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FLUORESCEIN ANGIOGRAPHY VERSUS OPTICAL COHERENCE TOMOGRAPHY-GUIDED PLANNING FOR MACULAR LASER PHOTOCOAGULATION IN DIABETIC MACULAR EDEMA

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Abstract

Purpose—To compare laser photocoagulation plans for diabetic macular edema (DME) using fluorescein angiography (FA) versus optical coherence tomography (OCT) thickness map superimposed on the retina.

Methods—Fourteen eyes with DME undergoing navigated laser photocoagulation with navigated photocoagulator had FA taken using the same instrument. Optical coherence tomography central retinal thickness map was imported to the photocoagulator and with same magnification aligned onto the retina. Three retina specialists placed laser spot marks separately on FA and OCT image in a masked fashion. The spots placed by each physician were compared between FA and OCT and among physicians. The area of dye leakage on FA and increased central retinal thickness on OCT of the same eye were also compared.

Results—The average number of spots using FA and OCT template was 36.64 and 40.61, respectively ($P = 0.0201$). The average area of dye leakage was 7.45 mm^2, whereas the average area of increased central retinal thickness on OCT of the same eye was 10.92 mm^2 ($P = 0.013$).

Conclusion—There is variability in the treatment planning for macular photocoagulation with a tendency to place more spots when guided by OCT than by FA. Integration of OCT map aligned to the retina may have an impact on treatment plan once such information is available.

Keywords

diabetic macular edema; laser photocoagulation; fluorescein angiography; optical coherence tomography

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Diabetic macular edema (DME) is one of the common causes of visual loss in patients with diabetes.[1] Although macular laser photocoagulation has been the mainstay for treating DME, several alternative treatments have emerged over the last years and have replaced laser photocoagulation as the first-line treatment for DME. In several clinical trials, treatments with antiangiogenic agents were found to be more effective than sham or focal/grid laser therapy in improving the best-corrected visual acuity and reducing the central retinal thickness in patients with visual impairment due to DME.[2–6] As a result, the role of macular laser has shifted to stabilize the improvement in vision and anatomy after the initial antiangiogenic treatment and to decrease the burden of subsequent intravitreal injections to maintain good initial therapeutic response. Moreover, cost-analysis shows laser treatment for DME to be cost effective in comparison with the current antiangiogenic injection therapy approved by the Food and Drug Administration.[7]

Laser treatments in DME clinical trials have used conventional slit-lamp photocoagulation delivery systems. The decision where to place the laser burns is guided by the previously acquired fluorescein angiograms (FA) and the area of macular edema appreciated using contact fundus lens. Optical coherence tomography (OCT) thickness map serves as an additional source of information in case the clinical edema is not apparent or clear from clinical examination. Information on the exact location and number of leaking microaneurysms from FA and/or the exact location and extent of macular edema from OCT thickness maps has to be remembered by physicians when placing laser burns.

Navigated laser photocoagulation technology uses a camera-based delivery system in which FA, acquired with the same system, is used as a template for making a treatment plan that is subsequently executed by the built-in laser photocoagulator. This, along with eye-tracking capability during the photocoagulation itself, has significantly increased treatment accuracy compared with conventional slit-lamp lasers.[8] Recently, integration of OCT thickness maps with proper alignment to the fundus photograph has become possible in navigated laser photocoagulation (Kozak et al, unpublished data, the Association for Research in Vision and Ophthalmology, Fort Lauderdale, FL, May 6–10, 2012).

Comparing navigated and conventional laser photocoagulation treatments in a recent study,[9] the authors have observed that the total number of laser spots placed by physician was higher with navigated laser than with conventional laser. They explain that in the navigated photocoagulation, the physician can directly observe the execution of the treatment plan in real-time and can see how many laser spots remain to be applied. That is why the physician is obliged to complete the treatment as outlined by his/her plan. Photocoagulation without an integrated template and plan is, therefore, more variable and can change during treatment itself, if biomicroscopy and FA are used solely for planning of treatment. The question where and how much to treat is further confounded by the integration of OCT thickness map, which can provide an additional layer of information on retinal pathology. The latter can be different from stereo-biomicroscopy.[10–12]

The aim of this study was to compare laser treatment plans for DME using FA versus OCT thickness map template superimposed on retinal images among retina specialists, which to the best of our knowledge has not been compared. We hypothesize that the information from integrated OCT retinal thickness map aligned onto fundus image will have an impact on treatment planning and that the treatment plans will differ among physicians based on the diagnostic modality they use.

Methods

Prospective randomized study of 14 eyes of 10 patients with symptomatic DME undergoing laser photocoagulation with navigated laser (NAVILAS, OD-OS, Inc, Berlin, Germany) that had FA and OCT imaging performed before treatment. Fluorescein angiography image was taken using the same instrument and superimposed onto a color fundus photograph. Standard OCT retinal thickness map acquired on the spectral domain OCT system (Spectralis; Heidelberg Engineering, Heidelberg, Germany) was imported to the laser photocoagulator unit and superimposed and aligned onto the fundus image of the same magnification as described previously (Kozak et al, unpublished data, the Association for Research in Vision and Ophthalmology, Fort Lauderdale, FL, May 6–10, 2012).

The inclusion criteria were good-quality images showing dye leakage on FA and red false color zone of retinal thickening in the macular area against the background fundus photograph on OCT. The treatment parameters included modified Early Treatment Diabetic Retinopathy Study method targeting all leaking microaneurysms and grid laser in the areas of edema. The treatment plans for each eye consisted of placing laser spot marks separately on FA and OCT images in a masked fashion. This step was saved on the screen. When making the plan on FA, physicians could use any phase of the angiogram sequence according to their preference or depending on each clinical case with preference to use earlier frames for focal and late frames for grid treatments. The area of dye leakage on FA and increased retinal thickness on OCT on the same eye was measured using the ImageJ software (NIH, Bethesda, MD). The final number of spots placed by the physician was compared between FA and OCT using matched-pair analysis and the difference among physicians was assessed by ANOVA test (SAS statistical software version 9.2, SAS, Inc, Cary, NC).

Results

The group consisted of 6 men and 4 women with the mean age of 64 ± 8.5 years. All eyes (n = 14) were diagnosed with DME for whom laser photocoagulation was to be performed. Three masked retina specialists created treatment plans. The average number of planed spots using FA and OCT template was 36.64 and 40.61, respectively ($P = 0.0201$) (Figures 1 and 2). The average area of dye leakage on FA was 7.45 mm^2, whereas the average area of increased retinal thickness on OCT superimposed on the fundus image of the same eye was 10.92 mm^2 ($P = 0.013$). In comparison of placing laser spots on OCT maps, there was no significant statistical difference among 3 physicians (Physician 1 vs. Physician 2, $P = 0.94$; Physician 1 vs. Physician 3, $P = 0.08$; and Physician 2 vs. Physician 3, $P = 0.15$) (Figure 3). No significant statistical difference among the 3 physicians was also present in comparison of placing laser spots on fluorescein angiograms (Physician 1 vs. Physician 2, $P = 0.98$; Physician 1 vs. Physician 3, $P = 0.95$; and Physician 2 vs. Physician 3, $P = 0.90$) (Figure 4).

Discussion

In the Early Treatment Diabetic Retinopathy Study, laser photocoagulation treatment was directed at all "treatable lesions" identified by biomicroscopy and/or FA. Fluorescein angiography was performed before the laser treatment to identify "treatable lesions" per the treatment criteria of Early Treatment Diabetic Retinopathy Study for those who follow that protocol[13] or to assess perfusion status of the retina and exclude other causes of vision loss in general. As such, the use of FA has been shown to improve the accuracy of photocoagulation treatment planning for clinically significant macular edema.[14]

Optical coherence tomography offers additional structural and quantitative information in characterization of DME, and because of its noninvasiveness, it has been surpassing the use of invasive FA. The topographic location and morphologic patterns of edema on the OCT retinal thickness map have served as useful predictors of treatment response in diffuse DME.[15] Optical coherence tomography thickness maps have been widely used as a guidance of macular laser therapy for DME, and in a small prospective study, they have produced similar clinical results as FA-based treatments.[16] For such reason, many physicians use OCT to guide laser photocoagulation, especially those preferring grid photocoagulation as their treatment approach.

Both FA and OCT are complementary in diagnosing the type and extent of DME.[17–19] Our study points to a wide variability in macular photocoagulation treatments among physicians when they base their treatment plan decision solely on one of them. We have studied this phenomenon using integrated imaging templates presented to different retina specialists. The images consisted of both the fluorescein angiograms and OCT thickness maps of each studied eye overlaid onto the fundus photographs of the patients.

Two major observations came out from this study. The first one, relating to our study hypothesis, is that the physicians placed different number of laser spots for the same DME pathology when they were guided by different imaging templates. They tend to treat more when the treatment is guided by OCT thickness map. Variation in macular photocoagulation treatment was recently studied by van Dijk et al.[20] They found differences in the assessment of DME with OCT or stereoscopic biomicroscopy, which then lead to different photocoagulation treatment decisions. They further measured areas of DME from the OCT thickness map simulating the Early Treatment Diabetic Retinopathy Study criteria yielding the concept of "treatable macular edema" to differentiate the assessment of DME using OCT from the assessment using biomicroscopy or stereoscopic fundus photography. Treatable macular edema is thus analogous to clinically significant macular edema, but thickening is derived from OCT. In addition, in their study, the retinal specialists markedly differed in the number and placement of planned laser spots when given identical information concerning the presence and location of DME and treatable lesions. Thus, there seems to be a natural variation in the treatment decision even with the same baseline information but the difference magnifies if the baseline information is somewhat different. We have not used any automated or custom-made software to compare the number of laser spots in treatment plans as van Dijk et al did. We performed manual count of laser spots. However, the advantage of our approach is overlaying of the aligned FA and OCT images onto fundus photos, which allows co-localization of structures and laser spots.

The second observation relates to the extent of the pathologic areas in the same eye (leakage on FA and thickening on OCT). We have found them to be different with the pathologic area on OCT measured larger than on FA. The exact explanation is not clear, but we speculate that the border retinal area adjacent to leakage on fluorescein angiography is still edematous, which is only detected by OCT. Discrepancies between FA and OCT in the detection of macular edema have been previously described.[17,18] Because the areas of thickening on OCT maps seemed larger than areas of leakage on FA in the same eyes could be a reason why physicians in this study had a tendency to place more treatment spots when they used information from OCT maps.

This report expands recent observations by others that treatment threshold and the number of laser spots differs depending on whether the macular edema is diagnosed by biomicroscopy, OCT, or FA. More common use of different photocoagulation approaches such as subthreshold, micropulse, or navigated lasers even further weakens the standardization of laser photocoagulation algorithms for the treatment of macular edema. This is of utmost importance in ongoing and future clinical trials studying comparisons or combination of macular laser photocoagulation and intravitreal pharmacotherapy. Although intravitreal injections have their defined pharmacokinetics and for most parts dosing regimens, this is not the case with laser arms of the trials. Most clinical trials use strict criteria of rescue therapy or retreatment in laser arms, but execution depends on study physicians, modes they use to diagnose the extent of DME, and their training and personal experience. This study shows that even in the hands of experienced retina specialists, there is a variation in laser treatment threshold. As such, it may be possible that we get variable treatment results with lasers and compare them with a very standardized pharmacotherapy protocols. Limitation of our study includes few patients and eyes. However, the comparisons did not apply to eyes but the number of planned photocoagulation marks, which were numerous in each eye. The strength includes using co-localization algorithms and masked fashion of comparison of treatment plans.

In summary, we show improved accuracy of treatment plan by incorporating information from FA and OCT overlay, and at the same time, variability in the treatment planning for macular laser photocoagulation. Further studies are warranted to evaluate clinical efficacy of OCT-guided laser treatments. We encourage experts to work on more standardized laser photocoagulation protocols to be used both in clinical trials and patient care.

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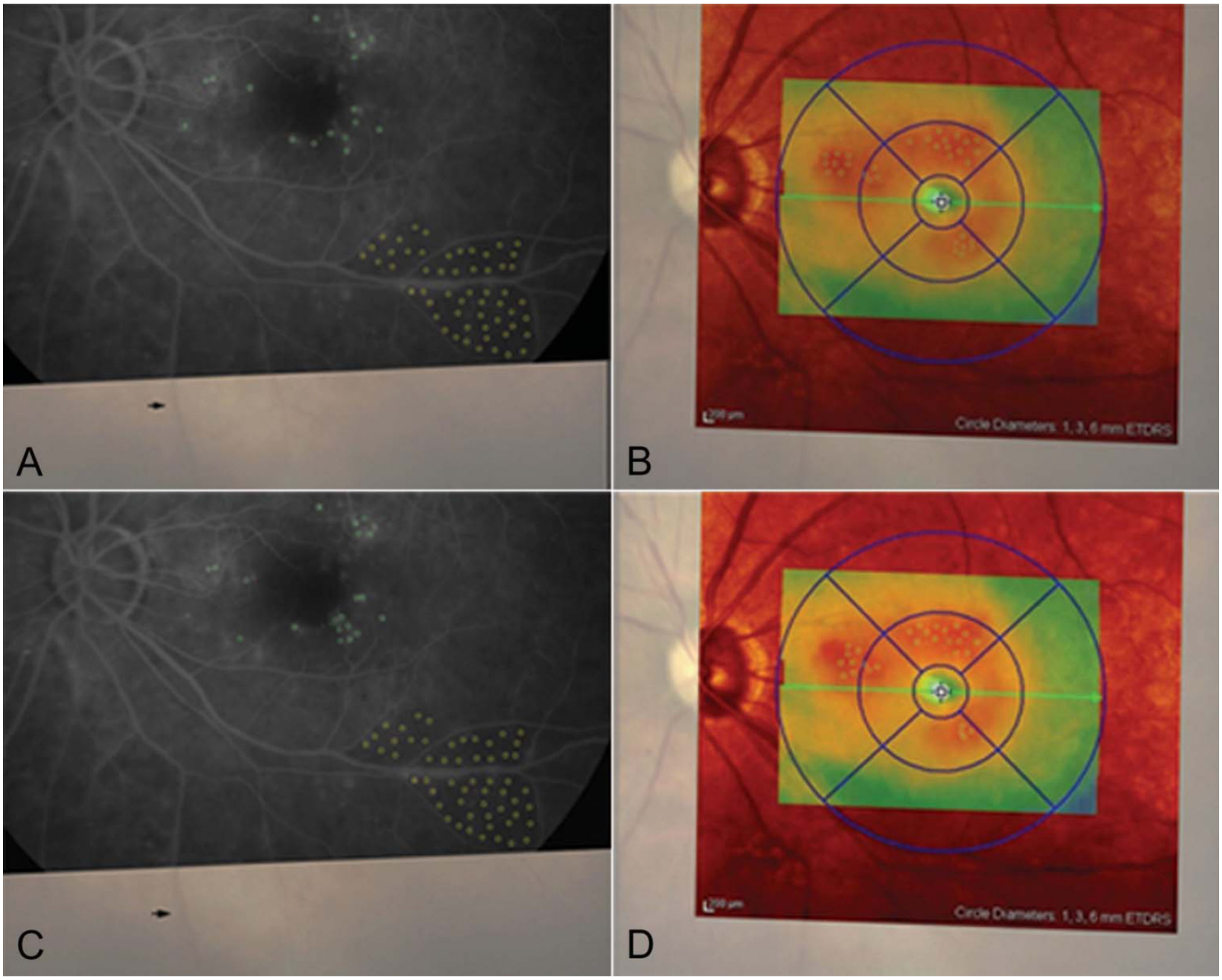

Fig. 1.

Fluorescein angiography versus OCT-guided treatment plan for macular laser photocoagulation. **A**. Fluorescein angiogram overlayed on fundus photograph of an eye with diabetic retinopathy and mild macular edema (black arrow points to proper alignment of blood vessels and correct image overlay). Green circles represent laser spots to be applied during macular photocoagulation as outlined by Physician 1 (n = 17); yellow circles represent extrafoveal spots. **B**. Optical coherence tomography overlayed on fundus photograph of the same eye. Green circles represent laser spots to be applied during macular photocoagulation as outlined by Physician 1 (n = 32). **C**. Fluorescein angiogram overlayed on fundus photograph of the same eye. Green circles represent laser spots to be applied during macular photocoagulation as outlined by Physician 2 (n = 21); yellow circles represent extrafoveal spots. **D**. Optical coherence tomography overlayed on fundus photograph of the same eye. Green circles represent laser spots to be applied during macular photocoagulation as outlined by Physician 2 (n = 28).

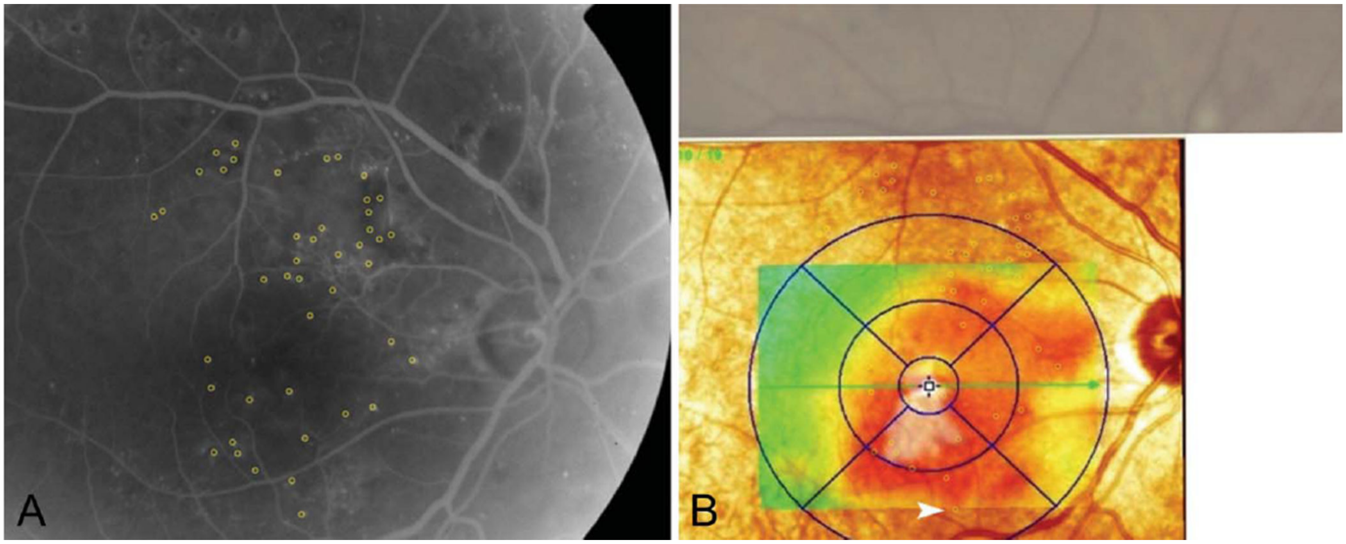

Fig. 2.

Fluorescein angiography versus OCT-guided treatment plan for macular laser photocoagulation. **A**. Fluorescein angiogram of an eye with diabetic retinopathy and macular edema used as a template for laser treatment planning. Yellow circles represent laser spots to be applied during photocoagulation as outlined by Physician 3 (n = 44). **B**. Optical coherence tomography overlayed on the same eye and used as a template for laser treatment planning. Yellow circles (white arrowhead) represent laser spots to be applied during photocoagulation as outlined by Physician 3 (n = 41).

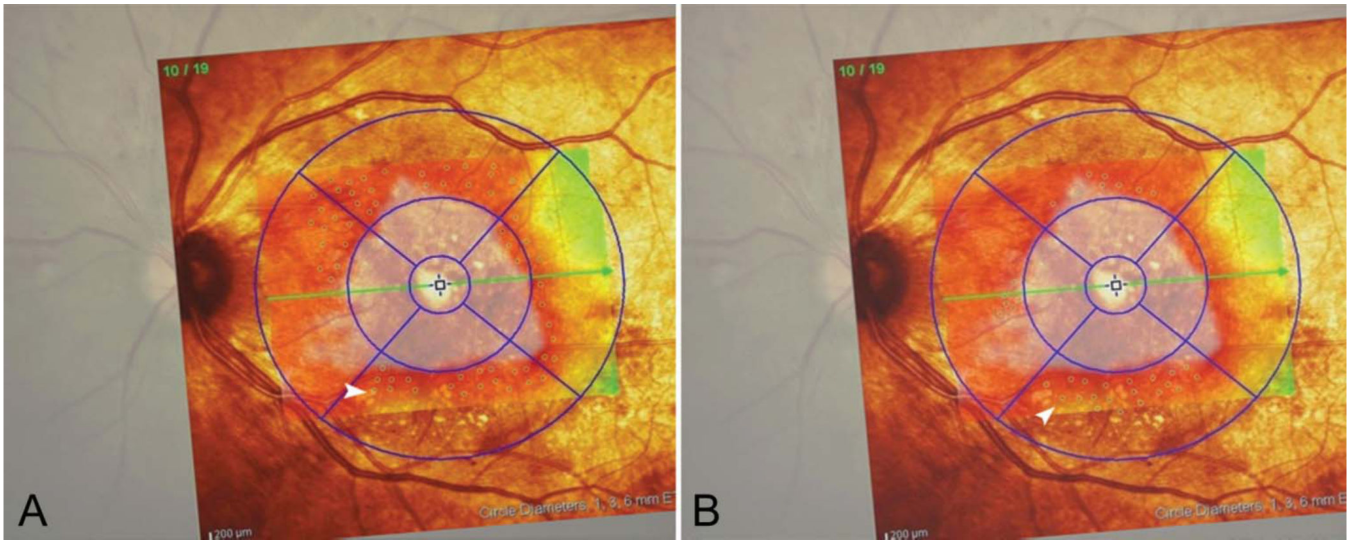

Fig. 3.

Comparison of OCT-guided treatment plans for macular laser photocoagulation. **A**. Optical coherence tomography retinal thickness map overlayed on fundus photograph with marked yellow spots (white arrowhead) for photocoagulation by Physician 1 (n = 61). **B**. The same template with marking by Physician 2 (n = 34).

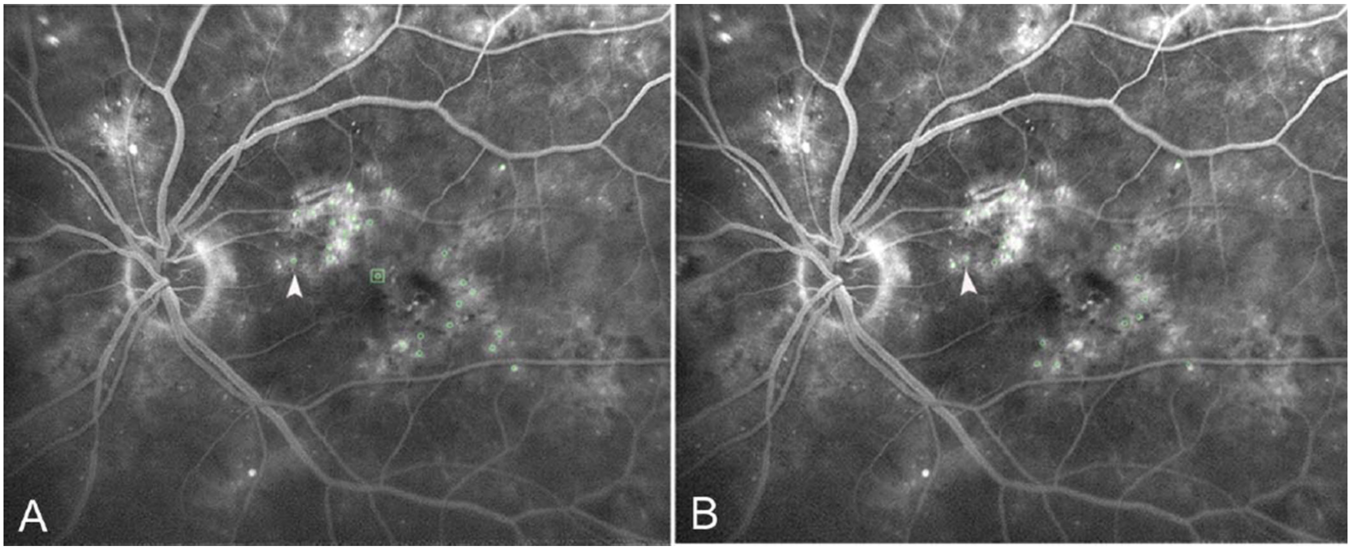

Fig. 4.

Comparison of FA-guided treatment plans for macular laser photocoagulation. **A**. Fluorescein angiogram of an eye with diabetic retinopathy and edema photograph with marked green spots (white arrowhead) for photocoagulation by Physician 1 (n = 25). **B**. The same template with marking by Physician 2 (n = 18).