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## **Efficacy and side effects of individualized panretinal photocoagulation**

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1 Title page

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3 Title: Efficacy and side effects of individualized panretinal photocoagulation

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5 Authors:

6 Anna Stage Vergmann<sup>1,2,4</sup>, Thao Thi Nguyen<sup>1</sup>, Thomas Lee Torp<sup>1,2</sup>, Ryo Kawasaki<sup>2,5</sup>, Tien Yin Wong<sup>6,7</sup>, Tunde  
7 Peto<sup>2,8</sup> and Jakob Grauslund<sup>1,2,3</sup>

8

9 <sup>1</sup> Department of Ophthalmology, Odense University Hospital, Odense, Denmark

10 <sup>2</sup> Research Unit of Ophthalmology, Department of Clinical Research, Faculty of Health Science, University of  
11 Southern Denmark, Denmark

12 <sup>3</sup> Steno Diabetes Center Odense, Odense University Hospital, Odense, Denmark

13 <sup>4</sup> OPEN, Open Patient data Explorative Network, Odense University Hospital, Odense, Denmark

14 <sup>5</sup> Department of Vision Informatics, Osaka University School of Medicine, Osaka, Japan

15 <sup>6</sup> Singapore Eye Research Institute, Singapore National Eye Centre, Singapore

16 <sup>7</sup> Duke-NUS Medical School, National University of Singapore, Singapore

17 <sup>8</sup> School of Medicine, Dentistry and Biomedical Sciences, Queen's University Belfast, Northern Ireland,  
18 United Kingdom

19

20 Corresponding author:

21 Anna Stage Vergmann

22 Department of Ophthalmology, Odense University Hospital

23 Kloevervaenget 5, entrance 132

24 DK-5000 Odense C, Denmark

25 Phone: +45 65 41 16 82

26 E-mail: [anna.stage.vergmann@rsyd.dk](mailto:anna.stage.vergmann@rsyd.dk)

27

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38

39 Running head:

40 Same efficacy for less retinal laser in PDR

41

42 Abbreviations:

43 Dark adaptation (DA)

44 Diabetic retinopathy (DR)

45 Panretinal photocoagulation (PRP)

46 Proliferative diabetic retinopathy (PDR)

47 Retinal quality of life (RQOL)

48 Vascular endothelial growth factor (VEGF)

49 Visual fields (VF)

50 Visual function questionnaire-25 (VFQ-25)

51

52 **Abstract**

53 This was a pilot study, where we demonstrated comparable efficacy and side effects of less extensive  
54 versus standard panretinal photocoagulation in patients with treatment-naïve proliferative diabetic  
55 retinopathy.

56 Panretinal laser photocoagulation (PRP) is considered the standard treatment of PDR<sup>1</sup>, but given the  
57 invasive nature of the treatment, side-effects like loss of visual fields (VF)<sup>2</sup> and night vision<sup>3</sup> as well as  
58 diabetic macular edema (DME)<sup>4</sup> can be expected.

59 To address this, we conducted a prospective, single-blinded randomized clinical trial (RCT) of patients with  
60 treatment-naïve PDR, where we investigated efficacy, side effects and retinal quality of life (RQOL) of  
61 patients treated with individualized PRP (targeting only affected retinal quadrants) as compared to  
62 standard (all quadrants) PRP.

63 The current study was a six-month 1:1 single-blinded RCT (<https://clinicaltrials.gov>, identifier:  
64 NCT03113006) including 53 eyes of 47 patients with treatment-naïve PDR. Patients were randomized to  
65 navigated retinal photocoagulation (Navilas<sup>®</sup>, OD-OS GmbH, Teltow, Germany) performed as standard  
66 treatment for all retinal quadrants (n=27) or individualized PRP addressing only quadrant(s) with retinal  
67 neovascularization (n = 26) (Fig. S1 available at [www.opthalmologyretina.org](http://www.opthalmologyretina.org)). The treatment was  
68 performed in two sessions, with one week in between treatments, at baseline (BL) in both groups.  
69 Participants were included at Odense University Hospital, Odense, Denmark between June 1st, 2017 and  
70 February 1st, 2019. Exclusion criteria were DME in the affected eye (central subfields thickness >300 µm),  
71 age <18 years, pregnancy and/or hazy optic media that could prevent PRP. Randomization was performed  
72 by Research Electronic Data Capture (REDCap) database under Open Patient data Explorative Network  
73 (OPEN). The study was conducted in accordance with the Helsinki Declaration II and in accordance with  
74 good clinical practice. Patients provided both written and oral consent to participation. The project was  
75 approved by the Research Ethics Committee of Southern Denmark (Project-ID: S-20160168) and The Danish  
76 Data Protection Agency.

77 Principal endpoint was defined as progression of PDR as given by disease progression, vitreous  
78 hemorrhage, need for additional retinal photocoagulation, or need for vitrectomy. Disease progression was  
79 evaluated at month (M) 3 and 6 by lesion growth (assessed by ophthalmoscopy and wide-field fundus  
80 photo) or increasing leakage by ultra-wide-field fundus fluorescein angiography (UW-FFA, Optos,  
81 Dunfermline, United Kingdom).

82 To evaluate side-effects at M6, we measured development in visual fields (VF, 30-2 perimetry, ZEISS  
83 Humphrey<sup>®</sup> Field Analyzer 3, Carl Zeiss, Oberkochen, Germany) and in dark adaptation (DA, Goldmann-  
84 Weekers dark adaptometer, Haag-Streit Holding, Köniz, Schweiz), while covering the fellow-eye. Mean  
85 Deviation (MD) and Visual Field Index (VFI) were recorded for VF. A validated Danish version of Visual  
86 Function Questionnaire-25 (VFQ-25) including the appendix VFQ-39<sup>5</sup> was filled out by the patients at BL  
87 and M6.

88 Mann-Whitney U test and Wilcoxon signed-rank test were used as appropriate to analyze differences  
89 between groups and time points. Chi2 test was used to evaluate if there were any differences in number of  
90 patients who progressed in the two groups.

91 A total of 53 eyes of 42 patients were included. Patients did not differ according to age (years), distribution  
92 of sex, ethnicity, body mass index (kg/m<sup>2</sup>), diabetes type, diabetes duration (years), smoking status, central  
93 retinal thickness (µm), blood pressure (mmHg), HbA1c (mmol/mol), or blood lipids (mmol/L) (Table S1,  
94 available at [www.opthalmologyretina.org](http://www.opthalmologyretina.org)).

95 Progression of PDR did not differ between patients treated by individualized and standard PRP (48.0% vs.  
96 59.3%,  $p=0.27$ , Table 1), even though the former by protocol received fewer photocoagulation spots  
97 ( $1524\pm 1096$  vs.  $2165\pm 915$ ,  $p=0.006$ ).

98 Visual fields and dark adaptation were obtained in 44 (individualized: 24, standard: 20) and 42  
99 (individualized: 23, standard: 19) eyes, respectively. VF did not differ between the individualized and  
100 standard group at M6 in either VFI ( $92.5\pm 7$  vs.  $95.5\pm 8$ ,  $p=0.13$ ) or MD ( $-4.70\pm 4.23$  vs.  $-3.47\pm 4.22$ ,  $p=0.25$ ).  
101 Dark adaptation analysis (log unit) showed no differences between the individualized and standard group  
102 at M6 ( $0.41666\pm 0.051$  vs.  $0.41340\pm 0.059$ ,  $p=0.76$ ).

103 VFQ-25 were obtained in 26 patients (individualized: 15, standard: 11). There were no differences between  
104 groups at M6 ( $90.9\pm 2.4$  vs.  $89.6\pm 10.4$ ,  $p=0.41$ ). Though, a statistically significant worsening between BL and  
105 M6 was found in the individualized group ( $93.5\pm 7.55$  vs.  $90.9\pm 2.40$ ,  $p=0.04$ ). However, in post-hoc analysis  
106 excluding the VFQ-39 appendix, we found no differences in the groups from BL to M6 (individualized  
107  $p=0.71$ , standard  $p=0.69$ ), or between the groups at M6 ( $89.1\pm 9.3$  vs.  $86.5\pm 10.9$ ,  $p=0.45$ ).

108 In this prospective RCT of patients with treatment-naïve PDR, we found that individualized PRP, targeting  
109 only affected retinal quadrants, had the same efficacy as full PRP. Furthermore, side effects and RQOL did  
110 not differ between the two groups.

111 VF and DA ability are determined by the function of the photoreceptor cells. In an earlier study, VF and DA  
112 were found to be affected in patients with PDR both before and after PRP<sup>2</sup>. In PRP, the retinal pigment  
113 epithelium and photoreceptors are altered and replaced by scar-tissue. A previous study reported that  
114 navigated laser leads to more uniform laser burns compared to conventional pattern scan laser<sup>6</sup>, and this  
115 might explain our results that were somewhat in opposition to the results of DRCR.net Protocol S that  
116 reported of VF-loss secondary to PRP<sup>7</sup>.

117 We conclude a less intensive, individualized retinal photocoagulation, targeting only retinal quadrants with  
118 retinal neovascularization, has a similar efficacy as standard PRP in patients who are regularly seen in the  
119 clinics. In addition, limited side-effects, balanced between groups, could indicate a gentler approach  
120 performed by the navigated laser system used in both treatment arms. This pilot-study adds to the ongoing  
121 discussion of individualizing and balancing efficacy and side-effects in PDR. While VA-loss was prevented at  
122 M6 in our study, we cannot speculate to the long-term sustainability of results. Hence, upcoming  
123 randomized trials, addressing long-term VA and treatment efficacy, and including additional relevant  
124 endpoints like electroretinography, would be important to confirm these findings.

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