Aus der Klinik für Augenheilkunde
(Prof. Dr. med. H. Hoerauf)
der Medizinischen Fakultät der Universität Göttingen

Funktionelle Veränderungen bei operativer Behandlung der epiretinalen Gliose

(Functional changes in surgical treatment of epiretinal membrane)

INAUGURAL-DISSERTATION
zur Erlangung des Doktorgrades
der Medizinischen Fakultät der
Georg-August-Universität zu Göttingen

vorgelegt von
Mohammed Haitham Khattab
aus
Nineveh, Irak

Göttingen 2020

Dekan:	Prof. Dr. med. W. Brück

Betreuungsausschuss

Betreuer/in:	Prof. Dr. med. N. Feltgen
Ko-Betreuer/in:	Prof. Dr. T. Gollisch

Prüfungskommission

Referent/in:	Prof. Dr. N. Feltgen
Ko-Referent/in:	Prof. Dr. T. Gollisch
Drittreferent/in:	Prof. Dr. T. Meyer

Datum der mündlichen Prüfung: 25.03.2021

Hiermit erkläre ich, die Dissertation mit dem Titel "Funktionelle Veränderungen bei operativer Behandlung der epiretinalen Gliose" eigenständig angefertigt und keine anderen als die von mir angegebenen Quellen und Hilfsmittel verwendet zu haben.

Göttingen, den 27.08.2020 ……

(Unterschrift)

List of Figures

List of Tables

List of Abbreviations

AMD®	A Metamorphopsia Detector
CFT	Central Foveal Thickness
Dpt	Diopter
ERM	Epiretinal Membrane
ETDRS	Early Treatment Diabetic Retinopathy Study
ILM	Internal Limiting Membrane
IOL	Intraocular Lens
LogMAR	Logarithm of Minimum Angle of Resolution
Meta-Index Score	Metamorphopsia Index Score
mmHg	mm of Mercury
NEI VFQ-25	National Eye Institute Visual Functioning Questionnaire - 25
OCT	Optical Coherence Tomography
PPV	Pars Plana Vitrectomy
PVD	Posterior Vitreous Detachment
RAND	Research and Development Corporation
RPE	Retinal Pigment Epithelium

1 Introduction

1.1 Epiretinal Membrane

Iwanoff first described an epiretinal membrane (ERM) in 1865 (Iwanoff 1865). ERM is a contractile fibrocellular, transparent, avascular membrane, composed of an extracellular matrix, which grows on the inner surface of the retina and covers the internal limiting membrane (ILM) (Johnson and Johnson 2004). ERM is shown in Figure 1.

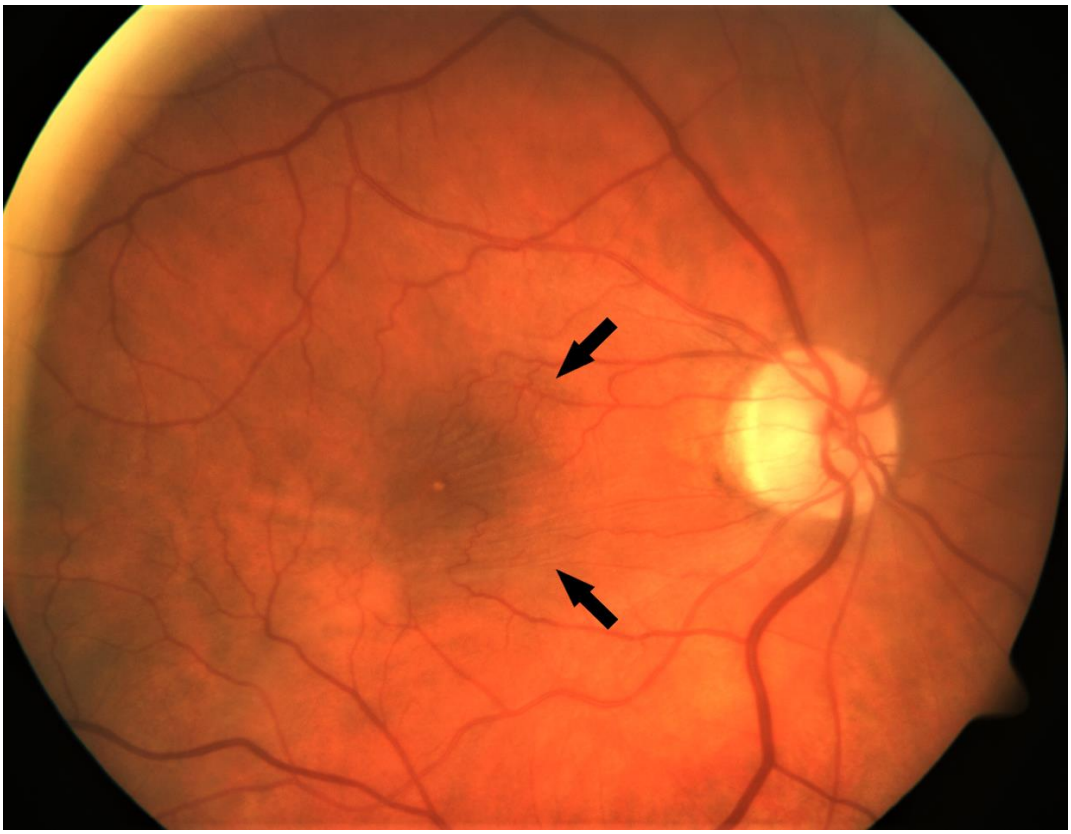


Figure 1: Fundus photograph of the right eye. It shows retinal vascular distortion produced by an epiretinal membrane (arrows). (Courtesy of Prof. Dr. Nicolas Feltgen)

ERM could be classified into primary (or idiopathic) ERM and secondary ERM. Primary ERM may occur in healthy eyes, whereas secondary ERM may occur as a result of different ocular disorders such as retinal vascular diseases, retinal breaks, rhegmatogenous retinal detachment, blunt or penetrating trauma. Other common synonyms of ERM are macular pucker, cellophane maculopathy, and premacular gliosis.

1.1.1 Epidemiology

The idiopathic ERM is more common than the secondary ERM. Its prevalence varies according to age group. The idiopathic ERM presents in about 5-7 % of all people over the age of 40, of which 15-20 % is bilateral (Pearlstone 1985; McCarty et al. 2005), whereas the prevalence for people above the age of 70 is about 12 % (Mitchell et al. 1997; Schuster et al. 2020). Young patients are occasionally affected (Barr and Michels 1982). ERMs were also identified in approximately 6 % of eyes examined at autopsy (Pearlstone 1985). According to many large series, the incidence of idiopathic ERM is higher in females than in males (Margherio et al. 1985; Pesin et al. 1991; Klein et al. 1994).

The incidence of secondary ERMs is 1-2 % following prophylactic laser therapy of peripheral retinal tears (Wilkinson et al. 1997) and 4-8 % following surgical repair of rhegmatogenous retinal detachment (Uemura et al. 1992).

1.1.2 Pathogenesis

Posterior vitreous detachment (PVD) has been heavily linked to the formation of the idiopathic ERM. PVD presents in 80-95 % of all eyes with idiopathic ERM (Wise 1975).

The cellular origin of ERMs is still under debate. Recent studies suggest that the proliferation of neural cells such as hyalocytes, glial cells, or retinal pigment epithelium (RPE) on the inner retinal surface results in ERM formation (Bu et al. 2014; Tsilimbaris et al. 2016). Furthermore, schisis of the posterior vitreous may leave portions of the vitreous adhered to the macula allowing hyalocytes to proliferate on posterior cortical vitreous remnants and glial cells to proliferate along the retinal surface (Kampik et al. 1980).

Secondary ERMs occur following retinal detachment and retinal bleeding, as well as secondary to abnormal vitreoretinal adhesions and inflammation. The following factors increase the risk of ERM development after retinal detachment surgery: older age, macula-off retinal detachment, large retinal breaks, preoperative vitreous hemorrhage, multiple operations, preoperative signs of proliferative vitreoretinopathy, and intraoperative use of cryotherapy (Uemura et al. 1992; Wilkinson et al. 1997).

Snead et al. (2008) examined ERMs in surgically removed specimens to find out the principal cell population that led to the formation of different types of ERMs; they found that laminocytes were the only cells present in almost all patients with idiopathic ERMs (Snead et al. 2008). Furthermore, in the case of ERM secondary to retinal tears, not only laminocytes but also groups of RPE cells were found. However, in patients with proliferative diabetic

retinopathy, capillaries, hyaline derived tissue, and groups of RPE cells were found in the absence of laminocytes (ibid.).
Also, recent studies have tried to illuminate the potential contribution of cytokines and growth factors such as nerve, glial cell line-derived, and basic fibroblast growth factors, since they may relate to ERM formation (Harada et al. 2006; Minchiotti et al. 2008; Iannetti et al. 2011).

1.1.3 Clinical Features

ERMs are present in most cases with slight visual symptoms. The severity of symptoms depends on the membrane's transparency, thickness, location, and the degree of retinal distortion. In the severe form, patients present with reduced and distorted vision, metamorphopsia, and nonspecific visual disturbances. Micropsia and monocular diplopia have also been reported in patients with ERMs (Wiznia 1982). ERMs that caused noticeable visual disturbances are located mainly in the central macula, more specifically in the fovea.
The decrease in vision may be due to the distortion of the inner retinal surface, the filtering effect of the membranes that prevent incoming light focus from spreading and reaching the light-sensitive cells in the retina, and macular edema.
ERMs tend to remain stable or show limited progression by most patients experiencing mild symptoms. According to Blue Mountains Eye Study, which follows up on cases with ERMs for five-years, ERM progression was reported in almost one third of cases, while stability was encountered in about 40 % of cases, and regression was seen in 25.7 % of cases (Fraser-Bell et al. 2003).

1.1.4 Diagnosis

The diagnosis of the ERM is based on clinical finding, mainly on a dilated fundus examination or fundus photograph. The clinical finding depends on the ERM's severity. In its mild stage, ERM appears as a slight shining light reflex on the posterior pole of the retina with retinal vasculature distortion. In severe cases, wrinkling of the retinal surface, intraretinal bleeding, vascular distortion (Figure 2), macular cystoid edema, as well as macular pseudohole may be noticed during the fundus examination.

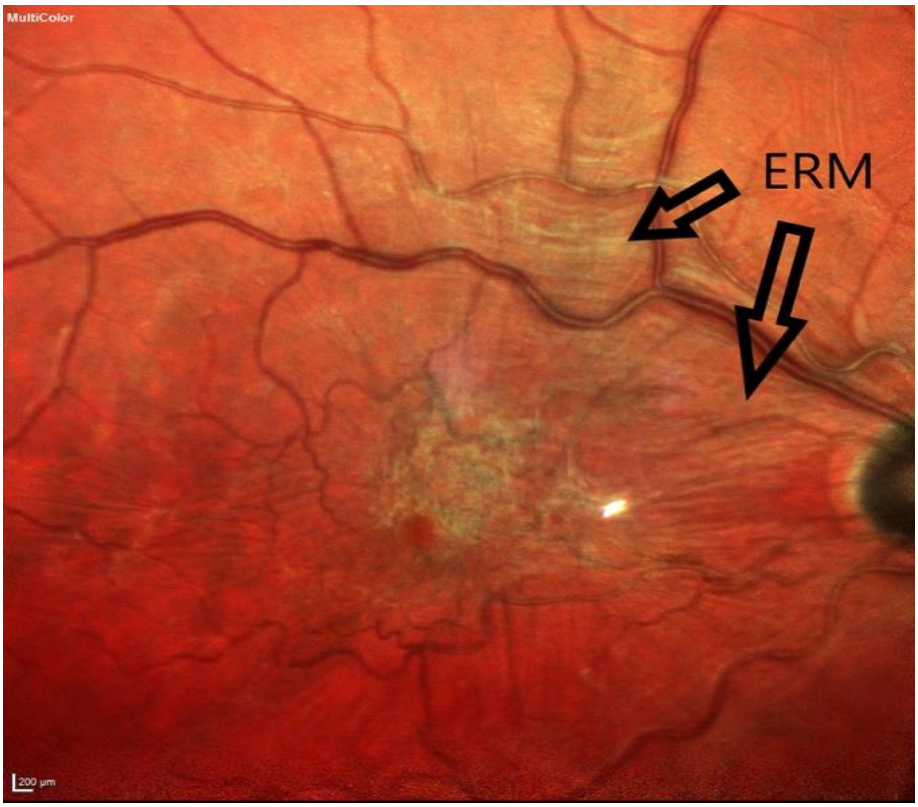


Figure 2: Fundus reflectance multicolor image using scanning laser ophthalmoscope. It shows an epiretinal membrane in the central macula with radiating striae and significant retinal vasculature distortion. (Courtesy of Prof. Dr. Nicolas Feltgen)

In order to diagnose ERM, the patient should undergo a complete examination to rule out other causative factors such as retinal breaks, detachments, trauma, retinal vascular, inflammatory diseases, and a history of previous retinal surgery.

Optical Coherence Tomography (OCT) is considered nowadays to be the definitive diagnostic tool for different retinal diseases. OCT is a non-invasive imaging tool that applies low-coherence interferometry to capture micrometer-resolution images (Huang et al. 1991). A sample of labeled OCT scan of a normal retina is shown in Figure 3.

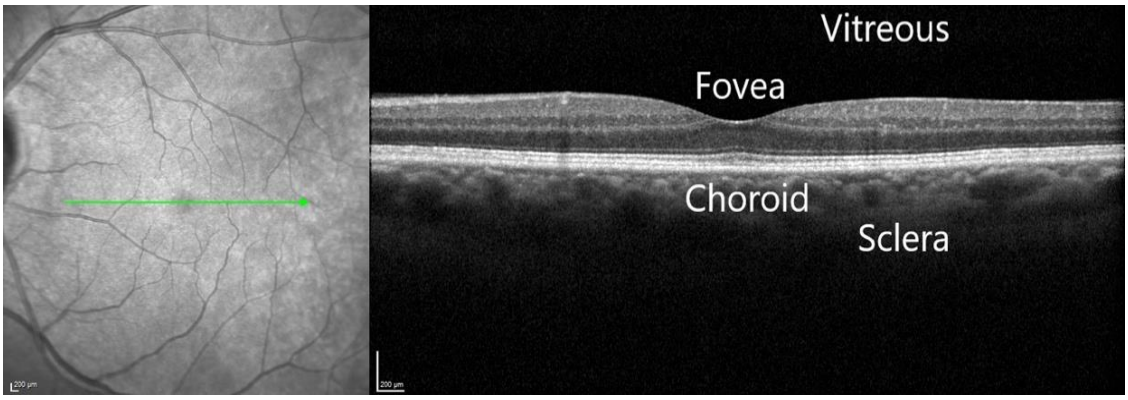


Figure 3: Sample labeled OCT scan of a normal retina.
(Courtesy of Prof. Dr. Nicolas Feltgen)

Moreover, using OCT cross-sectional images, a qualitative and quantitative analysis of the retina can be obtained, as illustrated in Figure 4.

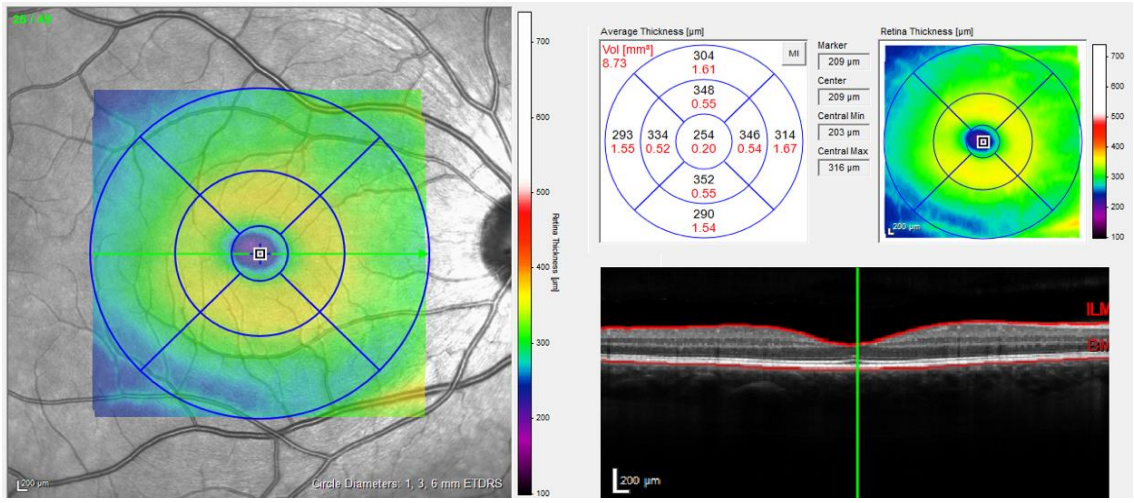


Figure 4: Quantitative measurements of a normal retinal using OCT. The central foveal thickness (CFT), total foveal thickness, and macular volume are 209 µm, 254 µm, and 8.73 mm^3, respectively. (Courtesy of Prof. Dr. Nicolas Feltgen)

The most common OCT findings in ERMs are a dense epiretinal reflective layer, retinal thickening, and loss of the normal retinal contour, which are shown in Figure 5. Occasionally cystic macular edema is seen in OCT images of ERMs, and sometimes a pseudohole may appear in the central macula (Figure 6).

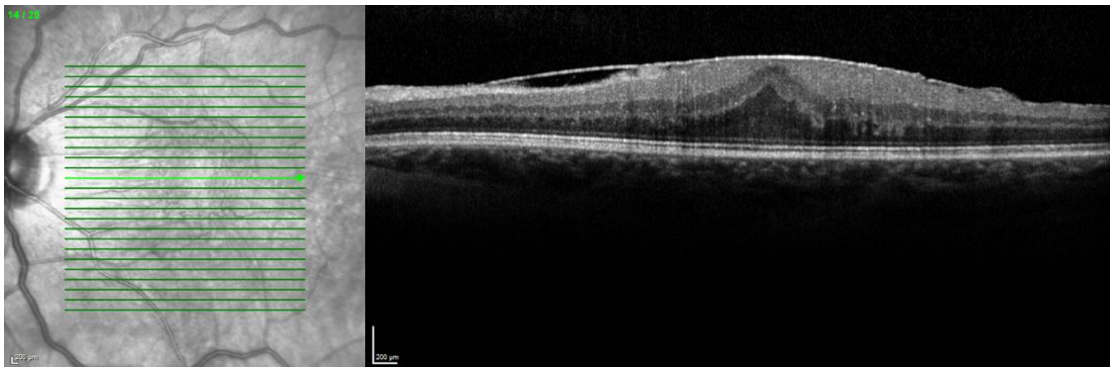


Figure 5: OCT scan through the fovea. It shows a dense epiretinal reflective layer, retinal thickening, and loss of the normal retinal contour. (Courtesy of Prof. Dr. Nicolas Feltgen)

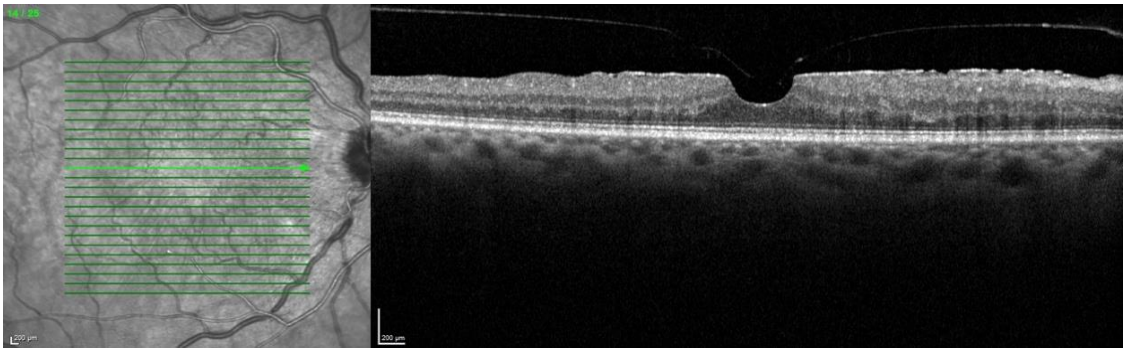


Figure 6: OCT scan showing a macular pseudohole forming by an ERM.
(Courtesy of Prof. Dr. Nicolas Feltgen)

OCT is also a very helpful device in preoperative evaluation of each patient and postoperative follow-up. In addition, fluorescein angiography test could serve as an ancillary diagnostic test in patients with ERM, which can demonstrate a macula edema, or show staining of the optic nerve. Gass proposed a grading system to differentiate ERMs based on biomicroscopic findings (Agarwal 2011). Grade 0 membranes are also known as cellophane maculopathy. These membranes are translucent and do not cause any retinal or visual distortion; therefore, cellophane maculopathy can be an accidental finding during a regular ophthalmic examination.

Grade 1 membranes are also known as crinkled cellophane maculopathy. These membranes cause an irregular wrinkling of the innermost layer of the retina due to their inherent contractile properties. These membranes cause distortion of vessels around the macula.

Grade 2 membranes are also known as macular pucker. These membranes are thick and opaque. They cause extreme retinal distortion and are often associated with cystic macular edema, exudates, and rarely with intraretinal hemorrhages. Therefore, a diagnosis of macular pucker is an indication of the surgical removal of the membrane.

1.1.5 Treatment

The ERM can be surgically removed in order to reduce metamorphopsia and improve visual acuity. However, for asymptomatic patients with ERMs or for patients with good vision, the intervention is usually not necessary. Instead, these patients should be monitored periodically and, in rare cases, an ERM may detach spontaneously from the retinal surface which leads to concomitant improvement in vision and symptoms (Yanoff and Duker 2018).
Although the operation may also be offered for patients with moderate to severe metamorphopsia despite the good visual acuity, it is important to put in mind that performing surgery in such cases bears to some extent raised hazards. Moreover, the surgery may not improve the visual acuity significantly, and may lead to unsatisfied patients, mainly because there is no significant improvement in vision. After all, the final decision to recommend surgery should be based on patients' needs and symptoms.

1.1.6 Pars Plana Vitrectomy (PPV)

PPV surgical techniques are used in order to remove the vitreous gel. After this, the extent of the ERM and ILM can be identified using different types of dyes such as brilliant blue, trypan blue, or indocyanine green, followed by elevating the ERM with vitreoretinal forceps. After that, the membrane is typically peeled as a single piece from the retina. This operation takes between 30 to 45 minutes. Preoperative and postoperative OCT pictures of one of the patients with ERM are shown in Figure 7.

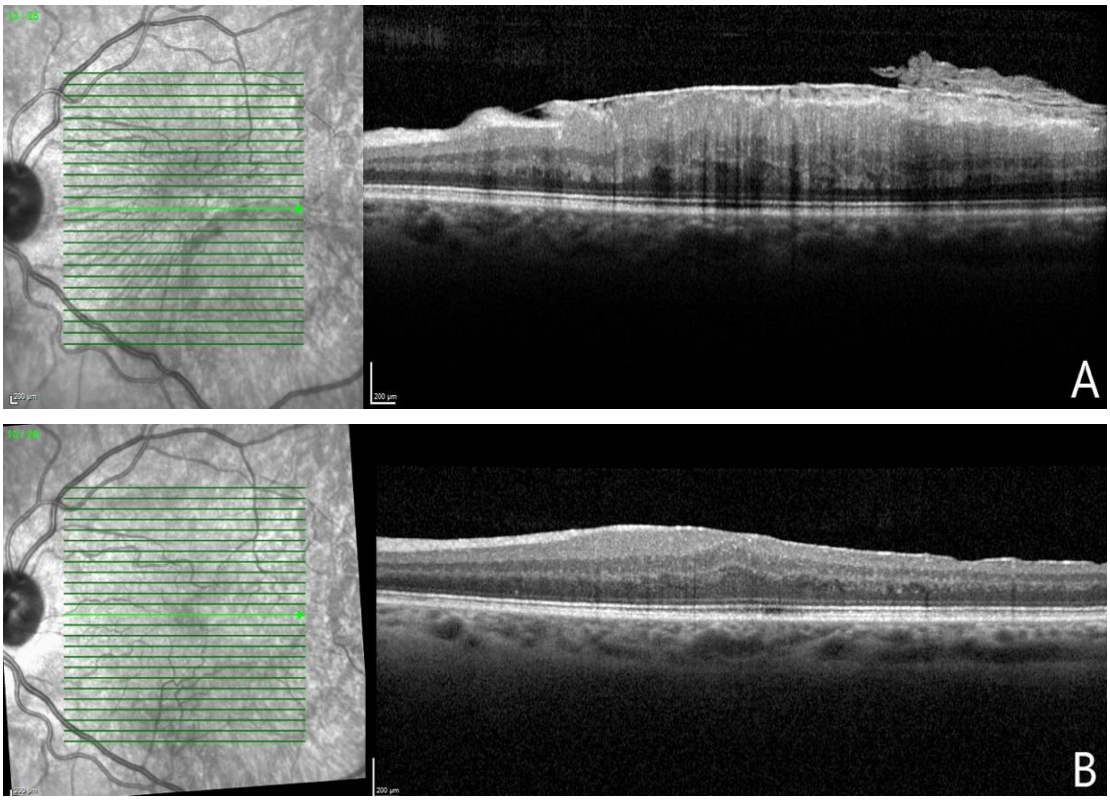


Figure 7: Preoperative and postoperative OCT pictures of a patient with ERM, who underwent PPV and ERM peeling. (A) is a preoperative OCT, showing ERM covering the entire fovea with a significant increase in retinal thickness; (B) is a postoperative OCT, showing the disappearance of ERM with a remarkable decrease in the retinal thickness. (Courtesy of Prof. Dr. Nicolas Feltgen)

Until the 1960s, surgical procedures on the vitreous body were avoided since the complications of vitreous loss often could not be controlled. After the introduction of PPV by Robert Machemer in the early 1970s, this surgical technique has been improved both in terms of instruments and in terms of indications (Machemer et al. 1972).

First, access to the vitreous cavity was gained by opening the conjunctiva via vertical sclerotomies using a 20-gauge instrument system (0.89mm diameter). Both the sclerotomies and the conjunctiva had to be sutured after surgery. Fujii et al. (2002) introduced a new 25-gauge (0.5mm diameter) vitrectomy surgical system. This system was characterized by sutureless, transconjunctival access, as well as, the use of cannulas. The main disadvantage of this system was its low instrument stability, a significantly longer vitrectomy period, and limited use of silicone oil. This urged the development of the 23-gauge vitrectomy surgical system (0.64mm diameter) by Eckardt in 2004 (Eckardt 2005). This system combines the advantages of traditional 20-gauge vitrectomy with those of 25-gauge sutureless sclerotomy and is, therefore,

a major advance in the field of vitreous and retinal surgery. The PPV is now one of the standard microsurgical procedures and is continuously being developed.
The most frequent surgical complication is the development of cataracts in phakic eyes, which occurs in 60–70 % of cases within two years (Cherfan et al. 1991; Pesin et al. 1991). Other less frequent complications include rhegmatogenous retinal detachment, peripheral retinal breaks, endophthalmitis, and light-induced phototoxic maculopathy. Late postoperative complications include the recurrence of symptomatic epiretinal tissue, which occurs in approximately 5 % of cases (Margherio et al. 1985; Pesin et al. 1991).

1.2 Aims and Objectives

Despite all the innovations in the field of vitreoretinal surgery, currently, there is not any possibility to capture the extent of the distortion, while other subjective testing methods such as visual acuity and central visual field, can be quantified. Therefore, the aim of the study is to measure functional changes after surgical treatment of epiretinal gliosis objectively, with the focus on the following objectives:
(1) To quantify the degree and the severity of metamorphopsia in patients with ERM pre- and postoperatively using a computer-based test (A Metamorphopsia Detector®, AMD®).
(2) To compare the subjective complaints of the patients and the objective findings pre- and postoperatively. Table 1 illustrates the primary and secondary objectives of the study and their measuring techniques.

Table 1: Overview of Primary and Secondary Objectives and Their Measuring Techniques.

Primary objectives	**Measuring techniques**
Quantify the degree of metamorphopsia using a computer-based test (A Metamorphopsia Detector®)	Non-contact metamorphopsia test
Secondary objectives	**Measuring techniques**
Best-refracted Snellen's vision, Logarithm of Minimum Angle of Resolution (logMAR), using Early Treatment Diabetic Retinopathy Study chart (ETDRS)	Visual acuity test
Retinal thickness of the macular region parameters: total foveal thickness, macular volume, and central foveal thickness (CFT)	Non-contact optical coherence tomography (OCT)
Corneal astigmatism	Non-contact corneal topography measurement
Complications e.g. macular edema, recurrence, cataract, retinal detachment, endophthalmitis	
Patient satisfaction	NEI-VFQ-25 questionnaire on eyesight

2 Patients and Methods

This clinical study was reviewed and permitted by the Ethics Committee at University Medical Centre Goettingen. It was conducted according to the doctrines of the Declaration of Helsinki. Furthermore, a written informed consent was collected in each case before each study-related examination.

2.1 Sample Design

In this prospective, monocentric study, 37 eyes of 37 patients with ERM and an indication of surgical treatment were included. The study was carried out as a part of the usual outpatient and inpatient treatment. The patients were recruited exclusively at the Department of Ophthalmology of University Medical Centre Goettingen between August 2016 and October 2018. For these patients, the usual surgical procedure – PPV with removal of the ERM and the ILM – have been performed. Patient recruitment was conducted in accordance with the inclusion and exclusion criteria, the study protocol, as well as the consent protocols.

Two retina specialists (Prof. Dr. N. Feltgen and Dr. S. Bemme) established the diagnosis of ERMs based on dilated fundus examinations and reviewing OCT images.

After the surgery was indicated in the outpatient preliminary examination, the patients were informed about the study and were given the study documents, as well as assess for the preliminary willingness to participate in the study. Regardless of their decision, the surgery was performed on the patients within four to eight weeks, with a hospitalization. On the day of admission, patients' consent to participate in the study was documented through a written document to ensure that they have sufficient time to consider the study content and participation in the study. If a patient provided written consent to participate in the study, the AMD® test, a computer-based evaluation, was performed in addition to the routine examination, and the patients were also interviewed about their complaints using the standardized and customary National Eye Institute Visual Functioning Questionnaire (NEI VFQ-25).

The surgery and inpatient stay did not differ from the usual procedure in clinical practice. Patients were hospitalized on a preoperative day and usually left the clinic three days later. The postoperative control after 42 days also corresponded to the usual procedure. However, further control after six months was only required in the context of the study. This additional visit, therefore, eliminated the usual control by the established ophthalmic colleagues.

The study took approximately 2.5 years with estimated recruitment. The first surgery was made on 19th August 2016 and the last one, as part of the study, on 12th April 2018.

2.1.1 Inclusion and Exclusion Criteria

The inclusion and the exclusion criteria for the recruitment of patients in the study are illustrate in Table 2.

Table 2: Overview of Inclusion and Exclusion Criteria.

Inclusion Criteria	Exclusion Criteria
Metamorphopsia	Patients with macular dystrophy
Surgical indication due to epiretinal gliosis	Previous eye operations with consecutive reduction of visual acuity or visual impairment (e.g., macular degeneration, retinal detachment, post macular surgery
Best-corrected decimal visual acuity equal to or more than 0.2	Best-corrected decimal visual acuity of less than 0.2
Age ≥ 18 year old, gender-independent	Age < 18 years
Written consent	Lack of written consent
Ability to participate in follow-up examinations	Bedridden patients for whom the measurements cannot be performed
	Pregnancy and breastfeeding period
	Visually relevant eye diseases, e.g., vitreous opacities and tractions, corneal disorders, advanced macular diseases associated with metamorphopsia (e.g., macular foramen, macular degeneration, diabetic maculopathy, uveitis, advanced glaucoma, retinal detachment with macular involvement)

2.2 Data Collection

2.2.1 Medical History

The medical history of the patients was obtained during baseline and admission examinations.

2.2.2 Ophthalmological Clinical Examination

The patients were examined one day before their operation, as well as 42 days and six months after surgery. For this purpose, the patient received scheduled representation appointments in accordance with the examination intervals. The examinations then took place on an outpatient basis and were organized in a way that the waiting times for the patients are kept as short as possible. A control group without therapy was omitted for ethical reasons because the spontaneous course is known and unfavorable.

Each patient underwent a comprehensive ophthalmological clinical examination, including routine examinations, which are carried out for all patients, and study-specific examinations which were carried out only for recruited patients.

Routine examinations include the following procedures:

- Autorefractometer and best-corrected visual acuity using a Snellen test;
- Measurement of the length of the eye and lens power using intraocular lens master device (IOL-Master®, Zeiss);
- Complete ophthalmic examination including slit-lamp biomicroscopy, indirect ophthalmoscopy, applanation tonometry, and dilated funduscopy;
- Measurement of retinal thickness using OCT (Spectralis OCT Heidelberg Engineering, Heidelberg, Germany).

Study-specific examinations include the following procedures:

- Metamorphopsia assessment using a computer-based test (A Metamorphopsia Detector®, AMD®), reading glasses, and best remote correction plus one diopter;
- Measuring the corneal astigmatism using corneal topography;
- NEI VFQ-25 questionnaire.

NEI VFQ-25 questionnaire is a vision-targeted questionnaire, which was developed at Research and Development Corporation (RAND) and sponsored by the National Eye Institute, and allowed the interviewing of patients regarding the influence of chronic eye diseases on their health-related quality of life (Mangione et al. 2001). The measurement of health-related quality of life during clinical studies helps to assess the result of treatment and intervention (ibid.).

An overall composite score was calculated before and after an intervention. The possible range of the score is 0-100. The complete questionnaire is available on the National Eye Institute website[1].

The detailed classification and schedule of the ophthalmological clinical examinations during the study are outlined in Table 3. Comparison of the results of the AMD® test, as well as results of the best-refracted vision Snellen test and OCT, are the most important methods of measurement that allow the determination of objective data.

Table 3: Classification and Schedule of Ophthalmological Clinical Examinations During the Study.

Preliminary examination before surgery ▼	
Routine examination	**Study-specific examination**
Autorefractometer and best-refracted vision Snellen test (ETDRS chart) Complete ophthalmic examination Optical coherence tomography (OCT) IOL-Master®	Metamorphopsia Detector test® Corneal topography NEI VFQ-25 questionnaire
▼ **Post-surgery routine examination I** **(42 days after surgery)**	▼ **Post-surgery study-specific examination I** **(42 days after surgery)**
Autorefractometer and best-refracted vision Snellen test (ETDRS chart) Complete ophthalmic examination Optical coherence tomography (OCT)	Metamorphopsia Detector test® Corneal topography
	Post-surgery study-specific examination II **(6 months after surgery)** ▼ Autorefractometer and best-refracted vision Snellen test (ETDRS chart) Complete ophthalmic examination Optical coherence tomography (OCT) Metamorphopsia Detector test® Corneal topography NEI VFQ-25 questionnaire

[1] https://nei.nih.gov/catalog/visual-function-questionnaire-25. Accessed 28.12.2018

2.2.3 Measurement of Retinal Changes with OCT

The complete macular area of both eyes was inspected with spectralis-OCT to confirm the presence of ERM and to detect any other clinical features that are often associated with it, including cystoid spaces, vitreomacular traction, and pseudohole. Quantitative measurements of ERM were also performed by OCT. The central foveal thickness (CFT), macular volume, and total foveal thickness were acquired through the OCT scan. The results for one of the patients are shown in Figure 8.

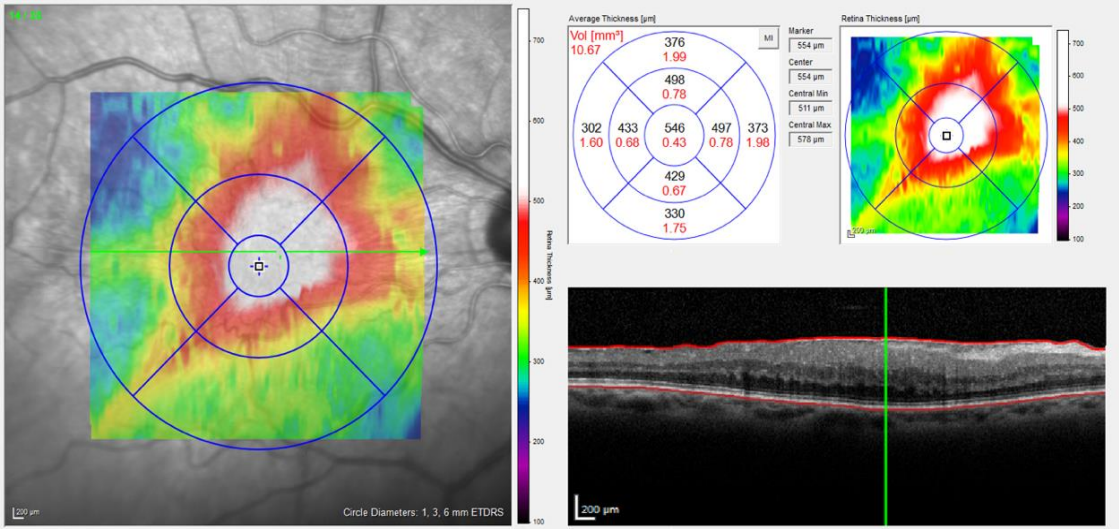


Figure 8: Quantitative measurements of retinal changes in a patient with ERM using OCT. CFT, total foveal thickness, and macular volume are 554 µm, 546 µm, and 10.67 mm^3, respectively. (Courtesy of Prof. Dr. Nicolas Feltgen)

2.2.4 Metamorphopsia Evaluation

In 1947, Marc Amsler, a Swiss ophthalmologist, described the Amsler grid – a black card with a white 10-cm squire on it, which is subdivided by vertical and horizontal parallel lines – as a method of examining qualitative disturbances in patients' vision and diagnosing the metamorphopsia (Amsler 1947; Amsler 1953). It was also reported that the Amsler test has a high sensitivity of 98.5 % in detecting metamorphopsia in patients with EMRs (Bouwens and Van Meurs 2003).

Claessens and Krüger (2015) presented a quantitative measurement of metamorphopsia using the Amsler grid. They developed a software *"AMD® – A Metamorphopsia Detector®,"* which allows to detect, measure, and control the degree of the metamorphopsia.

Compared to the Amsler grid, a computer-based test allows one to not only diagnose the metamorphopsia but also quantify the metamorphopsia by letting the patient straighten the line so that the degree and dimension of the distorted line can be then transformed into indices (ibid.). It also allows follow-ups.

Depending on the size of the screen, the program calculates the required distance of the subject from the screen to allow a comparable measurement. This distance is calculated so that the patient sees the lines at a distance of one degree to ensure the interoperability of the test. The patient receives the following brief written instructions about the test procedure that they can read at home in advance:

> *"Your task is to set the lines so that all lines appear straight. To do this, you should click on the lines that you want to see (check "horizontal lines" or 'vertical lines'). Then, one eye is covered with an eye patch. With the other eye, you should now fix the fixation point in the middle of the field. You should then move the mouse pointer to the position you want to change. You have now different options to change the lines.*
>
> *By using a mouse wheel – You should move the mouse to the place you want to change and then turn the mouse wheel.*
>
> *By mouse click – You should move first the mouse pointer to the place where you want to change the line. By clicking the line, it will be distorted to the current mouse position".*

The screenshot of the test can be seen in Figure 9.

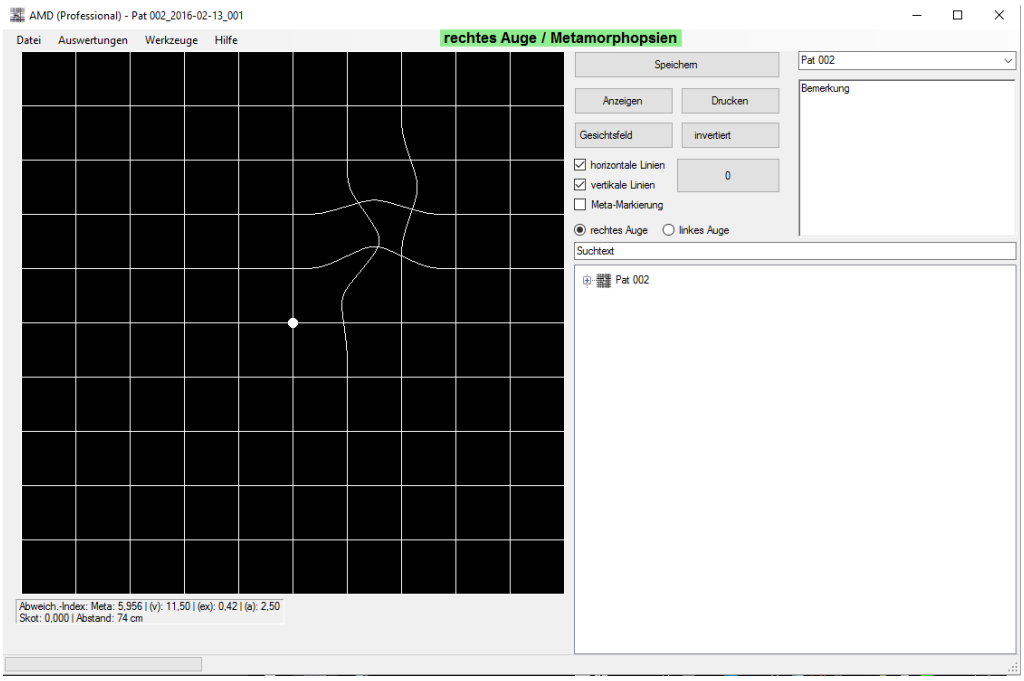


Figure 9: Screenshot of "A Metamorphopsia Detector®" test.

(Courtesy of Prof. Dr. Nicolas Feltgen)

Using the rolling wheel, the patient can distort the line at the point where the mouse pointer is located. If a mouse cannot be provided with a rolling wheel, then the patient can click near the line and distort the line gradually by clicking several times.

The procedure with the rolling wheel is the most sensitive because the patient can represent relatively small distortions with relatively large movements of the rolling wheel. After finishing the straightening of the lines with the right eye, the right eye of the patient is covered, and the horizontal and vertical lines should be straightened for the left eye. In this study, the AMD® test was presented on a 17-inch LCD monitor and patients were tested at a distance of 0.97 m.

Each visit involves two measurements per eye in a block design to evaluate the reproducibility of the test. In random order, either the right eye is tested first, then the left, and then the right eye (A-B-B-A), or vice versa (B-A-A-B). This must prevent systematic fatigue, for example, in an A-B-A-B design. Before starting the test, the patient first performs the test with a healthy eye.

There are three values for objective evaluation of the distortion which are shown at the left bottom of the software window and can be seen in Figure 10.

The value "*Metamorph*," which represents the degree of distortion weighted by the amplitude of the distortion, the size of the area, and the centricity.

The value "*Gesichtsfeld*," which means “visual field," that is a measurement of the size of the visual field loss.

The value "*Abstand*," which means “distance," and shows the distance of the patient (eye) to the screen, depending on the size of the screen and the number of lines in the field.

At the end of the test, a single index of the metamorphopsia is shown in the software window. A value equals zero means no metamorphopsia has been detected. The higher the value, the more the degree of distortion in the metamorphopsia. Other values which the test shows are: *"(v),"* which means the strength of the distortion; *"(ex),"* which means the eccentricity, high eccentricity in the central visual field and low eccentricity in the peripheral visual field; *"(a)*," which means the area of the metamorphopsia in relation to the measured visual field (Figure 10).

Figure 10: Screenshot of the results of the "A Metamorphopsia Detector®" test.

(Courtesy of Prof. Dr. Nicolas Feltgen)

2.3 Statistical Data Evaluation

The data was stored according to the data protection rules and evaluated with statistical programs. The statistical evaluation was carried out in collaboration with the Institute for Applied Research and Clinical Trials (Institut für anwendungsorientierte Forschung und klinische Studien, or IFS, namely Sebastian Pfeiffer). Statistical analysis was done using SAS® 9.4. All variables were analyzed descriptively and completed by selecting box plots for visualization (in case of continuous data). For pre-post comparison, the difference (postmeasure minus premeasure) was analyzed with the t-test. As a visual comparison of the two continuous variables, a scatterplot was created, and it includes a regression line. In addition to this, the parametric correlation coefficient and its 95 % confidence interval were calculated. We also applied a generalized linear mixed model for repeated measures to investigate the relationship between certain eye characteristics/measures and the metamorphopsia index score (meta-index score) in a single model.

For the purpose of statistical analysis, the best-corrected visual acuity was converted from letters to a logarithm of the minimum angle of resolution (logMAR) using the conversion chart (Table 4), taking into account that each letter has a score value of 0.02 log.

Table 4: Visual Acuity Conversion Table.

Decimal	LogMAR	Letter Score
0.10	1.00	35
0.125	0.90	40
0.16	0.80	45
0.20	0.70	50
0.25	0.60	55
0.32	0.50	60
0.40	0.40	65
0.50	0.30	70
0.63	0.20	75
0.80	0.10	80
1.00	0.00	85
1.25	−0.10	90
1.60	−0.20	95
2.00	−0.30	100

3 Results

3.1 Validation of the Measuring Methods

The accuracy of the results of this study was ensured through the use of a standardized protocol as well as through compliance with instrument maintenance and calibration. The AMD® test also was previously validated and verified by the study executors.

3.2 Patient Population

In this study, 37 eyes from 37 patients were examined in the period from August 2016 to October 2018 at the University Medical Centre Goettingen preoperatively and 42 days after surgery. However, two patients dropped out during the study so that six months after the surgery, 35 eyes from 35 patients were examined. The reason for the dropout for the two patients is not known.

Even though, the two patients dropped out by the third examination, their results during the first two examinations were included in the total results.

The mean patient age was 69.9 ± 6.6 years, and the range was from 47 years to 82 years. There were 21 (56.7 %) men and 16 (43.2 %) women. Of the 37 eyes, 22 were the right eye (59.4 %), and 15 were the left eye (40.5 %). Nine (24.3 %) patients were pseudophakic, and 28 (75.7 %) patients were phakic.

3.3 Preoperative Data

At baseline, the mean visual acuity was 0.374 ± 0.202 logMAR. The mean refraction error was +0.588 ± 2.121 diopters (dpt), and the mean astigmatism was -0.869 ± 0.755 dpt. The mean intraocular pressure was 16.2 ± 2.8 mm of mercury (mmHg). The mean CFT, total foveal thickness, and macular volume were 517.6 ± 113.3 μm, 526.0 ± 143.0 μm, and 10.988 ± 1.386 mm^3, respectively. All 37 (100 %) eyes showed ERM at the fovea; three (8.1 %) eyes showed vitreomacular traction syndrome, and six (16.2 %) eyes showed cystoid macular edema. The mean composite score of NEI VFQ-25 was 69.382 ± 15.853 at baseline visit. Table 5 summarized the baseline characteristics of the examined eyes.

Table 5. Baseline Characteristics of Eyes which were included in the Study.

Description	Value (mean ± standard deviation)
Age	69.9 ± 6.6 years
Gender	21 (56.7 %) men / 16 (43.2 %) women
Lens condition	28 (75.7 %) phakic / 9 (24.3 %) pseudophakic
Visual acuity	0.374 ± 0.202 logMAR
Astigmatism	-0.869 ± 0.755 dpt
Intraocular pressure	16.2 ± 2.8 mmHg
Central foveal thickness	517.6 ± 113.3 µm
Total foveal thickness	526.0 ± 143.0 µm
Macular volume	10.988 ± 1.386 mm^3
NEI VFQ-25	69.382 ± 15.853

Abbreviations: mmHg, mm of Mercury; LogMAR, Logarithm of Minimum Angle of Resolution; dpt, diopter; NEI VFQ-25, National Eye Institute Visual Functioning Questionnaire - 25.

3.4 Postoperative Data

Most of the examined eyes showed a significant improvement of visual acuity by both post-surgical examinations – the mean value decreased from 0.374 ± 0.202 at baseline to 0.251 ± 0.171 and to 0.210 ± 0.199 (p-value < 0.001), 42 days and six months after PPV surgery, respectively (Table 6). There was also a significant reduction in CFT, total foveal thickness, and macular volume with 435.0 ± 57.7 µm, 432.7 ± 81.4 µm, and 9.692 ± 0.767 mm^3, 42 days after the vitrectomy, respectively, and 404.1 ± 53.3 µm, 399.0 ± 77.1 µm, and 9.160 ± 0.587 mm^3, six months after the vitrectomy, respectively. However, no significant changes were observed in astigmatism and intraocular pressure. Table 6 provides the results of postoperative examinations.

Table 6. Measurement values at Baseline, 42 days, and Six Months after PPV Surgery.

Description	Mean value ± standard deviation (*p*-value)		
	Baseline	42 days after PPV surgery	six months after PPV surgery
Visual acuity, logMAR	0.374 ± 0.202	0.251 ± 0.171 (< 0.001)	0.210 ± 0.199 (< 0.001)
Astigmatism, dpt	-0.869 ± 0.755	-0.900 ± 0.581 (0.7239)	-0.921 ± 0.720 (0.458)
Intraocular pressure, mmHg	16.2 ± 2.8	17.5 ± 5.6 (0.172)	15.6 ± 3.8 (0.266)
Central foveal thikness, μm	517.6 ± 113.3	435.0 ± 57.7 (< 0.001)	404.1 ± 53.3 (< 0.001)
Total foveal thickness, μm	526.0 ± 143.0	432.7 ± 81.4 (< 0.001)	399.0 ± 77.1 (< 0.001)
Macular volume, mm^3	10.988 ± 1.386	9.692 ± 0.767 (< 0.001)	9.160 ± 0.587 (< 0.001)
NEI VFQ-25	69.382 ± 15.853		77.125 ± 14.804 (< 0.001)

Abbreviations: mmHg, mm of Mercury; LogMAR, Logarithm of Minimum Angle of Resolution; dpt, diopter; NEI VFQ-25, National Eye Institute Visual Functioning Questionnaire - 25.

The mean composite score of NEI VFQ-25 was also improved significantly and reached 77.125 ± 14.804 (*p*-value < 0.001) six months after surgery. The values by pre- and postoperative examinations are presented in Figure 11, where the box covers ranges between first and third quartiles, the line within the box indicates the median, and the cross shows the mean value. Meanwhile, neither meta-index nor visual acuity showed a statically significant correlation with NEI VFQ-25 score (*p*-value are 0.0392 and 0.0179 respectively), as shown in Figure 12.

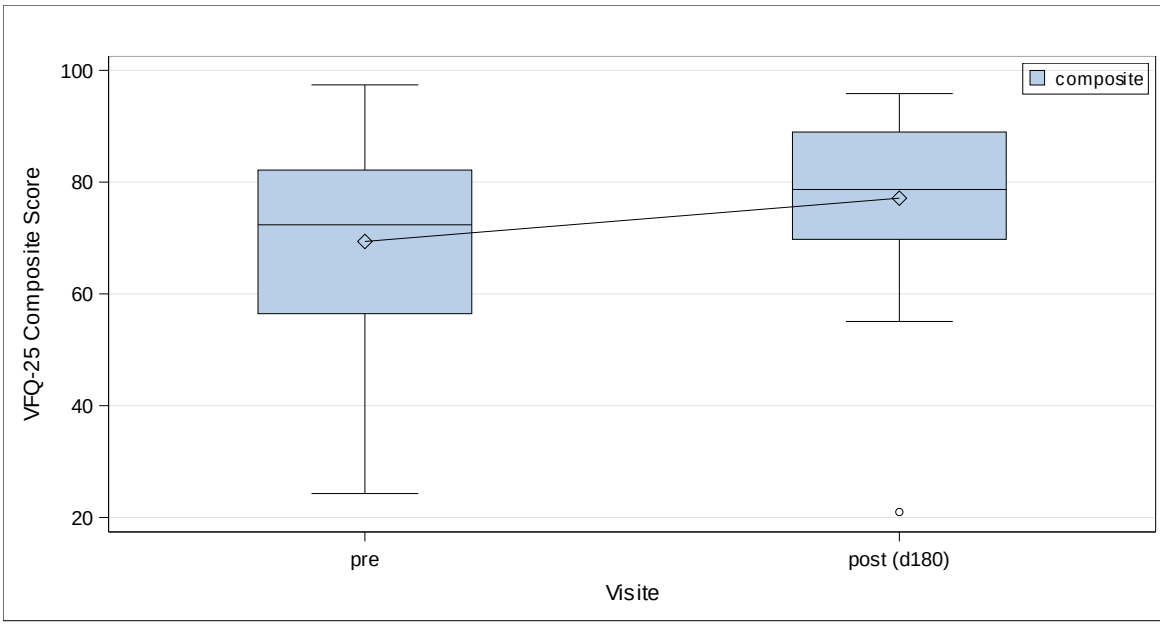


Figure 11: NEI VFQ-25 composite score – Boxplot[2].

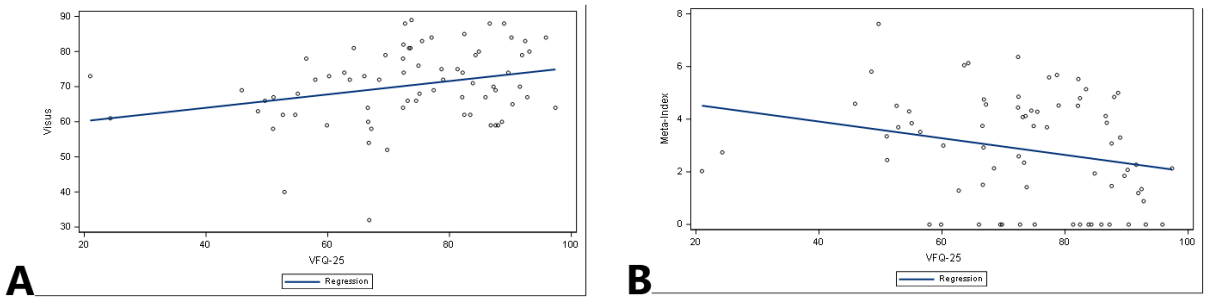


Figure 12. Correlations between (A) NEI VFQ-25 and visual acuity, (B) NEI VFQ-25 and meta-index score, in eyes with ERM that underwent a PPV surgery.

3.5 Intra- and Postoperative Complications

The first eye surgical operation in this study was performed on 19th August 2016, and the last one on 12th April 2018.

Twenty-five eyes had only PPV (67.5 %), and 12 eyes had PPV combined with cataract surgery (32.4 %). Thirty-four (91.8 %) eyes had undergone 25-gauge vitrectomy, and three (8.1 %) eyes 23-gauge vitrectomy. Air tamponade was used in 16 (43.2 %) eyes, gas tamponade in nine (24.3 %) eyes, and a balanced salt solution without tamponade in 12 (32.4 %) eyes.

[2] Whiskers range between the 1. quartile – 1.5*IQR and 3. quartile + 1.5*IQR (Inter quartile range). The Box (colored blue) ranges between the 1. quartile and 3. quartile. The line and the cross within the box represent median and mean, respectively. Outliers are indicated.

Intraoperative complications were noticed in four (10.8 %) eyes, of which three cases presented a retinal hole (8.1 %) and one case a lens touch (2.7 %). No endophthalmitis was recorded after surgeries in this study. There was one case of rhegmatogenous retinal detachment 42 days after surgery. The patient underwent a second PPV surgery immediately with gas tamponade to repair the retinal detachment. No retinal tear or break was detected during the operation.

3.6 Metamorphopsia Index

Metamorphopsia was quantified using a computer-based test, the AMD® test. Three (8.1 %) eyes had no metamorphopsia detected using AMD test; however, since the patients reported metamorphopsia subjectively, they were not excluded from the study. The mean value of the meta-index score decreased from 3.854 ± 1.809 at baseline, to 2.448 ± 1.948 42 days after vitrectomy surgery, and to 1.810 ± 1.762 six months postoperatively. The *p*-values are < 0.0001, which is statistically significant. That means that the change in the metamorphopsia index scores 42 days as well as six months after the PPV surgery correlated significantly with the baseline score (Table 7).

Table 7: Meta-Index Score at Baseline, 42 days, and Six Months after PPV Surgery.

	Meta-index score (mean ± standard deviation)	***p*-value**
Baseline	3.854 ± 1.809	
42 days after PPV surgery	2.448 ± 1.948	< 0.0001
Six months after PPV surgery	1.810 ± 1.762	< 0.0001

A better overview of the results of the metamorphopsia index scores, its mean, and median values are presented in Figure 13.

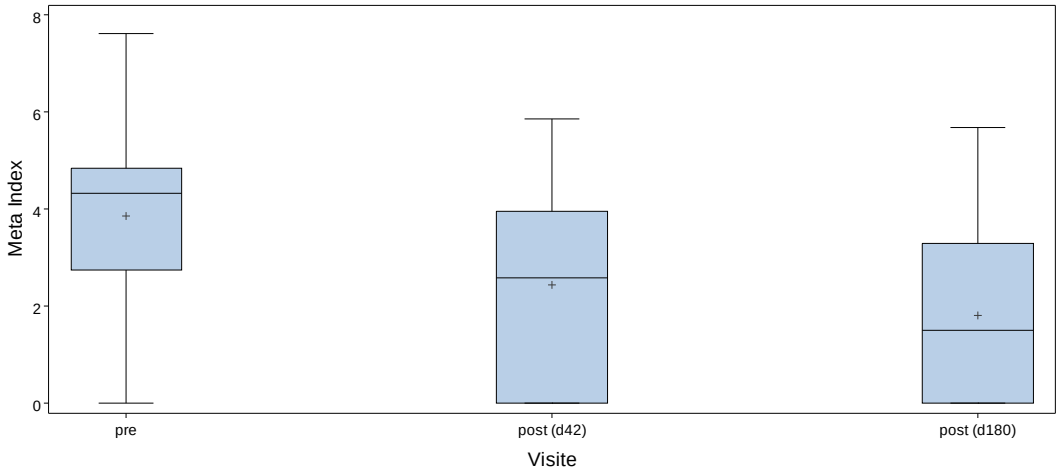


Figure 13: Meta-index score – Boxplot[3]

The meta-index score of non-study eyes had a mean value of 0.281 ± 0.874 at baseline. Even though a slight decrease to 0.213 ± 0.725 and 0.149 ± 0.625 was noticed in 42 days and in six months after PPV surgery, respectively, the *p*-values were 0.1238 and 0.1879, respectively, so that the values were considered to be statistically not significant.

Of 34 eyes, where the metamorphopsia was detected at baseline, it was completely eliminated in 10 (29.4 %) eyes six months postoperatively. Twenty-one (61.8 %) eyes showed improvement during postoperative examinations, although the metamorphopsia still persisted, and in three (8.8 %) eyes, the metamorphopsia increased.

During the study, it was found out that a meta-index score of more than 2.135 could be considered as a threshold, allowing to detect patients with symptomatic metamorphopsia.

Figure 14 shows a correlation between the meta-index score and other pathomorphological parameters such as visual acuity, astigmatism, foveal thickness, and macular volume, and the *p*-values for these correlations are summarised in Table 8. Since the *p*-values for visual acuity and astigmatism are quite high (*p*-values are 0.181 and 0.131 respectively), this means that the relationships between the metamorphopsia and these two parameters are not statistically significant. This could also be seen from Figure 14 A and Figure 14 B, respectively. However, the mean CFT, total foveal thickness, and macular volume were correlated with the meta-index score using the parametric Pearson correlation coefficient. Yet, the sensitivity analysis with the non-parametric Spearman coefficient provides comparable results (*p*-values are < 0.001).

[3] Whiskers range between the 1. quartile – 1.5*IQR and 3. quartile + 1.5*IQR (Inter quartile range). The Box (colored blue) ranges between the 1. quartile and 3. quartile. The line and the cross within the box represent median and mean, respectively. Outliers are indicated.

Table 8: Association Between the Meta-Index Score and Other Pathomorphological Parameters.

Pathomorphological parameters	*p*-value (Pearson correlation coefficient)
Visual acuity	0.181
Astigmatism	0.131
Central foveal thikness	< 0.0001
Total foveal thickness	< 0.0001
Macular volume	< 0.0001

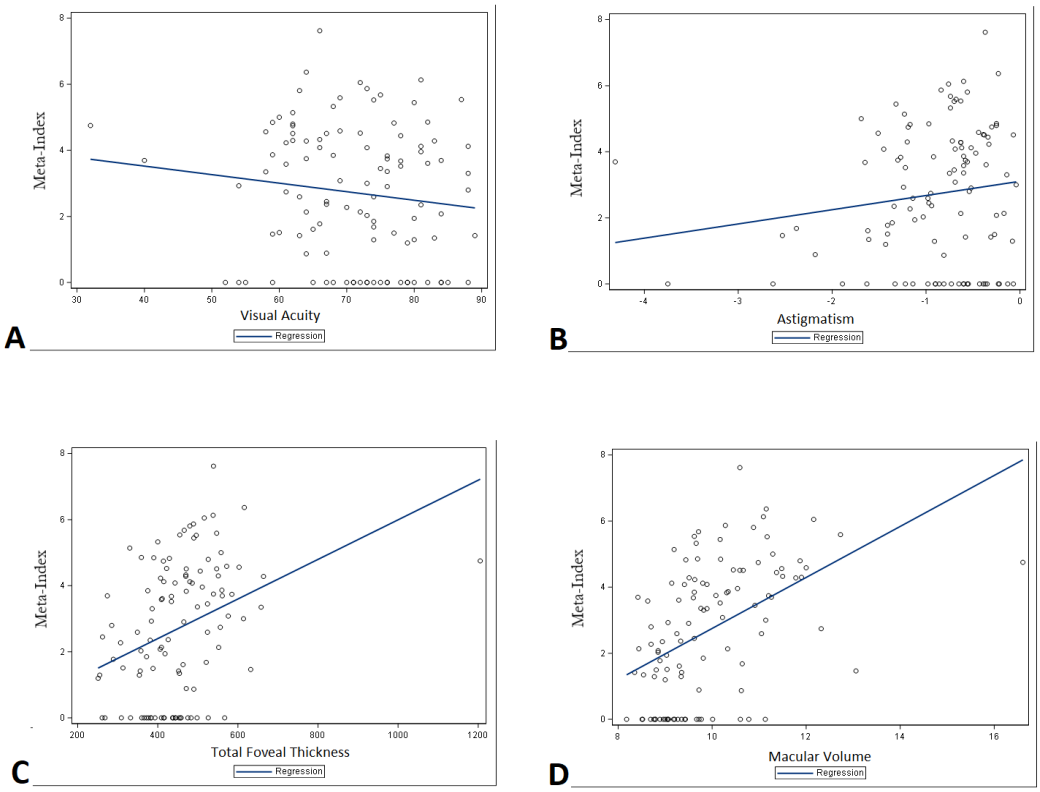


Figure 14: Correlations between meta-index and other pathomorphological parameters. (A) visual acuity, (B) astigmatism, (C) total foveal thickness, (D) macular thickness, in eyes with ERM that underwent a PPV surgery.

4 Discussion

4.1 Contribution

Metamorphopsia in patients with ERM pre- and postoperatively was quantified using the AMD® test. Metamorphopsia was found in 34 of 37 eyes (91.9 %), with the mean preoperative meta-index score 3.854 ± 1.809 at baseline. Results showed the meta-index score improved continuously throughout the six months postoperatively. During the first 42 days postoperatively, metamorphopsia significantly improved, and the mean meta-index score decreased to 2.448 ± 1.948. After that, the improvement progressed more slowly until six months, and the mean meta-index score reached 1.810 ± 1.762 six months postoperatively. However, three eyes (8.8 %) reported an increase in metamorphopsia six months after the PPV surgery. Two of the patients had macular edema, which might be the reason for the increase in the meta-index score. The other possible explanation is that, because of the severe visual impairment preoperatively, the metamorphopsia may not have been well-recognized in these patients.

In this study, most of the examined eyes showed a significant improvement in visual acuity postoperatively. This demonstrated the efficacy of surgical intervention in treating ERM and supported the results of the previous studies, which also showed the benefit of surgical intervention in improving visual acuity in patients with ERM (Bu et al. 2014; Folk et al. 2016).

Moreover, the study also demonstrated that there was no statistically significant relationship between the improvement of the meta-index score postoperatively and the visual acuity. Furthermore, even within the same visual acuity range the meta-index score varied. This leads to consider that the metamorphopsia is a new clinical aspect, which could be used besides the visual acuity in observing operation outcomes and follow-up patients.

As far as we know, no known studies have quantified the metamorphopsia using the AMD® test in patients with ERM. The Amsler chart, which is commonly used in daily clinical settings to detect the metamorphopsia, provides only rough detection of central visual field distortions, and no documentation or follow-up is possible. There are also other tests that can quantify the degree of metamorphopsia. One of the most used and commercially available tests is M-CHARTS. The M-CHARTS test was developed by Matsumoto et al. (2003). The authors reported a 97.3 % sensitivity for the test and a specificity of 100 % in detecting metamorphopsia (ibid.). Compared to these tests, the AMD® test has a sensitivity of 100 % and specificity of 85 % (Claessens and Krüger 2015). However, both M-CHARTS and the AMD® test examine the central 10° of the visual field, and both have difficulty in quantifying the metamorphopsia

on the peripheral line. That's because it may be a challenging task for a patient to change the peripheral line while fixing a central point, this may lead occasionally to less accurate results.

The study demonstrated that the new AMD® test can be used in clinical setting to detect and quantify the severity of metamorphopsia in patients with ERM. That can potentially make therapy more efficient by supporting compliance and adherence in the diagnosis and therapy of different macular diseases. Moreover, a computer or mobile application for the AMD® test allows self-monitoring at home, which could strengthen the patient's self-efficacy and has good promise of detecting metamorphopsia in the future. It can enhance self-efficacy, persistence, and adherence in different macular diseases by lowering the diagnostic threshold and supporting early detection, which could save unnecessary doctor visits. Especially taken into account the current situation with COVID-19 pandemic, when doctor visit is not always possible, in this case patients can monitor themselves at home and visit the ophthalmologist only when the score is changed.

The AMD® test has already been applied in different macular diseases. Claessens and Schuster (2019) examined the AMD® test in patients with diabetic maculopathy and age-related macular degeneration and found that a correlation between CFT and the metamorphopsia index was high in diabetic macula edema and moderate in age-related macular degeneration. This study showed that the meta-index scores correlated more with macular volume (Spearman's Rho = 0.5491, p-value < 0.0001) than with CFT or total foveal thickness.

Twenty-three patients were asked about their symptomatic metamorphopsia at baseline, from which 11 patients reported no symptomatic metamorphopsia six months postoperatively. The highest meta-index score in patients with no subjective metamorphopsia was 2.135. Since the test had been conducted monocularly, the patients could have a meta-index score of less than 2.135 and still have no subjective metamorphopsia. Since the normal eye is completely covered with an eye patch during the test, the brain can compensate for small distortions in the eye's visual field, and the patient sees no distortions binocularly. Thus, a meta-index score of more than 2.135 could be considered as a threshold, allowing to detect patients with symptomatic metamorphopsia.

To determine and evaluate the influence of metamorphopsia on the patients' quality of life, the ophthalmology questionnaire NEI VFQ-25 has been implemented. The results of the questionnaire showed that patients reported improvement in the metamorphopsia postoperatively. However, despite the reduction of macular thickness and increase in visual acuity six months postoperatively, some patients experience further a decreased life quality due to persistency of metamorphopsia.

4.2 Limitation and Implication

The main limitation of the study is the small sample size. The second limitation is a relatively short postoperative follow-up (six months). Larger studies with longer observation periods are crucial to evaluate the long-term morphological changes of metamorphopsia in patients with ERM.

Thirdly, there are several aspects of the test that might bias the results. First, the patients might lose the fixation point, which should be in the middle of the field, since the metamorphopsia is most significant in areas around the fixation point. If the patient loses the central fixation point and try to fix the distortion peripheraly, that will change the actual distortion, which leads to inaccurate results. In this case, an eye-tracking camera could be implemented to control the rate of the eye-fixation loss. Secondly, the test is conducted with the distance 0.97m but without head fixation so if patients change their head position, the distance and accordingly the degree of the visual field on the screen for the patient may be changed. Head fixation can solve this. The other suggestion for future research is a microperimetry test prior to AMD® test in order to detect large central scotoma in advance, which could be implicated to the meta-index score. Moreover, since the youngest patient was 47 years old and the oldest 82 years old, a computer-based test may be challenging for patients without prior computer knowledge. In such case, the patients needed more than 30 minutes to complete the test, which may be a reason for dropouts during the study. In these terms, the M-CHART is simpler, needs no computer knowledge, and requires less time for patients' preparation and less time conducting the test.

Finally, it was difficult to obtain the meta-index score using the AMD® test in patients with visual acuities less than 0.2 because they could not clearly recognize the lines on the screen. Therefore, these patients, as well as, patients with central scotoma, have not been included in this study since they have difficulties performing the test. Further studies should be conducted to examine the relationship between visual acuity and the meta-index score in lower visual acuity patients.

5 Summary

With the increasing aging in our society, ERM represents one of the treatable causes of vision impairment, especially in elderly people. Patients with ERM present with reduced and distorted vision, metamorphopsia, and nonspecific visual disturbances. The diagnosis of the ERM is based on clinical finding, mainly on a dilated fundus examination or fundus photograph. A qualitative and quantitative analysis of the retina can nowadays be obtained using OCT cross-sectional images. ERM can be surgically well manageable with consequent reduction of metamorphopsia and improvement in vision.

Despite all of the innovations in the field of vitreoretinal surgery, currently, there is not any possibility to capture the extent of the distortion, while other subjective testing methods such as visual acuity and central visual field, can be quantified.

The study demonstrated that the new AMD® test can be used in clinical setting to detect and quantify the severity of metamorphopsia in patients with ERM. Moreover, a computer or mobile application for the AMD® test allows self-monitoring at home, which could strengthen the patient's self-efficacy and has good promise of detecting metamorphopsia in the future. Especially taken into account the current situation with COVID-19 pandemic, when doctor visit is not alawys possible, in this case patients can monitor themselves at home and visit the ophthalmologist only when the score is changed.

In this study, the degree and severity of metamorphopsia in patients with ERM pre- and post-operatively was quantified using the AMD® test. Results showed a significant and continuous improvement in visual acuity and in metamorphopsia postoperatively. The metamorphopsia is a new clinical aspect, which could be used besides the visual acuity in observing operation outcomes and follow-up patients.

To the best of our knowledge, no other studies have yet quantified the metamorphopsia using the AMD® test in patients with ERM.

Larger studies with longer observation periods are crucial to evaluate the long-term morphological changes of metamorphopsia in patients with ERM.

6 Appendices

Appendix A Kurzprotokoll

Zentrum 13 – Augenklinik mit Poliklinik
Abteilung Augenheilkunde
Direktor: Prof. Dr. med. Hans Hoerauf
Studienleiter: Prof. Dr. med. Nicolas Feltgen
Robert-Koch-Strasse 40, 37075 Göttingen
Tel.: 0551-39 66776/ Fax: 0551-39 66787
E-mail: nicolas.feltgen@med.uni-goettingen.de

Kurzprotokoll

“Funktionelle Veränderungen bei operativer Behandlung der epiretinalen Gliose“

Einschlusskriterien:

- >18 Jahre, geschlechtsunabhängig, Operationsindikation aufgrund einer Epiretinalen Gliose
- Bestrefraktionierter Visus präoperativ 0,2
- Metamorphopsie
- Indikation zur vitreoretinalen Chirurgie

Ausschlusskriterien:

- Fehlende Einwilligungs-/Aufklärungsmöglichkeiten des Patienten
- Visusrelevante Augenerkrankungen (z.B. Visusrelevante Glaskörpertrübungen und -traktionen, Hornhauterkrankungen, fortgeschrittene Makulaerkrankungen, die mit Metamorphopsie einhergehen (z.B. Makulaforamen, Makuladegenerationen, diabetische Makulopathie, Uveitis, fortgeschrittenes Glaukom, Netzhautablösung mit Makualbeteiligung)
- Patienten mit Makuladystrophie
- Schwangerschaft und Stillzeit
- bettlägerige Patienten, bei welchen die Messungen nicht durchgeführt werden können
- vorausgegangene Augenoperationen, mit konsekutiver Visusreduktion oder Visusbeeinträchtigung (z.B. Ablatio-Operation mit Makulabeteiligung, Z. n. Makulachirurgie)

Wenn ein Patient für die Studie in Frage kommt/ teilnehmen möchte, bitte dem Studienbüro melden und das Kurzprotokoll in die Akte heften!

Bei Erstvorstellung:

- Nachdem die Indikationsstellung zur Operation in der ambulanten Voruntersuchung gestellt worden ist, werden die Patienten zusätzlich über die Studie informiert und erhalten die **Patientenaufklärung**.
- Stat. Op-Termin (innerhalb 4-8 Wochen durch Frau Krell) und stationäres Aufnahmemanagement (weil Patient am präop. Tag zuerst in die Poli geht).
- **Bitte den Patienten zur Voruntersuchung am Aufnahmetag in die Poli schicken!!!!**

1. Visite am **Aufnahmetag** in der **Poliklinik** (Voruntersuchung prä Op, zunächst nicht weit tropfen):
Patient meldet sich in Studienzentrale -> Aufklären und Unterschreiben für Studie

- **Patient zur Operation aufklären und Unterschrift einholen.**
- IOL-Master
- Autorefraktion
- NEI-VFQ 25 Fragebogen durch die **Study Nurse**
- Bestrefraktionierter Visus (ETDRS) durch die **Study Nurse**

- Amsler-Test (Metamorphopsia Detector) durch die **Study Nurse**
- Weit tropfen durch die **Study Nurse**
- HH-Topographie durch das Fotolabor
- Spectralis-OCT durch das Fotolabor
- Ophthalmologische Untersuchung und übliche Operationsaufklärung
- Bitte Patient mit dem Shuttle in die Hainbergklinik schicken (keine weiteren Untersuchungen oder Arztkontakt in Hainbergklinik benötigt**)**
- **bitte WV-Termin mitgeben!!!! (Study Nurse)**

2. Visite in der Poliklinik 6 Wochen post Op.:

- Autorefraktion
- Bestrefraktionierter Visus (ETDRS) durch die **Study Nurse**
- Amslernetz-Test (Metamorphopsia Detector) durch die **Study Nurse**
- Weit tropfen
- HH-Topographie durch das Fotolabor
- Spectralis-OCT durch das Fotolabor
- Ophthalmologische Untersuchung
- **bitte WV-Termin mitgeben!!!! (Study Nurse)**

3. Visite in der Poliklinik 6 Monaten post Op.:

- Autorefraktion
- NEI-VFQ 25 Fragebogen durch die **Study Nurse**
- Bestrefraktionierter Visus (ETDRS) durch die **Study Nurse**
- Amslernetze-Test (Metamorphopsia Detector) durch die **Study Nurse**
- Weit tropfen
- HH-Topographie durch das Fotolabor
- Spectralis-OCT durch das Fotolabor
- Ophthalmologische Untersuchung

Bei Unklarheiten bitte Rücksprache mit M.Khattab (919-6850) oder Prof. Feltgen (919-1164) oder mit dem Studienbüro!

Appendix B Visual Acuity

Name: _____Patienten Nr:_____ Visite: 1 2 3

UNIVERSITÄTSMEDIZIN GÖTTINGEN : UMG

Visual Acuity

Anleitung: Jeder richtig gelesener Buchstabe wird eingekreist. Falsche oder übersprungene Buchstaben werden nicht markiert. Nur das Studienauge wird Untersucht.

Datum der Untersuchung:____/____/____ Studienauge: ☐ rechts ☐ links

Refraktion:

RA Sphäre:_____Zylinder:_____Achse:_____° LA Sphäre:_____Zylinder:_____Achse:_____°

	Rechtes Auge						Korrekte		**Linkes Auge**						Korrekte
	Snellen	Chart R					Anzahl		Snellen	Chart R					Anzahl
Reihe	Äquivalent						4 meter	Reihe	Äquivalent						4 meter
1	20/200	H	V	Z	D	S	_____	1	20/200	H	V	Z	D	S	_____
2	20/160	N	C	V	K	D	_____	2	20/160	N	C	V	K	D	_____
3	20/125	C	Z	S	H	N	_____	3	20/125	C	Z	S	H	N	_____
4	20/100	O	N	V	S	R	_____	4	20/100	O	N	V	S	R	_____
5	20/80	K	D	N	R	O	_____	5	20/80	K	D	N	R	O	_____
6	20/63	Z	K	C	S	V	_____	6	20/63	Z	K	C	S	V	_____
7	20/50	D	V	O	H	C	_____	7	20/50	D	V	O	H	C	_____
8	20/40	O	H	V	C	K	_____	8	20/40	O	H	V	C	K	_____
9	20/32	H	Z	C	K	O	_____	9	20/32	H	Z	C	K	O	_____
10	20/25	N	C	K	H	D	_____	10	20/25	N	C	K	H	D	_____
11	20/20	Z	H	C	S	R	_____	11	20/20	Z	H	C	S	R	_____
12	20/16	S	Z	R	D	N	_____	12	20/16	S	Z	R	D	N	_____
13	20/12.5	H	C	D	R	O	_____	13	20/12.5	H	C	D	R	O	_____
14	20/10	R	D	O	S	N	_____	14	20/10	R	D	O	S	N	_____

Gesamt Anzahl korrekt gelesen bei 4 metern:* _____ Gesamt Anzahl korrekt gelesen bei 4 metern:* _____

*Wenn < 3 Buchstaben bei Reihe 1, dann 1 m *Wenn < 3 Buchstaben bei Reihe 1, dann 1 m

n.e.☐		Addiere + 0.75 Sphäre					Korrekte Anzahl 1 meter	n.e.☐		Addiere + 0.75 Sphäre					Korrekte Anzahl 1 meter
1	20/800	H	V	Z	D	S	_____	1	20/800	H	V	Z	D	S	_____
2	20/640	N	C	V	K	D	_____	2	20/640	N	C	V	K	D	_____
3	20/500	C	Z	S	H	N	_____	3	20/500	C	Z	S	H	N	_____
4	20/400	O	N	V	S	R	_____	4	20/400	O	N	V	S	R	_____
5	20/320	K	D	N	R	O	_____	5	20/320	K	D	N	R	O	_____
6	20/250	Z	K	C	S	V	_____	6	20/250	Z	K	C	S	V	_____

Gesamt Anzahl korrekt gelesen bei 1 metern: _____ Gesamt Anzahl korrekt gelesen bei 1 metern: _____

Visual Acuity Score – Rechtes Auge

A. Summe der Buchstaben 4 meter: + _____

B. Wenn ≥ 20, addiere 30, sonst 0 + _____

C. . Summe der Buchstaben 1 meter, sonst 0: + _____

Kleinste Reihe mit 3 gelesenen Buchstaben _____

Rechtes Auge: Summe von A, B und C

Visual Acuity Score – Linkes Auge

A. Summe der Buchstaben 4 meter: + _____

B. Wenn ≥ 20, addiere 30, sonst 0 + _____

C. . Summe der Buchstaben 1 meter, sonst 0: + _____

Kleinste Reihe mit 3 gelesenen Buchstaben _____

Linkes Auge: Summe von A, B und C

Datum: Unterschrift:

Appendix C Patienteninformation

Zentrum 13 – Augenklinik mit Poliklinik
Abteilung Augenheilkunde
Direktor: Prof. Dr. med. Hans Hoerauf
Studienleiter: Prof. Dr. med. Nicolas Feltgen
Robert-Koch-Strasse 40, 37075 Göttingen
Tel.: 0551-39 66776/ Fax: 0551-39 66787
E-mail: nicolas.feltgen@med.uni-goettingen.de

Patienteninformation

"Funktionelle Veränderungen bei operativer Behandlung der epiretinalen Gliose"

Sehr geehrte Patientin, sehr geehrter Patient,

wir möchten Sie um die freiwillige Teilnahme an einer wissenschaftlichen Studie bitten. Nachfolgende Punkte sollen Ihnen helfen unser Vorhaben besser zu verstehen und eventuell auftauchende Fragen im Voraus klären zu können. Natürlich stehen wir Ihnen während der Studie auch zur Verfügung und beantworten gerne Ihre Fragen.

Bei Ihrer Erkrankung hat sich ein zellophanartiges Häutchen auf der zentralen Netzhaut gebildet. Diese Membran verzieht die Netzhaut und legt diese in Falten. Die Folgen sind verzerrtes Sehen, Abnahme der Sehschärfe und des Bildkontrastes.
Das Häutchen kann durch eine Operation abgetragen werden. Hierbei geht der Operateur mit sehr feinen Instrumenten in das Auge ein und zieht das Häutchen ab. Der Eingriff erfolgt stationär und entweder in örtlicher Betäubung oder Vollnarkose.

Ihre Teilnahme an dieser Studie ist freiwillig. Sie werden in diese Studie also nur dann einbezogen, wenn Sie dazu schriftlich Ihre Einwilligung erklären. Sofern Sie nicht an der Studie teilnehmen möchten, entstehen Ihnen daraus natürlich keine Nachteile.
Bitte lesen Sie die nachstehende Information sorgfältig. Bei Unklarheiten wird Ihr Arzt Sie ausführlich beraten.

1. Was ist das Ziel der Studie?

In der Operation wird die auf der Netzhaut liegende Membran entfernt und die Netzhaut kann sich wieder entspannen. In den meisten Fällen kann mit dieser Operation das verzerrte Sehen reduziert oder behoben werden. Es gibt bisher tatsächlich keine Möglichkeit, das Ausmaß der Verzerrung zu erfassen.
Ziel der Studie ist es, den Grad des Verzerrtsehens vor und nach der Operation zu ermitteln.

2. Was sind die Voraussetzungen für eine Teilnahme?

Voraussetzung für eine Teilnahme ist, dass bei Ihnen eine operative Entfernung der Membran auf der Netzhaut geplant ist. Erst nachdem diese Entscheidung getroffen wurde, kommen Sie für die Studie in Frage. Nach eingehender mündlicher und schriftlicher Aufklärung über den Sinn und den Ablauf der Studie werden wir Sie bitten, schriftlich Ihr Einverständnis zur Teilnahme zu bekunden.

3. Studiendurchführung:

Wenn Sie sich mit der Teilnahm an der Studie einverstanden erklären, werden zusätztlich zu den Routinenuntersuchungen studienspezifische Untersuchungen des verzerrten Sehens bei Ihrer stationären Aufnahme am Tag vor dem Eingriff durchgeführt. Diese nicht-invasiven Messungen finden im Rahmen der Routinuntersuchung statt und haben keinen nachteiligen Einfluss auf die Operation und den Krankheitsverlauf.

Im Einzelnen sind folgende zusätzlichen Untersuchungen geplant:

1. Spezieller Sehschärfentest (5 min)
2. Ausfüllen eines Fragebogens (10 min)
3. Computertest zum Erfassen des verzerrten Sehens (10 min)

Die operative Behandlung und der Krankenhausaufenthalt (in der Regel 3 Tage) verändert sich durch die Studie nicht. Nach der Operation werden Sie 6 Wochen und 6 Monate erneut einbestellt und untersucht. Hierfür werden zwei Wiedervorstellungstermine mit Ihnen vereinbart. Bei der Kontrolluntersuchung nach 6 Monaten handelt es sich demnach um einen zusätzlichen Termin an der Universitäts-Augenklinik Göttingen. Dieser ersetzt den sonst üblichen Kontrolltermin bei Ihrem Augenarzt. Die Untersuchungen erfolgen ambulant und werden so organisiert, dass die Wartezeiten für die Patienten so kurz wie möglich gehalten werden.

4. Was sind die möglichen Risiken oder Nachteile einer Teilnahme an der Studie?

Es gibt keine Risiken. Bei allen studienspezifischen Untersuchungsmethoden handelt es sich um nicht-invasive Verfahren, es wird nur nach Ihrem Seheindruck gefragt.

Sie werden nur nach einer Teilnahme an der Studie gefragt, wenn die Operation ohnehin erforderlich ist. Die Behandlung in der Augenklinik erfolgt nach interner Leitlinie, allerdings über gesonderte Organisationswege (Studienbüro), sodass unangenehme Wartezeiten im ambulanten Bereich für Sie minimiert werden und eine persönliche Betreuung über unsere Studienärzte gewährleistet wird.

5. Welchen Vorteil haben Sie durch Ihre Teilnahme an der Studie?

Eigennutzen: Durch Ihre Teilnahme an der Studie kontrollieren wir Sie länger und regelmäßiger, als das im klinischen Alltag möglich wäre. Wir können Ihnen dadurch noch mehr Informationen über Ihre Sehfunktion geben. Durch die zusätzlichen Sehtest erfahren wir mehr über Ihre speziellen Probleme, die möglicherweise dann auch zu weiteren behandlungen außerhalb der Studie führen.

Der Nutzen für andere: Die Ergebnisse der Untersuchungen könnten in Zukunft helfen, Patienten mit verzerrtem Sehen aufgrund einer Netzhautmembran gezielter zu behandeln.

6. Risiken und Nebenwirkungen:

Risiken entstehen durch die Narkose und den Eingriff an sich (übliche Risiken der Operation, die gesondert aufgeklärt werden). Diese Risiken stehen aber nicht im Zusammenhang mit der Studie, sondern gehören zu den **allgemeinen Gefahren** bei der Diagnostik und Behandlung der Erkrankung. Es kommen also **keine Zusatzgefahren** auf Sie zu!

7. Erläuterungen anderer Therapien:

Die manuelle mikrochirurgische Abtragung der Membran von der Netzhautoberfläche stellt die **zurzeit einzige** Therapiemethode dar.

8. Versicherung:

Die Patienten sind im Rahmen der regelrechten klinischen Behandlung über die Haftpflichtversicherung der Universitätsmedizin Göttinngen versichert.

9. Was geschieht mit Ihren medizinischen Daten?

Es gilt die ärztliche Schweigepflicht. Jede Information über Sie wird zu jeder Zeit mit der größtmöglichen Vertraulichkeit behandelt. Die medizinischen Daten und Messergebnisse werden in einer zentralen Datenbank gespeichert, die den jeweils geltenden datenschutzrechtlichen Auflagen Rechnung trägt. In keiner wissenschaftlichen Veröffentlichung wird Ihr Name erscheinen. Ihre Daten werden auf keinen Fall bekannt gegeben. Ihre personenbezogenen Studiendaten werden für 10 Jahre gespeichert.

Im Falle einer Rücknahme der Einwilligung werden auf ihren Wunsch hin die bereits erhobenen personenbezogenen Daten gelöscht.

Hinweis zur Einwilligung: Die Teilnahme an dieser klinischen Prüfung ist freiwillig. Sie können diese Einwilligung jederzeit widerrufen und aus der Studie austreten, ohne es daraus Nachteil entsetehen.

Appendix D Kurzanleitung Metamorphopsie Detector-Test

Kurzanleitung Metamorphopsie Detector-Test:

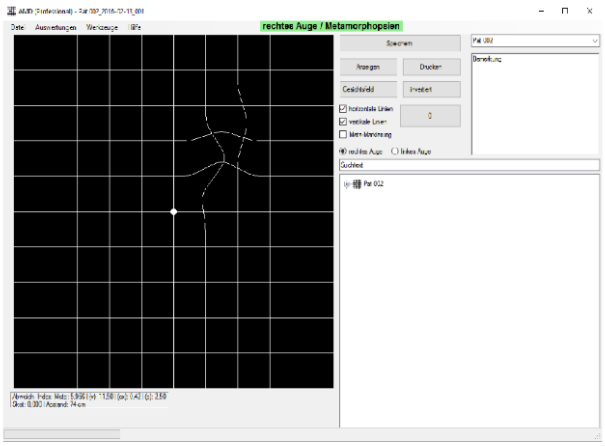
Ihre Aufgabe ist es, die Linien so einzustellen, dass alle Linien gerade erscheinen. Klicken Sie dazu die Linien an, die Sie sehen wollen (Häkchen bei "Horizontale Linien" oder "Vertikale Linien" setzen). danach wird mit einer Augenklappe ein Auge bedeckt. Mit dem anderen Auge sollen Sie nun den Fixationspunkt in der Mitte des Feldes fixieren. Bewegen Sie den Mauszeiger zu der Stelle die Sie verändern möchten.

Sie haben nun verschiedene Möglichkeiten die Linien zu verändern:

1. Mausrad

Gehen Sie mit der Maus an die Stelle, die Sie ändern wollen und drehen dann das Mausrad.

2. Mausklick. Gehen Sie an die Stelle mit der Maus, zu der Sie die Linie verändert haben wollen. Der Klick verzerrt die Linie zu der aktuellen Mausposition (Abb 1).



Mit Hilfe des Rollrades kann der Proband nun die Linie an der Stelle verzerren, an der sich der Mauszeiger befindet.

Abb. 1 Metamorphopsie Detector-Test

Kann keine Maus mit einem Rollrad zur Verfügung gestellt werden, so klick der Proband neben die Linie und verzerrt diese durch mehrmaliges Klicken um einen kleinen Betrag.

Appendix E Einwilligungserklärung

Zentrum 13 – Augenklinik mit Poliklinik
Klinik für Augenheilkunde
Direktor: Prof. Dr. med. Hans Hoerauf
Studienleiter: Prof. Dr. med. Nicolas Feltgen
Robert-Koch-Strasse 40, 37075 Göttingen
Tel.: 0551-39 66776/ Fax: 0551-39 66787
E-mail: nicolas.feltgen@med.uni-goettingen.de

"Funktionelle Veränderungen bei operativer Behandlung der epiretinalen Gliose"

Einwilligungserklärung

Patientenaufkleber

Teilnehmer-Nr. .....

Ich bin in einem persönlichen Gespräch durch den Prüfarzt

.....
Name der Ärztin/des Arztes

ausführlich und verständlich über Wesen, Bedeutung, Risiken und Tragweite der Untersuchung aufgeklärt worden. Ich habe darüber hinaus den Text der Patienteninformation sowie die hier nachfolgend abgedruckte Datenschutzerklärung gelesen und verstanden. Ich hatte die Gelegenheit, mit dem Prüfarzt über die Durchführung der Untersuchung zu sprechen. Alle meine Fragen wurden zufriedenstellend beantwortet.

Möglichkeit zur Dokumentation zusätzlicher Fragen seitens des Probanden oder sonstiger Aspekte des Aufklärungsgesprächs:

Ich hatte ausreichend Zeit mich zu entscheiden.

Mir ist bekannt, dass ich jederzeit und ohne Angabe von Gründen meine Einwilligung zur zusätzlichen Untersuchung zurückziehen kann (mündlich oder schriftlich), ohne dass mir daraus Nachteile entstehen.

Datenschutz:
Mir ist bekannt, dass bei dieser Untersuchung personenbezogene Daten, insbesondere medizinische Befunde über mich erhoben, gespeichert und ausgewertet werden sollen. Die Verwendung der Angaben über meine Gesundheit erfolgt nach gesetzlichen Bestimmungen und setzt vor der Teilnahme an der Untersuchung folgende freiwillig abgegebene Einwilligungserklärung voraus, das heißt ohne die nachfolgende Einwilligung kann ich nicht an der klinischen Prüfung teilnehmen. 1. Ich erkläre mich damit einverstanden, dass im Rahmen dieser klinischen Studie personenbezogene Daten, insbesondere Angaben über meine Gesundheit, über mich erhoben und in Papierform sowie auf elektronischen Datenträgern in der Universitäts-Augenklinik Göttingen aufgezeichnet werden. Die Daten einschließlich der pseudonymisierten werden an dritte nicht weitergegeben. 2. Die Einwilligung zur Erhebung und Verarbeitung meiner personenbezogenen Daten kann ich jederzeit widerrufen. Ich bin bereits darüber aufgeklärt worden, dass ich jederzeit die Teilnahme an der Studie beenden kann. Im Fall eines solchen Widerrufs meiner Einwilligung, können auf meinen Wunsch hin auch meine Daten aus der Studiensammlung gelöscht werden.

3. Ich erkläre mich damit einverstanden, dass meine Daten nach Beendigung oder Abbruch der Studie mindestens zehn Jahre aufbewahrt werden. Danach werden meine personenbezogenen Daten gelöscht, soweit nicht gesetzliche, satzungsmäßige oder vertragliche Aufbewahrungsfristen entgegenstehen (vertraglich vereinbarte Fristen müssen hier genannt werden).

4. Ich bin über folgende gesetzliche Regelung informiert: Falls ich meine Einwilligung, an der Studie teilzunehmen, widerrufe, müssen alle Stellen, die meine personenbezogenen Daten, insbesondere Gesundheitsdaten, gespeichert haben, unverzüglich prüfen, inwieweit die gespeicherten Daten für die in Nr. 3 genannten Zwecke noch erforderlich sind.
5. Nicht mehr benötigte Daten sind unverzüglich zu löschen.

6. Ich erkläre mich damit einverstanden, dass im Rahmen dieser Untersuchung personenbezogene Daten, Bestandteil meiner Patientenakte in der Universitäts-Augenklinik Göttingen wird.

7. Ich erkläre mich damit einverstanden, dass meine Daten ohne Hinweis auf die Person für eine Auswertung und Veröffentlichung verwendet werden kann.

8. Ich bin damit einverstanden, dass mein Hausarzt und Augenarzt über meine Teilnahme an der klinischen Prüfung informiert wird (**Falls nicht gewünscht, bitte streichen**.)

Ich erkläre mich freiwillig dazu bereit, an der Studie teilzunehmen.

Ein Exemplar der Patienteninformation und -Einwilligung habe ich erhalten.
Ein Exemplar verbleibt im Prüfzentrum.

.....
Name des Probanden in Druckbuchstaben

....
Datum Unterschrift des **Probanden**

Ich habe das Aufklärungsgespräch geführt und die Einwilligung des Probanden eingeholt.

.....
Name des Prüfarztes/der Prüfärztin in Druckbuchstaben

....
Datum Unterschrift des aufklärenden **Prüfarztes/der Prüfärztin**

7 References

Agarwal A (Hrsg.): Gass' Atlas of Macular Diseases: 2-Volume Set-Expert Consult: Online and Print. Band 1; Elsevier Health Sciences 2011, 672–674

Amsler M (1947): L'Examen qualitatif de la fonction maculaire. Ophthalmologica 114, 248–261

Amsler M (1953): Earliest Symptoms of Diseases of the Macula. Br J Ophthalmol 37, 521–537

Barr CC, Michels RG (1982): Idiopathic nonvascularized epiretinal membranes in young patients: report of six cases. Ann Ophthalmol 14, 335–341

Bouwens MD, van Meurs JC (2003): Sine Amsler Charts: a new method for the follow-up of metamorphopsia in patients undergoing macular pucker surgery. Graefes Arch Clin Exp Ophthalmol Albrecht Von Graefes Arch Klin Exp Ophthalmol 241, 89–93

Bu SC, Kuijer R, Li XR, Hooymans JMM, Los LI (2014): Idipathic epiretinal membrane. Retina 34, 2317–2335

Cherfan GM, Michels RG, de Bustros S, Enger C, Glaser BM (1991): Nuclear sclerotic cataract after vitrectomy for idiopathic epiretinal membranes causing macular pucker. Am J Ophthalmol 111, 434–438

Claessens D, Krüger RV (2015): AMD - A Metamorphopsia Detector. Invest Ophthalmol Vis Sci 56, 4109–4109

Claessens D, Schuster AK (2019): Correlation of Quantitative Metamorphopsia Measurement and Central Retinal Thickness in Diabetic Macular Edema and Age-Related Exsudative Macular Degeneration. Klin Monatsbl Augenheilkd 236, 877–884

Eckardt C (2005): Transconjunctival sutureless 23-gauge vitrectomy. Retina Phila Pa 25, 208–211

Folk JC, Adelman RA, Flaxel CJ, Hyman L, Pulido JS, Olsen TW (2016): Idiopathic Epiretinal Membrane and Vitreomacular Traction Preferred Practice Pattern(®) Guidelines. Ophthalmology 123, 152-181

Fraser-Bell S, Guzowski M, Rochtchina E, Wang JJ, Mitchell P (2003): Five-year cumulative incidence and progression of epiretinal membranes: the Blue Mountains Eye Study. Ophthalmology 110, 34–40

Harada C, Mitamura Y, Harada T (2006): The role of cytokines and trophic factors in epiretinal membranes: Involvement of signal transduction in glial cells. Prog Retin Eye Res 25, 149–164

Huang D, Swanson EA, Lin CP, Schuman JS, Stinson WG, Chang W, Hee MR, Flotte T, Gregory K, Puliafito CA, et al. (1991): Optical coherence tomography. Science 254, 1178–1181

Iannetti L, Accorinti M, Malagola R, Bozzoni-Pantaleoni F, Dalt SD, Nicoletti F, Gradini R, Traficante A, Campanella M, Pivetti-Pezzi P (2011): Role of the Intravitreal Growth

Factors in the Pathogenesis of Idiopathic Epiretinal Membrane. Invest Ophthalmol Vis Sci 52, 5786–5789

Iwanoff A (1865): Beiträge zur normalen und pathologischen Anatomie des Auges. Arch Für Ophthalmol 11, 135–170

Johnson TM, Johnson MW: Epiretinal Membrane. (Hrsg.): Ophthalmology. 3. Auflage; Elsevier, Netherlands 2004, 686–687

Kampik A, Green W, Michels R, Nase P (1980): Ultrastructural features of progressive idiopathic epiretinal membrane removed by vitreous surgery. Am J Ophthalmol 90, 797–809

Klein R, Klein BE, Wang Q, Moss SE (1994): The epidemiology of epiretinal membranes. Trans Am Ophthalmol Soc 92, 403–430

Machemer R, Parel JM, Norton EW (1972): Vitrectomy: a pars plana approach. Technical improvements and further results. Trans - Am Acad Ophthalmol Otolaryngol Am Acad Ophthalmol Otolaryngol 76, 462–466

Mangione CM, Lee PP, Gutierrez PR, Spritzer K, Berry S, Hays RD (2001): Development of the 25-list-item National Eye Institute Visual Function Questionnaire. Arch Ophthalmol 119, 1050–1058

Margherio RR, Cox MS, Trese MT, Murphy PL, Johnson J, Minor LA (1985): Removal of epimacular membranes. Ophthalmology 92, 1075–1083

McCarty DJ, Mukesh BN, Chikani V, Wang JJ, Mitchell P, Taylor HR, McCarty CA (2005): Prevalence and associations of epiretinal membranes in the visual impairment project. Am J Ophthalmol 140, 288–294

Minchiotti S, Stampachiacchiere B, Micera A, Lambiase A, Ripandelli G, Billi B, Bonini S (2008): Human idiopathic epiretinal membranes express NGF and NGF receptors. Retina Phila Pa 28, 628–637

Mitchell P, Smith W, Chey T, Wang JJ, Chang A (1997): Prevalence and associations of epiretinal membranes. The Blue Mountains Eye Study, Australia. Ophthalmology 104, 1033–1040

Pearlstone AD (1985): The incidence of idiopathic preretinal macular gliosis. Ann Ophthalmol 17, 378–380

Pesin SR, Olk RJ, Grand MG, Boniuk I, Arribas NP, Thomas MA, Williams DF, Burgess D (1991): Vitrectomy for premacular fibroplasia. Prognostic factors, long-term follow-up, and time course of visual improvement. Ophthalmology 98, 1109–1114

Schuster AK-G, Kluck A-K, Korb CA, Stoffelns B, Nickels S, Schulz A, Münzel T, Wild PS, Beutel ME, Schmidtmann I, et al. (2020): Characteristics and pathologies of the vitreomacular interface—results from the Gutenberg Health Study. Acta Ophthalmol (Copenh) 98, 273–e281

Snead DRJ, James S, Snead MP (2008): Pathological changes in the vitreoretinal junction 1: epiretinal membrane formation. Eye Lond Engl 22, 1310–1317

Tsilimbaris MK, Tsika C, Giarmoukakis GK and A (2016): Surgical Management of Epiretinal Membrane. Adv Eye Surg

Uemura A, Ideta H, Nagasaki H, Morita H, Ito K (1992): Macular pucker after retinal detachment surgery. Ophthalmic Surg 23, 116–119

Wilkinson CP, Michels RG, Rice TA: Michels Retinal Detachment. 2., illustrated Auflage; Mosby 1997

Wise GN (1975): Clinical Features of Idiopathic Preretinal Macular Fibrosis: Schoenberg Lecture. Am J Ophthalmol 79, 349–357

Wiznia RA (1982): Natural history of idiopathic preretinal macular fibrosis. Ann Ophthalmol 14, 876–878

Yanoff M, Duker J (Hrsg.): Ophthalmology. 5th Edition; Elsevier Inc. 2018, 616–621