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EDITORIAL

NICE guidelines reaffirm the key role of laser for treating proliferative diabetic retinopathy and diabetic macular oedema

Eye (2026) 40:3–6; https://doi.org/10.1038/s41433-025-04129-x

THIS WORK HAS NOT PREVIOUSLY BEEN PRESENTED AT A SCIENTIFIC MEETING

In August 2024 the National Institute for Health and Care Excellence (NICE) published the first guidance on the management and monitoring of people with diabetic retinopathy under the care of Hospital Eye Services (DR) [1]. The guidance highlighted the central role for panretinal photocoagulation (PRP) and macular laser to treat proliferative diabetic retinopathy (PDR) and diabetic macular oedema (DMO), respectively, as summarised in Box 1. We are aware that many patients who could benefit from macular laser are not offered this treatment and that, in some instances, PRP may not be delivered appropriately, with the potential for a reduced efficacy. Building on the NICE guideline, we propose a strategy to address these issues.

PRP FOR THE TREATMENT OF PDR

Photocoagulation of the retina was pioneered by Professor Gerhard Meyer-Schwickerath in Essen, Germany [2]. The argon laser, and subsequent equivalent continuous wave millisecond systems, superseded older xenon arc lasers. It has been proposed that, among other possible mechanisms, the thermal coagulation of the retinal pigment epithelium (RPE) and adjacent retina reduces the production of hypoxia-induced factors, including VEGF, leading to the regression of new vessels in PDR [3]. It is believed that the reduced consumption of oxygen due to cell demise in lasered areas increases the availability of oxygen to the macula. Untreated retina may also benefit from improved perfusion because of vascular remodelling [4].

Two early landmark RCTs provided the definitive evidence for the efficacy of PRP to treat PDR. The Diabetic Retinopathy Study (DRS), undertaken from 1971-9 [5, 6], compared PRP to observation for people with PDR in at least one eye or severe non-proliferative diabetic retinopathy (NPDR) in both eyes. A > 50% reduction in severe visual loss (defined as a loss of 30 ETDRS letters) was observed at 24 months. The ETDRS undertaken from 1979–89, demonstrated that PRP in NPDR or early PDR reduced the progression to high-risk characteristics PDR by 50% at 5 years in the full PRP group [7]. The ETDRS concluded that, provided people are carefully followed, PRP should not be recommended for eyes with mild/moderate NPDR, may be entertained in eyes with more severe retinopathy, depending on the circumstances, and that PRP should not be delayed in high-risk characteristics PDR.

The technique for PRP described in the DRS and ETDRS using argon laser remains the reference standard for treatment of PDR. The DRS recommended scatter laser (800-1600 spots in 1 or 2 sessions with follow-up treatment applied as needed at 4-month intervals) extending to or beyond the vortex vein ampullae (midperipheral retina) [5]. Current accepted treatment is 360-degree scatter laser of the midperipheral retina, with spacing 1 burn width apart to minimise effects on peripheral vision. Posterior extent of treatment is the vascular arcades superiorly and inferiorly, 500 µm from the optic disc nasally and 2 DD from the centre of the fovea temporally (assuming normal retinal anatomy). 2500 burns of approximately 200 µm diameter each is considered a standard treatment. Laser fluence is titrated to achieve an immediate grey-white, retinal burn. Very intense white spots are avoided to reduce complications including breaks in Bruch's membrane and secondary neovascular membranes.

There is limited evidence regarding the efficacy or safety of alternative strategies of PRP application or of alternative laser systems [8]. Nevertheless, we are aware that most eye units in the UK utilise multispot laser systems to perform PRP. These may reduce the time required for treatment, may be more tolerable for patients due to reduction in duration and thermal diffusion and may result in reduction in loss of retinal sensitivity when compared with conventional laser. However, the evidence of their efficacy regarding regression of PDR is limited to small studies. Indeed, in a *post hoc* analysis of DRCR.net Protocol S, eyes receiving multispot PRP, when compared with single spot standard laser, had a higher risk for worsening PDR [9].

Both the CLARITY and DRCR.net Protocol S RCTs investigated the efficacy of intravitreal anti-VEGF versus PRP for PDR. CLARITY demonstrated that aflibercept was non-inferior and superior to PRP in terms of visual acuity at 52 weeks [10]. In Protocol S, treatment with ranibizumab resulted in visual acuity that was non-inferior to PRP at 2 years [11]. Visual field sensitivity loss was initially worse, vitrectomy more frequent, and incidence of DMO more frequent in the PRP group [9]. However, anti-VEGF therapy does not reperfuse ischaemic retina, which would be expected to be required to achieve long-term stabilisation of the disease. Moreover, these RCTs were designed and powered as non-inferiority trials, thus, unable to determine whether both treatments were equivalent in terms of efficacy to control PDR, had short duration (one or two years) and did not have a pragmatic trial design. Thus, it is difficult to determine whether their results would be applicable to a real-world setting.

Protocol S subjects were followed to 5 years. Visual acuity in most study eyes that completed follow-up was very good; severe vision loss or serious PDR complications were uncommon in both groups. However, even in the context of this well-resourced study, 34% of subjects were lost to follow-up at 5 years [12]. Large real-world studies conducted in the US report lost-to-follow up rates after PDR treatment of between 11 and 17% [13, 14]. A recent study demonstrated worse visual acuity at the return visit for those lost to follow-up, with PRP monotherapy associated with a lower risk of complications on return compared with anti-VEGF therapy [15].

Received: 19 June 2025 Revised: 6 October 2025 Accepted: 7 November 2025
Published online: 4 December 2025

Hence in the NICE guidance, PRP is emphasised as the first line treatment for PDR. Anti-VEGFs should be considered only for eyes where complete PRP has been performed but PDR remains active. Vitrectomy is also an option in this group depending on the presence of other clinical features including any tractional retinal detachment (guideline recommendations 1.5.7-9). Few patients would be expected to have PDR which remains active in the presence of a complete and adequate PRP. In the future, sustained delivery systems, gene therapies or novel pharmacological therapies with longer duration and disease-modifying characteristics may replace the physical therapy of laser. For now, an international consensus supports PRP laser as the first line therapy for PDR. The health economic analysis undertaken as part of the NICE guidance further supports this position, demonstrating high cost-effectiveness of PRP [16].

Box 1. Recommendations from the NICE Guideline [1] pertaining to laser treatment for PDR and DMO

Note: NICE recommendations use the term "offer" when there is robust evidence of a benefit and "consider" when there is evidence but of less degree of certainty.

Proliferative diabetic retinopathy (PDR)

1.5.2 Offer panretinal photocoagulation to people when they are first diagnosed with PDR

1.5.5 Offer anti-VEGF treatment for people whose PDR remains active after complete PRP

Diabetic Macular Oedema (DMO)

1.6.1 Offer treatment to people with clinically significant macular oedema (CSMO) (centre-involving and non-centre-involving)

Non-centre-involving DMO

1.6.3 Offer macular laser treatment to people with non-centre-involving CSMO

Centre-involving DMO with good vision

1.6.4 For people with centre-involving DMO and good vision (79 letters or better) consider either macular laser treatment or observation. Discuss risks and benefits of these 2 options with the person.

Centre-involving DMO with impaired vision

1.6.5 For people with centre-involving DMO, visual impairment (worse than 79 letters) and central retinal thickness of 400 micrometres or more, offer anti-VEGF treatment. Discuss with the person the advantages and disadvantages of the available anti-VEGFs.

1.6.6 For people with centre-involving DMO, visual impairment and central retinal thickness of less than 400 micrometres, consider anti-VEGF or macular laser treatment. Discuss with the person the advantages and disadvantages of all available treatments.

MACULAR LASER IN DMO

The ETDRS demonstrated the benefit of macular laser in DMO. In participants with CSMO, macular laser photocoagulation reduced the risk of moderate vision loss (15 ETDRS letters) by 50% or more [17]. A modified macular laser technique adapted from that described in the ETDRS combining direct treatment of leaking microaneurysms and grid treatment of areas of diffuse leakage and non-perfusion [18] is an accepted standard for conventional macular laser (Box 2). Despite RCT evidence of its efficacy, the exact mechanism of action of macular laser has not been fully elucidated. Proposed mechanisms include closure of microaneurysms, stimulation of the RPE, hypoxia relief, oxygenation improvement, and changes in retinal vascular autoregulation [19]. The findings of the ETDRS are not redundant in the era of anti-VEGF. For people with CI-DMO with visual impairment anti-VEGF should be considered (recommendations 1.6.5 and 1.6.6). However, in people with CSMO that does not involve the centre of the fovea (i.e. not CI-DMO), laser reduces rate of progression to CI-DMO and, thus, the need for anti-VEGFs.

Even eyes with CI-DMO and good vision can benefit from macular laser. In the DRCR.net Protocol V study, participants with CI-DMO and good vision were randomised to initial management with aflibercept or focal/grid laser or observation. Participants in the later 2 groups were given aflibercept only if visual acuity worsened. There was no significant difference in vision loss at 2 years among groups [20]. Aflibercept was initiated in 25% and 34% of eyes in the laser photocoagulation and observation groups, respectively. Among eyes receiving at least 1 injection, the median number of injections over 2 years was 7 in the laser group and 9 in the observation group. A *post hoc* analysis from Protocol V reported characteristics that are associated with increased chance of requiring anti-VEGF following initial observation: baseline central subfield thickness at least 300μm; ETDRS level 47 retinopathy or worse; and non-study eye receiving DMO treatment within 4 months of randomisation [21]. Protocol V

Box 2. Modified ETDRS macular laser technique. Modified from [18]

Burn Characteristic	Modified-ETDRS technique
Direct treatment	Directly treat all leaking microaneurysms in areas of retinal thickening between 500 and 3000 μm from the centre of the fovea (but not within 500 μm of disc)
Colour change in microaneurysms with direct treatment	Not required, but at least a mild grey-white burn should be evident beneath all microaneurysms
Burn Size for Direct Treatment	50 μm
Burn Duration for Direct Treatment	0.05 to 0.1 s[a]
Grid Treatment	Applied to all areas with diffuse leakage or nonperfusion within area described below for treatment
Area Considered for Grid Treatment	500 to 3000 μm superiorly, nasally and inferiorly from centre of macula 500 to 3500 μm temporally from macular centre. No burns are placed within 500 μm of the disc.
Burn Size for Grid Treatment	50 μm
Burn Duration for Grid Treatment	0.05 to 0.1 s[a]
Burn Intensity for Grid Treatment	Barely visible (light grey)
Burn Separation for Grid Treatment	2 visible burn widths apart

[a]Treatment duration quoted for 'argon' lasers.

participants were seen every 2 months for 2 years; this schedule may not be reproducible in real-world practice.

All treatments have risks. No recent study has reported the risk of foveal burn during macular laser but this is commonly quoted as 1/1000 cases. The risk of endophthalmitis following a single intravitreal is around 1/3000 (with cumulative risk with a course of treatment) [22]. A course of anti-VEGF injections can be an important imposition on a patient's life, even if vision is maintained. Preventing the need for injections or reducing the number of injections required is a significant potential benefit of laser. NICE guidance aims to identify care which is high quality, good value and provides the best outcomes for people using health services within the budget available [23]. Health economic analysis undertaken as part of the NICE guidance demonstrates that macular laser for DMO is cost-effective [24].

Micropulse laser and other sub-threshold technologies aim to achieve the benefits of macular laser with no thermal damage to the neuroretina. The landmark DIAMONDS trial demonstrated that in subjects with CI-DMO and central subfield retinal thickness (central 1 mm) of <400um, micropulse laser is equivalent to conventional macular laser with regard to visual acuity at 24 months [25]. Participants maintained excellent vision at 2 years (median 80 ETDRS letters). The mean number of laser treatments was 2.4 and 1.9 in the micropulse and standard laser arms, respectively with 18% and 21% of micropulse and standard arm participants receiving anti-VEGF rescue therapy, respectively. There was no difference in adverse events between the 2 groups. The NICE guideline does not specifically refer to one or other method of macular laser.

COMPETENCY AND TRAINING FOR RETINAL SPECIALISTS

Clinicians counselling patients and benchmarking their results against those of RCTs should consider the characteristics of participants included in these RCTs as well as study treatment protocols as these will determine outcomes. The DRS, ETDRS and subsequent publications gave clear descriptions of how both PRP and macular laser are to be performed. Few studies have evaluated the quality and adequacy of real-world retinal laser treatments for DR and DMO [26]. However, anecdotal reports suggest variation in practice. It appears that the use of macular laser to treat DMO decreased greatly as anti-VEGFs were introduced. Reasons for this decline may include the influence of the pharmaceutical industry on the medical profession, shortcomings in retinal laser training to the new generation of retinal specialists and time pressure on busy clinical departments.

The RCOphth is a world leader in ophthalmic postgraduate education. The new RCOphth curriculum [27] mandates competency in both PRP and macular laser for general ophthalmologists. However, no minimum number of procedures is required. Health Education England has funded a course using a retinal laser simulation system [28], but not all UK specialist trainees have access to it. To tackle these serious shortcomings, we propose the following strategies:

- We call on retinal specialists in the UK and globally to promote the role of laser in DR and DMO, the latter particularly for patients with non-centre involving CSMO and centre involving DMO with good vision.
- We encourage the Royal College of Ophthalmologists in the UK, and parallel bodies abroad, to support the delivery of established and successful laser training courses to ensure that appropriate training on the delivery of laser treatments is provided to all ophthalmologists.
- We encourage retina societies across the world to ensure all retinal specialists are proficient in delivering laser treatment.
- We encourage clinicians to use the NICE guidance to advocate to their institutions for resources to deliver timely and appropriately treatments.
- We propose a national audit of DR and DMO treatment to understand variations in practice and outcomes with laser treatment and learn lessons from teams achieving clinical excellence.
- We encourage funding bodies to support further research into retina-sparing, disease-modifying treatment modalities and pathogenetic mechanisms of DR and DMO.

We believe these actions can re-establish the central role of laser in the treatment of PDR and DMO and encourage personalised treatments for people with PDR and DMO.

The guidance 'Diabetic Retinopathy: Management and monitoring ' is available at: https://www.nice.org.uk/guidance/ng242.

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AUTHOR CONTRIBUTIONS

All authors were members of the committee who produced the NICE Guideline 'Diabetic Retinopathy: Management and Monitoring'. MB was responsible for the concept of the editorial. PB drafted the manuscript. MB, CD and NL provided additions and corrections to the text. All authors reviewed and approved the final manuscript.

COMPETING INTERESTS

Dr Burgess has received compensation for consulting and speaker fees from Roche, Bayer and Alimera Sciences. Dr. Dinah has received compensation for consulting and speaker fees from Bayer, Boehringer Ingelheim, Roche, Eyepoint, Abbvie and Alimera Sciences and an institutional research grant from Roche. Professor Lois and Mr Burdon declare no potential competing interests.