Flinders
UNIVERSITY

This is the authors' version of an article published in *Ophthalmology.* The original publication is available at:
http://www.sciencedirect.com/science/article/pii/S0161642011000054

Please cite this as: Kelly, T.-L., Coster, D.J. and Williams, K.A., 2011. Repeat penetrating corneal transplantation in patients with keratoconus. Ophthalmology, 118(8), 1538-1542.

http://dx.doi.org/10.1016/j.ophtha.2011.01.002

Repeat Penetrating Corneal Transplantation in Patients with Keratoconus

Thu-Lan Kelly, PhD[1], *Douglas J. Coster, DSc, FRANZCO*[1], *Keryn A. Williams, PhD*[1]

Footnotes and Financial Disclosures

[1] Department of Ophthalmology, Flinders University, Adelaide Australia

[2]All data sourced from the Australian Corneal Graft Registry

Financial support: This research was funded by the Australian Organ and Tissue Donation Authority, Canberra, Australia. KAW was supported by a fellowship from the Australian National Health & Medical Research Council. The funding organizations had no role in the design or conduct of this research.

Conflict of interest: No conflicting relationship exists for any author.

Running head: Repeat penetrating grafts for keratoconus

Correspondence: Keryn A. Williams, Department of Ophthalmology, Flinders Medical Centre, Bedford Park, SA 5042, Australia.
Phone: +61 8 8204 5047
Fax: +61 8 8277 0899
Email: keryn.williams@flinders.edu.au

Abstract

Purpose: To determine factors influencing penetrating corneal graft survival in patients receiving repeat grafts in the same eye after a failed first graft for keratoconus.

Design: Large cohort study from a national Register of corneal grafts, in which data were recorded prospectively and analyzed retrospectively. Follow-up extended to 23 years.

Participants: Follow-up was available for 229 regrafts performed in 177 eyes of 173 patients. Regrafts were performed more than once in 16 eyes.

Methods: Corneal graft survival was analyzed using Kaplan-Meier survival plots and Cox proportional hazards regression, clustered by patient.

Main Outcome Measures: The primary outcome measure was graft survival.

Results: Graft survival was significantly worse ($P<0.001$) for second (n=176) and third or greater grafts (n=20), compared with first grafts for keratoconus (n=4,871). Kaplan-Meier survival at 1, 5 and 15 years post- graft was 88%, 69% and 46% for second grafts, and 65%, 49% and 33% for third and subsequent grafts, respectively ($P<0.001$). Risk factors associated with graft failure of repeat grafts in multivariate analysis were the geographic location of surgery ("center") ($P=0.04$), failure of the previous graft within 10 years of surgery ($P=0.02$), recipient age at graft ≥60 years ($P=0.04$), occurrence of rejection episodes ($P=0.007$), and corneal neovascularization post-operatively ($P=0.007$).

Conclusions: Repeat corneal grafts in eyes originally grafted for keratoconus showed better survival when the previous graft had survived ≥10 years, surgery was performed at a favourable location, the recipient was aged less than 60 years at graft, and graft rejection and neovascularization were circumvented.

Financial Disclosures: None of the authors have any financial interests to disclose.

Patients who have received a penetrating corneal transplant for keratoconus usually achieve favourable outcomes but some need their grafts replaced. Sometimes graft failure occurs early after surgery but more often it occurs late, sometimes decades later. The excellent outcome of first penetrating grafts performed for keratoconus is well known.[1-6] The outcome of regrafts done after a failed first graft for keratoconus is less well reported.[7-12] Various patterns of graft failure occur and the outcome of repeat corneal transplantation may be related to the cause of graft failure, just as the pre-operative diagnosis is associated with the outcome of first grafts.

Graft survival after penetrating corneal transplantation for keratoconus is high - at least in the short timeframe.[5,6] Nevertheless graft failure does occur. It can occur at the time of transplantation from primary graft failure. Sometimes it occurs early, especially if the early post-operative period is complicated by inflammation leading to allograft rejection. If the graft survives the early post-operative period of a year or two, a prolonged period of engraftment usually occurs. Eventually, a progressive increase in astigmatism may develop, which can be so marked that local surgical procedures are ineffective and repeat corneal transplantation with a larger graft is required.[7] In grafts that survive for two or more decades, the corneal endothelium may slowly fail, [2,13] resulting in corneal oedema. The biology of each of these patterns of failure is different, and this might be expected to influence the survival of a repeat graft in the same eye.

The purpose of this study was to measure the outcome of repeat penetrating corneal transplants in patients with keratoconus. We followed a large number of patients having corneal transplants, and observed prospectively over decades, in grafts reported to the Australian Corneal Graft Register. The Australian Corneal Graft Registry collects data prospectively on all corneal transplants performed in Australia. The Registry contains the records of 22,311 grafts, with some followed up to 23 years. Keratoconus is a major indication for corneal transplantation: twenty-nine percent of all grafts performed in Australia are for keratoconus.[14,15] A second graft for someone who originally had surgery for keratoconus is also common. Herein, we provide data on

the prognosis for patients having second and subsequent penetrating corneal grafts after a first graft for keratoconus.

Patients and Methods

Australian Corneal Graft Registry

The Australian Corneal Graft Registry was established in May 1985 to follow the outcomes associated with corneal transplants performed in Australia. The consent process for each patient is handled by individual surgeons according to local legislative requirements, permitting information to be lodged with the Register. The operations of the Register are overseen by the Institutional Ethics Committee of Flinders University and are carried out in accordance with the Declaration of Helsinki.

Data Collection

All corneal grafts performed in Australia are reported to the Registry by contributing ophthalmic surgeons. The workings of the Registry have been reported elsewhere.[16] For this study, follow-up data were collected from 634 contributors at 12 month intervals until graft failure, or until the death or loss to follow-up of the patient for surviving grafts. Missing data were sought directly from either the surgeon or the Eye Bank. Patient death was tracked using a national database of deaths. Information on the recipient at the time of entry, the donor, the eye bank procedures and the surgery was complete. Information pertaining to follow-up was not complete: not all recipients continued to present for annual follow-up.

A graft was determined to have failed when edema associated with loss of corneal clarity appeared in a previously thin, optically transparent graft. Primary graft non-functions were defined as grafts that never cleared in the immediate post-operative period. Allograft rejection was defined as graft edema resulting in increased corneal thickness and corneal opacity

associated with anterior segment inflammation in a previously non-inflamed eye.

Patient Demographics

At the census date of August 2010, the Australian Corneal Graft Registry contained records of 19,958 penetrating grafts, of which 16,293 (82%) had been followed on at least one occasion. Follow-up is requested annually for the life of the patient, or until graft failure or loss to follow-up. Of 4,871 followed first grafts for keratoconus (30%) in 4,098 patients, 371 grafts (8%) had failed. In this cohort of patients with failed grafts, follow-up was available for 229 regrafts performed in 177 eyes of 173 patients. Not all patients with failed first grafts for keratoconus have been regrafted as yet, and not all those who have been regrafted have yet undergone first annual follow-up. The time span for follow-up of these regrafts varied from one to approximately 20 years. In 33 cases, the reason for regraft was primary graft failure (14% of regrafts). Regrafts were performed more than once in 16 eyes: four times in one eye, three times in two eyes and twice in 13 eyes. Reasons for failure of first grafts for keratoconus and repeat grafts are shown in Table 1. In five patients with regrafts, the record of the first graft for keratoconus was not available, either because it was performed overseas or before the Registry was established, and these patients were excluded from multivariate analysis.

Statistical Analyses

All statistical analyses were performed using Stata v 11 (StataCorp, College Station, TX). The significance level was set at $P<0.05$. Graft survival amongst groups was compared with Kaplan-Meier plots, using the log-rank statistic to test significance. Trial time was defined as time from graft to failure for failed grafts and to time of most recent follow-up for surviving grafts. Variables that were significant in univariate survival analysis were included in a Cox proportional hazards regression model clustered by patient, to calculate adjusted risk factors

controlled for potential confounders. The final model was found using a backwards selection process, removing variables that were not significant in a stepwise manner. The Cox proportional hazards assumption was checked using a diagnostic test.[17]

Results

Graft Survival in Regrafts Compared with First Grafts for Keratoconus

Regrafts performed for primary graft failure showed no difference in graft survival compared with first grafts for keratoconus ($P = 0.15$), but had significantly better survival than regrafts performed for reasons other than primary non-function, as shown in Table 1 ($P = 0.003$). Subsequently, regrafts performed for primary graft failure were excluded, leaving 196 regrafts for analysis. Compared with first grafts for keratoconus, second and subsequent grafts exhibited significantly worse survival ($P<0.001$, Fig 1). Kaplan-Meier survival at 5, 10 and 20 years for first grafts was 94%, 88% and 46% and for regrafts was 67%, 51% and 45%, respectively ($P<0.001$).

Factors Associated with Graft Survival in Regrafts

Rejection (reversible or irreversible) was a risk factor for graft failure in regrafted eyes ($P<0.001$, Fig 2). Rejection was most likely to occur soon after graft, with a median time to first rejection of 13 months (range 13 days-10 years), and 90% of first rejection episodes occurred within the first four post-operative years. In regrafts for eyes with a previous failure from rejection, 50% of graft failures were also from rejection, and graft survival was significantly worse compared with regrafts performed for other reasons ($P = 0.04$). The time to failure of the previous graft affected survival of repeat grafts, with eyes in which previous grafts survived 10 years or longer showing significantly better survival than those in which previous grafts survived for less than 10 years ($P = 0.002$, Fig 3).

Multivariate analysis was performed to determine adjusted risk factors for graft failure in 191of 196 regrafts: 5 were excluded because the record of the first (preceding) graft for keratoconus was not available. Variables investigated for inclusion in the model were: geographic location (center effect, where the centers were Australian States); the survival time of the previous graft; rejection episodes in the preceding graft and in the current graft; vascularization at graft or post-graft; recipient age at graft; the number of ipsilateral grafts; inflammation at graft; and reason for failure of a previous graft for keratoconus (Table 2). Testing using the method of Grambsch and Therneau[17] showed that the assumption of proportional hazards that underlies the Cox model had not been violated (p=0.72). Significant risk factors for graft failure of repeat grafts were the center effect, recipient age at graft, occurrence of rejection episodes in the repeat graft, and corneal neovascularization post-graft. In addition, regrafts in eyes in which the previous graft had survived less than 10 years had more than four times the risk of failure than those regrafted after a previous graft that had survived for more than 10 years.

Discussion

Using data collected by a large national Registry, we report that the survival of a repeat graft in the same eye was reduced in patients for whom the first penetrating corneal graft had been performed for keratoconus. If the second graft failed and a subsequent graft was required, the probability of graft survival was further reduced.

Inflammation in the graft bed played a role in reducing repeat graft survival, as was the case for first grafts. Graft failures in the first ten years after surgery were often associated with an inflammatory condition – for example, allograft rejection. Allograft rejection after corneal transplantation for keratoconus tends to occur within the first few years, although it can occur at any time, sometimes after decades. Grafts that failed late, ten years or more after surgery, tended

to fail for non-inflammatory reasons. These patterns of failure were reflected in the graft survival data: regrafts in eyes in which the previous graft had survived *less* than 10 years were significantly more likely to fail than regrafts in eyes in which the previous graft had survived for *more* than 10 years. In some instances of late graft failure, recurrence of the ectatic process in the host led to uncorrectable astigmatism,[18,19] or in the graft resulted in recurrent keratoconus.[1,7] More often, graft failure occurred because the endothelium failed insidiously from unknown reasons after decades of engraftment.[2,4,20]

The risk factors associated with graft failure in the final multivariate analysis were largely related to inflammation: allograft rejection and corneal neovascularization post-operatively. Corneal transplants performed to replace grafts that failed because of graft rejection were prone to rejection in the regraft. Neovascularization of the graft is one mechanism by which chronic inflammation erodes immunological privilege. Increased recipient age (≥ 60 years) was also associated with an increased risk of graft failure, as has recently been reported in a meta-analysis of unselected cohorts of patients with penetrating keratoplasty.[21]

A curious finding, but consistent with many studies in other branches of clinical transplantation, was the center effect. Some centers did better than others even when the same protocols were followed. It might be expected that single surgeon academic facilities with a narrow spectrum of practice would do better than centers with multiple sites, many surgeons and comprehensive patterns of practice, as has been shown previously[14] The unexpected finding here was that large, state-wide groupings also demonstrated a significant center effect. Small variations in practice which may be widespread in a geographic location may explain the different outcomes in different jurisdictions. Such variations might include regional differences in regimens of immunosuppression for prophylaxis and treatment of corneal graft rejection. However, a registry study can identify associations but cannot always provide explanations.

A strength of the approach, especially for a nation-wide database, is that outcomes of a

large number of cases performed by a variety of surgeons in different centers over many years can be measured. A weakness, not restricted to registry studies, is loss to follow-up. Patients with surviving corneal grafts may fail to return to clinic appointments, leading to an under-estimate of graft survival over time. In the past, loss to follow-up because recipients deaths have not been reported to the contributing ophthalmologist has been a particular problem. Linkage of records with a national death register has now solved this issue.

Graft survival even of first penetrating grafts for keratoconus was not indefinite. The patient receiving a first graft for keratoconus is typically young and is likely to require the graft to be replaced in decades to come. As in previous studies,[10,12] third and subsequent grafts in general fared poorly, but if they survived the first three post-operative years, then the failure rate decreased somewhat. There is a move towards deep lamellar surgery for keratoconus to preserve the host endothelium.[22, 23] Only time and prolonged long-term prospective observation will reveal whether this approach provides a long-term advantage over penetrating keratoplasty.

In conclusion, we have shown that repeat penetrating corneal grafts after a failed first graft for keratoconus show poorer survival than first penetrating grafts. Second and subsequent grafts had a significantly worse risk of failure if the previous graft had survived for less than 10 years compared with regrafts in eyes in which the previous graft had survived for 10 years or more. Failures within the first 10 post-operative years were largely associated with episodes of inflammation of graft rejection, whereas those that occurred late were more likely to result from non-inflammatory conditions.

References

1. Praminik S, Musch DC, Sutphin JE, Farjo AA. Extended long-term outcomes of penetrating keratoplasty for keratoconus. Ophthalmology 2006;113:1633-8.

2. Jensen BJ, Hjortdal J, Ehlers N. Longterm follow-up of penetrating keratoplasty for keratoconus. Acta Ophthalmol 2009;88:347-51.

3. Fukuoka S, Honda N, Ono K, et al. Extended long-term results of penetrating keratoplasty for keratoconus. Cornea 2010;29:528-30.

4. Zadok D, Schwarts S, Marcovich A, et al. Penetrating keratoplasty for keratoconus. Long-term results. Cornea 2005;24:959-61.

5. Lim L, Pesudovs K, Coster DJ. Penetrating keratoplasty for keratoconus: visual outcome and success. Ophthalmology 2000;107:1125-31.

6. Javadi MA, Motlagh BF, Jafarinasab MR, et al. Outcomes of penetrating keratoplasty in keratoconus. Cornea 2005;24:941-5.

7. Patel SV, Malta JB, Banitt MR, et al. Recurrent ectasia in corneal grafts and outcomes of repeat keratoplasty for keratoconus. Br J Ophthalmol 2009;93:191-7.

8. Patel NP, Kim T, Rapuano CJ, et al. Indications for and Outcomes of Repeat Penetrating Keratoplasty, 1989-1995. Ophthalmology 2000;107:719-24.

9. Rapuana CJ, Cohen EJ, Brady SE, et al. Indications for and Outcomes of Repeat Penetrating Keratoplasty. Am J Ophthalmol 1990;109:689-95.

10. Bersudsky V, Blum-Hareweni T, Rehany U, Rumelt S. The Profile of Repeated Corneal Transplantation. Ophthalmology 2001;108:461-9.

11. Weisbrod DJ, Sit M, Naor J, Slomovic AR. Outcomes of repeat penetrating keratoplasty and risk factors for graft failure. Cornea 2003;22:429-34.

12. Yildiz EH, Hoskins E, Fram N, et al. Third or greater penetrating keratoplasties: indications, survival, and visual outcomes. Cornea 2010;29:254-9.

13. Armitage WJ, Dick AD, Bourne WM. Predicting endothelial cell loss and long-term graft survival. Invest Ophthalmol Vis Sci 2003;44:3326-31.

14. Williams KA, Lowe M, Bartlett C, et al. Risk factors for human corneal graft failure within the Australian Corneal Graft Registry. Transplantation 2008;86:1720-4.

15. Williams KA, Esterman AJ, Bartlett C, et al. How effective is penetrating corneal transplantation? Factors influencing long-term outcome in multivariate analysis. Transplantation 2006;81:896-901.

16. Williams KA, Lowe MT, Bartlett CM, et al. The Australian Corneal Graft Registry 2007 Report. Adelaide, Australia: Flinders University Press; 2007:186-91. Available at: http://hdl.handle.net/2328/1723. Accessed September 2, 2010.

17. Grambsch PM, Therneau TM. Proportional hazards tests and diagnostics based on weighted residuals Biometrika 1994;81:515–26.

18. de Toledo JA, de la Paz MF, Barraquer RI, Barraquer J. Long-term progression of astigmatism after penetrating keratoplasty for keratoconus: evidence of late recurrence. Cornea 2003;22:317-23.

19. Lim L, Pesudovs K, Goggin M, Coster DJ. Late onset post-keratoplasty astigmatism in patients with keratoconus. Br J Ophthalmol 2004;88:371-76.

20. Patel SV, Hodge DO, Bourne WM. Corneal endothelium and postoperative outcomes 15 years after penetrating keratoplasty. Am J Ophthalmol 2005;139:311-319.

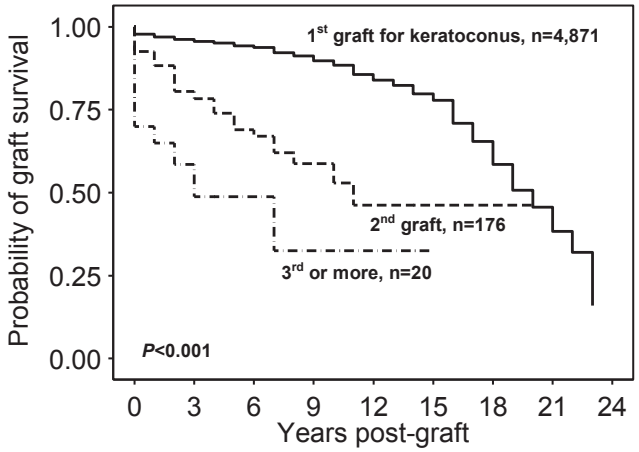
21. Bachmann B, Taylor RS, Cursiefen C. Corneal neovascularization as a risk factor for graft failure and rejection after keratoplasty: an evidence-based meta-analysis. Ophthalmology 2010;117:1300-5.e7. Epub 2010 Jun 3.

22. Watson SL, Ramsay A, Dart JK, et al. Comparison of deep lamellar keratoplasty and penetrating keratoplasty in patients with keratoconus. Ophthalmology 2004;111:1676-82.

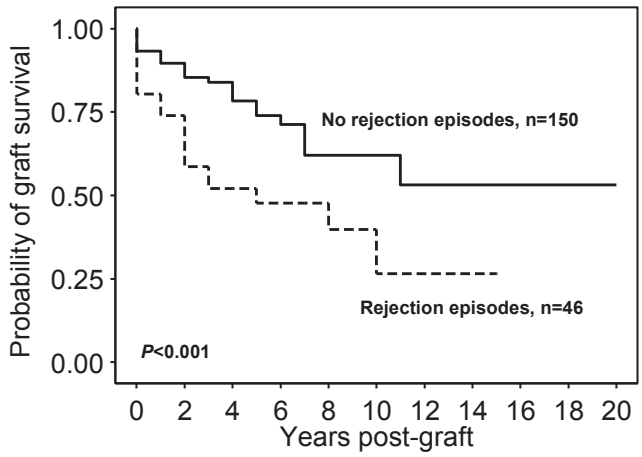
23. Han CY, Mehta JS, Por YM, et al. Comparison of outcomes of lamellar keratoplasty and

1 penetrating keratoplasty in keratoconus. Am J Ophthalmol 2009;148:744-51.

2



Number of grafts	Number initially at risk	Kaplan-Meier survival				
		1 year	5 years	10 years	15 years	20 years
1	4,871	0.97	0.94	0.88	0.78	0.46
2	176	0.88	0.69	0.53	0.46	0.46
3 or more	20	0.65	0.49	0.33	0.33	n/a



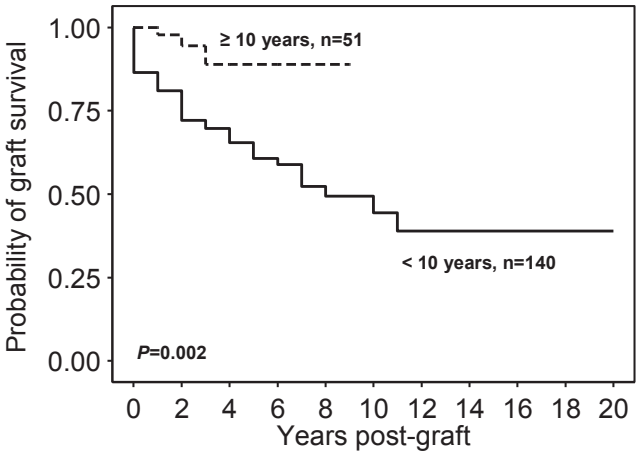


Table 1. Reasons for Graft Failure in The First 10 Years, or Later, in 4,871 First Grafts for Keratoconus and in 229 Regrafts.

	First grafts		Repeat grafts	
Reason for graft failure	Survival < 10 years n (%)	Survival ≥ 10 years n (%)	Survival < 10 years n (%)	Survival ≥ 10 years n (%)
Unspecified cause	53 (21%)	28 (24%)	13 (25%)	0 (0%)
Rejection	55 (22%)	12 (11%)	19 (37%)	0 (0%)
Primary graft failure	41 (16%)	0 (0%)	0 (0%)	0 (0%)
Endothelial cell failure	24 (9%)	19 (17%)	8 (15%)	1 (50%)
Astigmatism	18 (7%)	28 (24%)	1 (2%)	0 (0%)
Injury	18 (7%)	8 (7%)	0 (0%)	0 (0%)
Recurrent keratoconus/ectasia	6 (2%)	15 (13%)	0 (0%)	0 (0%)
Miscellaneous*	42 (16%)	4 (4%)	11 (21%)	1 (50%)
Total	257 (100%)	114 (100%)	52 (100%)	2 (100%)
Total failed grafts (percentage of total grafts)	371 (8%)		54 (24%)	

***** Includes infections, perforations, ulcers, corneal neovascularization and degeneration, scars, glaucoma, keratitis, wound dehiscence and uveitis**.**

Table 2. Multivariate Risk Factors for Graft Failure in Regrafts after a First Penetrating Graft Performed for Keratoconus – Final Cox Model (n=191).

Risk Factor	**Hazard Ratio (95% CI)***	***P* value**
Geographic location		
Center 1	1.0	
Center 2	0.86 (0.09, 8.62)	
Center 3	4.17 (1.16, 15.0)	0.04
Center 4	5.84 (1.59, 21.5)	
Center 5	5.42 (1.40, 21.0)	
Survival time of previous graft		
< 10 years	1.0	
≥ 10 years	0.25 (0.08, 0.78)	0.02
Rejection episodes in repeat graft		
None	1.0	
1 or more	2.12 (1.23, 3.66)	0.007
Vascularization post-graft		
No	1.0	
Yes	2.86 (1.33, 6.18)	0.007
Recipient age at graft		
< 60 years	1.0	
≥ 60 years	1.87 (1.02, 3.43)	0.04

Variables examined but removed from the final Cox model:		
Reason for failure of previous graft		
Reasons 1-4[†]	0.36 (0.04, 3.00) to 1.09 (0.53, 2.24)	0.81
Occurrence rejection in previous graft	1.56 (0.55, 4.47)	0.41
Each additional previous graft	1.07 (0.45, 2.54)	0.88
Vascularization at graft	1.22 (0.61, 2.44)	0.57
Inflammation at graft	1.55 (0.85, 2.83)	0.15

* 95% CI = 95% confidence interval.

[**] global *P*-values reported for risk factors with multiple categories.

[†] including endothelial cell failure, unspecified graft failure, astigmatism, other specified reason.