Original Article

Ten-Year Survival of Optical Penetrating Keratoplasty and Risk Factors for Graft Failure in Thai Patients

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Objective: To determine long-term graft survival and identify risk factors for secondary graft failure of optical penetrating keratoplasty (PK) in Thai patients.

Materials and Methods: A Retrospective study of patients that underwent optical PK at Siriraj Hospital between January 2002 and December 2005 was done.

Results: Of 131 eyes, primary graft failure was found in two eyes (1.5%) thus, 129 eyes were recruited. The three most common surgical indications were pseudophakic or aphakic bullous keratopathy (33.3%), corneal scars (post-trauma, post-infection) (20.9%), and regrafts (16.3%). Mean follow-up period was 93.2 months (1 to 183 months). One-year, 2-year, 5-year, and 10-year graft survival rates were 84.5%, 73.2%, 50.2%, and 24.7%, respectively. The leading cause of graft failure was irreversible allograft rejection (62.5%). Most (56.0%) of the first graft rejection happened within one year post-operatively. Graft survival was lower in eyes with regrafts, history of glaucoma, deep corneal vascularization, peripheral anterior synechiae, and occurrence of one or more rejection episodes. Multivariate regression analysis demonstrated that peripheral anterior synechiae and occurrence of one or more rejection episodes were the significant independent risk factors for graft failure. Considering patients with the clear grafts at the last follow-up, the final best-corrected visual acuity was 6/36 or better in 66.7% eyes and 6/18 or better in 31.6% eyes. Comparing to pre-operative vision, patients with the clear grafts at the last follow-up had improved visual outcome in most eyes (82.5%).

Conclusion: Ten-year survival and visual outcome of optical PK showed successful outcome, however, the survival rate decreased over time. The significant risk factors for graft failure should be cautiously evaluated before surgery.

Keywords: Corneal graft survival, Keratoplasty outcome, Optical penetrating keratoplasty

Received 26 March 2018 | Revised 21 October 2019 | Accepted 31 October 2019

J Med Assoc Thai 2020;103(9):883-90
Website: http://www.jmatonline.com

Corneal transplantation has been one of the most frequently performed solid organ transplantations. Even though, alternative surgical technique of lamellar keratoplasty has gained popularity, penetrating keratoplasty (PK), which could be the method of choice for all keratoplasty indications[1,2], is still the foremost surgery. Three indications of PK were for optical, therapeutic, and tectonic purpose. Unlike the other purposes, maintenance of clarity of the corneal graft in the long term is the main goal of optical PK surgery. Although many publications reported graft survival and visual outcome of PK in their population[3-6], few publications studied the long-term (more than 10 years) graft survival[7-10]. Reported graft survivals varied from country to country affected by different demographic patients' backgrounds and surgical circumstances.

In Thailand, indications and visual outcome of PK were previously studied[11-16]. However, to the authors' knowledge, corneal graft survival has never been studied in Thai patients. Therefore, in addition to reporting the surgical indications and visual outcome, the primary objective of the present study was to demonstrate the long-term (10 years) corneal graft survival of optical PK and to identify causes and risk factors of secondary graft failure.

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How to cite this article:

Chotikavanich S, Prabhasawat P, Satjapakasit O. Ten-Year Survival of Optical Penetrating Keratoplasty and Risk Factors for Graft Failure in Thai Patients. J Med Assoc Thai 2020;103:883-90.

doi.org/10.35755/jmedassocthai.2020.09.8667

Materials and Methods

Data collection

After the present study protocol was approved by the Siriraj Institutional Review Board [Siriraj Ethics Committee Number 179/2553(EC3)], a retrospective medical chart review of consecutive patients that underwent PK for optical purpose (for corneal clarity and improvement of vision) and had a minimum of 10-year follow-up at Siriraj Hospital was performed. Exclusion criteria included corneal transplants performed for therapeutic purpose for active corneal infection, inflammation, or neoplasia, for tectonic purpose in impending or presenting corneal perforation, patients younger than 20 years old, incomplete documentation, and primary graft failure.

One hundred thirty-one eyes in 129 patients underwent PK for optical reason between January 2002 and December 2005. Primary graft failure defined as irreversible corneal graft opacification occurring within two weeks after transplant was found in two eyes (1.5%). These failures had been considered to relate to donor tissue survivability and did not relate to recipient factors. Therefore, 129 eyes in 127 patients met the inclusion criteria.

Data including age, gender, laterality, and primary pre-operative diagnosis were collected. A secondary graft failure was defined as an irreversible loss of corneal graft clarity after the graft was initially clear for at least the first two weeks after PK, unresponsive to medical treatments. Causes of the secondary graft failure were recorded. Possible risk factors of secondary graft failure including pre-operative factors of surgical indication, history of glaucoma (having at least one anti-glaucoma medication or history of glaucoma surgery, which was trabeculectomy or tube-shunt surgery with or without medication), deep (stromal) corneal vascularization, peripheral anterior synechiae, and lens status, intra- and post-operative factors of type of operation, data about donor graft, occurrence of rejection episode, and other complications were reviewed.

Visual outcomes of the surgery including best-corrected visual acuity and other co-morbidities affecting visual acuity were recorded. The best-corrected visual acuity was categorized in eight levels, equal to or better than 6/18, worse than 6/18 to 6/36, worse than 6/36 to 6/60, worse than 6/60 to 3/60, worse than 3/60, hand movement, light projection or perception, and no light perception. Visual outcome was considered better when the best-corrected visual acuity improved one or more levels, worse when the best-corrected visual acuity decreased one or more levels, and stable when the best-corrected visual acuity was at the same level, compared to pre-operative vision.

Table 1. Indications for optical penetrating keratoplasty (n=129)

Primary pre-operative diagnosis	n (%)
Pseudophakic or aphakic bullous keratopathy	43 (33.3)
Corneal scars†	27 (20.9)
Regrafts	21 (16.3)
Stromal dystrophy	13 (10.1)
Idiopathic corneal decompensation	10 (7.8)
Fuchs' dystrophy	4 (3.1)
Interstitial keratitis	4 (3.1)
Glaucoma with corneal decompensation	3 (2.3)
Iridocorneal endothelial syndrome	3 (2.3)
Stevens-Johnson syndrome	1 (0.8)

† Corneal scars included post-traumatic scars and post-infectious scars

Statistical analysis

The data were analyzed using IBM SPSS Statistics for Windows, version 23 (IBM Corp., Armonk, NY, USA). Corneal allograft survival was determined with Kaplan-Meier survival analysis. The risk factors for secondary graft failure were identified by univariate regression analysis by Mantel-Cox (log-rank) test and by multivariate regression analysis with the Cox proportional hazards model, performed on the univariate risk factors to adjust for the effect of confounding by other risk factors. A p-value of less than 0.05 was considered statistically significant.

Results

Patient demographics and preoperative clinical data

One hundred twenty-nine eyes in 127 patients were included in the present study, of which 68 patients (53.5%) were male and 59 patients (46.5%) were female. Two patients received bilateral corneal grafts. Seventy-four eyes (57.4%) were right eye. The mean age of all recipients was 55.7 years (22 to 86 years). Their primary corneal diseases requiring optical PK are shown in Table 1. Pseudophakic or aphakic bullous keratopathy (43 eyes, 33.3%), corneal scars (27 eyes, 20.9%), and regrafts (21 eyes, 16.3%) were the three leading indications. According to lens status, 69 eyes (53.5%) were phakic, 47 eyes (36.4%) were pseudophakic, and 13 eyes (10.1%) were aphakic.

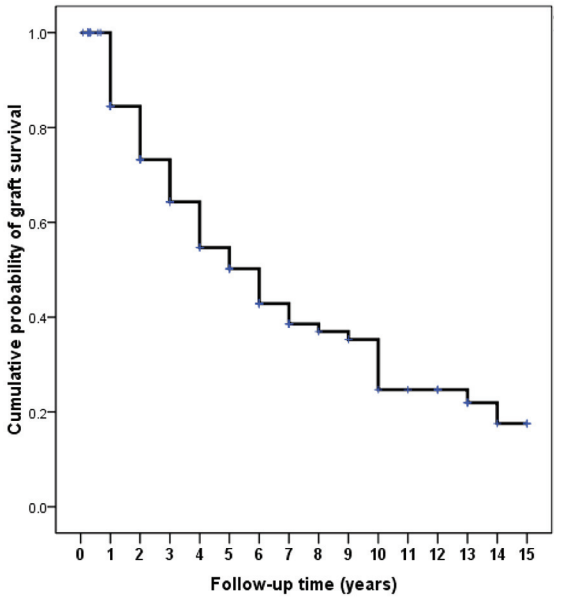

Figure 1. Kaplan-Meier survival curve of all corneal transplants.

Surgical data

Seventy-one eyes (55.0%) had PK surgery alone, whereas 58 eyes (45.0%) had PK combined with other operations including cataract removal with posterior chamber intraocular lens (IOL) implantation, primary or secondary IOL scleral fixation, or IOL exchange. Sixteen eyes (12.4%) had concurrent anterior vitrectomy surgery. One hundred twenty-seven eyes (98.4%) of recipient beds and all 129 donors' corneal buttons (100%) were in 7.0 to 8.5 mm diameter size. Two eyes (1.6%) of the recipient beds were less than 7 mm.

Most donors (113 eyes, 87.6%) were from the Thai Red Cross Eye Bank. The other 14 eyes (10.9%) and 2 eyes (1.6%) were from the Sri Lanka international eye bank in Sri Lanka and the Lions medical eye bank in USA, respectively. The ages of the donors were equal or less than 60 years in 78 eyes (65.5%) and more than 60 years in 41 eyes (34.5%). The donor storage time before surgery was within seven days in 118 eyes (98.7%) and more than seven days in two eyes (1.3%).

Postoperative data and corneal graft survival

Mean follow-up time for all patients was 93.2 months (1 to 183 months). The patients lost to follow-up increased over time. The percentage of patients with follow-up at 1, 2, 5, and 10 years was 90%, 74%, 41%, and 13%, respectively. The graft survival rates at 1, 2, 5, and 10 years were 84.5%, 73.2%, 50.2% and 24.7% respectively (Figure 1). At the last follow-up, secondary graft failure occurred in 72 eyes. Factors responsible for the graft failure are shown in Table 2. The most common cause of secondary graft failure was irreversible immunologic allograft rejection (62.5%), followed by ocular infection (18.1%), and corneal graft decompensation without history of allograft rejection (9.7%).

Table 2. Causes of secondary graft failure (n=72)

Cause	n (%)
Irreversible allograft rejection†	45 (62.5)
Ocular infection‡	13 (18.1)
Corneal graft decompensation without history of allograft rejection§	7 (9.7)
Recurrence of primary disease	3 (4.2)
Corneal surface problems¶	2 (2.8)
Ocular trauma	2 (2.8)

† Included epithelial rejection, stromal rejection, and endothelial rejection; ‡ Included corneal graft infection, infectious uveitis, and infectious endophthalmitis; § Caused by glaucoma, prolapsed vitreous, and idiopathic condition; ¶ Included persistent epithelial defect, and band keratopathy

Table 3. Post-operative duration of the first allograft rejection episode (n=75)

Post-operative duration (months)	n (%)
≤6	28 (37.3)
>6 to 12	14 (18.7)
>12 to 24	10 (13.3)
>24 to 36	11 (14.7)
>36 to 72	8 (10.7)
>72	4 (5.3)

Onset of allograft rejection, mostly occurred within the first year postoperatively (56.0%), especially within the first six months (37.3%) (Table 3). Not all patients with the first allograft rejection episode would finally develop graft failure. Of the ocular infection, causative organisms were bacteria (five eyes, including *Pseudomonas aeruginosa*, *Staphylococcus aureus* (MSSA), *Streptococcus viridans*, *Acinetobacter baumannii*, and *Citrobacter* spp., herpes virus (four eyes), fungus (two eyes, *Candida* spp., and *Acremonium* spp.) and negative culture (two eyes). Post-operative onset of infection ranged from 2 to 116 months.

Risk factors of corneal graft failure

A univariate regression analysis was performed

Table 4. Significant risk factors of secondary graft failure based on univariate regression analysis

Risk factor	Characteristic	Number (n=129)	Survival rate (%)				p-value
			1-year	2-year	5-year	10-year	
Pre-operative factor							
Surgical indication of regrafts	Presence	21	60	27.3	21.8	10.9	0.001
	Absence	108	89.6	82.8	56	25.5	
History of glaucoma†	Presence	54	80.8	66.3	34.3	15.2	0.01
	Absence	75	87.5	78.9	64.4	34.0	
Deep corneal vascularization	Presence	56	84	60.7	38.3	17.1	0.031
	Absence	73	84.8	81.7	58.3	30.5	
Peripheral anterior synechiae	Presence	23	60	32.7	10.9	-	<0.001
	Absence	106	89.6	81.6	58.7	28.5	
Post-operative factor							
≥ one rejection episodes	Presence	75	78.4	64.1	34	14.8	<0.001
	Absence	54	95.2	89.8	82.9	44.5	

† Included patients with history of having at least one anti-glaucoma medication or history of glaucoma surgery (trabeculectomy or tube-shunt surgery) with or without medication

to evaluate the risk factors of secondary graft failure. The significant risk factors ($p<0.05$) are presented in Table 4. The presence of regrafts, history of glaucoma, deep corneal vascularization, peripheral anterior synechiae in recipient eye, and post-operative occurrence of one or more allograft rejection episodes were significantly associated with an increased risk of graft failure, compared to the absence of each of these conditions ($p=0.001$, 0.01, 0.031, <0.001, and <0.001, respectively).

On the other hand, the other factors included donor age (60 years or younger versus older than 60 years), donor endothelial cell count (2,500 cells/mm² or less versus more than 2,500 cells/mm²), donor storage time (within seven days versus more than seven days), lens status (phakic versus pseudophakic or aphakic), operation type (PK alone versus PK combined with other operations, e.g., cataract extraction with IOL insertion, IOL exchange, or anterior vitrectomy) were not significant risks ($p>0.05$).

The variables that were significantly associated with graft survival in the univariate analysis were further analyzed using a multivariate regression analysis to identify independent risk factors for graft failure (Table 5). Two independent risk factors that reached statistical significance ($p<0.05$) with high risk ration (RR) were recipient peripheral anterior synechiae (RR 2.25, 95% CI 1.22 to 4.14) and occurrence of one or more allograft rejection episodes (RR 2.57, 95% CI 1.42 to 4.65).

Visual outcome

At the last follow-up, 57 clear corneal grafts were presented. The best-corrected visual acuity of the clear corneal grafts are presented in Figure 2. Of the patients who had clear corneal grafts, 66.7% achieved visual acuity of 6/36 or better and 31.6% achieved visual acuity of 6/18 or better. Thirty-eight eyes had ocular co-morbidities affecting visual outcome in addition to their primary corneal diseases. They were glaucomatous optic neuropathy (28 eyes, 73.7%), retinal and macular disease (four eyes, 10.5%), cataract (four eyes, 10.5%), open globe injury (one eye, 2.6%), and amblyopia (one eye, 2.6%). Comparing to pre-operative vision, the visual outcome of the clear grafts improved in 47 eyes (82.5%), was stable in six eyes (10.5%), and worsened in four eyes (7.0%) (Figure 3). The worsened vision included co-morbidities of advanced glaucoma (two eyes), retinal disease (one eye), and open globe injury (one eye).

Discussion

Among 129 eyes (127 patients) that underwent PK for optical purpose, the three most common surgical indications were pseudophakic or aphakic bullous keratopathy (33.3%), corneal scars (post-trauma or post-infection) (20.9%), and regrafts (16.3%), which accounted for nearly three-fourths of the surgical indications in the present study. Those three conditions were similar to the most common indications in other studies from Asia[4,10,17,18]. Moreover, pseudophakic or aphakic bullous keratopathy was the leading

Table 5. Risk factors of secondary graft failure and their associated risk ratios based on multivariate regression analysis

Risk factor	Characteristic	Risk ratio	95% CI	p-value
Pre-operative factor				
Surgical indication of regrafts	Presence	1.49	0.79 to 2.82	0.215
	Absence			
History of glaucoma†	Presence	1.09	0.62 to 1.90	0.769
	Absence	1		
Deep corneal vascularization	Presence	1.16	0.68 to 1.96	0.593
	Absence	1		
Peripheral anterior synechiae	Presence	2.25	1.22 to 4.14	0.009*
	Absence	1		
Post-operative factor				
≥ one rejection episodes	Presence	2.57	1.42 to 4.65	0.002*
	Absence	1		

CI=confidence interval

† Included patients with history of having at least one anti-glaucoma medication or history of glaucoma surgery (trabeculectomy or tube-shunt surgery) with or without medication

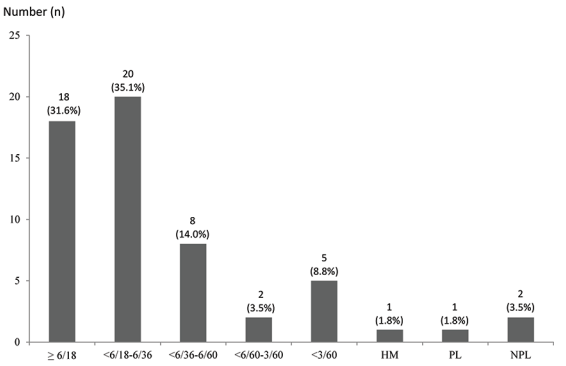

Figure 2. Best-corrected visual acuity of clear corneal grafts at last follow-up time (n=57).

HM=hand movement, PL=light perception, NPL=no light perception

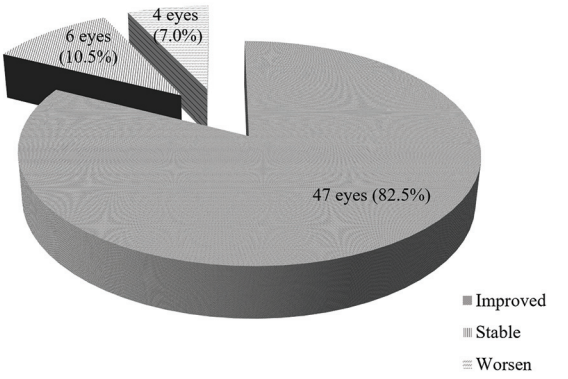

Figure 3. Visual outcome of clear corneal grafts at last follow-up time (n=57).

indication worldwide[19] because it happened after cataract surgery, which was the most common intraocular surgery performed. However, Fuchs' dystrophy and keratoconus, which were the other most common indications in western countries[3,5,7-9], were not as common in the present study. The prevalence of individual corneal pathologies and differences in decision making of patients or physicians based on different available resources might influence those surgical indications.

In the present study, corneal graft survivals at 1 year, 2 years, 5 years, and 10 years were 84.5%, 73.2%, 50.2%, and 24.7%, respectively. The finding showed that optical PK was an effective treatment for those indications, however, the survival rate decreased over time. At 1 year and 2 years, the survival rates were comparable with other studies, which reported 72% to 95% survival[3,5,9,10]. The long-term survival was lower than in some previous studies from western countries, which reported 5-year survival of 59% to 91% and 10-year survival of 50% to 71%[3,5,8,9]. However, the 1-year, 2-year and 5-year survival rates in the present study were higher than studies from India[4,17], which were 65% to 79.6%, 52.5% to 68.7%, and 46.5%, respectively. The results might be influenced by the majority of primary corneal diseases in the study including pseudophakic or aphakic bullous keratopathy, post-traumatic or post-infectious scars, and especially regrafts, which were categorized in worse survival in most studies[4,8,9,20].

In contrast, keratoconus or Fuchs' dystrophy, which were common indications in western countries, reported better survival[4,8,9,21,22]. About regrafts, Weisbrod et al studied to compare repeated PK with primary PK and found that the regrafts had a higher rate of peripheral anterior synechiae, were more likely to require anti-glaucoma medications prior to surgery, more likely to develop postoperative corneal neovascularization, and had significant worse graft survival rates[23].

The most common cause of secondary graft failure was irreversible immunologic allograft rejection (62.5%), similar to other studies[3,7,9,10]. More than half (56.0%) of the first allograft rejection happened within one year, post-operatively. The patients who had allograft rejection were sometimes lost to follow-up or had poor compliance, especially for instillation of topical steroids after surgery. The second most common cause of graft failure was ocular infection (18.1%). The causative agents in the present study were various including bacteria (both gram-positive and gram-negative organisms), virus, or fungus. Additionally, the infection could occur anytime in the postoperative course, similarly with the previous studies[24-27]. Besides requirement of prolonged use of topical steroids, ocular surface problems such as broken or loose suture, eye drops with preservatives, epithelial defects, and graft hypoesthesia contributed to associated risks of infection in the eye with corneal grafts and should be carefully managed[25,28,29].

Five significant risk factors of graft failure were identified based on univariate regression analysis (Table 4). This should be interpreted with caution because of potential confounding effect from other factors. After multivariate regression analysis, the two independent risk factors for graft failure were identified (Table 5). The presence of recipient peripheral anterior synechiae was a significant risk factor for graft failure (RR 2.25, p=0.009), similar to previous studies[5,30,31]. The presence of peripheral anterior synechiae exposed the donor endothelium to recipient vascular system and increased the risk of corneal graft rejection. Furthermore, peripheral anterior synechiae also increased the incidence of secondary glaucoma and endothelial cells loss from direct traction contributing to subsequent graft failure.

Occurrence of one or more allograft rejection episodes were the other significant risk factor (RR 2.57, p=0.002), which is in line with previous studies[5,32,33]. Wagoner et al reported that the low graft survivals were 42.6% at one year and 36.1% at three years in their patients after the onset of severe endothelial rejection[34]. Although, most of the rejection episodes occurred within six months postoperatively, it could occur at any time point (Table 3). However, Perera et al found that the treatment outcomes of graft rejections were not significantly different between early and late rejection (six months or earlier versus later than 6 months)[35].

At the last follow-up time (mean 93.2 months), 57 clear corneal grafts were presented. Of the clear grafts, the final best-corrected visual acuity was 6/18 or better in 31.6% and 6/36 or better in 66.7% (Figure 2). The visual outcome of clear graft was improved in 82.5% of the patients (Figure 3). The present study results were as good as previous studies[9,36,37]. Common comorbidities affecting visual acuity were glaucomatous optic neuropathy, cataract, and retinal and macular disease.

Limitations of the present study included the retrospective nature of the study that imposed incomplete data collection due to inadequate documentation of medical records or incomplete data of donor factors such as the imported donors that had no endothelial cell count records. However, the strength of the present study was that the data were representative of long-term outcome of optical PK covering essential aspects of graft survival, risk factors for graft failure, and visual outcome in Thai patients.

Conclusion

The ten-year follow-up of corneal graft survival and visual outcome after optical PK in the present study demonstrated successful outcome. However, the survival decreased over time. The significant risk factors for corneal graft failure could be used as prognostic guidelines for both surgeons and patients. As techniques for corneal transplant are continuously adapting, the results can be useful data for any further studies.

What is already known on this topic?

Indications and visual outcome of PK surgery in Thailand were previously reported. Those study periods were between one and five years.

What this study adds?

In addition to reporting the surgical indications and visual outcome of optical PK, the authors studied the long-term survival rate of the corneal graft, identified the cause, and analyzed the risk factors of secondary graft failure in Thai patients.

Acknowledgement

The authors are grateful to Julaporn Pooliam, MSc, from the Office for Research and Development, for her assistance with the statistical analysis.

Conflicts of interest

The authors declare no conflict of interest.

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