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Predictive factors associated with anatomical and functional outcomes following panretinal photocoagulation in people with proliferative diabetic retinopathy

Running title: **Predicting outcomes after PRP in PDR**

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Key Words

Diabetic retinopathy, diabetes, multi-spot laser, panretinal photocoagulation, PRP, pattern laser, proliferative diabetic retinopathy, PDR, retinal neovascularisation, single spot laser.

Summary Statement

People with proliferative diabetic retinopathy treated with panretinal photocoagulation remain at risk of experiencing progression and sight loss following treatment. People treated with multi-spot pattern laser took longer to stabilize and had higher risk of progression than those receiving standard, single spot laser and, thus, should be more closely monitored.

Abstract

Purpose: To determine effects of baseline characteristics and laser type performed on outcomes in people with proliferative diabetic retinopathy (PDR) undergoing panretinal photocoagulation (PRP).

Methods: Medical records of all consecutive patients with PDR naïve to PRP, identified using an electronic database, evaluated at the Macula Clinic, Belfast Health and Social Care Trust, receiving their first PRP between 1st January 2016 and 30th June 2017, and followed for a minimum of 6 months following stabilization of PDR, were retrospectively reviewed. Outcomes included time to stabilization following PRP, progression of PDR, and mean change in best-corrected visual acuity from baseline to last follow-up. Cox regression was used to estimate hazard ratios (HRs) for the effect of baseline characteristics and type of laser on outcomes following treatment.

Results: One hundred and fourteen patients (135 eyes) with a mean age of 57.6 (SD: 13.1) years were included, 67% males. People receiving pattern or mixed laser had a statistically significantly delayed stabilization (HR: 0.54, p=0.004; and HR: 0.41, p=0.001, respectively) and increased risk of progression (HR: 1.83, p=0.028; and HR: 2.04, p=0.018, respectively) when compared to those receiving standard laser. Among other potential predictors in multivariable regression analysis, only vitreous hemorrhage and fibrosis or traction at baseline increased risk of progression (HR: 1.70, p=0.017; and HR: 4.14, p<0.001 respectively). Baseline characteristics and type of laser had no statistically significant effect on vision.

Conclusion: These findings should be considered when selecting laser treatment, planning surveillance, and counselling patients with PDR undergoing PRP.

Introduction

Randomized controlled trials (RCTs) have demonstrated the merits of intensive control of hyperglycaemia and hypertension in delaying progression of diabetic retinopathy (DR)[1], [2]. It is unclear, however, whether progression to proliferative diabetic retinopathy (PDR), a major sight threatening complication of DR, has declined despite improvements in medical management of diabetes. Global estimates suggest a decreased prevalence of PDR from 7%[3] to 1.4%[4] between 1980-2008 and 2015-2019, respectively. In contrast, some large-scale epidemiological studies have detected a decline in NPDR but not PDR[5], [6], [7]. Prevalence of PDR is likely to increase globally due to the diabetes epidemic[8].

Anti-vascular endothelial growth factor (anti-VEGF) therapies have been shown to be non-inferior to panretinal photocoagulation (PRP) for treatment of PDR[9, 10]. Nonetheless, they appear to be cost-effective only in people with concomitant diabetic macular edema (DME)[11] and long-term outcomes are unknown. Reports have shown that people with PDR treated solely with anti-VEGFs, who become lost to follow-up, are at increased risk of blindness[12], [13]. Hence, PRP remains the mainstay therapy for managing PDR[14].

The Early Treatment Diabetic Retinopathy Study (ETDRS) stipulated PRP should be performed covering the mid-peripheral retina with 1200-1600, 500µm diameter argon laser burns, applied one half to one burn-width apart for 0.1 seconds[15]. Since then, several other treatment protocols and laser modalities have been introduced but evidence on their efficacy and safety compared to ETDRS PRP is limited[16]. One of these alternative technologies is the multi-spot pattern laser which enables multiple burns to be delivered simultaneously at the press of a foot pedal; potentially reducing treatment times, being more convenient to deliver and acceptable to patients. There has been, however, no large RCT comparing this technology against standard ETDRS PRP. Importantly, a post-hoc analysis of the DR Study

Clinical Research Network (DRCR.net) (protocol S) showed eyes receiving multi-spot laser were at higher risk of worsening compared with those undergoing single spot PRP[17].

The purpose of the current study was to evaluate influence of patients' baseline characteristics, laser type and parameters, on functional and anatomical outcomes of people with PDR treated with PRP in a clinical setting.

Methods

Retrospective analysis of clinical data obtained from Belfast Health and Social Care Trust (BHSCT) as a part of an audit (approval number 6024).

Eligibility criteria

Consecutive patients aged ≥18 years, with type 1 or 2 diabetes, and newly-diagnosed PDR who received their first session of PRP at the Macula Clinic, BHSCT, between 1st January 2016 and 30th June 2017, and followed for at least 6 months post-stabilization of PDR, were eligible for inclusion. Patients who did not meet these inclusion criteria and those receiving PRP for other conditions were excluded. PRP procedures performed during the study period were identified using an electronic database. The medical records of potentially eligible patients identified were then reviewed, and, if eligibility confirmed, data extraction undertaken.

Data collection

Data collected for each patient prior to first PRP session included: gender, date of birth, postcode, type and duration of diabetes, visual acuity with best current refraction (BCVA), presence of new vessels in the disc (NVD), elsewhere in the retina (NVE), iris (NVI) or anterior chamber (NVA), neovascular glaucoma (NVG), intra-/pre-retinal fibrosis related to

fibrovascular diabetic membranes, features of high-risk characteristics (HRC) and ocular co-morbidities. Anti-VEGF or macular laser treatments undertaken prior to initial PRP were also recorded. In some instances, particular disease features, such as presence of NVD, NVE or HRC, were not expressly recorded in medical records; this missing data was documented as unknown and considered in statistical analyses.

Postcodes were used to determine deprivation ranks using the Northern Ireland Multiple Deprivation Measure 2017 (https://www.nisra.gov.uk/statistics/deprivation/northern-ireland-multiple-deprivation-measure-2017-nimdm2017). In this system, the province is divided into 890 areas and ranked from 1-890, most to least deprived, based on income, employment, health, education, access to services, environment, and crime.

For each laser session, number of burns, spot size (microns), power (milliwatts) and duration (seconds) were recorded for each session undertaken. Whether laser was administered with single spot, multi-spot, or a combination (i.e., some sessions with single spot and others with multi-spot) was recorded. Both laser types were available in our clinic during the study period, and selection was based on preference of the treating ophthalmologist and availability when treatment was performed. PDR was considered to have stabilized following PRP, when no further laser was advised by the clinician but observation instead, and was measured from when the initial PRP treatment was received. Once stable, patients were followed and treated again only if active PDR occurred.

For the purpose of this study, follow-up data was collected at 6-monthly (+/- 3-months) intervals, capturing developments throughout the previous period. Information regarding development of previously existent/new NVD, NVE, NVI, NVA or NVG, vitreous hemorrhage, pre-retinal hemorrhage, and tractional retinal detachment (TRD) was recorded. The occurrence of any of these events, if not previously present, and need for supplemental

PRP indicated "progression" of PDR, and was measured relative to the time of stabilization. At each follow-up, BCVA, presence of DME and any other treatments undertaken were also collated.

Outcomes

The effect of baseline characteristics, laser type and parameters on anatomical (time to stabilization and risk of progression of PDR) and functional (mean change in BCVA from baseline to last follow-up) outcomes following PRP.

Statistical analysis

Descriptive statistics were used to present the cohort's baseline characteristics. Kaplan-Meier survival analysis estimated time required for patients to stabilize from when PRP was initiated, and risk of progression of PDR, accounting for loss to follow-up in the cohort. Eyes which did not progress were censored at their last follow-up.

Duration of diabetes, deprivation index, presence of NVD and/or NVE, HRC, vitreous hemorrhage, pre-retinal hemorrhage, NVI, NVG, fibrosis/traction or DME, and type of laser were evaluated in univariable linear regression analyses to identify possible associations with time to stabilization and progression. Anti-VEGFs received one month prior to enrolment and/or during stabilization period, and at any stage during the study, were assessed to determine possible effect on time to stabilization, and progression, respectively. Baseline characteristics of the laser groups were also compared to identify potentially confounding differences.

Variables identified as being statistically significant by univariable linear regression analysis and others considered to be clinically relevant to the outcomes of interest, were entered into Cox multivariable regression models to further assess the effect of covariates as

hazard ratios (HRs). For covariates with a significant effect, the proportional hazards assumption was assessed using log-log curves and based on Schoenfeld residuals. A robust standard error estimation with individuals as clusters was adopted to account for correlated data for eyes of the same individual.

Linear mixed models were used to model BCVA during follow-up, with individuals as random intercept and time as a random slope to account for longitudinal data correlation. The effect of categorical covariates on linear trend in BCVA over time was assessed with an interaction term between the covariate and time as a continuous variable. Continuous covariates such as baseline BCVA, deprivation rank and diabetes duration were made categorical using tertile values.

Results

Medical records of 348 PRP procedures performed during the study period were reviewed. Of these, 213 eyes were excluded for the following reasons: 159 were not naïve to PRP; 21 received laser for other conditions; eight had not reached PDR when receiving first PRP; in 12 clinical information was unavailable; four eyes (four patients) did not reach stabilization (three patients deceased prior to this point and one was lost to follow-up); and for nine eyes (seven patients) follow-up data was not available (four patients deceased or were discharged to other clinics prior to the 6-month follow-up visit, and in three patients (five eyes) although the 6-month follow-up visit did take place, it happened after all data was already collected for the purpose of this study and data analysis initiated.

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One hundred and fourteen patients (135 eyes) were eligible and included in this study with data from 135 (100%), 128 (95%), 119 (88%), 100 (74%), 68 (50%) and 39 (29%) eyes evaluated at 6-, 12-, 18-, 24-, 30-, and 36-months follow-up, respectively.

The mean age (standard deviation, SD) of patients was 56.9 (12.9) years and duration of diabetes was 22.2 (11.8) years. 76 out of 114 patients (66.7%) were male and 88 (65.2%) had type 2 diabetes. Mean deprivation index (SD) was 413.1 (263.7). Presenting clinical characteristics are shown in Table 1.

Anti-VEGF injections were administered one month prior to initial PRP and at any point during stabilization period in 41 eyes, to treat DME in 34 eyes (82.9%) and PDR in 7 (17.1%). There were no statistically significant differences in baseline characteristics or BCVA among single spot, multi-spot or mixed laser groups except for pre-retinal haemorrhage ($p=0.006$), NVI ($p=0.030$), DME ($p<0.001$) or having received anti-VEGF injections prior to study enrolment ($p<0.001$). (Table 2).

Outcomes of PDR

Stabilization was achieved in all patients after a median period of 6.0 months (interquartile interval: 3.7 – 10.6). 78 eyes (57.8%) progressed with 60 (48.9%) requiring supplemental laser post-stabilization. Median time to progression was 20.4 months. The cumulative risk of experiencing an episode of progression was 0.35, 0.55, and 0.65 at one, two and three years, respectively.

Mean BCVA was 0.32 logMAR (Snellen~20/40) at baseline and progressively decreased to 0.39 logMAR (Snellen~20/50), 0.42 logMAR (Snellen~20/50-1) and 0.44 logMAR (Snellen~20/50-2) at one, two, and three years, respectively. Although change from baseline was not statistically significant at any time point, the linear trend per year approached significance (0.05 logMAR per year, $p=0.024$) (Figure 1).

Table 3 shows the proportion of people with ≥20/40, 20/40- to 20/160 and ≤20/200 at baseline and final study visit. Survival analysis showed that cumulative probability of experiencing new episodes of visual loss below driving level (i.e. <20/40) (https://www.gov.uk/driving-eyesight-rules) in the affected eye increased from 14.0% at one year to 36.3% at two years, reaching 63.9% at three years. 16 (11.9%) eyes had BCVA ≤20/200 at their final follow-up visit, 5 of which entered the study with ≤20/200 vision. The causes of visual loss in these 16 eyes were vitreous hemorrhage in nine (56.2%), DME in three (18.8%), TRD in two (1.3%), and reason unclear in two.

Forty-three eyes of 40 patients (31.9%) developed vitreous hemorrhage; 28, 11 and 4 in the first, second and third years, respectively. Twenty-one eyes (15.6%) of 20 patients developed DME; 14, 5 and 2 in the first, second and third years, respectively. Nine eyes of 9 patients (7%) progressed to TRD, two had fibrosis/traction at baseline; 7 in the first year and 2 more within 3 years. Five of these required vitrectomy; the other four were observed as the macula was not compromised. Five other eyes required vitrectomy for non-clearing vitreous hemorrhage. Only one patient developed NVG during the study.

Influence of baseline characteristics and treatment parameters on outcomes

Univariable linear regression (Supplemental Table 1) revealed DME at baseline to be the only presenting characteristic associated with reduced time to stabilization (HR: 1.63, 95% confidence intervals [CI]: 1.12-2.37, p=0.011). Type of laser received was also statistically significantly associated with time to stabilization (p=0.002) with patients receiving multi-spot (HR: 0.54, 95%CI 0.35-0.82, p=0.004) and mixed laser (HR: 0.41, 95%CI 0.24-0.69, p=0.001) requiring approximately 3.6 months longer to stabilize than those receiving single spot (Figure 2).

In Cox multivariable regression models, only type of laser remained statistically significant, with an increased time to stabilization required by patients receiving multi-spot (HR: 0.57, 95%CI 0.35-0.92, p=0.020) or mixed laser (HR: 0.44, 95%CI 0.28-0.70, p<0.001), after adjusting for presence of HRC, NVD, vitreous hemorrhage, DME, and anti-VEGFs (Table 4) [the HR below 1 indicates the chances for stabilisation are reduced].

A statistically significantly increased number of laser sessions and total number of burns were also required in eyes treated with multi-spot and mixed laser compared to single spot (Supplemental Table 2). Number of sessions and laser burns were strongly correlated, with patients requiring more treatment sessions receiving an increased number of burns (Spearman correlation 0.82, p<0.001). Given this finding, only number of burns was included in further analyses. The ranges of laser power and burn duration for each of the laser groups are also presented in Supplemental Table 2.

From all potential predictors investigated in univariable models (Supplemental Table 3), presence of vitreous hemorrhage (HR: 1.70, 95%CI 1.10-2.63, p=0.017), fibrosis/traction at baseline (HR: 4.14, 95% CI 2.14-8.01, p<0.001) and use of pattern multi-spot (HR: 1.83, 95%CI 1.07-3.14, p=0.028) and mixed (HR: 2.04, 95%CI 1.13-3.68, p=0.018) laser, were associated with increased risk of progression compared to single spot . In Cox multivariable regression models, vitreous hemorrhage (HR: 1.58, 95%CI 1.01-2.50, p=0.047) and fibrosis/traction (HR: 4.29, 95%CI 2.33-7.93, p=0.000) at baseline, as well as use of multi-spot (HR: 1.87, 95%CI 1.02-3.45, p=0.045) or mixed (HR: 1.96, 95%CI 1.08-3.57, p=0.028) laser remained statistically significantly associated with increased risk of progression (Table 5) (Figure 3) [the HR above 1 indicates the increased risk of progression].

Although multivariable analysis would have considered and corrected all other factors investigated, including anti-VEGF use, given that a higher proportion of patients in the standard laser group had received anti-VEGFs, we undertook additionally a post-hoc

sensitivity analysis on the effect of the different laser types restricted only to patients naïve to anti-VEGF drugs (n = 94). Although the power of this analysis would have been diminished, given the smaller number of patients included, we still found that multi-spot and mixed laser types were statistically significantly associated with delayed stabilisation compared to single-spot laser **(**HR 0.56, p=0.038; and HR 0.53, p=0.042; respectively). When evaluating the risk of progression in this same group (eyes naïve to anti-VEGF treatment; n=94), sensitivity analysis did not reveal a statistically significantly increased risk in eyes treated with multi-spot (HR 1.74, p=0.068) or mixed (HR 1.58, p=0.225) laser compared to single spot laser, although significance was approached in the multi-spot laser group. The smaller sample size in this analysis may explain the lack of statistical significance observed on this outcome.

Neither baseline characteristics nor type of laser performed were found to be associated with change in BCVA from baseline to last follow-up (p>0.05 for overall interaction terms with time).

Discussion

This study showed in a hospital eye setting, a proportion of people with PDR treated with PRP still lose some sight over time and experience progression of their disease, despite treatment. Over a third of eyes developed vitreous hemorrhage, 16% DME, 7% TRD, and 7% required vitrectomy after a mean time of 13, 11, 13, and 19 months, respectively. Patients treated with multi-spot or mixed laser required an increased number of treatment sessions and laser burns, longer time to stabilize following PRP, and were at increased risk of progression of PDR. A statistically significantly increased number of patients in the single spot group had concomitant DME at presentation and received anti-VEGF injections prior to enrolment, compared with those in the pattern and mixed laser groups. However, anti-VEGF

use, prior to initiation and during the study, was included in univariable and multivariable regression models and, consistently found not to be statistically significantly associated with the outcomes, whereas laser type was highly significant. Presence of vitreous hemorrhage or fibrosis/traction at baseline were associated with increased risk of progression. None of the baseline characteristics or laser type performed impacted on change in BCVA from baseline to last follow-up.

Thus, our findings challenge the often-presumed adequate efficiency and efficacy of pattern lasers. Based on results of a RCT comparing single-session multi-spot and multiple-session single spot laser treatments, Muqit et al concluded both had similar efficacy[18]. The main outcome of this study was change in central subfield retinal thickness (CRT) on optical coherence tomography. As the trial was powered based on CRT (n=38 eyes, 19 per arm), it was most likely underpowered to detect differences in treatment efficacy with regard to control of disease process[18]. The value of subsequent studies comparing efficacy of single spot and multi-spot laser have similarly been restricted by inclusion of a modest number of patients (n=30-35 patients) followed for 12 months[19], [20]. Studies including higher numbers of patients (n=50-60 patients) followed them for only 6-months[21], [22]. Overall, there is limited evidence on the efficacy of pattern multi-spot laser.

In the present study, 64% and 51% of eyes receiving multi-spot and single spot laser, respectively, progressed. post-hoc analysis of DRCR.net RCT (protocol S) similarly found that eyes receiving pattern multi-spot were at increased risk of PDR progression, defined as first occurrence of vitreous hemorrhage, TRD, NVI, NVA, or NVG, than those receiving single spot laser (60%vs.39%, respectively; HR, 2.04; 99%CI 1.02-4.08 P ¼ 0.008)[17].

Vitreous hemorrhage or fibrosis/traction at baseline were the only presenting characteristics associated with risk of progression. Depending on its severity, vitreous

hemorrhage may make undertaking adequate PRP more difficult. Initiating PRP, as may also occur with anti-VEGFs, when there is contraction of the posterior hyaloid and pre-retinal fibrosis, may worsen these features due to the angio-fibrotic switch[23] and, occasionally, lead to development or progression of TRD. Parikh et al[24] also found that vitreous hemorrhage or fibrosis greatly increased risk of vitrectomy, emphasizing the need for a careful approach in the management and follow-up of patients with these characteristics.

In contrast to other studies[25], [26], [27] we found a decline in BCVA from baseline to last follow-up. Albeit small, this change may be significant, particularly in those who deteriorate below driving standards – an outcome selected as being important by people with diabetes[28]. The disparity may be explained, at least partly, by the higher number of eyes followed for a longer period of time in our study (100 eyes evaluated at 24 months, 68 at 30 months) compared to others (34 eyes followed for 11 weeks[25], 60 eyes followed for 11 weeks[27], 28 eyes followed for 12 weeks[18], 60 eyes followed for 6 months[21] and 36 eyes followed for 18 months[26]). Indeed, in our cohort, risk of both progression and visual loss increased with follow-up period. Therefore, patients with PDR should be counselled appropriately regarding the necessity of attending surveillance appointments, even on completion of PRP, especially as high rates of loss to follow-up have been found in those treated for PDR[10], [9].

This study has several limitations including its retrospective nature, the fact it was a single center study, and the limited demographic profile of the Northern Irish cohort, represented predominantly by a Caucasian population. The multi-spot and mixed laser groups were smaller than the single spot group. Despite the reasonable size of the cohort, this was not sufficient to evaluate risk factors associated with development of infrequently occurring events, such as TRD and vitrectomy. Furthermore, the effect of cataract on visual outcomes was not considered due to inconsistencies in recording. Strengths include the use of an electronic diagnostic database to identify eligible patients, consecutive inclusion of any

fulfilling eligibility criteria, the relatively high number of patients followed for a reasonable time and the longitudinal data analysis from real-world clinical practice. The cohort was well-characterized, including only patients with PDR naïve to PRP at baseline.

In conclusion, multi-spot pattern laser may not be as effective as standard laser in the treatment of PDR – requiring higher number of laser burns, treatment sessions and longer time to stabilization and increased risk of complications, many of which required subsequent treatment. This has important implications for patients and healthcare systems, including increased utilisation of resources and associated costs, particularly salient in the current climate when services are under pressure to meet demands. A methodologically sounded and appropriately powered RCT comparing acceptability, clinical and cost effectiveness is necessary to determine the real benefits, if any, pattern laser provides in treatment of PDR.

References

1. Control D and Group CTR. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. New England journal of medicine 1993; 329:977-986.
2. Turner RC, Holman RR, Cull CA et al. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). The Lancet 1998; 352:837-853.
3. Yau JW, Rogers SL, Kawasaki R et al. Global prevalence and major risk factors of diabetic retinopathy. Diabetes care 2012; 35:556-564.
4. Thomas R, Halim S, Gurudas S et al. IDF Diabetes Atlas: A review of studies utilising retinal photography on the global prevalence of diabetes related retinopathy between 2015 and 2018. Diabetes research and clinical practice 2019; 157:107840.
5. Brown JB, Pedula KL and Summers KH. Diabetic retinopathy: contemporary prevalence in a well-controlled population. Diabetes Care 2003; 26:2637-2642.
6. Mathur R, Bhaskaran K, Edwards E et al. Population trends in the 10-year incidence and prevalence of diabetic retinopathy in the UK: a cohort study in the Clinical Practice Research Datalink 2004–2014. BMJ open 2017; 7:e014444.
7. Tracey ML, McHugh SM, Fitzgerald AP et al. Trends in blindness due to diabetic retinopathy among adults aged 18–69 years over a decade in Ireland. Diabetes Research and Clinical Practice 2016; 121:1-8.
8. Saeedi P, Petersohn I, Salpea P et al. Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: Results from the International Diabetes Federation Diabetes Atlas. Diabetes research and clinical practice 2019; 157:107843.
9. Sivaprasad S, Prevost AT, Vasconcelos JC et al. Clinical efficacy of intravitreal aflibercept versus panretinal photocoagulation for best corrected visual acuity in patients with proliferative diabetic retinopathy at 52 weeks (CLARITY): a multicentre, single-blinded, randomised, controlled, phase 2b, non-inferiority trial. The Lancet 2017; 389:2193-2203.
10. Gross JG, Glassman AR, Jampol LM et al. Panretinal photocoagulation vs intravitreous ranibizumab for proliferative diabetic retinopathy: a randomized clinical trial. Jama 2015; 314:2137-2146.
11. Hutton DW, Stein JD, Bressler NM et al. Cost-effectiveness of intravitreous ranibizumab compared with panretinal photocoagulation for proliferative diabetic retinopathy: secondary analysis from a diabetic retinopathy clinical research network randomized clinical trial. JAMA ophthalmology 2017; 135:576-584.
12. Wubben TJ, Johnson MW, Sohn EH et al. Anti–Vascular Endothelial Growth Factor Therapy for Diabetic Retinopathy: Consequences of Inadvertent Treatment Interruptions. American journal of ophthalmology 2019; 204:13-18.
13. Obeid A, Su D, Patel SN et al. Outcomes of eyes lost to follow-up with proliferative diabetic retinopathy that received panretinal photocoagulation versus intravitreal anti–vascular endothelial growth factor. Ophthalmology 2019; 126:407-413.
14. Wong TY, Sun J, Kawasaki R et al. Guidelines on diabetic eye care: the international council of ophthalmology recommendations for screening, follow-up, referral, and treatment based on resource settings. Ophthalmology 2018; 125:1608-1622.
15. Group DRSR. Preliminary report on effects of photocoagulation therapy. American journal of ophthalmology 1976; 81:383-396.
16. Moutray T, Evans JR, Lois N et al. Different lasers and techniques for proliferative diabetic retinopathy. Cochrane Database of Systematic Reviews 2018.
17. Bressler SB, Beaulieu WT, Glassman AR et al. Factors associated with worsening proliferative diabetic retinopathy in eyes treated with panretinal photocoagulation or ranibizumab. Ophthalmology 2017; 124:431-439.
18. Muqit MM, Marcellino GR, Henson DB et al. Single-session vs multiple-session pattern scanning laser panretinal photocoagulation in proliferative diabetic retinopathy: The Manchester Pascal Study. Archives of Ophthalmology 2010; 128:525-533.

19. Seymenoğlu RG, Ulusoy MO and Başer EF. Safety and efficacy of panretinal photocoagulation in patients with high-risk proliferative diabetic retinopathy using pattern scan laser versus conventional YAG laser. The Kaohsiung journal of medical sciences 2016; 32:22-26.
20. Nemcansky J, Stepanov A, Nemcanska S et al. Single session of pattern scanning laser versus multiple sessions of conventional laser for panretinal photocoagulation in diabetic retinopathy: Efficacy, safety and painfulness. PloS one 2019; 14:e0219282.
21. Nagpal M, Marlecha S and Nagpal K. Comparison of laser photocoagulation for diabetic retinopathy using 532-nm standard laser versus multispot pattern scan laser. Retina 2010; 30:452-458.
22. Muraly P, Limbad P, Srinivasan K and Ramasamy K. Single session of Pascal versus multiple sessions of conventional laser for panretinal photocoagulation in proliferative diabetic retinopathy: a comparitive study. Retina 2011; 31:1359-1365.
23. Kuiper EJ, Van Nieuwenhoven FA, De Smet MD et al. The angio-fibrotic switch of VEGF and CTGF in proliferative diabetic retinopathy. PloS one 2008; 3:e2675.
24. Parikh R, Shah RJ, VanHouten JP and Cherney EF. Ocular findings at initial pan retinal photocoagulation for proliferative diabetic retinopathy predict the need for future pars plana vitrectomy. Retina 2014; 34:1997-2002.
25. Sanghvi C, McLauchlan R, Delgado C et al. Initial experience with the Pascal photocoagulator: a pilot study of 75 procedures. British Journal of Ophthalmology 2008; 92:1061-1064.
26. Muqit M, Marcellino G, Henson D et al. Pascal panretinal laser ablation and regression analysis in proliferative diabetic retinopathy: Manchester Pascal Study Report 4. Eye 2011; 25:1447-1456.
27. Salman AG. Pascal laser versus conventional laser for treatment of diabetic retinopathy. Saudi journal of ophthalmology 2011; 25:175-179.
28. Lois N, Gardner E, Waugh N et al. Diabetic macular oedema and diode subthreshold micropulse laser (DIAMONDS): study protocol for a randomised controlled trial. Trials 2019; 20:1-11.

Figure Legends

Figure 1. Survival analysis exhibiting the decline in best corrected visual acuity over time in the cohort (135 eyes).

Figure 2. Kaplan-Meier survival curves demonstrating more rapid time to stabilization in the group treated with single spot standard laser compared with the multi-spot pattern and mixed laser groups.

Figure 3. Kaplan-Meier survival curves representing the proportion of patients progressing in each laser group as a function of time following stabilization.

Supplemental Digital Content

Supplemental Digital Content 1. docx

Supplemental Digital Content 2. docx

Supplemental Digital Content 3. docx

Supplemental Table 1. Univariable Cox Regression Analysis Evaluating Associations Between Baseline Characteristics and Laser Type and Time to Stabilization

Variables	**Hazard Ratio**	***P* Value**	**95% CI**
Baseline characteristics			
Duration of diabetes (per 10 years)	1.05	0.574	0.90-1.22
Deprivation index (per 100 units)	0.96	0.282	0.89-1.03
NVD (yes vs. no)*	0.84	0.408	0.56-1.27
NVE (yes vs. no)*	1.14	0.524	0.76-1.73
NVD and NVE (yes vs. no)*	0.85	0.593	0.46-1.56
HRC (yes vs. no)*	1.19	0.385	0.80-1.78
HRNVD (yes vs. no)*	1.54	0.216	0.78-3.05
Vitreous hemorrhage	0.93	0.688	0.66-1.32
Pre-retinal hemorrhage	1.07	0.790	0.64-1.80
NVI	1.17	0.587	0.67-2.03
NVG	1.85	0.343	0.52-6.59
Fibrosis/traction	0.64	0.179	0.34-1.22
DME	1.63	**0.011**	1.12-2.37
Anti-VEGF use from 1 month prior to PRP to time of stabilization			
Anti-VEGF	1.27	0.277	0.83-1.94
Laser type			
Single spot	1.00		
Multi-spot	0.54	**0.004**	0.35-0.82
Mixed	0.41	**0.001**	0.24-0.69

NVD = new vessels in the disc; NVE = new vessels elsewhere; HRC = high-risk characteristics; HR-NVD = high-risk new vessels in the disc; NVI = new vessels in the iris; NVG = neovascular glaucoma; DME = diabetic macular edema; VEGF = vascular endothelial growth factor.

* See Table 1 for missing data (i.e. information about NVD, NVE, HRC, and HR-NVD not available in the clinical notes of some patients). When regression analysis was undertaken comparing missing data versus "not present" (rather than "yes" versus "no" as shown) for these characteristics, no statistically significant differences were found either (data not shown but available upon request).

Supplemental Table 2. Number of Laser Treatment Sessions and Burns, as well as Laser Parameters used by Laser Type (Single Spot Standard, Multi-Spot Pattern and Mixed Laser)

(n = 135 eyes).

Laser Type (n)	**Single Spot Standard**	**Multi-spot Pattern**	**Mixed**
Number of laser sessions	1.92	3.34 (<0.001*)	4.16 (<0.001*)
Number of burns	1244	2668 (<0.001*)	2923 (<0.001*)
Range of power (mw)	100-950	130-750	140-825
Range of burn duration (s)	0.1-0.15	0.02-0.08	0.02-0.1

n = number in group; * p value when compared against single spot standard laser

Supplemental Table 3. Univariable Cox Regression Analysis Evaluating Associations Between Baseline Characteristics and Laser Type and Risk of Progression

Variables	**Hazard Ratio**	***P* value**	**95% CI**
Baseline characteristics			
Duration of diabetes (per 10 years)	0.96	0.657	0.78-1.17
Deprivation index (per 100 units)	1.06	0.152	0.98-1.15
NVD (yes vs. no)*	1.14	0.627	0.67-1.97
NVE (yes vs. no)*	0.97	0.917	0.57-1.66
NVD and NVE (yes vs. no)*	0.91	0.821	0.90-2.64
HRC (yes vs. no)*	1.54	0.116	0.90-2.64
HRNVD (yes vs. no)*	1.02	0.942	0.56-1.86
Vitreous hemorrhage	1.70	**0.017**	1.10-2.63
Pre-retinal hemorrhage	1.39	0.239	0.80-2.41
NVI	0.54	0.150	0.24-1.25
NVG	0.63	0.605	0.11-3.64
Fibrosis/traction	4.14	**<0.001**	2.14-801
DME	0.82	0.399	0.51-1.30
Anti-VEGF use			
Anti-VEGF pre-stabilization	0.76	0.287	0.46-1.26
No. injections post-stabilization	1.03	0.893	0.63-1.70
Anti-VEGF pre- and/or post-stabilization	1.12	0.659	0.68-1.83
Laser type			
Single spot	1.00		
Multi-spot	1.83	**0.028**	1.07-3.14
Mixed	2.04	**0.018**	1.13-3.68

NVD = new vessels in the disc; NVE = new vessels elsewhere; HRC = high-risk characteristics; HR-NVD = high-risk new vessels in the disc; NVI = new vessels in the iris; NVG = neovascular glaucoma; DME = diabetic macular edema; VEGF = vascular endothelial growth factor.

* See Table 1 for missing data (i.e. information about NVD, NVE, HRC, and HR-NVD not available in the clinical notes of some patients). When regression analysis was undertaken comparing missing data versus "not present" (rather than "yes" versus "no" as shown) for these characteristics, no statistically significant differences were found either (data not shown but available upon request).

Table 1. Baseline Clinical Characteristics of the Cohort (n = 135 eyes)

Presenting Characteristic at Baseline	**Cohort (135 eyes)**
NVD	53/103 (51.5%)*
NVE	57/102 (55.9%)†
HRC	76/119 (63.9%)‡
HR-NVD	18/110 (16.4%)**
Vitreous haemorrhage	47/135 (34.8%)
Pre-retinal haemorrhage	26/113 (23.0%)††
NVI	14/135 (10.4%)
NVG	2/135 (1.5%)
Fibrosis/traction	3/135 (2.2%)
DME	54/135 (40.0%)
Previous anti-VEGF	41/135 (30.4%)
Previous macular laser	18/135 (13.3%)

NVD = new vessels in the disc; NVE = new vessels elsewhere; HRC = high-risk characteristics; HR-NVD = high-risk new vessels in the disc; NVI = new vessels in the iris; NVG = neovascular glaucoma; DME = diabetic macular edema; VEGF = vascular endothelial growth factor.

* Presence of NVD not specifically recorded in 32 cases; †presence of NVE not specifically recorded in 33 cases; ‡ presence of HRC not specifically recorded in 16 cases; ** presence of HR-NVD not specifically recorded in 25 cases; †† presence of pre-retinal haemorrhage not specifically recorded in 22 cases.

Table 2. Baseline Clinical Characteristics by Laser Type (Single Spot Standard, Multi-Spot Pattern and Mixed Laser)

	Single spot Standard (66 eyes)	**Multi-spot Pattern (33 eyes)**	**Mixed (36 eyes)**	**p-value**
Age, years (mean, SE)	57.6 (1.8)	53.5 (2.9)	58.9 (1.95)	0.190
Diabetes duration, years (mean, SE)	21.7 (2.2)	19.4 (2.0)	25.9 (1.8)	0.059
Deprivation index	391 (39)	434 (47)	434 (46)	0.696
Type 1 diabetes	20 (30.3%)	14 (42.4%)	13 (36.1%)	0.482
NVD (present)*	29 (53.7%)	10 (41.6%)	14 (56.0%)	0.539
NVE (present)*	28 (52.8%)	15 (62.5%)	14 (56.0%)	0.731
HRC (present)*	33 (58.9%)	17 (63.0%)	26 (72.2%)	0.429
HR-NVD (present)*	13 (23.6%)	1 (4.6%)	4 (12.1%)	0.091
Vitreous haemorrhage	22 (33.3%)	8 (24.2%)	17 (47.2%)	0.127
Pre-retinal haemorrhage	12 (18.2%)	3 (9.1%)	11 (30.6%)	0.006
NVI	11 (16.7%)	3 (9.1%)	0 (0%)	0.030
NVG	1 (1.5%)	1 (3.0%)	0 (0%)	0.582
Fibrosis/traction	1 (1.5%)	1 (3.0%)	1 (2.8%)	0.860
DME	38 (57.6%)	7 (21.2%)	9 (25.0%)	<0.001
Previous anti-VEGF	31 (47.0%)	3 (9.1%)	7 (19.4%)	<0.001
Previous macular laser	10 (15.2%)	4 (12.1%)	4 (11.1%)	0.825
LogMAR BCVA	0.32	0.31	0.34	0.486

NVD = new vessels in the disc; NVE = new vessels elsewhere; HRC = high-risk characteristics; HR-NVD = high-risk new vessels in the disc; VH = vitreous haemorrhage; PRH = pre-retinal haemorrhage; NVI = new vessels in the iris; NVG = neovascular glaucoma; DME = diabetic macular edema; VEGF = vascular endothelial growth factor; BCVA = best corrected visual acuity.

* See Table 1 for missing data (i.e. information about NVD, NVE, HRC, and HR-NVD not available in the clinical notes in some patients). When comparisons among laser types were undertaken taking into account missing data, no statistically significant differences were found among laser groups (data not shown but available upon request).

Table 3. Best Corrected Visual Acuity* at Baseline and at Last Follow Up (n = 135 eyes)

BCVA	Baseline n (%)	Last Follow Up n (%)
≤ 20/200	10 (7.4)	16 (11.9)
20/40- to 20/160	38 (28.1)	34 (25.2)
≥ 20/40	87 (64.4)	85 (63.0)

*= Best corrected visual acuity reflects visual acuity with best current refraction

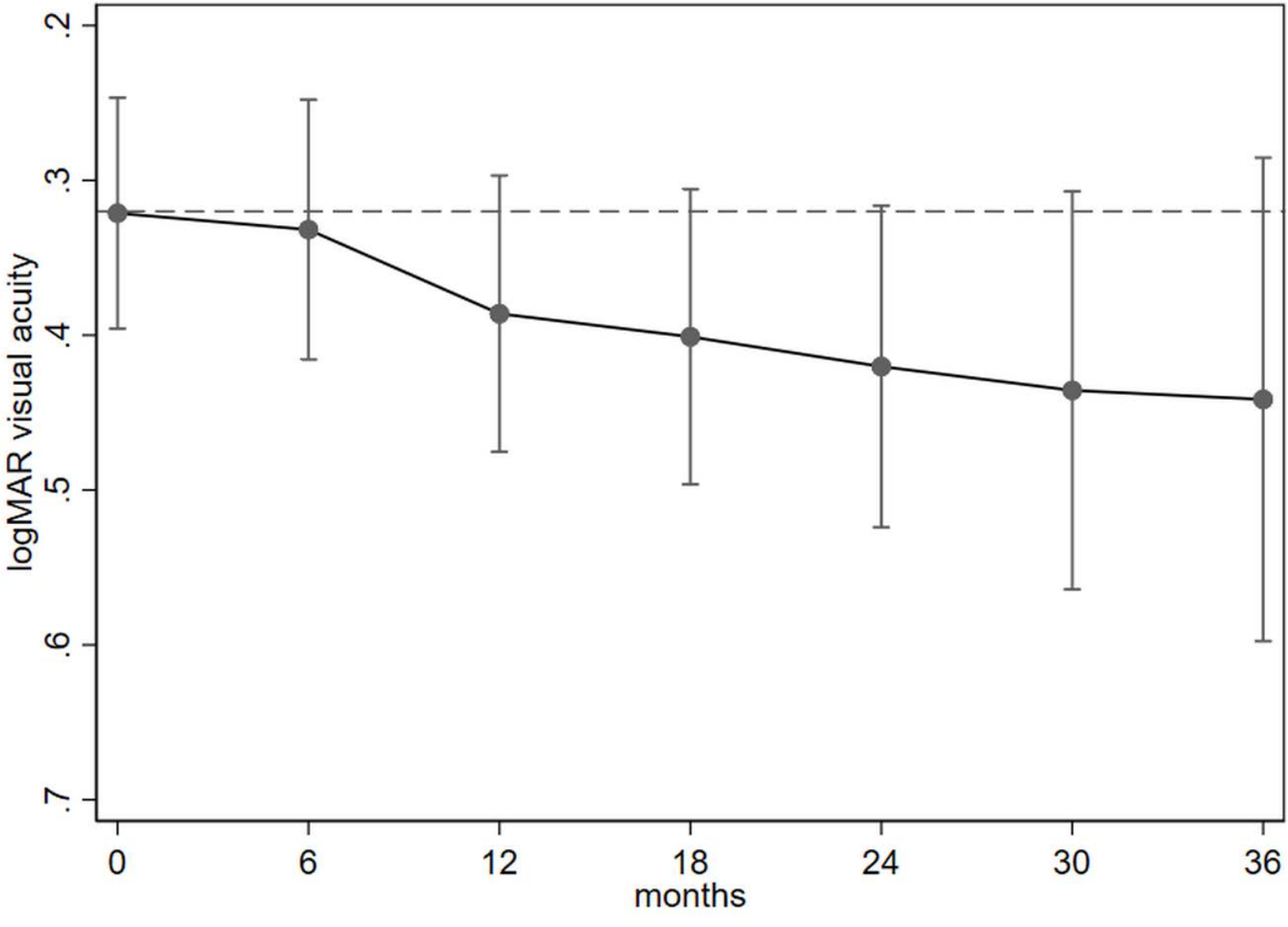
n = number; BCVA = Best corrected visual acuity

Table 4. Cox Multivariable Regression Model Evaluating Associations Between Baseline Characteristics and Laser Type, and Time to Stabilization.

Variable	**HR**	***P* value**	**95% CI**
Baseline characteristics			
DME at baseline	1.48	0.077	0.96-2.28
HRC at baseline	1.13	0.362	0.86-1.49
NVD at baseline	1.03	0.801	0.80-1.33
Vitreous hemorrhage at baseline	0.90	0.612	0.61-1.34
Anti-VEGF use from 1 month prior to PRP to time of stabilization			
Anti-VEGF	0.82	0.407	0.52-1.31
Laser type			
Single spot	1.00		
Multi-spot	0.57	**0.020***	0.35-0.92
Mixed	0.44	**<0.001**	0.28-0.70

* In bold, values which are statistically significant with a $p < 0.05$.

NVD = new vessels in the disc; HRC = high-risk characteristics; DME = diabetic macular edema; VEGF = vascular endothelial growth factor.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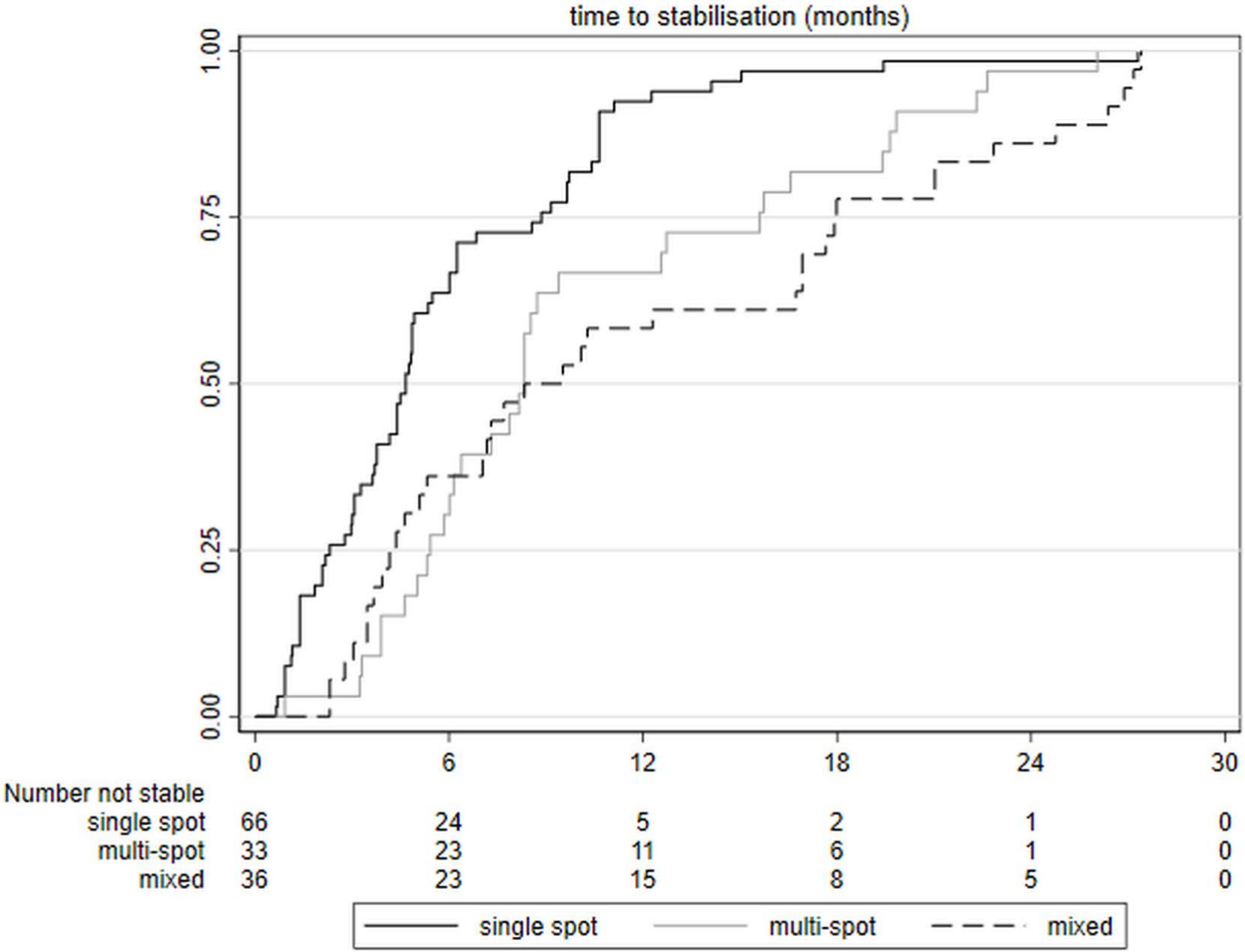
logMAR visual acuity
0
6
12
18
24
30
36
months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0.50
0.25
0.00
0
6
12
18
24
30
Number not stable
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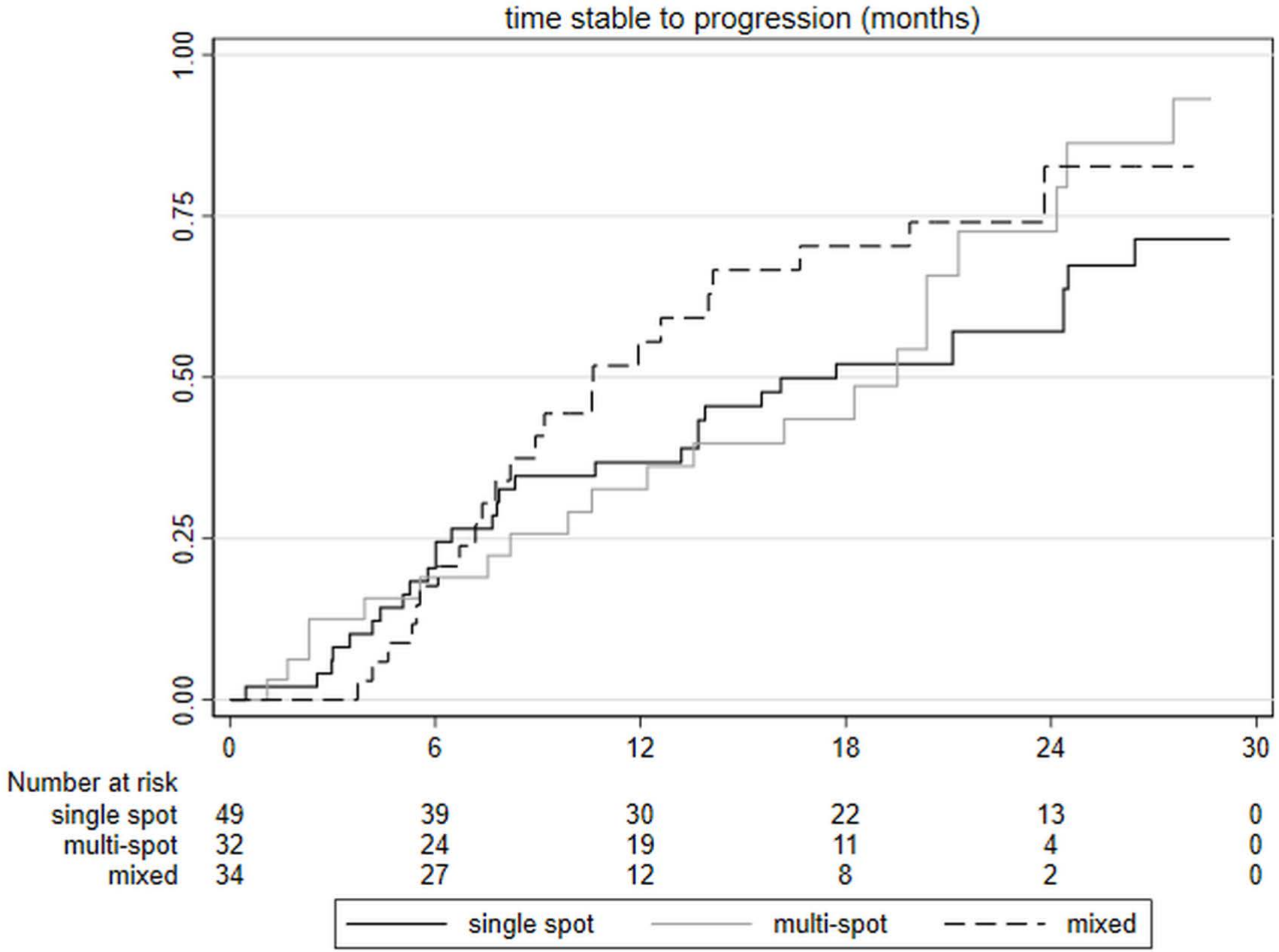
multi-spot 33 23 11 6 1 0
mixed 36 23 15 8 5 0
single spot
multi-spot
mixed


time stable to progression (months)
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0.75
0.50
0.25
0.00
0
6
12
18
24
30
Number at risk
single spot 49 39 30 22 13 0
multi-spot 32 24 19 11 4 0
mixed 34 27 12 8 2 0
single spot
multi-spot
mixed