Lisch W, Seitz B (eds): Corneal Dystrophies.
Dev Ophthalmol. Basel, Karger, 2011, vol 48, pp 116–153

Stage-Related Therapy of Corneal Dystrophies

Berthold Seitz[a] · Walter Lisch[b]

[a]Department of Ophthalmology, University of Saarland, Homburg/Saar, and [b]Department of Ophthalmology, City Hospital of Hanau, Hanau, Germany

Abstract

Corneal dystrophies typically result in a gradual bilateral loss of vision in a primary 'white eye' – often in conjunction with epithelial defects in later stages. Treatment of corneal dystrophies needs to be stage-related. To ensure a stage-related therapeutic approach, an adequate classification based on clinical, histopathological and genetic knowledge is indispensable. In principle, topical medications, contact lenses and various microsurgical approaches are applicable. In case of predominantly superficial dystrophies of the epithelium, basal membrane and/or Bowman's layer (map-dot-fingerprint, Meesmann, Lisch, Reis-Bücklers, Thiel-Behnke), recurrent epithelial defects may complicate the clinical picture. If conservative therapy with gels/ointments, application of therapeutic contact lenses and/or conventional corneal abrasion are not successful, phototherapeutic keratectomy (PTK) using a 193-nm excimer laser is the method of choice today. PTK can be repeated several times, thus postponing corneal transplantation (lamellar or even penetrating) for a long time. Three major goals may be achieved by PTK depending on the diagnosis: (1) to remove superficial opacities; (2) to regularize the surface and treat irregular astigmatism, and (3) to improve the adherence of the epithelium. In dystrophies with depositions predominantly in the stroma (e.g. granular, lattice, macular, recurrence on the graft), PTK may be a reasonable alternative to anterior lamellar or penetrating keratoplasty (PKP) depending on the exact localization of the lesions. Besides exact determination of the depth of depositions using a slit lamp, a preoperative topography analysis is indispensable. The therapy of endothelial dystrophies depends on diagnosis and age: Fuchs endothelial corneal dystrophy will need corneal transplantation (e.g. when visual acuity drops below 0.4). In contrast, transplantation will only be very rarely necessary in posterior polymorphous corneal dystrophy, but the intraocular pressure has to be checked frequently. Especially in elderly patients with reduced compliance, posterior lamellar keratoplasty – preferably in the form of Descemet stripping automated endothelial keratoplasty – may be performed instead of PKP. In case of congenital hereditary endothelial dystrophy, the best time point of PKP has to be determined with regard to amblyopia (surgery too late) and inadequate follow-up (surgery too early) together with parents and pediatric ophthalmologists on an individual basis. In conclusion, for stage-related therapy of corneal dystrophies, besides contact lenses, PTK and PKP, various techniques of lamellar keratoplasties represent an indispensable enrichment of our corneal microsurgical spectrum today.

Corneal dystrophies typically result in a gradual bilateral loss of vision in a primary 'white eye' – often in conjunction with epithelial defects in later stages. Treatment of corneal dystrophies needs to be stage-related. To ensure a stage-related therapeutic approach, an adequate classification based on clinical, histopathological and genetic knowledge is indispensable. In principle, topical medications, contact lenses and microsurgical interventions are applicable.

Over the past decades, there has been a shift in treatment of these conditions from corneal transplantation (penetrating keratoplasty – PKP) to excimer laser-assisted keratectomy, typically referred to today as phototherapeutic keratectomy (PTK), for visual restoration. PTK using the 193-nm excimer laser can produce significant visual improvement in these patients, and corneal transplantation or repeat transplantation can be delayed or even avoided. In addition, lamellar keratoplasty techniques [anterior lamellar keratoplasty (ALKP) and posterior lamellar keratoplasty (PLKP)] are widely discussed today.

Phototherapeutic Keratectomy Using an Excimer Laser

In case of predominantly superficial dystrophies of the epithelium, basal membrane and/or Bowman's layer (map-dot-fingerprint, Meesmann, Lisch, Reis-Bücklers, Thiel-Behnke), recurrent epithelial defects may complicate the clinical picture. If conservative therapy with gels/ointments, application of therapeutic contact lenses and/or conventional corneal abrasion are not successful, PTK using a 193-nm excimer laser is the method of choice today [1]. PTK can be repeated several times, thus postponing corneal transplantation (lamellar or even penetrating) for a long time. Three major goals may be achieved by PTK depending on the diagnosis: (1) to remove superficial opacities; (2) to regularize the surface and treat irregular astigmatism, and (3) to improve the adherence of the epithelium. These three goals may apply to variable degrees in a given pathology (fig. 1) [2].

In dystrophies with depositions predominantly in the stroma (e.g. granular, lattice, macular, recurrence on the graft), PTK may be a reasonable alternative to anterior lamellar keratoplasty or PKP depending on the exact localization of the lesions. Besides exact determination of the depth of depositions using a slit lamp, a preoperative topography analysis is indispensable. In principle, prominent lesions have a good, whereas localized lesions with stromal thinning have a limited prognosis.

Patient Counseling

The efficacy of PTK seems to be related to several factors, including (1) the nature of the corneal disorder; (2) the patient's subjective complaints; (3) the preoperative refractive error; (4) the treatment strategy, and (5) the tissue ablation properties

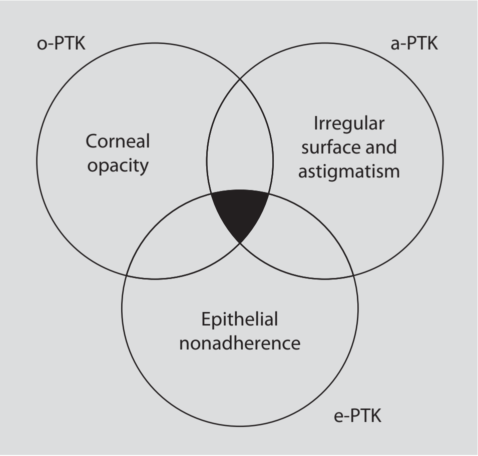


Fig. 1. Indications for PTK: (1) corneal opacity (o-PTK); (2) irregular corneal surface and astigmatism (a-PTK), and (3) epithelial nonadherence (e-PTK). Such indications may overlap in a number of corneal disease processes and may apply to variable degrees in a given pathology (modified after Hersh and Wagoner [2]).

of the laser. Careful attention should be directed toward the specific patient complaints to better determine if PTK may be expected to achieve the desired clinical goals. Certainly, the patient should be completely informed about the diverse surgical steps. Especially, characteristic phenomena referred to as 'sight', 'sound' and 'smell' have to be discussed with each patient in advance to avoid unexpected reactions intraoperatively.

Corneal Clarity

A crystal-clear cornea is typically not the goal of a PTK for superficial corneal dystrophies. The goal is to postpone or even avoid lamellar keratoplasty or PKP. Often removal of major central opacities leads to a considerable increase in visual acuity [3]. Typically some deposits are left in the midstroma (e.g. in granular dystrophy) without major disadvantages. The dystrophy may recur early after PTK, especially in macular dystrophy [4, 5] and Reis-Bücklers dystrophy [6, 7]. In contrast, map-dot-fingerprint dystrophy [8] and granular dystrophy [9, 10] will recur later. In case of recurrence of the dystrophy, repeat PTK or PKP/ALKP may be necessary [11, 12].

Visual Acuity and Refraction

Depending on the preoperative refraction, PTK may lead to an increased best-corrected visual acuity (BCVA), despite a decrease in the uncorrected visual acuity (UCVA). This may be due to a hyperopic shift after central PTK. A BCVA of 1.0 (20/20) is not the goal. Often the patient is highly satisfied when the visual acuity increases from 0.2–0.3 to 0.6–0.8. In some cases, even a hard contact lens may be necessary to achieve good vision. The patient must be aware of this potential problem in advance and should not be confronted with this issue for the first time after PTK in case a major hyperopic shift has occurred.

Recurrent Corneal Erosion Syndrome

Corneal dystrophies (especially epithelial basement membrane dystrophy – EBMD) are often associated with recurrent corneal erosion syndrome (RCES) [13]. Conservative treatment in case of RCES may include (1) gels and ointments; (2) lubricants (to be applied especially early in the morning and late at night); (3) nonpreserved artificial tears in severe cases; (4) autologous serum [14]; (5) therapeutic contact lenses, or (6) collagen shields.

Surgical alternatives include (1) abrasion and thorough removal of the basal membrane with a hockey knife, with or without (2) anterior stromal puncture [15]. Anterior stromal puncture should not be performed in the central optical zone to avoid glare, halos and visual impairment postoperatively. After PTK, the success rate is not 100% but somewhere between 85 and 90% [16, 17]. Artificial tears and/or gels are still necessary after PTK. Especially if PTK in corneal dystrophy is performed predominantly because of the pain caused by RCES, the patient must be aware of the potential loss of UCVA after PTK.

Diagnostic Approaches for Surgical Decision Making

Microsurgeons should realize that PTK is not the treatment of choice for all anterior corneal pathologies. 'Aiming and shooting' at all corneal pathologies should be avoided to prevent dissatisfaction and frustration. The primary diagnosis does not necessarily dictate the treatment of choice, since various clinical presentations of the same disorder may suggest different therapeutic approaches (table 1). Appropriate recommendations regarding treatment of choice can be made only after analyzing the horizontal/vertical distribution and the pattern of the pathology [3] and the applicability of manual versus PTK techniques.

However, the ultimate determinant of the appropriate technique is the functional objective of the procedure. (1) Visual objectives relate to final visual acuity. In assessing a patient's needs not only is the final BCVA important but any potential adverse alteration in UCVA that may result from undesirable hyperopic shift must be taken into account. (2) Nonvisual objectives include (a) reducing pain associated with RCES, which is a very typical complication of many progressive dystrophies [13], (b) decreasing optical problems such as glare, halo, monocular diplopia or triplopia, and/or (c) clearing the visual axis for subsequent cataract surgery.

Patient Selection

Besides clearly defining the expectations of patients and recheck whether these can be achieved with PTK, the individual corneal pathology itself is most critical for surgical decision making. Contact lens tolerance should be an issue in the process of decision making before surgery. In contrast to refractive surgery or even laser PKP, the PTK procedure has to be planned on an individual basis. Therefore, it is essential that the

Table 1. Principal therapeutic options for corneal dystrophies

Conservative
Topical (artificial tears, gels, ointment; antibiotics)
Contact lenses (soft/rigid; with/without keratoplasty)
Surgical
Corneal abrasion/pannus removal
Phototherapeutic keratectomy (with/without mitomycin C)
Corneal transplantation
Penetrating keratoplasty
Conventional
Excimer laser
Femtosecond laser
Deep anterior lamellar keratoplasty
Posterior lamellar keratoplasty (DSAEK, DMEK)

DSAEK = Descemet stripping automated endothelial keratoplasty; DMEK = Descemet membrane endothelial keratoplasty.

surgeon has a close look at the cornea using a slit lamp immediately before surgery, even if he/she has seen the patient at an earlier visit.

Refractometry

Identical morphological presentations do not necessarily dictate the same treatment of choice, since functional requirements may suggest different therapeutic approaches. Reis-Bücklers corneal dystrophy (RBCD) in a myopic eye may be successfully treated with PTK. In contrast, the same pathology in a hyperopic eye may suggest only manual superficial keratectomy, at least in case the patient is contact lens intolerant. For this reason, objective and subjective refractometry measurements of both eyes are mandatory in each patient before PTK to avoid anisometropia postoperatively.

Biomicroscopy with the Slit Lamp

Pattern Assessment

In all instances of assessment of corneal dystrophies, the light of the slit lamp must NOT be dimmed. For surgical decision making, the localization of the lesion is important: (1) multifocal (regular corneal tissue in between); (2) segmental contiguous, and (3) diffuse patterns of opacifications may be distinguished. Especially in cases of EBMD, the microsurgeon has to look carefully for subtle epithelial changes. In these cases, indirect illumination and retrograde illumination with dilated pupils may be required to detect the prevalent lesions.

Horizontal Extension

Modified after Hersh and Wagoner [2], corneal pathology may be categorized into the (1) central (optically relevant); (2) paracentral, and (3) peripheral zone.

The central zone is defined as the central 3–4 mm where the dystrophy may directly (through clouding of the visual axis) or indirectly (through the induction of irregular astigmatism) diminish visual function.

The paracentral zone is defined as the midperipheral area where pathology may indirectly affect visual function by the induction of irregular astigmatism and light scattering/glare. More often, however, treatment for disorders in this region is considered for recurrent epithelial erosions or potential extension into the visual axis. PTK in this region may produce alterations in visual function due to iatrogenic changes in the contour of adjacent corneal tissue in the visual axis.

The peripheral zone has little or no direct impact on visual function. However, in case of high elevation, for example peripheral nodules of Salzmann's corneal degeneration may induce irregular astigmatism due to tear film pooling. Multifocal (mid-) peripheral nodules may even induce considerable hyperopia and irregular astigmatism due to asymmetric tear film pooling resulting in an 'optical cornea plana' [18].

Vertical Extension

To evaluate the vertical extension, first a classification of the level of the corneal surface at the site of the lesion has to be made: (1) 'plus disease' is defined as an elevated (nodular) lesion compared to the surrounding corneal surface; (2) 'zero disease' is defined as a lesion within the level of the surrounding corneal surface, and (3) 'minus disease' is defined as a depressed lesion compared to the surrounding corneal surface. In addition, the vertical extension of corneal disorders may be divided into (1) pre-Bowman's layer; (2) involving Bowman's layer, and (3) anterior stroma, and midstroma. 'Pre-Bowman's' refers to dystrophies that involve the epithelium and basement membrane, but completely spare Bowman's layer, for example EBMD (eponym: map-dot-fingerprint dystrophy) [8].

'Bowman's' refers to all pathologies incorporated into Bowman's layer with or without epithelial and epithelial basement membrane involvement, for example Reis-Bücklers or Thiel-Behnke dystrophy [1, 2]. 'Anterior stromal' refers to dystrophies that have extended beneath Bowman's layer into the anterior 100–150 μm of the cornea, for example anterior variants of granular or lattice dystrophy [3, 9, 10]. 'Stromal' refers to disorders where excision of deep stromal lamellae (>150 μm) is required to achieve a satisfactory visual outcome, for example macular dystrophy [4, 5].

Topography Analysis and Assessment of Corneal Thickness Profile

Besides keratometry, topography analysis is indispensable to reflect the corneal power map over the central and midperipheral cornea. The effects of localized or diffuse lesions on the corneal curvature are best assessed with topography analysis. Refractive powers and individual axes of 4 or more hemimeridians are rounded up

Table 2. Strategic planning and surgical techniques of excimer laser PTK

Avoid 'aiming and shooting' at all corneal pathologies to avoid dissatisfaction and frustration
Remove as much of the diseased tissue with the blade
Remove as little tissue as possible with the laser (see fig. 2)
Use the laser predominantly for smoothing
Use 'masking agents' repeatedly during one session
Consider simultaneous refractive ablation
Prevention of hyperopic shift with deep ablation
High/irregular astigmatism and superficial opacities (topography-based ablation)
Asymmetric astigmatism after PKP and recurrence of dystrophies
Recentration of the apex with medium-stage keratoconus (in case of contact lens intolerance)
Take into account potential subsequent PKP (save peripheral Bowman's layer for suture fixation)

by system-specific indices, such as surface regularity index and surface asymmetry index of the TMS topography system [19].

Ultrasound pachymetry can only supply the microsurgeon with the entire corneal thickness at one spot. In contrast, slit scanning tomography (Orbscan) or Scheimpflug analysis (Pentacam) provide a thickness profile of the cornea including full information on the anterior and posterior corneal curvature. To assess the true vertical involvement of the lesion, anterior segment optical coherence tomography may be used. Nevertheless, slit lamp examination still is the most important qualitative examination technique to plan the surgical approach.

Strategic Planning and Surgical Techniques

PTK is not necessarily the treatment of choice for all anterior corneal pathologies. While in many circumstances it represents a significant advance in our ability to excise pathology that was once difficult to remove manually, it does not always guarantee a superior result. In some situations, it may produce an even less desirable outcome than manual superficial keratectomy (table 2).

General Concepts

In each individual patient, the actual ability of the PTK procedure to accomplish the desired objective of removing the pathologic process AND regularize the surface must be ascertained. Almost invariably, any dystrophy amenable to manual resection can be removed by PTK, although the converse is not true. Generally, the more posterior the pathology extends the more likely manual keratectomy is to be technically less desirable than PTK. At Bowman's layer, disorders such as Reis-Bücklers or Thiel-Behnke dystrophy may be easily resected manually. In contrast, anterior

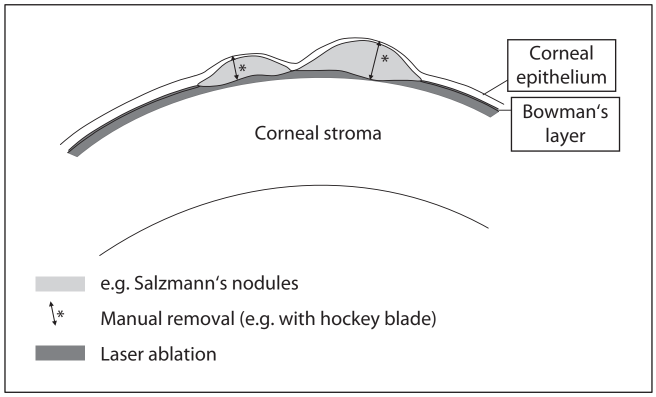


Fig. 2. Technical details: first major prominent subepithelial tissue is removed manually, e.g. with a hockey blade, before excimer laser ablation is applied to remove intrastromal opacifications and especially smoothen the surface (by use of masking fluids) [23, 24].

corneal dystrophies reaching into the stroma (e.g. granular or lattice dystrophy) are typically very difficult to remove manually with a blade but are amenable to PTK [3, 18].

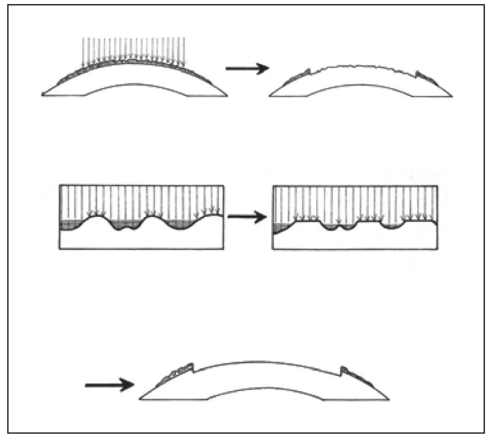
In general, PTK should be performed on a 'quiet eye'. Possible confounding problems such as blepharitis and active infection must be controlled before proceeding with surgery. In addition, intraocular inflammation should be controlled. The intended effects of PTK may be threefold: (1) removal of corneal opacities; (2) treatment of irregular corneal surface and astigmatism, and (3) increase and stabilization of epithelial adherence. Such indications may overlap in a number of corneal diseases and may apply to variable degrees in a given pathology (fig. 1).

Removal of Opacities

Generally, we recommend to remove as much of the diseased tissue with the blade or hockey knife and remove as little tissue as possible with the laser. This is especially true for all 'plus diseases' which are multifocally arranged. A cleavage plane is identified between abnormal tissue and Bowman's layer or stroma using the hockey knife to raise a tissue edge. To facilitate visualization and manipulation of the abnormal tissue, the corneal surface is kept dry. Traction may be applied with a forceps to strip the abnormal material along its natural cleavage plane while the tip of a dry cellulose sponge may be used as an atraumatic dissection instrument. In the case of strong adherence, the blade may be carefully used to lyse adhesions or to scrape residual abnormal tissue. Care is taken to leave limbal stem cells intact [20, 21]. Caution should be taken to remain in the cleavage plane, thus avoiding damage to Bowman's layer that may evoke further corneal scarring and irregularities. After mechanical scraping of residual tissue remnants with the hockey knife, laser ablation is performed. This technique may be called 'subepithelial PTK' (fig. 2).

In case of regular corneal topography – which is very rarely the case – a 'transepithelial PTK' may be advisable. In this case, the epithelium will mask the irregularities

Fig. 3. Application of masking fluid to smoothen the corneal surface. Upper left/right: schematic drawing of an irregular corneal surface before/after excimer laser ablation. Note how the irregular corneal surface pattern is preserved although the corneal substance is thinned. Middle left/right: using a masking fluid to protect the 'valleys' of the corneal surface by absorbing incoming laser energy will allow smoothing of the surface as the 'peaks' of the irregular surface are removed by photoablation leaving a smooth corneal surface (bottom) (modified after Hersh and Wagoner [2]).

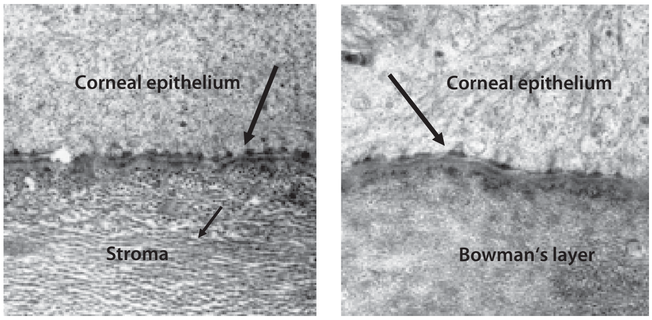


of the superficial stroma, acting as a biological 'masking agent' and contributing to a smoother postoperative stromal surface. However, different ablation rates in epithelium, stroma and scar tissue have to be taken into account.

Microsurgeons should be aware of the fact that corneal dystrophies typically recur after some time. Thus, removing as little tissue as possible (although the cornea may not be completely cleared) and leaving enough tissue to enable repeat PTK is mandatory. Especially in case of stromal involvement of dystrophies, corneal transplantation may be required later, if the outcome is not satisfactory for the patient. Therefore, peripheral Bowman's layer should be saved for suture fixation in case of subsequent PKP [22]. Typically, a treatment diameter of 7.0–8.0 mm with a small transition zone of around 0.5 mm is adequate.

Smoothening of Surface and Decreasing Irregular Astigmatism

It is important to note that, in general, the excimer laser will remove an equivalent amount of tissue over the entire area upon which it impinges (fig. 3). Although opacities will be removed, irregularities of the surface will be maintained because tissue is removed parallel to the surface. Therefore, during most PTK procedures it is mandatory to use so-called 'masking fluids' repeatedly during one session. Methylcellulose 1% has proven to fill in irregularities, thereby smoothing the surface to be ablated [2]. Hyaluronic acid 0.3% (e.g. Vismed®) may also be used successfully for this purpose [23]. The viscosity of these fluids is appropriate to fill in the 'valleys' of an irregular surface while leaving the 'peaks' exposed to the laser action [24]. This allows the surface to be smoothed with the laser while opacities are removed. The thickness of the masking fluid layer should be enough to smooth the valleys of the corneal surface, but not so much as to completely block the incoming laser beam. Collagen gels and other molding compounds have not been generally accepted in the community of corneal specialists.



Macular dystrophy after PTK;
Density of hemidesmosomes:
5,500 ± 800/mm

Macular dystrophy - Control
Density of hemidesmosomes:
3,500 ± 900/m

Fig. 4. Increased number of hemidesmosomes may be responsible for improved epithelial adherence after excimer laser PTK in macular corneal dystrophy. Without laser ablation, 3,500 ± 900 hemidesmosomes per millimeter of basal membrane length were measured. In contrast, after PTK, 5,500 ± 800 hemidesmosomes per millimeter of basal membrane length were measured [25].

The laser procedure is interrupted at frequent intervals and the patient may be examined with the slit lamp to monitor progress of the procedure and to determine areas to be treated further. If no slit lamp is available, typically 2–3 sessions with intended ablation depths of 40–50 μm over appropriate masking fluid are sufficient to regularize the corneal stromal surface after extensive mechanical debridement.

Improvement of Epithelial Adhesion

In case of nondystrophic RCES (e.g. traumatic origin), some microsurgeons advocate transepithelial PTK with treatment scheduled in the painless interval. However, RCES in the context of progressive corneal dystrophies should preferably be treated with subepithelial PTK (= treatment of Bowman's layer after generous removal of loose and irregular epithelium).

We know from histologic and ultrastructural studies that excimer laser ablation results in a significant increase in hemidesmosomes (fig. 4) thus improving epithelial adhesion to the underlying stroma [25]. For this reason, even dystrophies, such as the map-dot-fingerprint variant, that may be removed with mechanical corneal abrasion only should better be treated with additional PTK to regularize the surface and improve epithelial adherence [8].

Combination with Mitomycin C

Combining PTK with temporary application of 0.02 mg% mitomycin C on a merocel sponge for 30–60 s after laser action may prevent scarring and recurrence of certain corneal pathologies, such as granular dystrophy type 2 and Salzmann's nodular degeneration [26]. Potential problems with this antimetabolite include: hyperopic shift, epithelial healing problems, endothelial damage in thin corneas, and irreversible keratocyte damage with (late) melting. However, corneal toxicity of mitomycin C is not well established yet.

Medical Treatment

Preoperative Treatment

Typically, nonsteroidal anti-inflammatory drugs are applied 4 times a day the day before and at the day of surgery to reduce corneal inflammatory reaction after PTK. There is no need to apply topical or systemic antibiotics before PTK. In some cases, the operative eye may require pilocarpine 1% to constrict the pupil and thereby facilitate centration of the procedure and improve visualization of the pilot beam on the cornea.

Intraoperative Treatment

Most procedures are done using only topical anesthetic drops. In case of corneal dystrophies with intended subepithelial PTK, we prefer cocaine drops to break the hemidesmosomes thus making mechanical epithelial removal easier. Intraoperatively, masking fluids may be repeatedly used to achieve a regularization of the corneal surface depending on the degree of irregularity in a given eye.

At the end of surgery, we preferably apply cyclopentolate drops and ofloxacin ointment in conjunction with a pressure patch, to be changed daily until complete epithelial closure. Other microsurgeons prefer to apply ofloxacin eyedrops and a therapeutic contact lens.

To reduce pain, we supply the patient with tramadol orally for 2 days.

Postoperative Treatment

We do NOT recommend administering nonsteroidal anti-inflammatory drugs to reduce pain after PTK because of their well-documented adverse effects on epithelial wound healing. After epithelial closure, topical antibiotics are typically not necessary any more. However, lubricants or gels and nonpreserved artificial tears should be applied to promote epithelial remodeling without long-lasting superficial punctate keratopathy. Typically topical steroids (e.g. fluorometholone 0.1% or prednisolone acetate 1% in the presence or likelihood of more profound stromal inflammation after deep ablation) are tapered slowly over some weeks or months. Depending on the depth of ablation, it might be started to be administered 4 times a day and reduced by 1 drop a day every month.

Indications and Outcome

In table 3, the potential indications for PTK are summarized. In the following paragraph, only some specific details and/or recommendations concerning PTK in certain corneal

Table 3. Indications for excimer laser PTK

Corneal dystrophies
Epithelial basement membrane dystrophy (synonyms: map-dot-fingerprint dystrophy)
Bowman's layer dystrophies
Reis-Bücklers corneal dystrophies
Thiel-Behnke corneal dystrophies
Meesmann-Wilke corneal dystrophies
Granular corneal dystrophies [1, 2]
Lattice corneal dystrophies
Macular corneal dystrophies
Schnyder corneal dystrophies
Recurrences on the graft after keratoplasty
(Bullous keratopathy in Fuchs corneal dystrophies; combination with amniotic membrane transplantation)
Other superficial corneal pathologies
Scars
Herpetic origin (never without systemic acyclovir!)
Adenoviral keratoconjunctivitis
Scrofulous
Following other corneal infections
Traumatic
Salzmann's nodular degeneration
Pterygium (with involvement of optical zone; without involvement of optical zone – no indication for PTK!)
Subepithelial band keratopathy
Mechanical scraping
EDTA chelating
PTK just for smoothing
Keratoconus
Fibroblastic subepithelial nodules ('proud nebulae')
Irregular astigmatism (but: biomechanical stability of the cornea may further be decreased) – in combination with riboflavin-UVA cross-linking
Persisting epithelial defects
Erosions
Ulcers
Recurrent corneal erosion syndrome
Trauma
Epithelial basal membrane dystrophy (synonyms: Cogan-Guerry variant)
Idiopathic

dystrophies are given. It must be stressed in advance that not the class of dystrophy itself but the individual distribution of opacification, the amount of surface irregularities and the degree of RCES in combination with subjective symptoms are determining the decision for or against and the individual modality of PTK in a given patient.

Criteria of Outcome

Morphology

At the conclusion of the PTK treatment the cornea typically has a ground-glass appearance. After epithelial healing, which is typically completed after 3–4 days, corneal luster is regained and visual acuity may be markedly increased despite residual opacities in the deep stroma.

Persisting focal opacifications (typically in the deeper stroma and in the corneal periphery) must be distinguished from 'haze' early after laser ablation and from recurrences of the dystrophy, which typically appear in the subepithelial area after some years depending on the type of dystrophy.

Function

Criteria to determine visual function after PTK include: (1) UCVA; (2) BCVA; (3) subjective refraction and spherical equivalent of refraction; (4) astigmatism (refractive cylinder and keratometric/topographic astigmatism); (5) central corneal power (keratometric/topographic); (6) contrast sensitivity, and (7) patient's subjective assessment (photophobia, halo, glare, ocular surface discomfort).

The goal of PTK is to improve BCVA by 2–5 lines. BCVA of 1.0 (20/20) is not the goal! In previously emmetropic or even hyperopic eyes, UCVA may be worse after PTK due to a hyperopic shift. Typically, topographic regularity of the corneal surface will be improved after PTK. 'Plus diseases' with prominent lesions are good candidates. In contrast, 'minus diseases' (localized depressed lesions, e.g. foreign body scars) are bad candidates.

Although one of the important goals of PTK is to obviate the need for PKP, corneal transplantation may still be necessary in some cases. We found that preceding PTK does not appear to impair the outcome of subsequent PKP in patients with macular and granular dystrophy [22].

Recurrent Erosions

To assess the effects of the e-PTK component (i.e. PTK to improve epithelial adhesion), the patient's subjective report on ocular surface discomfort is valuable. Other important outcome measures are time period until complete epithelial closure after PTK and recurrence rate of corneal erosions. This should not only be given as a percentage but also as Kaplan-Meier curves [8, 17].

Until now it is still unclear what the exact mechanism is by which interaction between UV light and corneal tissue during PTK results in better epithelial adherence. However, we were able to show that after PTK the number of hemidesmosomes is significantly increased (fig. 4) [25].

Meesmann Corneal Dystrophy

Meesmann corneal dystrophy is a rare bilateral autosomal dominant exclusively epithelial dystrophy that usually appears very early in life. Tiny epithelial vesicles can be seen

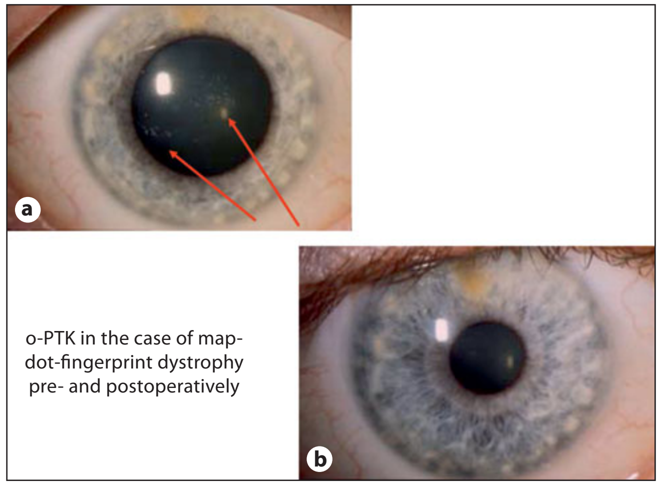


Fig. 5. Map-dot-fingerprint (epithelial basal membrane) corneal dystrophy: slit lamp appearance before excimer laser PTK (**a**), and no recurrence 4 years after excimer laser PTK (**b**) [8]. o-PTK = PTK to treat corneal opacity.

extending out to the limbus and may cause visual disturbance. Most patients are asymptomatic and hence require no treatment. Soft contact lens wear may help if patients show signs of RCES. Pure abrasion with a hockey knife should remove all the pathologic epithelium. Nevertheless, PTK may be used to enhance the adhesion of the corneal epithelium but results vary from good to bad with the possibility of inducing major haze [27].

Epithelial Basement Membrane Dystrophy

EBMD is the most common anterior corneal dystrophy [8, 20]. The so-called Cogan's microcystic dystrophy and the so-called map-dot-fingerprint dystrophy (Guerry) are variants or eponyms of EBMD. For both variants of EBMD, PTK using an excimer laser with low pulse energy and low number of pulses can be considered an effective and minimal invasive treatment modality to achieve a fast and durable epithelial closure, to prevent recurrent corneal erosions and to increase visual acuity in most patients (fig. 5) [8]. In this study, no recurrence of corneal erosion was observed during a mean follow-up of 4.8 years. Asymptomatic dystrophy signs in the midperiphery became visible in 2 out of 15 eyes at 3 and 5 years after PTK.

Granular Corneal Dystrophy

According to genetic studies, granular corneal dystrophy (GCD) is an epithelial rather than a stromal dystrophy. The multifocal opacities are usually superficial but can sometimes be located deeper in the stroma. In our department, GCD – besides RCES – was the dystrophy most frequently treated with PTK. To prevent a major hyperopic shift and to allow for repeat PTK in case of recurrence the primary ablation should be limited to less than 100 μm. The results are generally described as good (fig. 6) [9, 10].

Histomorphometric analysis of deposits in the cornea suggests that GCD is a better candidate than lattice dystrophy for PTK since the deposits are located more

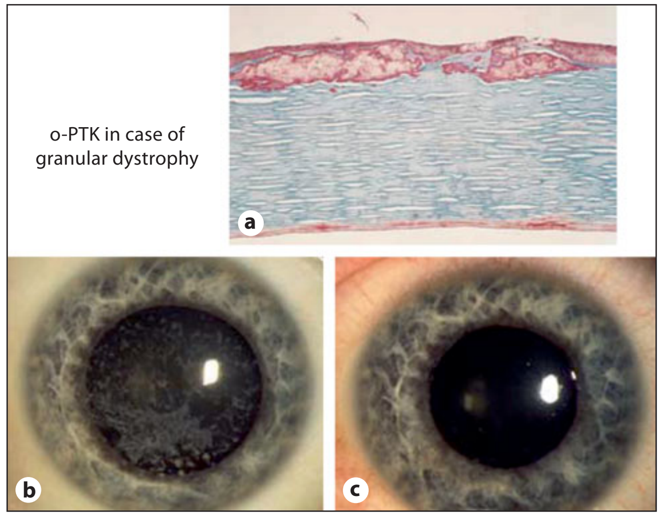


Fig. 6. GCD: superficial deposits of hyaline material (Masson's trichrome stain) (**a**), slit lamp appearance before excimer laser PTK (**b**), and 3 months after excimer laser PTK (**c**) [9]. o-PTK = PTK to treat corneal opacity.

superficially and the central clear optical zone after removal of 100 μm of tissue is significantly larger in granular (from 484 ± 389 μm to 1,451 ± 1,954 μm) than in lattice (from 258 ± 183 μm to 846 ± 784 μm) dystrophy. Deposits were completely removed in 22% of the GCD samples. In both dystrophies, a clear central 'pinhole' greater than 1 mm in diameter was achieved in around one third of corneas [3].

Lattice Corneal Dystrophy

Lattice corneal dystrophy (LCD) is characterized by the formation of branching filaments or bands in the corneal stroma. These are usually seen in the superficial part of the stroma, but it is not rare for them to penetrate deeper. The very center of the cornea is often opacified late in the disease but it is eventually overtaken by a general superficial opacification that reduces vision. Ablation of the superficial stroma removes the diffuse central opacity as well as some of the stromal branching filaments. Nevertheless, the average outcome in terms of visual acuity is decent but not impressive [9, 20]. The opacifications of LCD are often located too deeply to be completely removed. Spontaneous erosions are usual in LCD, but healing time is often longer than for other spontaneous erosions. In accordance, epithelial healing after PTK is typically delayed, too. It may require up to 3 weeks [28]. Recurrence rates are steady but fairly slow.

Bowman's Layer Dystrophies

Both types of Bowman's layer dystrophies have been confused for a long time. Both types are good candidates for PTK allowing for increased visual acuity and reduction of RCES. Eyes with Reis-Bücklers dystrophy seem to recur earlier than those with Thiel-Behnke dystrophy [20, 21].

Reis-Bücklers Corneal Dystrophy

RBCD is an autosomal dominant dystrophy where Bowman's layer is replaced with fibrocellular scar tissue that is classically described as 'saw tooth configuration'. The opacifications resemble geographic maps, but deposits reach deeper than in EBMD. PTK for RBCD is generally reported successful, but most recurrences appear within 1 year after PTK.

Thiel-Behnke Corneal Dystrophy

Thiel-Behnke corneal dystrophy (autosomal dominant inheritance) typically shows honeycomb opacifications of the superficial central stroma. In contrast to RBCD ('rod-shaped bodies'), Thiel-Behnke corneal dystrophy displays 'curly fibers' in Bowman's layer on transmission electron microscopic evaluation. Significant visual improvement may be achieved with PTK. Recurrences seem to appear more rarely and later than with RBCD.

Schnyder Corneal Dystrophy

Two changes characterize this dystrophy. One is a diffuse general, but not very dense opacification in the center of the corneal stroma. The other characteristic concerns the formation of subepithelial crystals in the center of the cornea in about half of the patients which scatter light very effectively. Schnyder corneal dystrophy is not very common. The treatment aims at removing the central superficial crystals. It seems that general stromal cloudiness does reduce vision to some extent as postoperative BCVA usually is about 20/40. However, visual acuity after PTK is maintained for a long time and recurrences seem to be very slow [20, 21, 27].

Macular Corneal Dystrophy

In the presence of superficial plaque-like opacities caused by macular corneal dystrophy PTK can moderately increase BCVA initially, although the diffusely scattered deep stromal opacities cannot be removed (fig. 7) [4]. In all patients with a follow-up of more than 1.4 years, a recurrence was observed leading to PKP in 6 of 10 eyes of this study. PTK should be considered after detailed explanation of limited long-term prognosis with the typically young patients (end of second decade). In addition, RCES may also be treated successfully by PTK. Despite possible complications primary PKP still seems to be the definite therapeutic option in patients with macular corneal dystrophy, because of the high recurrence rate after PTK and involvement of the corneal endothelium.

Recurrences of Dystrophies on Grafts after Keratoplasty

Various dystrophies seem to recur after different time periods following keratoplasty. Whereas GCD recurs very often and early, macular corneal dystrophy does recur very rarely and often not before 10–15 years after PKP.

In corneal grafts, the recurrence of GCD and LCD changes often take the form of superficial diffuse opacification (fig. 8). This type of opacification can be readily

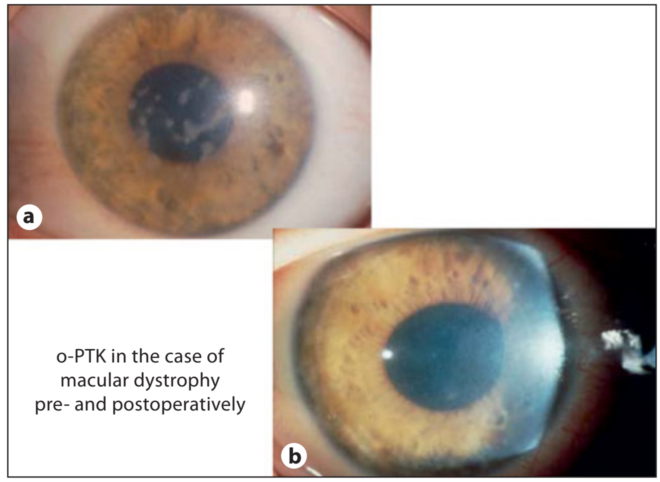


Fig. 7. Macular corneal dystrophy: slit lamp appearance before excimer laser PTK (**a**), and 6 weeks after excimer laser PTK (**b**). Note: only the superficial plaque-like opacifications can be removed with PTK [4]. o-PTK = PTK to treat corneal opacity.

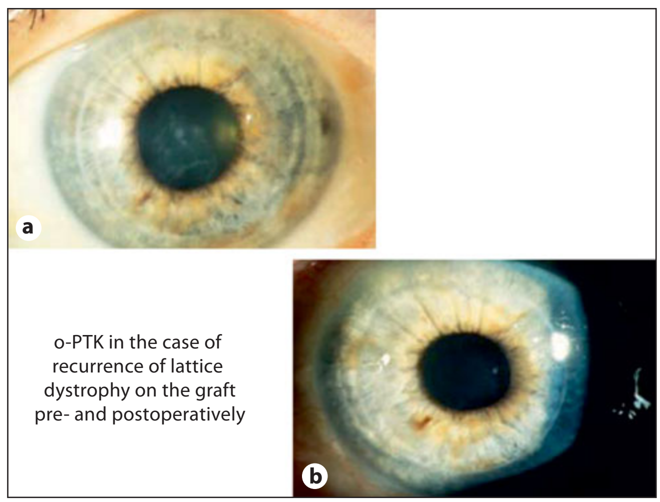


Fig. 8. Recurrence of LCD on the graft: slit lamp appearance before excimer laser PTK (**a**), and 6 months after excimer laser PTK (**b**). Be prepared for epithelial healing problems [28]. o-PTK = PTK to treat corneal opacity.

ablated and allow very acceptable vision for a few years. However, delayed epithelial healing has to be taken into account in LCD [28].

On a corneal graft, simultaneous correction of high astigmatism (in part) may be considered [29, 30]. In addition, prophylactic systemic corticosteroids may be helpful to avoid the induction of an immunologic graft rejection due to PTK [31, 32].

Fuchs Endothelial Corneal Dystrophy

Fuchs endothelial corneal dystrophy (FECD) is by definition an inherited disease. With progressive endothelial dysfunction due to increasing cornea guttata, it results in bullous keratopathy. There is no doubt that either PKP or posterior lamellar

Table 4. Complications of excimer laser PTK

Delayed epithelial healing (especially in lattice dystrophy)
Refractive and topographic changes
Hyperopic sift
Paradoxical myopic shift
Irregular astigmatism
Decentration
Stromal haze and scarring
Infectious ulcer/melting/perforation
Immunologic allograft rejection after PKP
Recurrence of disease
Corneal ectasia
Reactivation of herpes simplex keratitis
Intraocular lens power calculation for cataract surgery in eyes after PTK
(Subsequent penetrating keratoplasty needed)

keratoplasty are the treatment options of choice in eyes with good visual prognosis. However, in cases of low visual prognosis or patients with major noncompliance, superficial excimer laser ablation may be a palliative option. One of the rationales for PTK in bullous keratopathy is the chance to improve vision by ablating subepithelial scar tissue. However, exaggerated wound healing may lead to increased corneal scarring in those eyes [33]. Another reason for PTK concerns alleviation of pain. For this purpose, deeper ablation of up to 100 μm seems to be more effective than a more superficial approach. A combination with amniotic membrane transplantation (graft technique to ensure integration of amniotic membrane into the cornea) may even improve the outcome. Postoperatively, a long-term therapeutic contact lens seems to be helpful.

Complications

Three postoperative healing stages may be distinguished following PTK: (1) reepithelialization takes from 3–4 days (normal) to a few weeks (delayed) in some patients; (2) stromal remodeling occurs over the succeeding weeks and months, and (3) stabilization of topography and refractive changes may take months. Consequently, general postoperative goals include encouragement of epithelialization, minimization of stromal scarring and optimization of refractive and topographic outcome. Potential complications after PTK [34] are listed in table 4.

Delayed Epithelial Healing

Patients who have suffered previous ocular surface disease with loss of epithelial vitality may have problems with epithelialization following PTK. Eyes with severe ocular surface diseases such as chemical burns, ocular cicatricial pemphigoid, atopic keratoconjunctivitis and severe dysfunctional tear syndrome should be treated with extreme caution – if at all. However, even in eyes with 'pure corneal dystrophy' delayed epithelial healing may occur.

We performed a study to evaluate the time period necessary for complete epithelial healing after PTK carried out for various superficial corneal opacities [28]. One hundred and ninety-seven eyes were divided into 9 groups. One hundred and sixty-one eyes (95%) healed within 7 days. Overall, 63, 80, and 85% of epithelial defects were closed within 3, 4 and 5 days, respectively. Out of 9 eyes which showed delayed healing, 6 eyes (67%) belonged to the LCD category. The mean time taken for healing in the LCD group (8.6 ± 8.4 days) was significantly longer than in all other groups (mean 2.7 ± 3.7 days). Besides adequate counseling, these patients with LCD should be followed up closely until complete closure of the epithelium to avoid ulceration, scarring or even infection.

In general, potential reasons for delayed epithelial healing include: (1) systemic rheumatoid diseases (e.g. lupus erythematosus); (2) toxicity of topical medication (e.g. nonsteroidal anti-inflammatory drugs, steroids, gentamycin, preservatives); (3) presence of preoperative active ocular surface and lid inflammatory disease; (4) dry eye or dysfunctional tear syndrome, and (5) denervation after PKP. Those eyes with LCD might need additional treatment (perhaps prophylactic) such as hyaluronic acid drops, autologous blood serum drops [14], a bandage soft contact lens, punctal plugs/occlusion, simultaneous amniotic membrane patching or even temporary lateral tarsorrhaphy or botulinum toxin injection to induce a temporary ptosis. Lid surgery to correct malposition should preferably be performed before PTK.

Refractive and Topographic Changes

Ablation of the corneal surface will lead to refractive and topographic changes after PTK. Such effects may be predicted by the type of corneal disorder treated and the surgical strategy employed. The anticipated refractive changes should be considered during surgical decision making and strategic planning of technical details. Today, simultaneous hyperopic/astigmatic or even topography-based refractive ablation may be performed with acceptable results.

Hyperopic Shift

When performing PTK – at least with a broad-beam laser – the laser beam is of a fixed diameter. Since the energy is optimally homogeneous over the face, the ablation rate would theoretically be similar over the treated area of the cornea. Thus, with a direct ablation without polishing, the surface profile would be expected to be preserved without change in corneal power or topography, and the refraction similarly would be expected to be unchanged. However, studies and clinical practice indicate that a hyperopic shift is a frequent concomitant of PTK procedures [35]. There are several hypotheses to explain this phenomenon as outlined below.

1 The full-spot (= wide-field) laser beam in practice may exhibit somewhat attenuated fluence ('beam inhomogeneity') at its peripheral aspect. Thus, the peripheral ablation rate may be slightly less militating towards corneal flattening.
2 The induced corneal flattening may be caused by an unequal postoperative epithelial thickness with creation of an epithelial lens power different from the curvature of the underlying treated stroma. Epithelial hyperplasia at the periphery of the treated area could be implicated as a cause, especially if a metal mask is used to protect peripheral Bowman's layer.
3 The changing angle of incidence of the beam across the corneal dome might result in a lower fluence peripherally with a decrease in effective tissue ablation and consequent corneal flattening. An analogous phenomenon may result when focusing the laser on the apex of the cornea with the consequence of a peripheral defocus with potentially less tissue ablation. Both aspects may be of questionable clinical impact.
4 Other researchers suggest that removal of the central portion of corneal stroma lamellae may lead to centrifugal differential contraction of the remaining peripheral superficial lamellae with consequent central flattening. Dupps and Roberts [36] favor the model of differential swelling of midperipheral collagen fibers after removal of central superficial stromal tissue.
5 In addition, a peripheral meniscus of masking fluid (especially when using a metal mask) may prevent the (mid-)peripheral corneal tissue from being ablated to the same extent as the central tissue.
6 It may also be speculated that the laser plume may differentially block the periphery of the incoming beam thus leading to less peripheral ablation.

Paradoxical Myopic Shift
Steepening of the central cornea may occur when more tissue is removed peripherally than centrally. Although this may flatten the focal area of the cornea treated due to mechanisms discussed above, the overall optical contour of the cornea may steepen if peripheral tissue is removed. Typically, a paradoxical myopic shift occurs after removal of peripheral prominent pannus with the hockey knife before laser action (e.g. in case of Salzmann's nodular degeneration).

Irregular Astigmatism (Focal Ablation)
PTK to improve the adherence of the epithelium is supposed to smoothen the surface and reduce preexisting irregular astigmatism. However, irregular astigmatism may be induced inadvertently during the laser procedure. This may be caused by decentration of the ablation, which should be centered on the entrance pupil – not on the center of the pathology. If the pathology covers only half of the pupil, it is indispensable to ablate undiseased tissue to avoid irregular astigmatism. Uneven distribution of masking fluid with inadequately high viscosity may also result in focal hyperablation and irregular astigmatism. Typically, epithelial remodeling is able to compensate

for some degree of irregular astigmatism by focal hyperplasia and focal hypoplasia. However, this helpful mechanism may take some months.

Haze/Scars

In general, PTK has as one of its primary goals the amelioration of corneal opacity. Thus, postoperative stromal haze is of less concern for PTK than for PRK. Efforts promoting prompt closure of the epithelium should mitigate an adverse stromal wound healing response. In addition, adjunctive use of topical corticosteroids may also be helpful in avoiding excessive keratocyte activation and scar formation.

Early after PTK, a trace to mild reticular subepithelial stromal haze seems to be quite common. The intensity seems to depend on the depth of ablation and it seems to fade away over a few months. In case of preexisting scars, the probability of renewed scar formation is higher. In these eyes, the application of mitomycin C should be considered [26].

Infectious Ulcer/Melting/Perforation

The risk of microbial keratitis due to the iatrogenic introduction of an epithelial defect is very low, but this is a serious complication that can quite adversely affect the final visual outcome [37]. The greatest risk of microbial keratitis following PTK is either before reepithelialization is complete or within the first few weeks after reepithelialization before the risk of recurrent erosion is virtually eliminated. Moreover, the previously diseased cornea is at greater risk of infection following surgery than the healthy cornea. Persisting epithelial defects in such eyes may afford an inviting substrate for microbial keratitis. Thus, infection will be discouraged with prompt reepithelialization of the defect and strenuous efforts should be made to avoid persisting epithelial defects. We apply nonpreserved fluoroquinolone antibiotics as a routine after PTK because they are much less toxic to the epithelium than aminoglycosides. Following PTK, the patient should be closely followed in the face of a persistent epithelial defect especially if a bandage soft contact lens is in place. Any infiltrate and infection should promptly be treated with broad-spectrum antibiotic coverage or so-called 'fortified drops'.

In analogy to refractive surgery, systemic vasculitis or collagenolytic disease (e.g. Morbus Wegener, rheumatoid arthritis, systemic lupus erythematodes) are contraindications, because the cornea may melt resulting in a (perforated) nonreactive ulcer.

Immunologic Allograft Rejection after Penetrating Keratoplasty

Immunologic graft rejection after PKP may be prompted by any surgical procedure on the graft. PTK may be such a procedure, especially in case of provoked inflammation due to a prolonged time period until epithelial closure. There have been cases of immunologic graft rejection after PTK reported in the literature [31, 32]. It may happen even years after PKP. Although it is unclear what precipitated the immune reaction (laser treatment itself, manual epithelial removal, alterations in the patient's medical regimen), it is clear, however, that immediate topical and systemic treatment with corticosteroids is indispensable to manage this rare complication after PTK. It should be considered to administer a moderate dose of systemic corticosteroid (e.g. 80 mg prednisolone acetate orally) for a few days after PTK on a corneal graft as a prophylaxis.

Recurrence of Disease
Patients with corneal dystrophies undergoing PTK may suffer recurrences following the procedure. Disorders such as lattice/granular/macular corneal dystrophy, EBMD or Salzmann's nodular degeneration may recur at variable intervals after PTK. It is important to inform the patient of this possibility. PTK or manual superficial keratectomy while clearing and smoothing the cornea does not cure the underlying disorder of the epithelium or keratocytes. In cases where the disease presents itself again and becomes visually significant, PTK can be repeated as long as enough corneal tissue is available.

Our clinical impression based on scientific evaluation is that recurrences on the original cornea after PTK behave differently when compared to recurrences of the same dystrophy on the graft after transplantation: while granular dystrophy recurs quite often and quickly on the graft [6], it recurs late after PTK [9]. While macular dystrophy recurs after decades on the graft, superficial plaque-like opacities recur very quickly after PTK [4]. In contrast, map-dot-fingerprint dystrophy recurs very late. Some eyes did not show a morphologic recurrence of RCES after 9 years [8]. Presenting studies on recurrences of dystrophies after PTK should include cumulative Kaplan-Meier recurrence rates, not only relative risk as a percentage.

Reactivation of herpetic/adenoviral disease may be induced by UV light effects during PTK [38, 39]. Besides laser effects, manual trauma and postoperative use of corticosteroids may be factors in herpes reactivation. This may be true in case of concomitant corneal scars after herpetic keratitis. Thus, active herpes keratitis is an absolute, herpetic scars a relative contraindication for PTK. If PTK is performed on a herpetic scar, a quiescent period of 6–12 months is preferred before PTK and perioperative treatment with topical antiviral agents as well as oral acyclovir may act as prophylaxis against recurrent herpetic infection.

Corneal Ectasia
Corneas that are too thin (i.e. <400 μm) should not be treated with the laser, since additional tissue removal may destabilize the corneal biomechanics or may further distort the corneal surface with the consequence of progressive myopia. In addition, deep laser ablation may damage corneal endothelium by concomitant shock waves. An analogous problem may appear after PRK or laser-assisted in situ keratomileusis (LASIK) with too thin a residual stromal bed thickness [40].

Intraocular Lens Power Calculation for Cataract Surgery after Phototherapeutic Keratectomy
For more than one decade, it has been well known that intraocular lens power calculation after myopic PRK/LASIK results in postoperative hyperopia if no precautions

are taken. The deviation from the intended spherical equivalent increases with the amount of the myopic correction that precedes [41]. Since PTK inadvertently results in flattening of the cornea, this problem may also apply here – to some extent. Cataract surgeons should know about this potential risk of intraocular lens miscalculation after PTK. Nevertheless, patients after PTK are typically much less demanding than patients after PRK/LASIK in terms of achieving an optimal UCVA after phakoemulsification.

Anterior Lamellar Keratoplasty

Introduction

In case of deeper corneal stromal deposits sparing the endothelium, such as in special variants of granular or lattice dystrophy, PTK may not be sufficient whereas PKP may appear to be 'overtreatment'. In these cases, ALKP can be considered [42].

ALKP was developed more than 150 years ago [43, 44]. The first attempt to dissect near Descemet's membrane, in the sense of deep anterior lamellar keratoplasty (DALK), was described by Hallermann [44]. The main disadvantage of DALK is that it is both a technically more challenging and time-consuming procedure with a steep learning curve compared with PKP with a high possibility of Descemet's membrane perforations, particularly when the host stroma is manually removed layer by layer until the Descemet's membrane is exposed [45]. Another reason for surgeons to perform a PKP for anterior corneal disorders is that lamellar transplants often show decreased BCVA owing to irregular astigmatism and/or scarring at the donor-to-recipient interface [46, 47].

Archila [48] and Anwar [49] were the first to describe complete baring of Descemet's membrane in the recipient cornea. This technique promised to result in less interface opacity and hence improved visual acuity postoperatively, yielding vision comparable to that resulting from PKP. As concluded by Anwar [50] in 1972 when he described the dissection technique for ALKP, lamellar transplants are more advantageous since they are followed by fewer complications as the globe is not opened. Also, the donor material does not have to be as fresh as that required in full-thickness keratoplasty. He stressed the importance of improving the visual results of the lamellar operation as well as making it the first-choice intervention if the endothelium is found to be healthy.

Technique of Deep Anterior Lamellar Keratoplasty

Some corneal surgeons suggest starting by performing a separate corneal incision, 1 mm inside the limbus, using a 550-μm guarded limbal relaxing incision knife or

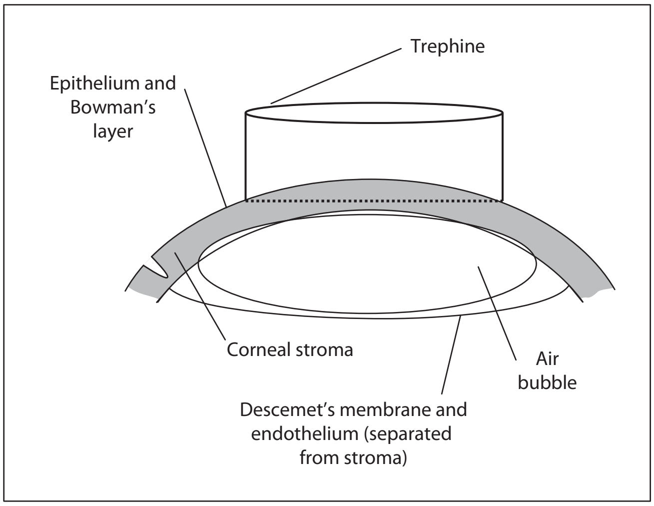


Fig. 9. Trephination of the recipient stroma after creating the air bubble separating Descemet's membrane in DALK.

even the femtosecond laser after performing pachymetry. A peripheral paracentesis is performed. Then a 27- or 30-gauge needle is attached to a 1- to 3-ml air-filled syringe. The needle is bent approximately 5.0 mm from its tip so that the terminal segment angles up approximately 60° while the bevel faces down. The tip is introduced, bevel down, into the corneal stroma at the chosen entry site, in the depth of the incision. Under direct visual control, the needle is carefully advanced towards the center of the cornea in a direction halfway between a tangential and a radial one until the bevel is completely buried, about 3.0 mm from the entry point. Air is injected progressively into the stroma, with the aim of achieving the formation of a large air bubble between the Descemet's membrane and stroma extending as peripheral as possible (fig. 9). This usually appears in the form of a white disk starting near the tip of the needle and gradually enlarging towards the periphery of the cornea. If no bubble is formed, air injection can be repeated by reentering from the incision site. When a sufficiently large bubble is achieved, a small amount of aqueous is allowed to escape to lower the intraocular pressure.

The size of trephination of the recipient bed is determined aiming to surround the entire superficial stromal pathology. Partial-thickness trephination of the cornea is performed to a depth between 350 and 400 μm using a Hanna suction trephine (Moria, France), the Guided Trephine System (GTS, Polytech, Germany) or a Hessburg-Barron vacuum trephine, which is less precise [12] but easy to use and disposable [51–53]. Lamellar superficial keratectomy is performed with a crescent knife aiming to leave a layer of corneal stroma in place anterior to the air bubble. A 15° slit knife is inserted into the large bubble, allowing the air to escape and collapsing the bubble. Viscoelastic material is injected from the opening done by the knife. Then the stroma is removed by blunt-tipped scissors.

The donor cornea is punched out from the endothelial side with a Hanna donor punch or a Barron donor punch (0.25 mm oversize) or from the epithelial side using the GTS (same size). The Descemet's membrane with endothelium is gently stripped off with a dry Weck-Cel sponge or using a forceps. The button is sutured in place using a double-running cross-stitch suture according to Hoffmann after copiously irrigating the Descemet's membrane to wash away all viscoelastic material.

Postoperative medications included topical prednisolone acetate 1% 4 times daily for 1 month, gradually tapered over 6 months, ofloxacin eyedrops 4 times daily for 1 week, and artificial tear preparations 4–6 times daily.

Discussion

DALK is a relatively new technique of lamellar corneal transplantation surgery used to treat corneal diseases that do not involve Descemet's membrane [54]. The technique allows the placement of a nearly full-thickness corneal donor button onto the host bed containing minimal or no stromal tissue on Descemet's membrane and is preferred over performing PKP for treating corneal stromal pathologies. It avoids the replacement of host endothelium with donor endothelium, thus removing the main antigenic load reducing the incidence of graft rejection. Also, it has less effect on endothelial cell count [55].

Other advantages of DALK over PKP as a treatment for corneal stromal disease are those of a lamellar procedure: avoiding most complications associated with 'open-sky' surgery, less chances of intraoperative complications such as expulsive hemorrhage and postoperative complications such as anterior synechiae or secondary glaucoma. Thus, DALK retains all the advantages of lamellar keratoplasty over PKP while providing a clear interface compared with that of conventional 'midstromal' lamellar keratoplasty.

In an attempt to facilitate dissection, Melles et al. [56] in 1999 injected air into the anterior chamber to improve visualization of Descemet's membrane during dissection. They started the dissection through a scleral incision 1 mm outside the limbus, and injected viscoelastic material in the dissected pocket before trephination. A more recent study by Marchini et al. [57] in 2006 used a similar technique, but started dissection from a limbal incision, using a specially designed set of instruments.

Although better microkeratomes have become available with the development of LASIK, microkeratome lamellar resections cannot be used for disorders with deep stromal opacities, variable corneal thickness, and surface irregularities [58]. The use of the femtosecond laser in fashioning the donor and recipient corneal lenticules faces the same problem of equipment availability (laser machine and artificial anterior chamber or whole donor globe) in addition to the expenses [59].

The technique of injecting air into the corneal stroma to facilitate dissection down to the Descemet's membrane led to reduced interface haze and better postoperative visual results. However, the rate of intraoperative perforation was high (39.2%) [57]. Descemet's membrane separation is essential in improving the postoperative visual function, as stated by Ardjomand et al. [60]. They suggested that the main parameter for good visual function after DALK for keratoconus is the thickness of the residual recipient stromal bed. DALK performed in an eye with a residual bed thickness of <20 μm can achieve a similar visual result as PKP, whereas the eyes with a recipient stromal bed thickness of >80 μm had a significantly reduced visual acuity.

In contrast to the other described techniques of ALKP, the big-bubble technique creates a perfect cleavage plane between Descemet's membrane and the rest of the corneal tissue and appears to be much safer than the manual technique of achieving deep stromal dissection regarding the incidence of macroperforations. The big-bubble technique also ensures a maximum possible depth dissection achieving a complete baring of Descemet's membrane so that no stromal tissue is left to cause interface haze in the future [61].

The importance of maintaining an intact Descemet's membrane was proven by Den et al. [62]. They found that the rate of endothelial decompensation was higher in patients with Descemet's membrane perforation. They attributed this to either direct insult to the cells associated with perforation or the ensuing pseudochamber formation or gas tamponade.

In case Descemet's membrane separation is not achieved or in case of macroperforation, the procedure is converted to a full-thickness transplantation. Using the excimer laser for lamellar trephination along metal masks, conversion to PKP can be performed without any disadvantage to the patient [63].

Posterior Lamellar Keratoplasty

Introduction

In case of solitary endothelial dystrophies, such as FECD, posterior polymorphous corneal dystrophy or even congenital hereditary endothelial dystrophy, only the diseased parts of the cornea may be replaced.

Today the procedure most widely applied is Descemet stripping automated endothelial keratoplasty (DSAEK). This technique refers to only removing Descemet's membrane in the recipient and then adding the transplant consisting of a thin stromal layer, Descemet's membrane and endothelium. 'Automated' refers to those techniques employing a microkeratome for preparation of the donor lamella [64–66].

In some centers, Descemet membrane endothelial keratoplasty (DMEK) is being tested, which includes removing the Descemet's membrane in the recipient and transplanting the Descemet's membrane and endothelium only [67]. This technique, still being under development, is obviously the most desirable from a theoretical standpoint, but needs further refinement before it can be introduced into routine clinical application due to major endothelial cell loss and technical difficulties potentially resulting in a major waste of precious donor tissue.

Advantages and Disadvantages of Posterior Lamellar Keratoplasty

The main advantages of posterior lamellar keratoplasty are [68]:

1 mechanical stability of cornea/globe basically unaltered;
2 fast visual rehabilitation;
3 almost neutral procedure concerning refraction;
4 'sutureless' procedure and therefore no suture-related complications;
5 intact corneal innervation;
6 lower risk of late wound dehiscence;
7 surgical procedure through small incisions in a closed system and thus less theoretical risk of choroidal hemorrhage and infection;
8 transplantation of less allogenic material and therefore less theoretical risk of graft rejection;
9 possibility of PKP remains if lamellar procedure does not satisfy the patient's visual needs;
10 repeatability of the transplantation.

The main disadvantages are (1) the problem inherent to all lamellar techniques, which is the construction of an interface with its negative impact on final visual acuity, and (2) the high amount of endothelial cell loss with current surgical techniques, which is attributed to the need for excessive manipulation of donor endothelium [65, 68].

Technique of Descemet Stripping Automated Endothelial Keratoplasty

First, an endothelial transplant is created by cutting a deep 'free' flap over the center of a donor cornea on an artificial anterior chamber and then punching the desired size (e.g. 9 mm) of the transplant from the endothelial side. After creating two opposite clear corneal incisions in the recipient, the Descemet's membrane is scored circularly and subsequently removed in the central corneal area with a special spatula ('stripping'). Then the transplant is introduced into the anterior chamber with various techniques, which all involve some kind of folding of the lamella. The transplant is then pressed against the back of the corneal stroma by injecting an air bubble into the anterior chamber, which may be partly removed at the end of surgery. The patient may then be advised to remain in back position (in order to press the transplant against the corneal back surface by the air bubble) depending on the surgeon. It may be advisable for the patient to lay down on his/her back until the next morning and have an Nd:YAG iridotomy performed preoperatively or a surgical iridotomy/

iridectomy intraoperatively to prevent papillary block with the consequence of dramatic pressure rise.

Indication and Limitations for Descemet Stripping Automated Endothelial Keratoplasty in Fuchs Endothelial Corneal Dystrophy

The principal requirement for successful posterior lamellar grafting is that the corneal stroma and surface be free of alterations which significantly impair vision (e.g. opacities or irregularities).

In partly or completely decompensated corneas, vision will usually be severely impaired and many patients will be symptomatic with edematous epithelium and with rupture of epithelial bullae. In these cases, the loose epithelium should be removed intraoperatively but the indication for surgery is usually straightforward.

In corneas in which guttae are present without decompensation, but to a degree/density which is visually symptomatic – especially by deterioration of contrast sensitivity – indication for surgery is relative and dependent on individual visual needs and demands of the patient.

Performing either penetrating or lamellar surgery is currently a matter of evolving opinion formation.

(1) In eyes with pronounced bullous keratopathy and symptomatology from discomfort to pain, DSAEK may be preferable – at least as a first-line treatment. If such eyes have reduced visual potential for other reasons than the corneal decompensation, the palliative indication being more or less prominent in the decision-making process, the lamellar option may also be superior. Even if the visual potential is full or close to it, lamellar surgery will have priority in older patients and those with average visual demand, while the potential for optimal and long-term visual result and endothelial survival is to be considered mainly in young and visually demanding patients.

(2) In patients/eyes with compensated corneal guttata, the above considerations require even more individual weighing of the above factors.

(3) In case of corneal opacities or irregularities, which would impede vision despite elimination of corneal edema, the penetrating option should be considered in accordance with the criteria outlined above [69].

Postoperative Course, Care and Complications

Once the transplant stays attached in the anterior chamber without air tamponade, it will not detach. Postoperative clarity of the recipient cornea usually occurs within days, resulting in ‘useful’ vision quickly. Over the following weeks, vision will gradually improve further. With full functional potential, vision may increase to >20/40 in about 80% of cases within a few months – but being highly dependent on the

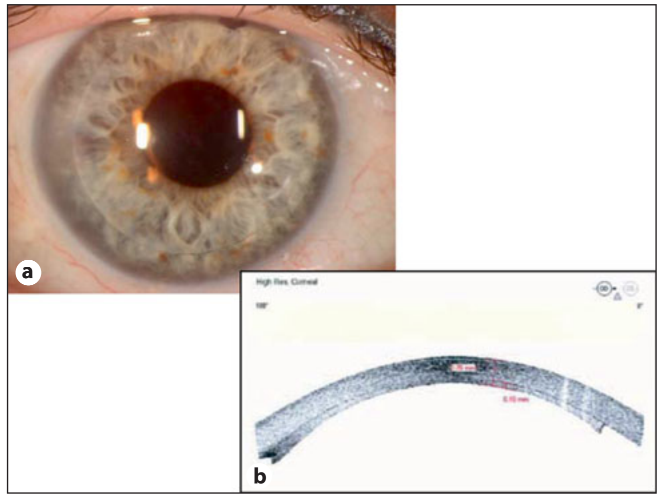


Fig. 10. DSAEK in FECD. **a** Anterior segment of an eye with an endothelial transplant. The transplant can bee seen as a round contour, attached to the inner corneal surface – without sutures. **b** Optical coherence pachymetry demonstrating a sagittal section through a cornea with an endothelial transplant (0.15 mm) after DSAEK [69].

surgeon's individual technique. Visual acuity of 20/25 may be achieved very rarely (fig. 10a) [70].

Postoperative treatment usually consists of topical steroids tapered over 6 months. Basically, the same criteria apply as after PKP. The rate of immune reactions seems to be in the same range as with PKP. Refractive changes introduced by the procedure usually consist of a slight hyperopic shift, which may be explained by the optical effect of the meniscus shape of the transplanted 'lenticule' (fig. 10b), i.e. it induced negative dioptric power [70, 71].

DSAEK can be combined with cataract surgery. In these cases, intraocular lens power calculation should account for the induced hyperopic shift (around 1.0–1.25 dpt). Nevertheless, the DSAEK procedure is preferably performed in primary pseudophakic eyes – especially during the learning curve of the microsurgeon.

To date there is no evidence for an artificially high intraocular pressure due to the thicker cornea after endothelial keratoplasty measured with Goldmann applanation tonometry [72].

Penetrating Keratoplasty

The classical option and gold standard in the surgical treatment of FECD has been PKP [73, 74]. Typically, our cutoff visual acuity for surgery is around 20/50 (0.4). However, we do modify this according to the needs of the patient. The outcome of PKP in FECD is generally good, due to the primary lack of vascularization, inflammation, uneven corneal thickness or other disadvantageous prognostic factors [75]. The 10-year graft survival in this condition has been reported as high as 80–90% in a recent series [76]. The risk profile of this intervention includes prolonged visual rehabilitation, high astigmatism, suture-related complications, wound dehiscence and immunologic graft rejection. To date the reason for an ongoing idiopathic endothelial cell loss which occurs in the graft is unclear [77].

Alternative Treatment Options in Fuchs Endothelial Corneal Dystrophy

Early stages of cornea guttata do not require any therapy at all. Patients should be counseled accordingly. Visually significant corneal edema is symptomatically treated with topical hyperosmotic agents such as 5% NaCl drops 4–6 times a day. Application is to be started in the morning upon awaking to promote early vision increase. In addition, artificial tears or gels during daytime and ointment at night might help to prevent bullous keratopathy from becoming painful. In case of bullous keratopathy, a bandage soft contact lens is typically helpful. In these cases, additional topical application of nonpreserved antibiotics (typically fluorochinolones) is advisable.

Several palliative options have been proposed for painful bullous keratopathy in case no corneal transplant is available. They include anterior stromal puncture, amniotic membrane transplantation as a graft – not only a patch [78]. This may or may not be combined with aggressive PTK to strengthen the adhesions between epithelium and superficial stroma.

Techniques of Penetrating Keratoplasty

A few general technical details concerning PKP need to be addressed [63, 73].

1 Donor topography should be attempted for exclusion of previous refractive surgery, keratoconus/high astigmatism.
2 General anesthesia has advantages over local anesthesia. The arterial blood pressure should be kept low as the eye is opened ('controlled arterial hypotension').
3 Donor and recipient trephination should be performed from the epithelial side with the same system, which is the predisposition for congruent cut surfaces and angles in donor and recipient. For this purpose, an artificial anterior chamber is used for donor trephination.
4 Graft size should be adjusted individually ('as large as possible, as small as necessary') [79].
5 Excessive graft over- or undersize should be avoided to prevent stretching or compression of peripheral donor tissue.
6 Horizontal positioning of head and limbal plane are indispensable for state-of-the-art PKP surgery in order to avoid decentration and vertical tilt.
7 Limbal centration should be preferred over pupil centration.

8 To protect the crystalline lens in phakic keratoplasty, usually the pupil is constricted.
9 Before recipient trephination, a paracentesis at the limbus is performed.
10 An optional iridotomy prevents pupillary block and acute angle closure glaucoma (so-called 'Urrets-Zavalia syndrome') in case of dilated pupil with iris sphincter necrosis.
11 The second cardinal suture exactly 180° away from the first suture is crucial for symmetrical graft alignment and to avoid horizontal torsion.
12 Orientation structures in the donor and host facilitate the correct placement of the first 8 cardinal sutures to avoid horizontal torsion.
13 As long as Bowman's layer is intact, a double-running cross-stitch suture (according to Hoffmann) is preferred since it results in higher topographic regularity, earlier visual rehabilitation and less suture loosening requiring only rarely additional suture replacement.
14 Intraoperative keratoscopy should be applied after removal of lid specula and fixation sutures. Unstable donor epithelium should better be removed to allow for reproducible results. Adjustment of double-running sutures or replacement of single sutures may be indicated.

Technique of Nonmechanical Excimer Laser Trephination for Penetrating Keratoplasty
A measurable improvement of PKP results seems to be possible, using the Krumeich GTS, the second-generation Hanna trephine and our technique of nonmechanical trephination with the excimer laser [80, 81]. Since 1989 more than 3,000 human eyes have been treated successfully with the Meditec MEL60® excimer laser in Homburg/Saar and Erlangen. Besides keratoconus, FECD has been by far the leading indication for PKP with this noncontact technique [82].

The main advantage of this novel laser cutting technique performed from the epithelial side in the donor and recipient is – in contrast to the femtosecond laser application – the avoidance of mechanical distortion by applanation during trephination, resulting in smooth cut edges which are congruent in the donor and patient potentially reducing 'vertical tilt'. Such cut edges in combination with 'orientation teeth' [83] at the graft margin and corresponding notches at the recipient margin for symmetric positioning of the 8 cardinal sutures minimizes 'horizontal torsion', thus potentially improving the optical performance after transplantation (fig. 11). Furthermore, recipient and donor decentration may be reduced [84]. The use of metal masks allows for arbitrary shapes of the trephination, e.g. elliptical [85].

These favorable impacts on major intraoperative determinants of postkeratoplasty astigmatism result in lower keratometric astigmatism, higher topographic regularity and better visual acuity after suture removal (table 5) [81, 86, 87]. After sequential removal of a double-running suture, keratometric astigmatism increased in 80% of eyes with conventional trephination, but further decreased in 52% of eyes with laser trephination.

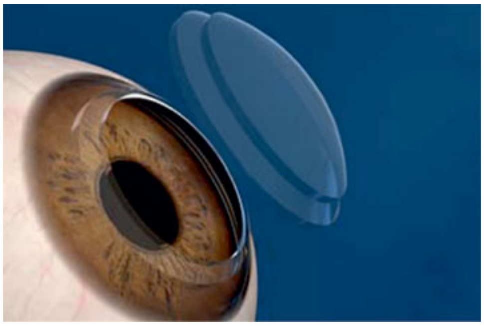
Fig. 11. Typical double-running 10-0 nylon cross-stitch suture with 8 bites each (according to Hoffmann) in macular dystrophy (7.5/7.6 mm, excimer laser trephination with 8 'orientation teeth/notches').

Table 5. Advantages of nonmechanical trephination with the 193-nm excimer laser along metal masks with 'orientation teeth/notches'

No trauma to intraocular tissues
Avoid deformation and compression of tissue during trephination
Reduction of horizontal torsion ('orientation teeth/notches')
Reduction of vertical tilt (congruent cut edges)
Reduction of host and donor decentration
Feasibility of 'harmonization' of donor and host topography
Reduction of anterior chamber inflammation early after PKP
Reduction of astigmatism after suture removal
Higher regularity of corneal topography
Significantly better visual acuity with spectacle correction
Feasibility of trephination with instable cornea
(e.g. 'open eye', descemetocele, after radial keratotomy, iatrogenic keratectasia after LASIK)
Arbitrary shape (e.g. elliptical)

Options of Femtosecond Laser Trephination for Penetrating Keratoplasty

Recently, the options for PKP have been expanded to include femtosecond laser-assisted trephination of contoured wound configurations. With this option, the construction of the recipient and donor can be adjusted to the requirements of the disease. For FECD, the so-called 'inverse mushroom' [88] or 'top hat' [89, 90] configuration of the transplant has been proposed, which describes a shape with a larger diameter on the endothelial side and a smaller diameter on the epithelial side (fig. 12). The main advantage of the contoured/shaped grafts is that less 'unnecessary' (in this case epithelium and anterior stroma) tissue is transplanted, and that



'Inverse Mushroom Graft'
=
'Top Hat Graft'

Fig. 12. Drawing of a 'top hat' = 'inverse mushroom' trephination using a femtosecond laser for PKP. The unsolved problem is the applanation of host cornea during trephination.

this wound configuration provides superior sealing characteristics thus being more stable against pressure [89, 90]. The major disadvantage of this technique is the need of suction and applanation of the cornea. At this time, no results concerning objective keratometric astigmatism with and without sutures, regularity of graft topography, and BCVA after suture removal are available in the literature in this exciting new field of corneal transplant surgery.

The Triple Procedure

Since the introduction of the triple procedure (= simultaneous PKP, extracapsular cataract extraction and implantation of a posterior chamber intraocular lens) in the mid-seventies, there has been an ongoing discussion among corneal microsurgeons concerning the best approach (simultaneous or sequential) for combined corneal disease and cataract [91, 92]. For the refractive results after the triple procedure, some intraoperative details are crucial: trephination of the recipient and donor from the epithelial side without major oversize (GTS or nonmechanical excimer laser trephination) should preserve the preoperative corneal curvature in FECD. The graft and the posterior chamber intraocular lens placed in the bag after large continuous curvilinear capsulorhexis should be centered along the optical axis. If possible, performing capsulorhexis under controlled intraocular pressure conditions prior to trephination may help to minimize the risk of capsular ruptures. In case of excessive corneal clouding, a capsulorhexis forceps is used via 'open sky'. Delivery of the nucleus is achieved via 'open sky' by means of manual irrigation, and removal of the lens cortex by automated irrigation-aspiration.

The major advantage of the triple procedure is the faster visual rehabilitation and less effort for the mostly elderly patients. In cases of large deviations from target refraction, toric sulcus add-on posterior chamber intraocular lenses can be implanted secondarily to minimize the refractive disadvantages of this procedure. In contrast, sequential cataract surgery has the potential of a simultaneous reduction of corneal astigmatism (appropriate location of the incision, simultaneous refractive keratotomies or implantation of a toric posterior chamber intraocular lens). Disadvantages may include the loss of graft endothelial cells and the theoretically increased risk of immunologic allograft reactions. After the triple procedure, major deviations from target refraction have been reported. Since suture removal after PKP may result in major individual changes of the corneal curvature, intraocular lens power calculation for the sequential approach requires all sutures to be removed at the time of cataract surgery [91–93].

In case of cornea guttata without corneal decompensation, a clinically significant cataract may be operated on during protection of the endothelium by a dispersive viscoelastic agent without simultaneous keratoplasty after extensive counseling of the patient.

In conclusion, the postulated better prediction of refraction after sequential keratoplasty and cataract surgery is opposed by a markedly delayed visual rehabilitation. Thus, we consider the triple procedure including cataract extraction via 'open sky' under general anesthesia as the method of choice for combined corneal and lens opacities in elderly patients [93].

Conclusions

Corneal dystrophies require stage-related therapy. To ensure stage-related therapy, adequate classification with respect to histological findings is indispensable. Excimer laser PTK is the treatment option of first choice in superficial corneal dystrophies. However, proper case selection is of paramount importance. In a properly selected and well-counseled patient, PTK can significantly improve vision and quality of life avoiding or at least postponing the need for corneal transplantation. In case of deep stromal deposits sparing the endothelium and Descemet's membrane DALK may be effective. In case of endothelial dystrophies without stromal scars, DSAEK appears to be the procedure of first choice today. Still, there are some corneal dystrophies that require PKP on principle (e.g. macular dystrophy). Excimer laser trephination for PKP results in: (1) lower astigmatism; (2) higher regularity of topography, and (3) better visual acuity – especially in younger patients with keratoconus. Femtosecond laser application is the 'excitement of today' in corneal microsurgery. However, superiority of this high-price and difficult-to-maintain option is not yet proven! Minimal requirements for comparative studies between lamellar and penetrating techniques or between various types of trephination for PKP include (1) endothelial cell count; (2) rate of immune reactions (Kaplan-Meier); (3) BCVA and central power; (4) keratometric or topographic astigmatism (not only refractive cylinder!), and (5) a measure for surface regularity (e.g. surface regularity index/surface asymmetry index of the TMS system) – both with all sutures in and with all sutures out.

References

1 Seitz B, Langenbucher A: Phototherapeutic keratectomy in corneal dystrophies; in Reinhard T, Larkin F (eds): Essentials in Ophthalmology – Corneal and External Eye Disease. Berlin, Springer, 2007.

2 Hersh PS, Wagoner MD: Excimer Laser Surgery for Corneal Disorders. New York, Thieme, 1998.

3 Seitz B, Behrens A, Fischer M, et al: Morphometric analysis of deposits in granular and lattice corneal dystrophy: histopathologic implications for phototherapeutic keratectomy (o-PTK). Cornea 2004;23:380–385.

4 Hafner A, Langenbucher A, Seitz B: Long-term results of phototherapeutic keratectomy with 193 nm excimer laser for macular corneal dystrophy. Am J Ophthalmol 2005;140:392–396.

5 Wagoner MD, Badr IA: Phototherapeutic keratectomy for macular corneal dystrophy. J Refract Surg 1999;15:481–484.

6 Dihn R, Rapauno CJ, Cohen EJ, et al: Recurrence of corneal dystrophy after excimer laser phototherapeutic keratectomy. Ophthalmology 1999;106:1490–1497.

7 Lee ES, Kim EK: Surgical do's and don'ts of corneal dystrophies. Curr Opin Ophthalmol 2003;14:186–191.

8 Pogorelov P, Langenbucher A, Kruse FE, Seitz B: Long-term results of phototherapeutic keratectomy for corneal map-dot-fingerprint dystrophy (Cogan-Guerry). Cornea 2006;25:774–777.

9 Das S, Langenbucher A, Seitz B: Excimer laser phototherapeutic keratectomy for granular and lattice corneal dystrophy: a comparative study. J Refract Surg 2005;21:727–731.

10 Nassaralla BA, Garbus J, McDonnell PJ: Phototherapeutic keratectomy for granular and lattice corneal dystrophies at 1.5 to 4 years. J Refract Surg 1996;12:795–800.

11 Auw-Haedrich C, Loeffler KU, Sundmacher R, et al: Characteristic distribution of deposits in recurrent granular corneal dystrophy. Ger J Ophthalmol 1996;5:132–136.

12 Talamo JH, Steinert RF, Puliafito CA: Clinical strategies for excimer laser therapeutic keratectomy. Refract Corneal Surg 1992;8:319–324.

13 Das S, Seitz B: Recurrent corneal erosion syndrome. Surv Ophthalmol 2008;53:3–15.

14 Ferreira de Souza R, Kruse FE, Seitz B: Autologous serum for otherwise therapy resistant corneal epithelial defects – Prospective study on the first 70 eyes. Klin Monatsbl Augenheilkd 2001;218:720–726.

15 Reinhard T, Sundmacher R: Therapeutic strategies in recurrent erosion: mechanical trauma, epithelial basal membrane dystrophies, and idiopathic genesis. Ophthalmologe 2000;97:157–172.

16 Cavanaugh TB, Lind DM, Cutarelli PE, et al: Phototherapeutic keratectomy for recurrent erosion syndrome due to anterior basement membrane dystrophy. Ophthalmology 1999;106:971–976.

17 Seitz B, Langenbucher A, Hafner A, et al: Phototherapeutic keratectomy for recurrent corneal erosion syndrome (e-PTK). Report on 116 consecutive interventions. Ophthalmologe 2002;99:703–708.

18 Das S, Langenbucher A, Pogorelov P, et al: Long-term outcome of excimer laser phototherapeutic keratectomy for treatment of Salzmann's nodular degeneration. J Cataract Refract Surg 2005:31:1386–1391.

19 Wilson SE, Klyce SD: Quantitative descriptors of corneal topography. A clinical study. Arch Ophthalmol 1991;109:349–353.

20 Fagerholm P: Phototherapeutic keratectomy: 12 years of experience. Acta Ophthalmol Scand 2003;81:19–32.

21 Rapuano CJ: Excimer laser phototherapeutic keratectomy: long-term results and practical considerations. Cornea 1997;16:151–157.

22 Szentmáry N, Langenbucher A, Hafner A, et al: Impact of phototherapeutic keratectomy on the outcome of subsequent penetrating keratoplasty in patients with stromal corneal dystrophies. Am J Ophthalmol 2004;137:301–307.

23 Kornmehl EW, Steinert RF, Puliafito CA: A comparative study of masking fluids for excimer laser phototherapeutic keratectomy. Arch Ophthalmol 1991;109:860–863.

24 Fasano AP, Moreira H, McDonnell PJ, et al: Excimer laser smoothing of a reproducible model of anterior corneal surface irregularity. Ophthalmology 1991;98:1782–1785.

25 Szentmáry N, Seitz B, Langenbucher A, et al: Histologic and ultrastructural changes in corneas with granular and macular dystrophy after excimer laser phototherapeutic keratectomy. Cornea 2006;25:257–263.

26 Marcon AS, Rapuano CJ: Excimer laser phototherapeutic keratectomy retreatment of anterior basement membrane dystrophy and Salzmann's nodular degeneration with topical mitomycin C. Cornea 2002;21:828–830.

27 Örndahl ML, Fagerholm PP: Treatment of corneal dystrophies with phototherapeutic keratectomy. J Refract Surg 1998;14:129–135.

28 Das S, Langenbucher A, Seitz B: Delayed healing of corneal epithelium after phototherapeutic keratectomy for lattice dystrophy. Cornea 2005;24:283–287.

29 Langenbucher A, Seitz B, Kus MM, et al: Topography-assisted correction of superficial irregularities of the cornea with the excimer laser. Klin Monatsbl Augenheilkd 1998;213:132–140.
30 Seitz B, Langenbucher A, Kus MM, et al: Experimental correction of irregular corneal astigmatism using topography-based flying-spot-mode excimer laser photoablation. Am J Ophthalmol 1998;125:252–256.
31 Epstein RJ, Jeffrey BR: Corneal graft rejection episode after excimer phototherapeutic keratectomy. Arch Ophthalmol 1994;112:157.
32 Hersh PS, Jordan AJ, Mayers M: Corneal graft rejection episode after excimer laser phototherapeutic keratectomy. Arch Ophthalmol 1993;111:735–736.
33 Alba M, Waring GO, Malaty A, et al: Increased corneal scarring after phototherapeutic keratectomy in Fuchs' corneal dystrophy. J Refract Surg 1997;13: 308–310.
34 Geerling G, Sekundo W: Phototherapeutic keratectomy – Undesirable effects, complications, and preventive strategies. Ophthalmologe 2006;103: 576–582.
35 Litwin KL, Moreira H, Ohadi C, et al: Changes in corneal curvature at different excimer laser ablative depths. Am J Ophthalmol 1991;111:383–384.
36 Dupps WJ, Roberts C: Effect of acute biomechanical changes on corneal curvature after photokeratectomy. J Refract Surg 2001;17:658–669.
37 Al-Rajhi A, Wagoner MD, Badr IA, et al: Bacterial keratitis following phototherapeutic keratectomy. J Refract Surg 1996;12:123–127.
38 Tervo T, Tuunanen T: Excimer laser and reactivation of herpes simplex keratitis. CLAO J 1994;20: 152–153, 157.
39 Vrabec MP, Durrie DS, Chase DS: Recurrence of herpes simplex after excimer laser keratectomy. Am J Ophthalmol 1992;114:96–97.
40 Seitz B, Rozsíval P, Feuermannova A, et al: Penetrating keratoplasty for iatrogenic keratoconus after repeat myopic laser in situ keratomileusis: histologic findings and literature review. J Cataract Refract Surg 2003;29:2217–2224.
41 Seitz B, Langenbucher A, Nguyen NX, et al: Underestimation of intraocular lens power for cataract surgery after myopic photorefractive keratectomy. Ophthalmology 1999;106:693–702.
42 Geerling G, Seitz B: Keratoplasty – A simple classification/terminology of current treatment options. Klin Monatsbl Augenheilkd 2005;222:612–614.
43 Anwar M, Teichmann KD: Big-bubble technique to bare Descemet's membrane in anterior lamellar keratoplasty. J Cataract Refract Surg 2002;28:398–403.
44 Hallermann W: Verschiedenes über Keratoplastik. Klin Monatsbl Augenheilkd 1959;135:252–259.
45 Fontana L, Parente G, Tassinari G: Clinical outcomes after deep anterior lamellar keratoplasty using the big-bubble technique in patients with keratoconus. Am J Ophthalmol 2007;143:117–124.
46 Richard JM, Paton D, Gasset AR: A comparison of penetrating keratoplasty and lamellar keratoplasty in the surgical management of keratoconus. Am J Ophthalmol 1978;86:807–811.
47 Lyons CJ, McCartney AC, Kirkness CM, et al: Granular dystrophy. Visual results and pattern of recurrence after lamellar or penetrating keratoplasty. Ophthalmology 1994;101:1812–1817.
48 Archila EA: Deep lamellar keratoplasty dissection of host tissue with intrastromal air injection. Cornea 1984–1985;3:217–218.
49 Anwar M: Technique in lamellar keratoplasty. Trans Ophthalmol Soc UK 1974;94:163–171.
50 Anwar M: Dissection technique in lamellar keratoplasty. Br J Ophthalmol 1972;56:711–713.
51 Sugita J, Kondo J: Deep lamellar keratoplasty with complete removal of pathological stroma for vision improvement. Br J Ophthalmol 1997;81:184–188.
52 Schor P, Rocha E, Cheema DP, Miller D: Calibration of trephine blade depth. J Refract Surg 1997;13: 89–90.
53 Shimmura S, Tsubota K: Deep anterior lamellar keratoplasty. Curr Opin Ophthalmol 2006;17: 349–355.
54 Anwar M, Teichmann KD: Deep lamellar keratoplasty: surgical techniques for anterior lamellar keratoplasty with and without baring of the Descemet's membrane. Cornea 2002;21:374–383.
55 Shimazaki J, Shimmura S, Ishioka M, Tsubota K: Randomized clinical trial of deep lamellar keratoplasty vs penetrating keratoplasty. Am J Ophthalmol 2002;134:159–165.
56 Melles GR, Lander F, Rietveld FJR, et al: A new surgical technique for deep stromal, anterior lamellar keratoplasty. Br J Ophthalmol 1999;83:327–333.
57 Marchini G, Mastropasqua L, Pedrotti E, et al: Deep lamellar keratoplasty by intracorneal dissection a prospective clinical and confocal microscopic study. Ophthalmology 2006;113:1289–1300.
58 Busin, M, Zambianchi L, Arffa RC: Microkeratome-assisted lamellar keratoplasty for the surgical treatment of keratoconus. Ophthalmology 2005;112: 987–997.
59 Yoo SH, Kymionis GD, Koreishi A, et al: Femtosecond laser-assisted sutureless anterior lamellar keratoplasty. Ophthalmology 2008;115: 1303–1307.
60 Ardjomand N, Hau S, McAlister J, et al: Quality of vision and graft thickness in deep anterior lamellar and penetrating corneal allografts. Am J Ophthalmol 2007;143:228–235.

61 Vajpayee RB, Tyagi J, Sharma N, et al: Deep anterior lamellar keratoplasty by big-bubble technique for treatment corneal stromal opacities. Am J Ophthalmol 2007;143:954–957.
62 Den S, Shimmura S, Tsubota K, Shimazaki J: Impact of the Descemet membrane perforation on surgical outcomes after deep lamellar keratoplasty. Am J Ophthalmol 2007;143:750–754.
63 Seitz B, Langenbucher A, Naumann GOH: Trephination in penetrating keratoplasty; in Reinhard T, Larkin F (eds): Essentials in Ophthalmology – Corneal and External Eye Disease. Berlin, Springer, 2006, pp 123–152.
64 Melles GRJ, Wijdh RHJ, Nieuwendaal CP: A technique to excise the Decemet membrane from a recipient cornea (descemetorhexis). Cornea 2004; 23:286–288.
65 Price MO, Price FW Jr: Endothelial cell loss after descemet stripping with endothelial keratoplasty: influencing factors and 2-year trend. Ophthalmology 2008;115:857–865.
66 Price MO, Price FW Jr: Descemet's stripping with endothelial keratoplasty: comparative outcomes with microkeratome-dissected and manually dissected donor tissue. Ophthalmology 2006;113: 1936–1942.
67 Melles GRJ, Ong TS, Ververs B, van der Wees J: Descemet membrane endothelial keratoplasty (DMEK). Cornea 2006;25:987–990.
68 Bahar I, Kaiserman I, McAllum P, Slomovic A, Rootman D: Comparison of posterior lamellar keratoplasty techniques to penetrating keratoplasty. Ophthalmology 2008;115:1525–1533.
69 Seitz B, Neuhann I, Neuhann T: Fuchs endothelial corneal dystrophy: current management. Contemp Ophthalmol 2009:8:1–8.
70 Koenig SB, Covert DJ, Dupps WJ Jr, Meisler DM: Visual acuity, refractive error, and endothelial cell density six months after descemet stripping and automated endothelial keratoplasty (DSAEK). Cornea 2007;26:670–674.
71 Holz HA, Meyer JJ, Espandar L, et al: Corneal profile analysis after Descemet stripping endothelial keratoplasty and its relationship to postoperative hyperopic shift. J Cataract Refract Surg 2008;34: 211–214.
72 Vajaranant TS, Price MO, Price FW, Wilensky JT, Edward DP: Intraocular pressure measurements following Descemet stripping endothelial keratoplasty. Am J Ophthalmol 2008;145:780–786.
73 Naumann GOH: Corneal transplantation in anterior segment diseases. The Bowman Lecture (Number 56). Part 2. Eye 1995;9:395–424.
74 Pineros O, Cohen EJ, Rapuano CJ, Laibson RP: Long-term results after penetrating keratoplasty for Fuchs' endothelial dystrophy. Arch Ophthalmol 1996;114:15–18.
75 Weiss JS, Moller HU, Lisch W, Kinoshita S, Aldave AJ, Belin MW, Kivela T, Busin M, Munier FL, Seitz B, Sutphin J, Bredrup C, Mannis MJ, Rapuano CJ, van Rij G, Kim EK, Klintworth GK: The IC3D classification of corneal dystrophies. Cornea 2008; 27(suppl 2):S1–S42.
76 Thompson RW Jr, Price MO, Bowers PJ, Price FW Jr: Long-term graft survival after penetrating keratoplasty. Ophthalmology 2003;110:1396–1402.
77 Langenbucher A, Seitz B, Nguyen NX, Naumann GOH: Graft endothelial cell loss after nonmechanical penetrating keratoplasty depends on diagnosis: a regression analysis. Graefes Arch Clin Exp Ophthalmol 2002;240:387–392.
78 Seitz B, Resch M, Schlötzer-Schrehardt U, Hofmann-Rummelt C, Sauer R, Kruse FE: Histopathology and ultrastructure of human corneas after amniotic membrane transplantation. Arch Ophthalmol 2006; 124:1487–1490.
79 Seitz B, Langenbucher A, Zagrada D, Budde W, Kus MM: Corneal dimensions in various types of corneal dystrophies and their effect on penetrating keratoplasty. Klin Monatsbl Augenheilkd 2000;217: 152–158.
80 Naumann GOH, Seitz B, Lang GK, Langenbucher A, Kus MM: 193 excimer laser trepanation in perforating keratoplasty. Report of 70 patients. Klin Monatsbl Augenheilkd 1993;203:252–261.
81 Seitz B, Langenbucher A, Kus MM, Küchle M, Naumann GOH: Nonmechanical corneal trephination with the excimer laser improves outcome after penetrating keratoplasty. Ophthalmology 1999;106: 1156–1165.
82 Seitz B, Langenbucher A, Nguyen NX, Kus MM, Küchle M, Naumann GOH: Results of the first 1000 consecutive elective nonmechanical keratoplasties with the excimer laser – A prospective study over more than 12 years. Ophthalmologe 2004;101: 478–488.
83 Behrens A, Seitz B, Küchle M, Langenbucher A, Kus MM, Rummelt C, Naumann GOH: 'Orientation teeth' in non-mechanical laser corneal trephination for penetrating keratopasty: 2.94 μm Er:YAG vs 193 nm ArF excimer laser. Br J Ophthalmol 1999;83: 1008–1012.
84 Langenbucher A, Seitz B, Kus MM, Vilchis E, Naumann GOH: Graft decentration in penetrating keratoplasty – Nonmechanical trephination with the excimer laser (193 nm) versus the motor trephine. Ophthalmic Surg Lasers 1998;29:106–113.

85 Szentmáry N, Langenbucher A, Kus MM, Naumann GOH, Seitz B: Elliptical nonmechanical corneal trephination: intraoperative complications and long-term outcome of 42 consecutive excimer laser penetrating keratoplasties. Cornea 2007;26: 414–420.
86 Seitz B, Langenbucher A, Küchle M, Naumann GOH: Impact of graft diameter on corneal power and the regularity of postkeratoplasty astigmatism before and after suture removal. Ophthalmology 2003;110:2162–2167.
87 Szentmáry N, Langenbucher A, Naumann GOH, Seitz B: Intra-individual variability of penetrating keratoplasty outcome after excimer laser versus motorized corneal trephination. J Refract Surg 2006; 22:804–810.
88 Seitz B, Brünner H, Viestenz A, Hofmann-Rummelt C, Schlötzer-Schrehardt U, Naumann GOH, Langenbucher A: Inverse mushroom-shaped nonmechanical penetrating keratoplasty using a femtosecond laser. Am J Ophthalmol 2005;139:941–944
89 Price FW, Price MO: Femtosecond laser shaped penetrating keratoplasty: one-year results utilizing a top-hat configuration. Am J Ophthalmol 2008;145: 210–214.
90 Steinert RF, Ignacio TS, Sarayba MA: 'Top hat'-shaped penetrating keratoplasty using the femtosecond laser. Am J Ophthalmol 2007;143:689–691.
91 Davis EA, Azar DT, Jakobs FM, Stark WJ: Refractive and keratometric results after the triple procedure. Experiences with early and late suture removal. Ophthalmology 1998;105:624–630.
92 Seitz B, Langenbucher A, Viestenz A, Dietrich T, Küchle M, Naumann GOH: Cataract and keratoplasty – Simultaneous or sequential surgery? Klin Monatsbl Augenheikd 2003;220:326–329.
93 Das S, Langenbucher A, Jacobi C, Nguyen N, Kruse FE, Naumann GOH, Seitz B: Long-term refractive and visual outcome after penetrating keratoplasty only versus the triple procedure in Fuchs' dystrophy. Graefes Arch Clin Exp Ophthalmol 2006;244: 1089–1095.

Berthold Seitz, MD, FEBO
Professor and Chairman
Department of Ophthalmology, University of Saarland
Kirrbergerstrasse 1, Building 22
DE–66424 Homburg/Saar (Germany)
Tel. +49 6841 162 2388, E-Mail berthold.seitz@uks.eu