Assessment of Retinal Nerve Fiber Layer Thickness Using Optical Coherence Tomography Before and After Ranibizumab Intravitreal Injection in Patients with Diabetic Macular Edema

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Abstract

Background: Anti-Vascular Endothelial Growth Factor (Anti-VEGF) therapy serves to decrease central retinal thickness in eyes affected with diabetic macular edema (DME). The Retinal Nerve Fiber Layer (RNFL) forms the basis of the optic nerve.

Objectives: Our study is concerned with studying the effects of Anti-VEGF injections in patients with DME on RNFL thickness.

Patients and methods: This was a prospective cohort interventional study conducted at South Valley University Hospital, Ophthalmology department outpatient clinic. It included 50 diabetic patients with diabetic macular edema whose RNFL thickness was measured before the anti-VEGF injections and again after the completion of the three injections treatment course using spectral domain optical coherence tomography (SD-OCT).

Results: This study included 50 eyes from 50 patients. 35 (70%) of them were females and 15 (30%) of them were males. 26 patients (52%) had their right eye injected, and 24 patient (48%) had their left eye injected. The superior quadrant of the RNFL showed a mean increase of 1.2 microns (SD = 38.4, 95% Confidence Interval CI = -9.7:12.1, p value = 0.829). The inferior quadrant showed a mean increase of 7.5 microns (SD = 35.6, 95% CI = -2.6:17.6, p value = 0.144). The nasal quadrant showed a mean increase of 8.3 microns (SD = 23, 95% CI = 1.8:14.9, p value = 0.014). The temporal quadrant showed a mean increase of 4.1 microns (SD = 33.2, 95% CI = -5.3:13.6, p value = 0.386).

Conclusion: There is no statistically significant correlation between intra-vitreal injections of anti-VEGF and the RNFL thickness.

Keywords: Anti-VEGF; retina; DME; CME; RNFL.

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Introduction

Diabetic retinopathy is a very dangerous complication of diabetes mellitus owing to its progressive nature as well as to its effect on visual acuity (**Lutty, 2013; Kelkar et al., 2016**). In assessing the effects of diseases on the eye, it is essential to consider the Retinal Nerve Fiber Layer (RNFL) which forms the basis of the optic nerve fibers once it passes through the optic disc (**Lupión et al., 2021**).

Anti-Vascular Endothelial Growth Factor (Anti-VEGF) therapy serves to decrease central retinal thickness in eyes affected with diabetic macular edema (DME) through a reduction in the angiogenesis aspect of DME pathogenesis. Ranibizumab is one of the types of Anti-VEGF drugs used in treatment. It is administered as an intravitreal injection of 0.5 or 0.3 mg (**Yang et al., 2017**).

Intravitreal ranibizumab is mainly indicated for center involving DME (**Wykoff et al., 2018**). Treatment is initiated with one injection every 4 weeks (which should be the minimum time between two consecutive injections). Several protocols suggest at least three consecutive injections initially (**Kertes et al., 2019**). Visual acuity, clinical examination, and imaging (including Optical Coherence Tomography or OCT and angiography) can be used to assess retreatment needs in pro re nata (PRN) treatment protocols (**Silva et al., 2018**).

Treat-and-extend regimens have been also proposed, and in these protocols, once maximum visual acuity is achieved and/or there are no signs of disease activity, the treatment intervals can be extended stepwise until signs of disease activity or visual impairment recur. If disease activity recurs, the treatment interval should be shortened accordingly (**Dervenis et al., 2017**). Our study is concerned with studying the effects of Anti-VEGF injections in patients with DME on the RNFL thickness.

Patients and methods

This was a prospective cohort controlled interventional study conducted at South Valley University Hospitals, Ophthalmology department outpatient clinic between May and November of 2022. It included 50 diabetic patients with diabetic macular edema. Inclusion criteria included patients of either sex with type 2 diabetes mellitus who developed diabetic macular edema and were being considered for intra-vitreal Ranibizumab injections.

Exclusion criteria included children and uncooperative patients with disturbed conscious levels, patients with very dense cataracts precluding visualization of the fundus or proper assessment of visual acuity, patient with other types of retinopathies, patients who had previous laser or ocular surgery, and patients with ischemia (macular or retinal) or proliferative diabetic retinopathy detected on fundus fluorescein angiography.

Our study adhered to the Declarations of Helsinki. The current study has been approved by the Ethics Committee of Faculty of Medicine, South Valley University, Qena, Egypt and the ethical approval number is SVU-MED-OPH026-1-22-6-409. An official latter was taken to approach the director of ophthalmology department in SVU hospital for permission to conduct the

study. Written consent was obtained from all patients.

This study included 50 eyes from 50 patients. Fellow eyes of those 50 patients were used as controls. Consent was obtained from all patients and then they underwent full history taking and clinical examination. All the patients underwent Spectral Domain Optical Coherence Tomography (SD-OCT) preoperatively and once (one to four weeks) postoperatively following intravitreal Ranibizumab (Anti-VEGF). These scans were marked as the patient's baseline and were used for referencing the subsequent scans using the "follow-up" function of the SD-OCT, assuring us that the scans were performed in the same position. All images were taken as close to the optic disc as possible to ensure, to the best extent possible, that the same retinal area was being scanned.

To achieve this study purpose, patients were injected with Ranibizumab (Lucentis) in a dose of 5 mg/ml (Novartis, Switzerland) then we evaluated and compared retinal nerve fiber layer thickness changes using SD-OCT using OCT-Spectralis (Heidelberg Engineering GmbH 69121 Heidelberg / Germany, SN: TR-KT-2069, Manufactured 02/13) with the software Heidelberg Eye Explorer version 1.9.10.0 (**Pazos et al., 2017**), before starting intra-vitreal Ranibizumab injections and again after finishing the three months treatment regimen.

The primary (main) outcome was the retinal nerve fiber layer thickness pre- and postoperatively. The secondary outcomes included visual acuity using the logMAR scale (uncorrected visual acuity UCVA and best corrected visual acuity BCVA) and central foveal thickness.

Statistical analysis

Data was analyzed using Statistical Package for Social Sciences (SPSS) software program (version 26) (**IBM Corp., 2019**). Qualitative variables were recorded as frequencies and percentages and were compared by Chi-square test. Quantitative measures were presented as means ± standard deviation (SD) and were compared by Student t-test. Regression correlation and analysis between different variables were performed as indicated. A P-value of < 0·05 was considered to be significant.

Results

This study included 50 eyes from 50 patients. Fellow eyes of those 50 patients were used as controls. 35 (70%) of them were females and 15 (30%) of them were males. 26 patients (52%) had their right eye injected, and 24 patient (48%) had their left eye injected. The mean age of the patients was 60 years (SD = 7.9 years, Range = 43:75 years) and the mean duration of their diabetes mellitus was 11.5 years (SD = 6.5 years, Range = 2:24 years).

The mean preoperative UCVA of the injected eyes using logMAR was 1.06 on LogMAR (SD = 0.27, Range = 0.6:1.8) and the mean preoperative BCVA was 1 (SD = 0.29, Range = 0.6:1.8). The mean postoperative UCVA was 1.03 (SD = 0.25, Range = 0.6:1.8) and the mean postoperative BCVA was 0.98 (SD = 0.27, Range = 0.6:1.8). The average UCVA of the non-injected (control) eye at the start of the follow up period was 0.94 (SD = 0.24, Range = 0.3:1.3) and the mean BCVA of the non-injected (control) eye was 0.88 (SD = 0.24,

Range = 0.3:1.2). The UCVA and BCVA of the non-injected (control) eyes after the end of the assessment period of 3 months was the same.

For the injected eyes, the mean preoperative RNFL thickness in the superior quadrant preoperatively was 120 microns (SD = 33 microns, Range = 29:194 microns) which postoperatively became 121 microns (SD = 29 microns, Range = 59:165 microns). For the inferior quadrant, preoperatively it was 123 microns (SD = 31 microns, Range = 76:224 microns), and postoperatively it became 130 microns (SD = 29 microns, Range = 81:191 microns). For the nasal quadrant, it was 74 microns (SD = 21 microns, Range = 35:127 microns) and it became 83 microns (SD = 22 microns, Range = 49:120 microns). And, lastly, for the temporal quadrant, preoperatively it was 98 microns (SD = 28 microns, Range = 64:169 microns), and postoperatively it became 102 microns (SD = 21 microns, Range = 66:126 microns) (**Fig.1, 2**).

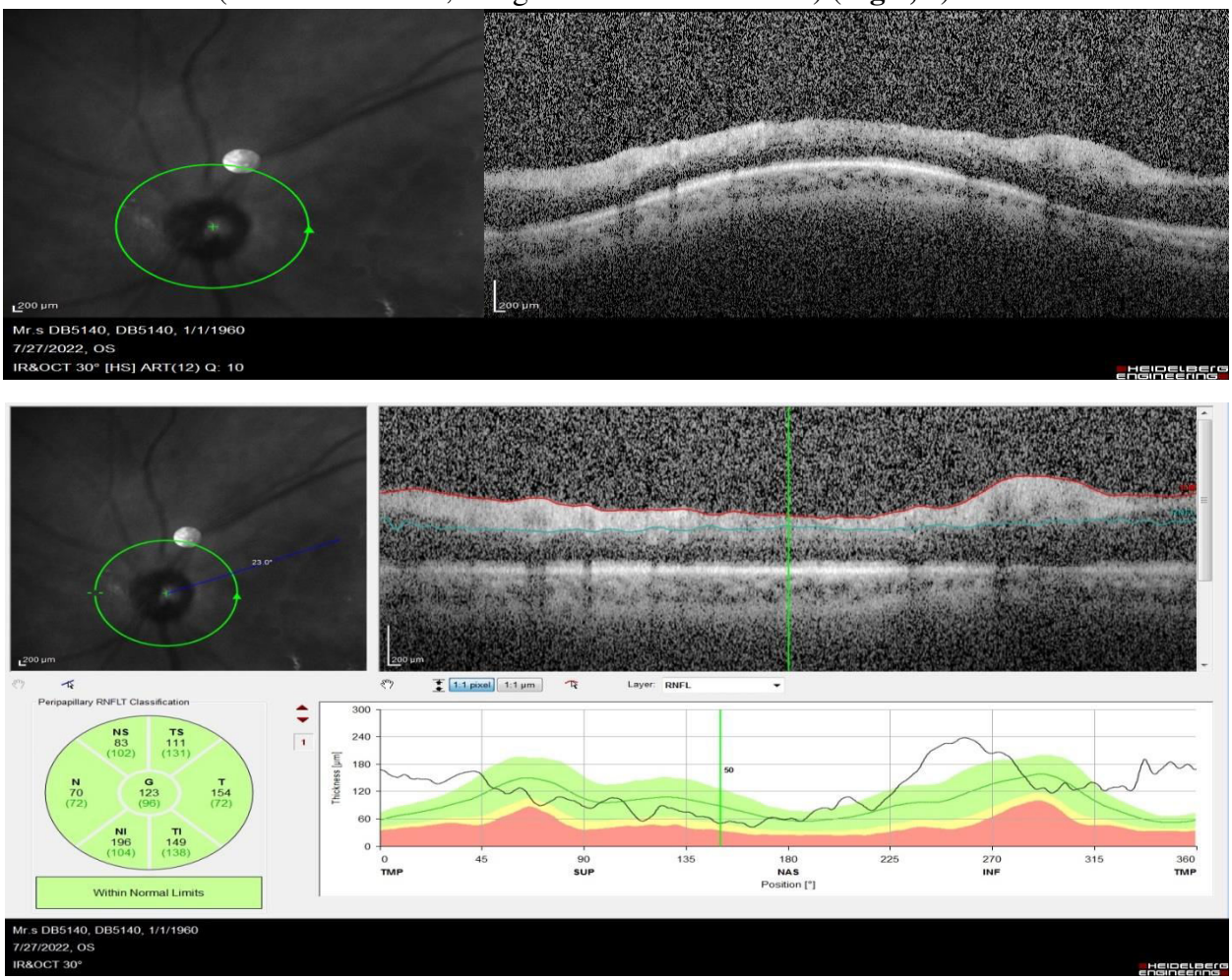


Fig.1. Preoperative OCT image of the RNFL thickness in different quadrants of the left eye of a diabetic macular edema patient. These images were taken from a 69-year-old woman who has been diabetic for 15 years.

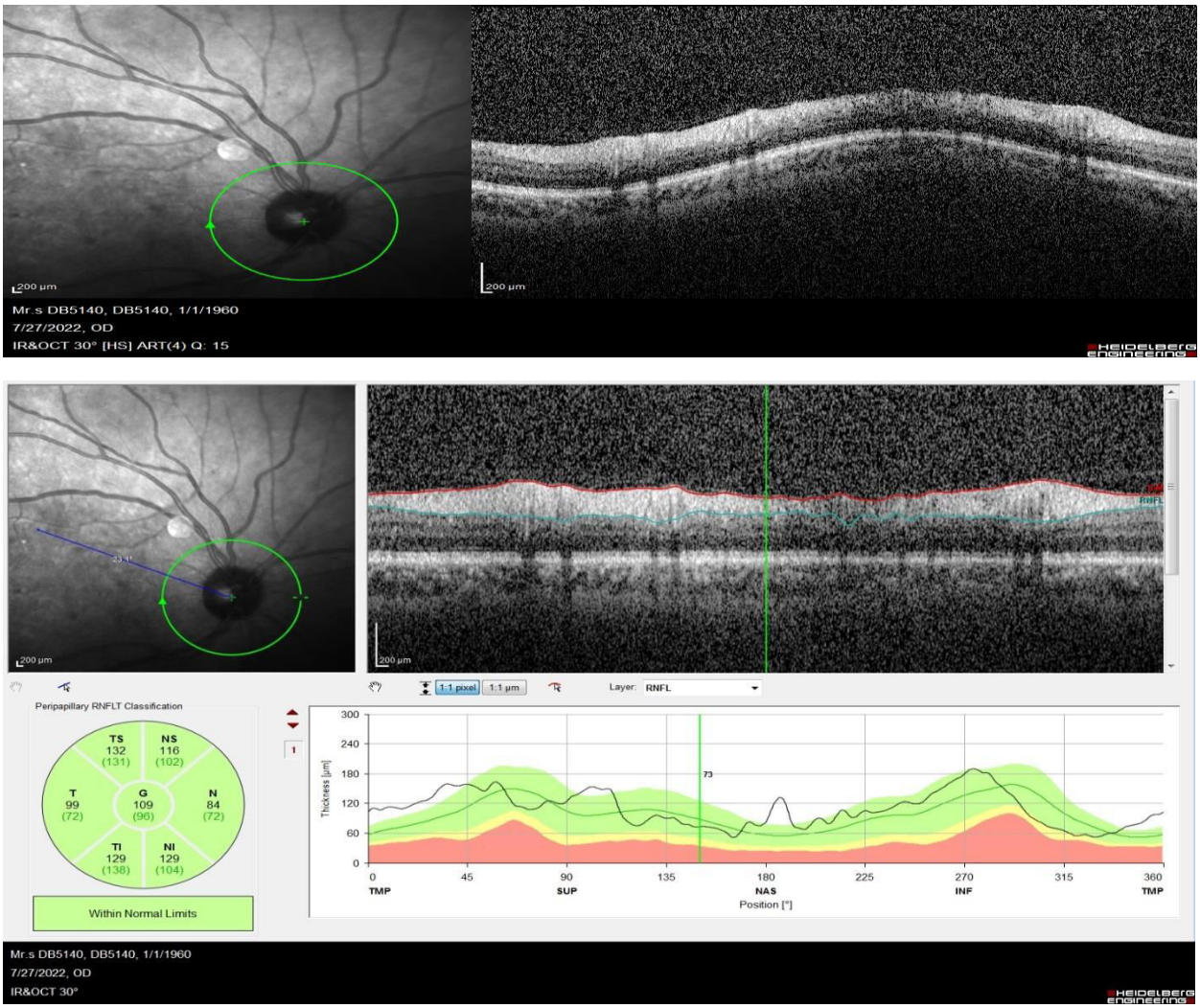


Fig.2. Preoperative OCT image of the RNFL thickness in different quadrants of the right eye of a diabetic macular edema patient. These images were taken from a 69-year-old woman who has been diabetic for 15 years.

For the non-injected (control) eyes, the mean RNFL thickness at the start of the follow up period in the superior quadrant preoperatively was 129 microns (SD = 36 microns, Range = 68:232 microns) which at the end of the follow up period became 132 microns (SD = 29 microns, Range = 95:189 microns). For the inferior quadrant, it was 128 microns (SD = 40 microns, Range = 56:229 microns), and at the end of the follow up period it became 135 microns (SD = 37 microns, Range = 83:201 microns). For the nasal quadrant, it was 83 microns (SD = 35 microns, Range = 33:195 microns) and it became 93 microns (SD = 39 microns, Range = 49:170 microns). And, lastly, for the temporal quadrant, it was 99 microns (SD = 28 microns, Range = 61:168 microns), and at the end of the follow up period it became 100 microns (SD = 35 microns, Range = 62:158 microns) (**Table 1** & **Fig. 3-6**).

Table 1. Preoperative & Postoperative Retinal Nerve Fiber Layer Thickness in Injected and Non-injected (control) Eyes

Variables	Injected Eyes		Non-injected (control) Eyes	
	Preoperative Mean RNFL thickness (SD)	Postoperative Mean RNFL thickness (SD)	Preoperative Mean RNFL thickness (SD)	Postoperative Mean RNFL thickness (SD)
Superior Q	120 (33)	121 (29)	129 (36)	132 (29)
Inferior Q	123 (31)	130 (29)	128 (40)	135 (37)
Nasal Q	74 (21)	83 (22)	83 (35)	93 (39)
Temporal Q	98 (28)	102 (21)	99 (28)	100 (35)

Q = Quadrant, SD = Standard Deviation. Measurements are all in microns

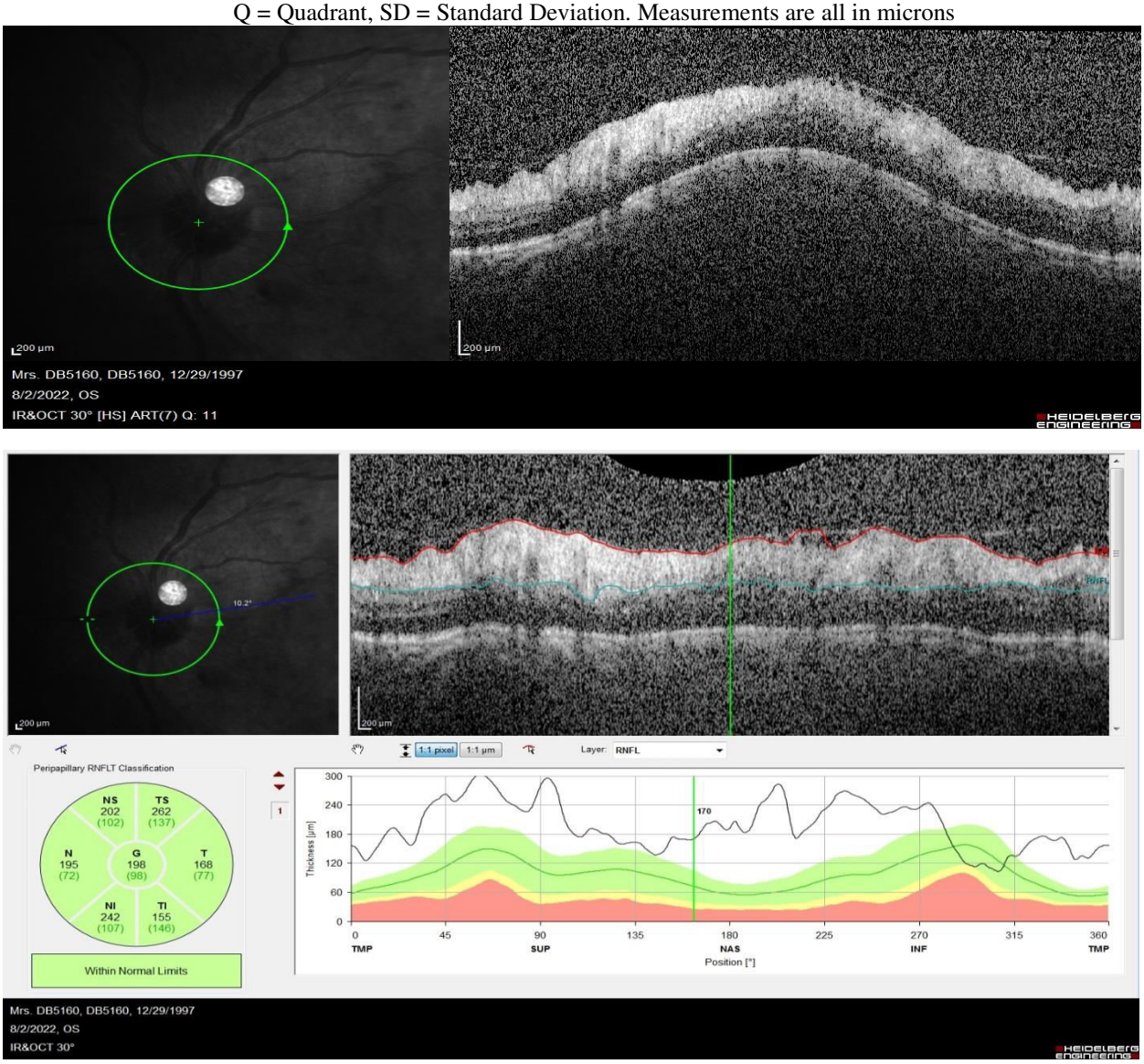


Fig.3. Preoperative OCT image of the RNFL thickness in different quadrants of the left eye of a diabetic macular edema patient. These images were taken from a 43-year-old woman who has been diabetic for 10 years.

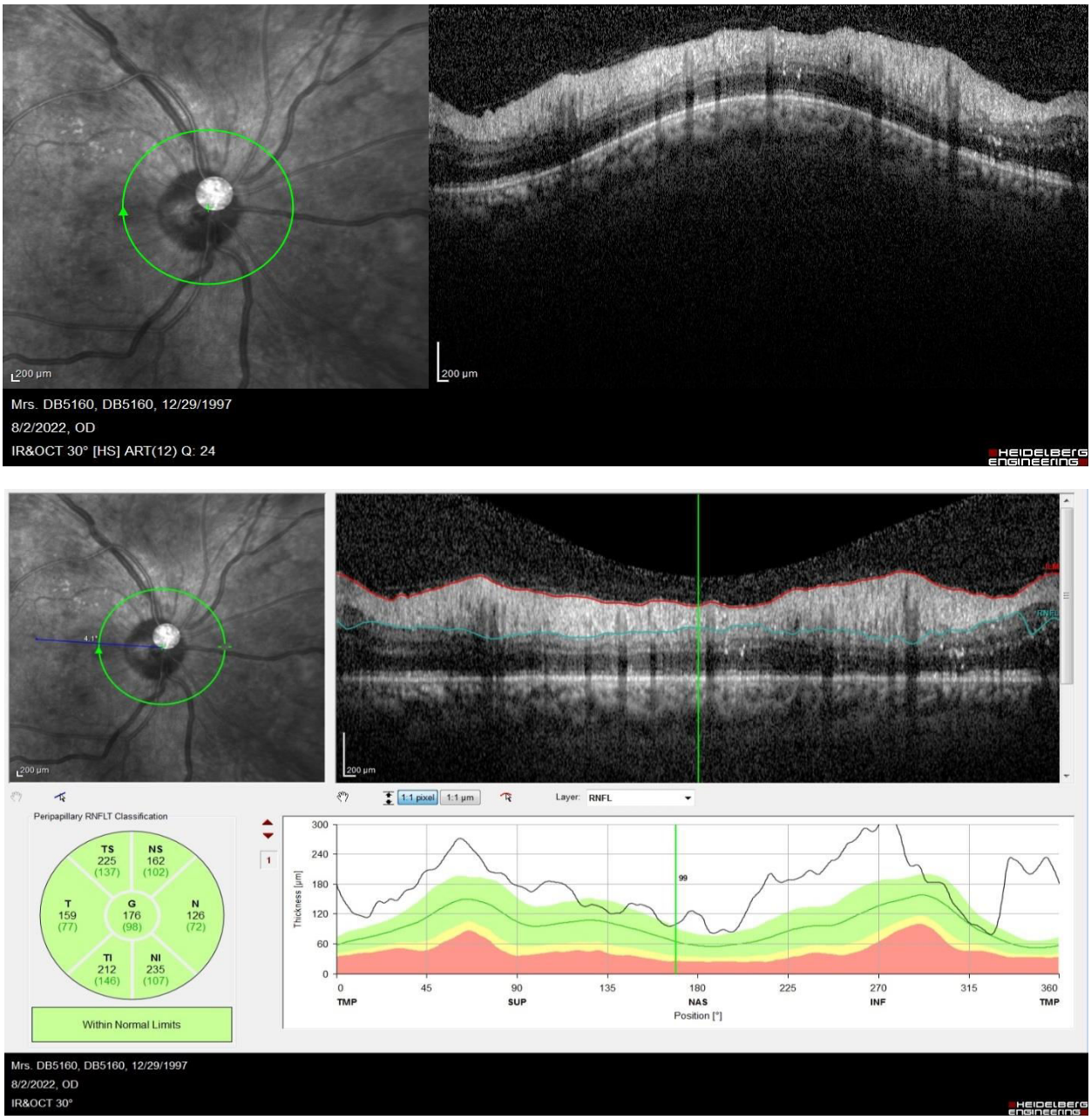


Fig.4. Preoperative OCT image of the RNFL thickness in different quadrants of the right eye of a diabetic macular edema patient. These images were taken from a 43-year-old woman who has been diabetic for 10 years.

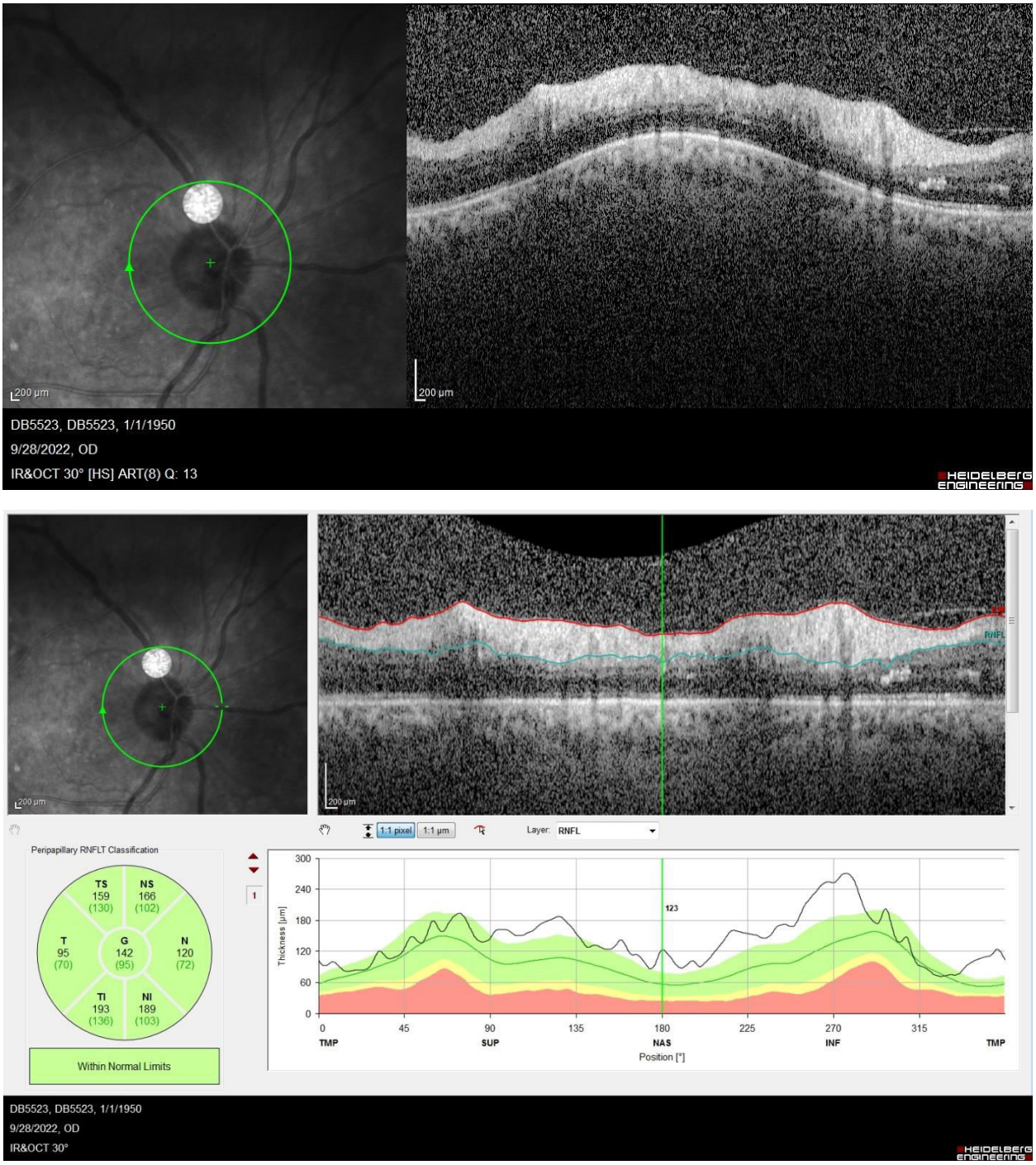


Fig.5. Postoperative OCT image of the RNFL thickness in different quadrants of the right eye of a diabetic macular edema patient. These images were taken from a 43-year-old woman who has been diabetic for 10 years.

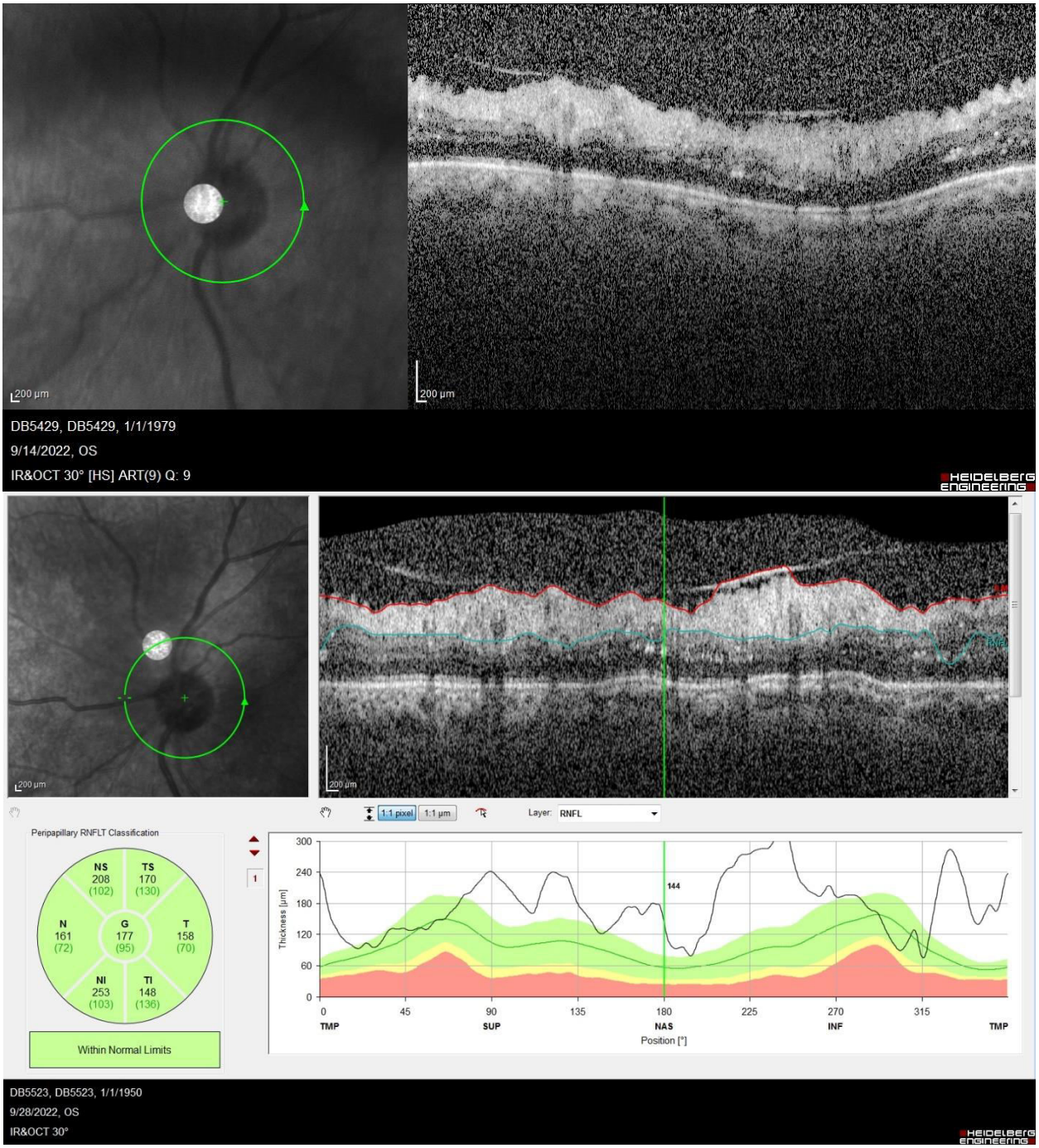


Fig.6. Postoperative OCT image of the RNFL thickness in different quadrants of the left eye of a diabetic macular edema patient. These images were taken from a 43-year-old woman who has been diabetic for 10 years.

For the injected eyes, the superior quadrant of the RNFL showed a mean increase of 1.2 microns (SD = 38.4, 95% Confidence Interval CI = -9.7:12.1, p value = 0.829). The inferior quadrant showed a mean increase of 7.5 microns

(SD = 35.6, 95% CI = -2.6:17.6, p value = 0.144). The nasal quadrant showed a mean increase of 8.3 microns (SD = 23, 95% CI = 1.8:14.9, p value = 0.014). The temporal quadrant showed a mean increase of 4.1 microns (SD = 33.2, 95% CI = -5.3:13.6, p value = 0.386). The central foveal thickness showed a mean decrease of 8.5 microns (SD = 159, 95% CI = -36.8:53.8, p value = 0.706) (**Fig. 7, 8**).

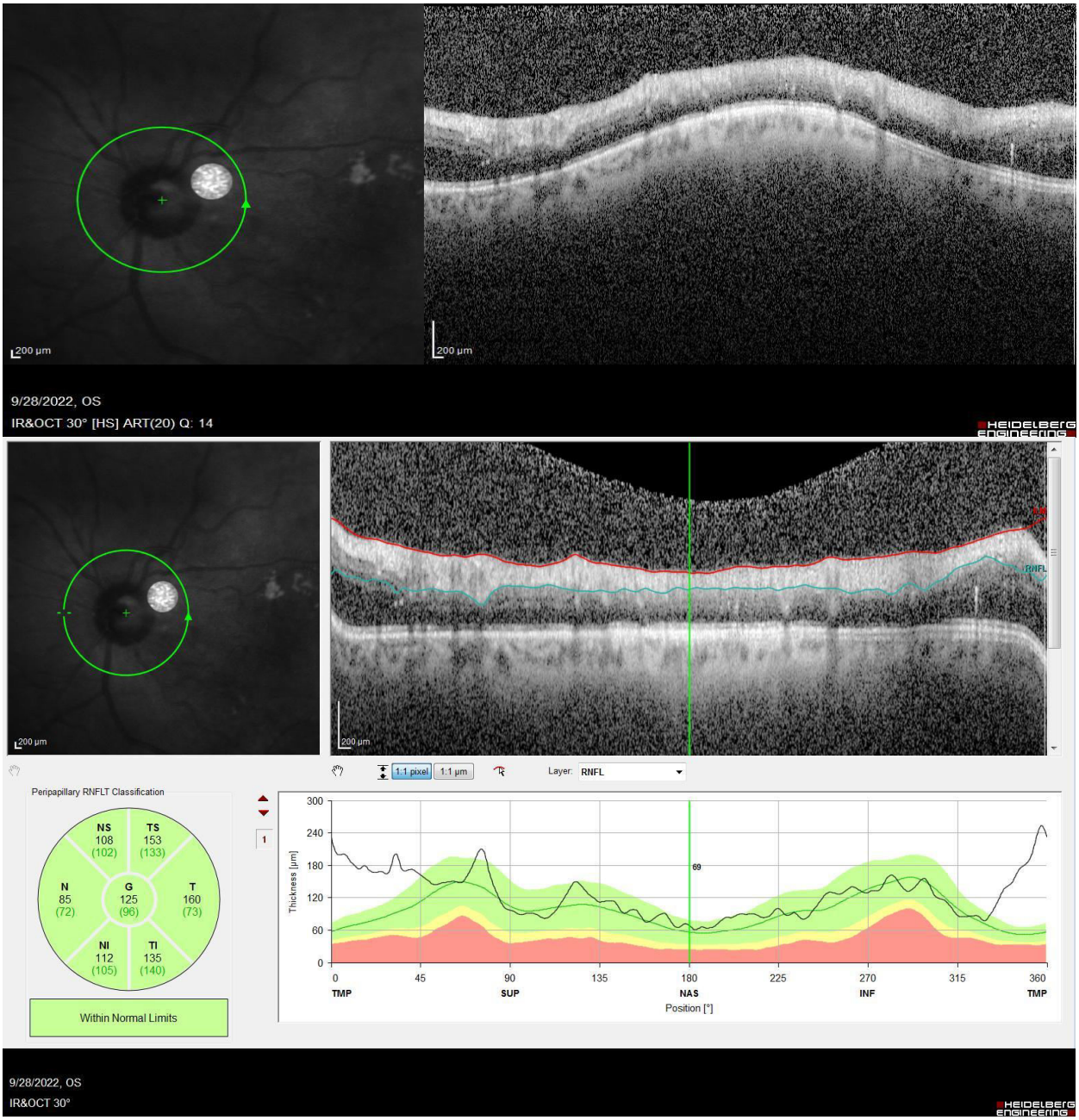


Fig.7. Postoperative OCT image of the RNFL thickness in different quadrants of the left eye of a diabetic macular edema patient. These images were taken from a 53-year-old woman who has been diabetic for 15 years.

Fig.8. Postoperative OCT image of the RNFL thickness in different quadrants of the right eye of a diabetic macular edema patient. These images were taken from a 53-year-old woman who has been diabetic for 15 years.

For the non-injected (control) eyes, the superior quadrant of the RNFL showed a mean increase of 3 microns (SD = 44, 95% CI = -9.6:15.7, p value = 0.626). The inferior quadrant showed a mean increase of 7.3 microns (SD = 45, 95% CI = -5.4:20, p value = 0.256). The nasal quadrant showed a mean increase of 10.4 microns (SD = 48, 95% CI = -3.4:24.1, p value = 0.136). The temporal quadrant showed a mean increase of 1.5 microns (SD = 43, 95% CI = -10.8:13.8, p value = 0.807). The central foveal thickness showed a mean increase of 17.4 microns (SD = 60, 95% CI = 0.215:34.6, p value = 0.047) (**Table 2**).

Table 2. Mean Change in Retinal Nerve Fiber Layer Thickness Before & After Anti-VEGF injections.

Variables	Injected Eyes					Non-Injected Eyes				
	Mean	SD	95% CI		p value	Mean	SD	95 % CI		p value
			lower	upper				lower	upper	
Superior Q	1.2	38.4	-9.7	12.1	0.829	3	44	-9.6	15.7	0.626
Inferior Q	7.5	35.6	-2.6	17.6	0.144	7.3	45	-5.4	20	0.256
Nasal Q	8.3	23	1.8	14.9	0.014	10.4	48	-3.4	24.1	0.136
Temporal Q	4.1	33.2	-5.3	13.6	0.386	1.5	43	-10.8	13.8	0.807

All measurements in microns. CI = Confidence Interval, Q = Quadrant, SD = Standard Deviation.

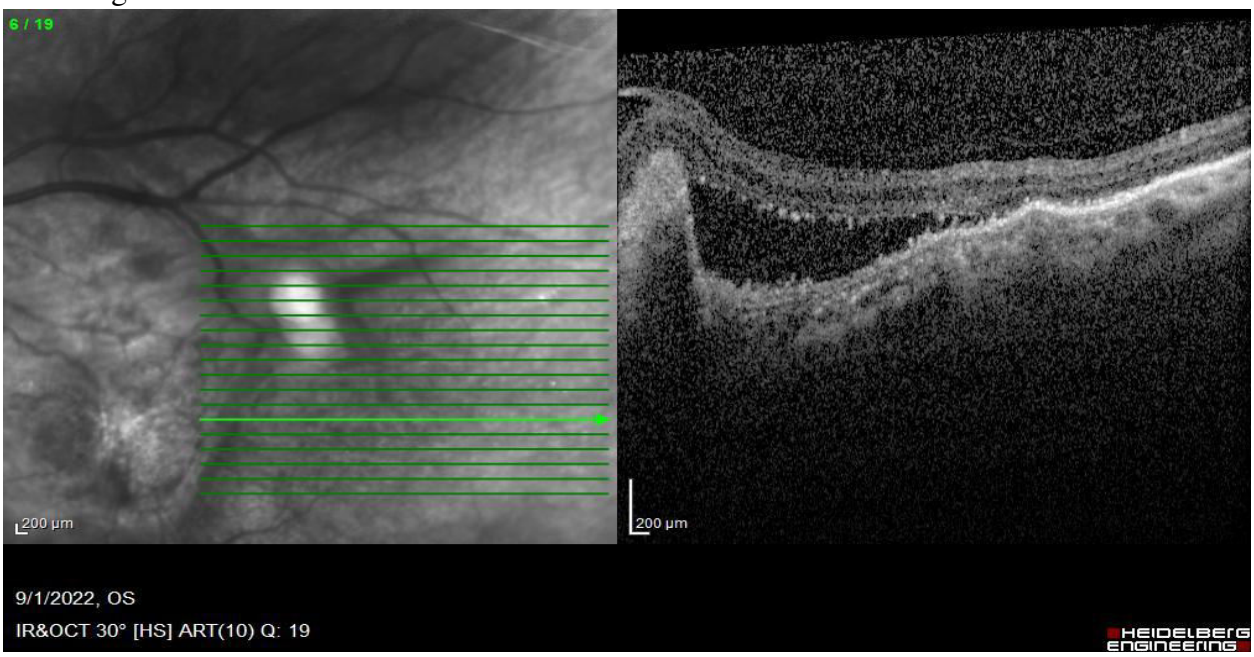
The mean preoperative central foveal thickness of the injected eyes was 400 microns (SD = 141 microns, Range = 189:942 microns) which became 391 microns (SD = 119 microns, Range = 222:745 microns) postoperatively. The mean central foveal thickness of the non-injected (control) eyes at the start of the follow up period was 294 microns (SD = 52 microns, Range = 224:500 microns) which changed to 312 microns (SD = 34 microns, Range = 256:348 microns) at the end of the assessment period of 3 months (**Fig. 9-12**).

Discussion

For years, the effects of anti-VEGF injections on the eye were studied, with their effect on the peripapillary RNFL thickness being the most controversial owing to the different results of different studies conducted on the subject. Furthermore, the majority of literature focused on the effect of anti-VEGF on eyes afflicted with wet or exudative age-related macular degeneration (AMD) and not DME. This study is focused on the effect of anti-VEGF on peripapillary RNFL thickness in eyes affected with DME. Our study found that there was no statistically significant difference between the RNFL thickness pre- and post- injection.

Previous studies found that, at 6 months, the peripapillary RNFL decreased in thickness in eyes affected with DME and treated with anti-VEGF. However, when adjusted for peripapillary retinal thickness, there was no significant change in the peripapillary RNFL thickness. Furthermore, the researchers went on to recommend using this new retinal nerve fiber layer index which corrects for the component of retinal edema in patients with DME (**Yang et al., 2017**). This goes in accordance with the suggestions of other researchers who

speculated that changes in the RNFL thickness in DME is due to retinal changes as a whole and not related to any individual pharmacological therapy (**Prager et al., 2018**).



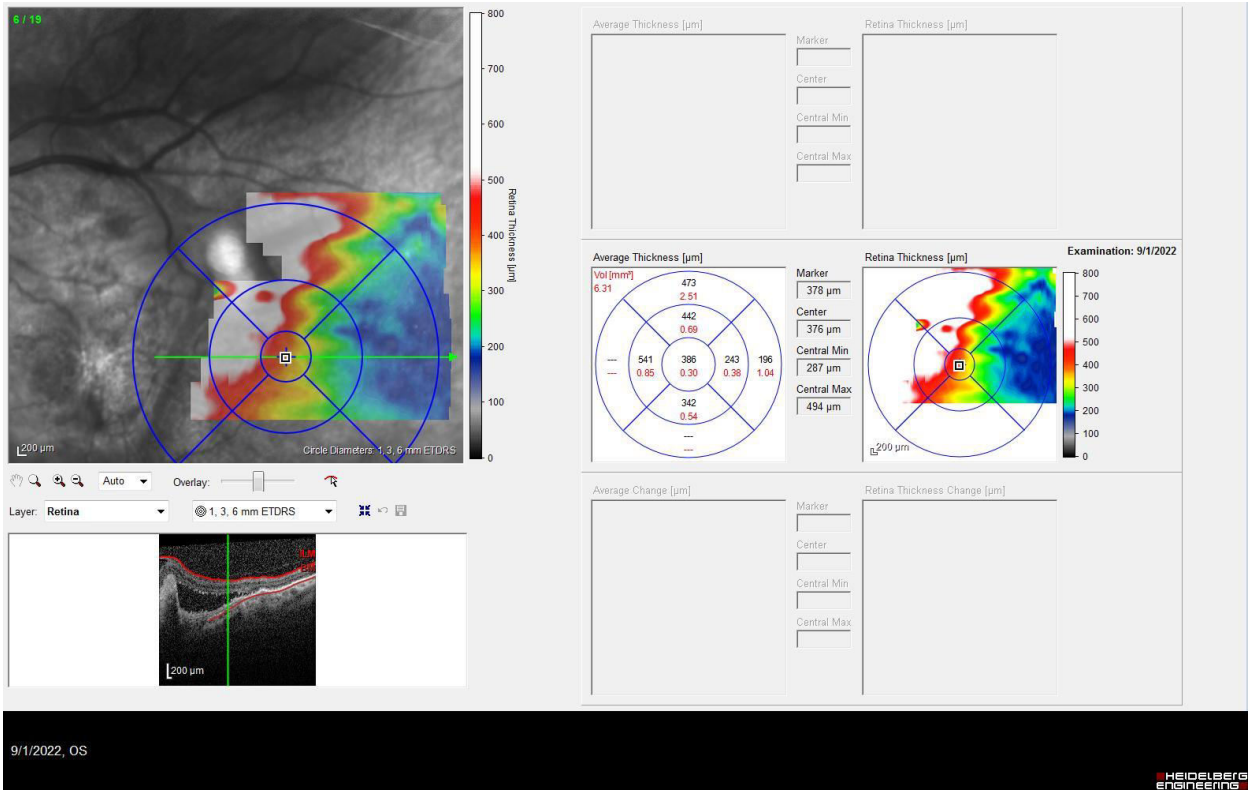


Fig.9. Preoperative Central Foveal Thickness in the left eye of a 75-year-old female patient with DME who had been diabetic for 22 years.

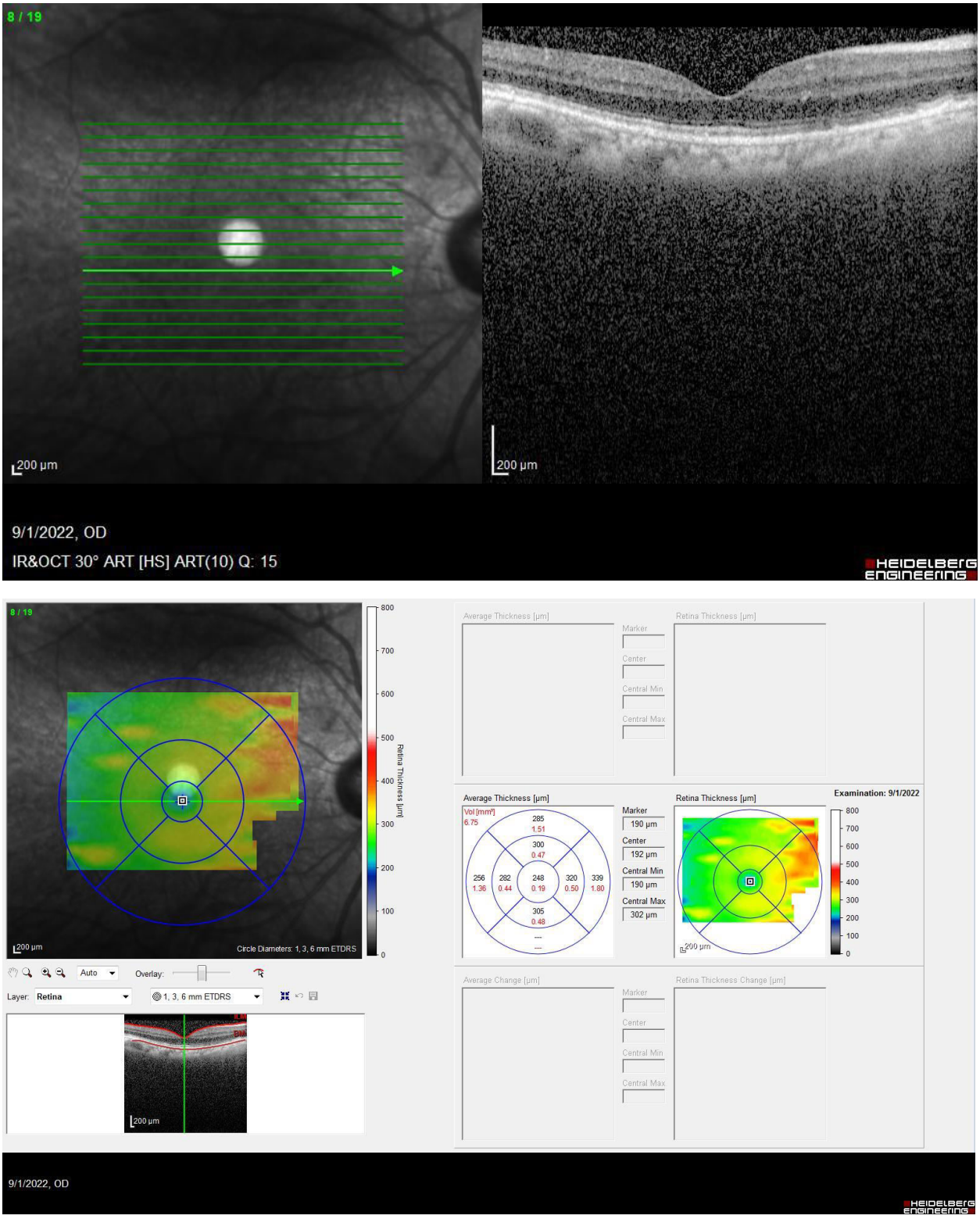


Fig.10. Preoperative Central Foveal Thickness in the right eye of a 75-year-old female patient with DME who had been diabetic for 22 years.

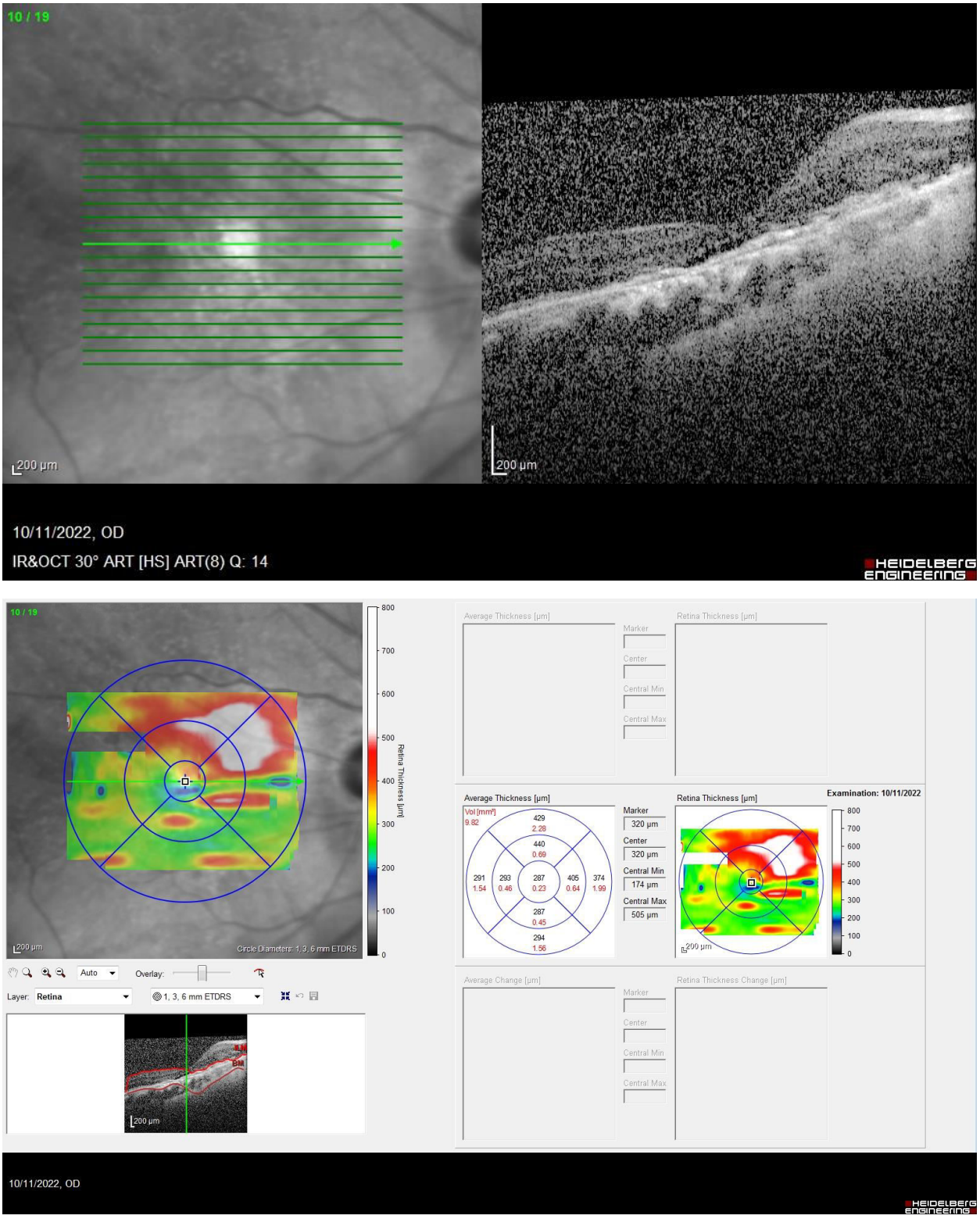


Fig.11. Postoperative Central Foveal Thickness in the right eye of a 75-year-old female patient with DME who had been diabetic for 22 years.

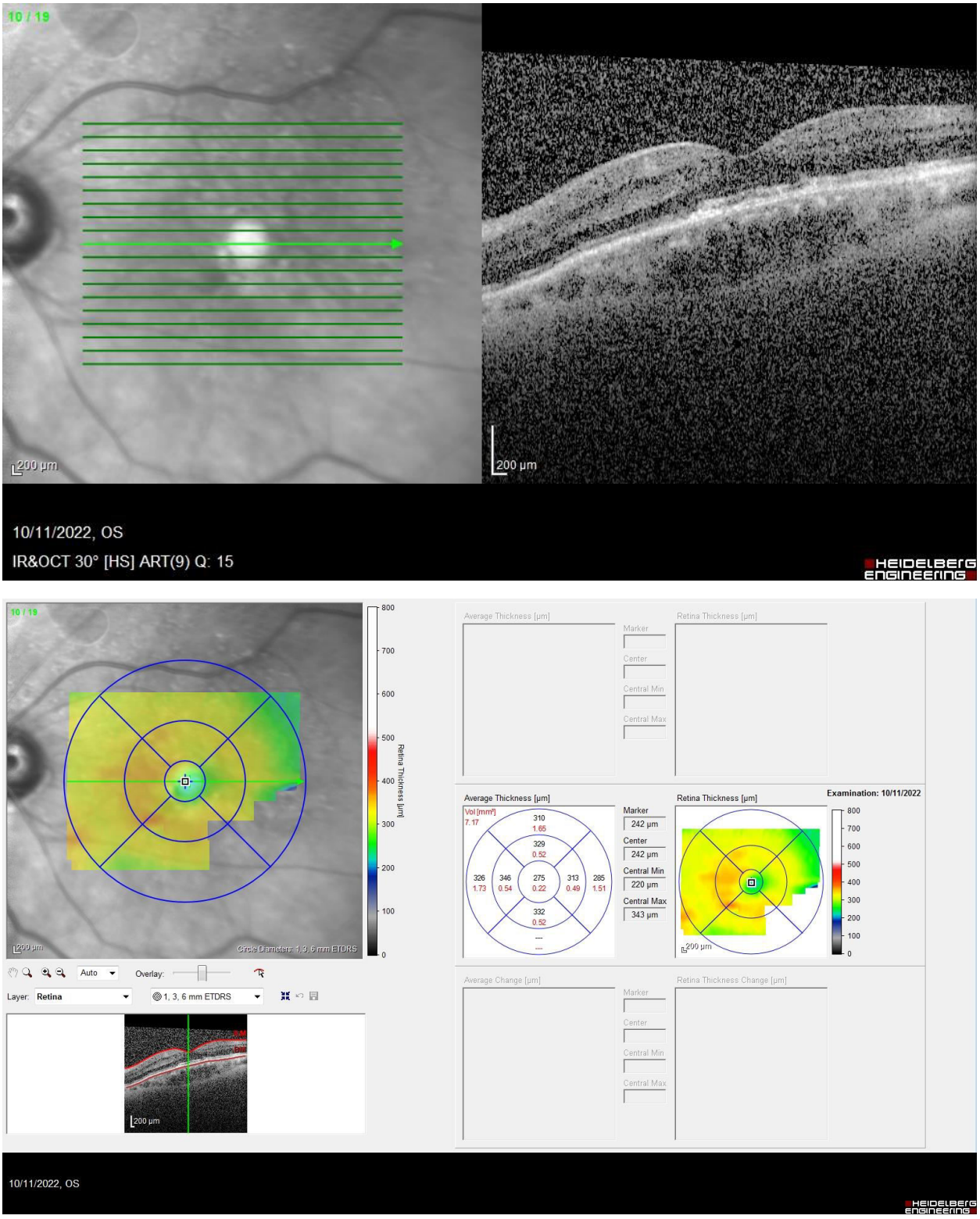


Fig.12. Postoperative Central Foveal Thickness in the left eye of a 75-year-old female patient with DME who had been diabetic for 22 years.

A previous paper found that the RNFL thickness in DME patients were greater than the RNFL thickness in age and diabetes duration matched diabetic retinopathy non-DME patients. They attributed this finding to the retinal edema found in DME patients. However, their analysis was retrospective and all DME patients had had intra-vitreal Bevacizumab injections, thus confounding the effects of the treatment itself on the RNFL thickness in the eyes of those patients (**Hwang et al., 2014**).

When compared to panretinal photocoagualtion, it was found that there's greater RNFL thinning with anti-VEGF therapy than with pan-retinal photocoagulation. They explained that by either a decrease in retinal edema or a loss of ganglion cell layer, which is the origin cell for the RNFL, through interruption of the neuroprotective effect of VEGF (**Jampol et al., 2019**). Both of these theories could explain why the RNFL thickness changed in both the injected and non-injected (control) eyes in our analysis.

Literature also described a thinning of 2 microns in the RNFL thickness in eyes treated with anti-VEGF, but this study had a small sample size of 29 eyes. It also included patients with different retinal conditions such as wet AMD, DME, or retinal venous occlusion (RVO) (**Gómez-Mariscal et al., 2019**).

Futhermore, on examining the literature, there's no relationship between RNFL thickness and anti-VEGF injection regardless of what disease is affecting the eye. It was found that patients with AMD who were put on anti-VEGF treatment go on after 48 months to develop increased thickness in their RNFL temporal quadrant while all other quadrants remained the same (**Yau et al., 2015**). It was also found that patients with AMD who received anti-VEGF injections were subject to thinning of their RNFL, probably owing to the fact that the researchers in this study included patients with recent diagnosis of wet AMD, hence their baseline RNFL measurements were probably artificially elevated, and their decrease was a return to baseline (**Martinez-de-la-Casa et al., 2012**).

Researchers found that there was no significant difference in the thickness of RNFL before and after anti-VEGF injections in patients with AMD and confirmed or suspected glaucoma (**Swaminathan et al., 2021**). This agrees with the results of Kopic et al. 2017 who found that at 12 months there was no difference in RNFL thickness in eyes that had glaucoma and AMD and were treated with anti-VEGF but there was thinning in RNFL in eyes that had glaucoma and DME (**Kopic et al., 2017**).

Almost all of the literature found that in eyes affected with wet AMD and treated with repeated anti-VEGF agents, there was no difference in the thickness of RNFL (**Horsley at al., 2010; Entezari et al., 2014; Shin et al., 2014; Sobacı et al., 2013; Parlak et al., 2015; Demirel et al., 2015; El-Ashry et al., 2015; Jo et al., 2016; Beck et al., 2016; Valverde-Megías et al., 2019; Demir et al., 2021; Lüke et al., 2022**). It was also further emphasized that finding by providing a comparison between Ranibizumab and Bevacizumab in the treatment of wet AMD, and found that neither of those anti-VEGF agents had

an effect on the thickness of the peripapillary RNFL (**Sobacı et al., 2013**).

The limitations of our study include a low statistical significance to the changes detected in RNFL thickness, probably owing to a reduced magnitude of effect rather than a small sample size, owing to the great number of studies that detected no relationship between RNFL thickness and anti-VEGF injections, and also owing to the fact that our sample size falls on the greater edge of the spectrum of sample sizes dedicated to studies in this regard.

Conclusion

There is no statistically significant correlation between intra-vitreal injections of Ranibizumab and the Retinal Nerve Fiber Layer thickness.

Declarations

Ethical approval: The current study has been approved by the Ethics Committee of Faculty of Medicine, South Valley University, Qena, Egypt and the ethical approval number is SVU-MED-OPH026-1-22-6-409.

Consent to participate Patients signed consent to participate in this research.

Conflict of interest: The authors declare no competing interests.

Data availability: Data are available from the first author upon request.

Funding: No funding was received.

Authors' Contribution: All authors participated in study conception and design. Patient collection was done by Amr K. Hassan. Data analysis was done by Amr K. Hassan. Amr K. Hassan wrote the first draft of the manuscript. Ahmad H. Aldghaimy, Ahmad A. Mohalhal, and Osama A. Ali revised and edited the manuscript. All authors read and approved the final manuscript.

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