Comparative Study of Long-term Graft Survival Between Penetrating Keratoplasty and Deep Anterior Lamellar Keratoplasty



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- PURPOSE: Endothelial failure and immunological graft rejection remain long-term complications leading to late graft failure in penetrating keratoplasty (PK). Deep anterior lamellar keratoplasty (DALK) has emerged as a viable alternative that enables preservation of the host's endothelial cells to eliminate risks of endothelial rejection and failure. The aim of this study was to compare long-term graft survival between PK and DALK.
- DESIGN: Retrospective clinical cohort study.
- METHODS: All consecutive primary grafts of DALKs (n = 362) and PKs (n = 307) performed for optical indications in a tertiary eye center from the ongoing, prospective Singapore Corneal Transplant Study. Ten-year graft survival outcomes were compared. Cases in which endothelial pathologies were diagnosed were excluded, as DALK was not performed for such cases. Main outcome measurements were mean graft survival rate.
- RESULTS: The survival rate for PK was 94.4%, 80.4%, and 72.0% at 1, 5, and 10 years, respectively; and 95.8%, 93.9%, and 93.9% at 1, 5, and 10 years, respectively, for DALK (P=.001). Patients who underwent PK developed more complications of glaucoma (29.3% vs. 11.6%, respectively; P<.001), allograft rejection (16.6% vs. 1.7%, respectively; P<.001), epithelial problems (10.4% vs. 5.5%, respectively; P=.018), and nonimmunological failure (7.8% vs. 1.9%, respectively; P<.001), compared to DALK. Rates of graft failure attributable to rejection (36.7% vs. 5.9%, respectively; P=.015) and endothelial failure (36.7% vs. 5.9%, respectively; P=.015) were lower in DALK.
- CONCLUSIONS: The 10-year graft survival for primary DALK was superior to that for PK for corneal pathologies with functional endothelium. Primary DALK resulted in fewer post-operative complications and lower rates of graft rejection and failure. This study strengthens the case in favor of performing DALK over PK when

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PENETRATING KERATOPLASTY (PK) HAS BEEN SHOWN to be a safe and effective surgery for patients with corneal stromal diseases with good visual outcomes. In the 2019 Eye Bank Association of America statistical report, PK was performed for more than 90% of corneal grafts for nonendothelial and stromal disease. However, endothelial failure and immunological graft rejection remain long-term complications, even up to 15 years post-operatively, leading to a graft failure rate of 18%-50% of cases depending on cause. Furthermore, persistent endothelial cell loss occurred over time in the Cornea Donor Study, demonstrating in excess of 76%-79% of endothelial cell loss 10 years after undergoing primary PK.

Refinements of surgical techniques, instruments, and microscopes have led to an evolution from replacement of full-thickness cornea to selected diseased layers. Beep anterior lamellar keratoplasty (DALK) enables preservation of the host's endothelial cells to eliminate the risks of immune-meditated endothelial rejection and resultant failure. This technique has been refined over the years to a removal of almost all the corneal stroma in a lamellar dissection while preserving the healthy endothelium of the host. In addition, it avoids the potentially serious complications of an open sky surgery of PK such as expulsive hemorrhage and endophthalmitis and requires less strict criteria for selection of donor corneal tissue. 1,10 DALK also results in better tectonic integrity of the globe and provides faster visual recovery due to possibility of earlier suture removal. One of the drawbacks of DALK remains light scattering at the host-donor interface, which may lead to poorer final visual acuity. 11 However, advancements in surgical techniques, most notably Anwar's "bigbubble" technique, has resulted in a smoother interface and resultant better visual outcomes. 12-14 Therefore, DALK has emerged as a viable alternative to PK for the treatment of eyes with corneal stromal opacities and a normal endothelium, such as keratoconus, stromal dystrophies, trauma, and resolved microbial keratitis with residual stromal scarring.

Various studies comparing DALK with PK in keratoconus patients have shown similar 3- and 5-year graft survival

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outcomes.^{15–18} Although graft survival can be influenced by a number of factors including host and donor factors, refinements of surgical technique, and possibly a surgeon learning effect, DALK has been shown to be a safe alternative to PK in keratoconus.¹⁷ DALK has also shown comparable outcomes to PK for other stromal diseases with normal endothelium such as stromal dystrophies¹⁹ and infectious keratitis.²⁰ Borderie and associates²¹ postulated model-predicted higher graft survival for DALK than for PK for corneal disease not involving the endothelial layer. However, evidence is limited regarding actual comparative long-term graft survival.

Patients presenting with these corneal diseases are usually younger, which makes a long graft survival necessary. The accelerated progressive endothelial cell loss⁷ and high rates of late graft failure^{4–6} after undergoing PK have highlighted the possible long-term benefits of DALK. The present authors previously showed that the visual acuity outcomes for DALK are comparable with those for PK, with good graft survival rates 3 years postoperatively.¹⁸ Therefore, the main objectives for this study were to compare the long-term graft survival outcomes of PK relative to those of DALK performed for optical indications over 10 years and to identify high-risk characteristics and causes of graft failure in both groups.

METHODS

THIS WAS A PROSPECTIVE COHORT STUDY IN WHICH CLINical data were extracted from the database of the ongoing prospective Singapore Corneal Transplant Study. From January 2000 to December 2014, all patients who underwent PK or DALK at the Singapore National Eye Centre were included. The database was anonymized with respect to patient and surgeon information. This study adhered to the tenets of the Declaration of Helsinki, and Institutional Review Board approval was obtained (CIRB: 2018/2688).

Inclusion criteria were primary grafts for both PK and DALK performed for optical indications, and patients were followed for a minimum of 1 year. Cases diagnosed with endothelial pathologies such as bullous keratopathy, Fuchs' endothelial dystrophy, and other forms of endothelial decompensation (ie, glaucoma, post-laser) were excluded because DALK was not performed for such cases. Only the primary graft of each patient was included and analyzed in the study. A total of 669 grafts consisting of 362 cases of DALK and 307 cases of PKs were identified.

The primary outcome measurement was graft survival time. Graft survival over time was defined on the basis of graft clarity. ²² Confirmation of graft failure was defined as an irreversible loss of optical clarity, with the date of onset of corneal clouding selected as the clinical date of failure. ^{5,22} The survival period was defined as the interval between date of surgery and the date of failure. Post-operative complications

extracted from the database were scored as events and subsequently analyzed. Patients were divided into 2 groups based on high or low risk of graft failure. Eyes with high risk for graft failure were defined as the presence of at least 1 of the following: deep vascularization of more than >1 quadrant; concomitant glaucoma; active inflammation; ocular surface disease; and the presence of peripheral anterior synechiae.

The surgical technique used for DALK was either Descemet's membrane (DM) baring or non-DM baring anterior lamellar keratoplasty. The modified Anwar technique involved an initial manual dissection of the anterior stromal layer prior to entry of the air needle close to the Descemet's membrane for big-bubble separation as previously described. 18 In cases where the big bubble was not successfully achieved or the modified Anwar technique was deemed not feasible, for example, in cases with deep corneal stromal scarring, a manual dissection technique was performed. In such cases, deep lamellar dissection was performed in several layers, but baring of the DM membrane was not achieved. DALK donor size was generally not oversized but was occasionally done to balance the power between the 2 eyes or in very steep cones. PK was performed as previously described⁵ with a full-thickness trephine of the recipient cornea, followed by 0.25-0.50 mm suturing of an oversized donor cornea on to the host.

The statistician who performed the analysis was masked for post-operative outcomes. Kaplan-Meier survival plots were used to illustrate the differences in survival probability between PK and DALK. The Mantel-Cox log rank test was used to compare 2 survival curves. For comparisons of categorical data, χ^2 tests or Fisher exact tests were conducted where appropriate. A P value of <.05 was considered statistically significant. Statistical analysis was performed using SPSS version 25.0 software (IBM, Armonk, New York, USA) for Windows (Microsoft Word, Redmond, Washington, USA), and Statistical Software version 15 (STATA Corp, College Station, Texas, USA).

RESULTS

A TOTAL OF 669 GRAFTS WERE ANALYZED, CONSISTING OF 362 cases of DALK and 307 cases of PK. At the time of surgery, patients had a mean age of 41.0 \pm 20 years (range: 1-90.3 years old). A total of 380 were male (56.8%), and 46.6% were Chinese as shown in Table 1. The mean follow-up period was 40.0 \pm 38.9 months.

A total of 307 cases of PK were performed throughout the 10-year study period, accounting for 45.9% of all corneal transplants performed. Initially, PK was the most commonly used technique at the start of the study period in 2000 and slowly decreased in frequency. The decreasing trend coincided with an increase in frequency of DALK being performed for similar optical indications. This gradual change in surgical technique continued as more surgeons were trained in DALK, and DALK overtook PK as the

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	-	Total	PK (n = 307)	DALK	(n = 362)	P Value
Sex							.469ª
Male	380	56.8%	179	58.3%	201	55.5%	
Female	289	43.2%	128	41.7%	161	44.5%	
Race							.005ª
Chinese	312	46.6%	162	52.8%	150	41.4%	
Malay	112	16.7%	53	17.3%	59	16.3%	
Indian	96	14.3%	32	10.4%	64	17.7%	
Others	149	22.3%	60	19.5%	89	24.6%	
Age, y							<.001 ^b
Mean \pm SD	41.0 ± 20.3		45.3 ± 20.7		37.5	± 19.4	
Median	38.9		45.8 32.7		32.7		
Range	0.2-90.3		0.2	2-90.3	0.2	2-83.1	

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

^bMann-Whitney *U*-test.

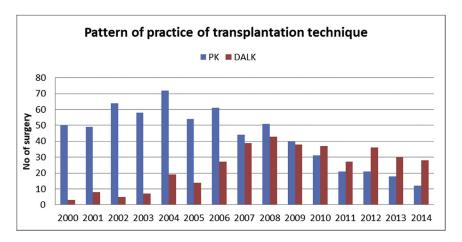


FIGURE 1. Number of PK and ALK corneal transplantations performed in Singapore from year 2000 to 2014. ALK = anterior lamellar keratoplasty; PK = penetrating keratoplasty.

primary corneal transplantation procedure of choice from the year 2010 onward for corneal stromal disease (Figure 1).

Patients were stratified by their underlying diagnoses, where the 3 most common indications for corneal transplantation were post-infectious scars (23.8%; n = 73 for PK and 27.9%: n = 101 for DALK), keratoconus (23.5%; n = 72 for PK and 37.6%, n = 136 for DALK), and post-traumatic scars (13.7%, n = 42 for PK and 7.2%%, n = 26 for DALK) (Table 2). There were no significant differences between the proportion of high-risk PK patients and DALK patients for keratoconus (P > .999), postinfectious scars (P = .063), and traumatic scars (P = .537).

• KAPLAN-MEIER COMPARATIVE GRAFT SURVIVAL RATES: The overall average survival period for all corneal

grafts was 143.5 months (95% confidence interval [CI]: 136.5 to 150.5). Kaplan-Meier survival curves for PK and DALKs were then compared over the same time period. The mean survival period was 133.5 months (95% CI: 124.0 to 143.0) for PK and 141.4 months (95% CI: 137.4 to 145.5) for DALK. The graft survival rate for PK was initially high at 94.4% at the 1-year mark, gradually declining over time to 80.4% at the 5th year and further declining to 72.0% at the 10-year mark. In contrast, the graft survival rate for DALK was 95.8% at the 1-year mark and maintained good graft survival rates at 93.9% at both the 5-year and 10-year marks with no late graft failures occurring from the 5th-10th years (P = .001) (Figure 2, Table 3).

Graft failure were than analyzed in eyes with high risk of failure as identified earlier. The overall graft survival period

 $a\chi^2$ test.

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TABLE 2.	Underlying	Diagnosis	of All	Cases

Major Diagnosis	PK		DALK	
	n	(%)	n	(%)
Post-infectious scars	73	23.8	101	27.9
Keratoconus	72	23.5	136	37.6
Traumatic corneal scars	42	13.7	26	7.2
Other corneal scars (nontraumatic/noninfectious)	59	19.2	39	10.8
Corneal dystrophies (excluding endothelial dystrophies)	38	12.4	38	10.5
Pediatric corneal scars and opacities	13	4.2	1	0.3
Corneal degenerations	10	3.2	13	3.6
Post-refractive surgery complication	0	0.0	8	2.2
Total	307	100	362	100

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

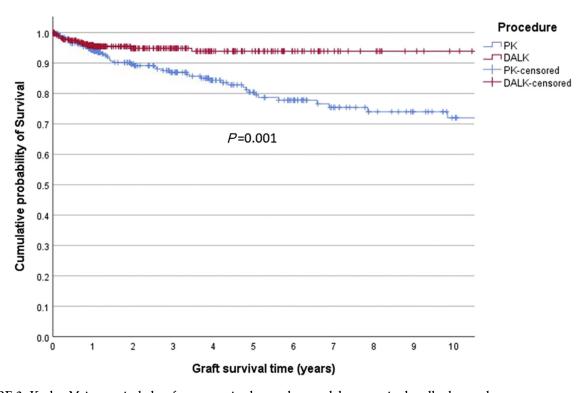


FIGURE 2. Kaplan-Meier survival plots for penetrating keratoplasty and deep anterior lamellar keratoplasty.

for high-risk eyes was expectedly lower at 100.5 months for PK and 106.0 months for DALK, compared to 150.0 months for PK and 144.2 months for DALK in low-risk eyes. In high-risk eyes, the graft survival rate for PK were 90.3%, 59.0%, and 48.7% at 1, 5, and 10 years, respectively, whereas for DALK, they were higher at 84.6%, 82.1%, and 82.1%, respectively (P = .403) Similarly, in low-risk eyes, the graft survival rates for PK were 96.0%, 88.9%, and 81.1% at 1, 5, and 10 years, respec-

tively, compared to 97.6%, 95.8%, and 95.8%, respectively, for DALK (P = .011) (Figure 3).

Graft survival rates were then stratified by major diagnoses between the 2 procedures to analyze survival rates. The 10-year survival rates between PK and DALK, respectively, were 93.7% and 95.9% for keratoconus (n = 13 vs. n = 6; P = .796) and 76.7% and 91.5% for post-infectious scars (n = 11 vs. n = 5; P = .951). For traumatic scars, the 5-year survival rate was 45.7% and 87.3% for PK and

TABLE 3. Graft Survival Rates for PK and DALK

Survival time Number at risk	PK			DALK		
	Survival Rate	95% CI	Number at risk	Survival Rate	95% CI	
Year 0	306	100%		361	100%	
Year 1	234	94.4%	91.7-97.1%	255	95.8%	93.7-98.0%
Year 2	175	89.7%	85.9-93.5%	158	94.9%	92.3-97.4%
Year 3	149	86.9%	82.6-91.3%	113	94.9	92.3-97.4%
Year 4	117	84.3%	79.4-89.3%	82	93.9%	90.8-97.0%
Year 5	96	80.4%	74.6-86.2%	61	93.9%	90.8-97.0%
Year 10	35	72.0%	63.9-80.1%	12	93.9%	90.8-97.0%

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

DALK, respectively (n = 11 vs. n = 2; P = .592) (Figure 4). Subgroup analysis of DM-baring versus manual dissection DALK procedures was also performed, with graft survival rates for DM-baring DALK at 99.2%, 99.2%, and 99.2% at 1, 5, and 10 years, respectively, compared to manual dissection DALK at 93.9%, 90.4%, and 90.4%, respectively (P = .005).

• COMPLICATIONS AND CAUSES OF GRAFT FAILURE: Post-operative complications were significantly higher in eyes that underwent PK than in eyes that underwent DALK. A significantly larger proportion of patients who underwent PK developed glaucoma or raised intraocular pressure (29.3% vs. 11.6%, respectively; P < .001), allograft rejection (16.6% vs. 1.7%, respectively; P < .001), epithelial problems (10.4% vs. 5.5%, respectively; P = .018), and nonimmunological failure (7.8% vs. 1.9%, respectively; P < .001) (Table 4).

DM perforation is a complication unique to DALK, which was described in a prior publication. ²³ A total of 101 DALK cases (18.7%) sustained intraoperative DM perforation, of which 79 cases were microperforation (14.6%) and 15 cases were macroperforation (2.8%). Cases were treated with a combination of intracameral air tamponade, stromal patching, fibrin glue, and suturing of the defect. All cases of microperforation had successful completion of the DALK surgery, whereas 2 cases of macroperforation necessitated conversion to PK.

The major causes of graft failure for PK were rejection (18 of 49; 36.7%) and endothelial failure (18 of 49; 36.7%). In contrast, the rates of failure attributed to rejection and endothelial failure were significantly lower in patients who had DALK, 1 of 17 (5.9%) (Table 5).

DISCUSSION

THE RESULTS OF THIS STUDY DEMONSTRATED THAT GRAFT survival for DALK was significantly better than for PK for a

range of corneal pathologies (ie, keratoconus, post-infectious scars, and traumatic scars). In addition, recipients who had high-risk factors for graft failure and underwent DALK also had better graft survival than patients who underwent PK (Figure 3). This study also showed that PK was associated with higher risk of late post-operative complications of glaucoma, rejection, and nonimmunological failure than DALK, illustrating the long-term safety profile of DALK compared to PK. The 2 highest causes of graft failure of rejection and endothelial failure were significantly higher in PK than in DALK.

To the best of the authors' knowledge, this is the first comparative study of long-term 10-year graft survival outcomes of PK and DALK for a range of corneal pathologies with a healthy endothelium. This study demonstrated significantly better long-term graft survival of 93.9% with DALK than with PK 10 years post-operatively. Clinical results are also in agreement with the statistical theorem of Borderie and associates, ²¹ who used statistical models based on postoperative endothelial cell loss to predict significantly better long-term graft survival in DALK than in PK. In contrast, Coster and associates²⁴ reported lower survival outcomes for DALK than for PK over a 5-year period. However, information for the DALK surgical technique is lacking, and given that 20% of graft failures were due to interface haze, it may be inferred that surgical technique might have been a factor resulting in suboptimal outcomes in that large series. Other registry studies comparing PK and DALK survival outcomes have largely focused on keratoconus, with some studies showing comparable graft survival of up to 5 years. 15-17 A diagnosis of keratoconus is generally associated with better graft survival even in eyes with PK. Findings of the present study also confirm comparable graft survival of keratoconus at 10 years postoperatively. However, given that keratoconus patients tend to be younger, as well as the fact that endothelial attrition in DALK is much lower, longer term studies, beyond 10 years, are needed to assess graft survival rates in those patients.

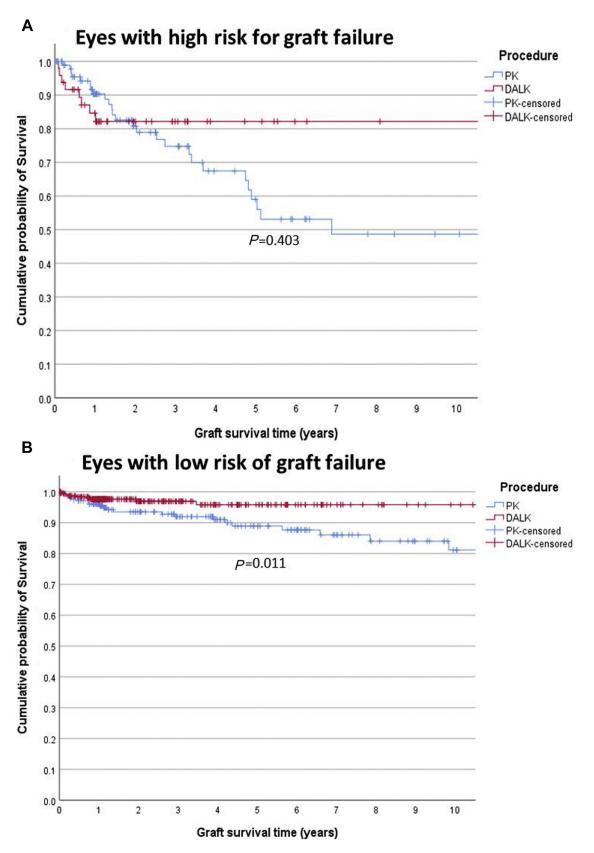


FIGURE 3. Kaplan-Meier survival plots for penetrating keratoplasty and deep anterior lamellar keratoplasty by presence of high-risk (A) and low-risk (B) factors of graft failure.

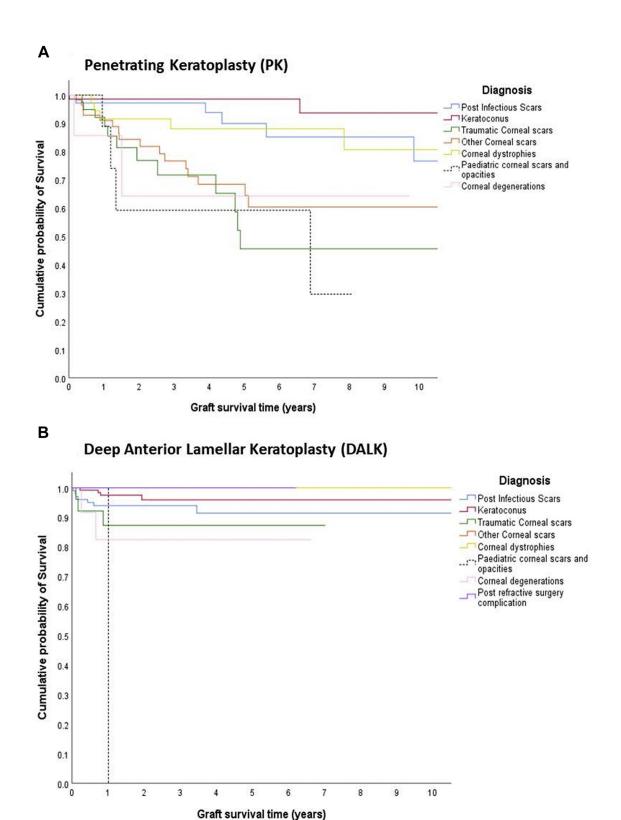


FIGURE 4. Kaplan-Meier survival plots of penetrating keratoplasty (A) and deep anterior lamellar keratoplasty (B) by primary corneal disease groups.

TABLE 4. Post-Operative Complications for Both PK and DALK

	PK	(n = 307)	DALK (n = 362)			
Major complications	n	%	n	%	P Value	
Glaucoma/raised IOP	90	29.3%	42	11.6%	<.001	
Allograft rejection	51	16.6%	6	1.7%	<.001	
Epithelial problems	32	10.4%	20	5.5%	.018	
Nonimmunological failure	24	7.8%	7	1.9%	<.001	
Cataract	11	3.6%	13	3.6%	.996	
Wound dehiscence	9	2.9%	3	0.8%	.041	
Activation of HSV	7	2.3%	9	2.5%	.862	
Microbial keratitis	5	1.6%	3	0.8%	.480	
Recurrence of primary disease	3	1.0%	9	2.5%	.143	

DALK = deep anterior lamellar keratoplasty; HSV = herpes simplex virus; IOP = intraocular pressure; PK = penetrating keratoplasty. Some patients can have more than 1 complication.

TABLE 5. Reasons for Failure for Both PK and DALK

Failure causes	PK (n = 49)		DAL	K (n = 17)	
	No	%	No	%	P Value
Rejection	18	36.7%	1 ^b	5.9%	.015
Endothelial failure	18	36.7%	1	5.9%	.015
Glaucoma	8	16.3%	2	11.8%	>.999
Infection	4	8.2%	1	5.9%	>.999
Epitheliopathy	3	6.1%	4	23.5%	.066
Recurrence of primary disease	1	2.0%	3	17.6%	.050
Others ^a	6	12.2%	9	52.9%	.001

DALK = deep anterior lamellar keratoplasty; PK = penetrating keratoplasty

at 94.4% at 1-year post-operatively. However, over a longer term, PK graft survival was not as optimal at 72% at 10 years following surgery. This can be attributable to a progressive attrition in endothelial cell density (ECD) over a long follow-up period.²⁵ Current medical literature shows widely varied graft survival outcomes, with 10-year graft survival ranging from 79%-80% reported in Western studies^{6,7} and 50%-72% survival in Asian populations.²⁶ ²⁸ This variability among studies is due to multiple factors including differing proportions of various diagnosis and nonuniform exclusion criteria. For example, studies with a higher percentage of grafts performed for keratoconus, as well as grafts performed for optical indications, report higher survival rates. In contrast, populations with a larger proportion of high-risk grafts, or those performed for tectonic or therapeutic indications report lower survival rates.⁵ Taking that into account, even in studies with a high reported graft survival rate of

Graft survival rates for PK were better in the short term

79%, Ings and associates⁷ demonstrated an accelerated loss of ECD of 70% at 10 years after PK.

Our results for DALK have been encouraging, with 95.8% at the first year and 93.9% at 10 years. Our results are similar to that of Sarnicola and associates, 22 which reported good post-DALK graft survival of up to 99% at 10 years in a study population consisting largely of keratoconus and post-herpetic scarring patients. In contrast, our series have included many anterior corneal pathologies with indications more in line with an Asian context, with a higher proportion of post-infectious and post-traumatic scars (Table 2) with keratoconus only, accounting for approximately one-third of all cases. Our previous study showed 100% graft survival at 3 years for both PK and DALK performed for keratoconus at the 3-year mark.¹⁸ Looking forward, the rates of performing of DALK in keratoconus may decrease even in the Western populations, and the main indications for DALK may shift towards post-infectious and post-traumatic scars.

^aIncludes corneal scar of unknown cause, post-pterygium corneal scarring, and scarring due to lid disease.

^bEpithelial rejection which resolved with a course of intensive topical steroids.

A limitation in the present study is that due to the nature of a registry study, the comparative data in the PK and DALK groups were unmatched and may suffer from selection bias. Coster and associates²⁴ previously argued that registries, although imperfect, provide arguably the best available evidence for long-term outcomes of different forms of corneal transplantation in the real world, as follow-up can be maintained indefinitely. Randomized controlled trials comparing DALK and PK are difficult to implement partly due to the changing trends in surgeon preference as shown by the pattern of practice from our study (Table 1) as well as from the Eye Bank Association of America, ²⁹ which may make timely randomization not possible. Although in the present study the PK and DALK groups were not matched and differed for race and age, these 2 factors have previously shown not to affect long-term graft survival.³⁰ Another limitation was that the number at risk in the DALK group after 10 years was small, as PK was the more commonly used technique at the start of the study period in 2000, with frequency of DALK being performed for similar optical indications gradually increasing from 2004.

Van Dooren and associates³¹ reported that, following a small initial drop in ECD induced by surgical trauma, no continued post-operative accelerated cell loss occurred in the eye that underwent DALK, approaching the physiological cell loss of normal corneas³² with no drop off of ECD up to 5 years post-operation.³³ In contrast, corneal endothelial cell loss continues to occur at a higher rate than the physiological cell loss in PK, with a cumulative cell loss of more than 50% within the first 10 years.²⁵ In the latest Cornea Donor Study, post-PK eyes experienced substantial cell loss of 76% at 10 years, with only 14% of patients having a residual ECD of >1,000 cells/mm².³⁴ Furthermore, a comparative study of corneal endothelium survival showed an ECD loss of 50% in PK and 22% in DALK at 5 years, with increased accelerated loss in PK every year. 21 This lends credence to the finding that, by preserving the host corneal endothelium, DALK has the potential to offer much better, longer graft survival than PK. Another limitation in the present study was the lack of corroborating ECD data, hence analysis of ECD was not performed.

The main causes of graft failure in PK are allograft rejection and late endothelial failure, each accounting for 36.7% of graft failures in the present series. This rate is similar to that in a previous study. In contrast, only 1 patient in the DALK group had endothelial failure over the study period, and that patient was already noted to have pre-existing endothelial compromise prior to DALK. No patients in the present DALK group had endothelial rejection. As the host corneal endothelium is preserved in DALK, donor endothelial immune-mediated rejection does not occur as it would in PK.35 Although epithelial and stromal rejection can still occur in DALK, they usually respond well to a course of topical corticosteroids and generally do not affect graft clarity if early treatment is instituted.³⁶ The present DALK series had a single case of epithelial rejection which resolved with a course of intensive topical steroids. However, a case series by Watson and associates³⁷ showed that stromal inflammation from stromal rejection can result in secondary endothelial function compromise and progressive graft failure, especially in patients with high-risk of rejection and noncompliance with immunosuppressive therapy. The results of this study are also commensurate with evidence in the medical literature showing graft failure of 13%-28% after a rejection episode in PK. 17,35,38

In summary, this study describes the long-term graft survival outcomes of up to 10 years for DALK compared to PK for optical indications in eyes with a healthy endothelium. It is expected that the survival differential will widen with even longer periods of follow-up due to continued accelerated endothelial cell loss in PK. We have also demonstrated that DALK results in a significantly lower rate of long-term complications, including graft rejection and failure. This information, together with current knowledge of equivalent visual outcomes for DALK and PK, only strengthens the case in favor of performing DALK over PK where possible.

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