Eye (2008) 22, 782–789

www.nature.com/eye

CLINICAL STUDY

Optical coherence tomography on autologous translocation of choroid and retinal pigment epithelium in age-related macular degeneration

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Received: 25 May 2006
Accepted in revised form: 12 December 2006
Published online: 2 March 2007

Proprietary interest: none for all authors

Abstract

Purpose **To analyse structural changes after autologous translocation of choroid and retinal pigment epithelium (RPE) in patients with age-related macular degeneration (AMD) using optical coherence tomography (OCT).**
Methods **We performed a prospective nonrandomised study in 29 consecutive patients, who underwent submacular surgery with translocation of an autologous full-thickness graft of RPE, Bruch's membrane, and choroid. All patients had recent loss of reading vision due to AMD. OCT was performed before surgery and at 3- and 6- month follow-up to analyse the morphological appearance of the graft and the overlying retina.**
Results **Maximum retinal thickness decreased from mean 408 μm (standard deviation (SD) 127 μm) preoperative to mean 373 μm (SD 104 μm) at 6-month follow-up ($P = 0.094$). In 11 cases (40%), a nearly physiological shape of the retina was seen at this time point. A macular hole persisted in two eyes after silicone oil removal. In most eyes, the highly reflective band of the graft presumably corresponding to RPE was continuous with the surrounding RPE band in all six OCT scans. Eyes with flat appearance of the graft at 6-month follow-up (<300 μm) showed a significantly better functional outcome than eyes with more prominent grafts. Interestingly, most patients did not complain about metamorphopsia, even though the graft was prominent or wrinkled in some cases.**
Conclusion **OCT is a useful tool in monitoring intra- and subretinal changes after subretinal surgery with graft translocation. We demonstrated that graft translocation may lead to a normalisation of retinal thickness and stabilisation of visual acuity.**
Eye (2008) **22,** 782–789; doi:10.1038/sj.eye.6702761; published online 2 March 2007

Keywords: OCT; age-related macular degeneration; submacular surgery; graft; translocation

Introduction

Age-related macular degeneration (AMD) is the most common cause of severe visual acuity loss in individuals 65 years of age or older.[1] Neovascular AMD is responsible for over 80% of severe visual loss due to AMD,[2] whereas the dry form of AMD comprises about 90% of all cases. Visual loss related to neovascular AMD is, at least in part, related to vascular leakage resulting in macular thickening.

Photodynamic therapy (PDT) and antivascular endothelial growth factor (VEGF) therapies have been shown to slow the course of the disease in subtypes of wet AMD.[2–5] Simple surgical removal of the membrane did not result in improvement of visual acuity,[6] and attempts to transplant suspensions of retinal pigment epithelial (RPE) cells resulted in a temporary improvement but did not result in a long-term functional monolayer.[7] After 360° macular translocation, late macular oedema, as well as rapid recurrence of geographic atrophy have been documented.[8–12]

Peripheral autologous translocation of the choroid is a novel approach to stabilise visual acuity.[13–15] In this surgery, a full thickness graft of choroid, Bruch's membrane, and RPE is taken from the midperipheral fundus and positioned under the macula. The reaction of the retinal tissue to the transplanted graft and the interaction between retina, RPE, and choroids, however, are not yet fully understood. Funduscopy and angiography allow only limited assessment of epi-, intra-, and subretinal changes. Fukuchi *et al*[16] and Toth *et al*[17] have demonstrated that the pseudo-color banding of retinal optical coherence tomography (OCT) images correlate well with histology. Contemporary literature is focusing on the detection of intra- or subretinal fluid,[18–20] vitreo-macular traction,[21] or macular hole formation.

In our study, we performed OCT imaging to analyse the epi-, intra-, and subretinal changes after translocation of autologous RPE and choroid.

Methods

Patients and surgical treatment

Included into this analysis were 29 patients recruited within the 'patch-study' (peripheral autologous translocation of the choroid),[13,14] who were examined by OCT preoperatively and 3 and 6 months postoperatively (complete cases). Sixteen patients were female, 13 were male. All patients presented with a loss of vision due to AMD. Surgery was performed owing to classic membrane in two cases, occult membrane in eight cases, vascularised pigment epithelium detachment in 10 cases, rip of pigment epithelium in one eye, massive subretinal bleeding in three eyes, and geographic atrophy in five cases. The target group of patients were those with large subfoveal lesions (>5 papillary diameter) or poorly demarcated lesions to which laser photocoagulation or PDT was judged to be inappropriate. Similarly, classic lesions that failed to improve after the first PDT and patients seeking alternative treatment options were included in the study because of patient's preference after discussion of pharmacological and surgical options.

Translocation surgery is described elsewhere.[13,14] In short, a present subretinal membrane was excised via a central retinotomy medial within the arcade region after standard pars plana vitrectomy. An area of about 5–6 disc areas was demarcated and excised in the mid periphery. The graft consisting of intact RPE, Bruch's membrane, and the underlying choroid was positioned underneath the macula. In eyes with dry AMD, Bruch's membrane was incidentally damaged to allow for vascularisation of the graft. As vitreous tamponade either SF6 20% (first four eyes), silicone oil (5000 cst, 11 eyes), or heavy silicone oil (Densiron®, Fluoron GmbH, Neu-Ulm, Germany, last 14 eyes) was used. The surgeon used different endotamponades throughout the study to enhance mechanical protection against peripheral PVR that was developed in some patients to avoid PVR retinal detachments. Heavy silicone oil was chosen in patients with inferior excision areas of the graft. After a minimum of 3 months silicone oil was removed.

Assessment of macular thickness and the graft by OCT

OCT was performed with Carl Zeiss Meditec Model 3000, OCT3 system equipped with software version 4.0 (Zeiss-Humphrey, Zeiss Oberkochem, Germany).

The 'Fast Macular Thickness' acquisition protocol was used to acquire six 6 mm line scans. In addition, cross hair scans (horizontal and vertical 6 mm scans with 512 A scans per B scan for higher resolution) were performed to obtain better quality of the scans. Scans for evaluation were carefully selected to avoid errors in images due to movements of the patient's eye.

If the patients were unable to detect the intersection of the red scan lines because of low visual acuity or if they fixated eccentrically, they were asked to look straight forward and the scan lines were manually positioned over the graft.

In all eyes, maximum retinal thickness of the macula was measured using the computer algorithm provided by the Stratus OCT software, which determines the inner and outer retinal boundaries. If the computer did not identify the boundaries correctly, thickness measurements were performed by manual positioning of the callipers.

In addition, in eyes with central fixation on the graft, retinal thickness was measured at the point of fixation (also if this was not in the fovea) in all of the six scans and the mean value was used for correlation with visual acuity.

The morphological appearance of the retina and the graft was analysed in all eyes by two independent examiners using the 'scan selection' mode providing non-aligned images. The retina covering the graft was classified into five groups: (1) macular oedema, (2) atrophy, (3) 'mixed' appearance with atrophic and oedematous areas, (4) normal retinal appearance, and (5) macular hole (Figure 1). Macular oedema was defined as retinal thickness of more than 250 μm in contrast to atrophy with a retinal thickness below 150 μm throughout the scan.

Furthermore, the appearance of the graft was described either as flat (0–300 μm), prominent (300–500 μm), or very prominent (>500 μm). Thickness of the graft was measured using commercially available software (Adobe Photoshop). The highly reflective band

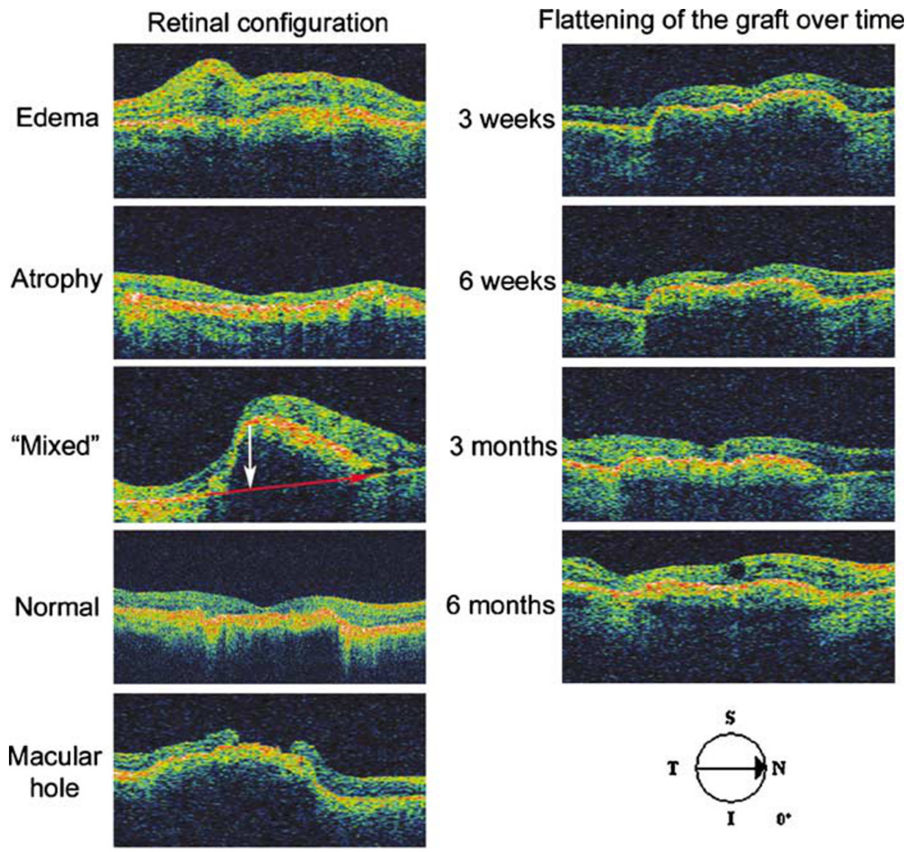

Figure 1 Retinal appearance after graft translocation: oedema, atrophy, mixed appearance, normal configuration, and macular hole. Thickness of the graft is defined as the maximum height (white arrow) from the 'normal position' of the RPE (red arrow) to the RPE of the graft (measurement demonstrated in a case with mixed appearance of the retina). Most grafts appeared prominent early after surgery, flattened within the first postoperative weeks and stayed flat during follow-up.

seen on the elevated area of the scan assumedly resembles the RPE layer of the graft. We chose the outer borders of the graft to be the normal position of the RPE band, which means the guessed line between clearly identifiable, surrounding RPE. Thickness of the graft was then defined as the maximum height from the normal position of the RPE to the RPE of the graft (Figure 1, red and white arrow).

Visual acuity testing

Best-corrected visual acuity testing was performed after full subjective ETDRS protocol refraction preoperatively and at each follow-up visit (logMAR).[13] Reading performance was measured by a standardised reading test according to Radner *et al*.[22,23] Reading acuity was calculated using a logRAD value.

Data analysis and statistical methods

Statistical analysis was carried out using SAS (The SAS System, Release 9.1. 3 SP2; SAS Institute Inc., Cary, NC, USA). Values are given as means and standard deviation (SD). Pearson correlation coefficients were calculated with analyse interrelation between visual acuity and retinal thickness (eligible only for patients with central fixation on the graft). Evaluation of the time effects (difference between 6-months and preoperative values) was performed using paired *t*-tests.

Results

Morphology of the graft

OCT examination was performed 6 weeks after surgery in 21 of 29 eyes, when the thickness of the graft measured 371 μm (SD 192 μm), with nine of 21 grafts demonstrating a thickness of $>300\,\mu$m. Flattening of the graft occurred in 16 out of 27 patients during the follow-up (Figure 1), usually seen from 3 months onwards after surgery. After 6 months, average thickness of the graft was 332 μm (SD 186 μm) with a moderate correlation to far vision ($r=0.46$, $P=0.01$) but no correlation to reading vision ($r=-0.19$, $P=0.52$). Eyes with a flat graft ($<300\,\mu$m,

$n = 18$) at 6-month follow-up had the best mean distant visual acuity followed by those with prominent (300–500 μm, $n = 8$) grafts. Eyes with very prominent grafts (>500 μm) had the worst mean visual acuity ($n = 3$) (Figure 2).

Although the highly reflective band of the graft presumably corresponding to RPE was mostly attached to the hyper-reflective band of the recipient RPE in all six scans, in four cases each one of the six OCT scans intersect an area in which the edge of the graft seems to be not continuous with the surrounding RPE band or in which the margin of the graft was wrapped (Figure 3a and b). In selected patients, we saw a hypo-reflective window towards the choroid and the presence of two highly reflective bands of the graft (Figure 3c–f).

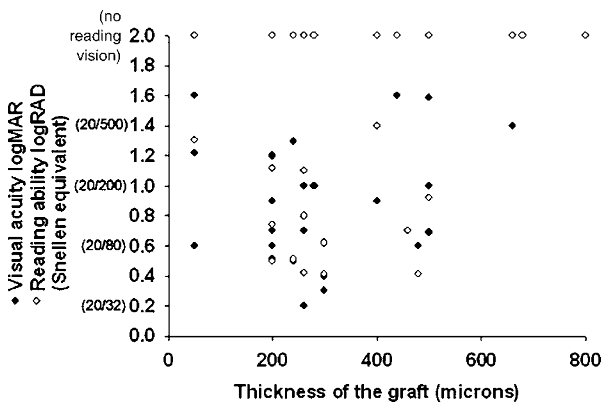

Figure 2 Scatter plot showing the correlation between visual acuity and thickness of the graft. Eyes with a flat appearance of the graft had a tendiously better far visual acuity than eyes with prominent or very prominent grafts (not statistically significant). ●, distant visual acuity; ○, reading ability.

Few grafts had an uneven surface. The cavities of these uneven grafts were filled with retinal tissue, resulting in a straighter surface of the overlaying retina (Figure 3a and b). Most of these patients did not complain about distortion in their daily life, even though the graft surface was wrinkled. In eyes with central fixation and visual acuity better than 1.6 logMAR (19 out of 29 eyes) only two patients complained about disturbing metamorphopsia. In both eyes the graft was flat, but one eye showed a macular hole and one demonstrated a fibrosis close to the point of fixation. A total of four patients reported a reduction of metamorphopsia after graft translocation.

Retinal morphology and function

Maximum retinal thickness in all eyes ranged from 179 to 681 μm (mean 408 μm, SD 127 μm, $n = 29$) preoperative and from 191 to 700 μm (mean 373 μm, SD 104 μm, $n = 29$) at the 6-month follow-up. Decrease in maximum retinal thickness from baseline to 6-months examination showed a tendency; however, this was not statistically significant ($P = 0.1768$). Mean visual acuity was 0.8 logMAR (SD 0.34 logMAR) preoperatively and 1.01 logMAR (SD 0.52 logMAR) at 6 months. There was no relevant

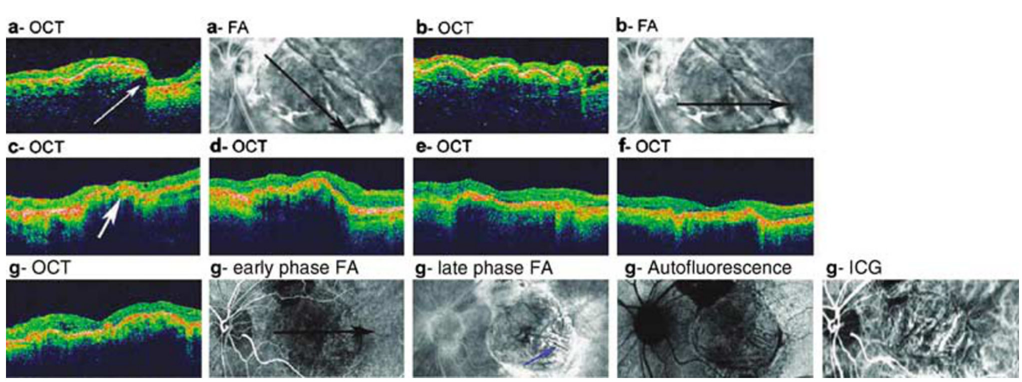

Figure 3 In some eyes the margin of the graft was wrapped and the RPE seemed to be not continuous with the surrounding RPE (white arrow in (a) OCT). Fluorescein angiography (FA) did not show signs for recurrence of CNV in this area (a) FA. The black arrow marks the position of the OCT scan). Some grafts appeared wrinkled (b) OCT). Nevertheless, most of these patients did not complain about metamorphopsia. The cavities of the graft are filled with retinal tissue, so that the overlaying retina appears straighter (black arrow in panel b—FA mark the position of the OCT scan). In some eyes, two bands of high reflectivity are present (c–f). Although the upper band is likely to be corresponding to RPE, the origin of the lower band (white arrow in panel c) is unknown. We presume that this line might represent choroidal vessels underneath the RPE of the graft. Case (**g**) presents with a foveal depression on OCT 6 months postoperative. Nasal from the fovea, a cystoid space is visible whereas in temporal the retina appears normal ((g) OCT, the black arrow in panel g— early phase FA marks the position of the OCT scan), autofluorescence is intact ((g) autofluorescence) and the graft is vascularised ((g) ICG angiography). Fluorescein angiography shows a hyperfluorescence in the temporal half side of the graft in mid- and late phase of fluorescein angiography. Hypofluorescent lines were visible in the area of the graft (blue arrow in panel g—late phase FA).

correlation between retinal thickness measured at the point of fixation (preoperative mean 290 μm, SD 129 μm, $n = 15$; at 6-month follow-up mean 203 μm, SD 82 μm, $n = 12$) and visual acuity.

Retinal morphology was further classified into five subgroups according to the presentation upon OCT analysis (Figure 1). Preoperatively 14 eyes presented with macular oedema, one eye with a retinal atrophy and 14 eyes with a normal appearance of the central retina (Table 1). At 6-month follow-up, central retinal oedema was seen in six eyes, with six more demonstrating a variable retinal thickness over the graft (mixed group).

Thirteen cases showed an improvement or stabilisation in visual acuity postoperative. In seven (54%) out of these cases, a normal retinal configuration was seen at 6-month follow-up. In three eyes, visual acuity decreased during follow-up in the presence of a normal appearing retina.

In one eye with geographic atrophy, Bruch's membrane was not damaged during surgery. Postoperative vascularisation of the graft appeared

Table 1 Morphology of the Retina 6 months postoperatively

6 months preoperative	*Macular oedema (6)*	*Atrophy (4)*	*Mixed appearance (6)*	*Normal configuration (11)*	*Macular hole (2)*
Macular edema (14)	3	2	4	4	1
Atrophy (1)	1	0	0	0	0
Normal configuration (14)	2	2	2	7	1

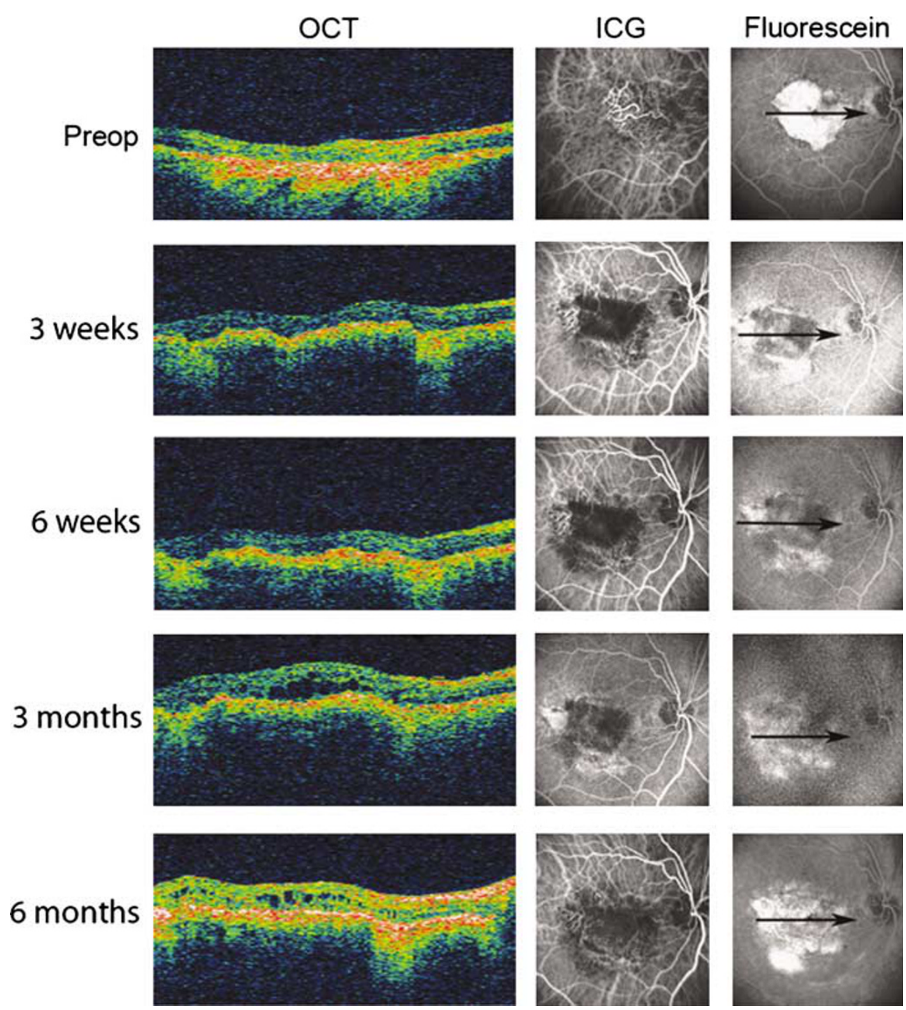

Figure 4 Patient with preoperative geographic atrophy. Three weeks postoperative, no vascularisation of the graft was seen on ICG angiography. Three months later, vascularisation slowly appeared associated with macular oedema, seen on OCT and fluorescein angiography. The black arrow marks the OCT scan.

delayed on ICG angiography associated with macular oedema (Figure 4). In all patients with postoperative macular oedema or mixed appearance of the retina, angiography confirmed late hyperfluorescence. In seven eyes without signs of macular oedema on OCT, fluorescein angiography demonstrated hyperfluorescence in the area of the graft in mid and late phase (Figure 3g). In most eyes, hypofluorescent lines were visible in the area of the graft (Figure 3g, early phase FA).

Complications of surgery included intraoperative bleeding, postoperative development of fibrosis, and macular pucker formation. In two eyes, persistent macular holes were seen after silicone oil removal surgery.

Discussion

In this report, we analyse the morphology of the graft and the overlying retina after a free transplant of choroid and RPE in patients with AMD.

OCT images demonstrate that the highly reflective band of the graft presumably corresponding to the RPE and the surrounding RPE layer appear as one continuous red band as early as 3 weeks after surgery. Previous studies reported reperfusion of the graft visible on indocyanin green angiography 3 weeks postoperative as well as early recovery of visual acuity in patients after graft surgery.[13,14] Accordingly it might be speculated, although it could only be proven with histology, that the graft is integrated into the surrounding RPE choroidal complex early after surgery. Interestingly, a disconnection between graft and recipient RPE apparent on single OCT scans (Figure 3a and b) was not associated with recurrent CNV formation in our series. It cannot be proven without histology that the gap between both RPE bands seen in single OCT scans is not only simulated by shadowing from overlying structures but may also exist and be missed during the imaging procedure because they are not cut by one of the six OCT scans.

Few weeks after surgery, the patch appeared more or less prominent in most cases. Grafting results, at least in part, in a double sandwich-like structure with the underlying recipient choroid, Bruch's membrane, and RPE covered by the full thickness graft consisting of donor-RPE, Bruch's membrane, and donor choroid. Additionally, fluid due to intraoperative trauma and irritation may accumulate in the grafted tissue. During follow-up, flattening of the patch was visible in most cases (Figure 1).

At 6-months follow-up, there was a moderate correlation between thickness of the graft and far visual acuity ($r = 0.46$, $P = 0.01$); however, there was no correlation with reading vision. The reason for the worse functional outcome in eyes with prominent grafts is yet unknown. In our series, we found no correlation with development of fibrosis, macular pucker formation, or vascularisation pattern.

On OCT scans, two high-reflective bands can be distinguished in the area of the graft in several patients (Figure 3c–f). Although it is likely that after graft surgery the upper band reflects the RPE layer of the graft, it seems possible that the lower high-reflective band represents blood vessels of the graft. The presence of dilated, large calibre choroidal vessels is reported in a study analysing histological findings after translocation of RPE and choroid in a pig model.[24]

Although histology would be needed to assign the different hypo- and hyper-reflecting layers of the graft visible on OCT with certainty to specific anatomic structures, OCT is of prominent value for determination of intraretinal fluid and oedema and is of increasing interest for monitoring treatment effects of different therapies.[25–28] In our series, maximum retinal thickness decreased from mean $408 \pm 127\,\mu$m preoperative to mean $373 \pm 104\,\mu$m at 6-month follow-up; however, this was not statistically significant ($P = 0.094$). A late macular oedema is described to be a frequent complication after macular translocation surgery or pigment cell transplantation.[7,10] In our series, one patient with geographic atrophy showed delayed vascularisation of the graft and increasing macular oedema after 3 months (Figure 4). Two eyes showed macular oedema at 6-month follow-up due to epiretinal membrane formation. Despite this, so far no late macular oedema has been observed.

The reduction of retinal thickness is commonly used as a morphological outcome parameter after treatment, but interestingly does not necessarily correlate with functional benefit.[29,30] In our study, eyes with normal retinal appearance reached better distant visual acuity than eyes with retinal oedema, atrophy, or mixed appearance of the retina; however, this was not statistically significant. Our findings indicate that a functional interaction between photoreceptors and functioning graft-RPE is possible after graft translocation, and in turn may lead to a normalisation of the covering retina. Even several eyes with atrophic or oedematous retina showed functional stabilisation or improvement.

Most eyes demonstrated lines of blocked fluorescence visible on fluorescein angiography that correlated with hyperpigmented lines upon funduscopy. These hypofluorescent lines presumably represent pleats of the RPE layer. In seven eyes without macular oedema on OCT, hyperfluorescent areas were visible in mid and late phase of fluorescein angiography. Presumptions that this hyperfluorescence is at least partially explained by RPE disturbance seem possible, but may eventually indicate leakage of newly formed or reperfused vessels of the graft, or more likely in the absence of retinal oedema and subretinal fluid represent the staining of graft tissue.

Metamorphopsia is a common symptom in patients with AMD. Interestingly, although the graft appeared prominent or wrinkled, most patients did not complain about disturbing metamorphopsia, which were more frequently present in eyes with fibrosis or macular hole formation. This phenomenon has also been described in patients with PED.[31] In our series, the lack of metamorphopsia in some patients might be explained by reduced visual acuity. However, 90% of the eyes with visual acuity better than 1.6 and central fixation did not complain about metamorphopsia.

In conclusion, this study indicates that a normal retinal morphology can be achieved after graft surgery. Flat appearance of the graft seems to be an important factor to achieve good functional results. However, being limited by the small number of patients; however, there was no statistically significant correlation between retinal configuration and functional outcome. Interpretation of OCT scans in this study is limited because of the lack of histological correlation.

These data identify OCT as a valuable diagnostic tool for eyes after surgery for AMD and as a supplement to angiographic evaluation. Further improvements in visualisation of intra- and subretinal morphology,[32–34] advances in the understanding of anatomic correlates as well as refinements of measurements[35,36] are anticipated and may enhance the analysis of retinal images in clinical trials.

Acknowledgements

We thank Beate Prinz and Erica Menrath for expert technical assistance. This work was supported by DFG Jo 324/6-2 (Emmy Noether) and DFG Ki 743/5-1.

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