Comparison of Penetrating Keratoplasty and Deep Lamellar Keratoplasty for Macular Corneal Dystrophy and Risk Factors of Recurrence

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Purpose: To compare the therapeutic effects of penetrating keratoplasty (PK) and deep anterior lamellar keratoplasty (DALK) on patients with macular corneal dystrophy (MCD) and to analyze the risk factors of postoperative recurrence.

Design: Retrospective, interventional, comparative case series.

Participants: Fifty-one patients (78 eyes) with MCD treated by PK or DALK at Shandong Eye Institute between January 1992 and December 2010.

Methods: The medical records of the patients were reviewed retrospectively.

Main Outcome Measures: Best-corrected visual acuity, corneal endothelial density, complications, recurrence, graft survival, and risk factors for recurrence.

Results: Penetrating keratoplasty was performed in 57 eyes, and DALK was performed in 21 eyes. The mean follow-up time was 5.1±4.1 years (range, 1.0–18.0 years). The best-corrected visual acuity of the PK group was much better than that of the DALK group at 1, 2, 3, and 5 years. The corneal endothelial density was reduced to 1000 cells/mm^2 or less within 5 years in 21.6% (11/51) of eyes treated by PK and in none of the eyes treated by DALK. The 1-year incidence rate of complications was 21.1% in the PK group, higher than the 4.8% rate in the DALK group. At the last visit, the rate of graft clarity was 87.7% and 85.7% in the 2 groups, respectively. Ten eyes (17.5%) treated by PK had recurrent MCD, with a rate of 0.8%, 7.7%, and 40% at 1, 5, and 10 years, respectively, whereas 9 eyes (42.9%) treated by DALK demonstrated recurrence, with a rate of 14.3% and 49.5% at 1 and 5 years, respectively. The recurrence risk was higher in patients whose age was 18 years or younger at onset or younger than 30 years at surgery. The recurrence risk after DALK was 5.066 times higher than that after PK.

Conclusions: Penetrating keratoplasty more often immediately improves the visual acuity of patients with MCD, but many complications seem to be inevitable, especially continuous loss of corneal endothelium. Despite poor visual acuity and recurrence after surgery, DALK may produce fewer complications overall and more durable stability of the ocular surface compared with PK. The selection of PK or DALK for MCD should depend on the actual need and situation of certain patients.

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Classic corneal stromal dystrophies include macular corneal dystrophy (MCD), granular corneal dystrophy, and lattice corneal dystrophy, among which MCD, a recessively inherited disorder, is most severe but least common.[1] Such dystrophies usually are diagnosed based on clinical manifestations and histopathologic examination. At the early stage, a number of small, white, irregularly shaped, and ill-defined patchy dense opacities are scattered in the light matrix of the central cornea. These opacities gradually fuse and expand to the periphery and deep corneal stroma as the disease progresses and eventually invades the entire cornea. Histopathologically, MCD is characterized by an accumulation of glycosaminoglycans between the stromal lamellae, within and underneath the epithelium, and within keratocytes and endothelial cells.[2] Eventual treatment for corneal stromal dystrophy often involves penetrating keratoplasty (PK) or deep anterior lamellar keratoplasty (DALK). In China, 4% of corneal transplantation procedures and 7.1% of pediatric keratoplasty procedures were performed for any corneal dystrophy,[3,4] whereas in Europe, the United States, Japan, and Saudi Arabia, 4% to 24% of patients treated by keratoplasty had corneal dystrophy.[5–8] Some ophthalmologists believe the risks of endothelial rejection, intraocular complications, and corneal endothelial cell loss after DALK are less than with PK. Deep anterior lamellar keratoplasty theoretically is a better choice because the corneal endothelium is not involved in the disorder.[9] However, there are 2 common and important problems after DALK for MCD:

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postoperative turbidity between the graft and bed and recurrent disease.[10–12] This study compared the therapeutic effects of PK and DALK on MCD and analyzed the postoperative risk factors for MCD recurrence.

Patients and Methods

This study was approved by the institutional review board of Shandong Eye Institute and conformed to the guidelines of the Declaration of Helsinki. The medical records of every patient who underwent PK or DALK for MCD at the authors' institution between January 1992 and December 2010 were reviewed retrospectively. Patients were included in the study if the diagnosis of MCD was confirmed histopathologically and more than 12 months of follow-up were available. Four patients with fewer than 12 months of follow-up were excluded.

The surgical procedure was performed to improve vision after being selected on the basis of the disease severity. Examined by slit lamp and RTVue optical coherence tomography (Optovue, Fremont, CA), patients with deep stromal and endothelial opacity underwent PK, whereas those with anterior to middle stromal opacity underwent DALK. Penetrating keratoplasty surgeries were performed between 1992 and 2010; DALK was used for MCD from 2000. In the DALK procedure (Video 1, available at http://aaojournal.org), recipient corneal stroma was trephined 400 to 450 μm using the Barron radial vacuum trephine (Katena Products, Denville, NJ) before the opaque stroma was excised with lamellar microsurgical knives (no. 74-1010, Sharpoint, Angiotech, Surgical Specialties, Inc., Reading, PA). The excision was continued until the clear portion was visible. Donor corneas were trephined using the Barron vacuum donor cornea punch (Katena Products) with a diameter 0.25 mm larger than the recipient bed, and the endothelium and Descemet membrane were dissected. Penetrating keratoplasty was performed routinely using the Barron radial vacuum trephine (Video 2, available at http://aaojournal.org). In both procedures, corneal grafts were sutured with 16 interrupted 10-0 nylon sutures. The recipient size ranged from 7.25 to 8.25 mm in eyes treated with DALK and from 7.25 to 8.0 mm in those treated with PK.

Topical antibiotics were administered for 2 weeks after surgery. Steroids were given topically for 1 year after DALK and for at least 2 years after PK. In addition, 1% cyclosporine A eyedrops (North China Pharmaceutical Group Corporation, Shijiazhuang, China) were used from week 2 and were continued for 1 year in eyes that underwent DALK and for at least 2 years in those that underwent PK. Suture removal was based on the topographic astigmatism pattern in both groups.

Most patients were evaluated at 1 day; 1 week; 1, 3, 6, 9, 12, 18, and 24 months after surgery; and yearly thereafter. Best-corrected visual acuity (BCVA), changes in the corneal endothelial cell density (ECD), complications, disease recurrence, graft survival rate, and recurrence risk factors were recorded. Visual acuity of counting fingers, hand movements, and light perception were converted to 0.004, 0.002, and 0.001, respectively, and the results were converted into logarithm of the minimum angle of resolution units for statistical analysis. The endothelium was photographed using a noncontact specular microscope (SP-3000P, Topcon Tokyo, Japan). Approximately 50 cells were analyzed for the mean cell density. The percent of endothelial loss was calculated by subtracting postoperative ECD from baseline ECD and then dividing by baseline ECD and multiplying by 100. The baseline ECD was the donor ECD in the PK group, whereas in the DALK group, it was the recipient's ECD before surgery or at 7 to 14 days after surgery when the preoperative ECD could not be counted because of corneal opacity. Graft failure was defined as irreversible loss of central graft clarity, regardless of the level of visual acuity. Moreover, a simple recurrence was defined as biomicroscopic findings of the recurrent disease in the graft button without decreased visual acuity or recurrent erosions. A clinically significant recurrence was defined as biomicroscopic findings of the recurrent disease located in the central graft with decreased visual acuity of 2 lines or more and associated with recurrent erosion symptoms.[13]

Statistical analysis was carried out with SPSS software version 15.0 (SPSS, Inc., Chicago, IL). The BCVA, age, and follow-up time between the PK and DALK groups were compared with independent samples t test. The BCVA before and after surgery were compared using the paired t test. Complications between the 2 groups were compared using chi-square analysis. Kaplan-Meier and log-rank tests were used to compare simple recurrence and graft survival, whereas the risk factors for recurrence were analyzed using a Cox multivariate proportional hazards regression model. A P value of less than 0.05 was considered significant.

Results

Seventy-eight eyes of 51 patients, 24 men (47.1%) and 27 women (52.9%), with histologically proven MCD were included. The average age at onset and surgery was 22.3±10.9 years (range, 1–64 years) and 37.9±13.5 years (range, 3–76 years), respectively. Penetrating keratoplasty was performed in 57 eyes, and DALK was performed in 21 eyes. The mean follow-up was 5.7±4.5 years (range, 1.0–18.0 years) after PK and 3.4±2.1 years (range, 1.0–8.5 years) after DALK ($P = 0.003$). There was no significant difference in age, sex, or preoperative BCVA between the 2 surgical groups. In the PK group, 3 eyes had amblyopia (including exotropia in 2 eyes) and 2 eyes underwent cataract extraction and intraocular lens implantation concomitantly. In the DALK group, 2 eyes had amblyopia and 1 eye had trachoma. There was no significant difference in these pre-existing ocular conditions between the 2 groups. None of the eyes had a history of glaucoma.

Visual Outcome

The visual outcomes are summarized in Table 1 and Figure 1. There was no significant difference in preoperative BCVA between the 2 groups, but the postoperative BCVA at 1, 2, 3, and 5 years in the PK group was much better than that in the DALK group ($P<0.05$).

Corneal Endothelial Cell Density

Corneal ECD decreased over time in eyes undergoing PK. The mean cumulative loss rate of endothelial cells was 20.1%, 44.1%, 57.1%, 57.2%, and 62.7% at 1, 3, 5, 7, and 10 years after surgery, respectively. The density reduced to 1000 cells/mm^2 or less in 11 of 51 eyes (21.6%) within 5 years and in 20 of 51 eyes (39.2%) at the last visit. In comparison, the downtrend of ECD was milder in the DALK group, with a rate of 14.6%, 16.5%, 24.1%, and 24.8% at 1, 3, 5, and 7 years, respectively, and only 1 of 18 eyes (5.6%) had a density of less than 1000 cells/mm^2 6 years after surgery (Fig 2).

Complications

In the PK group, complications were detected in 19 eyes (33.3%) during the follow-up period. Graft rejection occurred in 13 eyes, once in 4 eyes and twice or more in 9 eyes, leading to

Table 1. Best-Corrected Visual Acuity after Keratoplasty for Macular Corneal Dystrophy

	Preoperative Best-Corrected Visual Acuity	Postoperative Best-Corrected Visual Acuity				
		6 Months	*1 Year*	*2 Years*	*3 Years*	*5 Years*
PK	1.49±0.83	0.37±0.37	0.30±0.36	0.25±0.42	0.27±0.48	0.26±0.53
DALK	1.22±0.59	0.53±0.29	0.51±0.29	0.64±0.65	0.62±0.62	0.84±0.67
P value	0.109	0.071	0.023	0.010	0.050	0.017

DALK = deep anterior lamellar keratoplasty; PK = penetrating keratoplasty.
Data are presented as mean±standard deviation unless otherwise indicated.

endothelial decompensation in 4 eyes. Two eyes had transiently increased intraocular pressure, 2 eyes had complicated cataract, 1 eye had continued corneal epithelial defect, and 1 eye had traumatic graft laceration 8 years after surgery. In the DALK group, 3 eyes (14.3%) experienced postoperative complications, including graft rejection in 2 eyes and complicated cataract in 1 eye. The incidence rate of complications within 1 year was 21.1% (12/57) in the PK group, higher than 4.8% (1/21) in the DALK group.

Recurrent Disease

Ten eyes (17.5%) that underwent PK had recurrence of MCD. The mean interval between surgery and diagnosis of simple recurrence was 6.3±3.1 years (range, 1–10.5 years). The cumulative percentage of simple recurrence was 0.8%, 7.7%, and 40% at 1, 5, and 10 years, respectively. Three eyes (5.3%) had clinically significant recurrence, 2 of which underwent a secondary PK. The diseased corneal grafts were confirmed histopathologically as recurrence.

Macular corneal dystrophy also recurred in 9 eyes (42.9%) that underwent DALK, and the mean time for a simple recurrence was 2.3±2.1 years (range, 0.5–7 years). The percentage of simple recurrence was 14.3% and 49.5% at 1 and 5 years, respectively. Three eyes (14.3%) had clinically significant recurrence. Compared with DALK, PK seemed to have a lower recurrence rate and seemed to delay disease recurrence (log rank, 14.566; $P = 0.000$; Fig 3).

Graft Survival

At the last visit, 50 grafts (87.7%) in the PK group remained clear. The graft survival rate was 87.2% at 5 years. Graft failure was caused by corneal endothelial decompensation in 4 eyes and by clinically significant recurrence of MCD in 3 eyes. In the DALK group, 18 grafts (85.7%) were clear, and the graft survival rate was 72.7% at 5 years. Graft failure in 3 eyes was attributed to clinically significant recurrence. There was no significant difference in the rate of graft survival between the 2 groups (log-rank, 1.307; $P = 0.253$; Fig 4).

Risk Factors for Recurrence

The possible risk factors for disease recurrence were subjected to univariate analysis by the Kaplan-Meier and log-rank tests, showing that the patients who were male ($P = 0.059$), 18 years of age or younger at onset ($P = 0.001$), younger than 30 years at surgery ($P = 0.003$), and treated with DALK ($P = 0.000$) were liable to experience recurrence. In the Cox multivariate proportional hazards regression model, the risk rate was approximately 3.2 times higher in patients 18 years of age or younger at onset than in those older than 18 years, 2.8 times higher in patients aged younger than 30 years at surgery than in those 30 years of age or older, and 5.1 times higher in patients who underwent DALK than in those who underwent PK. Sex was not found to be related to the recurrence (Table 2).

Trauma and the need for repeat surgery may be related to recurrence. In 1 patient who sustained a traumatic graft laceration and retinal detachment 8 years after surgery, there was no sign of recurrence during the 8-year follow-up. But at 10 months after graft resuture, vitrectomy, and retinal detachment repair, obvious signs of recurrence were observed on the margin of the graft (Fig 5).

Discussion

Macular corneal dystrophy is a rare, autosomal recessive genetic eye disease. Surgical intervention is indicated in

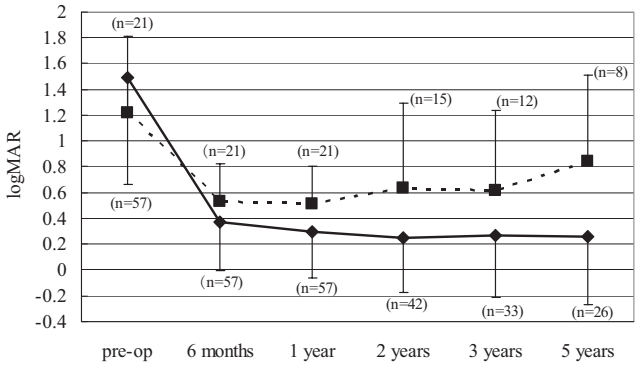

Figure 1. Graph showing change in best-corrected visual acuity after deep anterior lamellar keratoplasty (DALK) and penetrating keratoplasty (PK). logMAR = logarithm of the minimum angle of resolution. -◆- = PK; -■- = DALK.

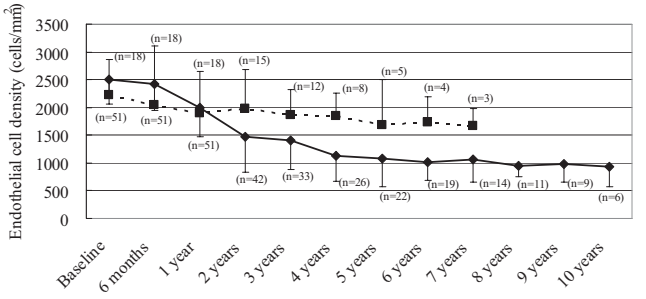

Figure 2. Graph showing change in corneal endothelial cell density after deep anterior lamellar keratoplasty (DALK) and penetrating keratoplasty (PK). -◆- = PK; -■- = DALK.

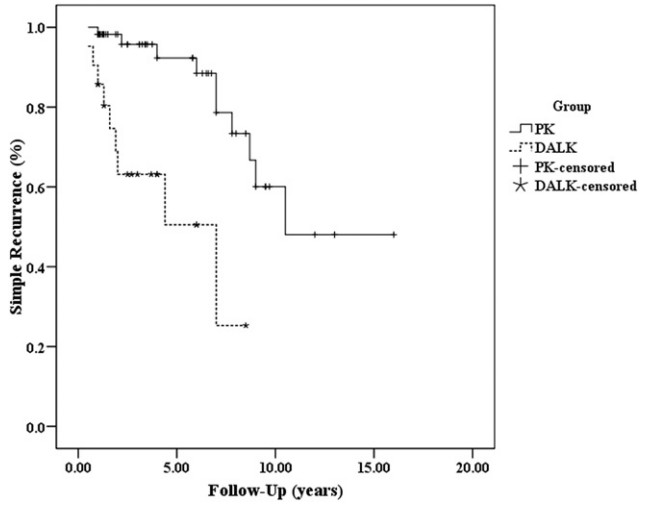

Figure 3. Graph showing simple recurrence after deep anterior lamellar keratoplasty (DALK) and penetrating keratoplasty (PK) for macular corneal dystrophy.

patients with severe visual impairment or discomfort from recurrent corneal epithelial erosions. Penetrating keratoplasty,[14] DALK,[14,15] and phototherapeutic keratectomy[16,17] have been used to improve BCVA, to relieve symptoms, or both. However, the preferred surgical option for the management of MCD has not been established clearly.

Penetrating keratoplasty may remove the diseased cornea completely, may increase visual acuity immediately, and may achieve good visual quality in patients with MCD, whereas the visual acuity and quality after DALK is affected if the recipient bed becomes opaque. In this series, the postoperative BCVA of the patients undergoing PK was much better than in those who underwent DALK. The rate of corneal graft clarity was reported to be as high as 92% after PK for MCD.[18]

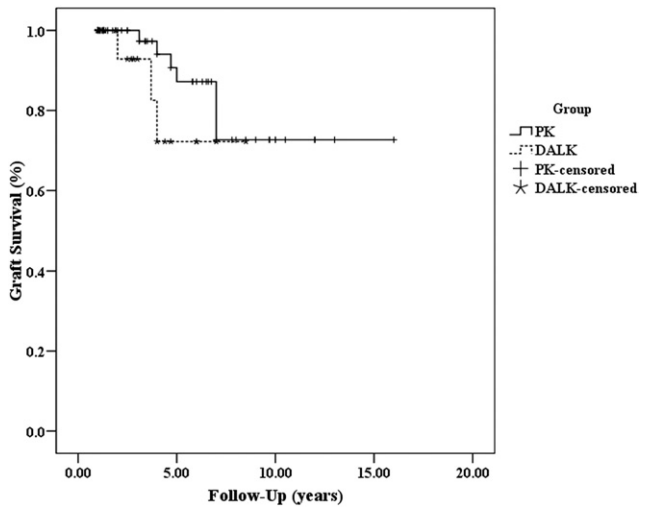

Figure 4. Graph showing graft survival after deep anterior lamellar keratoplasty (DALK) and penetrating keratoplasty (PK) for macular corneal dystrophy.

Table 2. Risk Factors for Recurrent Macular Corneal Dystrophy after Keratoplasty

Variable	B Value	Relative Risk (95% Confidence Interval)	*P* Value
Age at onset (yrs)			
≤18			
>18	1.169	3.218 (1.218–8.500)	0.018
Age at surgery (yrs)			
<30			
≥30	1.038	2.822 (1.073–7.420)	0.035
Therapy			
DALK			
PK	1.623	5.066 (1.768–14.520)	0.003

DALK = deep anterior lamellar keratoplasty; PK = penetrating keratoplasty.

However, major complications after PK include increased intraocular pressure, graft rejection, and complicated cataract. These occur more frequently than those that occur after DALK, almost certainly because the intraocular tissues are not disturbed during DALK.[19] In the current study, 4 eyes had corneal endothelial decompensation resulting from continuous loss of corneal endothelial cells after PK. The ECD reduced to 1000 cells/mm^2 or less in 20 eyes (39.2%), all of which had a risk of endothelial decompensation. Therefore, to achieve permanent intraocular stability and safety, DALK—based on the authors' experience—seems to be a better choice for patients with MCD than PK.

Recurrent MCD after PK often presented as patchy opacities in the light matrix of the graft margin, which usually developed around the sutures, then gradually fused into pieces, and finally expanded to the center of the graft. The recurrence after DALK manifested as gradually aggravated opacification of the recipient bed with a white substance depositing on the juncture of graft and recipient bed, after which the graft was involved, and the opacity in the graft margin became more obvious. By light microscopy and histochemical study, Robin et al[10] concluded that recurrence of MCD in the corneal graft resulted from replacement of the donor keratocytes by genetically defective host cells. Because the corneal endothelium, Descemet's membrane, and partial corneal stroma did not need to be removed during DALK, more genetically defective tissues were retained compared with PK. Therefore, the higher rate and the earlier onset of recurrence in the eyes treated by DALK may be attributed to the more active replacement of the donor keratocytes than those treated by PK.

It has been reported that the incidence of disease recurrence after keratoplasty correlated with the length of follow-up and inversely with the size of the donor graft and the recipient trephination.[11–13,20,21] The clinically significant recurrence rate was 8.4% in eyes with a recipient trephination of 7.0 mm or less, and only 1.9% in those with a recipient trephination of 7.25 mm or more.[22] In the current series, the recipient trephination in all cases was 7.25 mm or more. Recurrence also was correlated with the age at onset and surgery. In this study, the risk rate of recurrence was compar-

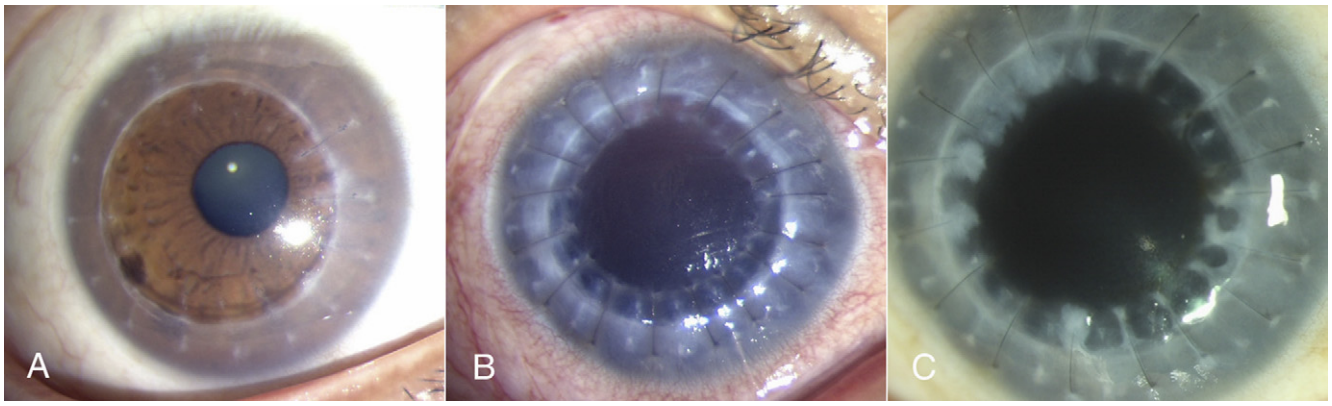

Figure 5. **A**, Photograph showing clear graft and no recurrence 8 years after penetrating keratoplasty. **B**, Photograph showing clear graft at 1 month after graft resuture. **C**, Photograph showing disease recurrence and white substance on the margin of the graft 10 months after graft resuture.

atively higher in patients 18 years of age or younger at onset or in those younger than 30 at surgery, which was different from the study by Al-Swailem et al[22] in which recurrence occurred more frequently in patients older than 40 years of age. Trauma and repeated surgery also may trigger recurrence. One patient in this series who had no recurrent disease for 8 years after PK demonstrated obvious recurrence signs after the graft was resutured for traumatic corneal laceration. This was probably because of the accelerated replacement of donor keratocytes with host cells and the accumulation of glycosaminoglycans in cells during the wound healing. Related mechanisms need to be investigated further.

The decision regarding the type of transplantation performed for MCD was made based on the patient's disease severity. There were more PK than DALK procedures in this study, mainly because the DALK procedure was adopted for a shorter period than PK, and MCD had become severe in many patients when they visited the authors' institution. Nevertheless, the baseline features of the 2 groups were similar except for the follow-up time. The comparison was made at the same time points, so the results were reliable. In consideration of the low incidence of MCD, both eyes of the bilateral cases were included in the study to increase the sample size. This could contribute to a bias because of a correlation effect in statistical analyses, and it was a limitation of this study.

In summary, PK may improve the visual acuity and quality of vision immediately in patients with MCD, but the incidence of complications seems to be higher than with DALK, which can bring permanent stability and safety of the graft and intraocular tissues. Comparatively poor postoperative visual acuity and recurrence of disease are major problems with DALK. No significant difference was detected in graft survival rates between eyes treated by PK and DALK for MCD. Therefore, selection of specific keratoplasty for MCD should be dependent on the actual need and situation of patients. For young patients with severe corneal opacity, PK can be recommended for immediate improvement in visual function, whereas for older patients with mild to moderate corneal opacity, DALK or phototherapeutic keratectomy may be preferred for its apparently better safety.

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Footnotes and Financial Disclosures

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