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Laser Treatment for Diabetic Macular Edema in the 21st Century

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Abstract: Diabetic macular edema (DME) is the leading cause of blindness in the diabetic population. The diabetes Control and Complications Trial reported that 27% of patients affected by type 1 diabetes develop DME within 9 years of onset. Other studies have shown that in patients with type 2 diabetes, the prevalence increased from 3% to 28% within 5 years of diagnosis to twenty years after the onset. At the present time, despite the enthusiasm for evaluating several new treatments for DME, including the intravitreal therapies for DME (*e.g.*, corticosteroids, and anti-VEGF drugs), laser photocoagulation remains the current gold standard and the only treatment with proven efficacy in a wide range of clinical trials for this condition. Despite being the standard technique for comparison and evaluation of the emerging treatments, we have generally poor understanding of the ETDRS recommendations, and we often forget about the results of laser in DME. The purpose of this review is to update our knowledge on laser photocoagulation for DME with an extensive review of the ETDRS results and discuss the laser techniques. Furthermore, we will describe the new developments in laser systems and review the current indications and results. Finally, we will discuss the results of laser treatments versus the current pharmacological therapies. We conclude by trying to provide a general overview that which laser treatment must be indicated and what types of lasers are currently recommended.

Keywords: Laser, grid laser, focal laser, pan-retina-photocoagulation, anti-VEGF injections, diabetic retinopathy, diabetic macular edema, clinically significant macular edema, diffuse macular edema, focal macular edema.

INTRODUCTION

Diabetes is a chronic disease that typically causes changes in the small vessels of the whole body, changes that are referred to as diabetic microangiopathy. The ocular form is called diabetic retinopathy (DR). Approximately 25% of the people with diabetes have at least some form of diabetic retinopathy, and the incidence increases with the duration of the disease [1]. Eye diseases in diabetic population are the leading cause of blindness in adults under 75 years of age in developed countries [2]. There are two main complications of DR that cause visual loss: the proliferative diabetic retinopathy (PDR) and the presence of diabetic maculopathy [3].

Diabetic maculopathy may appear in two forms:

1) Diabetic macular edema (DME)

2) Diabetic macular ischemia (DMI)

DME is defined as an accumulation of fluid between the outer plexiform and the inner nuclear layers, as well as a swelling of the Müller cells of the retina, causing expansion of the retinal extracellular space, in some cases involving the intracellular, both in the macular area. The prevalence of DME is higher in type 2 (DM2) than that in type 1 (DM1) diabetic patients. Our study group in 2007 found a prevalence of DME of 12.9% in DM2 patients and 7.86% in DM1 patients [4].

The Diabetes Control and Complications Trial (DCCT) [5] reported that 27% of DM1 patients develop DME within 9 years of diabetes onset. Other studies have shown that in patients with type 2 diabetes, the prevalence increased from 3% to 28% within 5 years of diagnosis to twenty years after the onset [6]. DME tends to be a chronic disease, although it is important to recognize that about 33% to 35% of patients with DME resolve the condition spontaneously after 6 months [7, 8]. The edema in the macular area occurs secondary to an abnormal permeability of the capillaries surrounding the macula (failure of inner retinal blood barrier), and in turn to a failure in the outer retinal barrier (formed by the retinal pigmented epithelium). These two mechanisms are responsible for the accumulation of interstitial fluid at the macula [9, 10].

While there is currently no treatment for DMI, there are different treatments for patients with macular edema, including the photocoagulation treatment with focal or grid laser, which remains the gold standard of treatment for DME. In recent years new treatment regimens with intravitreal corticosteroid or anti-VEGF injections and anti-VEGF drugs, and

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combined treatments of laser and intravitreal injections have been studied. Finally, in cases where vitreous traction is demonstrated, the treatment of choice is to perform a posterior vitrectomy surgery (VPP). The use of the laser source as a method of treatment for DME was first evaluated in a protocol within the Diabetic Retinopathy Study (DRS) in 1981 [11]. The effectiveness of the xenon arc source and argon laser light in the treatment of proliferative diabetic retinopathy was verified, with a reduction in visual acuity of less than 5/200 in 50% of cases, and with a stability of visual acuity for at least 4 months. The next clinical trial of diabetic retinopathy, the Early Treatment Diabetic Retinopathy Study (ETDRS) evaluated the efficacy of laser treatment in 3.711 patients, assigning patients randomly into two groups, the first receiving laser treatment immediately and the second, subjected to treatment with aspirin and laser, being delayed until five years [11-14].

The ETDRS results suggested that scatter laser photocoagulation should be considered for all eyes with severe nonproliferative diabetic retinopathy or worse, because the rate of severe loss was reduced by more than 50% of those treated with early laser photocoagulation compared with eyes assigned to deferred laser photocoagulation. Regarding macular edema treatment, the ETDRS, further concluded that focal or grid laser photocoagulation was effective [13, 15]. Despite the fact that ETDRS study has been the gold standard in the classification and treatment of diabetic retinopathy and macular edema, it seems that DME photocoagulation laser treatment has been replaced by the new intravitreal drugs. This work aims to review the knowledge we currently have on the importance of laser photocoagulation, the different techniques and laser sources, and the current indication in patients with DME.

DEFINITION OF MACULAR EDEMA AND CLINICALLY SIGNIFICANT MACULAR EDEMA

In clinical care we use two different terms to define macular edema secondary to diabetes mellitus [16, 17]:

1) Diabetic macular edema (DME)
2) Clinically significant macular edema (CSME)

Both terms are different and are a source of confusion. In many studies, the terms are used indifferently and have led to confusing results.

Diabetic macular edema (DME) is defined as retinal thickening (associated with the typical lesions such as microaneurysms, retinal edema and hard exudates) within 1 disc diameter from the foveal centre and with two disc diameters wide (1 disc diameter = 1500 μm); it can either be focal or diffuse in distribution.

Clinically significant macular edema (CSME) is a form of DME that was precisely defined by the ETDRS [32] as any of the following criteria being met:

1) Any retinal thickening within 500 μm of the centre of the macula.
2) The presence of hard exudates at or within 500 μm of the centre of the macula, if associated with thickening of the adjacent retina (not residual hard exudates remaining after the disappearance of retinal thickening).
3) A zone, or zones, of retinal thickening 1 disk area or larger, any part of which is within 1 disk diameter (1 disc = 1500 μm) of the centre of the macula.

The most useful classification used for clinical diagnosis, and subsequent DME treatment, is based on macular distribution [18, 19], which classifies them as focal or diffuse macular edema:

1) Focal macular edema is associated with circinate rings of hard exudates resulting in leakage from microaneurysms that would lead to macular edema. Focal macular edema can be unique, with only one focus of macular edema, or multi-focal (with more than one focus).
2) Diffuse macular edema represents a more extensive breakdown of the blood retinal barrier with leakage from both microaneurysms and retinal capillaries (Fig. **1**). This type is observed during late hyperfluorescence angiography of a significant size (typically more than two papillary diameters) with scarce microaneurysms and hard exudates.

DIFFERENT LASERS USED IN OPHTHALMOLOGY

Classification of the ocular tissue lesion produced by laser [20]

1) Photocoagulation: thermal effect. Lesions are caused by an increase in tissue temperature, causing vaporization of liquids within and outside tissues and denaturalizing proteins, resulting in cellular death (apoptosis). Lasers of this kind are called photocoagulators, some of which are of argon (514.4 green and 488 blue-green nanometers) and krypton (647.1 red nanometers), which require a water refrigeration system. Currently, the most commonly used are double-diode (532 nanometers) and double-YAG (532 nanometers), which do not require cooling systems.
2) Disruption: electromechanical effect. These lasers use a burst of optical pulses of high power and short duration, achieving ionization of the tissue, forming plasma that expands at high temperature, which causes an acoustic shock wave that breaks the target tissue. Lasers of this type are called photodisruptors and Neodimio YAG (Yttrium-Aluminum-Garnet) operated with a longitudinal wave of 1064 nanometers is the one most commonly used. Its usefulness is in carrying out a capsulotomy after opacification following cataract surgery, and peripheral iridotomy to prevent risks of acute angle-closure glaucoma.
3) Photochemical, in which the lasers are used to alter the chemical composition of the target tissue, producing a molecular alteration of the cells subjected to a prior photosensitization. This type of treatment is called photodynamic therapy. In this type of laser, the treatment is carried out by photosensitization of the tissues, using photosensitizing agents like verteporfin (with a laser light absorption peak of 689 nm), which binds to the lipoproteins LDL-cholesterol. The activation is done by a non-thermal diode laser of 689 nm for 83 seconds, giving a dose of 50 jules/cm^2 luminous light intensity of 600mW/cm^3. Once activated, verteporfin radicals release oxygen, a process that alters the membranes of en-

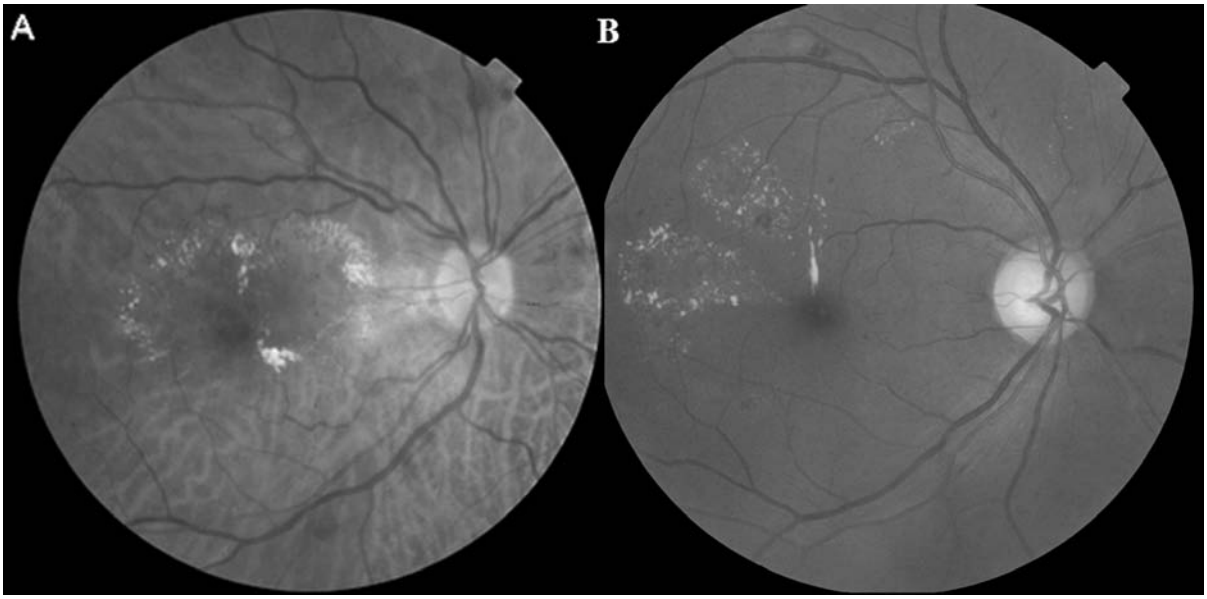

Fig. (1). Red-free fundus photography showing diffuse diabetic macular edema.

dothelial cells of the ocular blood vessels. This produces a platelet aggregation and forms a thrombus, resulting in an occlusion of the vessels. This technique is currently used in the treatment of exudative AMD (age related degeneration).

4) Photodecomposition. This is the result of the interaction of the laser with the tissues, which emits ultraviolet light at the target tissue. In this case, the laser photons are absorbed at the molecular level, resulting in fragmentation of the molecules. They emit ultraviolet radiation of 193 nanometers in pulses of 10 nanoseconds and the emitted radiation destroys molecular unions forming a volatile phenomenon called photodecomposition. The Excimer lasers (Argon - Fluoride) used in refractive surgery sculpt the corneal stroma using the photoablation.

Of the lasers described above, the treatment of DR and the DME appearing there is carried out with photocoagulator lasers. The first of their type used were argon and krypton, which were very cumbersome owing to the need for water cooling facilities. These have been replaced by the so-called solid lasers, which use diode or YAG, doubled to a produced radiation of 532 nanometers.

One type of laser also used in DME is the diode of 810 nanometers and acts in micropulses of 0.1 ms duration.

PHOTOCOAGULATION

The initial laser used in retina treatment with a thermal effect was the xenon arc photocoagulator. It is, in fact, not a true laser; it was introduced by Meyer-Schwickerath [21, 22] who, in a large series of publications, demonstrated in proliferative diabetic retinopathy the effectiveness of light burns over new vessels. This technique changed to a long, slow, moderately intense burning, turning the retina white adjacent to the new vessels, and sometimes causing them to narrow, slowing the flow within them. A true laser was made later; the first to be introduced was the argon laser. This produced a blue-green beam with sufficient intensity to reproduce the effects of a xenon arc with more intensity and a narrower beam. At the same time, the ruby laser was being evaluated [23]; the long wavelength and very brief exposure time of the ruby laser limited burns mainly to the outer layers of the retina, without immediate visible effects in new vessels, leading to the abandonment of the technique.

Diabetic retinopathy and diabetic macular edema are treated by lasers that produce thermal photocoagulation. As commented, the first laser used in retina treatment was the argon laser, which was then followed by the red krypton laser and finally the dye laser (which allowed the light to change from yellow to green, according to the needs of the retina. These types of lasers have been changed for solid lasers (doubled-diode or doubled-YAG). Unlike the argon and krypton lasers, the doubled diode or YAG lasers are much more power efficient, allowing them to be connected to standard power outlets available in any hospital or clinic. The laser emission is located in the green 532 nm, being much more effective than conventional argon lasers. The tissue response at wavelength 532 nm is more similar to that with the dry yellow-green argon (514 nm) and almost the same as the Krypton yellow (568 nm). Compared with the argon (514 nm) laser, doubled diode or YAG lasers have higher absorption of oxyhaemoglobin (HbO) and haemoglobin (Hb), less dispersion (the long wavelength) and low absorption of xanthophyll pigment.

The first clinical trial was initiated by a British multicentre research that used xenon arc photocoagulation [24], and later by the National Eye Institute's Diabetic Retinopathy Study [25], known as the DRS, which compared xenon arc and argon laser photocoagulation. The DRS studied patients with proliferative diabetic retinopathy in at least one eye or severe non-proliferative DR in both eyes, with a visual acuity of at least 20/100 in each eye. Patients were assigned to xenon arc or argon laser photocoagulation treatment, and followed at four months intervals. At two-years follow up, the DRS concluded that prompt laser treatment for eyes with severe non-proliferative DR or proliferative DR was effective. Furthermore, the DRS concluded that because the harmful effects were higher with xenon arc than argon laser, the

latter laser was a preferable treatment for diabetic retinopathy [26].

Laser Effect Mechanism

The effect of laser photocoagulation on the retina for diabetic retinopathy is still unknown, although different explanations have been put forward. The first is the occlusion of microaneurysms. In focal laser treatment in cases of focal macular edema, it is thought that direct microaneurysm photocoagulation around macular area reduces the leakage from the MA with a consequent decrease in macular edema. However, in the grid laser treatment technique, this mechanism might only function partially, so other possible mechanisms have been suggested:

1) Oxygen increases through the laser scar. One explanation involves laser-induced destruction of oxygen-consuming photoreceptors; the laser scars produce an apoptosis of photoreceptors, retinal pigment epithelium and choriocapillaries, and the scars allow oxygen (that normally diffuses from the choriocapillaries into the outer retina) to diffuse through the laser scar into the inner retina, thus relieving the inner retinal hypoxia [27].

2) A decrease in autorregulatory vasoconstriction. In diabetic retinopathy (also in DME), retinal vascular perfusion is increased with an arteriolar and venular dilatation. Following laser photocoagulation, Gottfredsdottir et al found that arteriolar branches constricted by 20.2% and the venular branches by 13.8%. The authors hypothesized that the improved retinal oxygenation leads to autoregulatory vasoconstriction with subsequent improvement in the DME [28].

3) A decrease in the whole area of abnormal leakage. Wilson et al demonstrated a reduction in the retinal capillary area in the laser photocoagulation zone, and suggested that when the area of abnormal leaking vessels is reduced, the amount of leakage would be reduced, which would result in the macular edema being resolved [29].

4) Restoration of retinal pigment epithelium (RPE) barrier. The RPE cells might respond to the laser injury in several ways: if the lesion is small (<125 μm) the RPE defect can be filled by spreading, but if the defect is relatively large the RPE cells proliferate to resurface the area, and the new RPE cells produce cytokines (*e.g.* TGF-β) that antagonize the effects of VEGF (the most important vasculogenic molecule, implicated in DME production) [30, 31].

DIABETIC MACULAR EDEMA, TREATMENT TECHNIQUES

Laser treatment was defined by the ETDRS study in its Reports number 3 and number 4, [32-34]. According to the ETDRS, there are two different techniques:

Focal Laser, Focal treatment is required for focal lesions located between 500 and 3000 μm from the centre of the macula. The term 'focal lesions' according to the ETDRS classification includes: microaneurysms, intraretinal microvascular abnormalities (IRMA) and short capillary segments that show focal fluorescein leakage. The treatment consists of burns of 50 to 100 μm of moderate intensity and 0.05 to 0.1 second duration, the end point of treatment is whitening or darkening of focal lesions. Microaneurysms below 40 μm in diameter had successful results with low laser intensity, but microaneurysms with more than 40 μm diameter needed more intense laser burns (a more whitening result) and sometimes needed a re-treatment. The clusters of microaneurysms, in particular those with hard exudate rings, may be treated with larger spots (200 to 500 μm), with subsequent re-treatment of any large microaneurysms within the cluster with 50 μm spots to obtain darkening or whitening. The treatment of lesions of more than 3000 μm from the centre is recommended if prominent leaks are present and associated with retinal thickening or hard exudates that extend closer to the center (Table **1**).

Grid laser, in which mild power laser impacts were made with a spot size of 50 to 200 μm, for a duration of 0.05 to 0.5 sec obtained a mild retinal pigment epithelium whitening, with power adjustment to prevent the burns from spreading to more than 200 μm in diameter. Grid treatment is not placed within 500 μm of the center of the macula or within 500 μm of the disc margin, but may be placed in the papillomacular bundle. Grid can extend up to 2 disk diameters (3000 μm) from the centre of the macula or to border panretinal photocoagulation treatment, if present (Fig. **2**). Any focal leaks within the areas of the grid treatment are treated focally. The laser burns are placed approximately two visible burn widths apart in the areas of the macular edema (retinal thickening) that are thought to be related to diffuse leakage or capillary loss (Table **1**).

Mild Macular Laser Photocoagulation (MMG)

This new approach to macular laser photocoagulation has recently become the focus of interest for ophthalmologists. In this new method, the burns are applied to the entire area (as described below) for treatment (including unthickened retina). Burns are focused/located over 500 to 3000 microns above, nasally and under the center of macula, and 500 to 3500 microns towards the temples [35]. There are no burns within 500 microns of the disc. The burn intensity of the grid laser is barely visible (light grey); 200 to 300 burns in total are distributed evenly over the treatment area (approx. 2 to 3 burn widths apart). The MMG burns are lighter and more diffused in nature and are distributed over the whole macula in both areas of thickened and unthickened retina. Microaneurysms are not directly photocoagulated (Table **1**). In contrast, the ETDRS focal/grid photocoagulation comprised of treating only areas of thickened retina (and areas of retinal nonperfusion) and leaking microaneurysms. The Diabetic Retinopathy Clinical Research Network (DRCR.net) compared this technique [35] with the previously described modified-ETDRS gold standard technique. Between July 2003 to October 2004, 263 patients (with a total of 323 eyes) were enrolled and assigned randomly to each technique (n = 162 eyes to the mETDRS technique and n = 161 eyes to the MMG technique). Despite the hopes for this new method, there was no indication that the eyes treated with MMG had a better outcome after 12 months of follow up than those receiving mETDRS treatment. In fact, eyes in the mETDRS group experienced a slightly greater reduction in retinal thickening and a trend towards a slightly better visual acuity outcome. In conclusion, despite potential advantages in theory

Table 1. Laser photocoagulation techniques for DME, attending the original ETDRS, modified ETDRS and the MMP technique.

	Direct/ Grid Photocoagulation Original ETDRS	Direct/ Grid Photocoagulation Modified ETDRS	Mild Macular Grid Photocoagulation Technique
Characteristic of direct treatment	Directly treat all leaking MA in areas of retinal thickening between 500 and 3000 microns from the centre of the macula (but not within 500 microns of disc)	Directly treat all leaking MA in areas of retinal thickening between 500 and 3000 microns from the centre of the macula (but not within 500 microns of disc)	Lighter and more diffuse in nature and are distributed throughout the macula in both areas of thickened and unthickened retina
Change in microaneurysms colour with direct treatment	Required at least a mild white burn should be evident beneath all MA	Not required, but at least a mild gray-white burn should be evident beneath all MA	Microaneurysms are not directly photocoagulated
Burn size for direct treatment	50 to 100 microns	50 microns	Not applicable
Burn duration	0.05 to 0.1 sec	0.05 to 0.1 sec	Not applicable
Grid treatment	Applied to all areas with diffuse leakage or nonperfusion within area described below for treatment	Applied to all areas with diffuse leakage or nonperfusion within area described below for treatment	Applied to entire area described below for treatment (including unthickened retina)
Area considered for grid treatment	500 to 300 microns superiorly, nasally and inferiorly from the centre of macula. 500 to 3500 microns temporally from macula centre. No burns are placed within 500 microns of disc	500 to 300 microns superiorly, nasally and inferiorlyfrom the centre of macula. 500 to 3500 microns temporally from macula centre. No burns are placed within 500 microns of disc	500 to 300 microns superiorly, nasally and inferiorly from the centre of macula. 500 to 3500 microns temporally from macula centre. No burns are placed within 500 microns of disc
Burns size for grid treatment	50 to 100 microns	50 microns	50 microns

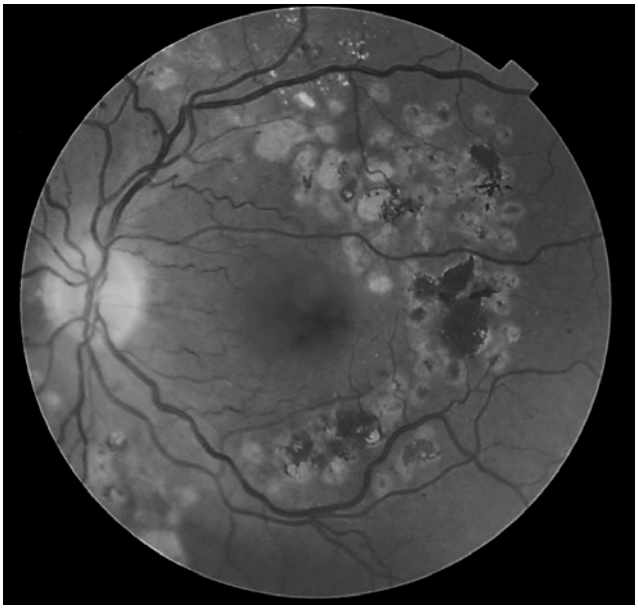

Fig. (2). Macular fibrosis secondary to a grid laser treatment. Spectral Domain-OCT image shows the subretinal fibrosis. The red-free fundus photography shows a scar located at fovea, surrounded by the laser impact sites.

after 12 months of follow up the MMG laser technique is less effective in reducing OCT measure retinal thickening than the mETDRS technique frequently used in current clinical practice. Having said that, the visual acuity outcomes with either approach are not significantly different. This study does not therefore provide data to suggest that a larger long-term trial of the MMG technique is likely to show substantial clinical benefit over the current mETDRS approach.

Subthreshold Diode Micropulse Laser Photocoagulation (MPD)

This recent technique uses a subthreshold laser micropulse, using an 810 nanometre diode laser; the desired effect is to reduce the laser damage to ocular tissue; its application in the macular area is very promising in order to treat DME with the less retinal damage. Although conventional photocoagulation is a destructive procedure, chorioretinal damage can be minimized by modifying laser parameters and clinical endpoints in the following ways: by decreasing wavelength, spot size, retinal irradiance or pulse duration. In continuous wave mode, the laser energy is delivered as a single pulse, with a typical width in the range of 0.1-0.5 seconds exposure. In micropulse mode, the laser energy is delivered with a train of repetitive short pulses (typically 100x300 msec. each) in packets. The greatest limitation of MPD laser procedures is the difficulty of the treatment without the feedback of an ophthalmoscopically visible endpoint. Conversely, minimizing chorioretinal laser damage allows confluent therapy and re-treatment of the same areas, which may be needed in macular edema. Re-treatment is feasible after MPD, because it does not produce chorioretinal scars that might expand or increase the risk of choroidal neovascularization. The treatment protocol is not yet well established in terms of the exact laser irradiance (power per unit of area) that should be delivered to the retina.

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