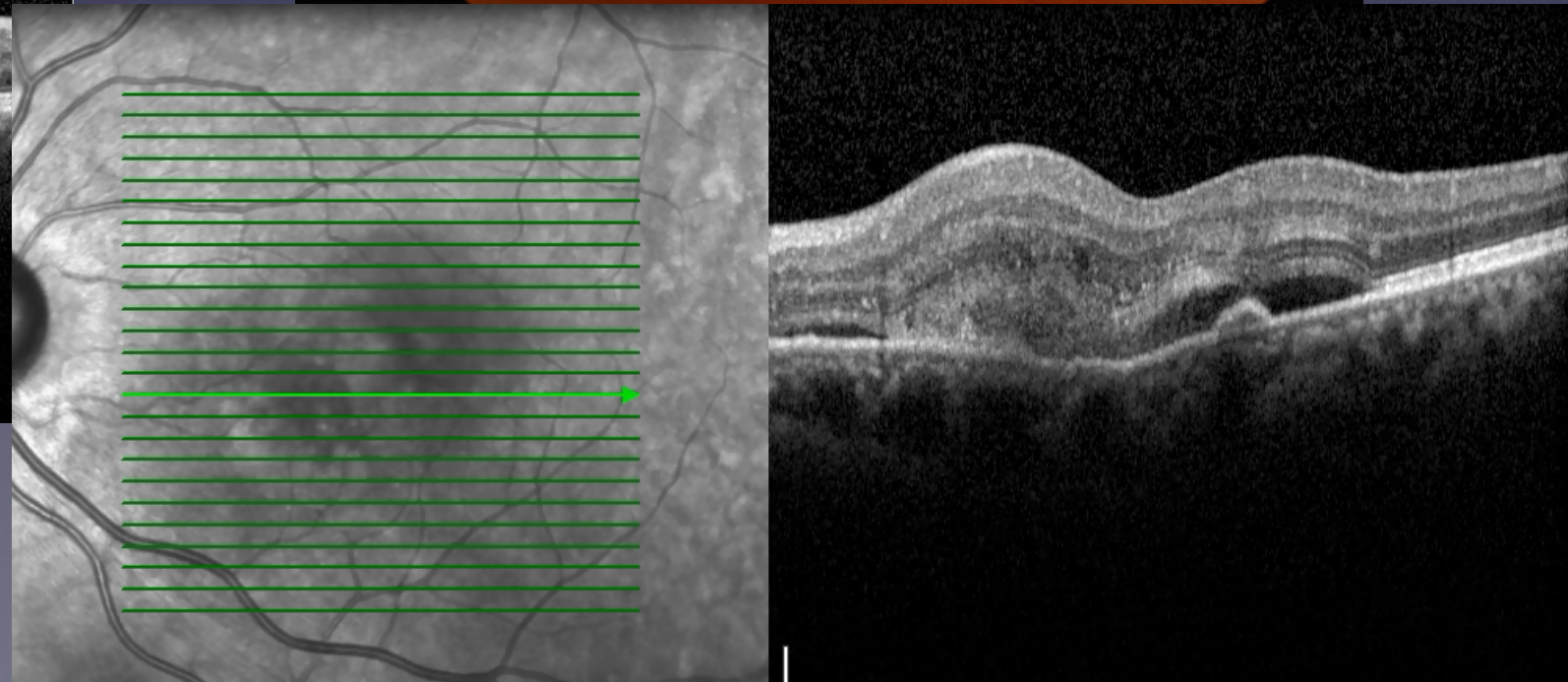
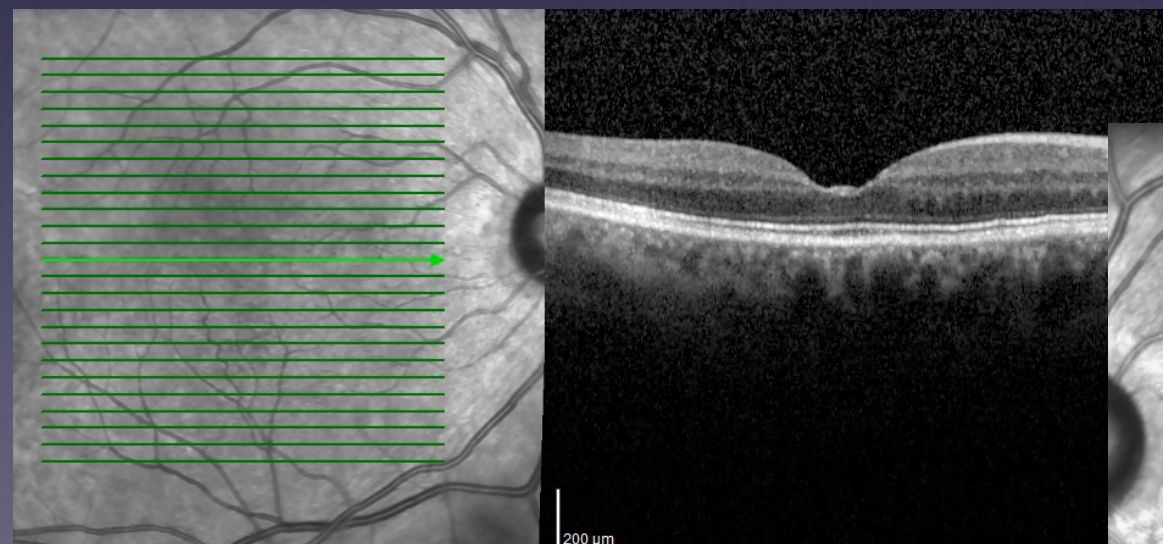
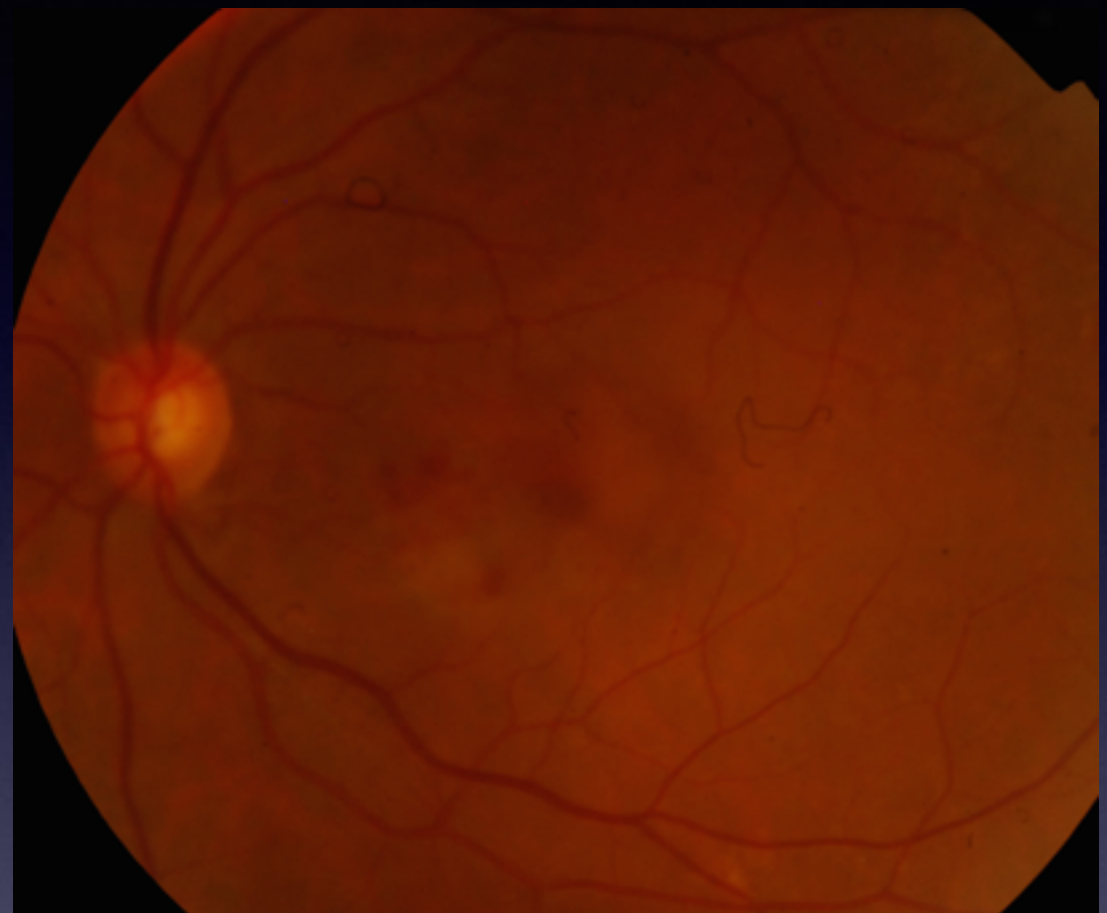


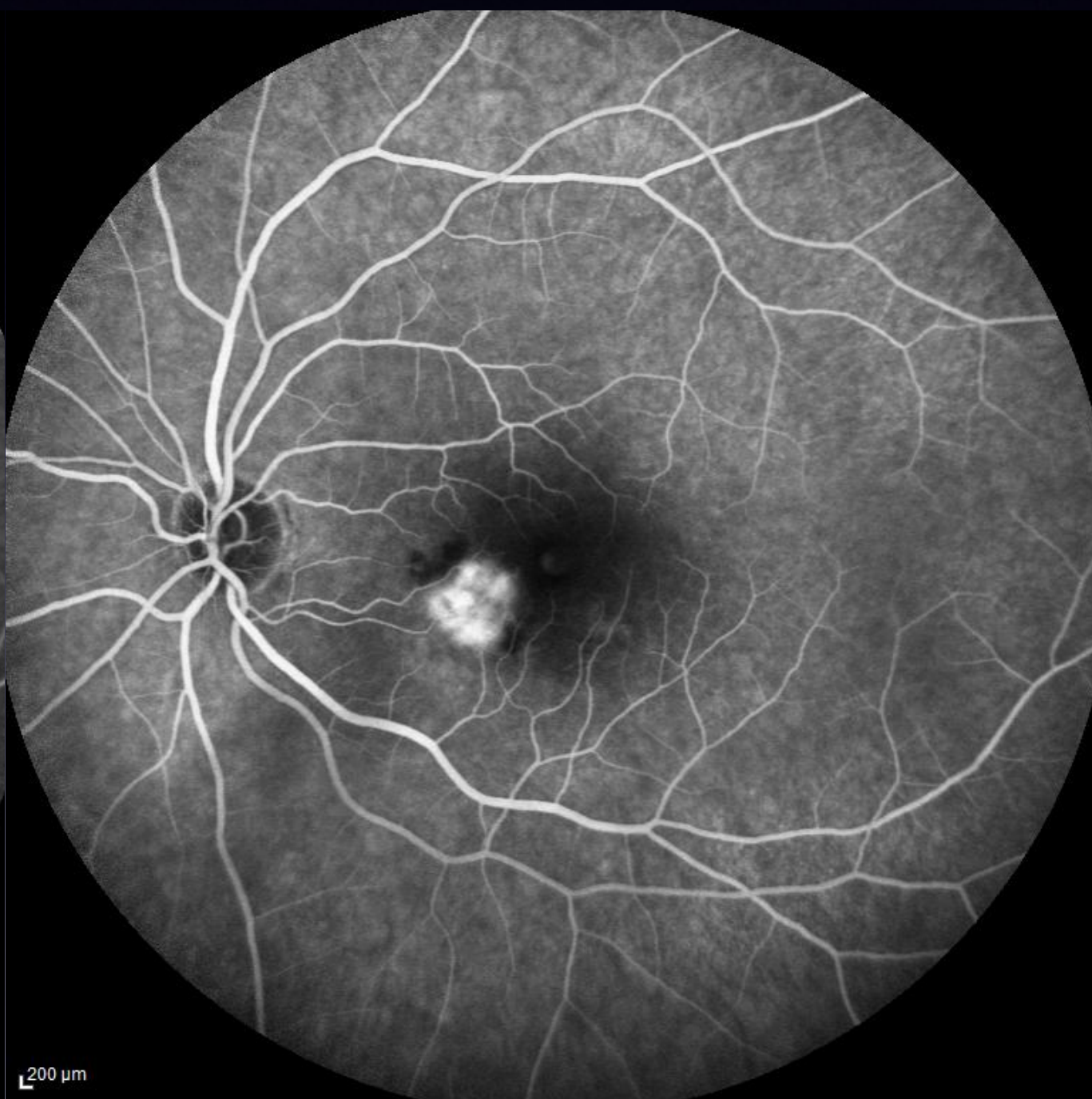
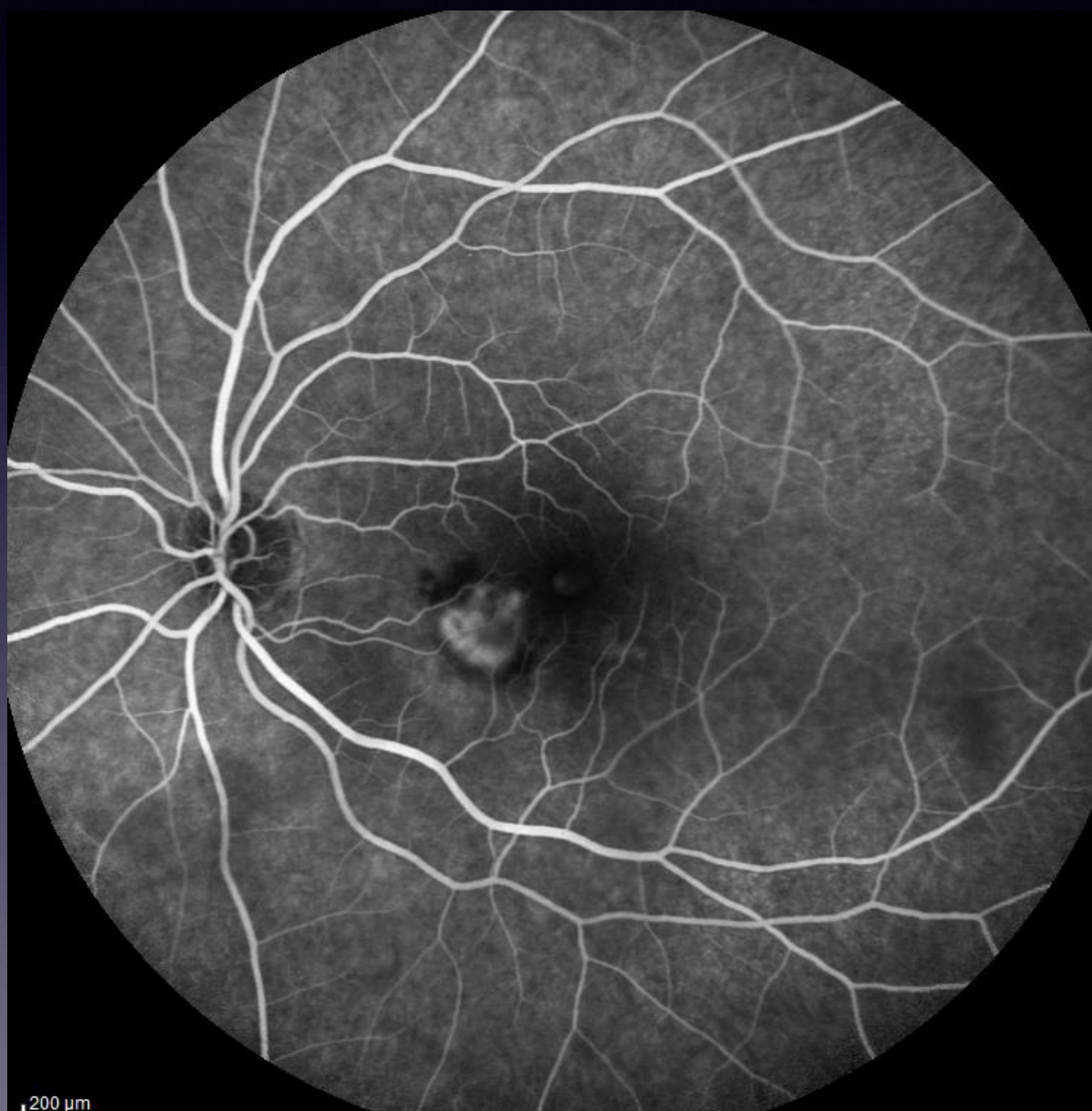
HEMORRHAGIC RESPONSE

SG, 63y, VA: 0.6, Type 2 CNV



11/2013





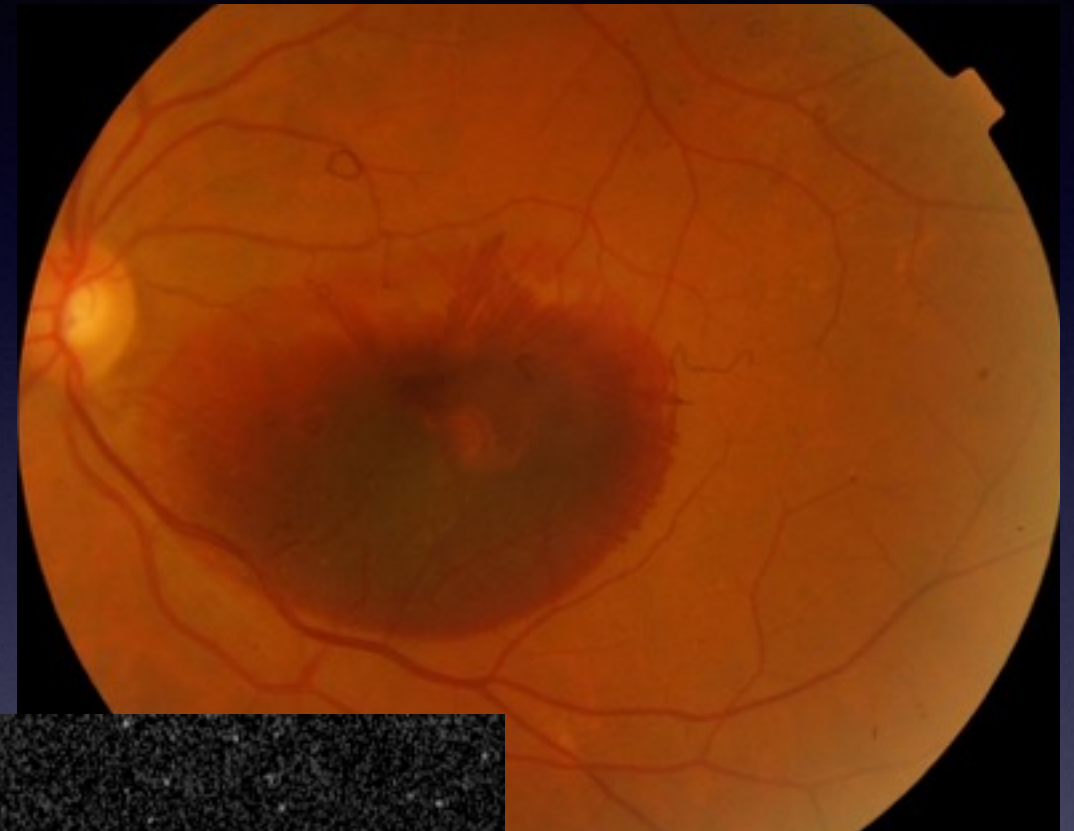
IV Lucentis

HEMORRHAGIC RESPONSE

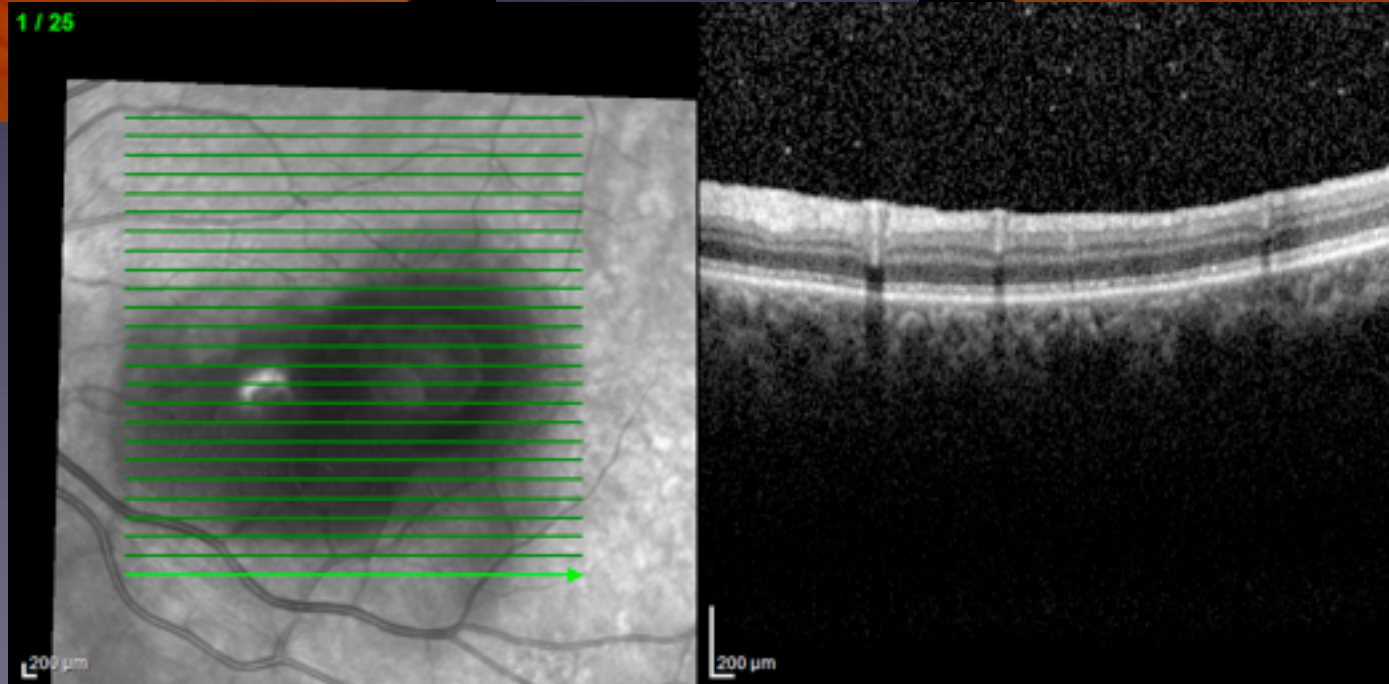
IV Lucentis+tPA+SF6+Face down



→
3 days



12/2013

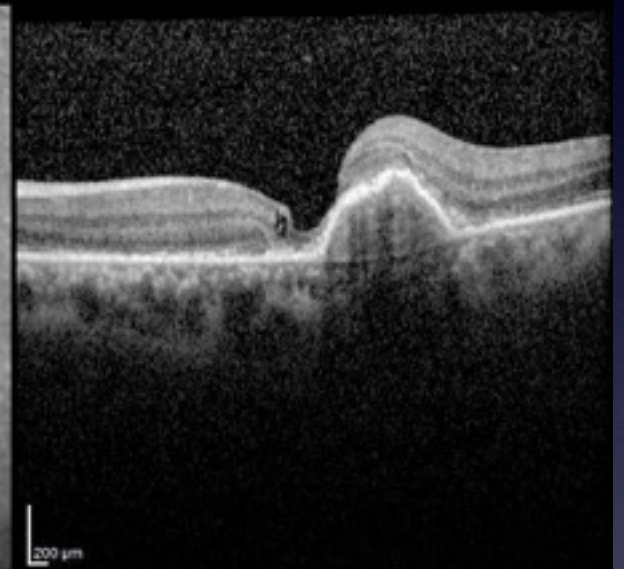
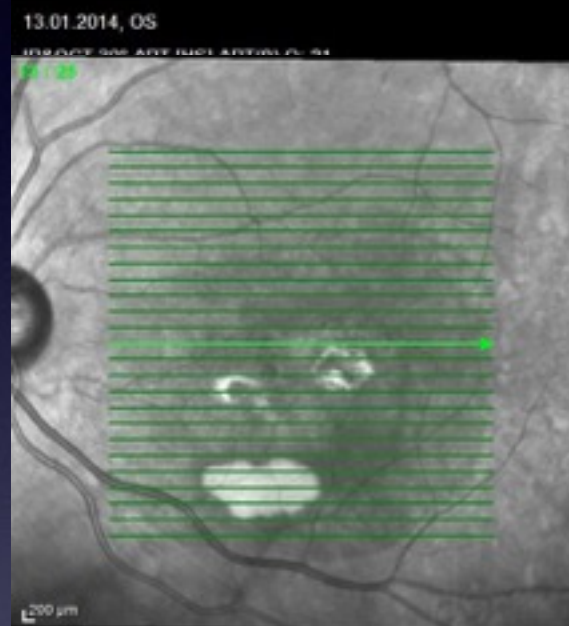
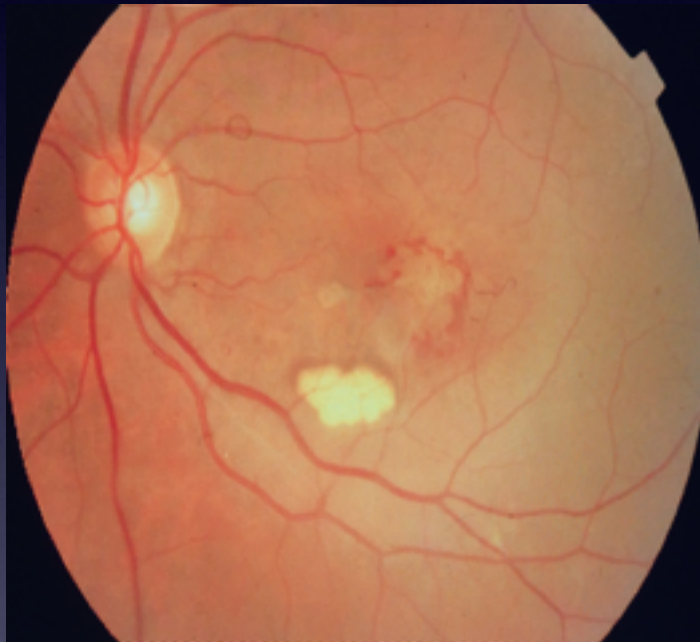
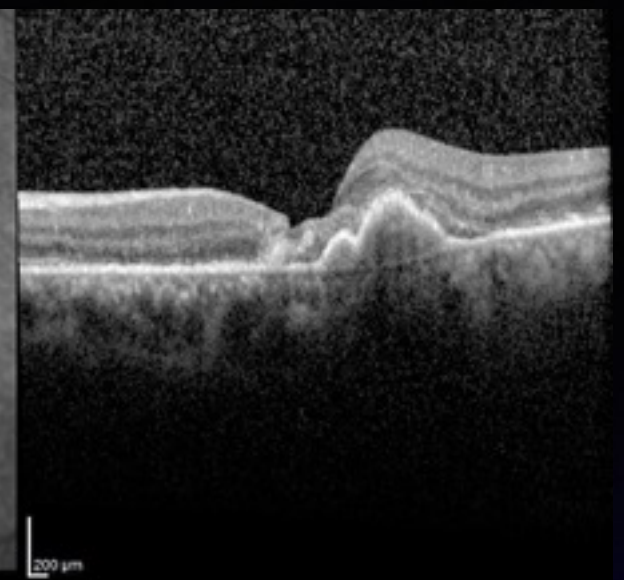
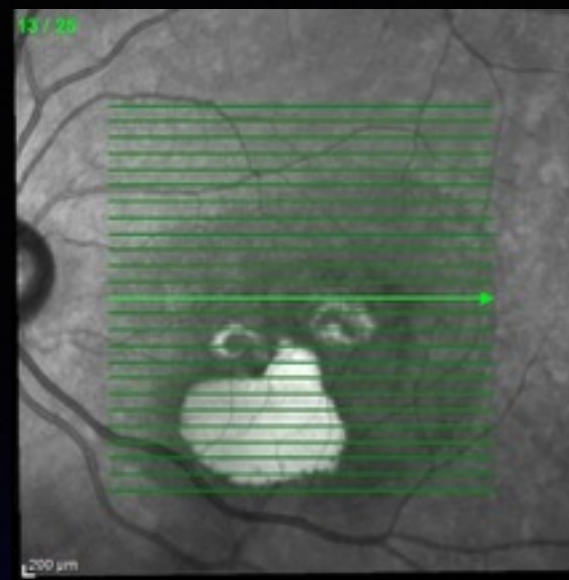
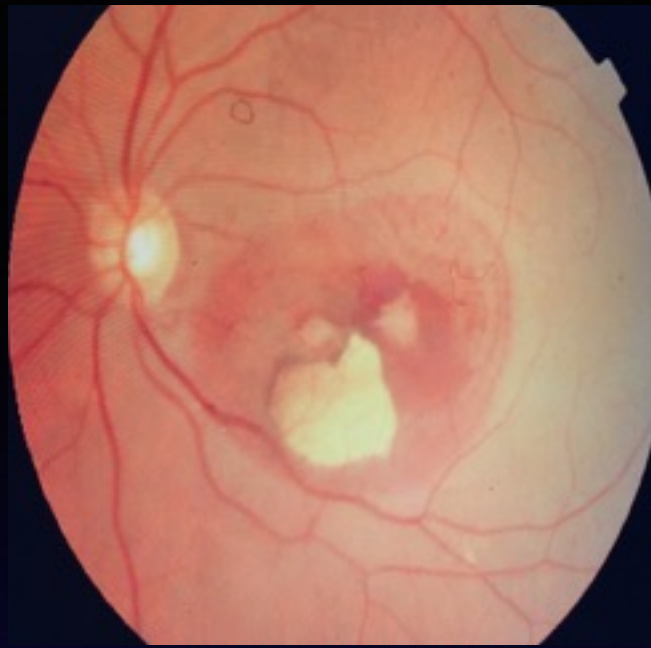


13.12.2013, OS

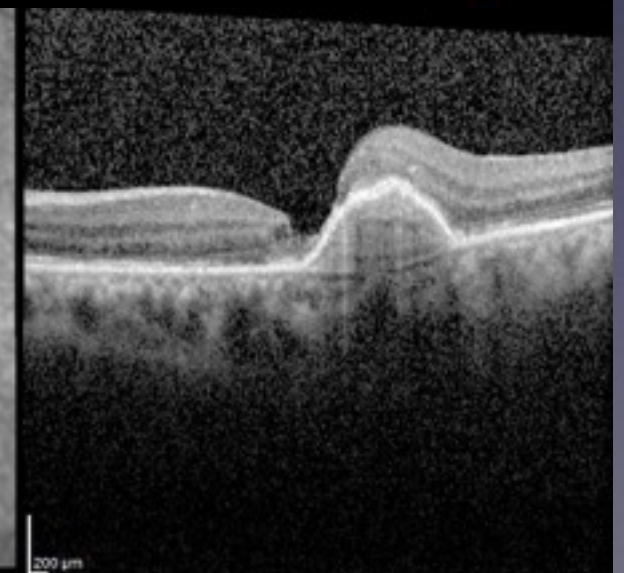
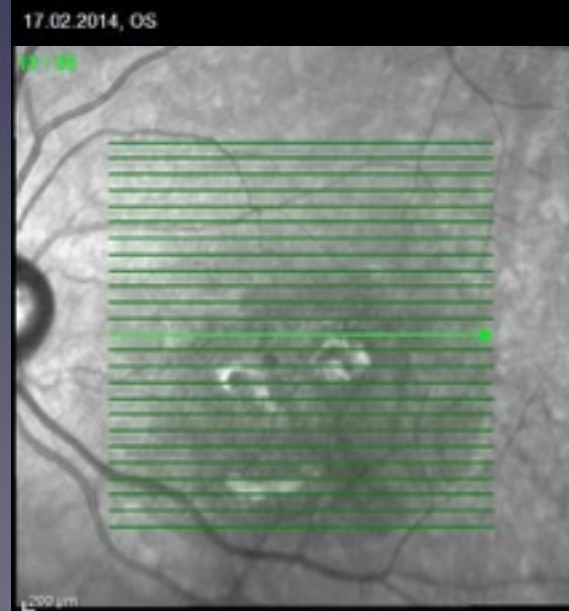
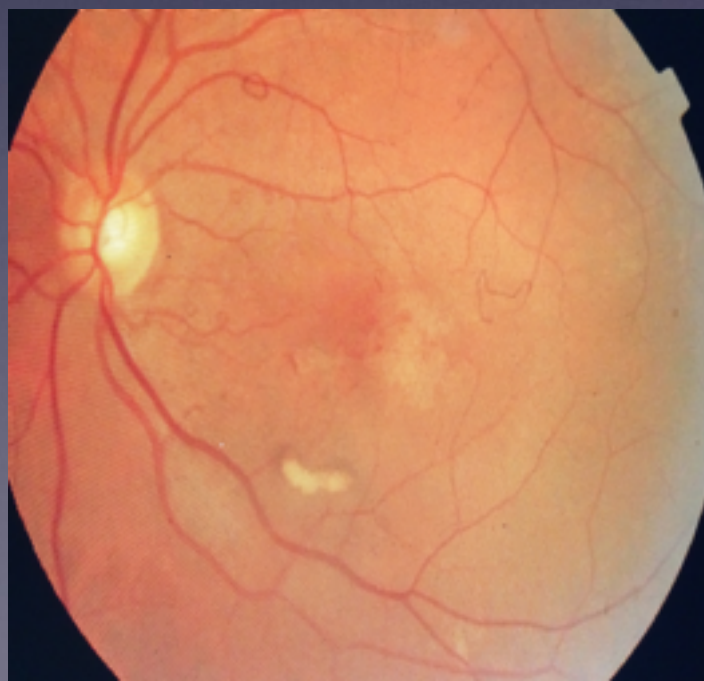
IR&OCT 30° ART [HS] ART(9) Q: 21

HEIDELBERG
engineering

1st mo:
VA: 0.4



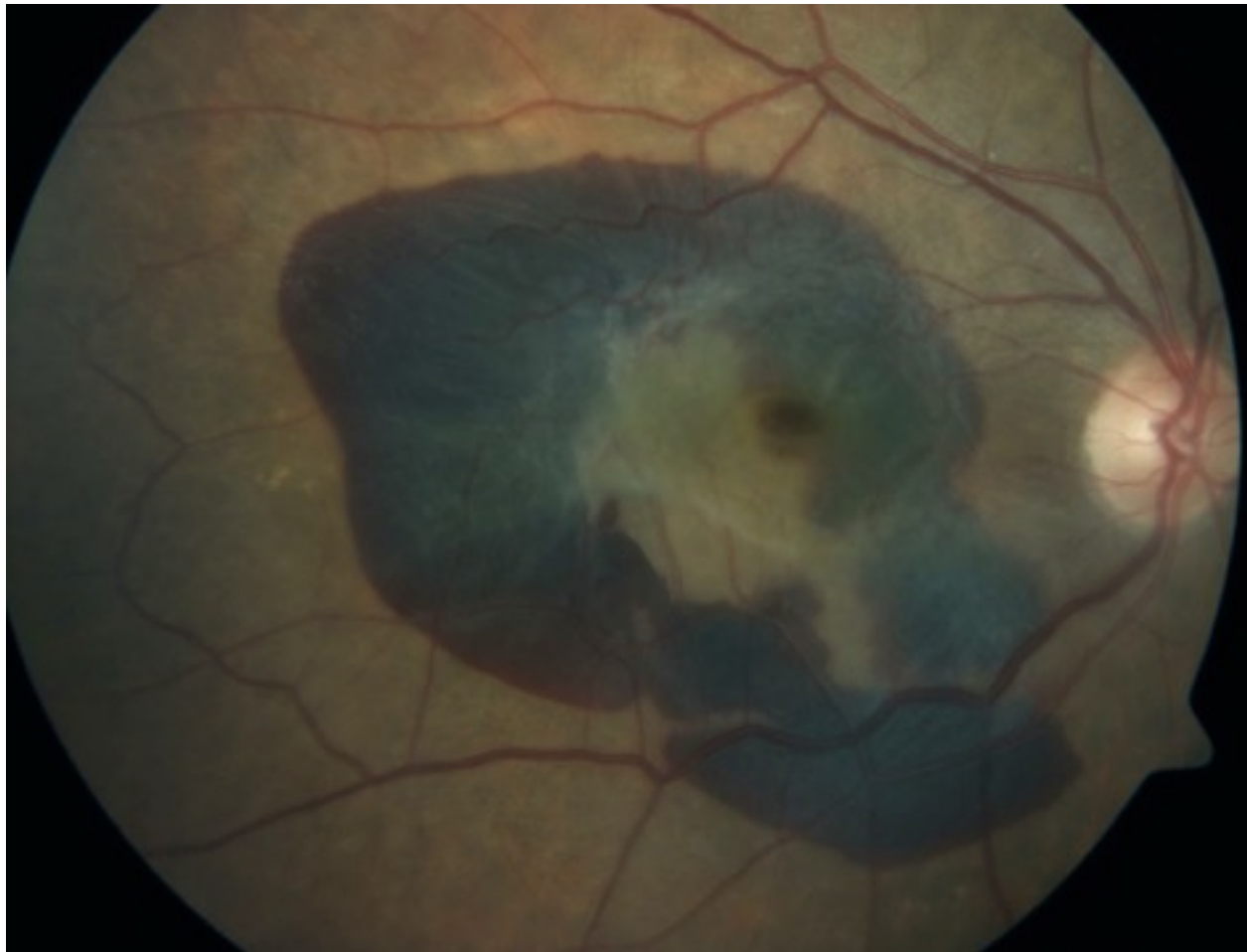
4x Lucentis
VA: 0.7

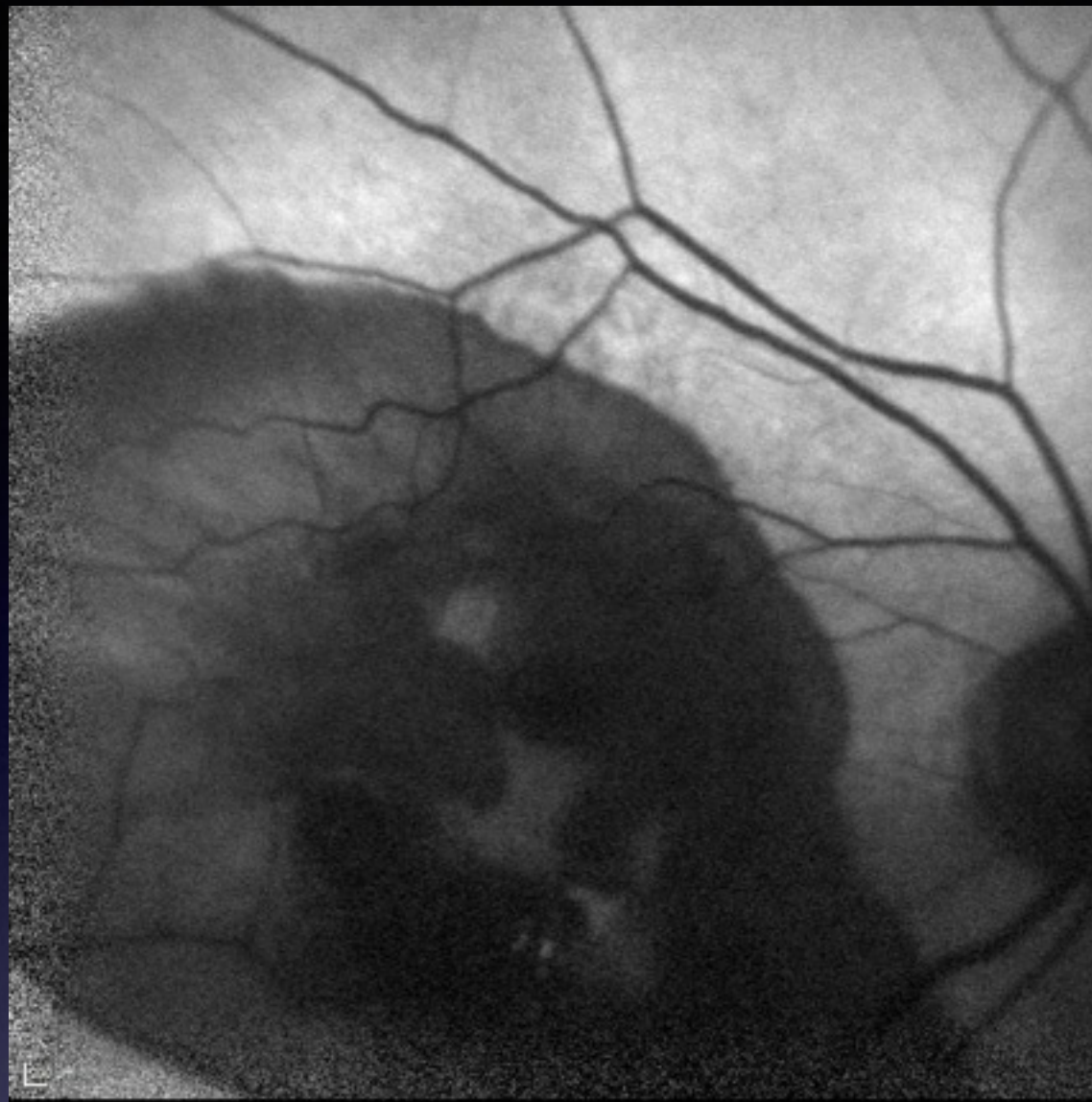


19.03.2014, OS
IR&OCT 30° ART (HS) ART(9) Q: 19

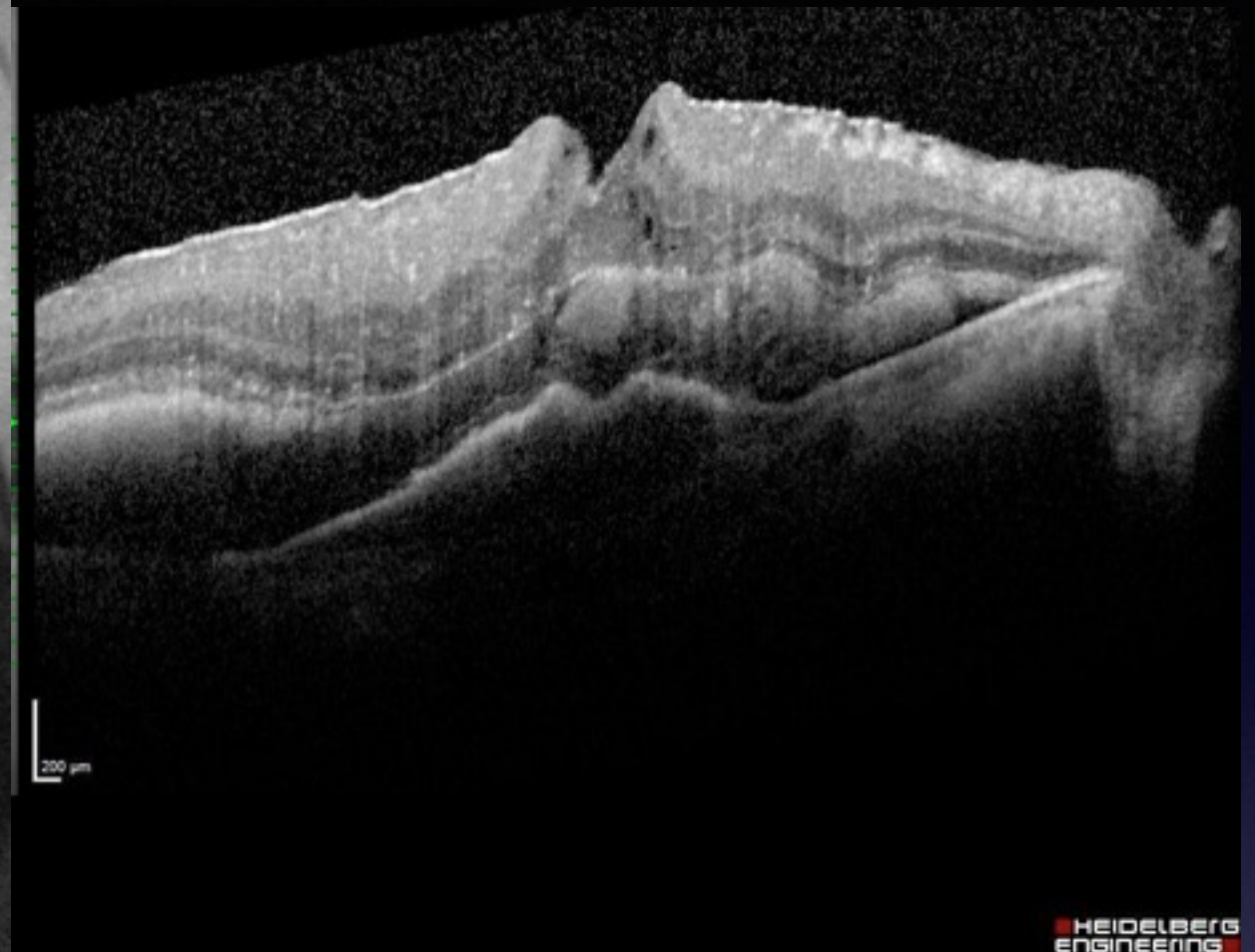
HEMORRHAGIC RESPONSE

NT, 65y, VA: CF 1m, ERM, M. hole

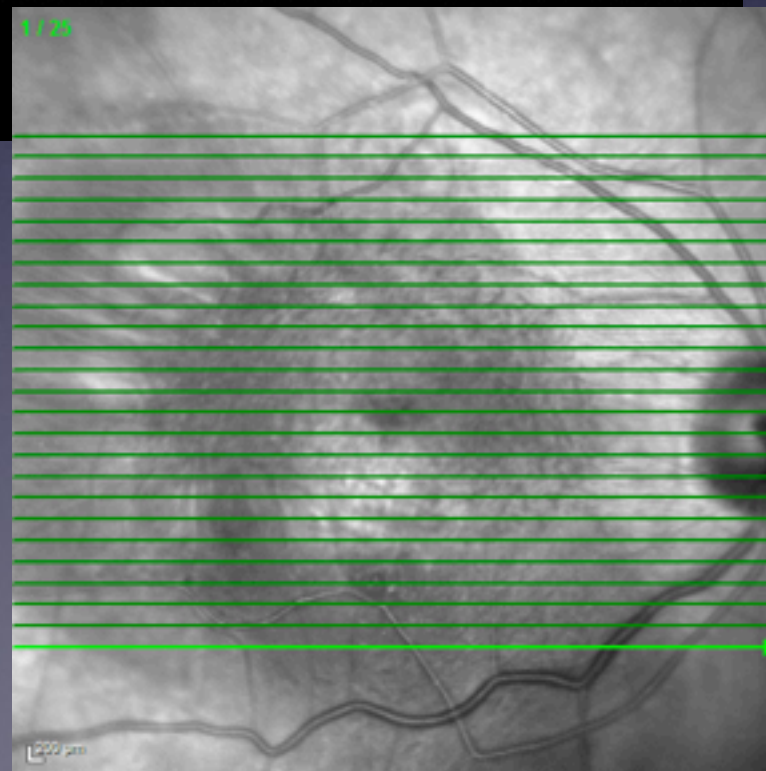




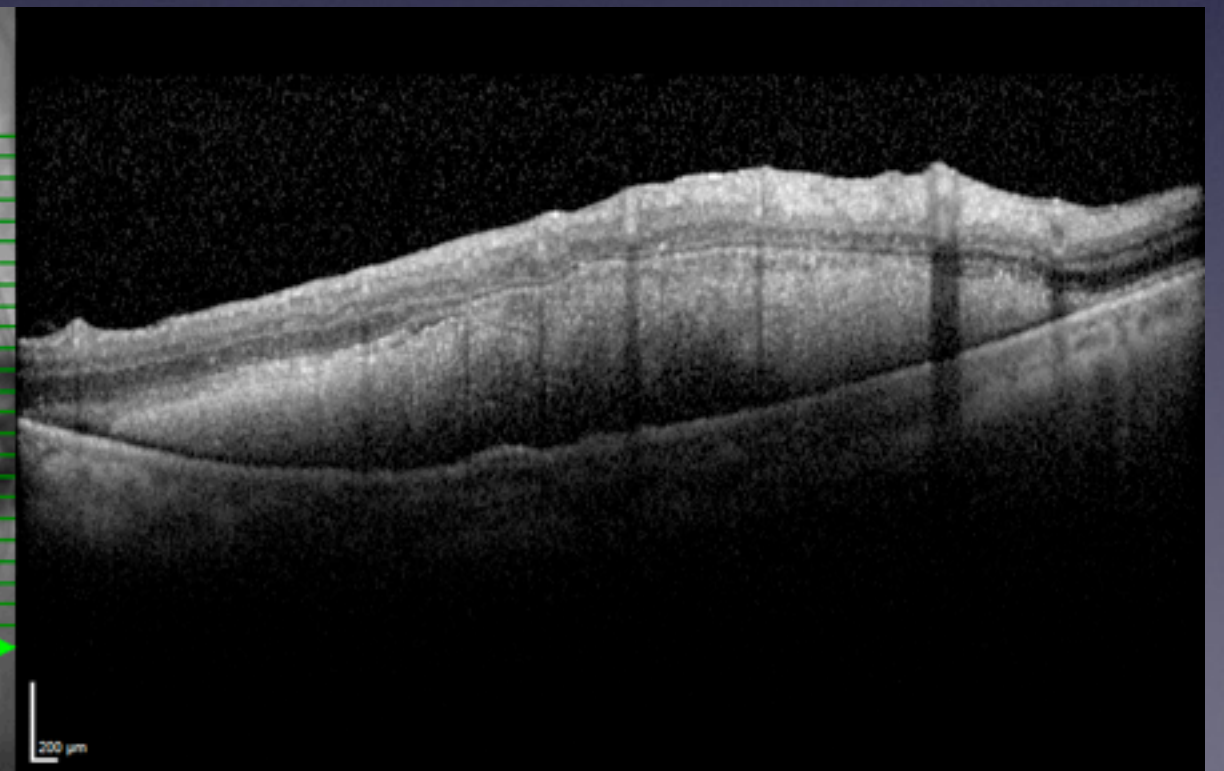
17.3.2014, OD
BAF 30° ART(50)



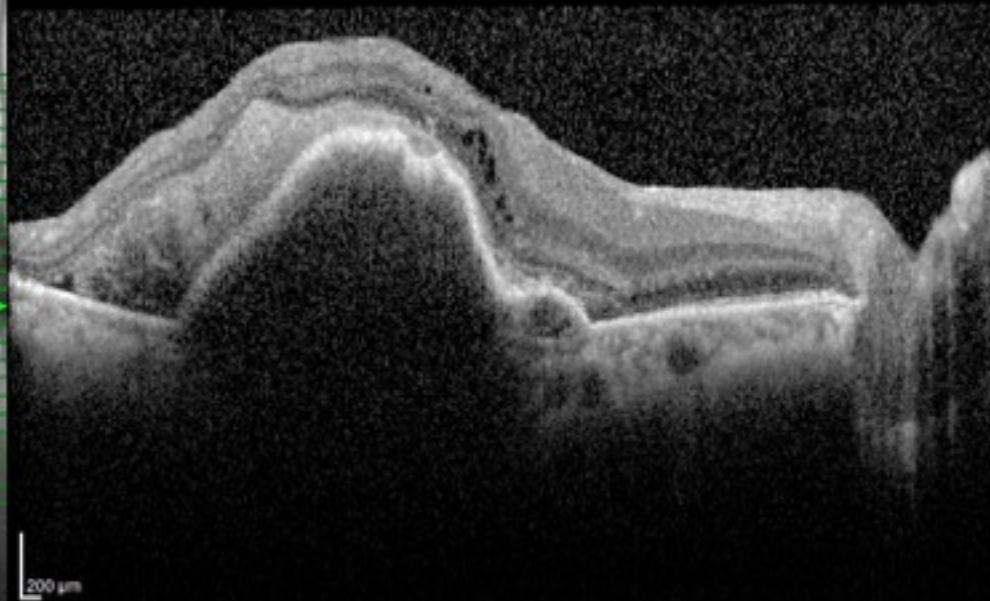
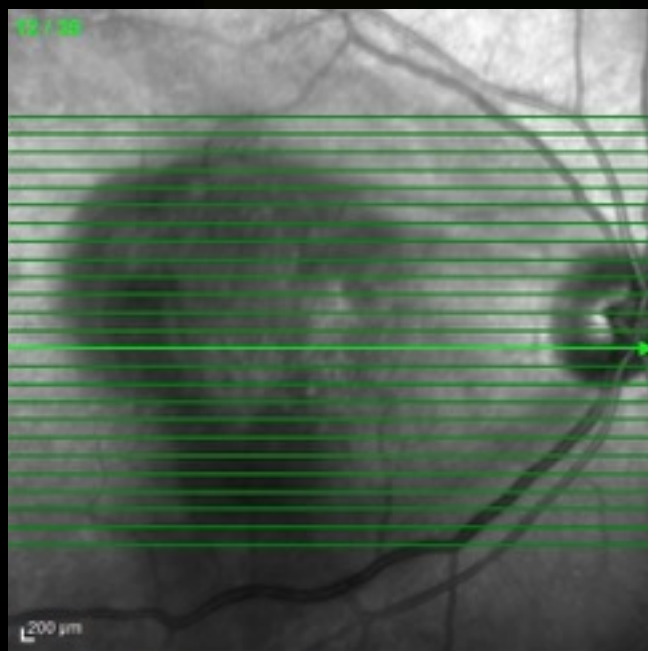
HEIDELBERG
ENGINEERING



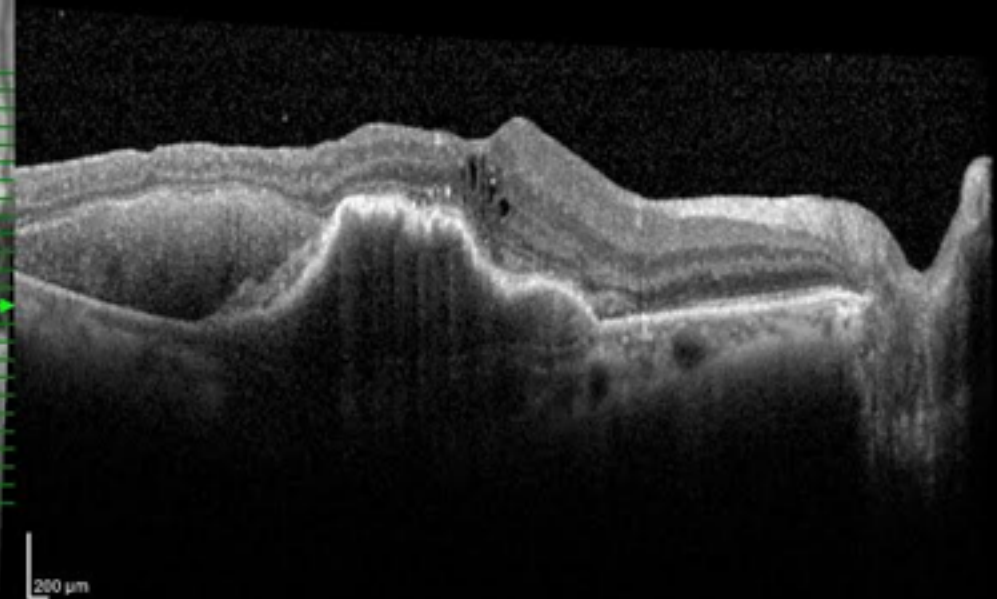
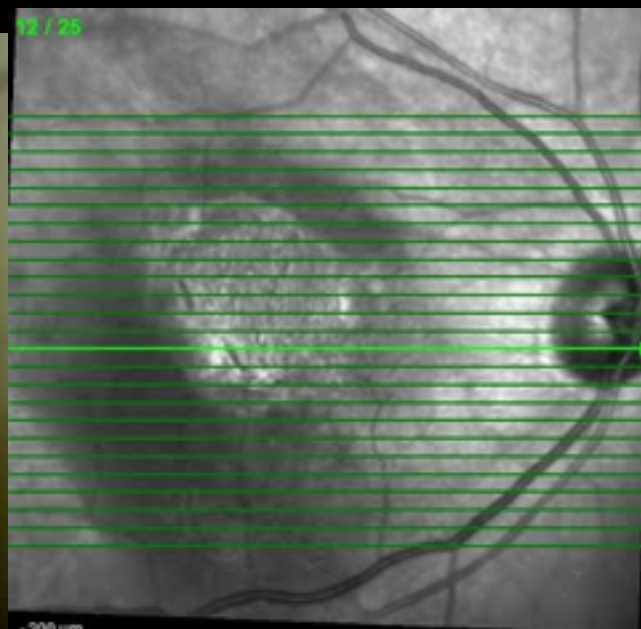
17.3.2014, OD



PPV-MP-ILMP-Subretinal tPA-Gas

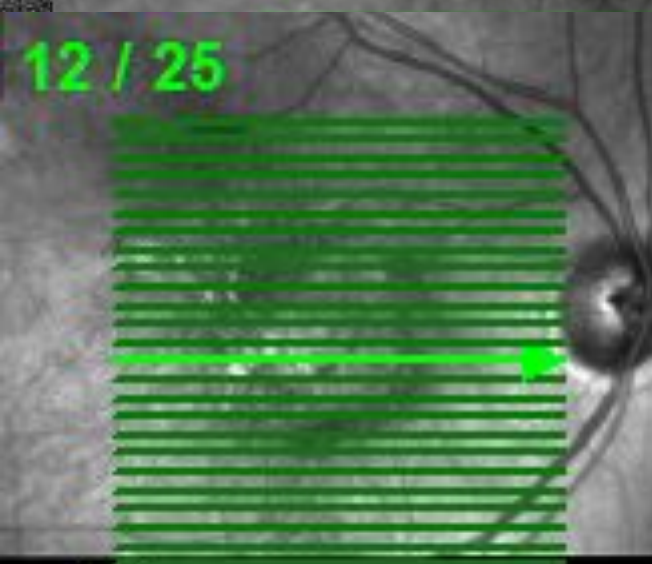
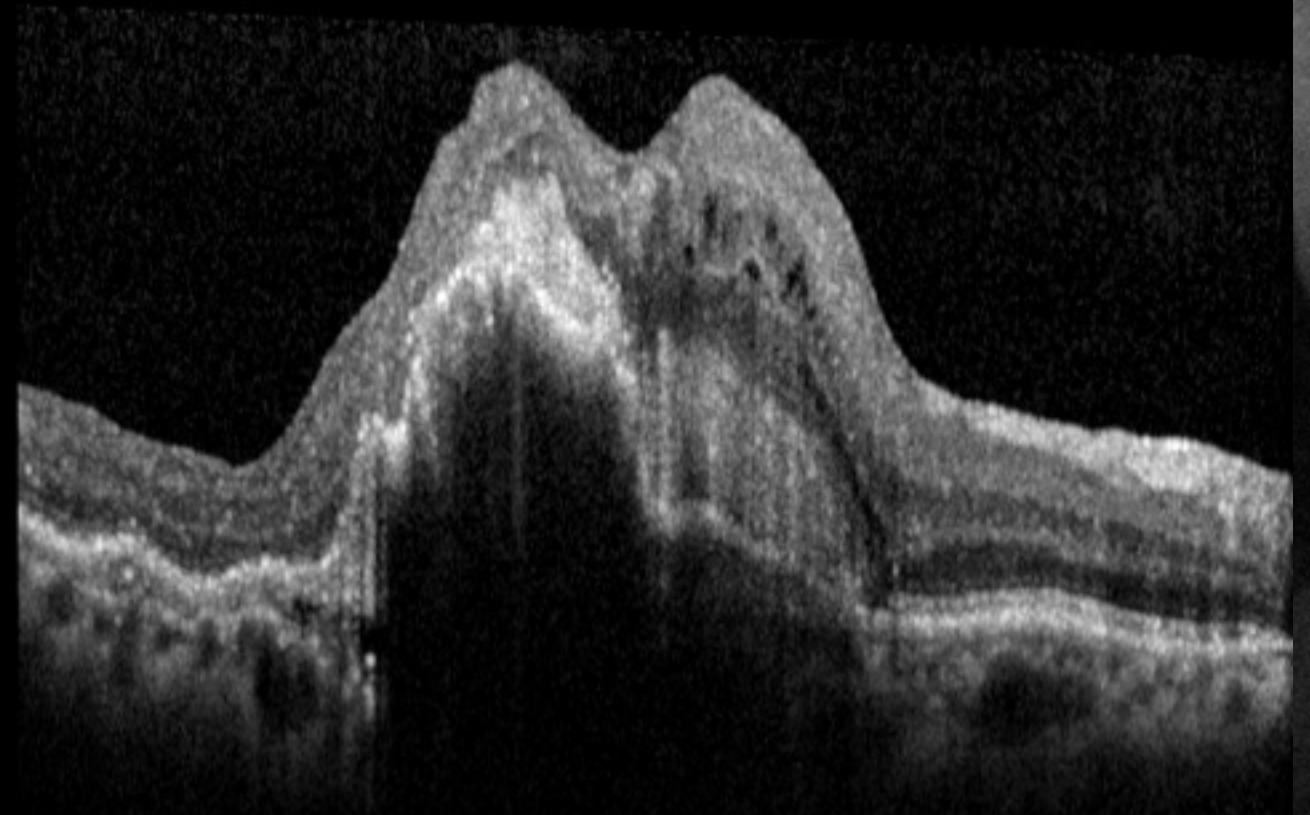
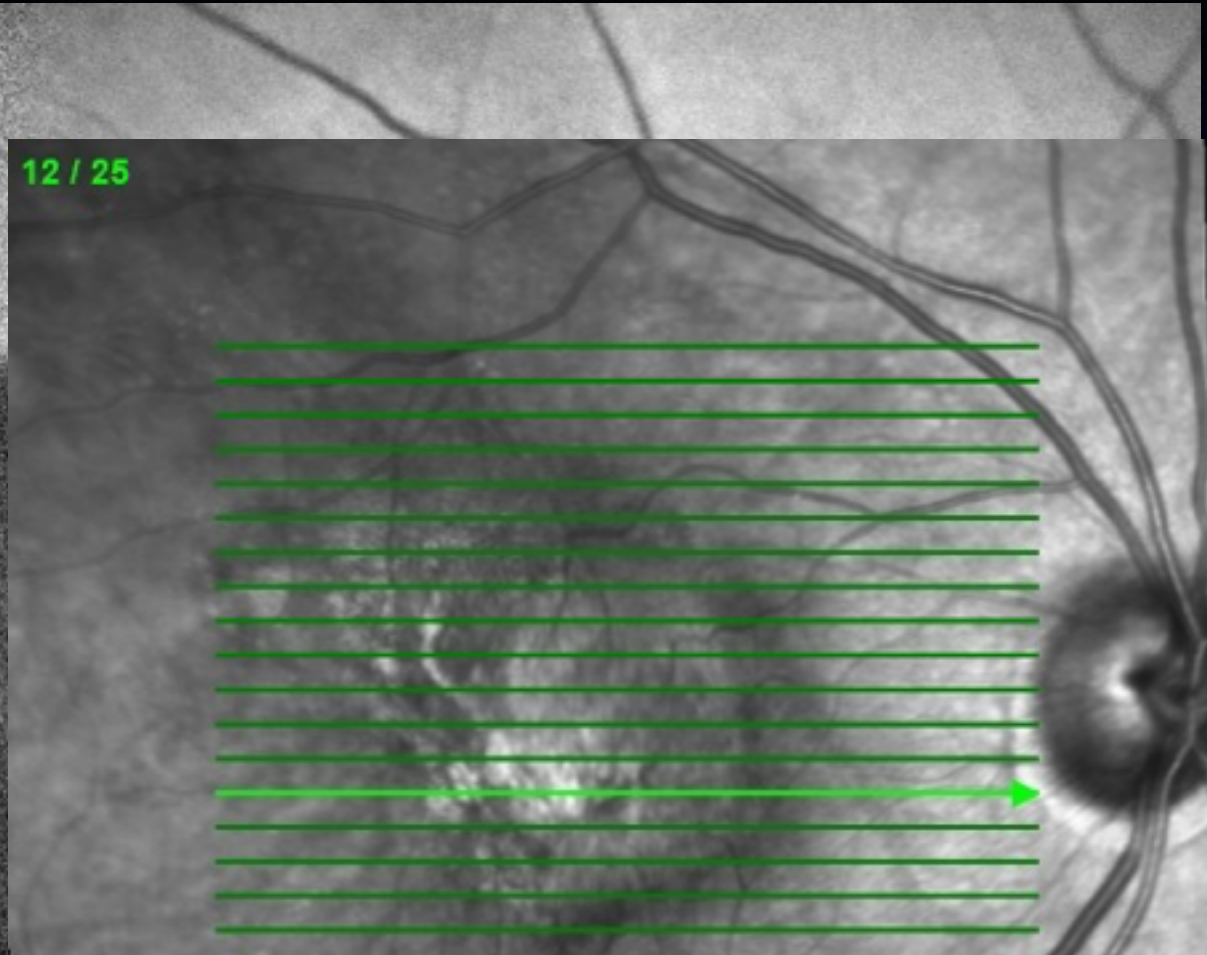


TASBAS, NIGAR, 01.01.1939
28.03.2014, OD
IR&OCT 30° [HS] ART(9) Q. 23

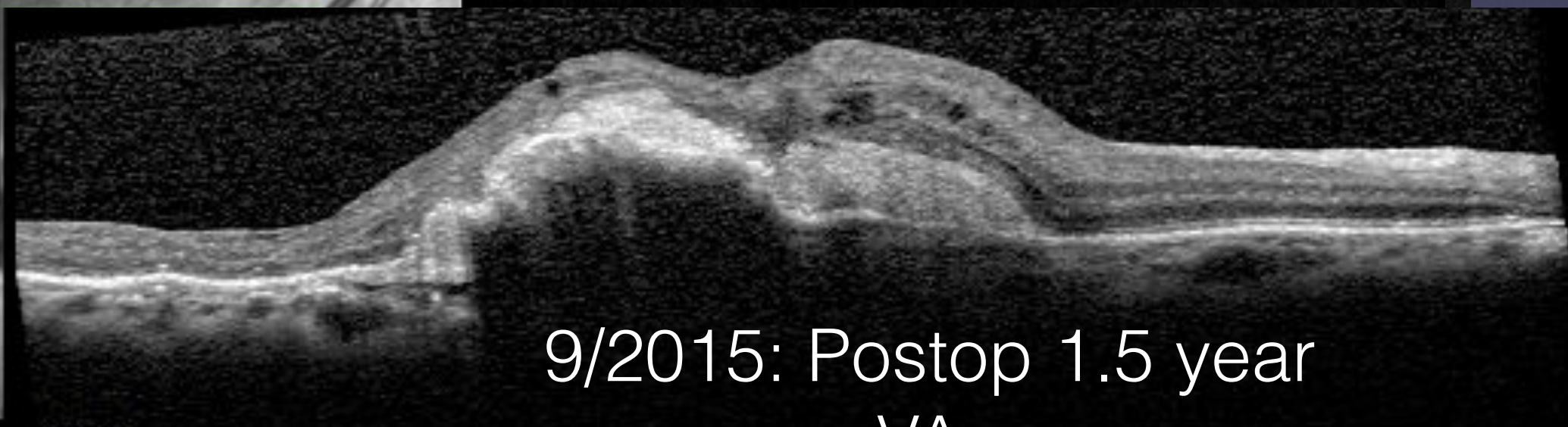


TASBAS, NIGAR, 01.01.1939
15.04.2014, OD
IR&OCT 30° [HS] ART(9) Q. 28

Postop 1st mo VA↑:0.2



200 μ m



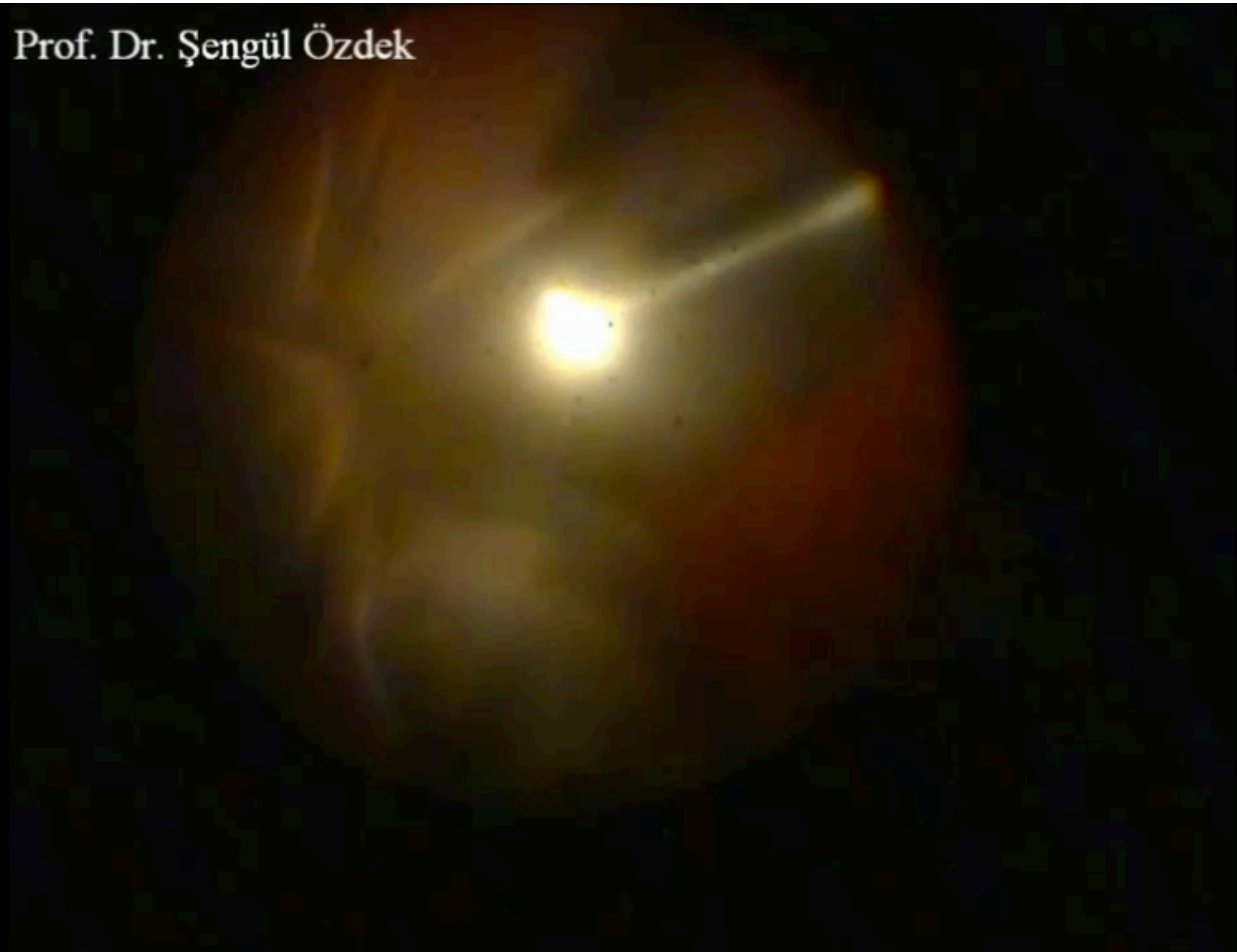
200 μ m

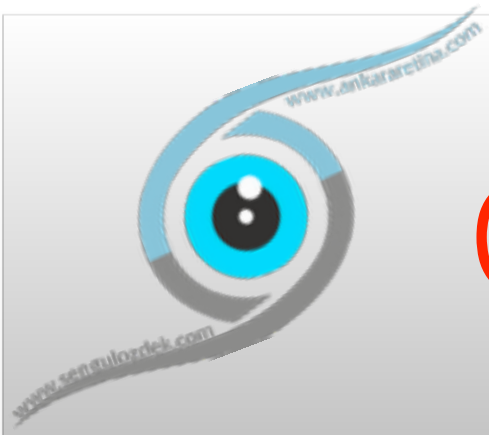
9/2015: Postop 1.5 year
VA:

HEMORRHAGIC RESPONSE

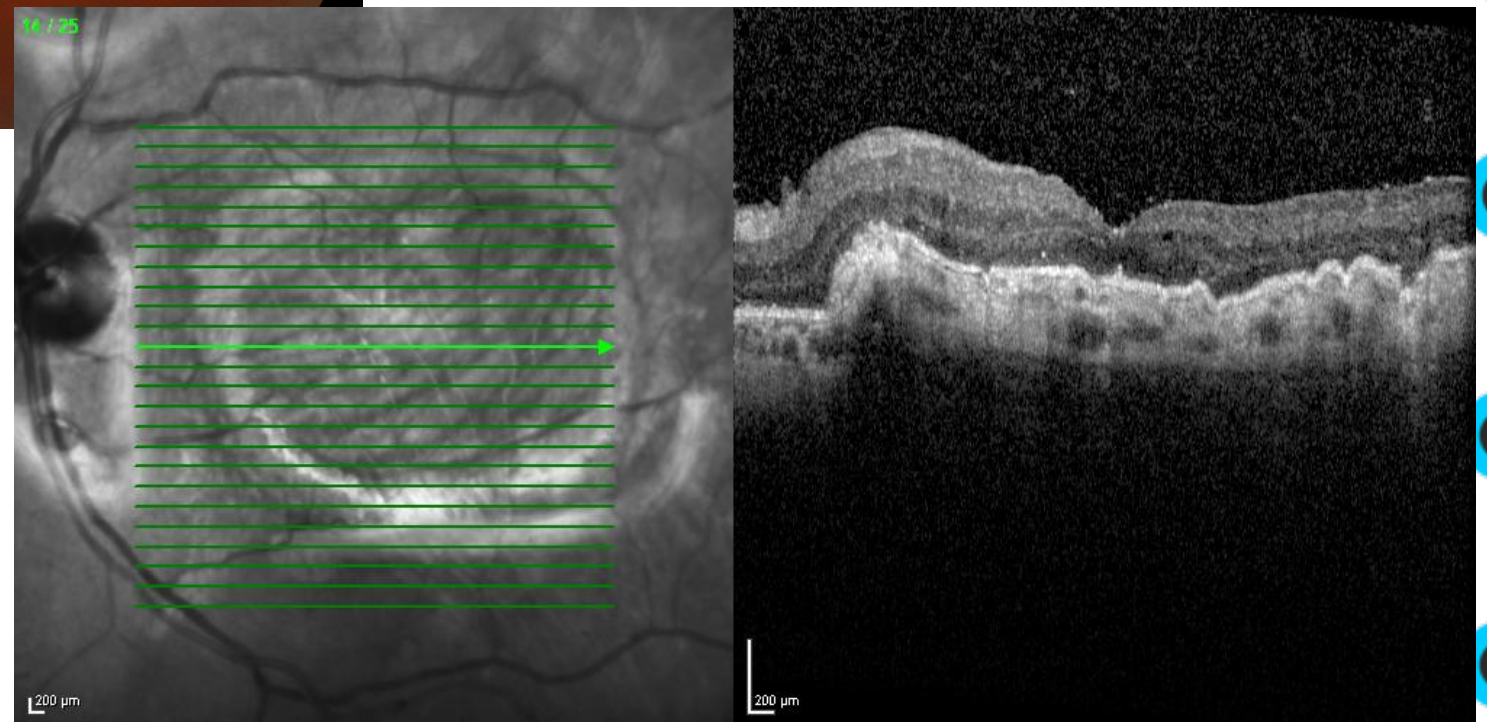
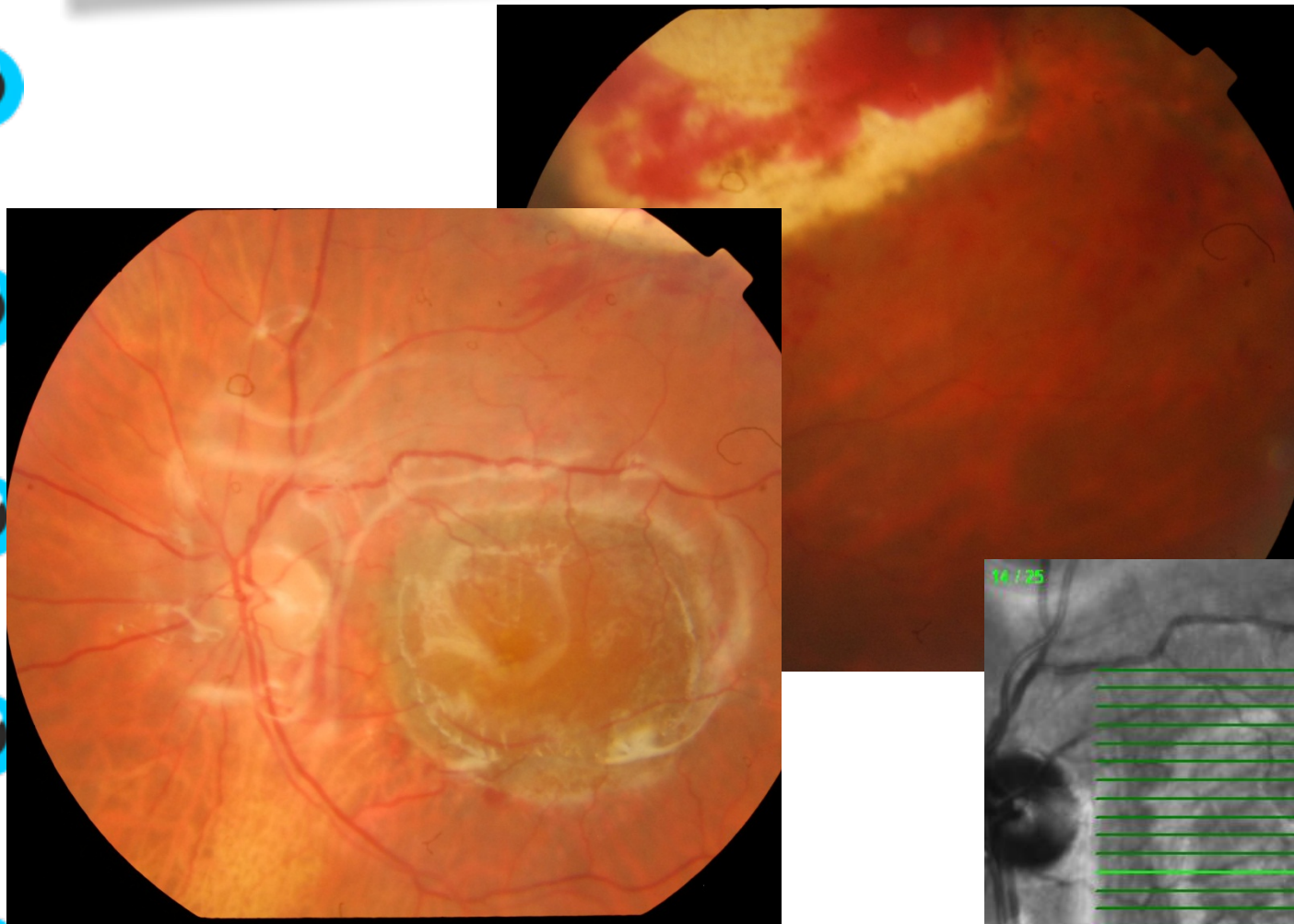
64y, VA: HM (better eye), Hemorrhagic
retinal detachment 2 days ago

Prof. Dr. Şengül Özdek

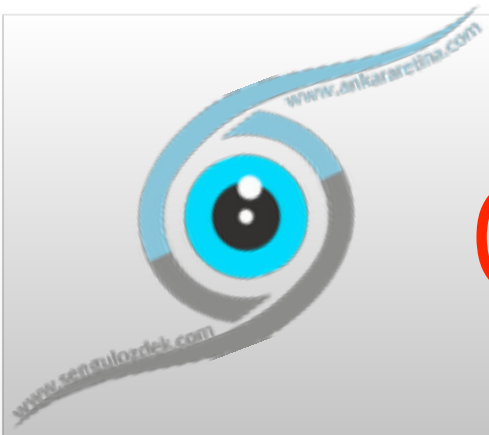




Choroidal patch graft



15.10.2012, OS
IR&OCT 30° ART [HS] ART(9) Q: 24



Choroidal patch graft



VA: 0.4, Can read J1

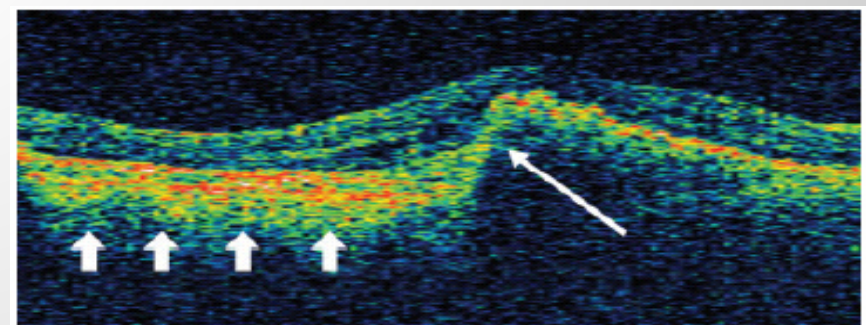
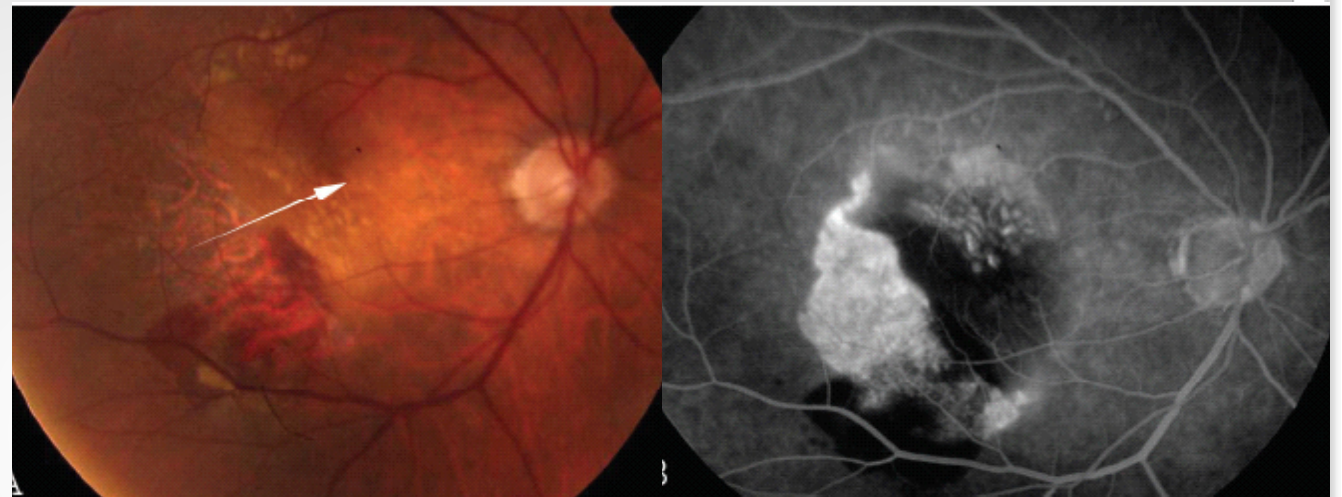
RESISTANCE TO ANTI-VEGF TREATMENT

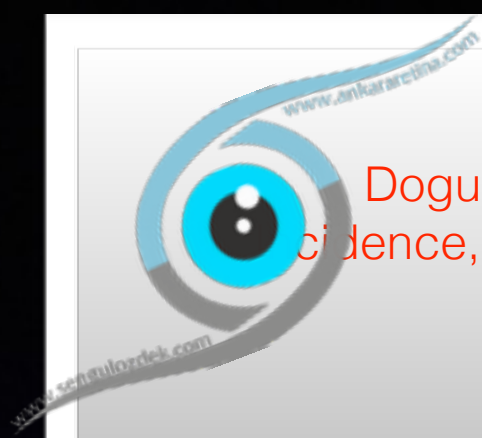
- WRONG DIAGNOSIS (46.2%)
 - PCV, RAP, VITELLIFORM (AOVMD), CSCR
- TACHYPHYLAXIS-TOLERANCE (22%)
- NONRESPONDERS (26.9%)
- **COMPLICATIONS:** RPE tear, atrophy, scarring/fibrosis (11.6%)
- GENETIC BASIS FOR RESISTANCE



ANTI-VEGF TREATMENT COMPLICATIONS

- RPE Tear
- RPE atrophy,
- Scar formation





Doguizi S, **Ozdek S**. PIGMENT EPITHELIAL TEARS ASSOCIATED WITH ANTI-VEGF THERAPY: Incidence, Long-term Visual Outcome, and Relationship with Pigment Epithelial Detachment in Age-related Macular Degeneration. **Retina**. 2014 Jun;34(6):1156-62.

PIGMENT EPITHELIAL TEARS ASSOCIATED WITH ANTI-VEGF THERAPY

Incidence, Long-term Visual Outcome, and Relationship with Pigment Epithelial Detachment in Age-related Macular Degeneration

SIBEL DOGUIZI, MD, SENGUL OZDEK, MD

Purpose: To evaluate the prevalence of retinal pigment epithelium (RPE) tears associated with anti-VEGF therapy and its relation with retinal pigment epithelial detachment (PED).

Methods: A total of 226 patients with exudative age-related macular degeneration treated with intravitreal anti-VEGF were included retrospectively in the study. The presence of RPE tears; the effect of the presence, height, and duration of PED on the rate of RPE tears; and change in visual acuity during follow-up were recorded.

Results: Among 226 study patients, 28 (12.3%) had RPE tears. The RPE tear rate was significantly higher in patients with vascularized PED (vPED) than in those without PED (19.7% vs. 2.1%; $P < 0.001$). The change in visual acuity after the formation of RPE tear was not statistically significant (on logMAR scale: 0.92 ± 0.49 initially, 0.89 ± 0.41 after the RPE tear, 0.96 ± 0.45 at the last follow-up; $P = 0.613$). Pigment epithelial detachment height $>580 \mu\text{m}$ (odds ratio = 69.4; 95% confidence interval = 16.7–288.1) and PED duration ≤ 4.5 months (odds ratio = 166.7; 95% confidence interval = 15.2–1000) were found to be significant risk factors for RPE tear formation.

Conclusion: The RPE tears are not infrequent among eyes treated with intravitreal anti-VEGFs. The presence, increased height, and shorter duration of vPED are potential risk factors for RPE tears associated with anti-VEGF therapy.

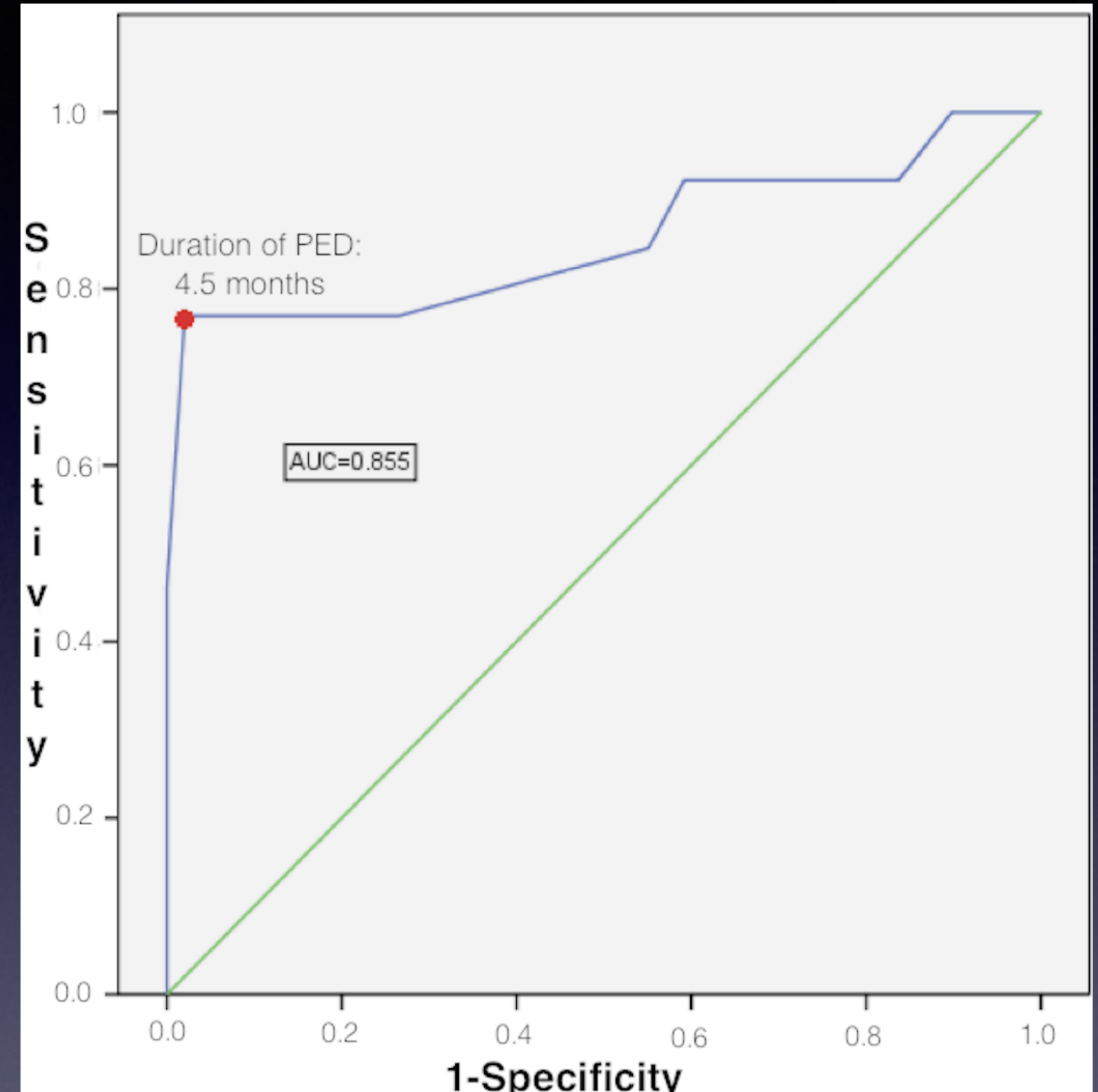
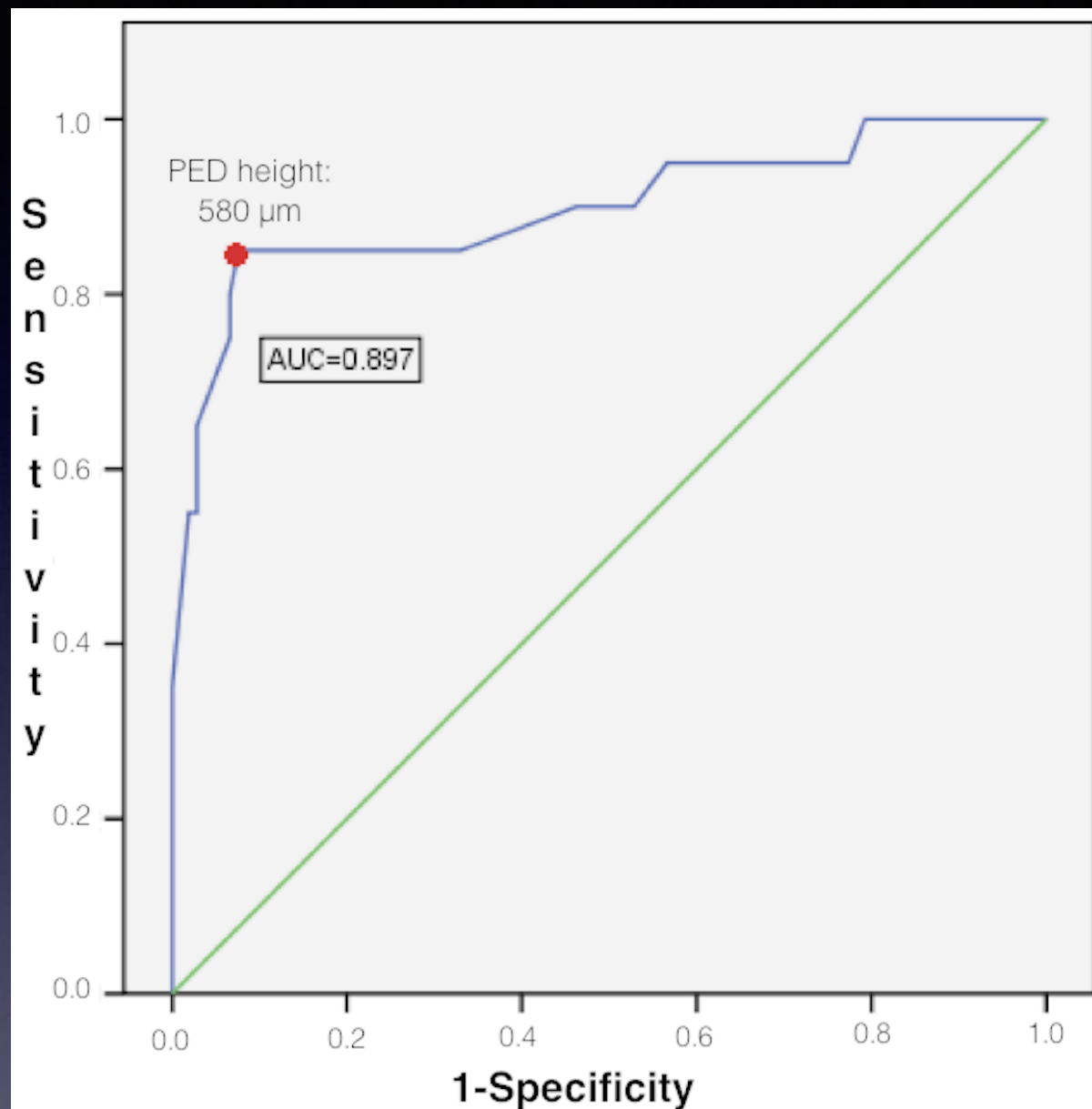
RETINA 0:1–7, 2013

ANTI-VEGF TREATMENT COMPLICATIONS

RPE TEAR

- Retrospective analysis of 226 patients with neovascular ARMD treated with anti-VEGF
- The rate of RPE tears; 12.3%
- The rate in patients with PED 19.7%
- The rate in patients without PED 2.1%, ($p < 0.001$).

PED Size&Duration-RPE tear



PED height $>580 \mu\text{m}$, and PED duration ≤ 4.5 months were significant risk factors for RPE tear formation.

*PED duration predicts RPE tear risk with 77% sensitivity and 98% specificity.

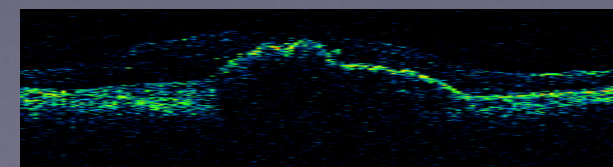
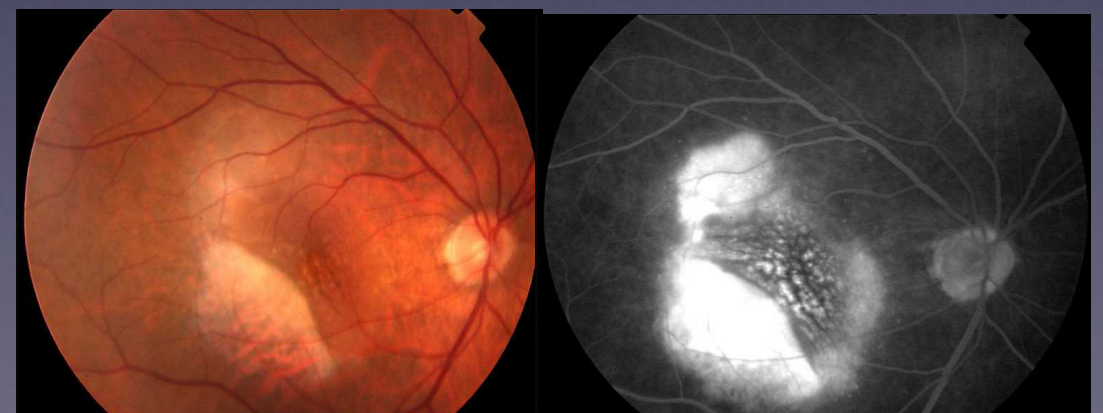
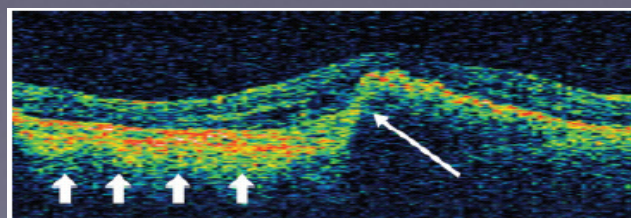
*PED height predicts RPE tear risk with 85% sensitivity and 92% specificity

Duration of PED

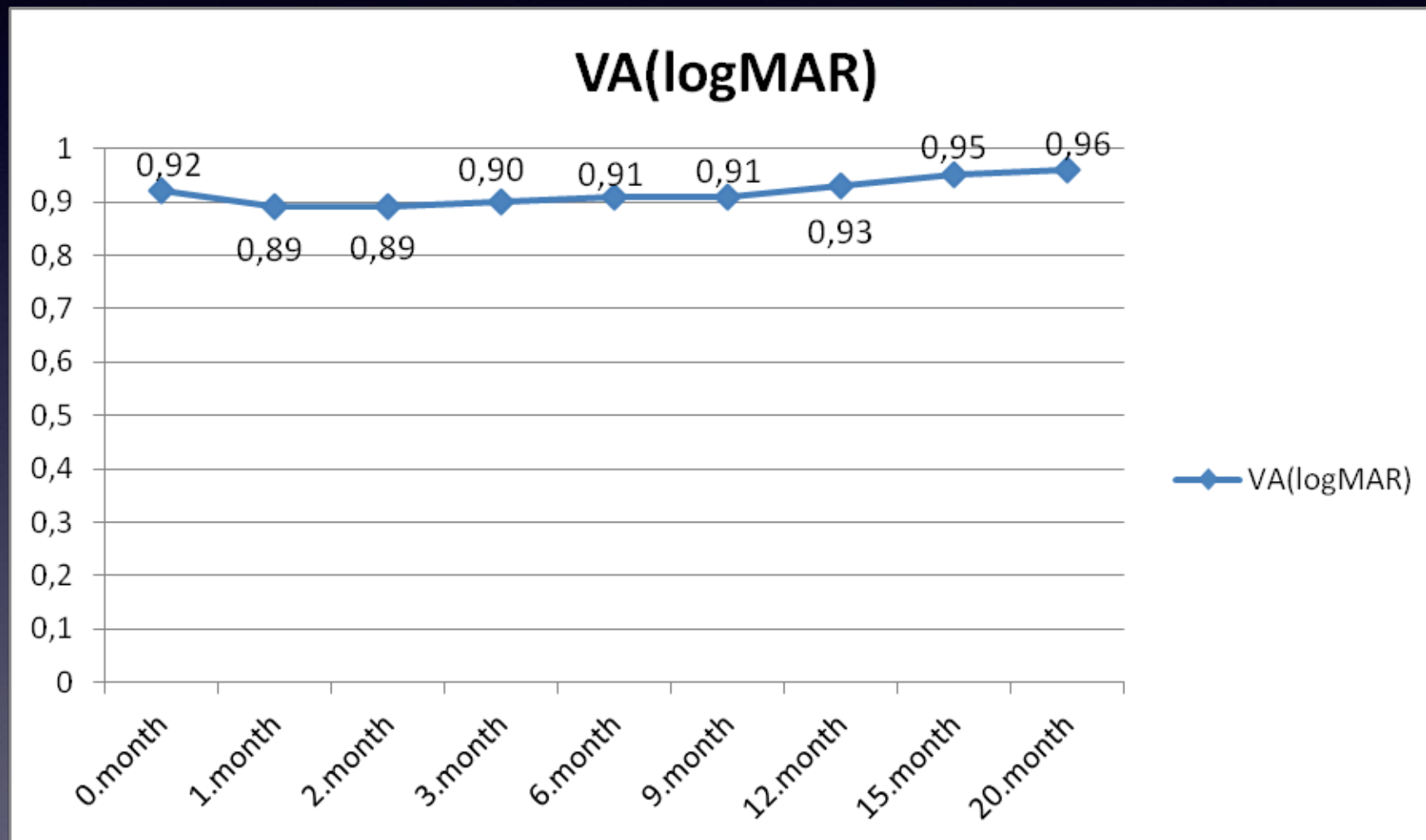
- The first study demonstrating an inverse relationship bw the duration of PED and RPE tear formation
- The neovascular process is fresh, with immature vessels.
- More susceptible to anti-VEGFs,
- Response to anti-VEGF therapy more dramatic
- Contraction of CNV.....RPE TEAR!

PROGNOSIS

- The visual prognosis of RPE tears was not so guarded (parallel to the literature).
- Major determinant factor for the poorer visual prognosis: foveal involvement with RPE tear resulting in an RPE-free central retina.

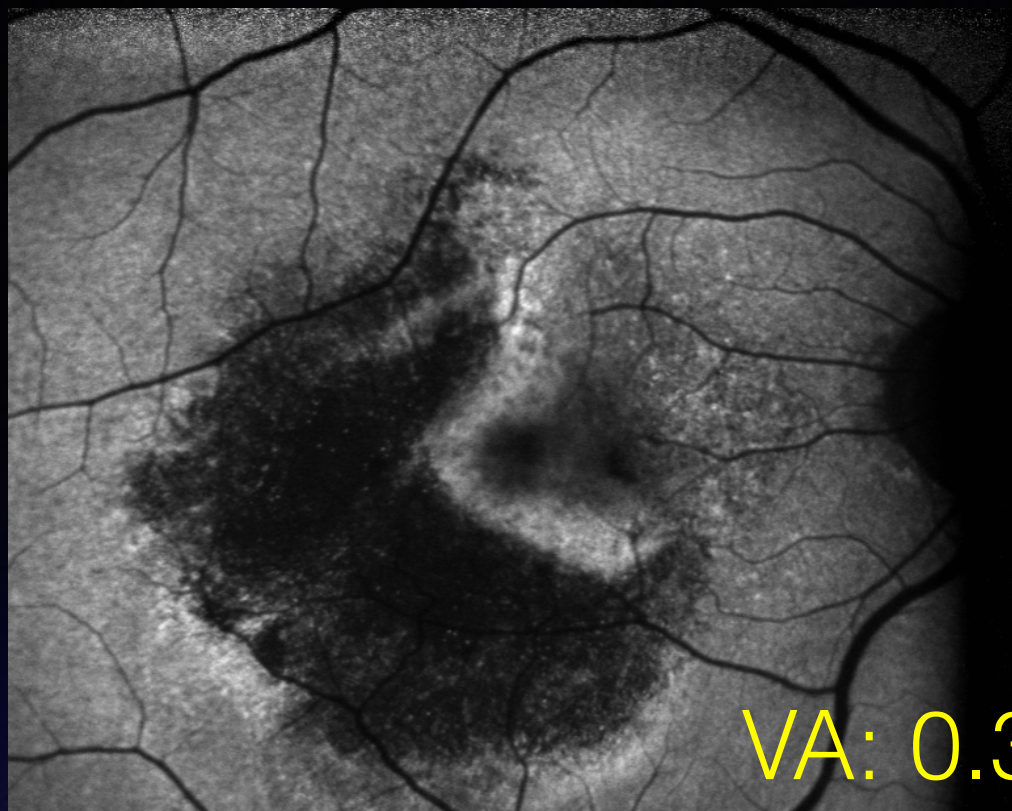


The mean VA score in eyes with RPE tears

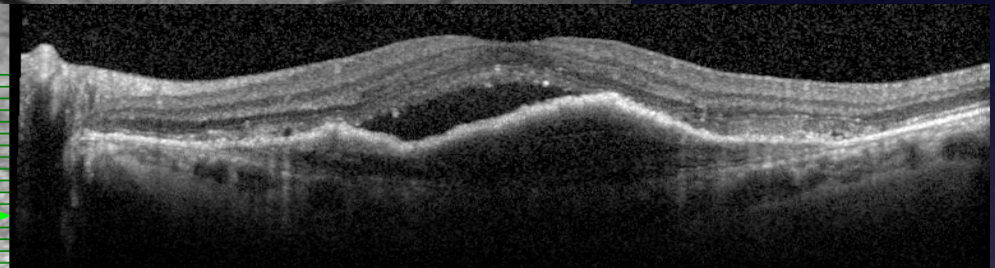
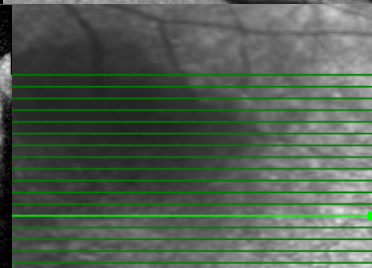
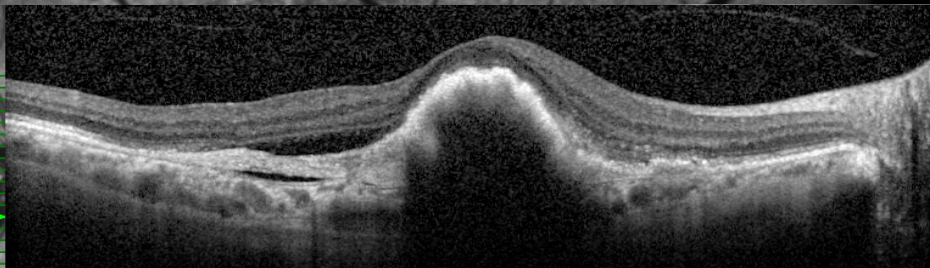
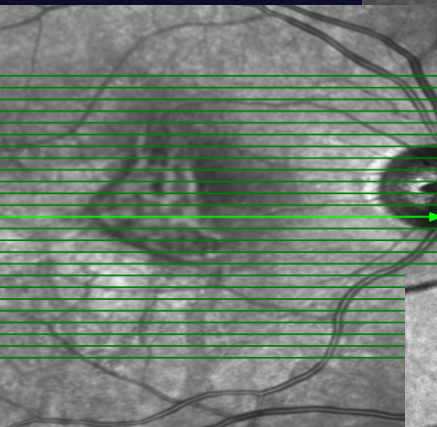


RPE tear occurred within a month following the first injection in 26 of 28 eyes

No significant change in VA during follow-up.



VA: 0.3/0.6



EL, 01.01.1947
ART(9) Q: 24



VA: 0.3/0.4



KURTULUS, EMEL, 01.01.1947
19.09.2014, OD
BAF 30° ART(23)

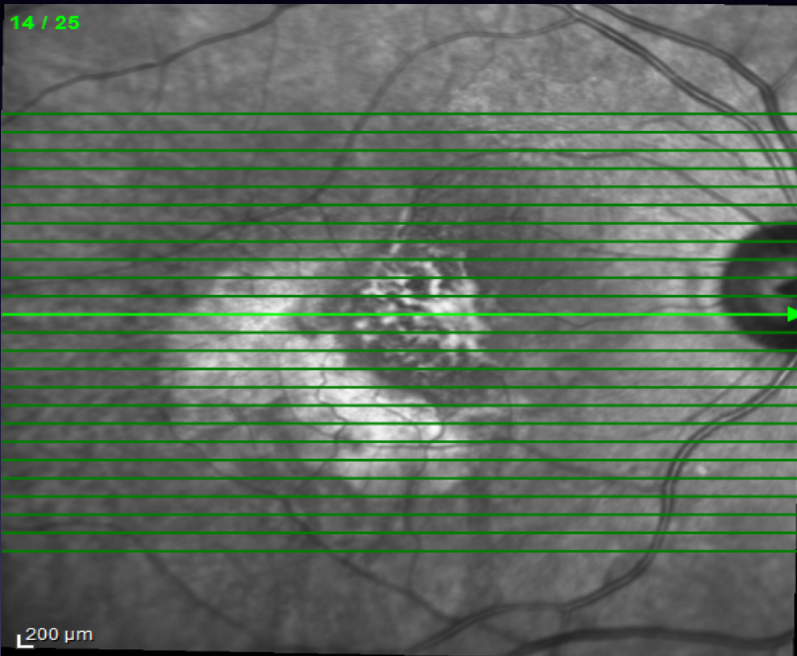
KURTULUS, EMEL, 01.01.1947
19.09.2014, OS
BAF 30° ART(40)

HEIDELBERG

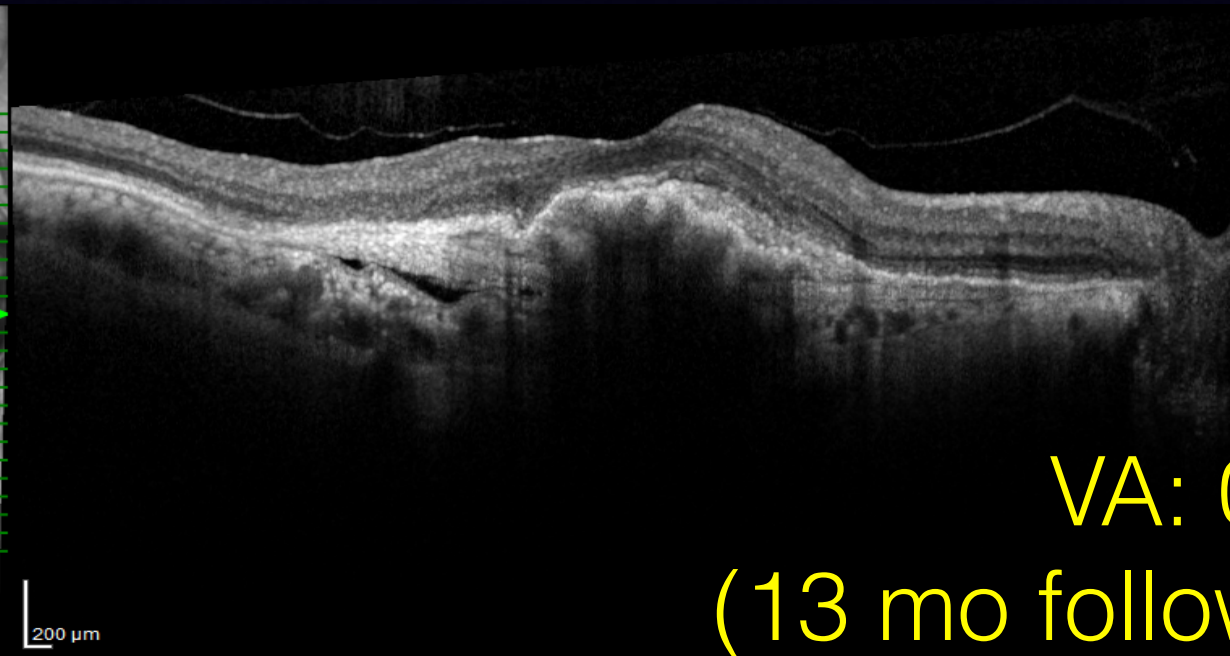
HEIDELBERG
ENGINEERING

RPE TEAR

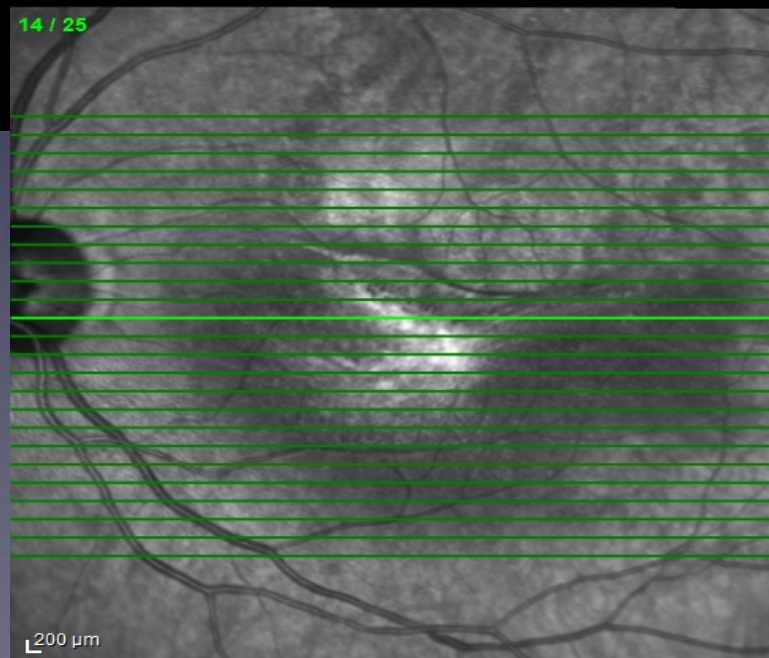
Continued Anti-VEGF treatment



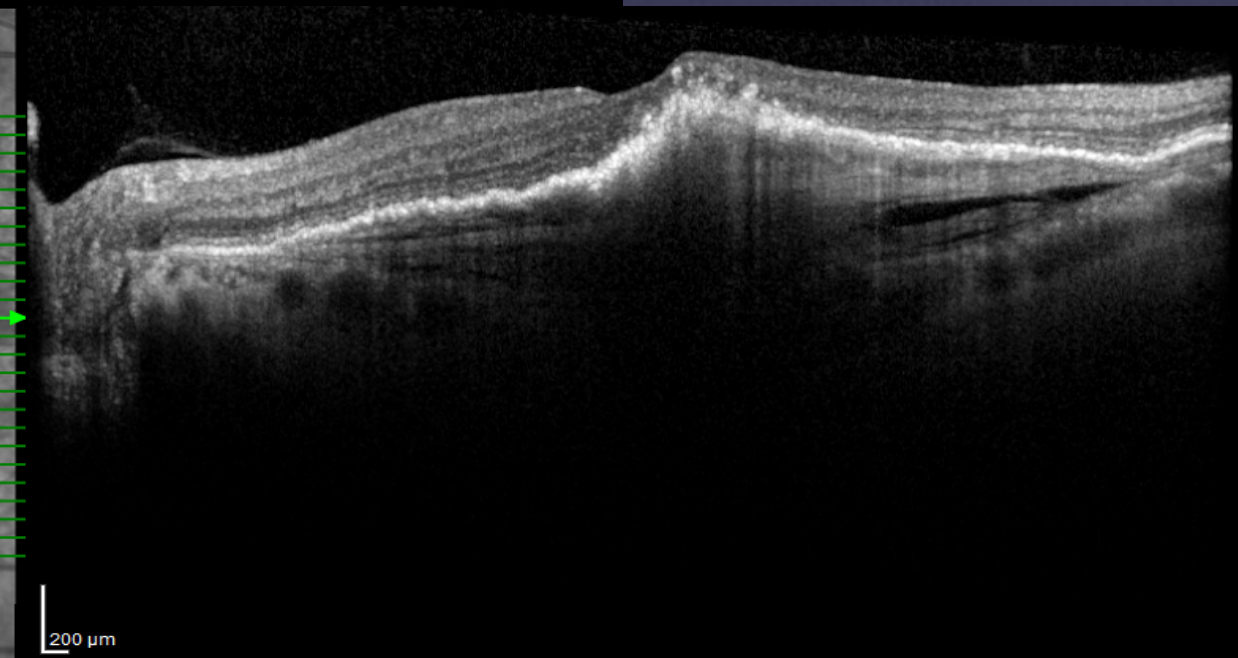
01.10.2015, OD
IR&OCT 30° [HS] ART(9) Q: 36



VA: 0.6/0.7
(13 mo following RPE tear)



01.10.2015, OS
IR&OCT 30° ART [HS] ART(9) Q: 32



ANTI-VEGF TREATMENT COMPLICATIONS

RPE TEAR-CONCLUSIONS

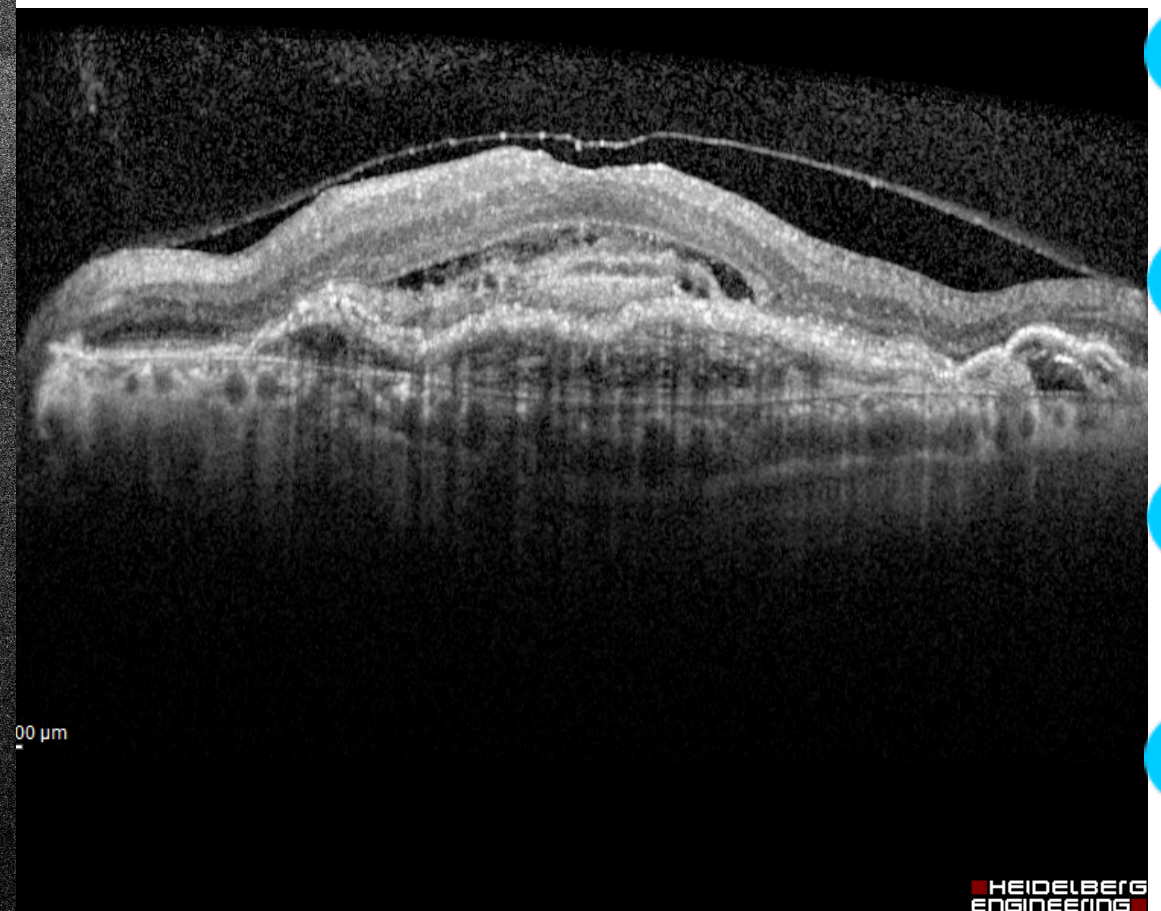
- Patients appear to maintain good VA in most cases, especially with extrafoveal involvement and continued anti-VEGF treatment.
- The high PED height and the short duration of PED are potential risk factors for developing RPE tear.

ANTI-VEGF TREATMENT COMPLICATIONS

SUBFOVEAL FIBROSIS-SCAR

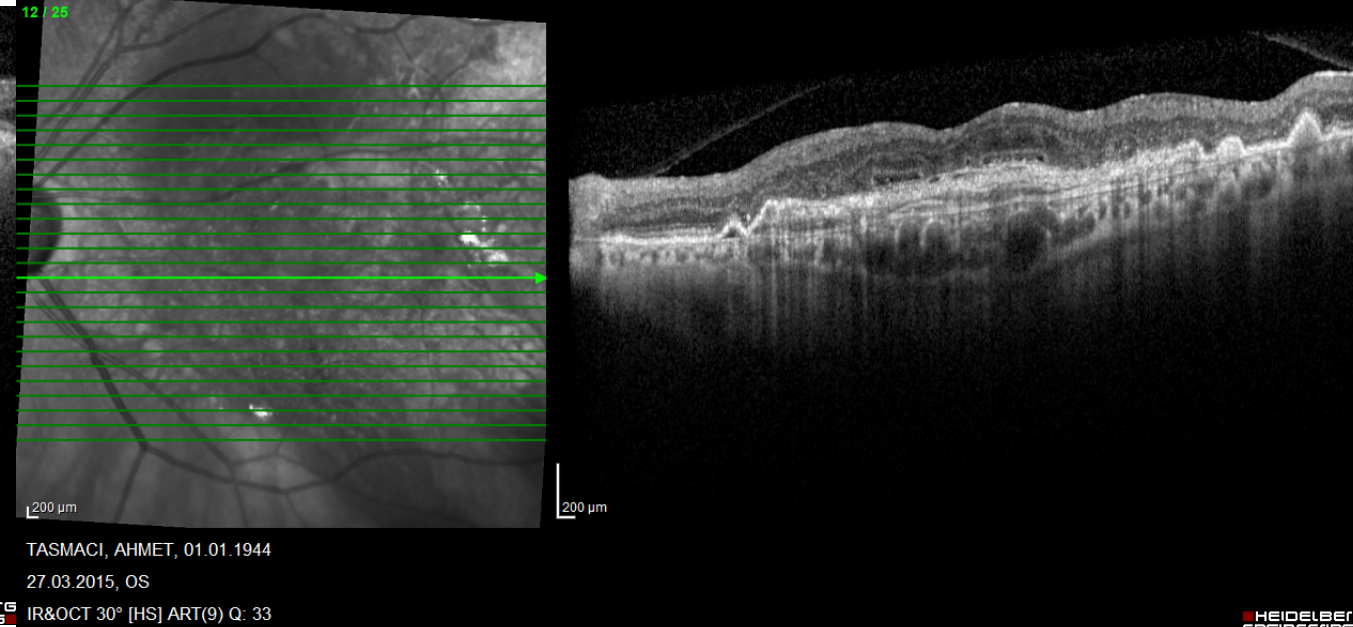
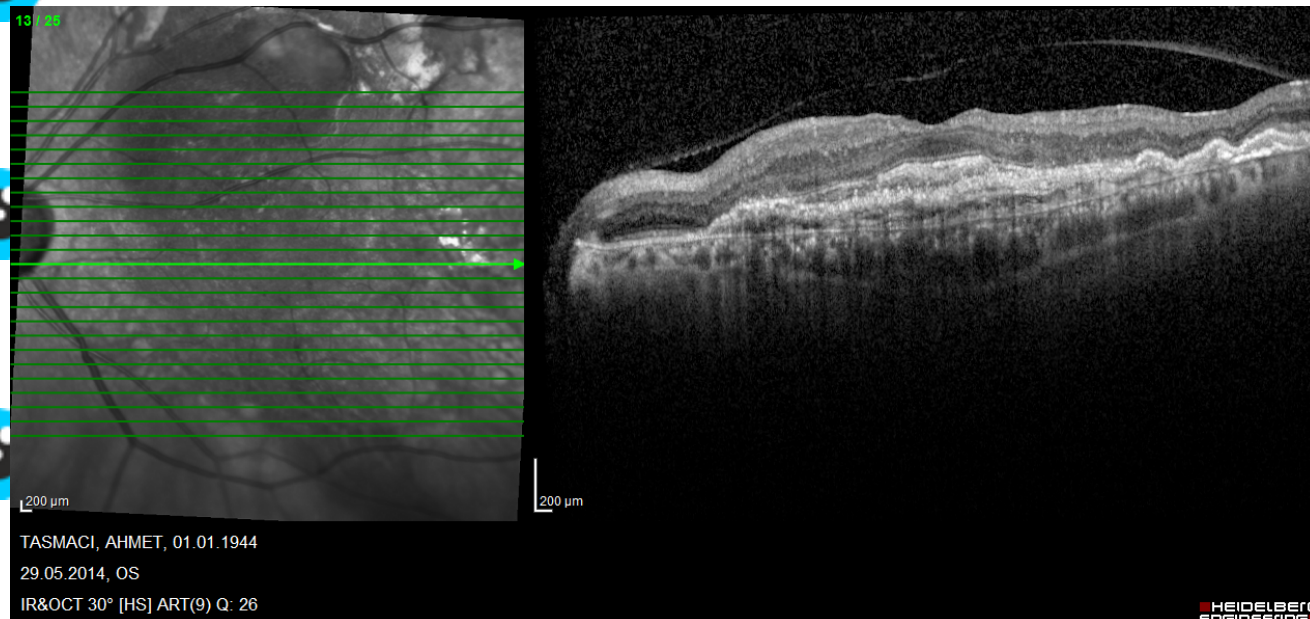
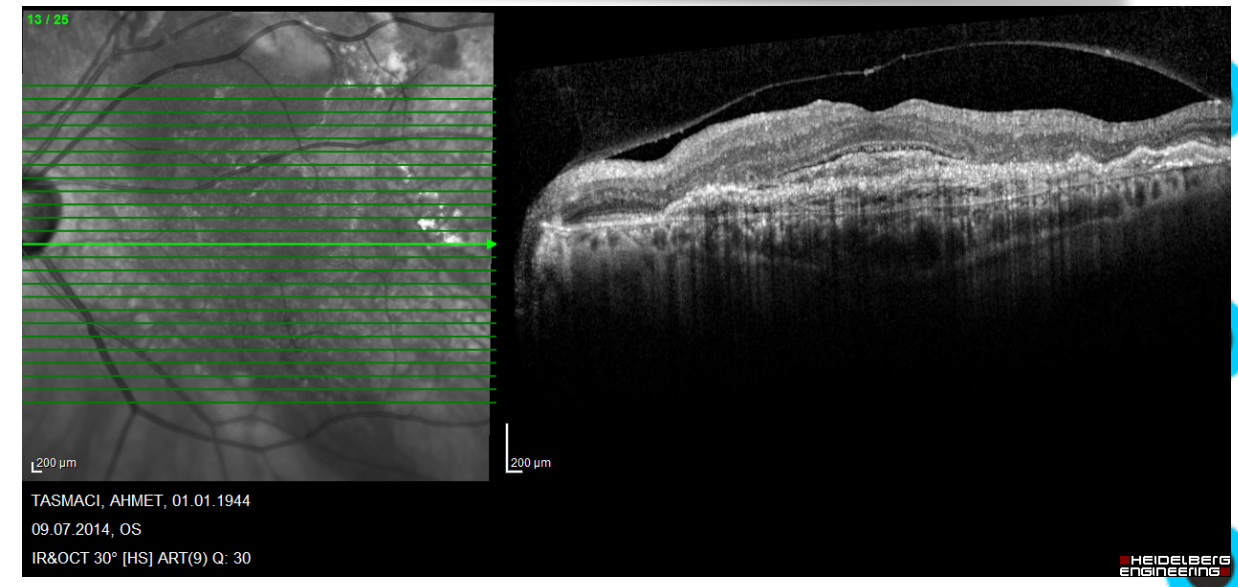
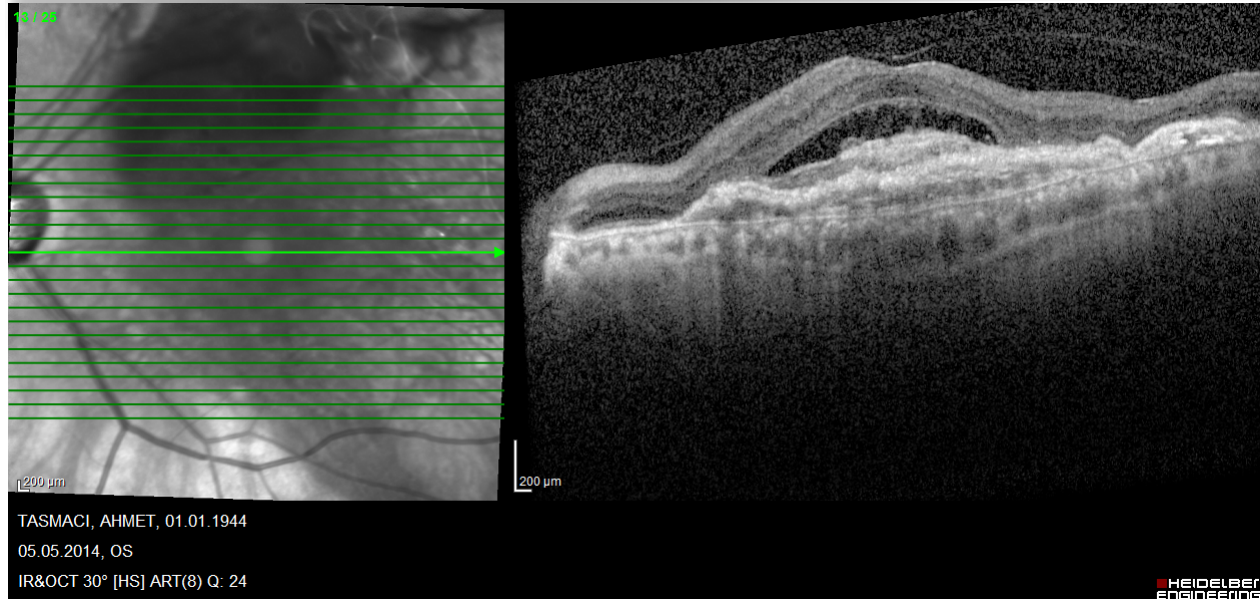


VA: 0.4



ANTI-VEGF TREATMENT COMPLICATIONS

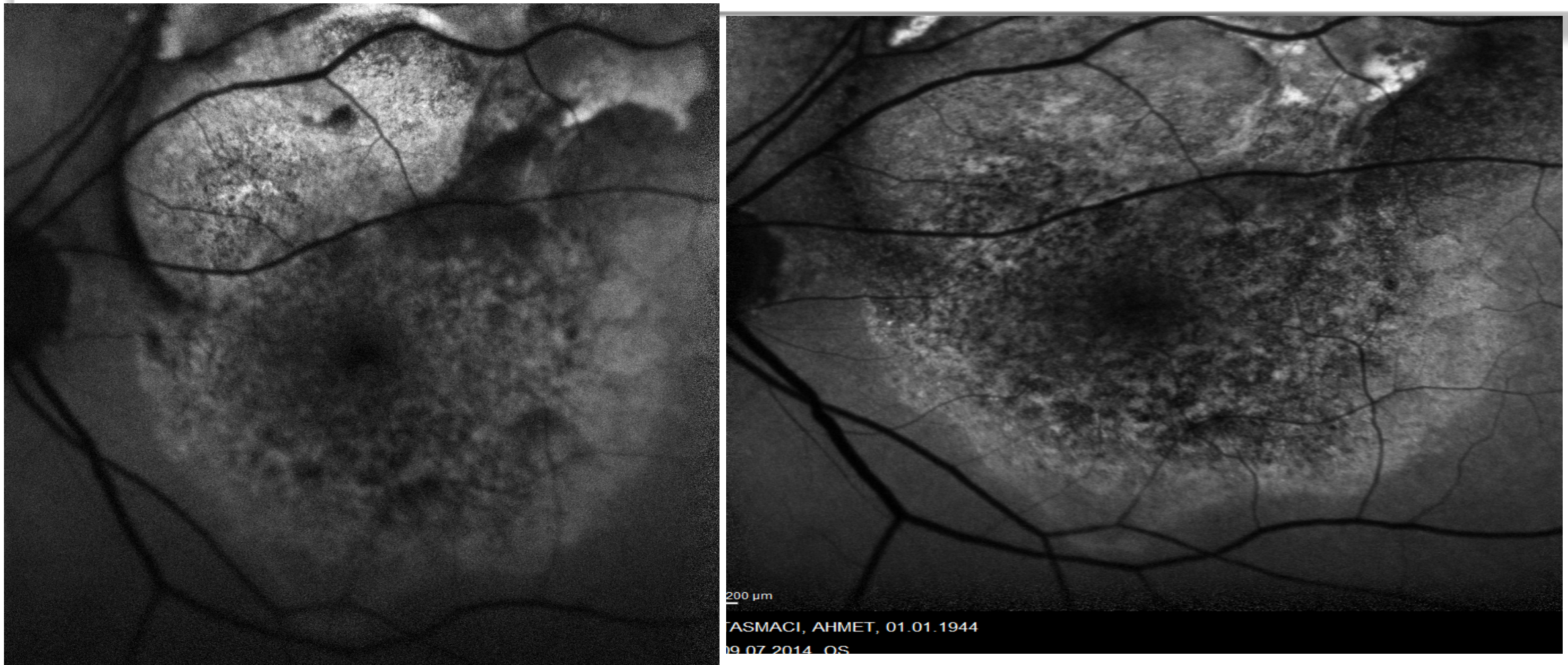
SUBFOVEAL FIBROSIS-SCAR



VA↓: 0.05

ANTI-VEGF TREATMENT COMPLICATIONS

SUBFOVEAL FIBROSIS-SCAR



VA↓: 0.05

RESISTANCE TO ANTI-VEGF TREATMENT

- WRONG DIAGNOSIS (46.2%)
 - PCV, RAP, VITELLIFORM (AOVMMD), CSCR
- TACHYPHYLAXIS-TOLERANCE (22%)
- NONRESPONDERS (26.9%)
- COMPLICATIONS: RPE tear, atrophy, scarring/fibrosis (11.6%)
- GENETIC BASIS FOR RESISTANCE

Anti-VEGF Treatment Response

Genetic Factors

- No effect of CFH (Y402H) and VEGF rs2146323,rs699947 SNPs on anti-VEGF treatment response in Turkish population.*
- CFH gene rs1061170 polymorphism is a predictor for ARMD anti-VEGF response. (treatment effect decreases 1.6x in homozygote mutants)**
- No relation bw CFH, ARMS2, HTRA1 gene and treatment response***

*Yıldız BK, **Özdek Ş** et al. EKSUDATİF YAŞA BAĞLI MAKULA DEJENERASYONUNDA ANTI-VEGF TEDAVİ ETKİNLİĞİNİN GENETİK POLİMORFİZM İLE İLİŞKİSİ. TOD Ulusal Kongre, 2013

**Chen H, Yu KD, Xu GZ. Association between variant Y402H in age- related macular degeneration (AMD) susceptibility gene CFH and treatment response of AMD: a meta-analysis. PLoS One. 2012;7(8)

***Orlin A, et al. Association between high-risk disease loci and response to anti-vascular endothelial growth factor treatment for wet age related macular degeneration. Retina. 2012;32:4–9.