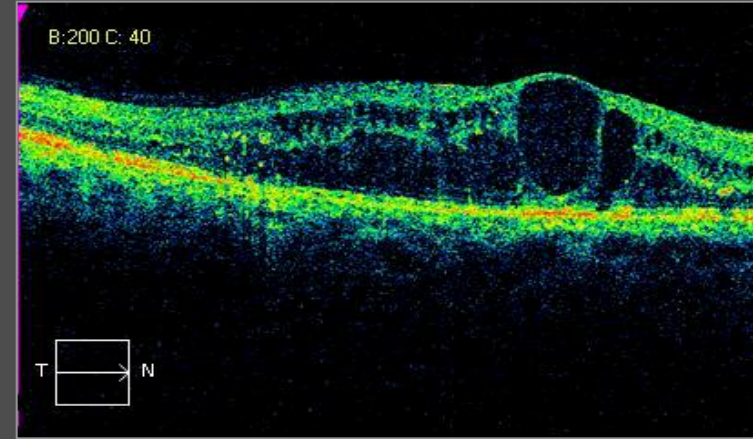




# Diabetik Maküla Ödeminin Tedavisinde Laserin Yeri



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Ankara Üniversitesi – Vehbi Koç Göz Hastanesi

2. Retina Günleri, 2015 İstanbul

# DMÖ – Görme Kaybı

- DM hastalarının % 20'sinde 10 yıl içinde DMÖ gelişir.



- Görme bozukluğunun eşlik ettiği DMÖ, diyabetli kişilerin yaklaşık % 1-3'ünü etkiler.

(dünya genelinde yaklaşık 10 milyon kişi)



# DMÖ – Görme Kaybı



N C K Z O  
R H S D K  
D O V H R  
C Z R H S  
O N H R C  
D K S N V  
Z S O K N  
C K D N R  
S R Z K D  
H Z O V C  
N Y D O K  
K S D N R  
S R Z K D

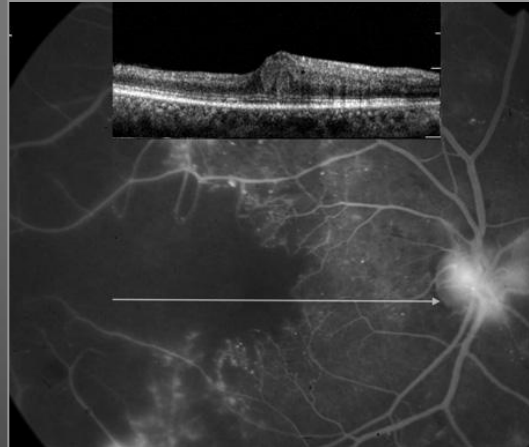
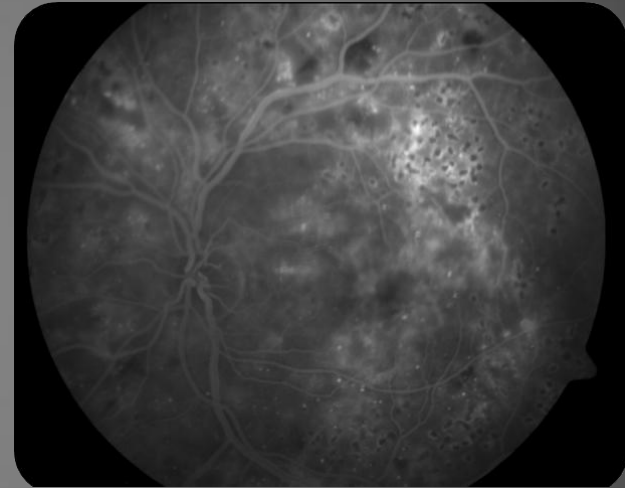
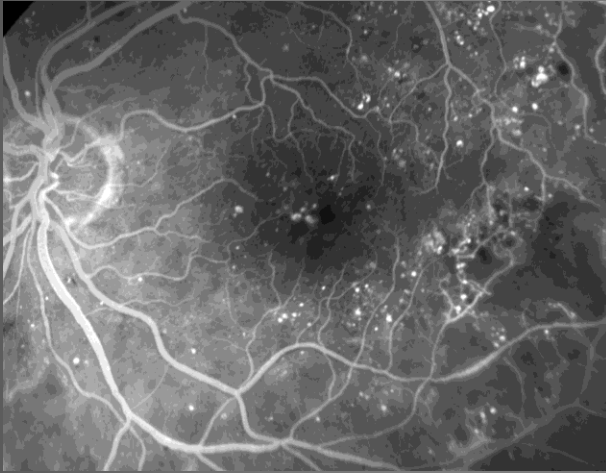
Tedavi edilmezse,  
2 yıl içinde



N C K Z O  
R H S D K  
D O V H R  
C Z R H S  
O N H R C  
D K S N V  
Z S O K N  
C K D N R  
S R Z K D  
H Z O V C  
N Y D O K  
K S D N R  
S R Z K D

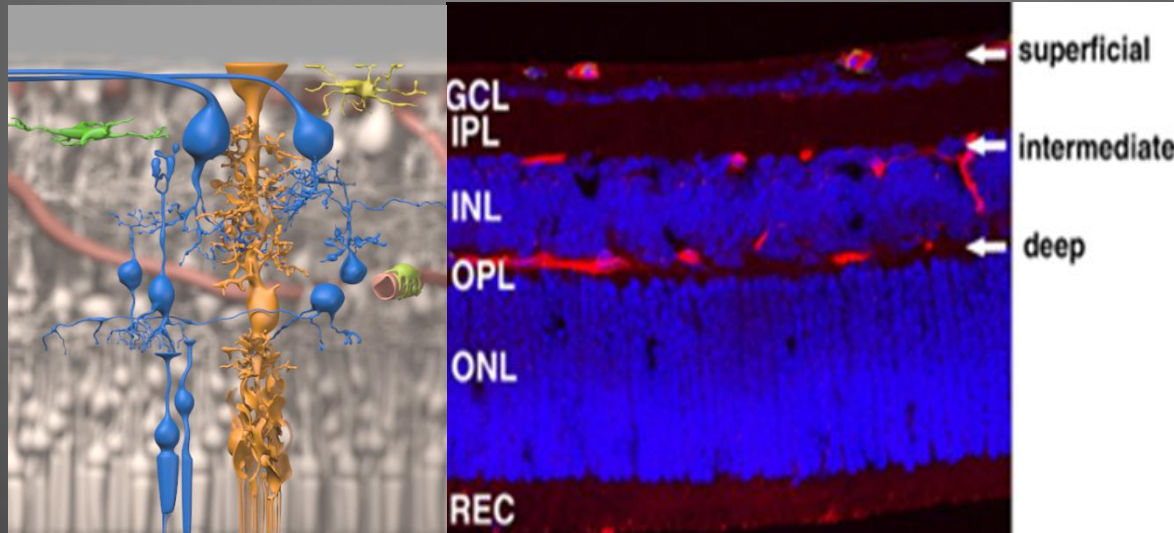
Hastaların  
% 50'sinde  
2 sıradan  
fazla görme  
kaybı

# DMÖ SADECE BİR DAMAR PATOLOJİSİ MİDİR?



# Diyabetik retinopati/diyabetik makula ödemi fizyopatolojisi

- Diyabet retinanın tüm hücre tiplerini etkiler
  - Retinal / koroidal damarlar
  - Glial hücreler
  - Nöronal hücreler



Boyer D. *Retina Today* 2011;4–7.

Images provided by A Jousen, Charité Universitätsmedizin Berlin, Germany, and E. Midena, University of Padova, Italy.



# İnsanda diyabetik retinopatide aközde inflamatuvar sitokinler artar

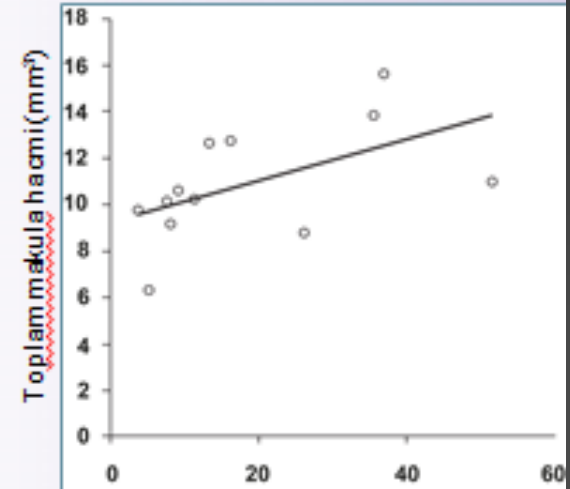
**Table 2** Aqueous concentrations (pg/ml) of angiogenic and inflammatory cytokines in the DMO, BRVO-MO groups

Variable	Control group (n=16)	DMO group (n=18)	BRVO-MO group (n=12)	p Value	
				Among 3 groups*	DMO vs BRVO-MO†
IL-2	3.0±0.3	3.1±0.3	3.1±0.2	0.745	0.851
IL-5	1.6±0.0	1.6±0.0	1.6±0.0	0.834	0.662
IL-6	28.8±39.2	66.8±70.4	17.7±26.9	0.007	0.003
IL-8	8.9±11.5	20.4±11.4	18.7±15.3	0.001	0.415
IL-12p70	1.7±0.3	1.6±0.2	1.6±0.1	0.796	0.545
IL-13	3.0±0.4	2.7±0.3	2.8±0.2	0.013	0.113
MCP-1	1225.1±421.3	3095.6±1918.3	136.3±524.8	<0.001	0.004
MIP-1α	0.0±0.0	2.6±11.1	0.0±0.0	0.459	0.819
TGF-α	3.1±0.4	2.8±0.3	3.0±0.3	0.205	0.325
IFN-γ	3.7±0.2	3.6±0.1	3.7±0.2	0.242	0.172
PDGF-AA	74.8±33.1	112.0±49.5	97.1±33.3	0.020	0.158
EGF	3.9±3.5	4.8±2.6	5.2±2.4	0.479	0.692
FGF2	3.0±4.8	0.8±1.9	1.9±3.0	0.389	0.415
VEGF	45.5±51.8	128.4±116.6	107.1±132.2	0.050	0.950

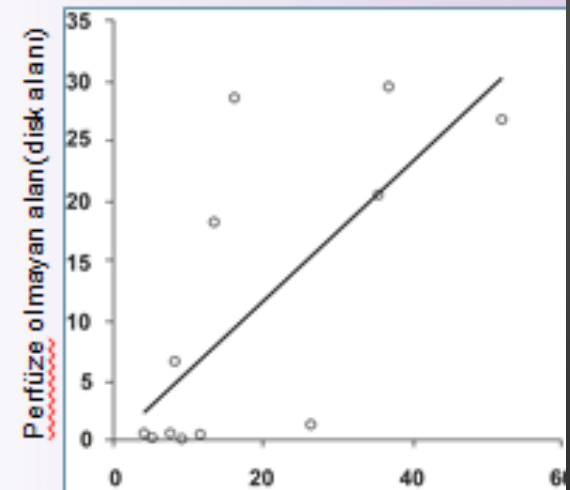
\*Kruskal-Wallis test.

†Mann-Whitney U test.

BRVO-MO, branch macular oedema secondary to retinal vein occlusion; DMO, diabetic macular oedema; EGF, epidermal growth factor; IL, interleukin; IFN-γ, interferon-γ; MO, macular oedema; MCP-1, monocyte chemoattractant protein-1; MIP-1α, macrophage inflammatory protein-1α; PDGF, platelet-derived growth factor; TGF-α, transforming growth factor-α (TGF-α); TNF-α, tumour necrosis factor-α; VEGF, vascular endothelial growth factor.



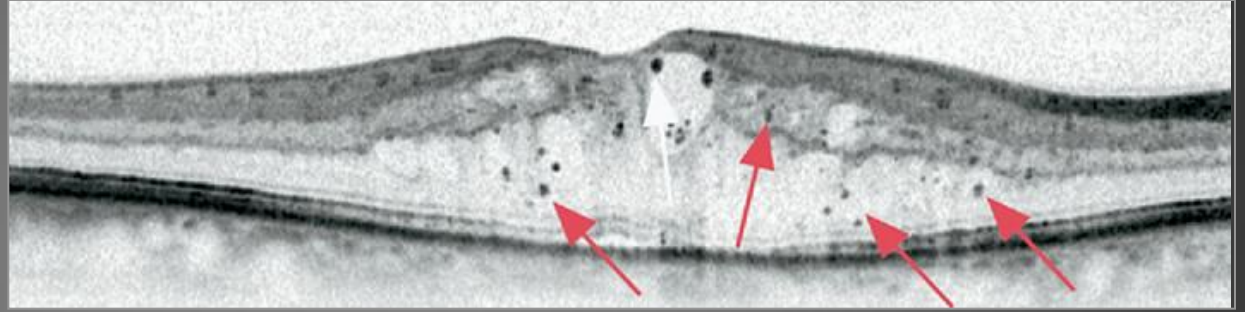
IL-8 aköz düzeyleri (pg/ml)



IL-8 aköz düzeyleri (pg/ml)

# RETİNA İÇİ DEĞİŞİKLİKLER

Hiperreflektif noktalar ---- Retinal mikroglial aktivasyon  
Anti-inflamatuar tedavi ?



- DMÖ'de OKT'de düzgün sınırlı hiperreflektif noktalar mikroglial aktivasyon, makrofaj
- Sıklıkla dış nükleer ve pleksiform tabakada
- KRB bariyeri bozulmasının erken subklinik bulgusu ? (damar dışına sızan lipoprotein ve/veya proteinler)
- Diabette tüm ödem tiplerinde bulunabilir
- İnflamatuar sürecin veya ödem nüksünün işareti ?

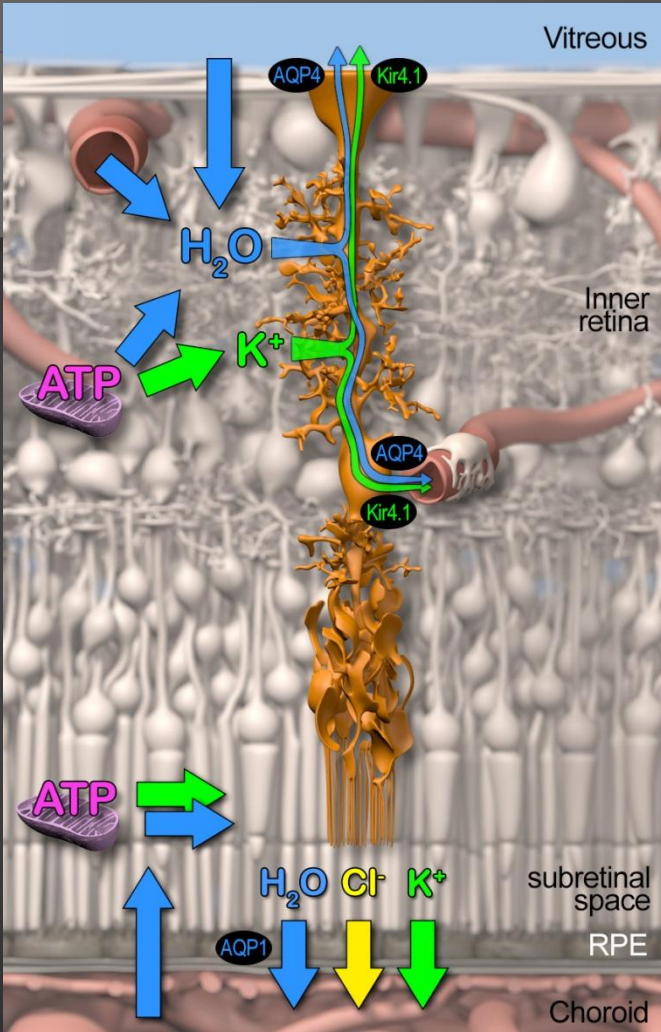
# Retinal makroglia: Müller hücreleri

## Cell Biology of the Müller Cell

Andreas Reichenbach, Andreas Bringmann

Chapter

17



## Damarlar ve nöronlar arasında "iletişim" hücreleri

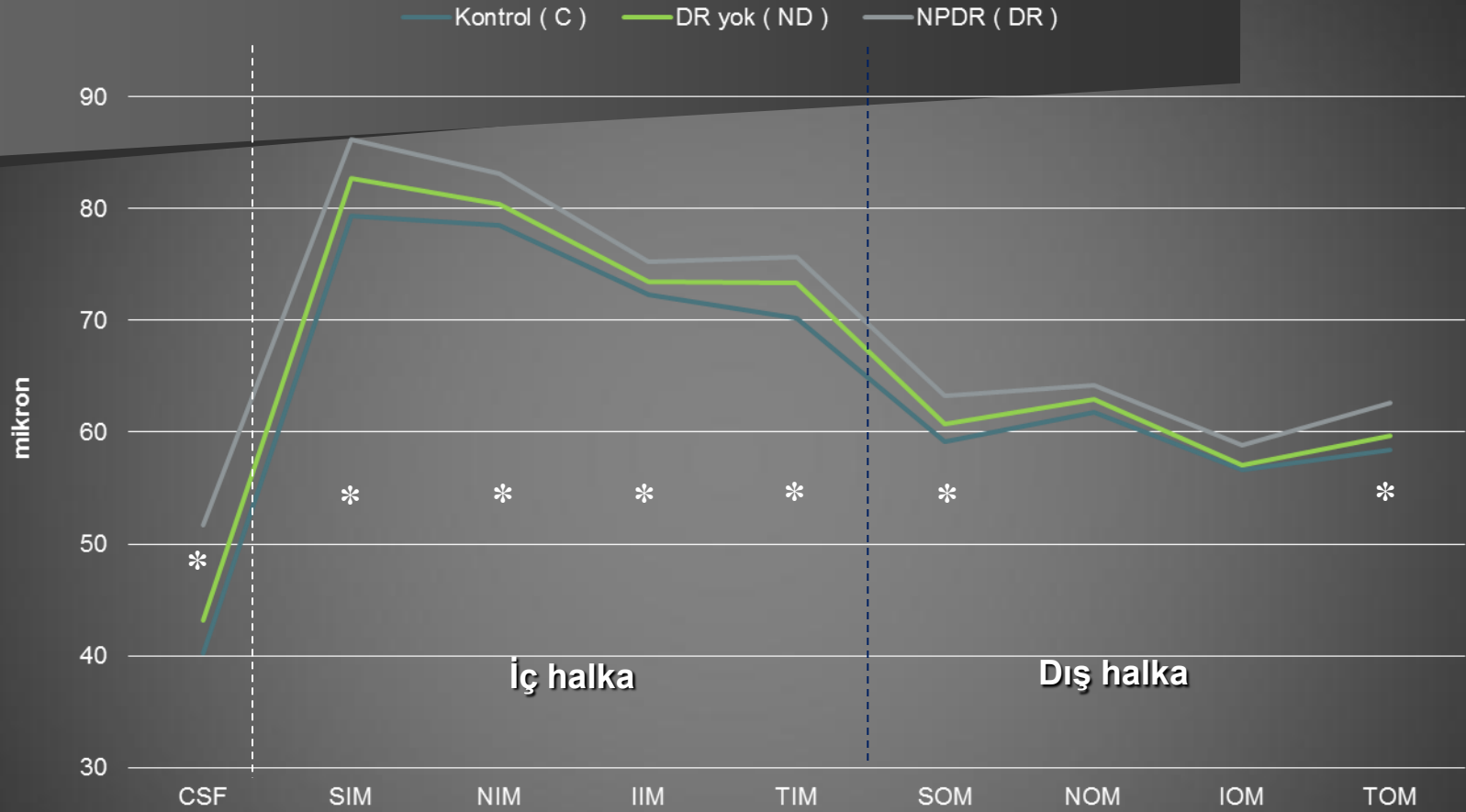
- Su ve ion kanalları ile, retina boyunca sıvı transferini düzenleme
- KRB rolü, DMÖ' e katkı
- Yapıştırıcı protein (MMP) sekresyonu
- GFAP ve AQP4 up-regülasyonu
- VEGF artışı / PEDF azalması

AQP: aquaporin;  
GFAP: glial fibriller asidik protein;  
MMP: matriks metalloproteinaz.

1. Mizutani M et al. *Diabetes* 1998;47:445–9;
2. Rungger-Brändle E et al. *Invest Ophthalmol Vis Sci* 2000;41:1971–80;
3. Barber AJ et al. *Invest Ophthalmol Vis Sci* 2000;41:3561–8;
4. Bringmann A, Wiedmann P. *Ophthalmologica* 2012; 227:1–19.



# Müller hücre aktivasyonu



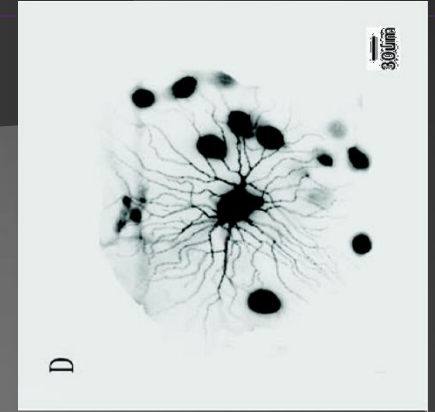
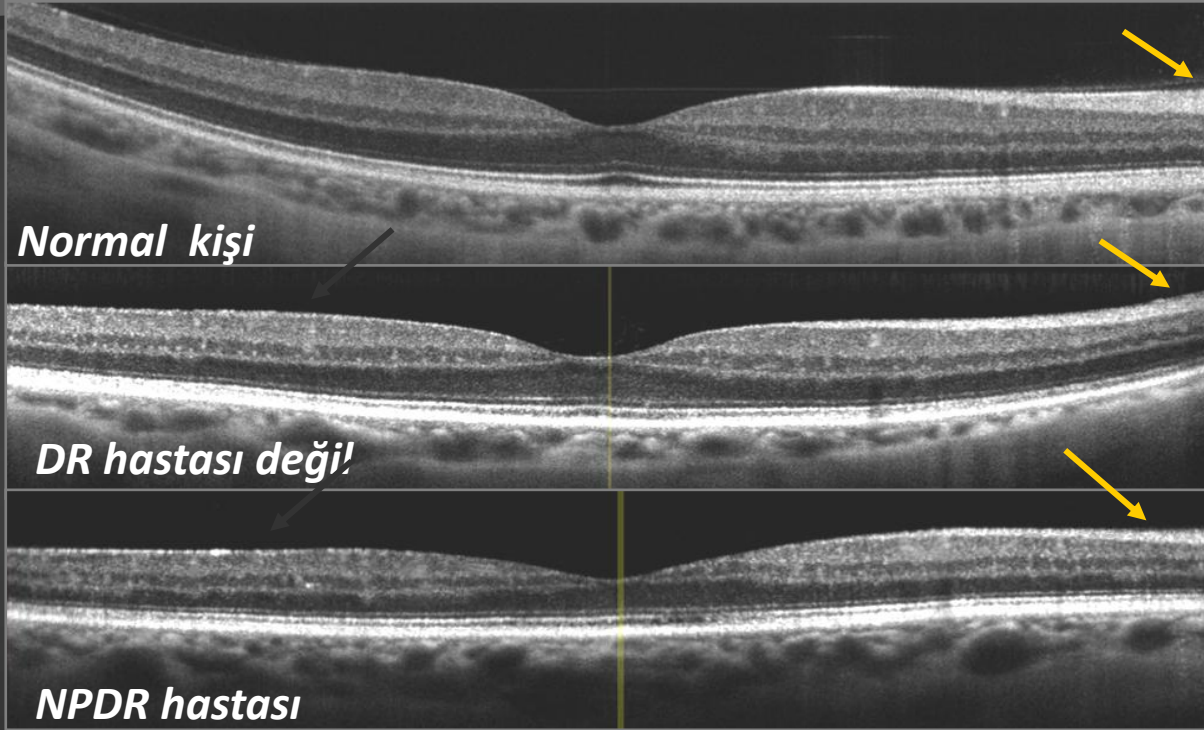
\* $p < 0.05$  of C to DR

Erken retinopatisi olan ve olmayan diyabet hastalarında iç nükleer tabaka kalınlığında artış Müller hücre aktivasyonunun bir bulgusu (iç nükleer tabaka hücresi ile en çok ilişkili)

Vujosevic S, Midena E. *J Diabetes Res* 2013;2013:905058.

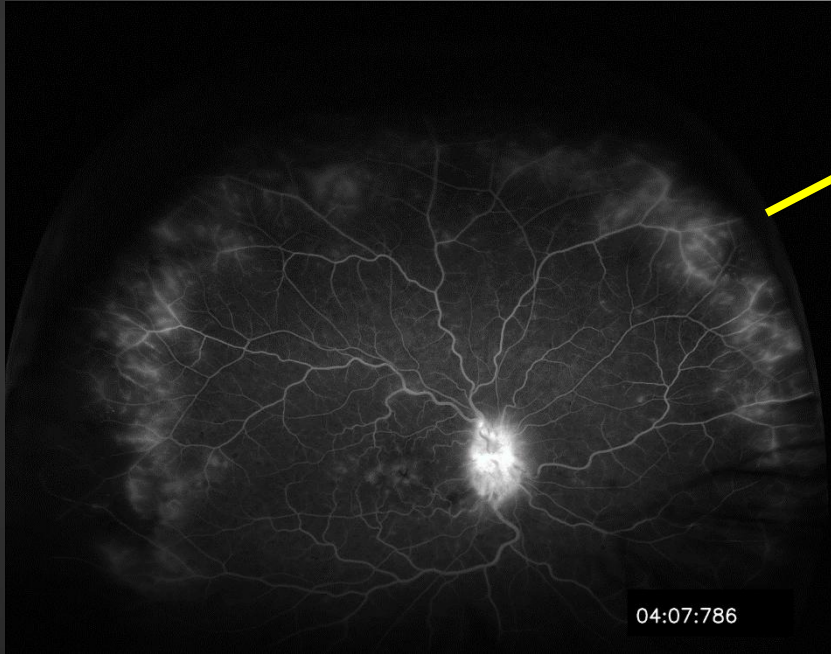
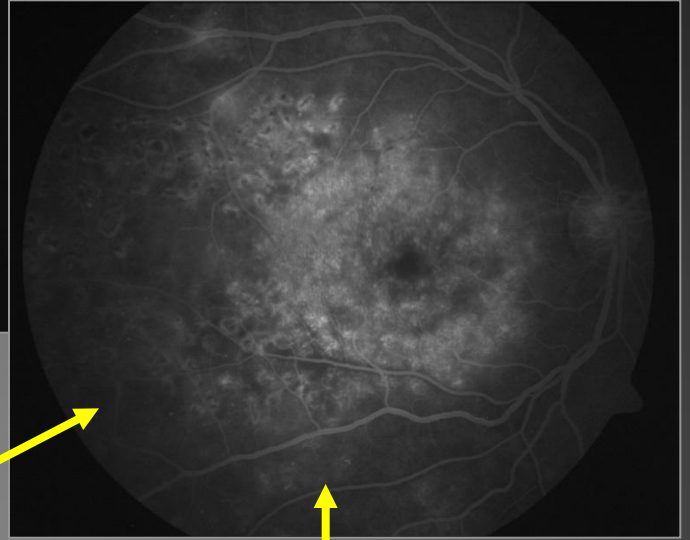
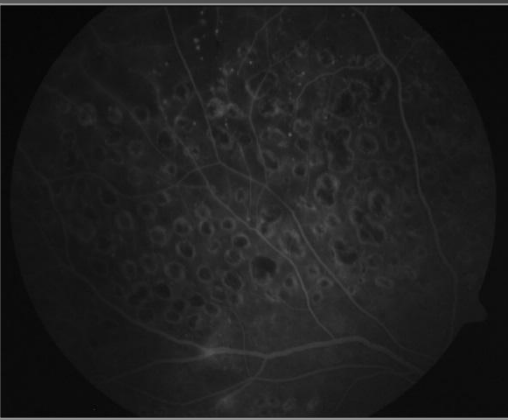
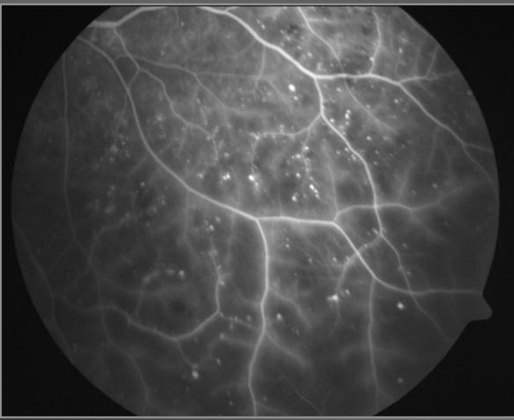
# Nöronal hücreler

- Hücre kaybı (başlıca apoptosis yoluyla)
- Retinal tabaka(lar)da incelme



Hasara cevap olarak,  
RGC dendrit sayısında artma

Barber AJ et al. *Invest Ophthalmol Vis Sci* 2011;52:1156–63.  
van Dijk HW et al. *Invest Ophthalmol Vis Sci* 2010;51:3660–5.  
Vujosevic S et al. *J Diabetes Res* 2013;2013:491835. doi:  
10.1155/2013/491835.



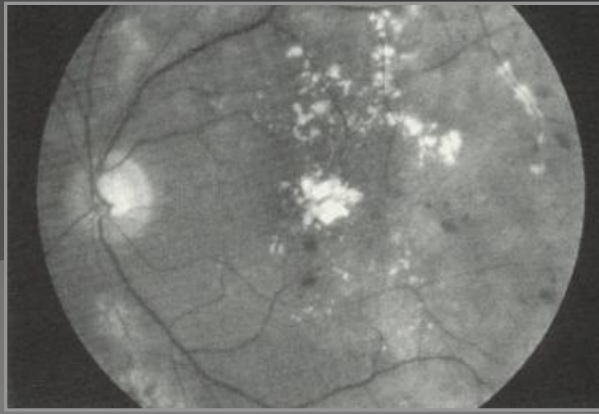
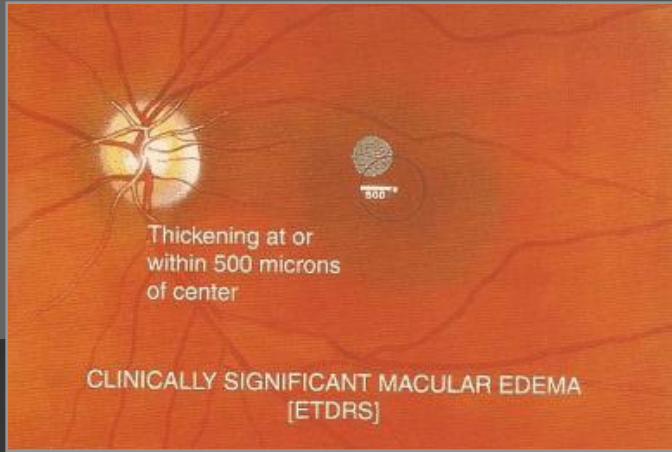
- Sistemik regülasyonun bozukluğu
- Mikroalbüminüri, anemi
- A. Carotis Interna
- Hb A 1 C % 7 üstü olması
- Uyku apne sendromu
- Periferik retina
- Glitazone grubu oral anti- diabetik alımı

# DMÖ' de tedavi kombinasyonları

- Anti-VEGF, Anti-PIGF, anti-PDGF
- Uzun salınımlı intravitreal steroidler
- Laser: **modifie ETDRS, eşik altı, mikropulse**
- Pars plana vitrektomi / arka hiyaloid, İLM soyma

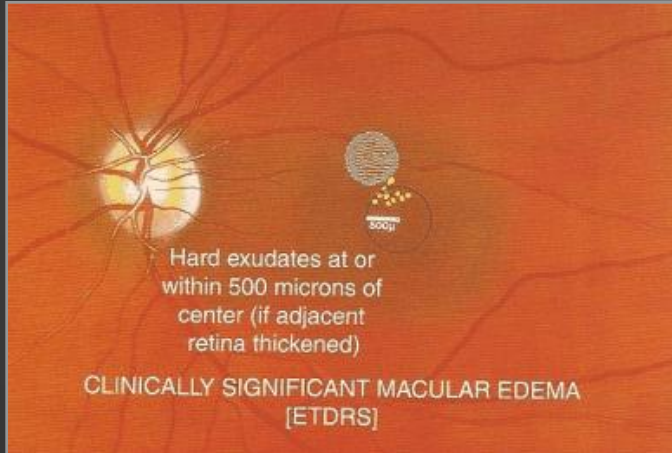


# ETDRS (1987) – KÖMÖ: Biomikroskopi veya fundus stereofotografı ile

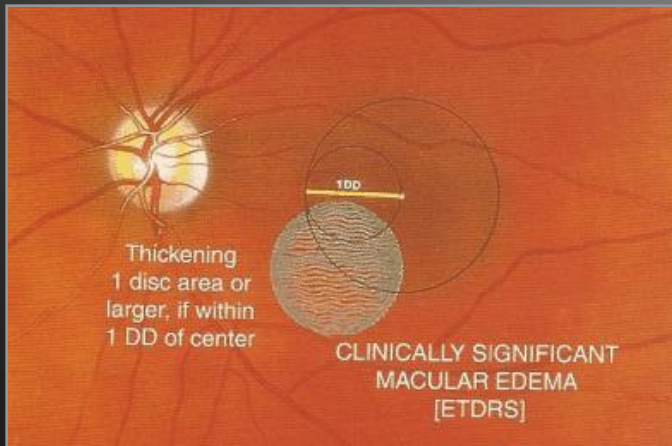


Retinal kalınlaşma

Veya



Sert eksuda + Eğer komşu retinada kalınlaşma



En az 1 disk alanı retinal kalınlık

# Klinikman önemli maküla ödeminin önemi

- Eşik ödemi gösterir, tedaviye başlama kriteridir
- 3 yılda % 30 görme kaybı riski var
- Görme tam bile olsa laser tedavisi yapılır
- Tedavi ile 15 harf kaybında ( orta ) % 50 azalma
- Retinal kalınlığı değerlendirmez

DMÖ de, görme ile en iyi korele olan retinal kalınlık =  
aksiyel kalınlıktır



SD - OCT

## ETDRS / KÖMÖ ( 1987)

Fokal / grid pattern maküler argon laser tedavisinden yararlanır ( tedavisiz kontrol grubuna göre)

### Fokal tedavi:

Yeşil / sarı dalga boyu

Merkezden 500 – 3000  $\mu\text{m}$  arasına

50 – 100  $\mu\text{m}$  spot size

Süre 0.1 sn veya daha az

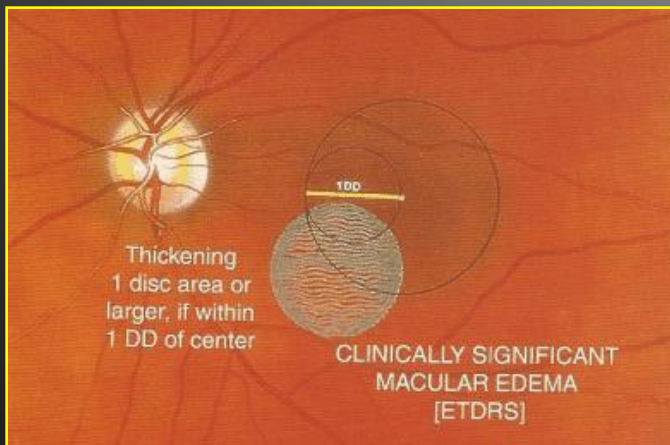
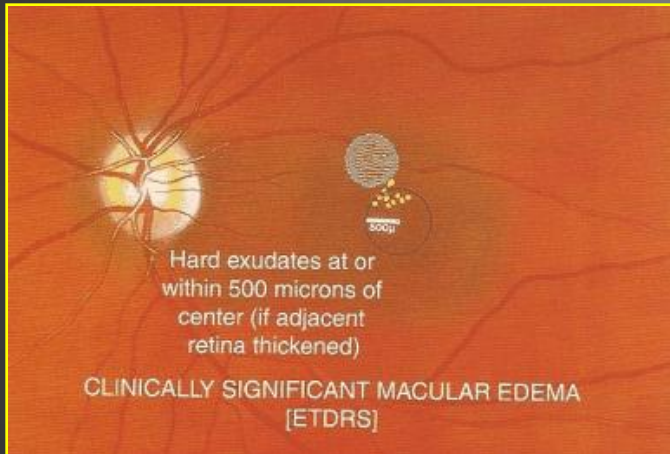
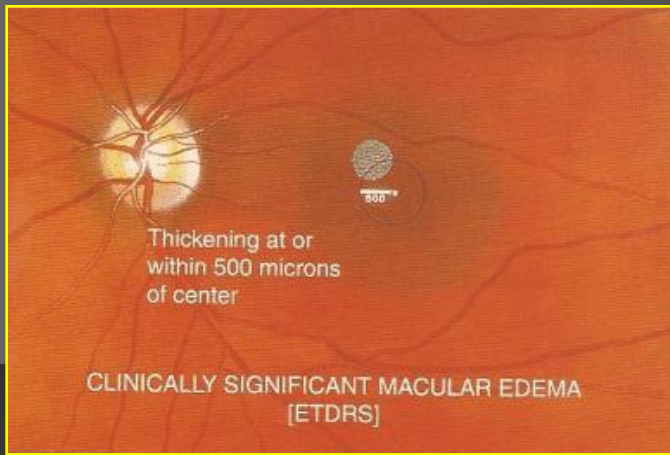
M.a.'nın beyazlanması veya kararması amaçlanır

### Grid tedavi:

Hafif yoğunlukta grid pattern

Spotlar, en azından 1 spot aralıklarla yerleştirilir

Aynı parametreler

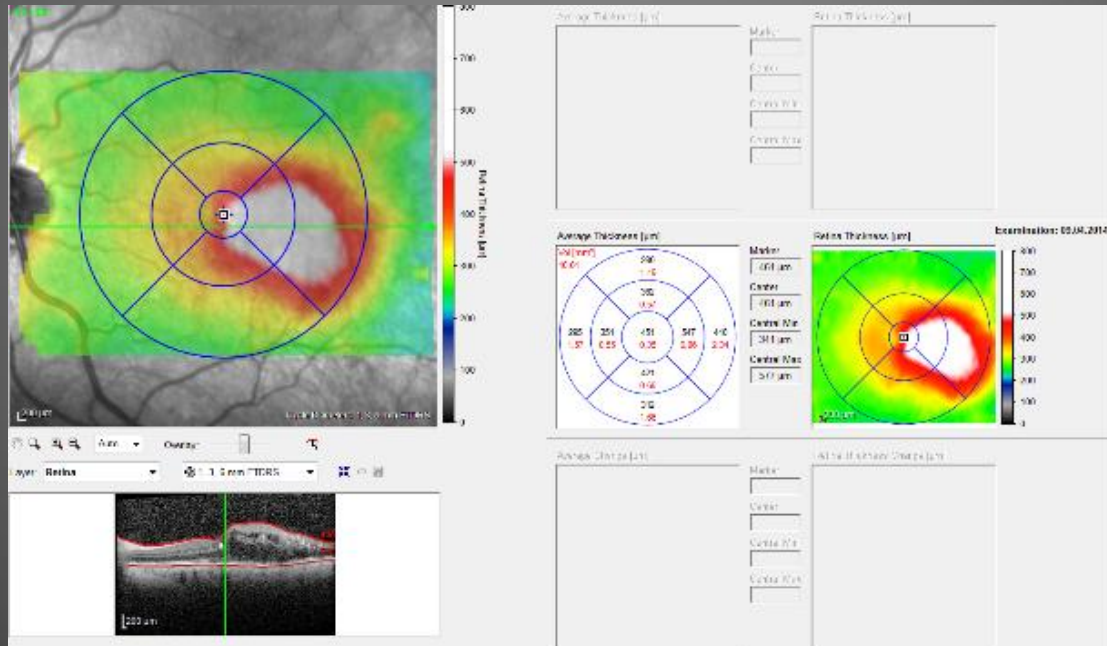
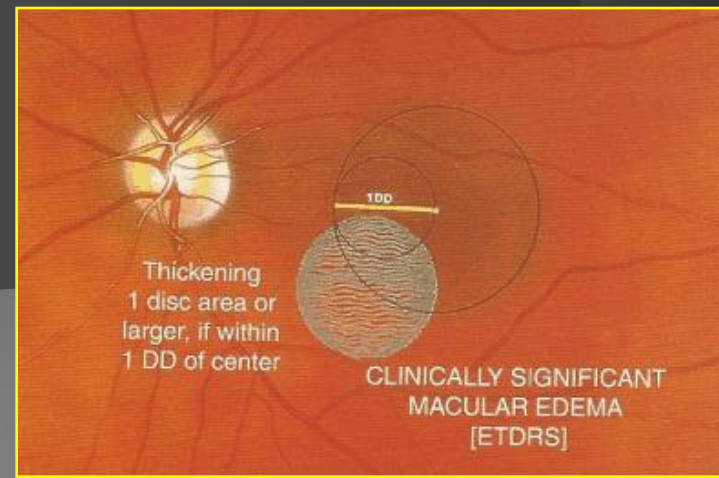
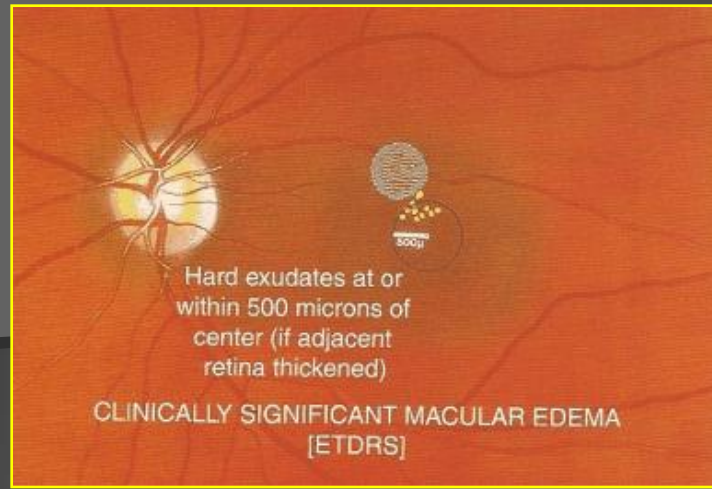


# Modifiye ETDRS tekniđi

DMÖ' de klasik eşik fotokoagülasyon (2007)

- Yan etkileri azaltmak için:
  - \* Daha büyük spot size
  - \* Zorlukla görülebilir spot oluşturan güç
  - \* Azaltılmış süre
- Direkt m.a.' ya atmaya gerek yok
- FAZ sınırında tedavi yapılmaz
- Santral sızıntıda: iyi sistemik kontrol ile takip



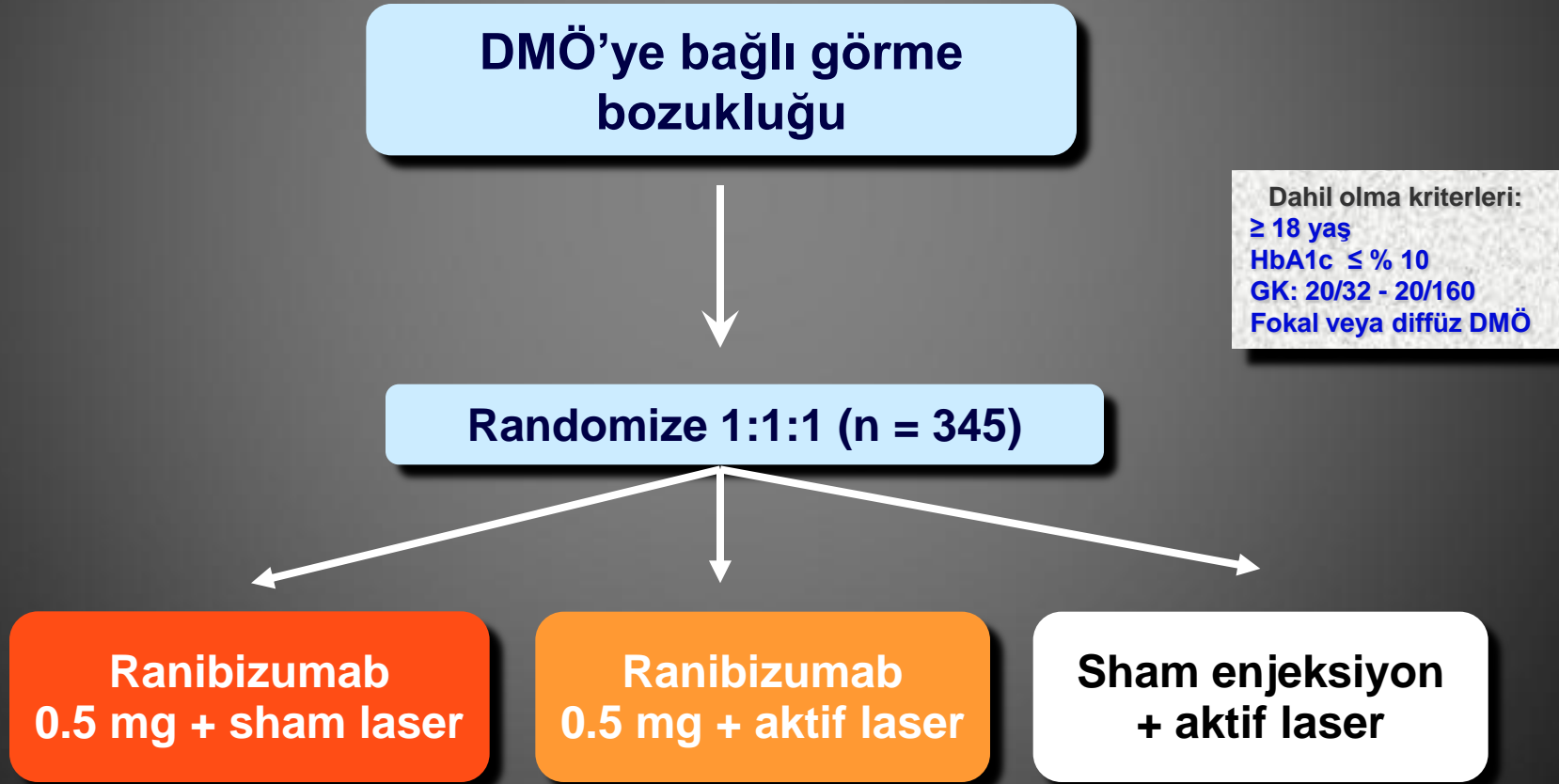


**Klinikman Önemli Maküla Ödemi:** 1000-3000 µm çaplı daire

**SD-OCT:** 1000 µm / 3000 µm / 6000 µm çaplı daireler

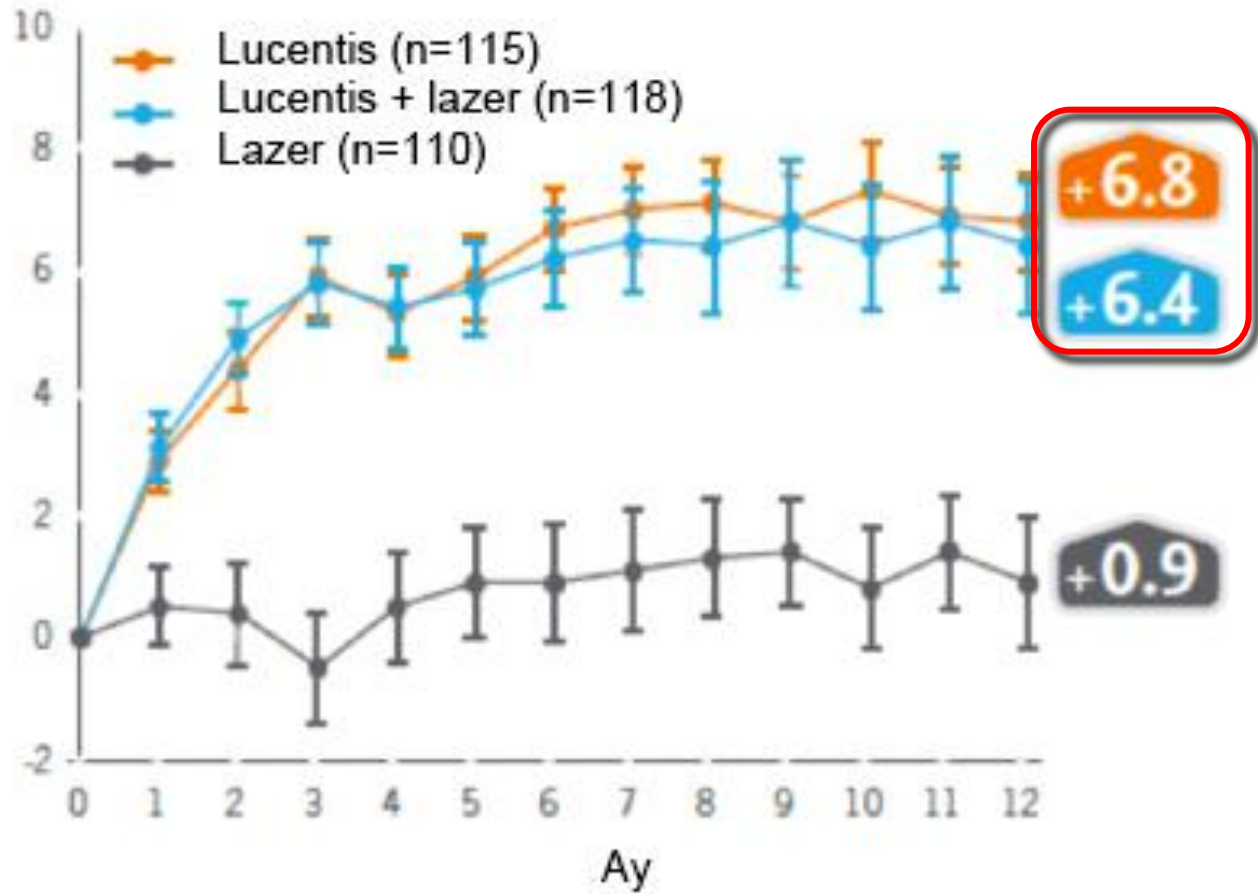
# RESTORE (Faz III)

**Amaç:** Laser tedavisine karşı ranibizumabın (0.5mg), tek başına veya lazer tedavisi ile kombine olarak GK üzerine üstünlüğünü göstermek



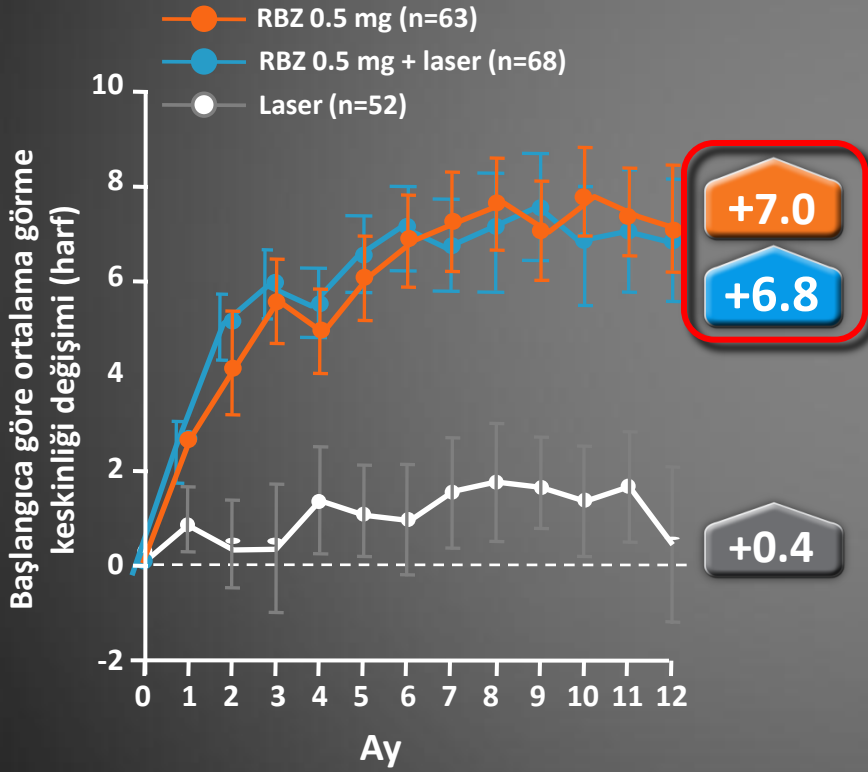
# RESTORE – Fonksiyonel Sonuçlar

Başlangıca kıyasla BCVA'da meydana gelen ortalama değişim (ETDRS harfleri)

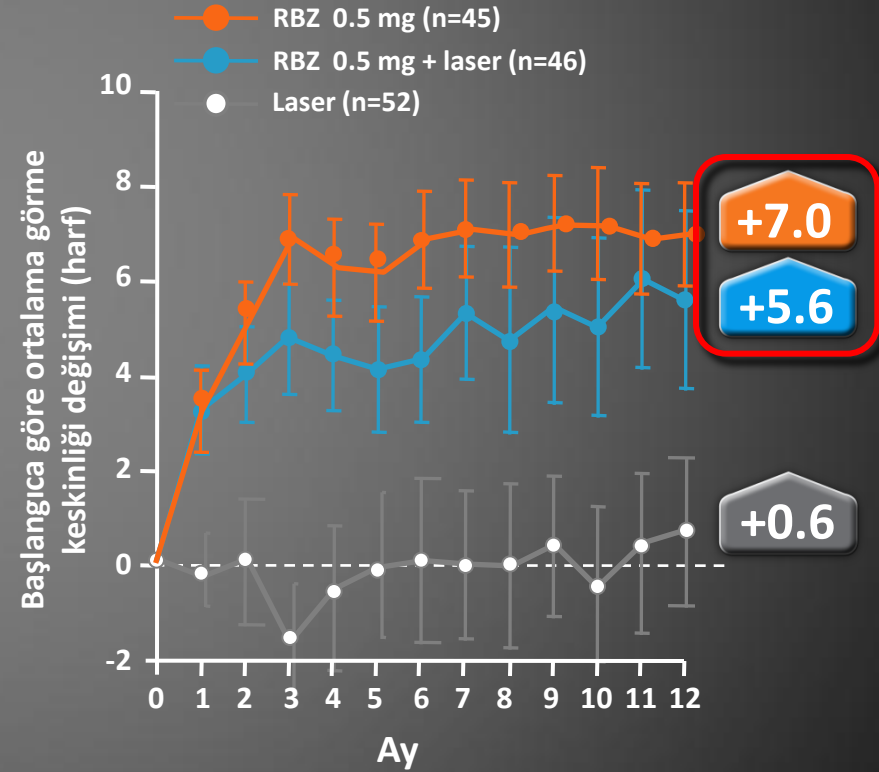


# RESTORE – Fonksiyonel Sonuçlar

## Fokal

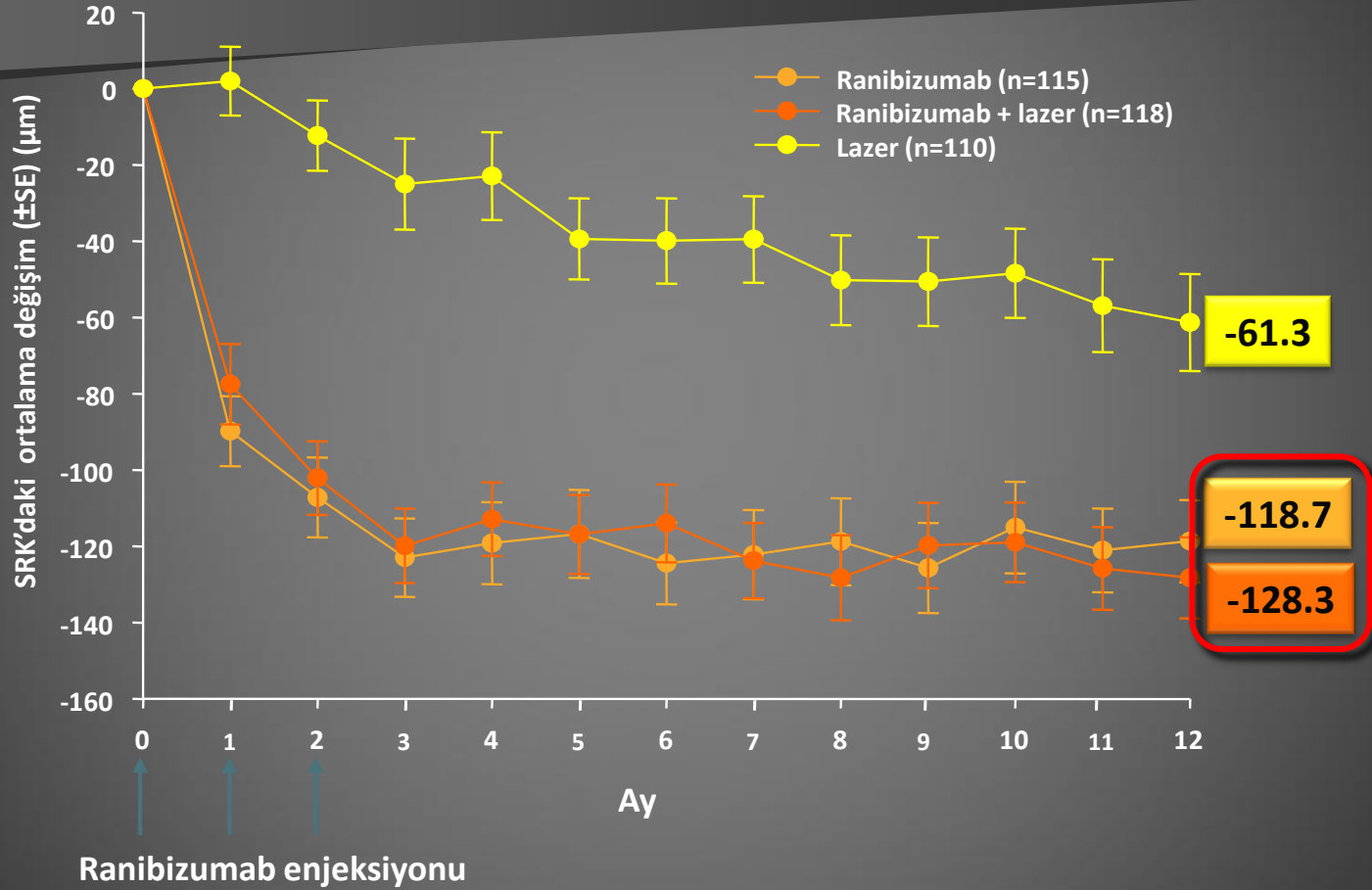


## Diffüz

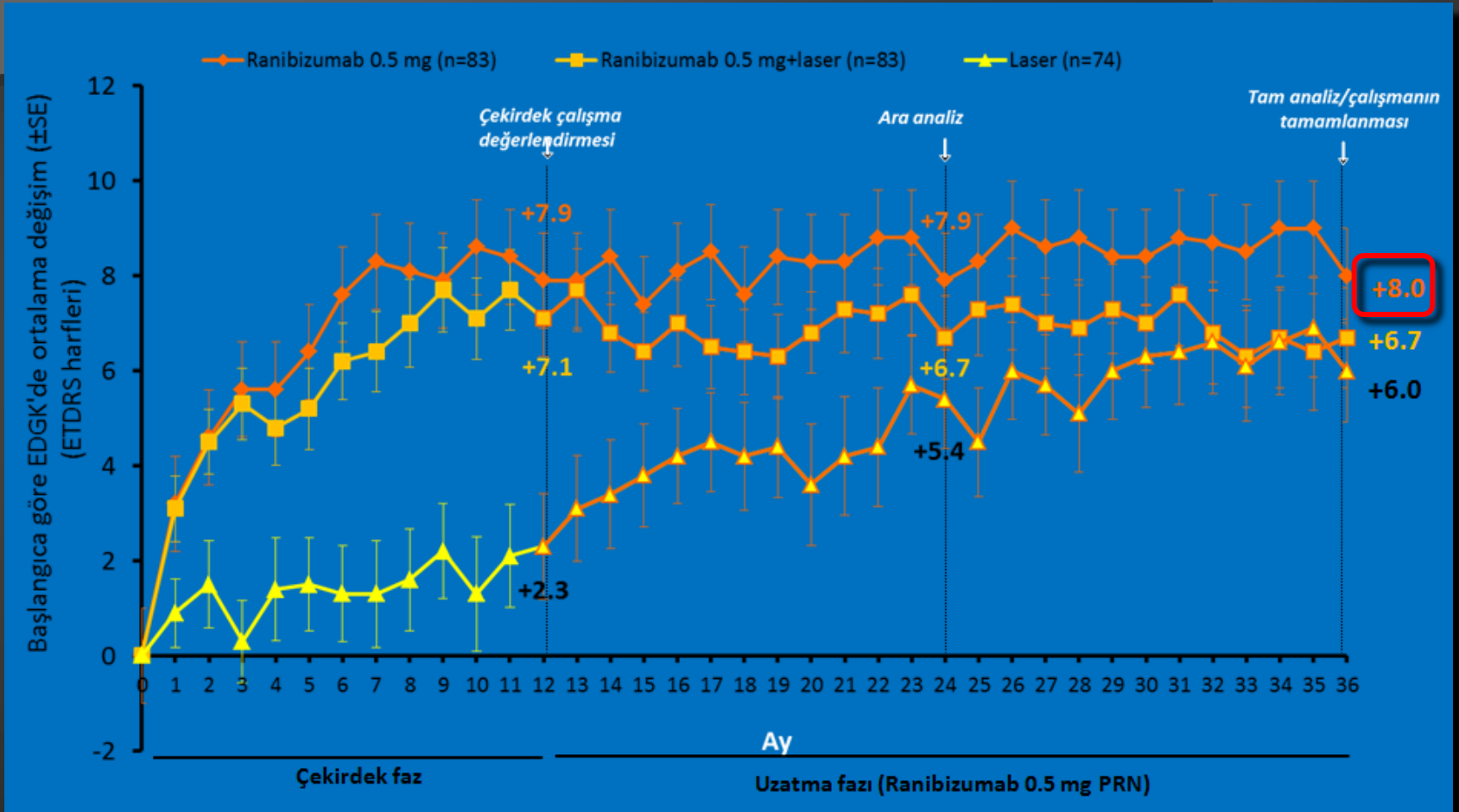




# RESTORE – Anatomik Sonular



# RESTORE Uzatma - Fonksiyonel Sonuçlar



# VIVID / VISTA (Faz III)

Klinik açıdan anlamlı, santral tutulumlu DMÖ  
bulunan ETDRS EDGK 20/40 ila 20/320 olan hastalar

N=406 (VIVID) N=466 (VISTA)

Randomize edilen hastalar  
1:1:1

Aflibersept  
2 mg q4 hafta

Aflibersept  
2 mg q8 hafta\*

Laser  
Fotokoagülasyon

Primer sonlanım noktası:  
Ortalama EDGK değişikliği

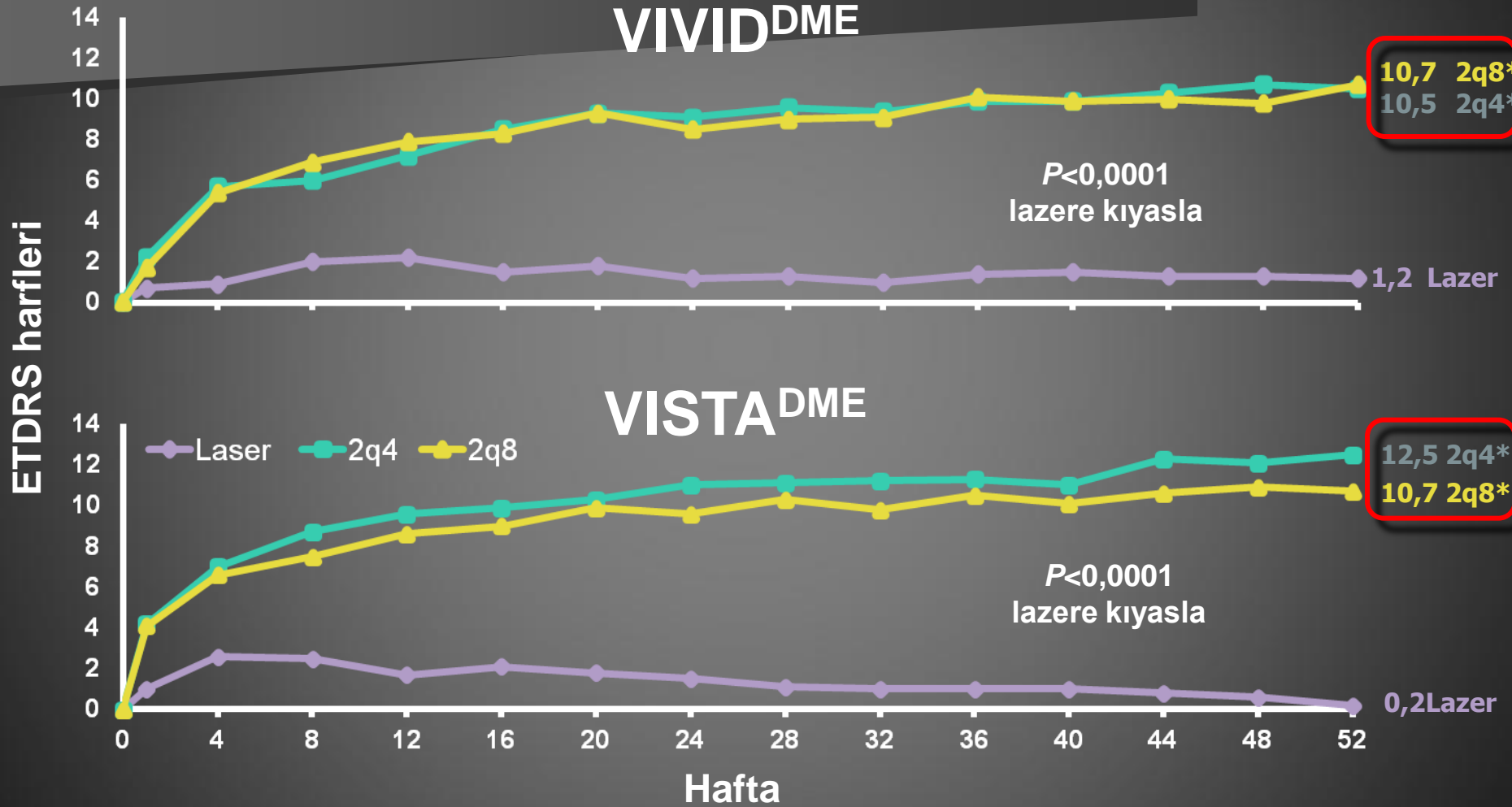
Primer sonlanım noktası:  
52. hafta

Temel sekonder sonlanım  
noktası:  
DRSS değişikliği

Tedavi 3. yıla kadar sürdürülmüştür

\*Aylık 5 başlangıç dozundan sonra

# VIVID / VISTA – Fonksiyonel Sonuçlar



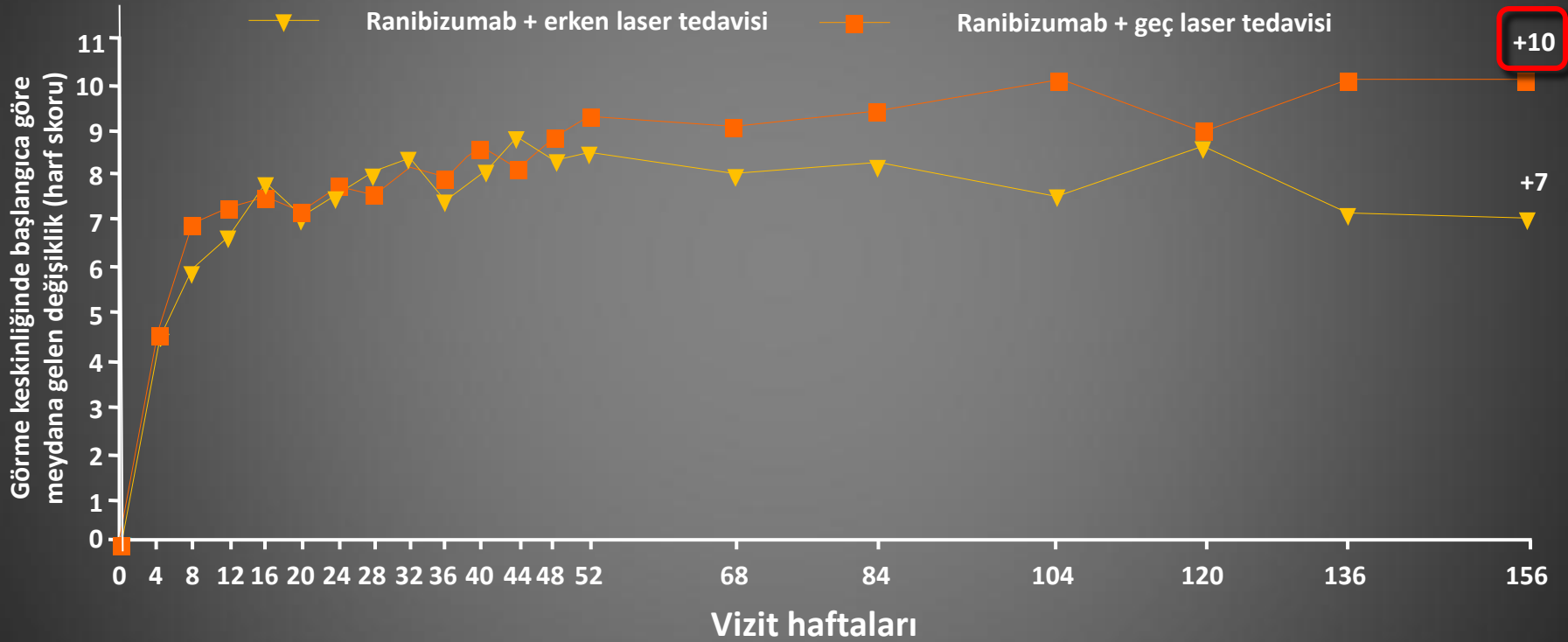
Lazere kıyasla fark testi (ANCOVA)  $P < 0,0001$ .

# DRCR-net (Faz III)





# Fonksiyonel Sonuçlar



- Geç tedavi grubundaki hastalar, erken tedavi grubuna kıyasla anlamlı olarak daha iyi GK sonuçları elde etmiştir (P=0.02).

# DRCR-net – Laser Uygulamaları

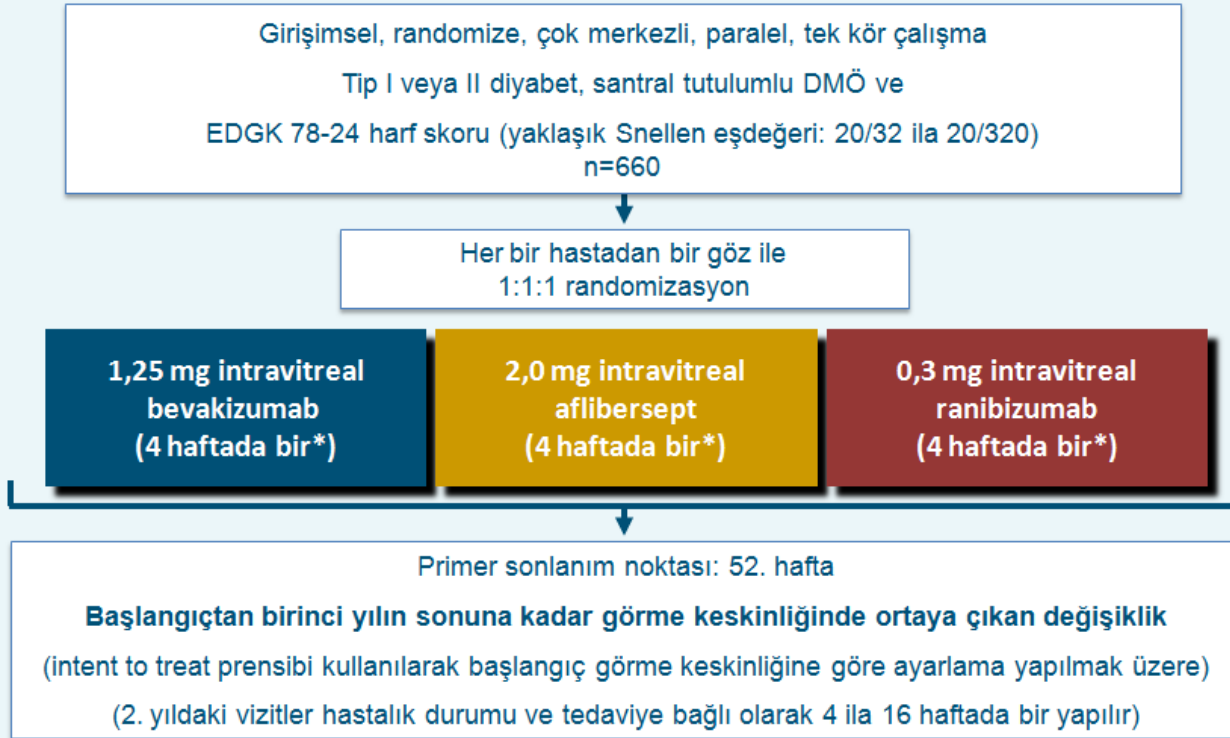
	Ranibizumab + erken laser n = 144	Ranibizumab + geç laser n = 147
1. yıldaki	% 100	% 32
2. yıldaki	% 100	% 43
3. yıldaki	% 100	% 46
4. yıldaki	% 100	% 44

# Protokol T – Uygulamalar

	Aflibersept	Bevakizumab	Ranibizumab
Medyan enjeksiyon sayısı (25., 75. persentil)*	9 (8, 11)	10 (8, 12)	10 (8, 11)
En az bir fokal/grid lazer tedavisi**	%37	%56	%46

# DRCR-net – Protokol T

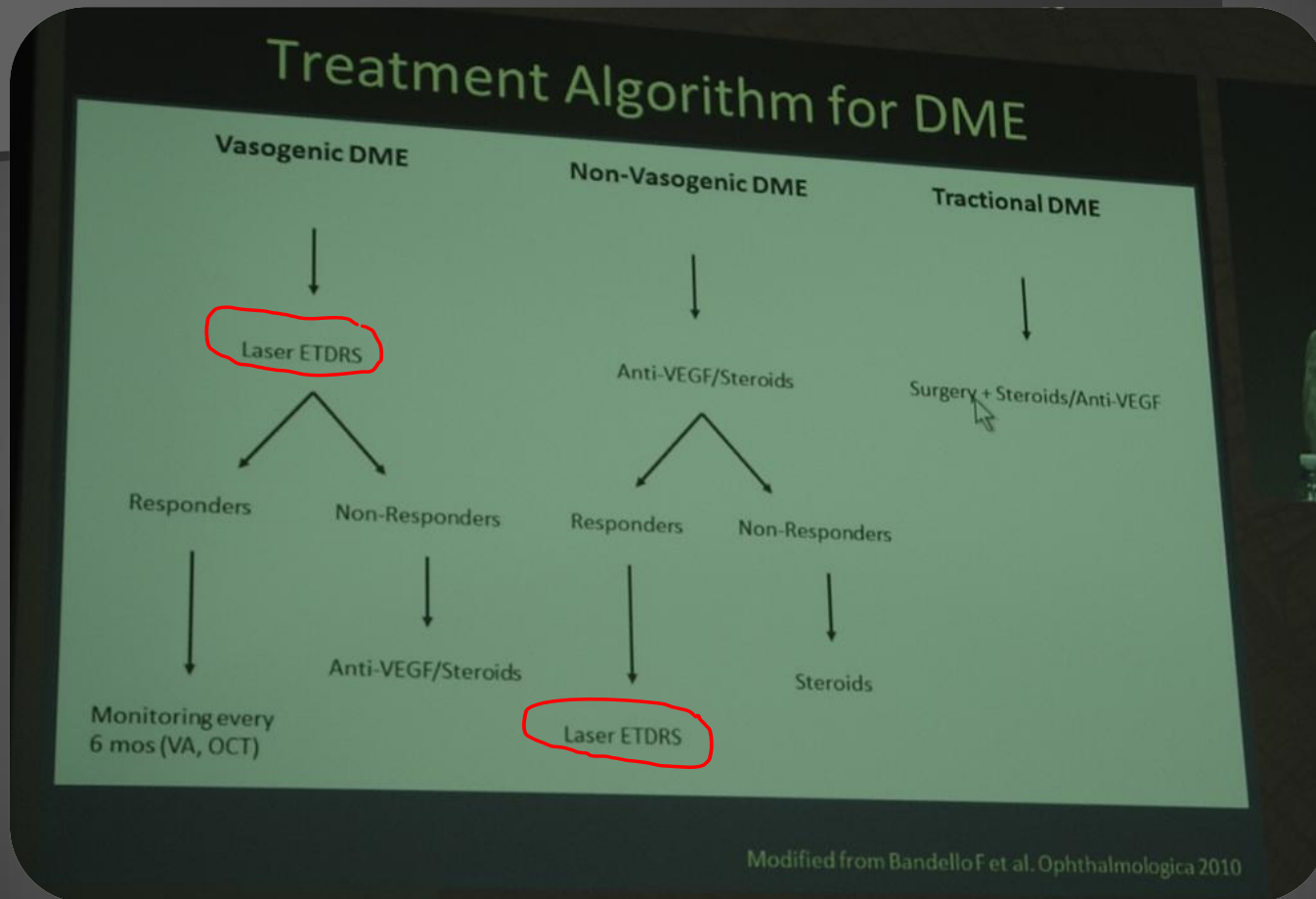
## Çalışma Tasarımı



\*OKT veya GK kriterlerine dayanan tedavi kararı; enjeksiyon öncesi ve sonrası topikal antibiyotikler araştırmacının takdirinde kullanılmıştır.  
DMÖ, diyabetik makula ödemi; ETRDRS, Diyabetik Retinopatide Erken Tedavi Çalışması; OKT, optik koherens tomografisi; GK, görme keskinliği

Görmesi: 20/20 – 20/32 arası olanlarda hangi tedavi ???

# Termal laser tedavisi, tedavinin bir parçasıdır

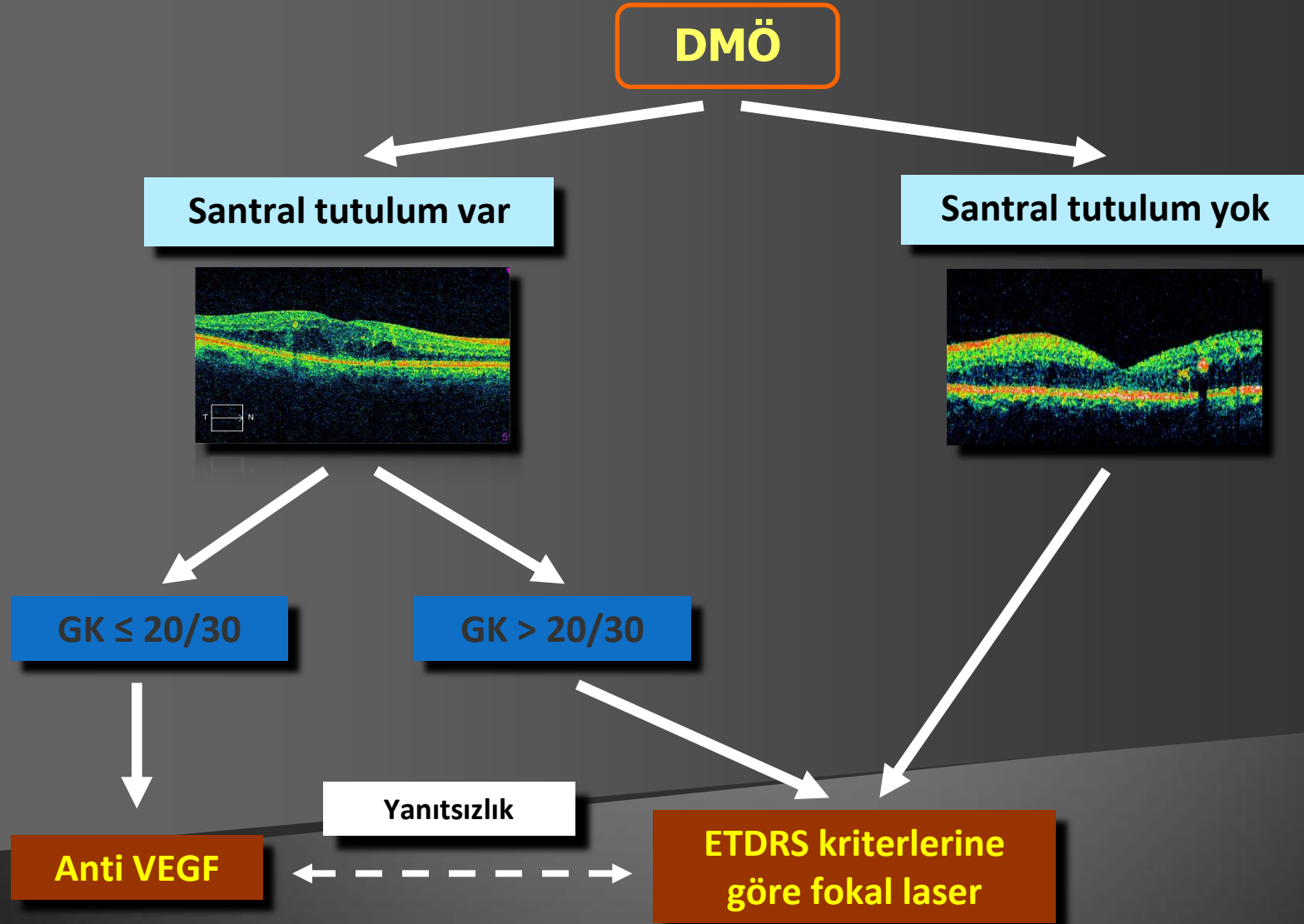


Reduced the risk of moderate visual loss ( > 15 letters ) by 50 % in eyes with severe NPDR and CSME

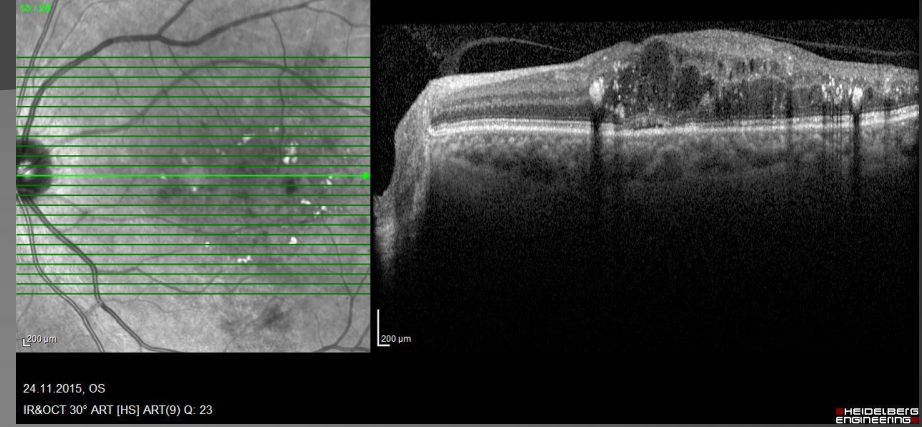
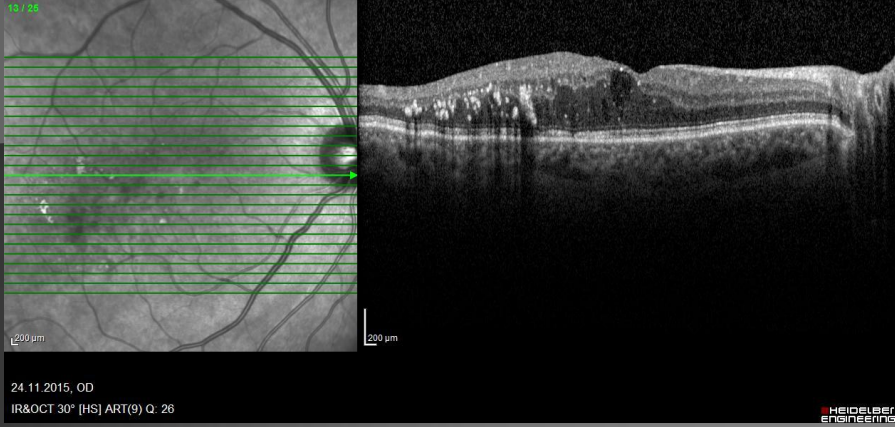
ETDRS Study Report 1 Arch Ophthal 1985



# DMÖ Tedavi Modeli



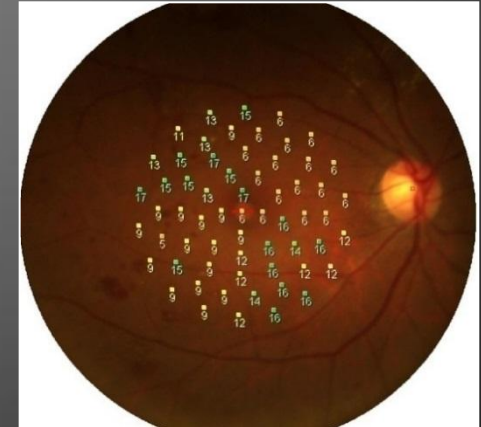
# ZH: Sağ-sol DMÖ, insülin bağımlı



Sadece DMÖ var, retinopati yok  
Her iki gözde görmeler tam  
İnce işle uğraşan bir meslek



ETDRS kriterlerine göre  
klasik fokal laser

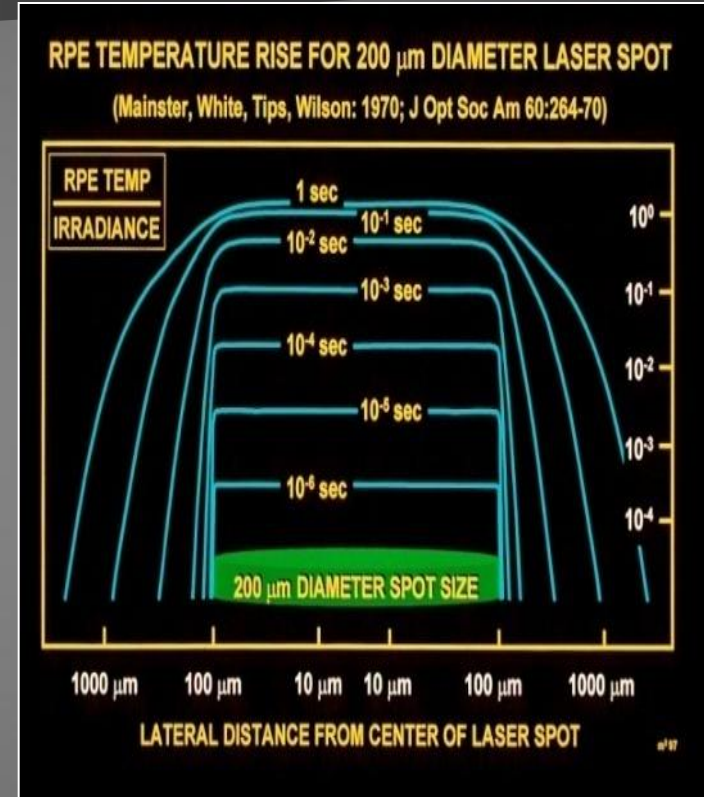


# Günümüzde DMÖ' i için tedavi seçenekleri

- Steroid
- Anti-VEGF
- Kombine tedaviler
- Laser tedavisi:

Termal laser ile:

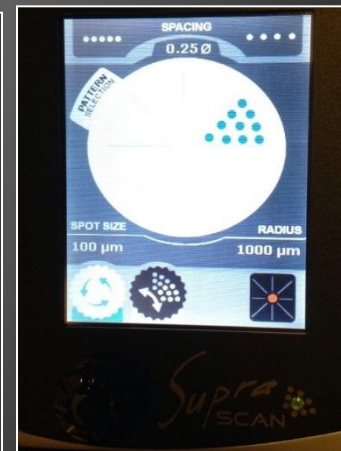
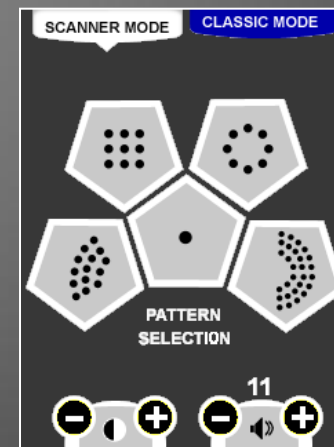
Verilen enerjinin % 10-40' ı komşu dokuyu zedeler



Kollateral termal hasar

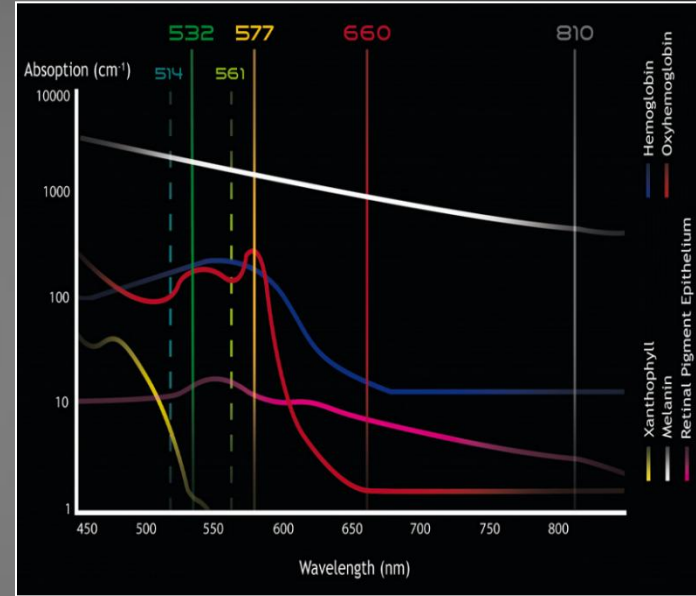
# Klasik termal laserin yan etkilerini azaltma

- Modifiye – ETDRS protokol
- 577 nm sarı dalga boyunu, 532 nm yeşil dalga boyuna tercih etmek
- Klasik CW termal laseri, hafif yanık / eşik-altı olarak kullanmak
- CW termal laser ile pattern scanning (multispot) eşik-altı spotlar (Pascal, Navilas)
- Doku koruyan mikropulse laser stimulation:  
Mikropulse laser + pattern (multispot)  
577 nm sarı dalga boyu



# 577 nm sarı dalga boyu

- RPE & Koriokapillarisden maksimum emilim
- Az güç ile daha homojen laser spotu
- Optik ortam bulanıklıklarında daha iyi penetrasyon
- Maküla pigmentinden emilmeme, FAZ' a daha yakın tedavi



Mainster MA: Wavelength selection in macular photocoagulation. Tissue optics, thermal effects, and laser systems. Ophthalmology. 1986;93:952-958

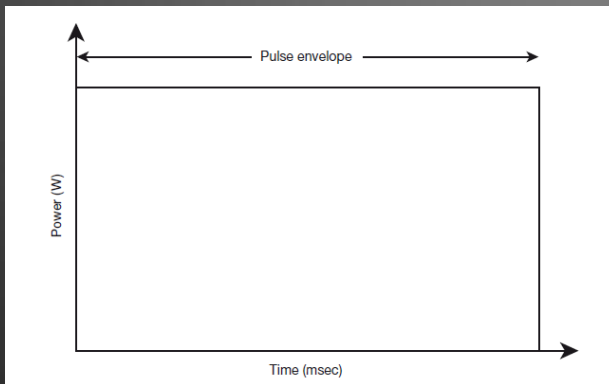
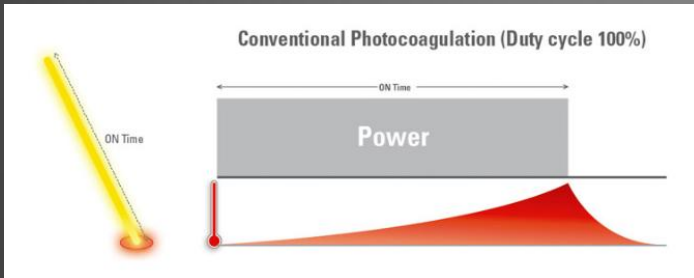


# Mikropulse mode

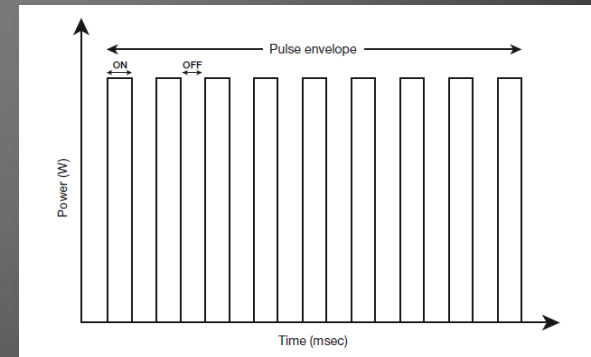
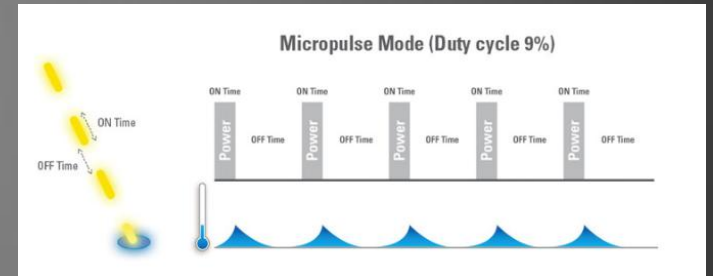
## Fotokoagülyasyondan fotostimülyasyona

- Komşu dokuya termal hasar yok
- Retinaya minimal enerji gönderilir
- Pulslar arası dokunun soğuması için zaman var
- Laser skarları oluşmaz ve çok az görülebilir (FFA,FAF)
- Retinal doku canlı olup, restoratif doku mediatörleri salınır ve dengelenir

FAZ' yakın tedavi, skotom yok, tekrarlanabilme

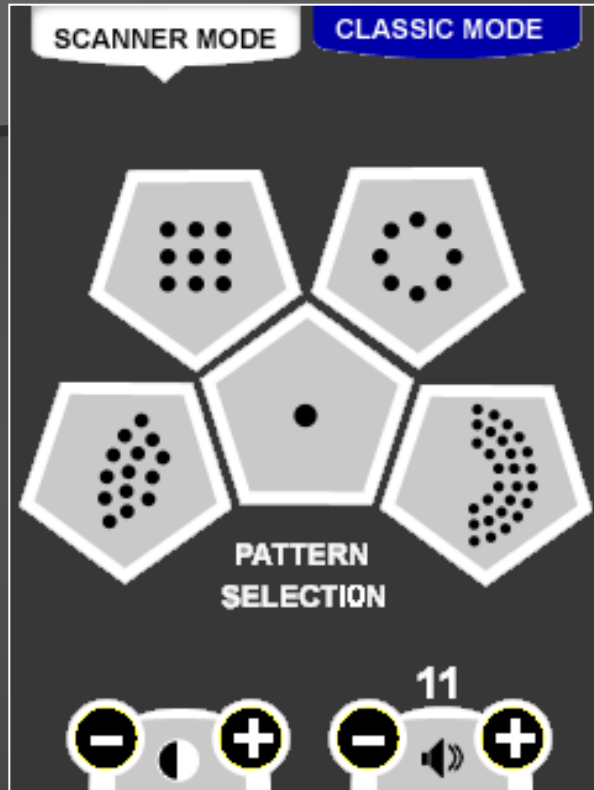


Continuous (CW) laser

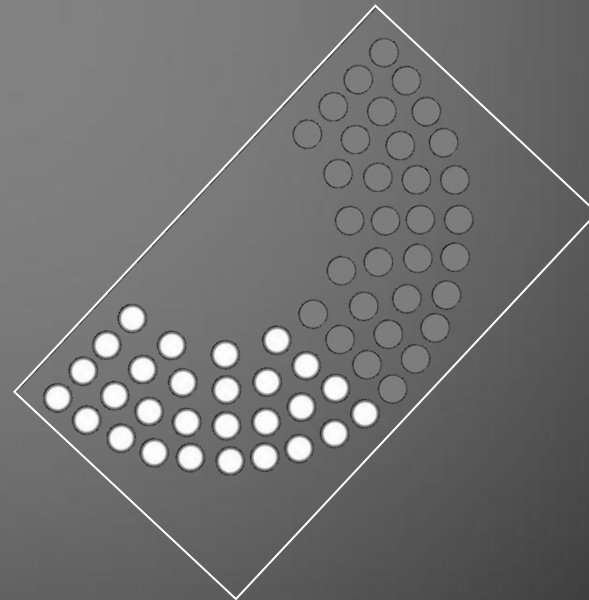


Mikropulse laser

# Mikropulse / Multispot ( pattern ) laser stimulation

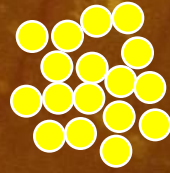


- **Power:** MPL, barely visible spot / 2
- **Duration:** 200 ms
- **Spot size:** 160 micron
- **Duty Cycle:** % 5
- **Çeşitli pattern seçimi**

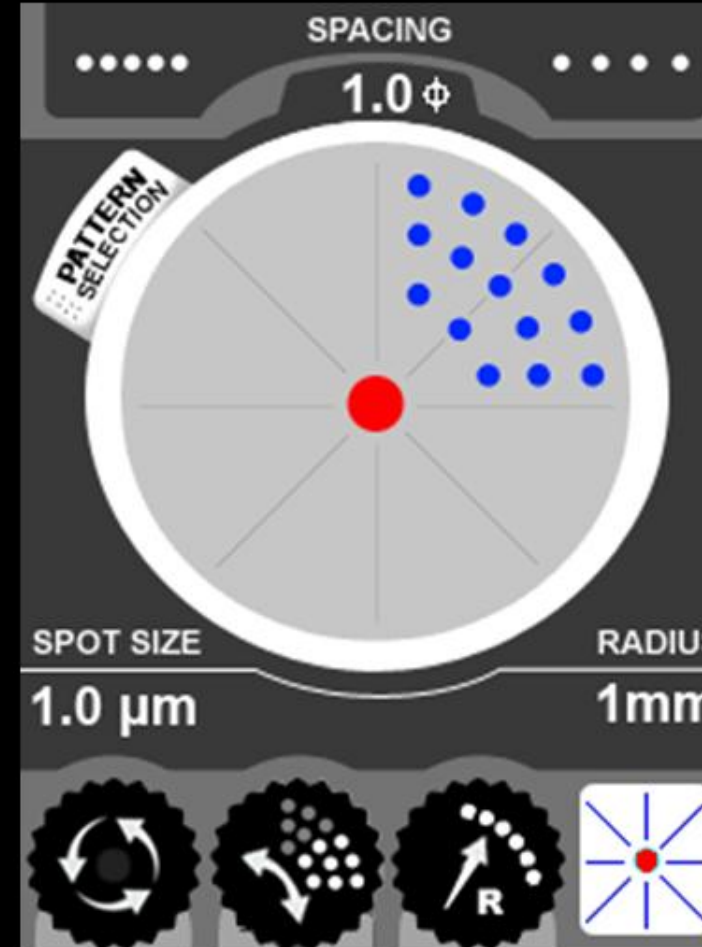
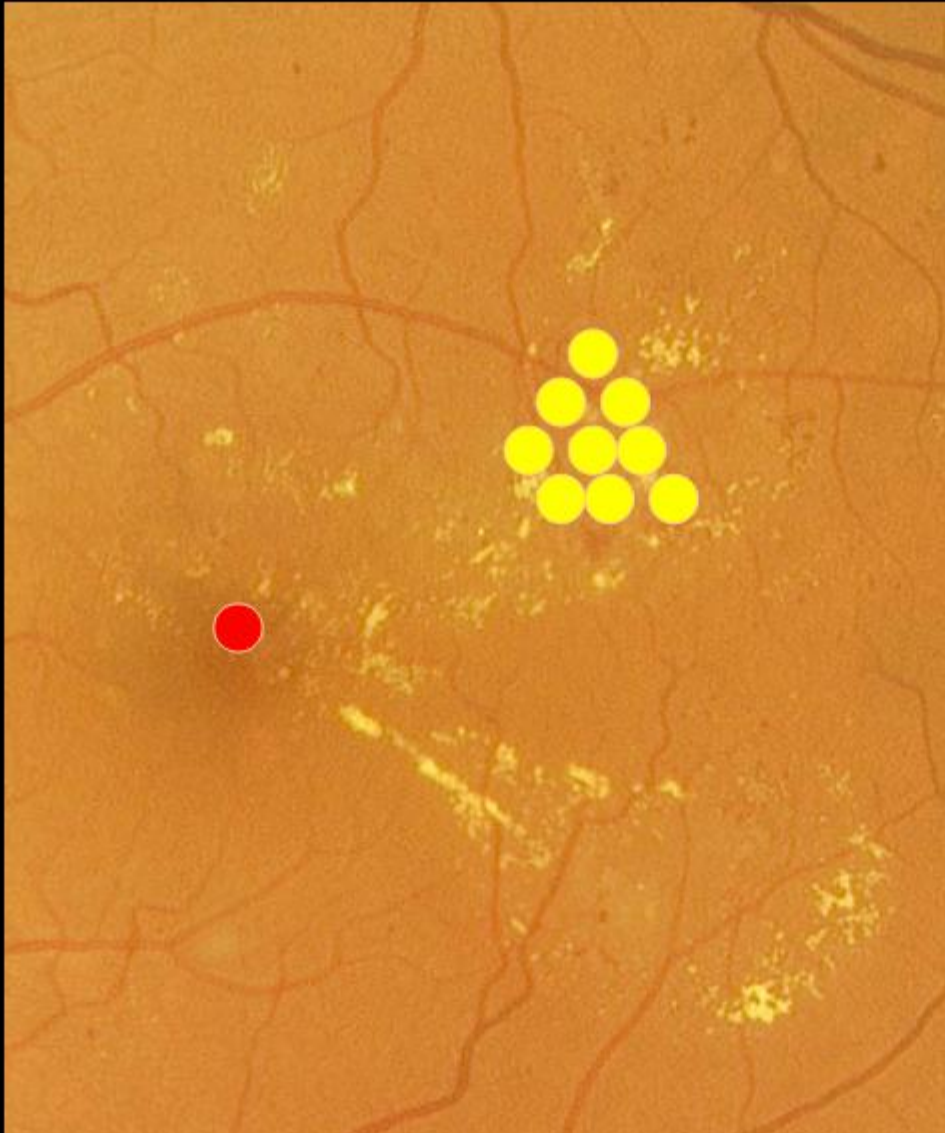


Low intensity: % 5 Duty Cycle

High density : bitişik spotlar uygulamaları ( üst üste binme yok )



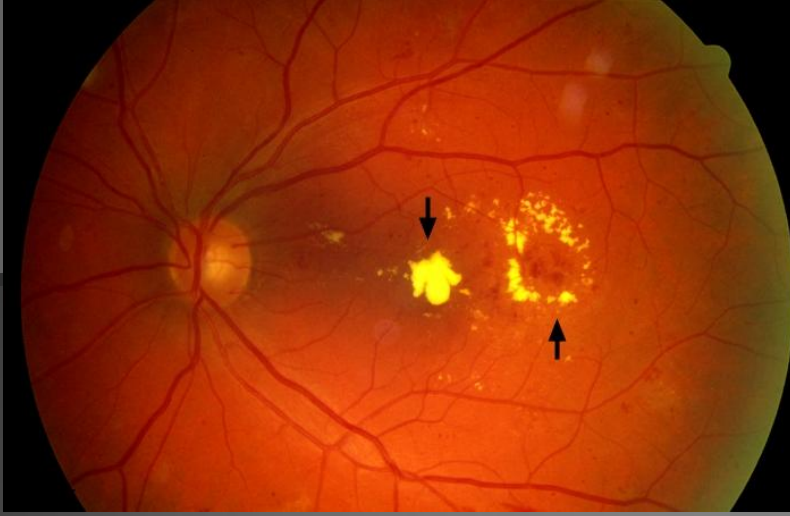
# Fovea tutulumu olmayan KÖMÖ



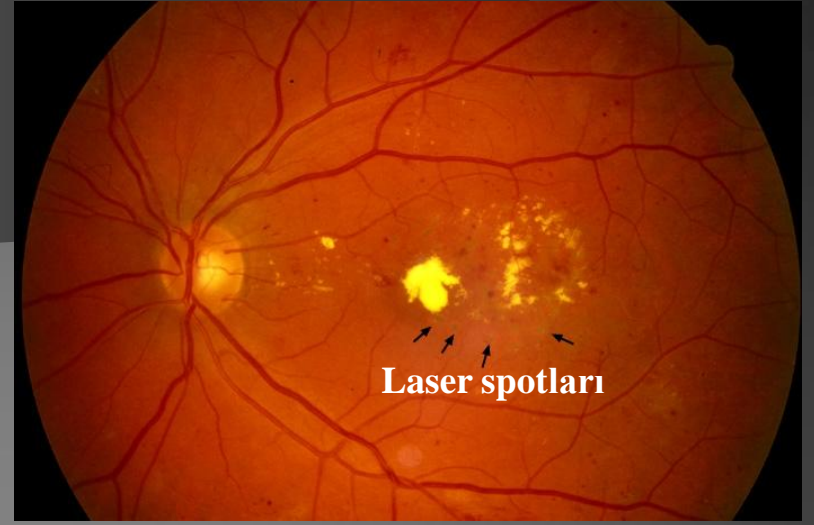
Maküler Grid



# Klasik termal laser



Laser öncesi



Laser sonrası 4. ay



Laser sonrası 8. ay

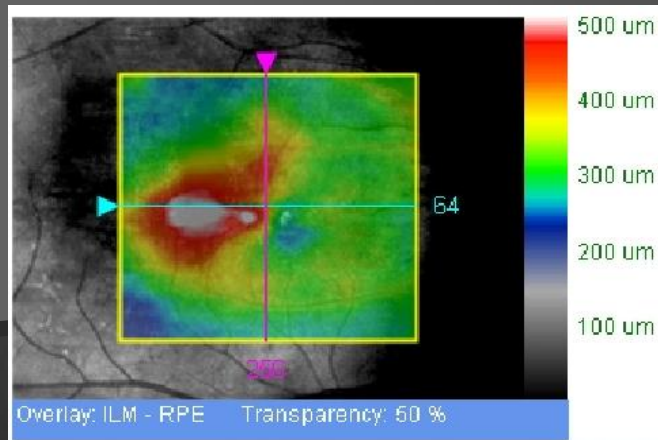
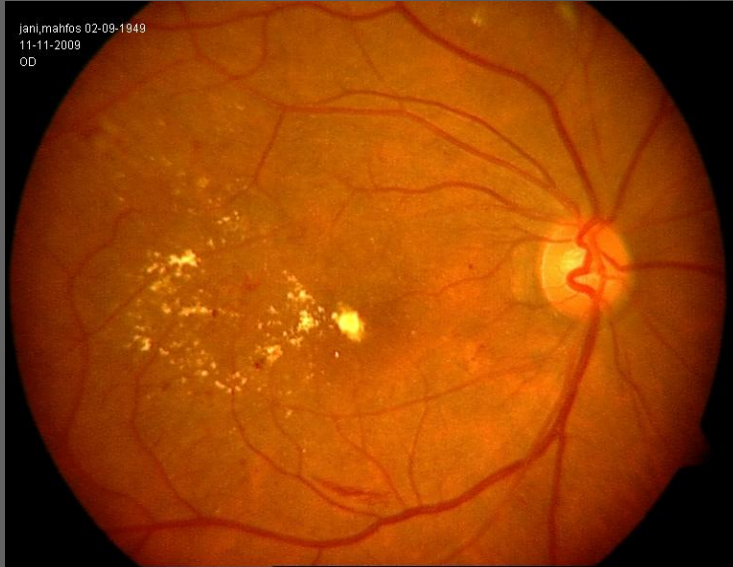


Laser sonrası 12. ay

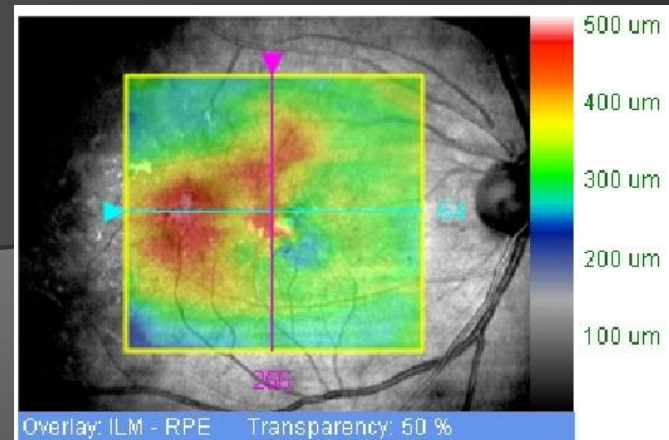
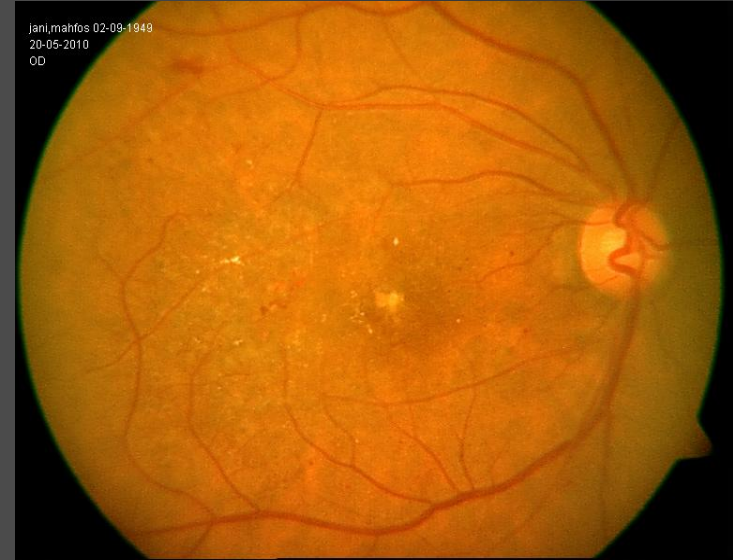


# Klasik termal laser

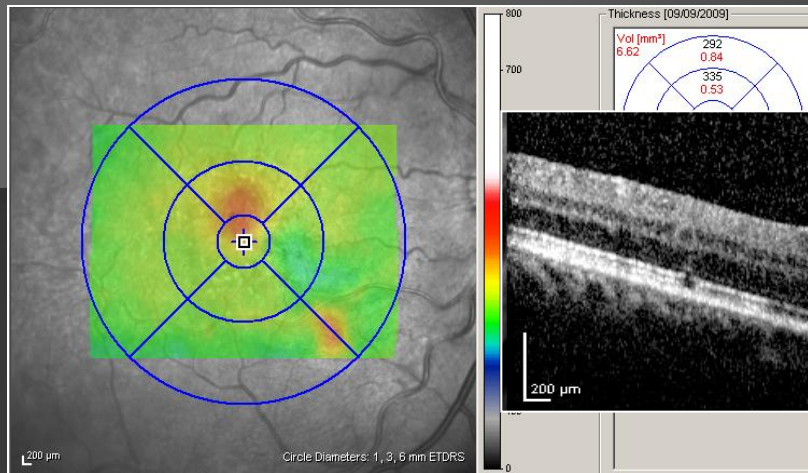
Laser öncesi



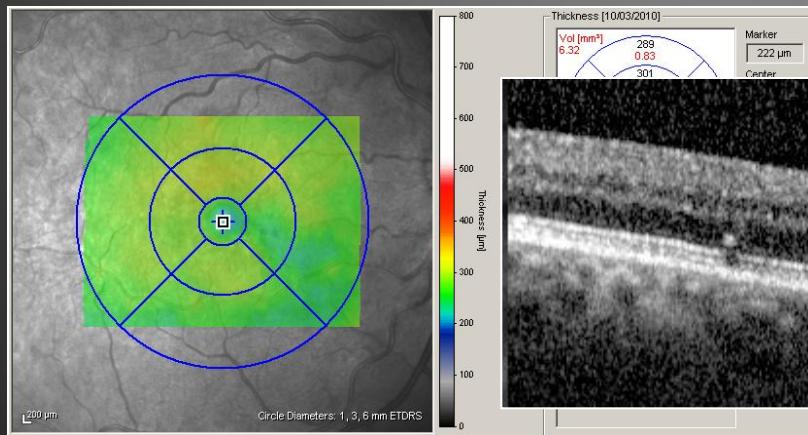
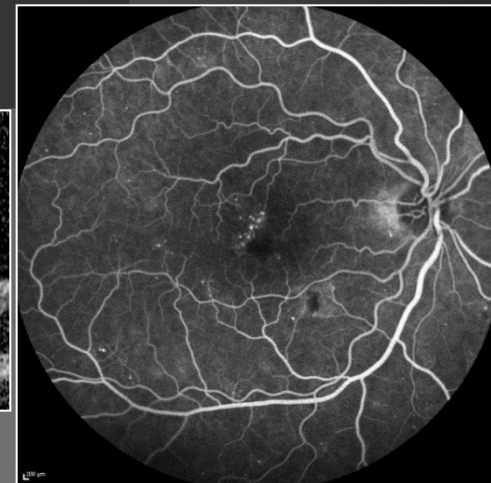
Laser sonrası 12. ay



# OCT- guided mikropulse tedavi / DMÖ



Pre op OCT – VA 0.5

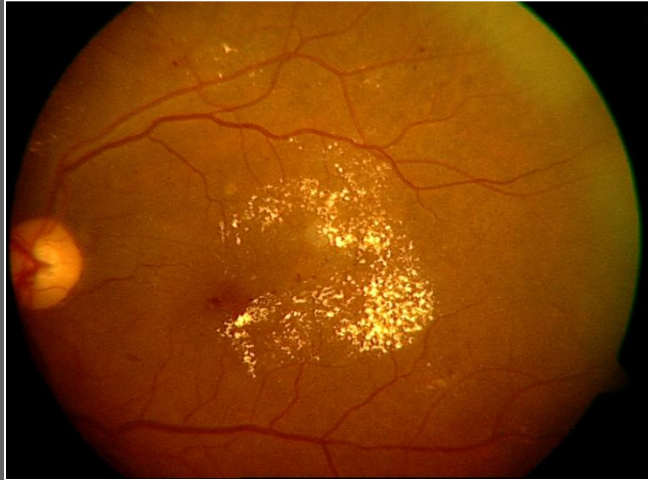


Post op OCT – VA Tam

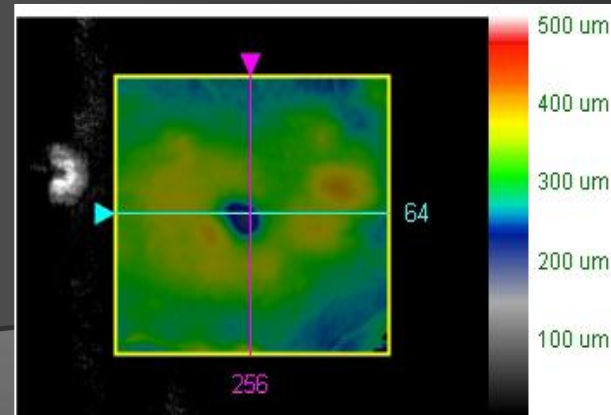
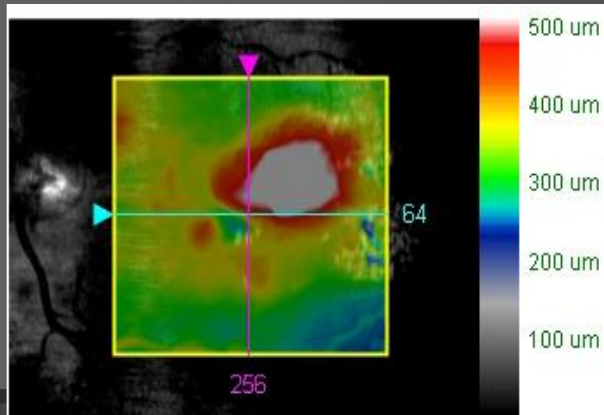


# Mikropulse Sarı Laser

Laser öncesi (VA 37 harf)

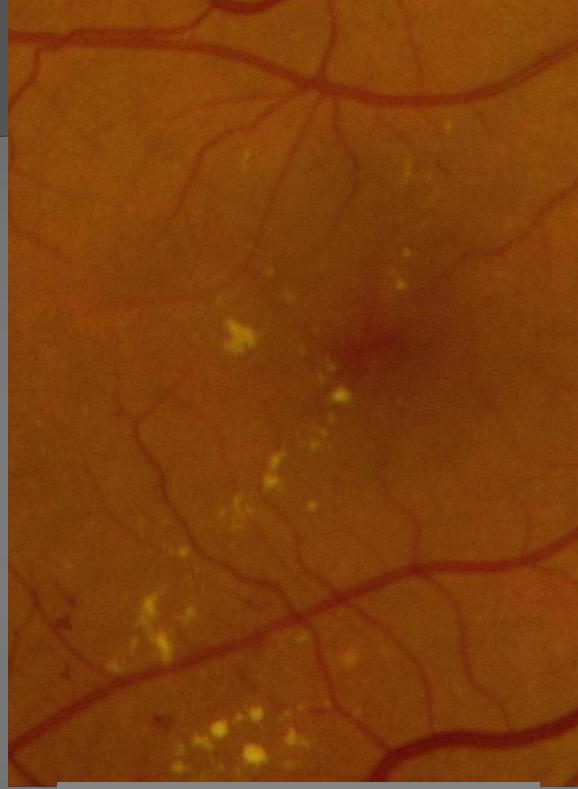
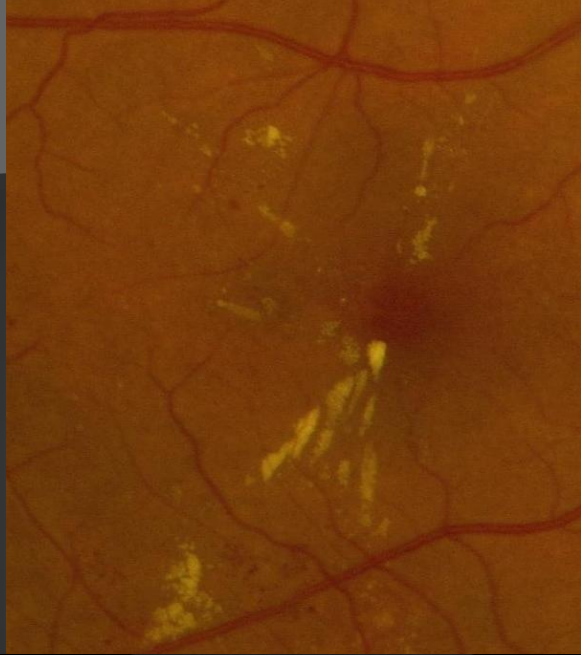


Laser sonrası 12. ay (VA 57 harf)

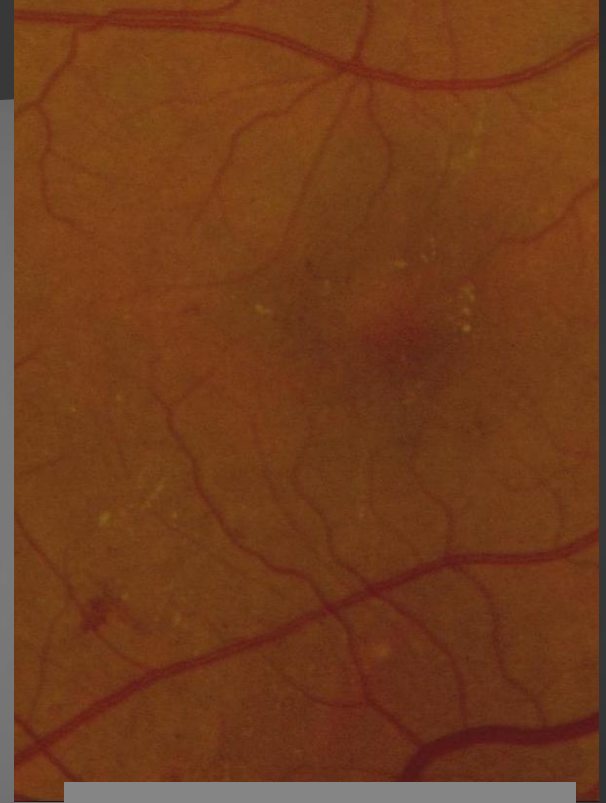


# Mikropulse Multispot laser tedavisi

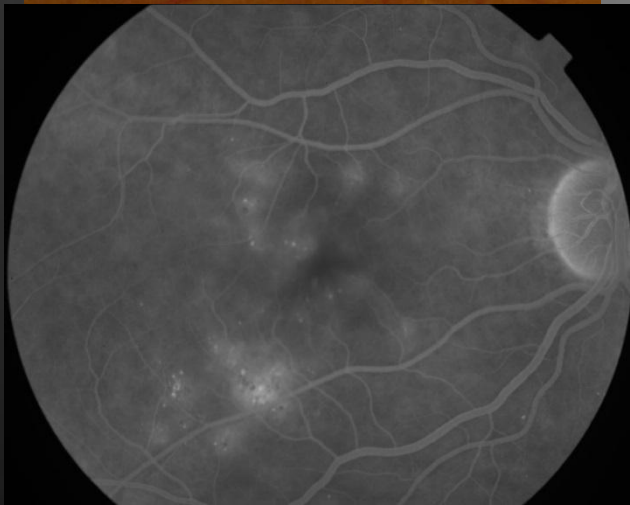
Laser öncesi



Laser sonrası 4. ay

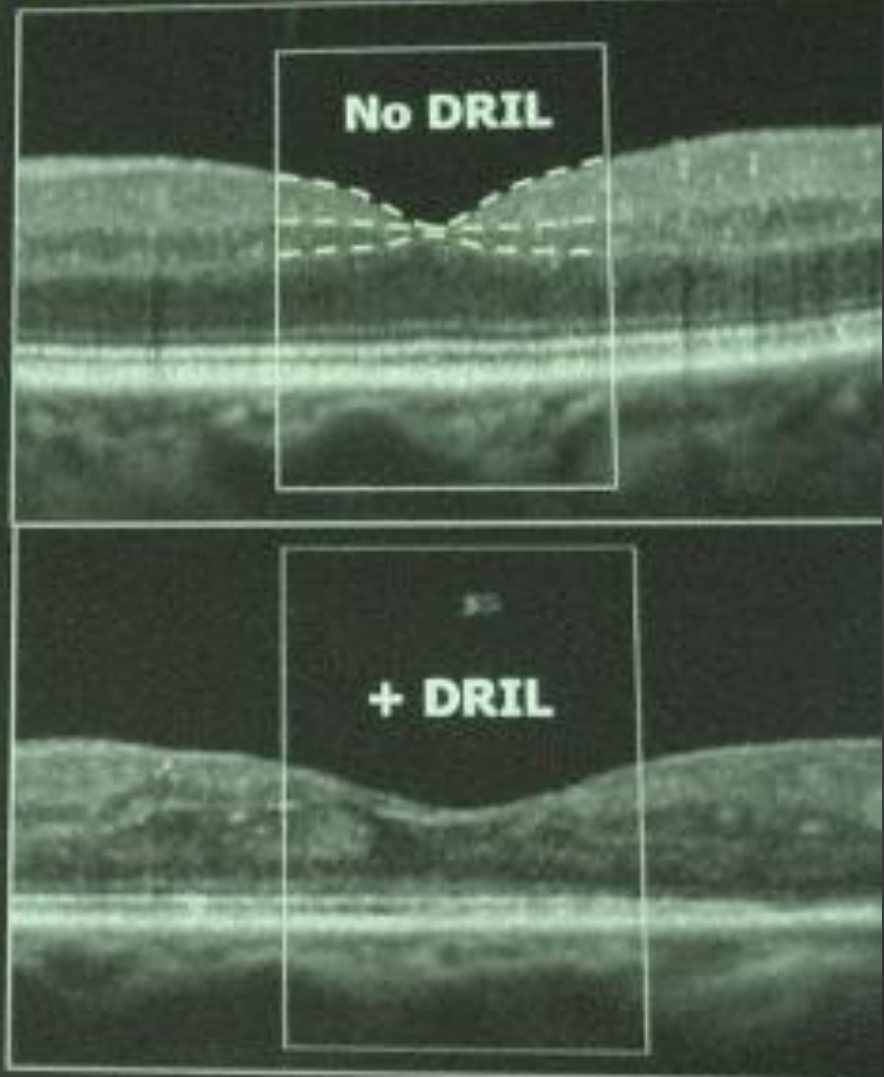


Laser sonrası 12. ay



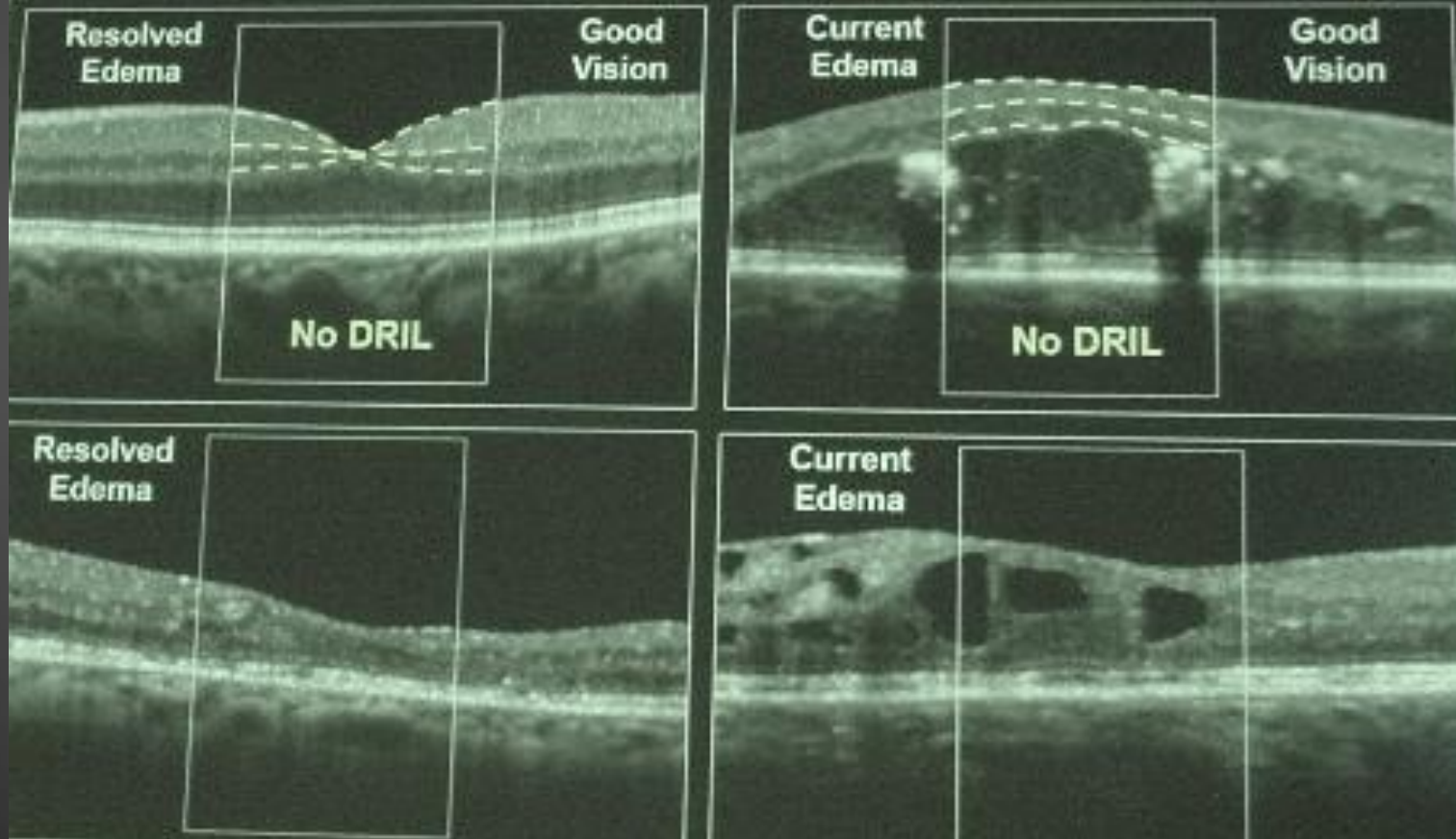
# Spectralis SDOCT Features

- Outer layer disruption
- Cysts
- Hyperreflective foci
- Ring sign
- Disorganization of the Retinal Inner Layers (DRIL) →



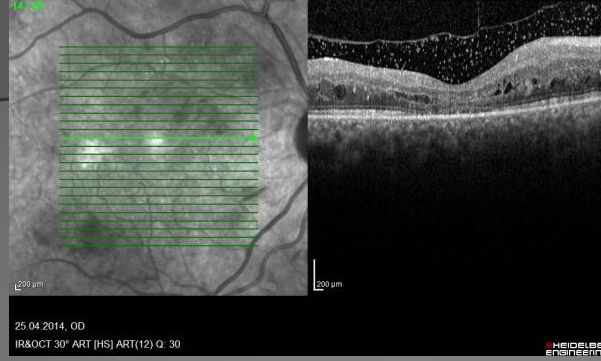
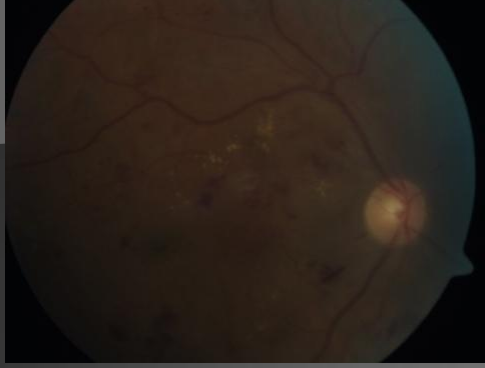


# Disorganization of Retinal Inner Layers (DRIL) and Vision

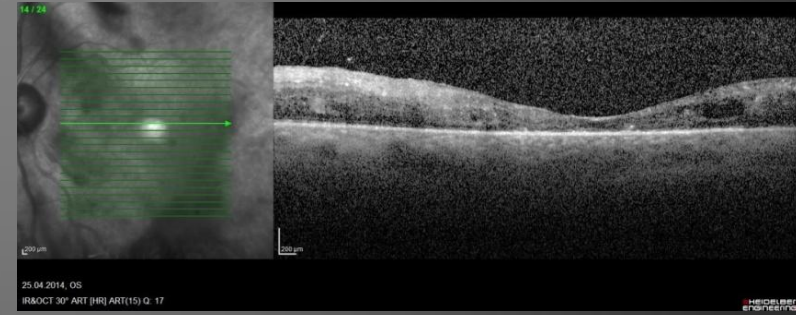
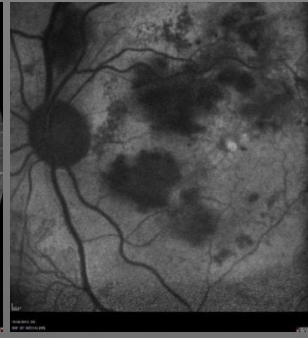
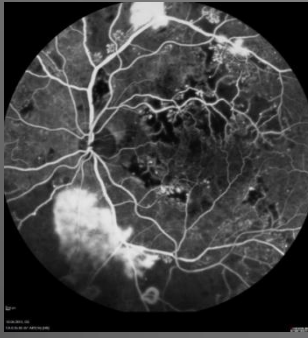
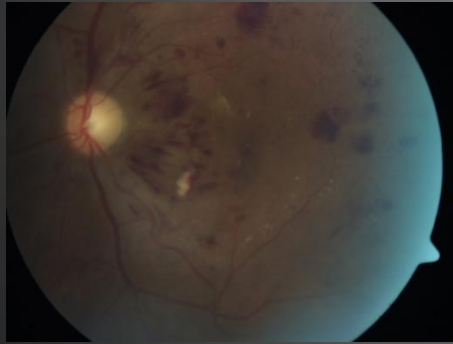




# Diabetik iskemik makülopati / OCT

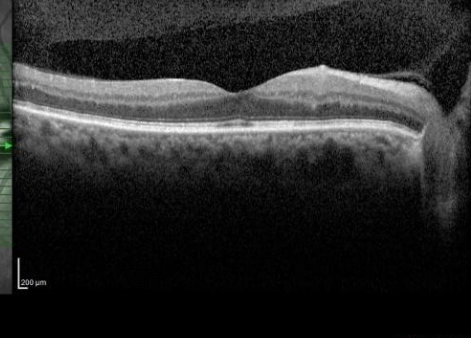
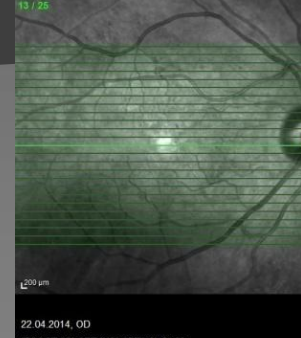
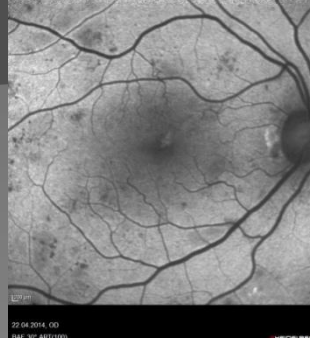
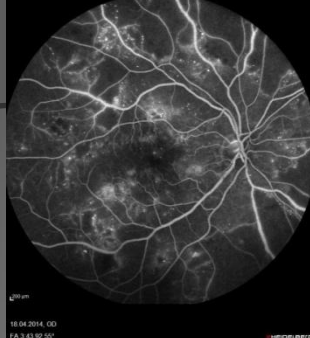


GCL, maküler iskemide ilk hasarlanır

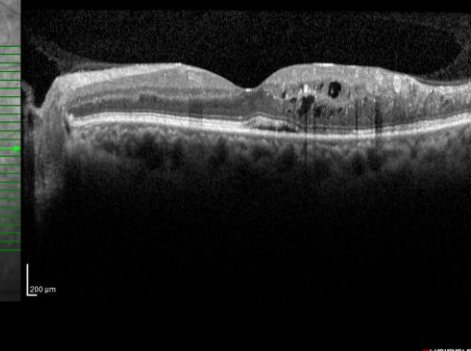
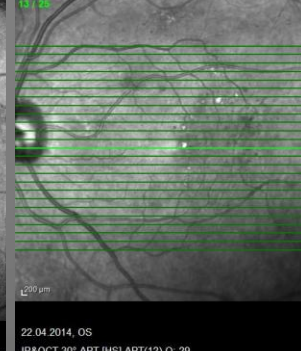
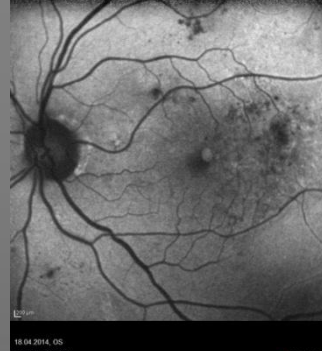


İncelmiş ve homojen hale gelmiş (tabakaları kaybolmuş) retina

# HG: Diabetik retinopati, her iki göz



İskemik hasar yok

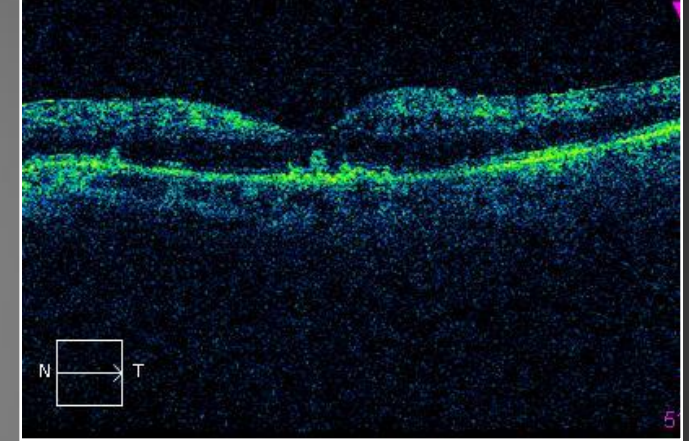
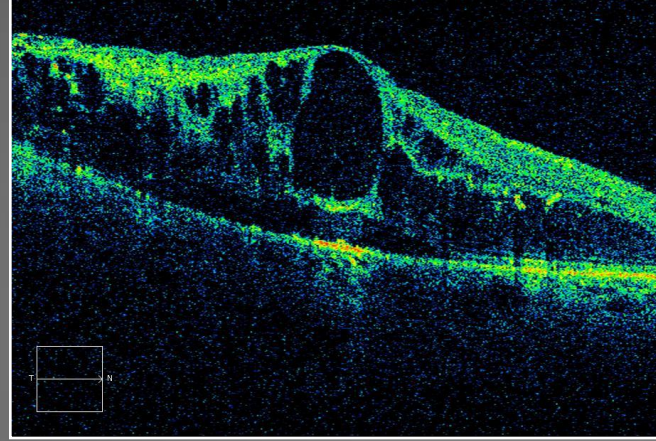
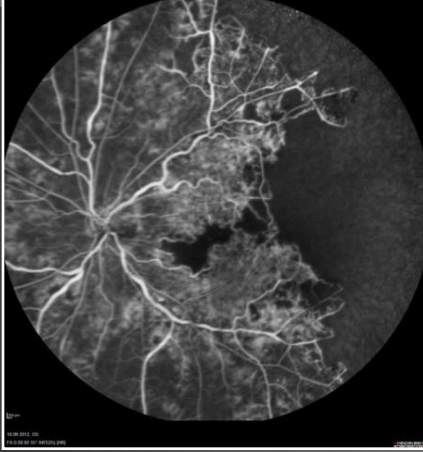


İç retinal iskemik değişiklikler  
Temporalde retinal atrofi

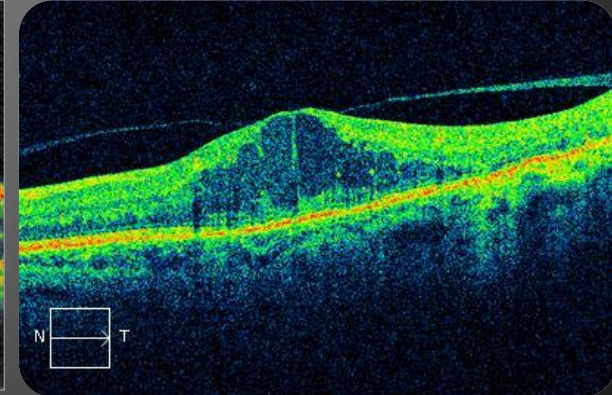
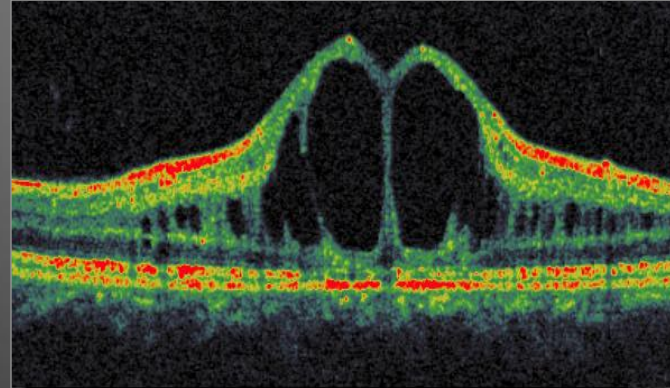
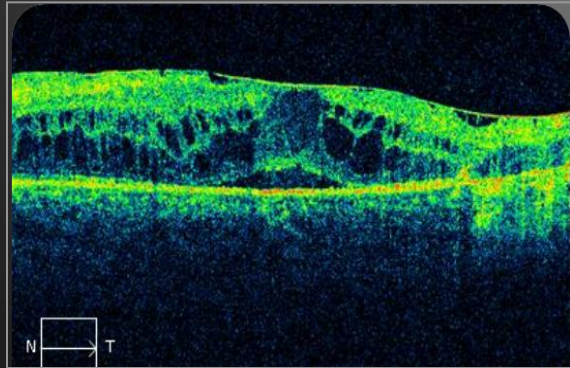


# DIŐ RETİNAL İSKEMİ

- \* Ciddi olarak hasarlanmış KRB' inden koroidal eksudasyon
- \* Bozulmuş koriokapillaris, RPE atrofik deęişiklikleri
- \* Dıő segment – RPE arasında yüksek yansıtıcı birikintiler
- \* Dıő retinada pigment birikintileri



## Dıő retinal iskemi yok



# Mikropulse laserin etki mekanizması

- Isınmış ama ölmemiş doku stres cevabı oluşturur (RPE stimülasyonu)
  - \* Faydalı intraselüler biyolojik faktörlerin salınması /dengelenmesi ( PEDF, TSP1, SDF1,  $\beta$ -Actin, VEGF )
  - \* Sitokinlerin normalleşmesi
  - \* Bu faktörler anti-anjiogenik ve tamir edici
- RPE hücreleri, çevre alandan proliferer olur ve göçer  
Birkaç gün içinde tedavisi bölgesini örter

Shafiee A, IOVS 2000; Figueroa J, BJO 2009; Vojosevic S, Retina 2010  
Lavinsk D, Retina 2014

# DRIL ve dış retinal iskemi varlığında

İntravitreal steroid ???

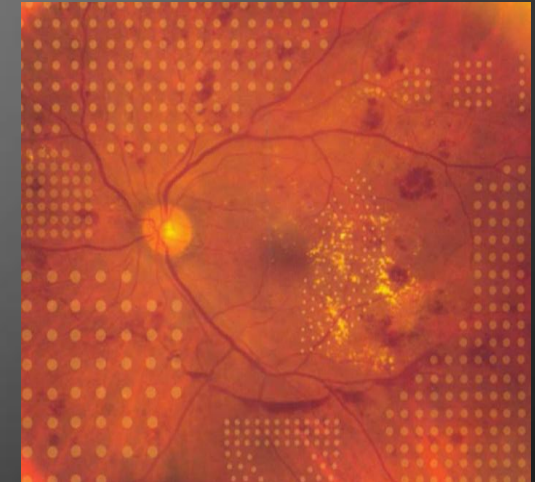
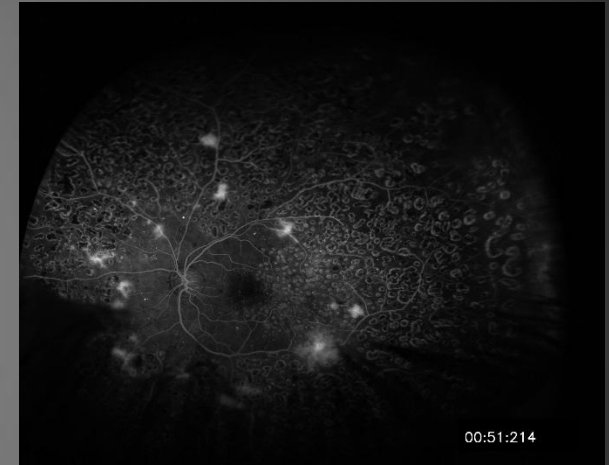
Anti-VEGF ???

Mikropulse laser ???



# Pattern scan (multispot) klasik termal CW laserler PASCAL, NAVILAS

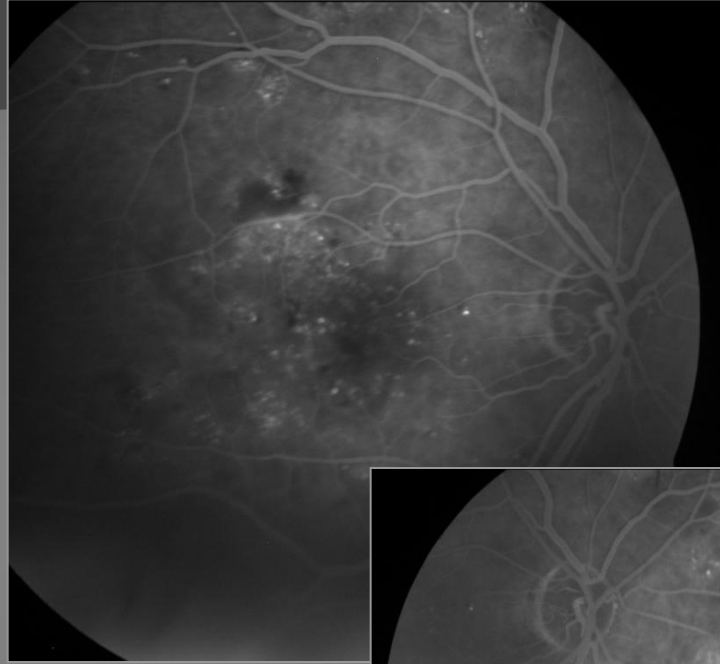
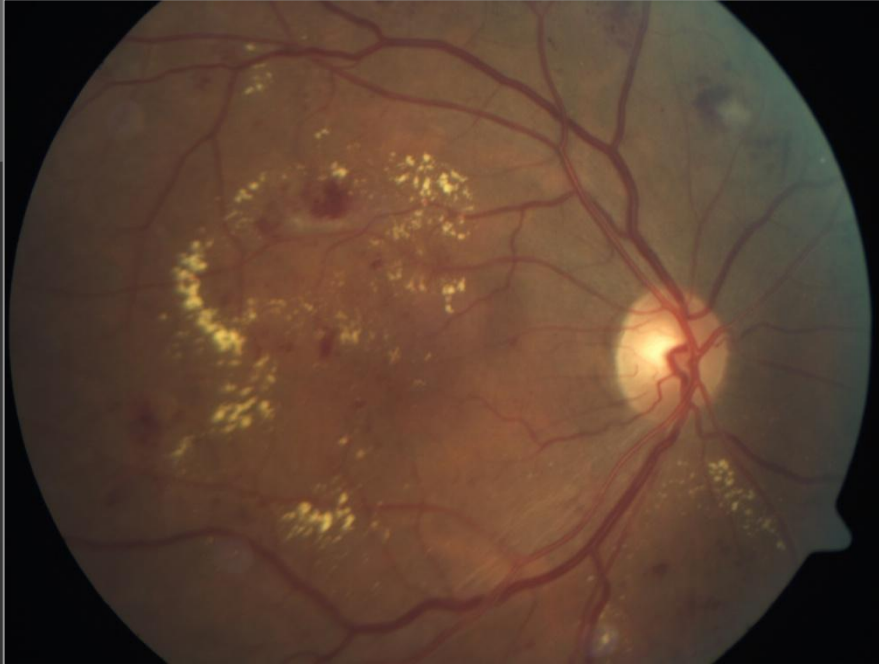
- CW termal laser: yeşil, sarı dalga boyu
- Çok hafif yanık / eşik altı
- Pattern scan ( multispot array): multiple laser yanıklarının bir defada uygulanması
- Çok kısa süreli laser atışı (20msn)
- Geniş açılı FFA' daki non-perfüze alanlara hedeflenmiş laser fotokoagülasyonu



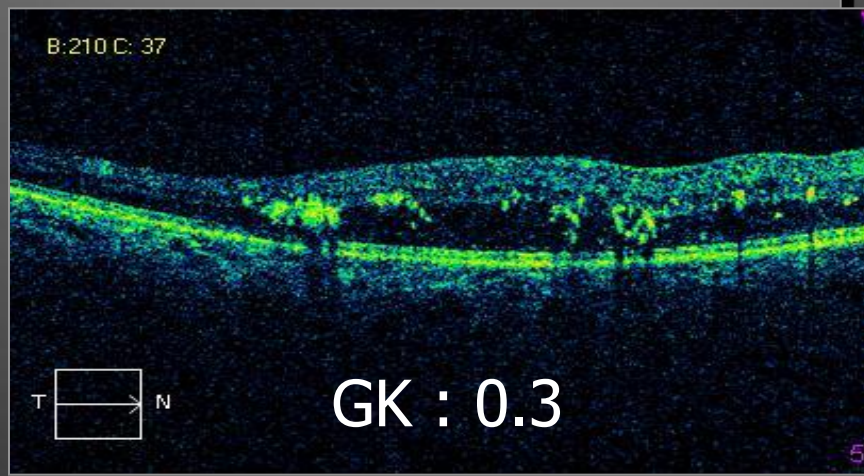


**Olgu**

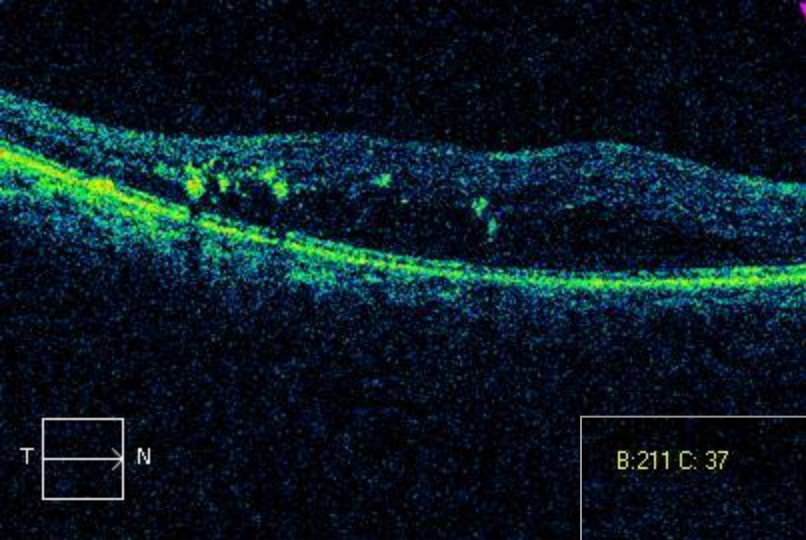
61 yaş, kadın, Tip 2 DM (15 yıl)  
5 x ranibizumab



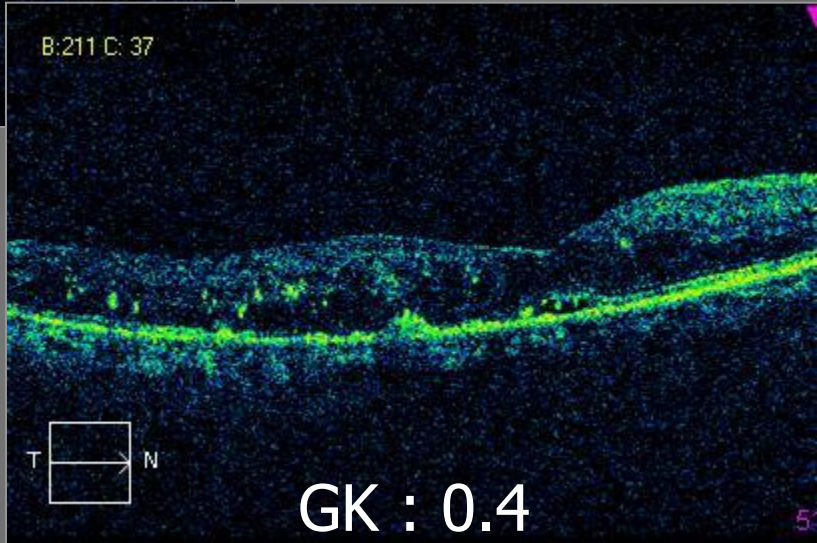
Perifer iskemi



laser

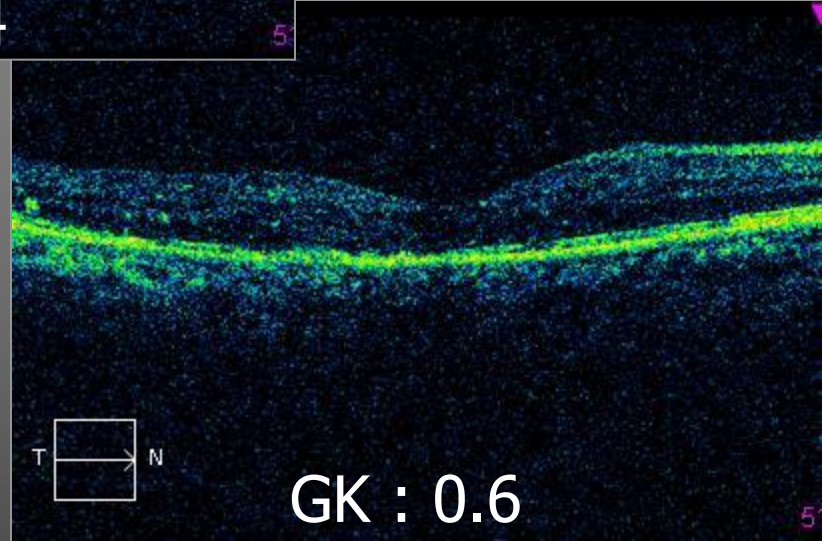


B:211 C: 37



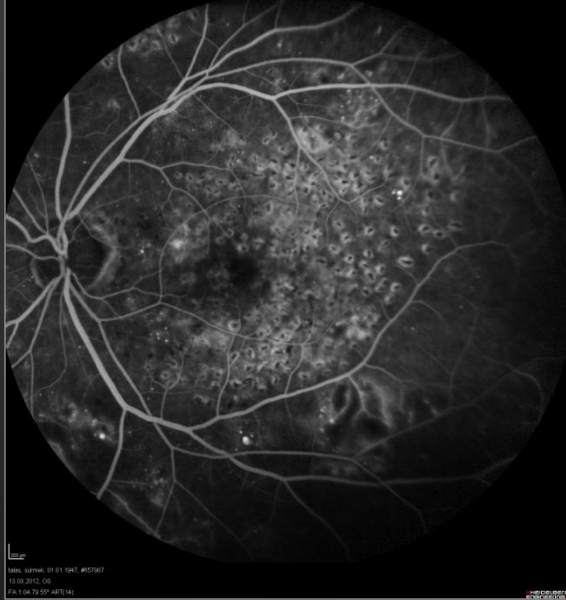
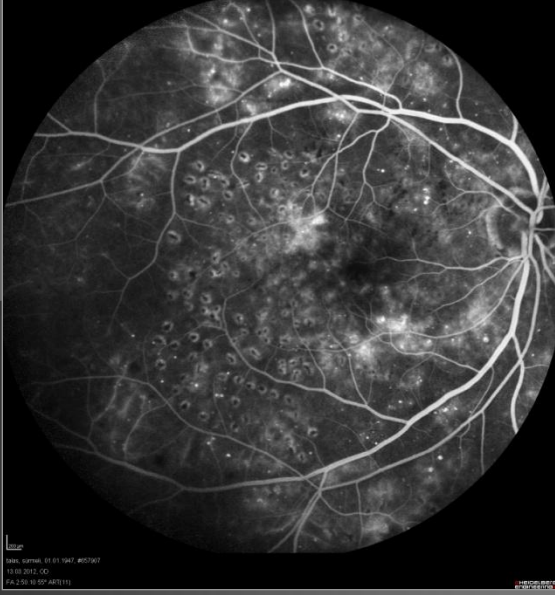
GK : 0.4

1 yıl sonra



GK : 0.6

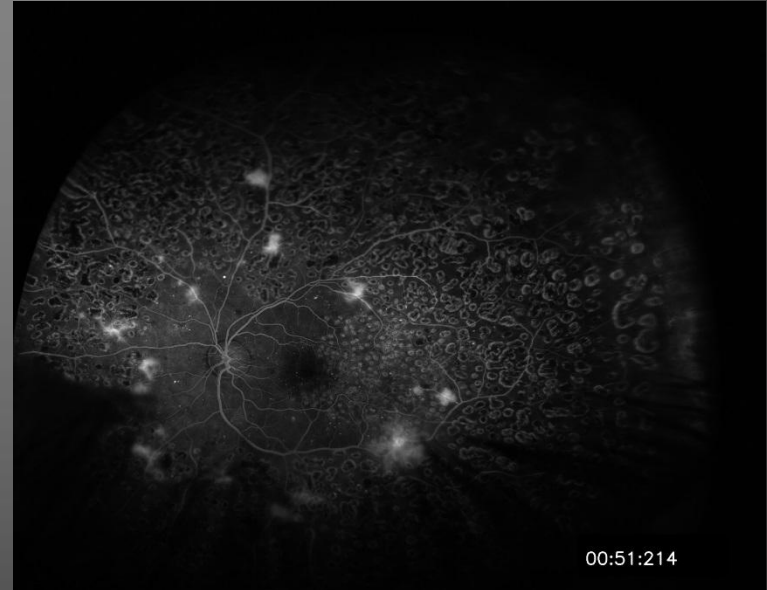
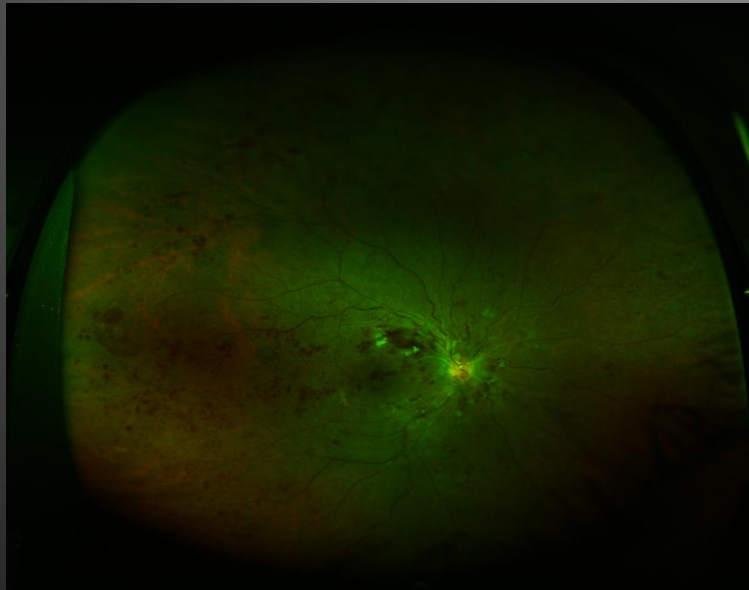




Maküler lasere rağmen  
DMÖ' nin gerilememesi

Periferdeki hipoksik alanlara  
dağınık laser ilavesi

# Geniř aılı FFA rehberlięinde hedeflenmiř pattern laser uygulamaları



# DMÖ tedavisinde laserin yeri vardır

- Klasik CW termal laser ile, modifiye ETDRS protokolü (light) Pattern eşik-altı, mikropulse laserler
- **Laserin primer endikasyonu:**
  - \* Görmesi 0.7 – tam arası, retinopatinin olmadığı foveal / parafoveal DMÖ
  - \* DMÖ ile birlikte periferik iskeminin bulunması (Geniş açılı görüntüleme)
- **Laserin sekonder endikasyonu:**

Anti-VEGF / steroid tedavisi sırasında, residüel maküla ödemi varlığında, 6 aydan sonra laser ile kurtarma
- **Araştırma:** DRIL, dış retinal iskemide sarı dalga boylu mikropulse laserin etkinliği ???