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Laser Treatment in Diabetic Retinopathy

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Abstract

Diabetic retinopathy is a leading cause of visual impairment and blindness in developed countries due to macular edema and proliferative diabetic retinopathy (PDR). For both complications laser treatment may offer proven therapy: the Diabetic Retinopathy Study demonstrated that panretinal scatter photocoagulation reduces the risk of severe visual loss by >50% in eyes with high-risk characteristics. Panretinal scatter coagulation may also be beneficial in other PDR and severe nonproliferative diabetic retinopathy (NPDR) under certain conditions. For clinically significant macular edema the Early Treatment of Diabetic Retinopathy Study could show that immediate focal laser photocoagulation reduces the risk of moderate visual loss by at least 50%. When and how to perform laser treatment is described in detail, offering a proven treatment for many problems associated with diabetic retinopathy based on a high evidence level.

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Introduction

Diabetic retinopathy is a leading cause of visual impairment and blindness in developed countries. Macular edema is the major cause of vision loss in diabetic pa-

tients, while proliferative retinopathy is another common cause [1]. For both of these retinal complications of diabetes laser treatment can, if timely applied, greatly reduce the probability of vision loss. Of course, the other modifiable risk factors of disease progression have to be optimized in adjunction to any laser therapy, especially optimizing blood glucose control [2, 3] and tight blood pressure control [4].

History of Laser Treatment

While H.G. Wells foresaw the development of lasers in his book *The War of the Worlds* in 1897, it was not until 1960 that Maiman built the first working laser. A flash of light was used to deliver light energy to a ruby crystal. Due to 1 totally and 1 partially reflecting mirror at each end a light amplification by stimulated emission of radiation (LASER) device is obtained. The typical characteristics are monochromatic light, spatial coherence and a high density of electrons. Several different wavelengths have been and are being developed, including ruby (694 nm), argon green (514 nm), krypton (647 nm), Nd:YAG (1,064 and frequency doubled to 532 nm), diode (810 nm), excimer (193 nm).

The previously used xenon light photocoagulator had been developed by the German ophthalmologist Meyer-Schwickerath together with Littmann from Zeiss in the 1950s and made photocoagulation independent of sunlight and weather conditions. Its spot size was variable

ranging from 3° to 8° (i.e. minimum spot size approx. >500 μm) and the burns had greater power than laser burns, therefore usually yielding full thickness burns. In contrast, the laser effects include (depending on laser type, tissue characteristics and settings) photochemical effects, photoirradiation, photocoagulation and photodisruption. Lasers became available for ophthalmologic applications in the late 1960s and became more frequently used in the 1970s. Coagulation treatment of the retina for diabetic retinopathy became a standard of care since the Diabetic Retinopathy Study (DRS) results were published in the late 1970s. It showed a great reduction of severe vision loss in high-risk proliferative disease for both xenon and argon laser photocoagulation [5].

Panretinal Laser Treatment for Proliferative Diabetic Retinopathy

The DRS enrolled 1,742 patients, 876 of whom were randomized to the argon group and 875 to the xenon group [6]. Argon photocoagulation involved the placement of 800–1,600 burns with 500 μm diameter or 500–1,000 burns with 1,000 μm diameter, both at 0.1 s of duration. The areas treated included the retina to or beyond the vortex veins in 1 or 2 sessions, also covering neovascularization of the optic disc (NVD), which is no longer typically performed today. The primary endpoint of the study was a visual acuity of <5/200 on 2 consecutive visits 4 months apart. After 3 years argon laser coagulation could decrease the rate of severe visual loss to 13.3%, and xenon coagulation to 18.5%, while untreated eyes had 26.4%. Thus at least a 50% reduction in the rate of severe visual loss could be demonstrated for panretinal laser treatment, which was maintained during a 5-year follow-up period [7]. The harmful effects of photocoagulation were more pronounced for xenon coagulation than for argon laser coagulation and included a reduction of visual acuity due to treatment and loss of peripheral visual field. For laser treatment a decrease by ≥1 lines occurred in 10% and a mild constriction of visual fields in 5% [7]. Macular edema, which may be exacerbated by panretinal photocoagulation and will be discussed in detail later, was not evaluated in the DRS. Finally the so-called high-risk characteristics, for which the benefits of peripheral coagulation outweigh the risks, were defined as [7, 8]:

1 NVD ≥1/4 to 1/3 disc area in extent
2 New vessels on or within 1 disc diameter of the optic disc (NVD)
3 Any new vessels within 1 disc diameter of the optic disc and associated with vitreous or preretinal hemorrhage
4 Proliferation elsewhere at least 1/2 disc area in size and associated with vitreous or preretinal hemorrhage

The risk of severe visual loss was 26% for eyes exhibiting these high-risk characteristics (at least 3 of 4 signs) as compared to 7% in proliferative diabetic retinopathy (PDR) without those characteristics after 2 years [9]. Photocoagulation reduced this risk by 50%. Therefore the DRS recommends panretinal laser treatment for (1) eyes with new vessels and preretinal or vitreous hemorrhage; and (2) eyes with new vessels on or within 1 disc diameter of the optic disc (NVD) ≥1/4 to 1/3 disc area in extent (with or without preretinal or vitreous hemorrhage) [7]. It was not able to give recommendations on earlier stages such as severe nonproliferative patients.

The current international clinical diabetic retinopathy disease severity scale distinguishes 5 levels of retinopathy [10]: (0) no apparent retinopathy; (1) mild nonproliferative diabetic retinopathy (NPDR, only microaneurysms); (2) moderate NPDR; (3) severe NPDR (including any of: >20 intraretinal hemorrhages in each quadrant, venous beading in ≥2 quadrants, intra-retinal microvascular abnormalities (IRMA) in ≥1 quadrant, but no proliferations), and (4) proliferative retinopathy (defined by neovascularization and/or vitreous/preretinal hemorrhage). The subgroup with high-risk characteristics has been described by the DRS above.

A summary of current treatment recommendations for laser therapy using this disease scale [11–13] is given in figure 1. In supplementation to the DRS criteria it is recommended at a high evidence level [9] to perform panretinal laser coagulation for PDR, NVD, proliferation elsewhere >1/2 disc area, vitreous/preretinal hemorrhage and neovascularization of the iris under certain conditions. Additionally, for severe NPDR scatter laser coagulation may be indicated in some cases (see fig. 1). Laser treatment should be performed over a period of 4–6 weeks at 500 μm spot size, spaced 0.5 burn widths from each other with 0.1–0.2 s of duration (for green lasers). Intensity should be regulated so that mild white bleaching is obtained, the treatment area reaches from the temporal arcade to the equator and up to 2 disc diameters temporal from the macular center. Around the optic disc some space (e.g. 1 disc diameter) should be spared (see fig. 2) to avoid central visual field defects [14].

Fig. 1. Algorithm for panretinal scatter coagulation of the retina [11–13]. For details of the used classification see text. A macular edema must be assessed separately (see text and fig. 2). Type 2 diabetes (older patients) may benefit more from early scatter photocoagulation [60].
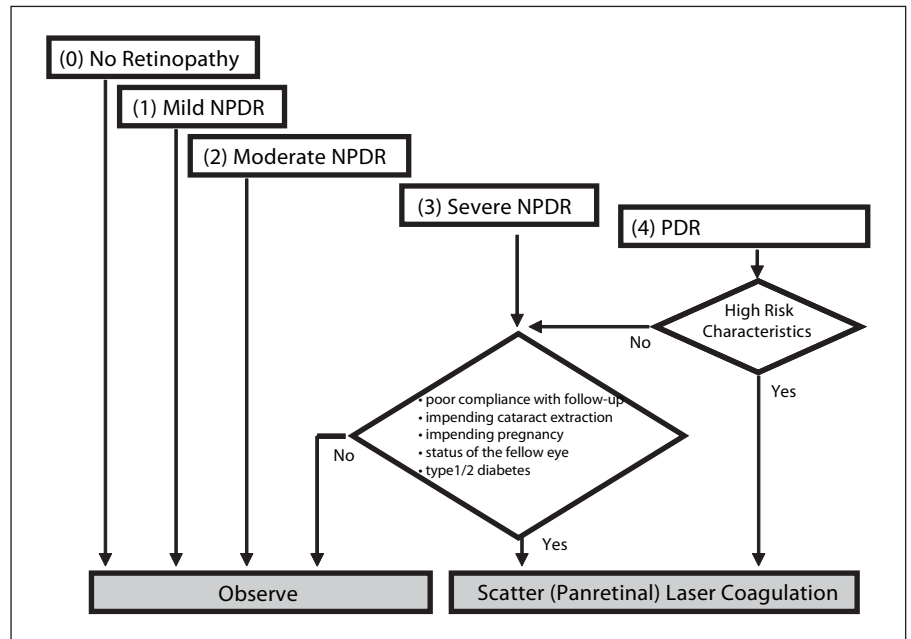
Flowchart content:

(0) No Retinopathy
(1) Mild NPDR
(2) Moderate NPDR
(3) Severe NPDR
(4) PDR

High Risk Characteristics

• poor compliance with follow-up
• impending cataract extraction
• impending pregnancy
• status of the fellow eye
• type1/2 diabetes

No / Yes

Observe

Scatter (Panretinal) Laser Coagulation

Ora

Equator

Usual Treatment Area for Panretinal Laser Coagulation

Fig. 2. Illustration of treatment area for panretinal scatter photocoagulation on widefield imaging (Optomap, Optos, Dunfermline, Fife, Scotland, UK). For details please see text.
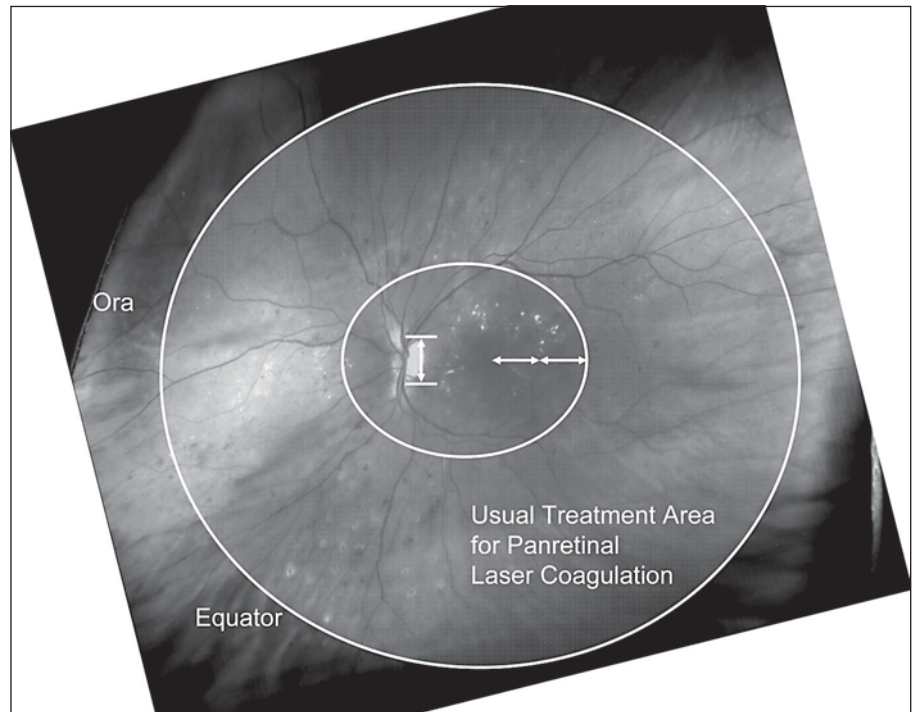
Laser Treatment of Macular Edema

Macular edema is responsible for a major part of visual impairment associated with diabetic retinopathy [1]. Correct and timely treatment is of vital importance to avoid severe visual loss. The Early Treatment of Diabetic Retinopathy Study (ETDRS) formed the basis of current treatment regimens by laser. The multicenter randomized study was designed to investigate the effect of photocoagulation and aspirin treatment in patients with

Fig. 3. Algorithm for laser treatment for macular edema. Please note that proliferative disease must be assessed separately as discussed in the text and shown in figure 1. CSME = clinically significant macular edema.
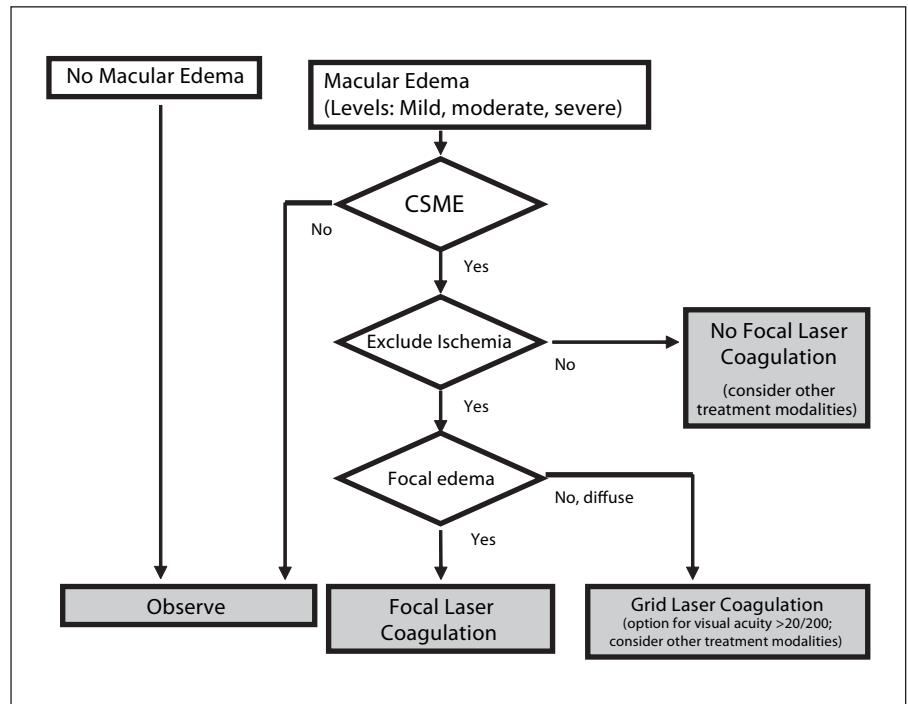
NPDR and early proliferative retinopathy. It enrolled a total of 3,711 patients between 1980 and 1985 who met the following criteria: (1) no macular edema with visual acuity >20/40 and (2) macular edema with visual acuity >20/200.

As one result the ETDRS showed that the randomized intake of 650 mg aspirin per day did not alter the clinical course [15]. It also investigated as a second question when in the course of diabetic retinopathy panretinal laser coagulation is most effective. To answer both these questions, patients without macular edema were randomized to either early (mild or full) scatter photocoagulation or deferral. Eyes with macular edema were randomized to either deferral or immediate focal or immediate panretinal plus follow-up focal photocoagulation. Full scatter photocoagulation was defined as in the DRS, and mild scatter photocoagulation consisted of 500-μm spots spaced 1 burn width apart from each other. For eyes without macular edema, no benefit resulted from immediate photocoagulation (either mild or full scatter, focal where needed) to prevent moderate or severe visual loss. For eyes with macular edema and more severe retinopathy a small reduction of the risk for severe visual loss was found with early photocoagulation [16]. However, there was an increased risk of moderate visual loss in the treatment group after 6 weeks, which after 1 year reversed. The least visual loss was in the group treated by mild scatter to-

gether with immediate focal photocoagulation [16]. This supports the algorithm given in figures 1 and 3 regarding timing of scatter photocoagulation and further justifies photocoagulation in non-high-risk characteristic eyes [16].

The third and main question to be answered by the ETDRS was the efficacy of laser treatment for macular edema (fig. 3). Macular edema was defined as: (1) thickening of the retina at or within 500 μm of the center of the macula; (2) hard exudates at or within 500 μm of the center of the macula, if associated with thickening of adjacent retina, and (3) a zone of retinal thickening ≥1 disc area, any part of which is within 1 disc diameter of the center of the macula.

Any of these 3 criteria defined clinically significant macular edema (CSME, see fig. 4). Focal laser treatment consisted of 50- to 100-μm laser burns of 0.05–0.1 s duration directed at microaneurysms between 500 and 3,000 μm from the macular center achieving whitening around or (if >40 μm) color change of the microaneurysm. Treatment closer than 300 μm from the fovea was not recommended (rarely <500 μm). Diffuse leakage or nonperfusion were treated in a more indirect way focused at the retinal pigment epithelium: within 2 disc areas of the fovea a grid pattern with 50- to 200-μm spots, spaced 1 burn width apart, was applied [17]. Figure 4 illustrates the size relationships. Moderate visual loss, defined as >15
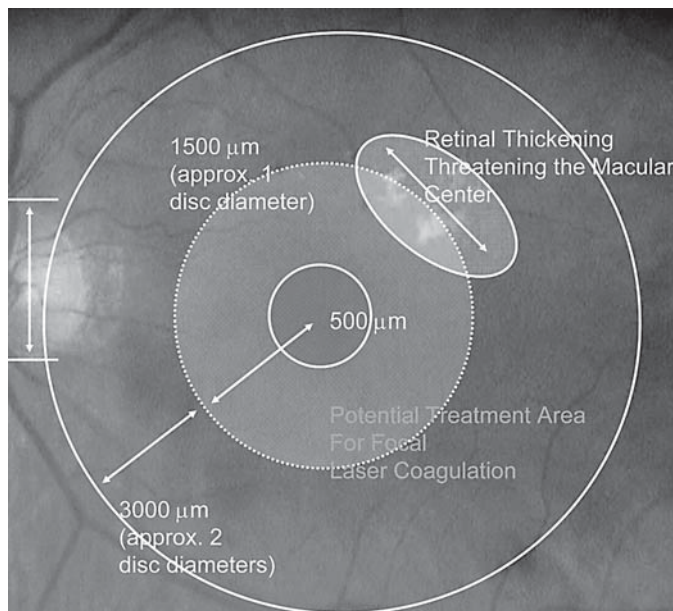
Fig. 4. Illustration of treatment area for focal (and grid) photocoagulation for CSME. For details please see text and figure 3.

letters (i.e. ≥3 lines), was the primary endpoint. In brief, the ETDRS could show that immediate focal laser coagulation in eyes with CSME could reduce the percentage of eyes with moderate visual loss by at least 50%. This effect was maintained over follow-up time, for example after 3 years 12% as opposed to untreated 24% was achieved [16]. However, visual improvement was observed in a minority of cases; for the majority of cases the goal of photocoagulation is to stabilize visual acuity. Therefore patients with good visual acuity and CSME should definitely be considered for treatment [18]. On average 3–4 treatment sessions 2–4 months apart were needed [19]. The side effects of focal photocoagulation include an initial decrease in central vision and rarely subretinal fibrosis with choroidal neovascularization. The development of subretinal fibrosis is associated with the degree of subretinal exudates and only 8% were directly attributable to laser coagulation [20]. Paracentral scotomas may be noted by the patient with burns close to the macular center, especially when confluent [21].

Diffuse Macular Edema
In focal macular edema well-defined focal areas of leakage with retinal thickening are seen. As described above for the ETDRS, treatment may consist of either direct treatment of leaking microaneurysms or indirect treatment of the retinal pigment epithelium, usually applied in a more grid-like fashion directed towards thickened areas. In contrast, in diffuse macular edema, leakage occurs diffusely from the retinal capillaries. Retinal microaneurysms, hard exudates and retinal hemorrhages tend to be few in number and small in size. Subtypes include central diffuse edema caused by leakage of the capillaries immediately adjacent to the foveal arcade and generalized diffuse edema [22]. In the latter a more widespread retinal thickening is observed across the posterior pole. Laser treatment has been evaluated using 100- to 200-μm spot size and just threshold burns at the level of the pigment epithelium. Usually spots are applied spaced 1 spot size apart and 100–200 burns are required. The so-called 'grid' pattern depends on the pattern of leakage and may be performed circularly around the macular center (including the papillomacular bundle). Visual acuity <20/200 (0.1) is a contraindication for grid laser treatment [11, 12]. The results of such treatment are contradictory [23, 24] and not of high evidence. Other treatment modalities such as pars plana vitrectomy [25] or different medical treatment options [26, 27] may be more promising.

Ischemic Macular Edema
While the accompanying edema may be variable, central ischemia is characterized by a loss of foveal capillaries/capillary nonperfusion. The clinical diagnosis is difficult, while fluorescein angiography shows an enlarged foveal avascular zone (i.e. >500 μm diameter) [12, 28, 29]. An example is shown in figure 5. Laser therapy should not be applied if significant ischemia exists [22]. The complete algorithm for laser treatment of macular edema is given in figure 3.

Coexistent Macular Edema and Proliferative Disease

When scatter photocoagulation is to be carried out in eyes with coexisting CSME, there is evidence that first performing focal laser treatment may be beneficial. Both the DRS and ETDRS showed that full scatter photocoagulation may exacerbate macular edema leading to moderate visual loss [16]. This effect was quantified later [30]. The ETDRS could also show some advantage for immediate focal as compared to delayed focal coagulation together with panretinal laser therapy. Therefore it is advisable to first perform focal before panretinal photocoagulation. In cases with high-risk PDR simultaneous focal and scatter photocoagulation should be performed [11, 13].
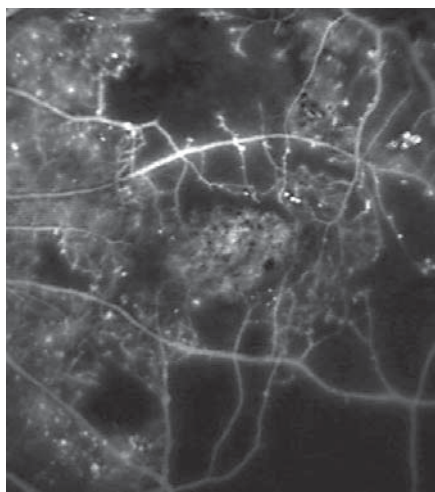
Fig. 5. Illustration of severe macular capillary dropout, i.e. macular ischemia. Focal laser coagulation should be avoided in such cases.

Cataracts

Various studies suggest that diabetic retinopathy, especially macular edema, may progress following cataract surgery [9, 31, 32]. Therefore, if the ocular media are clear enough, necessary laser therapy should be performed preoperatively. If this is impossible due to media opacities, re-evaluation and necessary therapy should be performed as soon as possible [11]. Regarding the implanted intraocular lens it is important to choose a model with a large optical zone facilitating further photocoagulation. Silicone material should definitely be avoided, since in the case of vitrectomy, especially with silicone oil, precipitates will occur [33].

Laser Therapy for Subhyaloidal Hemorrhage

In case of dense subhyaloidal hemorrhage located at the macular center disrupting the inner limiting membrane by an Nd:YAG laser [34] or green laser [35] may allow the blood to dissolve in the vitreous and be absorbed much faster. Panretinal laser treatment should be performed beforehand to avoid unnecessary delays. Complications of the method include macular hole formation and retinal detachment [36]. Other treatment options such as vitrectomy should also be considered in such cases.

Diode Laser Treatment

The diode laser is widespread due to its ease of maintenance, small size and lower costs. Due to its wavelength of 810 nm the biologic properties are different from other wavelengths such as the green lasers. Especially more profound effects of the diode laser in the choroid are known, which may be more painful for the patient during application. Regarding the effectiveness of avoiding progression of PDR no differences exist [37, 38]. On the other hand functional parameters such as color contrast sensitivity or pattern electroretinograms after panretinal photocoagulation may be more in favor of diode laser treatment [39], while expansion of laser spots over time appears to be more likely with the longer wavelength of the diode laser [40].

Regarding macular edema, gentle threshold diode laser coagulation is suitable for focal laser therapy [41], although some studies suggest that it may be to some degree less effective than green laser wavelengths [42]. Subthreshold treatment minimizes damage but is to some extent less effective in promoting resolution of edema, though the difference was not significant [43]. Micropulsed application of subthreshold diode laser burns may increase its effectiveness [44, 45].

Objective Retinal Thickness Measurements

While the ETDRS used stereoscopic clinical examination and stereo fundus photographs to define macular changes [46, 47], over the last decade much more sensitive methods have become available to quantify retinal thickness objectively. Optical coherence tomography (OCT, Carl Zeiss Meditec, Jena, Germany) has rapidly become a standard method of analyzing macular changes [48] offering high resolution cross-section images. OCT and another instrument, the retinal thickness analyzer (Talia Technology, Neve-Ilan, Israel) having less resolution, can reliably detect small increases of retinal thickness of at least 20–40 μm [49–51]. Stereoscopic fundus examination usually only detects retinal thickening of approximately 100 μm [52]. The new objective methods have been shown to be superior to clinical examination for investigating the extent of diabetic macular edema [53, 54]. By these means it could also be shown that non-clinically significant retinal thickening occurs in most diabetic patients even in the absence of visible retinopathy [55]. This raises the question whether treatment of non-clinically significant ('subclinical') macular edema may

be indicated under certain conditions – no such groups had been identified with the methods used in the ETDRS [16]. On the other hand methods like OCT and retinal thickness analyzer offer sensitive tools to follow changes in retinal thickness objectively, which allows better assessment of treatment success of e.g. focal laser treatment. The OCT can also identify membranes and vitreomacular traction [56, 57], cases in which pars plana vitrectomy might be more beneficial than other treatment modalities [25, 58, 59].

Conclusions

Laser therapy remains the main treatment modality for diabetic retinopathy. The DRS demonstrated that panretinal scatter photocoagulation reduced the risk of severe visual loss by >50% in eyes with high-risk characteristics. It may also be beneficial in other PDR and severe NPDR under certain conditions. The ETDRS could show that immediate focal laser photocoagulation reduced the risk of moderate visual loss for CSME by at least 50%. Usually several treatment sessions are required. In cases of both PDR and CSME, first the macula should be addressed unless high-risk characteristics warrant simultaneous panretinal treatment.

In summary, laser treatment offers proven treatments for many problems associated with diabetic retinopathy at a high evidence level. However, for certain situations such as macular ischemia, tractive components, severe proliferations and maybe diffuse macular edema other treatment modalities may be more beneficial. Surgery is definitely indicated for some situations and recently emerging medical therapies offer a variety of new approaches, which alone or in adjunction with laser therapy may help to further improve the outcome of treating diabetic retinopathy. However, their value still has to be proven at the same high level of evidence as that which exists for laser therapy.

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