The Evolution of Retinal Laser Technology and Retinal Photocoagulation as Therapeutic Modality

Kfir Azoulay,[1] Pazit Pianka[2] and Anat Loewenstein[3]

1. General Manager, Ophthalmology Department, Lumenis, Amsterdam, Netherlands; 2. Senior Ophthalmologist and Medical Director, Lumenis, Yokneam, Israel; 3. Vice Dean, Faculty of Medicine and Chairperson, Department of Ophthalmology, Tel Aviv Medical Centre, Tel Aviv, Israel

Abstract

The effect of thermal insult to ocular tissue was first recorded in Western literature over two millennia ago. During the early scientific period and the ensuing eras, our understanding of this phenomenon, as well as our ability to accurately deliver dose-controlled therapeutic thermal energy to retinal tissue, have improved greatly. Since their commercial introduction in 1970, ophthalmic photocoagulation laser systems have been playing a cardinal role in the treatment and/or management of various ocular pathologies, predominantly though not limited to, retinal pathologies. Seminal studies, such as the Diabetic Retinopathy Study (DRS) and Early Treatment Diabetic Retinopathy Study (ETDRS), have solidified the role of such tools in the ophthalmologist's therapeutic armamentarium; and to this day, as either stand-alone treatment or in combination with pharmacological agents, retinal laser therapy is recognised as the 'gold standard' for treating diabetic macular oedema (DME) and proliferative diabetic retinopathy (PDR). The continuous elucidation of the role that the retinal pigmented epithelium (RPE) plays in the emergence of retinal pathologies has prompted researchers and clinicians to further investigate selective RPE treatments – featuring significantly reduced or altogether devoid of collateral thermal damage to inner neural retinal structures with limited regenerative capacity. The convergence of electronic dosimetry, diagnostics imaging and new therapeutic laser modalities into a singular entity may serve as the technological platform for successfully employing such therapies in the near future.

Keywords

Ophthalmic lasers, history of lasers, laser technology, laser evolution, thermal damage to retina, photocoagulation, multi-wavelength lasers, Diabetic Retinopathy Study (DRS), Early Treatment Diabetic Retinopathy Study (ETDRS), scanning lasers, selective retina therapy (SRT), image-guided laser therapy

Disclosure: Kfir Azoulay and Pazit Pianka are employed by Lumenis, manufacturer of ophthalmic lasers. Anat Loewenstein is a paid consultant to Lumenis.
Received: 15 June 2012 **Accepted:** 23 July 2012 **Citation:** *European Ophthalmic Review*, 2012;6(3):185–9 *DOI: 10.17925/EOR.2012.06.03.185*
Correspondence: Kfir Azoulay, Lumenis Holland, Locatellikade 1, 1076 AZ Amsterdam, The Netherlands. E: kazoulay@lumenis.com

Support: The publication of this article was supported by Lumenis.

One of the earliest recorded descriptions of thermal energy effect on ocular tissue in general and the retina in particular is ascribed to the Greek scholar and philosopher Plato,[1] who admonished of the deleterious impact of gazing directly at a solar eclipse. However, it was not until the 17th century AD that the first scientific-like description of a central scotoma resulting from solar thermal insult to the macula was produced by Swiss scholar Theophilus Bonetus.[2]

The advent of the telescope in the 17th century, along with the subsequent increase in astronomy and stargazing, led to several contemporaneous reports of inadvertent retinal coagulation resulting from inappropriate utilisation of this novel technology, particularly when employed for directly viewing the sun or sun-related events. With the invention of the ophthalmoscope by Hermann von Helmholtz in 1851 (although, for the sake of historical accuracy, the ophthalmoscope had been invented four years earlier by the English Charles Babbage without Von Helmholtz's knowledge), such reported cases could be further elucidated by direct ophthalmoscopic observation and correlation of clinical manifestations to the morphological changes in the retinal tissue subjected to thermal insult.

A series of animal experimentations on the impact of focused sunlight and retinal damage was pioneered by Czerny in 1867.[3] Additional work also involving artificial light (produced from carbon arc rods), was conducted by Deutschman and Widemark in the decades that followed.

The first extensive clinical study on the impact of thermal damage to the retina ('Solar Retinopathy') was conducted by Birch-Hirschfeld in 1912.[4] Birch-Hirschfeld was the first scientist to postulate that the humanly visible portion of the solar spectrum was responsible for the retinal changes occurring from eclipse blinding. However, it was Verhoeff and Bell who in 1916 concluded[5] that solar retinopathy resulted from thermal damage, rather than from photochemical effects of light on the retina.

Research in the ensuing three decades shifted focus from brief intense exposures to chronic and prolonged exposures, as evident in

the works of Cordes[6] (1944), Smith[7] (1944), Churchill[8] (1945) and Dekking[9] (1947). Some of the clinical manifestations described in their work are presumed to have been the result of dietary deficiencies (malnutrition) coupled with chronic and prolonged sunlight exposures of navy crewmen at sea or in prison camps in the Pacific during World War II (a condition termed as 'camp eyes' in those days).

Early Non-laser Photocoagulation Technology

The proverbial father of modern photocoagulation was German ophthalmologist Gerhard (Gerd) Meyer-Schwickerath. Meyer-Schwickerath observed the existence of scars in the retinas of patients who had been exposed to the solar eclipse of 10 July 1945. He noted that the observed scars resembled such that are formed following surface diathermy. To employ the technique in a controlled manner, Meyer-Schwickerath constructed a Galilean telescope connected to a mirror and utilised it to focus sunlight onto the retina.[10] However, this novel approach suffered from numerous flaws, predominantly the reliance on external weather conditions, the lengthy exposure time needed to achieve the desired clinical outcome and the ability to control the accurate location and spot size of the burn. Recognising these challenges, Meyer-Schwickerath pursued the development of a coagulator equipped with artificial light source. In cooperation with Carl Zeiss Laboratories, a xenon arc lamp was constructed and came into use as the first commercial non-laser retina coagulator. However, the xenon arc lamp was not bereft of challenges either, such as long exposure times of 250–1,000 milliseconds (ms), a wavelength encompassing the entire range of 400–1,600 nanometres (nm), very large spot sizes in the range of 1000 microns (µm) and significant discomfort to the patient during treatment and post-operatively.

The Laser Era

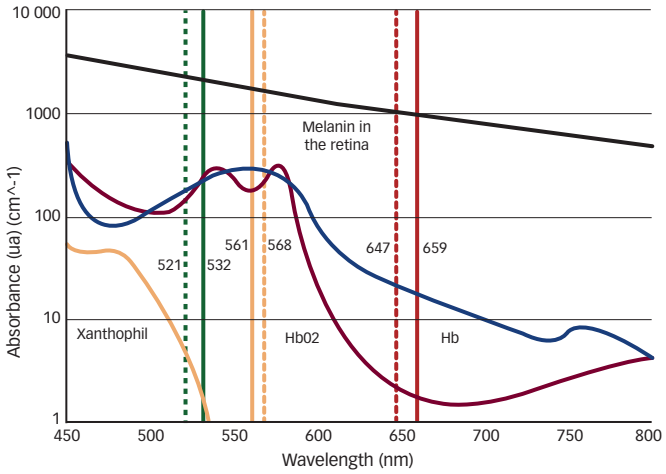
The development of the first working light amplification by stimulated emission of radiation (LASER) by Theodore H Maiman in 1960 – based on theoretical concepts set forth by Albert Einstein in 1916 and the work of Townes and Schawlow on the microwave amplification by stimulated emission of radiation (MASER) in the 1950s – heralded a new era in ophthalmology. Maiman's laser design utilised a solid-state flashlamp-pumped synthetic ruby crystal, emitting a red laser beam at 694 nm wavelength.

In 1961, Zaret conducted early experimental work with the new ruby laser, initially in animal model, with clinical trials on humans by Zweng, Flocks, Campbell and others in the following years.

Technical challenges presented by the first ruby laser included inconsistencies in the beam diameter, irregular laser pulses and restricted output control. From a clinical perspective, the red (694 nm) wavelength was outside the optimal absorption range of melanin and haemoglobin (the primary target chromophores in retinal photocoagulation); it was poorly absorbed by blood or vascular lesions (estimated at under 20 % absorption rate); and penetrated deep into the choroid. Treatments often resulted in haemorrhage due to the treatment parameters entered in order to achieve the necessary clinical outcomes.

The argon laser, developed in 1964 by William Bridges at Hughes Labs, was considered a viable alternative to the ruby laser. Francis L'Esperance (Columbia University Presbyterian Medical Centre, New York, US) who had already gained extensive experience treating retinopathy with the ruby laser, was one of the first physicians to recognise[11] the advantages presented by argon-based lasers over ruby lasers, and was also the first to treat human patients with the argon laser in February 1968. The first commercial argon photocoagulator was introduced to the market during the annual conference of the American Academy of Ophthalmology (AAO) in 1970 (Model 800, Lumenis Inc., formerly Coherent Medical, Santa Clara, CA, US).

Figure 1: Wavelength Absorption in Different Ocular Chromophores



Hb = haemoglobin; Hb02 = oxyhaemoglobin.

Multi-wavelength Lasers

In the mid-1970s the first tunable dye lasers became commercially available (Model CR-599, Lumenis Inc., Santa Clara, CA, US). Tunable dye lasers offered a myriad of advantages over single-wavelength lasers,[12] predominantly a selectable wavelength within the wide range of 360–960 nm. This novel technology allowed for the first time (theoretically) a more selective targeting of ocular tissue by using a particular wavelength that was highly absorbed by specific ocular chromophores (see *Figure 1*). Simultaneously, selecting or avoiding other wavelengths allowed for reduced collateral damage to structures adjacent to the target tissue; by avoiding or reducing absorption in competing chromophores. Furthermore, longer wavelengths of the spectrum offered better penetration through lenticular opacities (such as a sclerotic crystalline lens) and red or infrared wavelengths penetrated better through haemorrhage and other vitreous opacities. The red wavelength is also the preferred wavelength for treating pre-term infant eyes afflicted with retinopathy of prematurity (ROP), as the red wavelengths penetrate through the tunica vasculosa lentis – the extensive capillary network spreading over the posterior and lateral surface of the lens that normally regresses shortly after birth. Newer multi-wavelength laser media, such as gas and later semiconductor-based devices, eventually displaced dye lasers.

Diabetic Retinopathy Study and Early Treatment Diabetic Retinopathy Study

The significance of the argon laser for the treatment of diabetic retinopathy was first demonstrated by the Diabetic Retinopathy Study (DRS),[13,14] which has set the current standard of care for proliferative diabetic retinopathy, followed by the Early Treatment Diabetic Retinopathy Study (ETDRS),[15–20] which has set the current standard of care for diabetic macular oedema.

Figure 2: Lumenis Vision One – A Modern Multi-wavelength Retinal Laser Platform

The DRS was designed to evaluate whether pan-retinal photocoagulation (PRP) (also known as 'scatter laser treatment') could reduce vision loss associated with proliferative diabetic retinopathy. A total of 1,758 patients were recruited and following a two-year follow-up period it became evident that retinal photocoagulation was of meaningful benefit. Results showed that severe vision loss (defined as best acuity of 5/200 or worse) was seen in 15.9 % of untreated eyes, compared with 6.4 % of treated eyes. Furthermore, only 11 % of treated patients from the high-risk characteristics group progressed to severe visual loss, compared with 26 % of the non-treated group.

The ETDRS was a multicentre, randomised clinical trial (which began in 1979) designed to evaluate argon laser photocoagulation and aspirin therapy in delaying or preventing progression of early diabetic retinopathy, to more severe stages of visual loss and blindness. A total of 3,711 patients were recruited to be followed-up for a minimum of four years, to provide long-term information on the risks and benefits of the treatments under study.

The ETDRS demonstrated that in cases of macular oedema, photocoagulation meaningfully reduced the risk of moderate vision loss, especially in eyes with macular oedema that involved or threatened the centre of the macula. Focal/grid photocoagulation reduced the risk of moderate vision loss (defined as doubling of visual angle) by 50 % or more and increased the chance of a small improvement in visual acuity. Furthermore, in eyes with macular oedema and pre-treatment visual acuity of 20/40 or worse, an improvement in visual acuity of six or more letters was more frequent ($1.96 \leq z < 2.58$ at 36 months follow-up) in eyes treated with focal/grid photocoagulation than in eyes assigned to deferral to treatment.[21]

Prior to the DRS and ETDRS studies, the prognosis for patients with proliferative diabetic retinopathy was blindness within five years for more than 50 % of patients. Rates of blindness in ETDRS patients following the development of proliferative diabetic retinopathy were remarkably lower. Legal blindness was reduced to less than 5 % in five years for patients with proliferative retinopathy. Severe vision loss was reduced to 1 %. Laser photocoagulation surgery in both the DRS and the ETDRS was beneficial in reducing the risk of further visual loss, but generally not beneficial in reversing already diminished acuity.

The Semiconductor Era

The first viable and commercially successful alternatives to gas-based lasers (e.g. argon and krypton), or liquid-based lasers (e.g. dye) came in the early 1990s, with the introduction of the first infrared diode lasers (Iris Corporation, now Iridex, Mountain View, CA, US) emitting in the range of 810 nm. Diode infrared lasers offered several advantages compared with gas-based lasers, such as reduced scatter (allowing better penetration through occluded media, such as cataracts and vitreous haemorrhage) and deeper choroidal penetration for targeting retinal and choroidal tumours.[22] However, similar to ruby lasers, absorption in the target tissue was sub-optimal (estimated at 20 %) compared with more than 90 % in argon green lasers,[23] and treatments also resulted in significant patient discomfort due to the longer exposure time and higher energy required to achieve clinical endpoints.

Modern Laser Consoles and Modified Early Treatment Diabetic Retinopathy Study

Since the early 2000s, argon lasers have largely been displaced by diode, diode pumped solid state (DPSS) and most-recently optically pumped semiconductor lasers (OPSL) (see *Figure 2*), with wavelengths ranging from 532 to 810 nm. Concurrently, the trend towards minimally invasive procedures in medicine in general has led to the investigation of an alternative laser methodology for the treatment of diabetic retinopathy. The ETDRS protocol required placement of high intensity burns close to the centre of the macula, in the parafoveal and perifoveal areas. However, this approach is associated with central scotomas and decreased colour vision. While this treatment was proven clinically effective, a modified ETDRS approach[24] where lighter burns are placed in the macula and especially close to the fovea, was adopted by many retinal physicians. The lighter burns are theoretically less likely to result in significant thermal injury to the neurosensory retina and cause less discomfort to the patients.

Over the past seven years the Diabetic Retinopathy Clinical Research Network (DRCR.net) (a National Institutes of Health [NIH] sponsored clinical trial research network dedicated to the treatment of diabetic retinopathy) has conducted a series of studies[25,26] comparing focal/grid laser treatment with macular grid (no advantage); focal/grid laser treatment with intravitreal injection of steroids[27–29] (focal/grid laser treatment showed superior results compared with intravitreal injection of triamcinolone alone); or in combination with focal/grid laser treatment. In addition, there was no long-term benefit of intravitreal injection of triamcinolone relative to focal/grid photocoagulation and outcomes slightly favoured the laser group compared with either of the two triamcinolone groups) and, more recently, focal/grid laser treatment compared with intravitreal injections of an Anti-VEGF agent (ranibizumab).[30] While ranibizumab had a more dramatic effect on improving visual acuity and avoiding further vision loss compared with focal/grid laser alone, the anti-VEGF group required, nonetheless, application of laser therapy in 40 % of cases over the two-year follow–up period, due to persistent oedema that did not improve within six months or more after initiating therapy. Currently, a combination approach of anti-VEGF injections and deferred focal/grid laser treatment for at least six months may become the standard care for diabetic macular

oedema (DME). Furthermore, laser continues to be needed for pan–retinal photocoagulation for cases developing proliferative diabetic retinopathy.

Reduced Fluence, Sub-threshold and Selective Laser Treatments

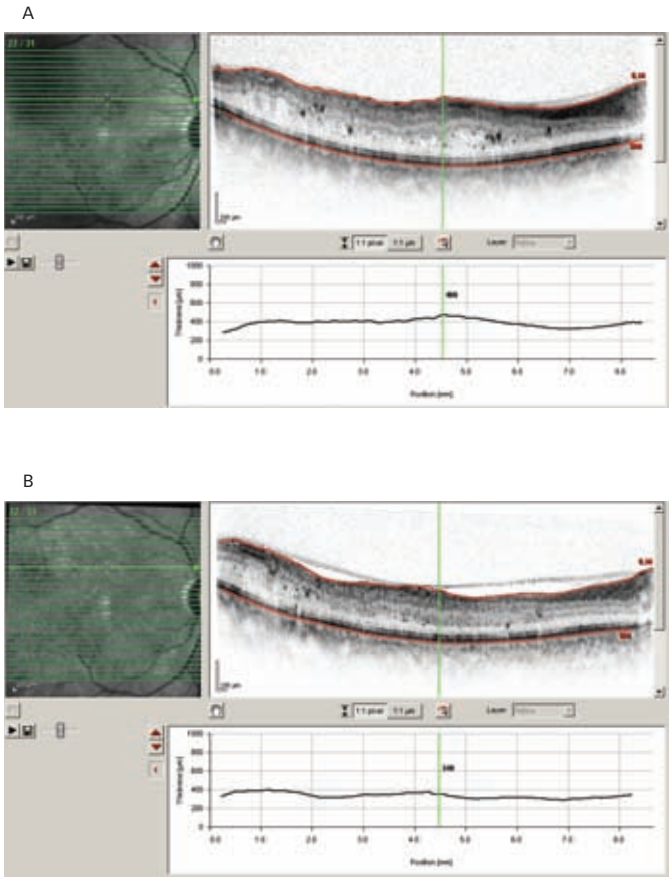
Micropulse mode was initially introduced using 810 nm (infrared) laser wavelength, and more recently incorporated into 532 nm (green) and 577 nm (yellow) wavelengths. In micropulse mode, continuous wave laser energy is electronically 'chopped' to create short (microsecond) 'on' and 'off' pulses. The length of the pulse can be determined by changing the duty cycle. The laser lesions are sub-visual (i.e. in principle, no visible burn is evident on the retina during treatment). However, even at the lowest setting, the pulse duration is longer than the retinal pigmented epithelium (RPE) thermal relaxation time and thus the term 'sub-threshold' should be used more conservatively.

The major published studies (in small series of patients) are predominantly using the 810 nm wavelength.[31] A recent paper compared treatment with conventional laser with normal-density sub-threshold diode-laser micropulse (ND-SDM) (two spots apart) and high-density sub-threshold diode-laser micropulse (HD-SDM) (confluent treatment).[32] At 12 months, the HD-SDM group showed higher improvement in best corrected visual acuity (BCVA), followed by the mETDRS group (0.08 logarithm of the minimum angle of resolution [logMAR]), whereas no improvements were seen in the ND-SDM group (0.03 logMAR). All groups showed statistically significant progressive reduction of central macular thickness. The HD-SDM group exhibited the greatest central macular thickness (CMT) reduction and was not significantly different from that of the mETDRS group. The ND-SDM group showed the least reduction in CMT. Notably, the author commented that while no visible laser burns were normally found in patients treated with micropulse photocoagulation, in some patients, very light laser-induced lesions were evident upon clinical examination.

The multi-spot pattern scanning laser was introduced in 2006 (OptiMedica, Santa Clara, CA, US) and since then has gained acceptance due to its rapid delivery of laser burns in a predetermined semi-automated sequential manner.[33] The primary benefits of scanning lasers over conventional single-spot lasers are speed and reduced fluence, allowing for significantly shorter PRP treatment times, reduced thermal damage to inner retinal layers and less patient discomfort. Unlike standard laser photocoagulation, scanning lasers feature shorter pulse durations in the range of 10–30 ms. Plus, in light of the fact that heat diffusion with shorter exposures is decreased, the applied laser lesions tend to be lighter and smaller than conventional ones.[33–35]

A further advance towards a truly minimally invasive retina treatment was the development of selective retina therapy (SRT, Lumenis Inc., Santa Clara, CA, US), based on the scientific and clinical work of Birngruber, Roider et al. While all previous treatments employed a continuous wave (CW) laser with pulse duration in the millisecond range, this laser treatment is based on a sequence of 1.7 micro-second pulses that are delivered to the retina and absorbed by the RPE. Animal studies have shown that these ultra-short pulses affect the RPE, however, no heat is conducted to the overlaying retina thus minimising the risk of photoreceptor damage and the resultant central scotoma.[36,37] After selective RPE treatment, the RPE is hypothesised to regenerate and the photoreceptors survive. The RPE response resembles that of mild continuous wave photocoagulation. The tissue repair of the RPE cells occurs mainly by the neighbouring RPE cells. While this methodology is still under clinical investigation (see *Figure 3*), several studies have shown the efficacy of SRT for the treatment of DME.[38–40]

Figure 3: Cross-sectional Spectral-domain Optical Coherence Tomography Images



A: baseline; B: 12 m post selective retina therapy laser treatment. In comparison with the baseline there is no scar formation on spectral-domain optical coherence tomography Images (SD-OCT). Courtesy of the Ophthalmology Department, Tel Aviv Medical Centre (TAMC), Israel.

Near Future

Looking ahead, within the currently foreseeable future, retinal photocoagulation lasers are likely to remain a viable treatment modality in the ophthalmologists' armamentarium. Based on most recent clinical studies, combination therapy offers the optimal results in DME and no alternative exists (other than resolving the underlying cause of diabetes) for pan-retinal photocoagulation (PRP) in managing proliferative diabetic retinopathy. The convergence of diagnostics and therapeutic modalities (also known as image-guided therapy), along with sub-threshold and/or selective laser treatments, will set the clinical and technological trend in the coming years, allowing clinicians to achieve more precise and consistent outcomes, with minimal collateral thermal damage to neurosensory structures in the retina and reduced patient discomfort. ■

1. Plato. Phaedo. Jowett B, trans. Lawrence, KS: Digireads.com Publishing; 2006.
2. Hamm, H, Zentralskotom nach Sonneblendung, dissertation, Hamburg, 1947.
3. L'Esperance FA, Ophthalmic Lasers, St Louis, US: C.V. Mosby, 1977;3.
4. Birch-Hirshlfeld B, Zum kapitel der sonnenblendung des Auges, *Zeitschrift für Augenheilkunde,* 1912;28:324–47,444–9 and 509–30.
5. Verhoeff FH, Bell L, Thermic Effects of Radiant Energy upon the Retina P, The Pathological Effects of Radiant Energy on the Eye, Boston, *US: Proc Am Acad Arts Sci,* 1916;51(13):697–9.
6. Cordes FC, A type of foveo-macular retinitis observed in the US navy, *Am J Ophth,* 1946;27:803–16.
7. Smith H, Actinic macular retinal pigment degeneration, *US Naval Med Bull,* 1944;42:675–80.
8. Churchill MH, Diatary deficiency among prisoners of war, *J Roy Army Med Corps,* 1945;35:294–8.
9. Dekking HM, Tropical nutritiona amblyopia ("camp eyes"), *Ophthalmologica,* 1947;113:63–92.
10. Meyer-Schwickerath G, Light coagulation, St Louis, *US: CV Mosby,* 1960.
11. L'Esperance FA Jr, An opthalmic argon laser photocoagulation system: design, construction, and laboratory investigations, *Trans Am Ophthalmol Soc,* 1968;66:827–904.
12. L'Esprance FA Jr, Trans-spectral organic dye laser photocoagulation, *Trans Am Ophthalmol Soc,* 1985;83:82–113.
13. Photocoagulation treatment of proliferative diabetic retinopathy: the second report of diabetic retinopathy study findings, *Ophthalmology,* 1978;85(1):82–106.
14. Fine SL, Patz A, Ten years after the Diabetic Retinopathy Study, *Ophthalmology,* 1987;94(7):739–40.
15. Early Treatment Diabetic Retinopathy Study Research Group, Treatment techniques and clinical guidelines for photocoagulation of diabetic macular edema. Early Treatment Diabetic Retinopathy Study Report Number 2, *Ophthalmology,* 1987;94:761–74.
16. Early Treatment Diabetic Retinopathy Study Research Group, Techniques for scatter and local photocoagulation treatment of diabetic retinopathy. Early Treatment Diabetic Retinopathy Study Report Number 3, *Int Ophthalmol Clin,* 1987;27:254–64.
17. Early Treatment Diabetic Retinopathy Study Research Group, Photocoagulation for diabetic macular edema. Early Treatment Diabetic Retinopathy Study Report Number 4, *Int Ophthalmol Clin,* 1987;27:265–72.
18. Early Treatment Diabetic Retinopathy Study Research Group, Early Treatment Diabetic Retinopathy Study design and baseline patient characteristics. ETDRS Report Number 7, *Ophthalmology,* 1991;98:741–56.
19. Early Treatment Diabetic Retinopathy Study Research Group, Early photocoagulation for diabetic retinopathy. ETDRS Report Number 9, *Ophthalmology,* 1991;98:766–85.
20. Early Treatment Diabetic Retinopathy Study Research Group, Focal photocoagulation treatment of diabetic macular edema. Relationship of treatment effect to fluorescein angiographic and other retinal characteristics at baseline: ETDRS report Number 19, *Arch Ophthalmol,* 1995;113:1144–55.
21. Early Treatment Diabetic Retinopathy Study Research Group: Photocoagulation for diabetic macular edema. Early Treatment Diabetic Retinopathy Study report Number 1, *Arch Ophthalmol,* 1985;103:1796–806.
22. Fankhauser F 2nd, Giger H, Niederer P, Seiler T, Transpupillary laser phototherapy of tumors and vascular anomalies of retina and choroid: theoretical approach and clinical implications, *Technol Health Care,* 2000;8(2):93–112.
23. Balles MW, Puliafito CA, D'Amico DJ, et al., Semiconductor diode laser photocoagulation in retinal vascular disease, *Ophthalmology*, 1990;97:1553–61.
24. Writing Committee for the Diabetic Retinopathy Clinical Research Network, Fong DS, Strauber SF, Aiello LP, et al., Comparison of the modified Early Treatment Diabetic Retinopathy Study and mild macular grid laser photocoagulation strategies for diabetic macular edema, *Arch Ophthalmol,* 2007;125(4):469–80.
25. Diabetic Retinopathy Clinical Research Network, The course of response to focal/grid photocoagulation for diabetic macular edema, *Retina,* 2009;29(10):1436–43.
26. Scott IU, Danis RP, Bressler SB, et al., Effect of focal/grid photocoagulation on visual acuity and retinal thickening in eyes with non-center-involved diabetic macular edema, *Retina,* 2009;29(5):613–7.
27. Diabetic Retinopathy Clinical Research Network, A randomized trial comparing intravitreal triamcinolone acetonide and focal/grid photocoagulation for diabetic macular edema, *Ophthalmology,* 2008;115(9):1447–9.
28. Lauer AK, Bressler NM, Edwards AR, et al., Frequency of intraocular pressure increase within days after intravitreal triamcinolone injections in the diabetic retinopathy clinical research network, *Arch Ophthalmol,* 2011;129(8):1097–9.
29. Elman MJ, Bressler NM, Qin H, et al., Expanded 2-year follow-up of ranibizumab plus prompt or deferred laser or triamcinolone plus prompt laser for diabetic macular edema, *Ophthalmology,* 2011;118(4):609–14.
30. Diabetic Retinopathy Clinical Research Network, Elman MJ, Aiello LP, Beck RW, et al., Randomized trial evaluating ranibizumab plus prompt or deferred laser or triamcinolone plus prompt laser for diabetic macular edema, *Ophthalmology,* 2010;117(6):1064–77.e35
31. Luttrull JK, Sramek C, Palanker D, et al., Long-term safety, high-resolution imaging, and tissue temperature modeling of subvisible diode micropulse photocoagulation for retinovascular macular edema, *Retina,* 2012;32(2):375–86.
32. Lavinsky D, Cardillo JA, Melo LA Jr, et al., Randomized clinical trial evaluating mETDRS versus normal or high-density micropulse photocoagulation for diabetic macular edema, *Invest Ophthalmol Vis Sci,* 2011;52(7):4314–23.
33. Blumenkranz MS, Yellachich D, Andersen DE, et al., Semiautomated patterned scanning laser for retinal photocoagulation, *Retina,* 2006;26:370–6.
34. Jain A, Blumenkranz MS, Paulus Y, et al., Effect of pulse duration on size and character of the lesion in retinal photocoagulation, *Arch Ophthalmol,* 2008;126:78–85.
35. Nagpal M, Marlecha S, Nagpal K, Comparison of laser photocoagulation for diabetic retinopathy using 532-nm standard laser versus multispot pattern scan laser, *Retina,* 2010;30:452–8.
36. Roider J, Michaud NA, Flotte TJ, Birngruber R, Response of the retinal pigment epithelium to selective photocoagulation, *Arch Ophthalmol,* 1992;110:1786–92.
37. Roider J, Hillenkamp F, Flotte F, Birngruber R, Microphotocoagulation: selective effects of short laser pulses, *Proc Natl Acad Sci U S A, 1993;90:8643–7.*
38. Roider J, El Hifnawi ES, Birngruber R, Bubble formation as primary interaction mechanism in retinal laser exposure with 200-ns laser pulses, *Lasers Surg Med,* 1998;22(4):240–8.
39. Roider J, Brinkmann R, Wirbelauer C, et al., Subtreshold (retinal pigment epithelium) photocoagulation in macular diseases: a pilot study, *Br J Ophthalmol,* 2000;84(1):40–7.
40. Roider J, Liew, SHM, Klatt C, et al., Selective retina therapy (SRT) for clinically significant diabetic macular edema, *Graefes Arch Clin Exp Ophthalmol,* 2010;248:1263–72.