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# How new generation lasers are different from each other?

**Victor Chong**

Consultant Ophthalmic Surgeon, Optegra Eye Hospital, University of Oxford and Royal Free Hospital, London, United Kingdom

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## HIGHLIGHTS

The author would explain how laser works in macular diseases, how the treatment protocol has been modified and also how new generation lasers are different from each other?

## NAJWAŻNIEJSZE

Autor opisuje sposób działania laseroterapii w chorobach plamki, a także historię zmian protokołów prowadzenia laseroterapii oraz nowe generacje urządzeń i cechy odróżniające je od poprzedników.

## ABSTRACT

Laser has changed a lot over the years, the newer laser can deliver energy in different ways, by reducing the duration to 10–20 ms, in a train of pulses of 0.1 ms as in the micropulse / subliminal laser, and extremely short duration of 0.0017 ms as in the nanosecond laser. Clinical studies have shown that micropulse laser is efficacious in multiple macular conditions. Reducing the power and duration using end-point management has yet to demonstrate clinical efficacy beyond CSR. The ability to reduce the progression of intermediate AMD is intriguing, after all the LEAD (Laser intervention in early stages age-related macular degeneration) trial failed the primary endpoint. Nonetheless, there is evidence to support that it may be effective in a highly selected sub-group of intermediate AMD patients. More studies are required to see whether other lasers such as micropulse laser can have the same effect, and whether micropulse lasers with a slightly higher energy leading to a few RPE cell deaths is needed to have the same effect.

**Key words:** macular diseases, diabetic macular edema, micropulse laser, subliminal laser, non-damaging laser, nanosecond laser

## STRESZCZENIE

Lasery okulistyczne do leczenia schorzeń siatkówki przeszły znaczną ewolucję w ciągu ostatnich lat. Najnowsze urządzenia zapewniają krótszy czas dostarczania energii (10–20 ms): w impulsach trwających 0,1 ms w laserze mikropulsowym/podprogowym i w impulsach o ultrakrótkim czasie trwania – 0,0017 ms – w laserze nanosekundowym. Badania kliniczne wykazały, że laser mikropulsowy jest skuteczny w wielu stanach chorobowych plamki żółtej. Trwają badania nad określeniem skuteczności klinicznej przy zastosowaniu mniejszej mocy i krótszego czasu aplikacji, uzyskanych dzięki metodzie *end-point management* we wskazaniach innych niż centralna retinopatia surowicza. Możliwości spowolnienia progresji średnio zaawansowanego zwyrodnienia plamki żółtej (AMD) wydają się realne, mimo że w badaniu LEAD (*Laser Intervention in Early Stages Age-related Macular Degeneration*) nie udało się osiągnąć tego założonego pierwszorzędowego punktu końcowego. Dysponujemy jednak licznymi poszlakami wskazującymi, że sukces jest możliwy w precyzyjnie wyselekcjonowanej podgrupie pacjentów z AMD. Potrzebne są zatem kolejne badania, aby jednoznacznie stwierdzić, czy urządzenia takie jak laser mikropulsowy mogą zapewnić satysfakcjonujący efekt terapeutyczny i czy lasery mikropulsowe o nieco większej energii, które powodują zniszczenie większej liczby komórek RPE, są niezbędne do osiągnięcia tego efektu.

**Słowa kluczowe:** choroby plamki, cukrzycowy obrzęk plamki, laser mikropulsowy, laser podprogowy, laser nieuszkadzający, laser nanosekundowy

## BASIC PRINCIPLE OF LASER FOR MACULAR DISEASES

In order to understand the how new generation lasers are different from each other, we would have to first try to understand how and why lasers work in macular diseases. It is important to separate the role of laser in the coagulation of tissue, such as treating a vascular tumor, or using laser to coagulate the retina around a retinal hole to create a ring of scar tissues in forming a physical barrier. In those circumstances, the laser generates heat and the heat energy leads to coagulation and the tumor tissues are destroyed or scars form.

In macular diseases such as diabetic macular edema (DME), we were initially taught to "shoot at the red dots". The red dots are the microaneurysms, which are leaking leading to DME. However, before we had modern lasers and biomicroscopic laser lenses, it was not uncommon to miss these microaneurysms. However, the treatment stills seemed to work. Then when the red laser came along. A red laser light would not be absorbed by the microaneurysms, so shooting at them should not work but it still worked [1]. Then over the years, we were taught to reduce the power so we can see a barely visible burn, and that also worked [2]. It is unlikely a barely visible burn will coagulate the microaneurysms directly. So why would did that work?

It turns out that the most of the laser energy is absorbed by the retinal pigment epithelium (RPE) and the choroid. And it is believed that the laser energy induces a change in the RPE cells and by changing that micro-environment, the edema improves. So several questions were raised.

## WHAT IS THE GREY COLOR CHANGE THAT WE SEE WHILE WE ARE LASERING, WHAT DO WE MEAN BY "BARELY VISIBLE" OR "THRESHOLD"?

When we laser, if there is enough energy, you would see a grey color change and with increasing energy, it would look white. If you think about it, the retina is translucent, and if you try to heat it up, it changes color, as you are denaturing the neurosensory retina. That is why you have a color change. If you increase the energy of the laser, the retina becomes even more opaque, and hence it looks white. If the energy is reduced, the reaction can barely be seen, and that is called "barely visible". This is considered as threshold, that is the threshold energy with which a color change can be obtained. To be fair, some retinal specialists would consider a clearly visible reaction as threshold, and that has caused confusion if the power setting is based on the threshold power. The latter would set a higher treatment power as more energy is needed to get a clearly visible reaction as compared to a barely visible reaction. You need to use a different correction ratio to correct for that.

## HOW MANY PARAMETERS CAN WE CHANGE IN LASER PROCEDURES?

Within a given laser, you can change the spot size, the duration and the power. So if you have a larger spot size, you would need to give either more power or a longer duration to deliver the same amount of energy to the individual RPE cell. There is a trend of using a smaller spot size, it was 200 microns in 1980s, and now most people would use 50 to 100 microns. Similarly, the duration of a single spot (energy) delivered was also reduced from 200 ms to 50 ms. The move to smaller spot size and shorter duration appears to give the surgeon more control and less scarring, but with similar efficacy.

The wavelength of laser can alter things a bit, for instance an infrared 810 nm laser would be absorbed more by the choroid as compared to a yellow 577 nm laser which is more absorbed by the RPE. The different laser lenses one uses also have a different laser correction factor, hence affecting the spot size on the retina. Finally, if you are not in focus or the lens is slightly tilted, you would have less energy reaching the retina. Furthermore, when there is edema, you cannot always be sure that you are in focus. Many were taught to increase the power in these edematous areas to get the same level of visible change as in other areas but unfortunately, that is also a fundamental mistake to equate the color change while performing the laser to the key of success. In fact, it is commonly seen that these areas ended up with very heavy laser burns due to the increased energy.

## DO WE NEED TO SEE VISIBLE CHANGES WHILE WE ARE DOING THE LASER FOR THE TREATMENT TO BE EFFECTIVE?

As mentioned, you would like to deliver energy to the RPE cells without damaging the photoreceptors. It is now clear that no visible changes are needed as multiple studies have shown efficacy without any visible changes on the retina.

## NEW GENERATION LASERS

### End-point management / Non-damaging

The history of short duration (10 to 20 ms) in laser treatment was initially based on the desire to perform multiple spots within a short period of time through a single press on the laser foot pedal. It was found that the size of the laser scar does not expand. The reduction of the energy can still induce RPE changes without killing the RPE cells. Animal experiments in rabbit have shown that it is around 25% to 30% of the so called threshold power [3]. Threshold power is the power at which the surgeon can see a change in the retina

during the laser procedure. It is claimed that the treatment window is very narrow and has to be carefully titrated using the so called end-point management software by reducing the power and the duration used in the test spot, and to achieve no visible retinal scarring but positive clinical effect. The principle sounds great but it is unclear how to translate animal experiment to human as rabbit choroid and choroidal pigmentation are very different from human. In general, the best way to look at these principles would be clinical studies. So far, there is only one case series showing clinical success without retinal damage on central serous chroio-retinopathy (CSC), hence the term non-damaging was coined [4]. No controlled trial has been published in DME. Indeed, independent investigators have shown RPE changes / scarring can be detected by autofluorescence (AF) imaging and optical coherent topography (OCT) [5].

## MICROPULSE / SUBLIMINAL / MINIPULSE LASER

Instead of strictly reducing the duration of each laser energy delivery, micropulse laser was pioneered by Iridex to deliver the laser energy with a train of short pulses over a historic standard duration [6]. As the standard duration of 200 ms per laser energy delivery is commonly used, using 5% duty cycle, 100 pulse of 0.1 ms with the laser ON and 1.9 ms with the laser OFF. Hence the total time of laser on over the 200 ms is in fact 10 ms. The conceptual idea is that the laser OFF period allows the lasered tissue (RPE cells) to cool off before the next laser ON period comes along. This concept has been challenged. Some would argue that there was not enough time for the RPE to cool off and all the micropulse laser would achieve is the same as using 10 ms. So why waste the time and energy to use micropulse laser?

Frankly, it is very difficult to prove what micropulse laser really does. However, there are over 50 studies using micropulse laser showing efficacy in DME and CSC, including controlled trials by a number of investigators using a number of different treatment protocols [7]. Comparing with end-point management, the same group of investigators did not see any RPE changes / scarring using AF or OCT.
So comparing end-point management and micropulse, both are delivering about 10 ms of laser energy and both are using the power selected based on the threshold power. The key differences are that somehow, end-point management continues to show RPE changes / scarring with very limited published efficacy and micropulse laser has demonstrated efficacy by many group of investigators in multiple clinical trials. Furthermore, there were no visible RPE changes using current clinical retinal imaging.

FIGURE 1a

Cartoon of conversation laser treatment.

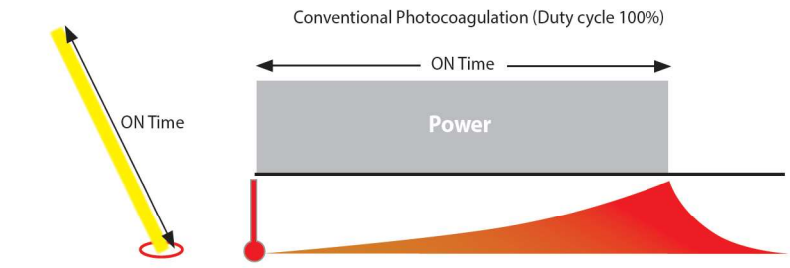



FIGURE 1b

Cartoon of micropulse laser treatment.

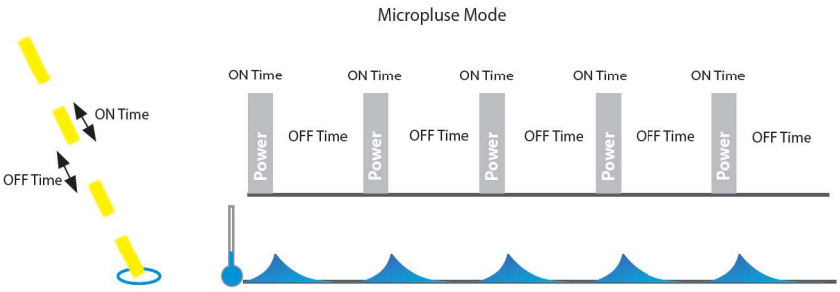


FIGURE 1c

Scanning electron microscopy of RPE after micropulse laser.

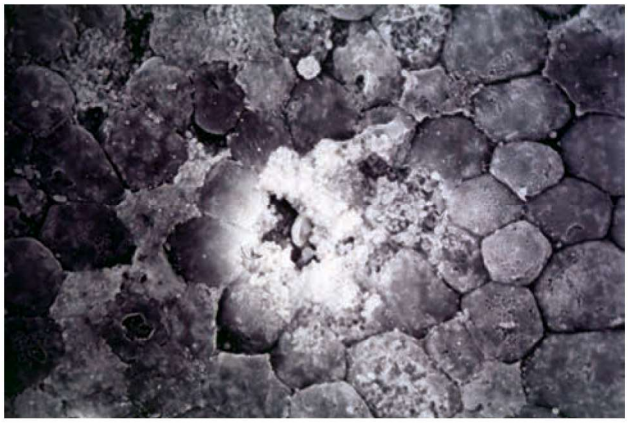


FIGURE 2a

Fundus photo of pre-laser in patients with DME.

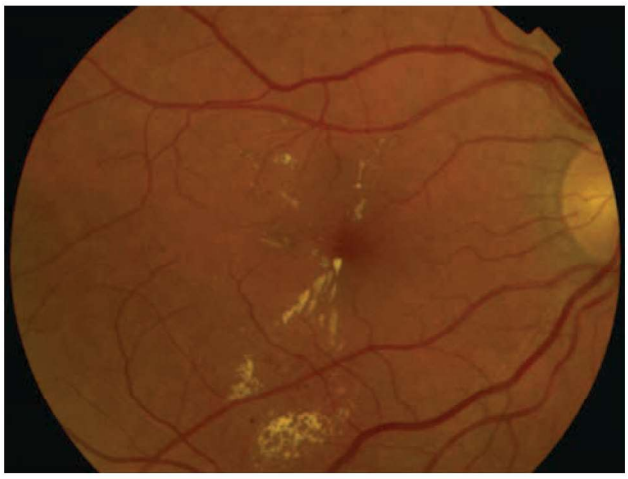


FIGURE 2b

Fundus photo of patients with DME, 4 months after a single micropulse laser treatment.

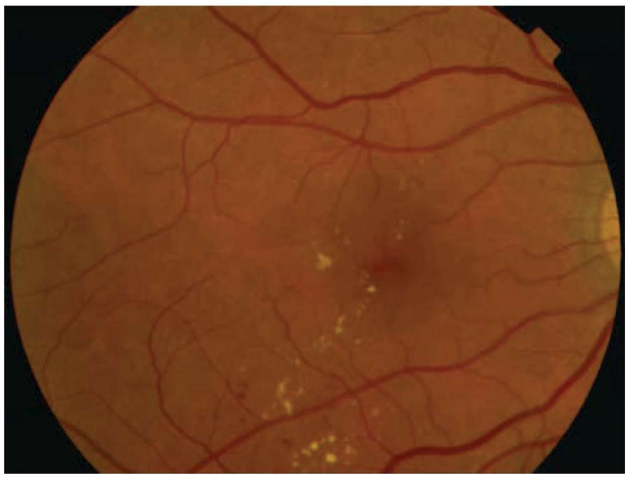
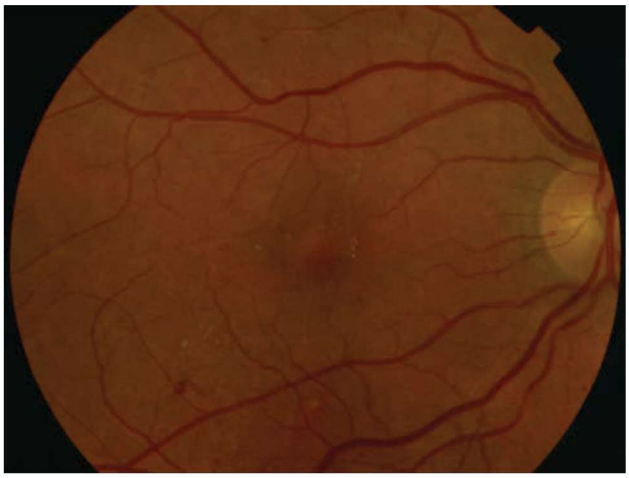


FIGURE 2c

Fundus photo of patients with DME, 12 months a single micropulse laser treatment showing exudation reduction and no visible laser scar.



***So what is SubLiminial or minipulse?***

As mentioned, micropulse laser was pioneered by Iridex. For many years, micropulse is the standard terminology. More recently, other companies have also developed "micropulse" technology but they cannot call that micropulse. Quantel Medical called it SubLiminal and OD-OS called it Minipulse. I am not a patent lawyer, so I am not sure who is right or wrong, but my understanding is that "micropulse" technology from different companies are similar if not identical, at least from the laser surgeon point of view.

***Is power testing needed for micropulse laser?***

There are generally two schools of thought, one is to test power titrate to a barely visible reaction, and then reduce that by 50%. Some retinal specialists titrate to clearly visible reaction and then reduce that by 30%. Both give similar results. The alternate method would be using the same power for everyone [8]. I prefer to test power, as first, I can be sure the laser is working and can cause some laser reaction, and second, I do find less power is needed in non-European races such as Asian Indian and African. It is reasonable to test power on the first case on the day. Assuming the laser would work on the same session, and if all your patients on the list are of European descent with relatively clear lenses, then use the same power for the rest of the day. In general, most experienced surgeons can perform the titration very quickly, so the key disadvantage of titration would be extra 30 seconds of surgery time, and the key advantage is being more precise and ensuring the laser is working without needing a power meter.

## NANOSECOND / REJUVENATION LASER

Most laser surgeons would be familiar with SLT laser. The retinal nanosecond / rejuvenation (2RT) laser is a modified SLT laser, however, the principle is similar. The 2RT laser uses an extremely short duration, and multiple beams are delivered to the retina at 400 microns spot size. The treatment energy is based on power testing to a threshold color change. It has gained a lot of recent attention as it might reduce the progression of intermediate AMD without reticular pseudodrusen [9].

It is suggested that the laser can kill RPEs without any damage to the retina, and RPE death is needed, as the surrounding RPE cells will slide over and cover the defect, and this leads to a biological effect. RPE changes after treatment are clearly visible, and it was shown that the retinal sensitivity is similar over these RPE changes and nearby retinal areas. However, the changes in retinal sensitivity as measured by microperimetry has poor sensitivity in detecting changes. Nonetheless, it is clear that there was no massive retinal sensitivity loss associated with conventional laser.

The main claim is that this sliding RPE cells would not occur in other forms of laser treatment [10]. It is unclear to me why. I can accept that the laser might be able to kill RPE cells without damaging the photoreceptors. However, micropulse laser does not appear to damage the photoreceptors either. It remains to be seen whether micropulse or indeed any other forms of laser can reduce the progression of intermediate AMD.

TABLE 1

Comparison of new generation lasers.

| | Micropulse / Subliminal | Endpoint management / Non-damaging | Nanosecond / Rejuvenation |
|---|---|---|---|
| Duration of laser in each pulse | 0.1 ms | 10 to 20 ms | 0.000003 ms |
| OCT changes after treatment | None visible | Clearly visible | Seen in some cases |
| AF imaging after treatment | None visible | Clearly visible | No published data but RPE changes visible on color fundus photos |
| Randomized controlled trials published | Several in DME and CSC | None | Reduce AMD progression (in post-hoc analysis) |

**CORRESPONDENCE**
Victor Chong, MD
Optegra Eye Hospital, London W1G 9HT, 25 Queen Anne Street
e-mail: victor@eretina.org

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