Clinical outcomes and graft survival after Descemet membrane endothelial keratoplasty

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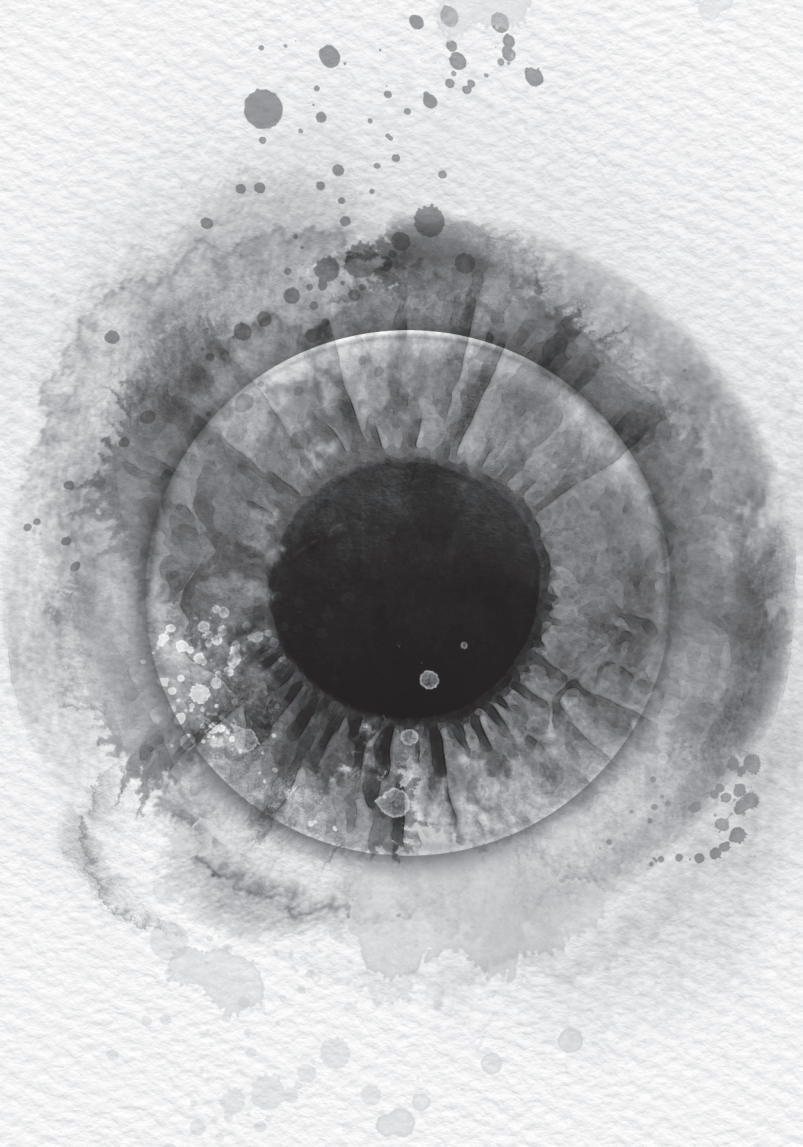

Chapter 5

Descemet Membrane Endothelial Keratoplasty: Ten-Year Graft Survival and Clinical Outcomes

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ABSTRACT

Purpose: To evaluate the 10-year graft survival and clinical outcomes of the first case series after Descemet membrane endothelial keratoplasty (DMEK).

Design: Retrospective, interventional case series.

Methods: After excluding the very first 25 DMEK eyes that constitute the technique learning curve, the following 100 consecutive primary DMEK eyes (88 patients) were included. Main outcome parameters (survival, best-corrected visual acuity (BCVA), central endothelial cell density (ECD), central corneal thickness (CCT)) were evaluated up to 10-years postoperatively and postoperative complications were documented.

Results: At 5 and 10 years after DMEK, respectively 68 and 57 out of 100 eyes were still available for analysis. Of those eyes, 82% and 89% reached a BCVA of ≥20/25 (Decimal VA ≥0.8) at 5- and 10 years postoperatively, respectively. Preoperative donor ECD decreased by 59% at 5 years and 68% at 10 years postoperatively. CCT averaged 668 (±74) µm preoperatively, and 540 (±33) µm and 553 (±43) µm at respectively 5 and 10 years after surgery. Within 10 years, 4% of eyes developed allograft rejection, no primary graft failures occurred and 6% of the eyes developed secondary graft failure. Graft survival probability was 0.83 [95% Confidence Interval (CI), 0.75-0.92] and 0.79 [95% CI, 0.70 -0.88] at 5- and 10-years postoperatively, respectively.

Conclusion: Most eyes operated in the pioneering phase of DMEK show excellent and stable clinical outcomes with low postoperative complication rates and promising graft longevity over the first decade after surgery. This suggests that DMEK may be a safe long-term treatment option for corneal endothelial diseases.

INTRODUCTION

The first Descemet membrane endothelial keratoplasty (DMEK) surgery was performed in 2006.[1-2] Now, more than a decade later, this selective endothelial keratoplasty technique has gained wide global acceptance and is being offered as a standard procedure for the treatment of corneal endothelial disorders.[3-5] The increasing popularity of DMEK results from the excellent visual recovery and clinical outcomes accompanied by low allograft rejection rates as reported in several short-term studies.[6-11] First mid-term results showed promising graft survival rates that are comparable to earlier endothelial keratoplasty techniques while clinical outcomes remained stable and postoperative complication rates remained low.[12-16] However, so far no studies on long-term outcomes are available.

We now evaluated the 10-year clinical outcomes and graft survival rates for the first 100 consecutive DMEK cases (cases 26-125) excluding the very first 25 DMEK cases that we define as the learning curve of the technique. These 25 DMEK cases were excluded as they do not represent the classical learning curve of a surgeon, but rather the technique learning curve as those were the very first 25 DMEK surgeries ever performed. During the first months when starting to perform DMEK, the technique was standardized and e.g. the protocol for treating eyes with a graft detachment was adapted (first eyes with a graft detachment underwent re-surgery within the first weeks after DMEK).[17]

In this study we present the first 10-year graft survival data for a large cohort of DMEK eyes and also to assess if clinical outcomes remain stable up to 10-years after DMEK.

METHODS

Patient data

One hundred consecutive eyes of 88 patients that underwent primary DMEK surgery for Fuchs endothelial corneal dystrophy (94%), failed previous transplant (4%), or bullous keratopathy (2%) between October 2007 and June 2009 were evaluated retrospectively. Mean recipient age was 68 ± 12 years (range, 41-89 years) and 84%

of eyes were pseudophakic (**Table 1**). Out of the first 125 consecutive primary DMEK surgeries, the first 25 DMEK cases operated worldwide (cases 1-25), that represented the learning curve of the DMEK technique, were excluded from the study. All patients included in this retrospective study had signed an informed consent prior to surgery for research participation and the study was carried out according to the Declaration of Helsinki. No IRB/Ethics Committee approval was required due to the retrospective study design under national legislation.

Table 1. Demographics of Descemet membrane endothelial keratoplasty eyes and donors.

Baseline parameters	Total group (n=100)
Number of eyes / patients (n)	100 / 88
Gender (n)	
Male / female	36 / 52
Mean patient age ±SD (years)	68 ±12
Indication for DMEK (n)	
FECD	94
Pseudophakic BK	2
Failed PKP / DSEK	4
Preoperative lens status (n)	
Phakic / pseudophakic	16 / 84
Eyes OD / OS (n)	53 / 47
Donor gender (n)	
Male / female	56 / 44
Donor age ±SD (years)	62 ±9
Donor cause of death (n)	
Cardiovascular	54
Respiratory	23
Cancer	18
Trauma	3
Other	2
Graft storage time in medium ±SD (days)	13.3 ±3.9

SD: Standard deviation
DMEK: Descemet membrane endothelial keratoplasty
FECD: Fuchs endothelial corneal dystrophy
BK: Bullous keratopathy
PKP: Penetrating keratoplasty
DSEK: Descemet stripping endothelial keratoplasty

DMEK graft preparation and surgery

Donor tissue was prepared at Amnitrans EyeBank Rotterdam, as previously described.[18] After assessing endothelial cell morphology and viability, the DMEK grafts were stored free-floating in organ culture medium (CorneaMax; Eurobio, Courtaboeuf, France) until the time of the transplantation (**Table 1**).

The surgery was performed as previously described.[19] Postoperative medication included topical chloramphenicol 0.5% 6 times daily for the first and 2 times daily for the second week, ketorolac tromethamine 0.4% and topical dexamethasone 0.1% 4 times daily for 4 weeks, followed by fluorometholone 0.1% 4 times daily, that was tapered to once daily over a period of 1 year. Further on, patients were recommended to continue using fluorometholone once a day or every other day indefinitely.

Data collection and statistical analysis

Patients were examined preoperatively and at 6 and 12 months postoperatively, followed by yearly examinations up to 10 years.

Outcome measures included best-corrected visual acuity (BCVA), endothelial cell density (ECD), central corneal thickness (CCT) and complications.

Best-corrected visual acuity (BCVA) was measured using a Snellen letter chart and outcomes were converted to the logarithm of the minimum angle of resolution units (LogMAR) for statistical analysis. Eyes with low visual potential (LVP) due to ocular co-morbidities unrelated to the cornea were excluded from the BCVA analysis. The percentage of excluded LVP eyes was 8% or less at any analyzed time-point. ECD was assessed with non-contact auto-focus specular microscopy (Topcon Medical Europe BV, Capelle a/d IJssel, The Netherlands). For ECD counting an average of three central measurements were used in the analysis. CCT was measured using rotating Scheimpflug corneal tomography (Pentacam HR, Oculus Optikgeräte GmbH, Wetzlar, Germany).

Graft detachment was assessed by anterior segment optical coherence tomography (Heidelberg Engineering GmbH, Heidelberg, Germany) and Scheimpflug imaging.

Graft detachment was defined as minor (≤1/3 of the graft surface area) or major detachment (>1/3 of the graft surface area). Allograft rejection was defined as the presence of an endothelial rejection line or keratic precipitates (with or without an increase in corneal thickness), anterior uveitis, and/or ciliary injection on slit-lamp biomicroscopy. Primary graft failure (PGF) was defined as an absence of corneal clearance in an eye with full graft attachment. Secondary graft failure was defined as corneal decompensation after an interval of corneal clearance.

Graft survival was estimated by Kaplan-Meier survival analysis using the log-rank test. The second operated eyes of patients undergoing bilateral DMEK (n=12) were excluded from the survival analysis. Survival time was calculated as the time between the surgery and the last available follow-up time-point of an eye, or as the time between the surgery and graft failure. All secondary graft failures (endothelial failures), as well as re-transplantations performed for graft detachment (technical failures) were included in the survival analysis.[20] Patients that were unable to attend the 10-year follow-up examination were contacted for medical record updates to be included in the graft survival analysis (n=11).

Continuous data were analyzed by Student's t test and categorical variables by Chi-squared test. All data analysis was performed using SPSS 25.0 and Excel Software for Windows. P values less than 0.05 were considered significant.

RESULTS

At 5 and 10 years after DMEK, 68 and 57 out of 100 eyes were still available for analysis, respectively (**Supplemental Data Table**). Patients who reached the 10-year follow-up were on average 64 (±11) years at the time of surgery, compared to 68 (±12) years for the entire study group (*P*=0.001).

Supplemental Data Table: Overview of available and unavailable data up to 10 years after Descemet membrane endothelial keratoplasty.

	Total group (n=100)			
	6m FU	1y FU	5y FU	10y FU
Available data				
Survival analysis*	82	75	59	48
BCVA	86	79	55	44
ECD	85	81	59	44
CCT	84	81	57	44
Unavailable data				
LTFU	**1**	**3**	**16**	**24**
Passed Away	0	0	6	11
Own Ophthalmologist	1	3	10	13
Re-surgery	**5**	**10**	**16**	**19**
Missing data				
BCVA (LVP)	8 (8)	8 (6)	13 (5)	13 (2)
ECD	9	6	9	13
CCT	10	6	11	13

*: The second operated eyes of patients undergoing bilateral DMEK were excluded from the survival analysis.
LVP: Number of eyes excluded from BCVA analysis because of low visual potential; these eyes are included in the number of eyes with missing
BCVA: Best corrected visual acuity
CCT: Central corneal thickness
ECD: Endothelial cell density
LTFU: Lost-to-follow-up
BCVA values
m: Month
y: Year

Best corrected visual acuity

At 1-year after DMEK, 96% of the eyes had a BCVA of ≥20/40 (Decimal VA ≥0.5), 81% had ≥20/25 (≥0.8), and 49% had ≥20/20 (≥1.0). At the 5-year follow-up, 98% of the eyes had a BCVA of ≥20/40 (0.5), 82% had ≥20/25 (≥0.8), and 53% had ≥20/20 (≥1.0). At 10-years after DMEK, 98% had ≥20/40 (0.5), 89% ≥20/25 (≥0.8), and 64% ≥20/20 (≥1.0) (**Table 2, Figure 1**). BCVA outcomes (in logMAR) between 5- and 10-year postoperatively reached a statistically significant difference (*P*=0.022). At 10-years postoperatively, BCVA outcomes (in logMAR) did not differ between eyes with fully attached and ≤1/3 detached grafts (*P*=0.281).

Table 2. Best corrected visual acuity, endothelial cell density and pachymetry results pre- and post- Descemet membrane endothelial keratoplasty.

	Total group (n=100)				
	Preoperative	6m FU	1y FU	5y FU	10y FU
BCVA in Snellen (Decimal)	**(n=99)**	**(n=86)**	**(n=79)**	**(n=55)**	**(n=44)**
< 20/40 (< 0.5)	71 (72%)	8 (9%)	3 (4%)	1 (2%)	1 (2%)
≥ 20/40 (≥ 0.5)	28 (28%)	78 (91%)	76 (96%)	54 (98%)	43 (98%)
≥ 20/25 (≥ 0.8)	5 (5%)	64 (74%)	64 (81%)	45 (82%)	39 (89%)
≥ 20/20 (≥ 1.0)	0	37 (43%)	39 (49%)	29 (53%)	28 (64%)
Mean BCVA ±SD, (logMAR)	0.36 ±0.20 (n=99)	0.11 ±0.22 (n=86)	0.07 ±0.12 (n=79)	0.04 ±0.12 (n=55)	0.03 ±0.1 (n=44)
Mean ECD ±SD, (cells/mm²)	2593 ±178 (n=100)	1711 ±525 (n=85)	1605 ±530 (n=81)	1083 ±432 (n=59)	845 ±342 (n=44)
Mean ECD Decrease ±SD, (%) *		34 ±19 (n=85)	38 ±19 (n=81)	59 ±15 (n=59)	68 ±13 (n=44)
Mean Pachymetry ±SD, (μm)	668 ±74 (n=79)	533 ±42 (n=84)	536 ±37 (n=81)	540 ±33 (n=57)	553 ±43 (n=44)
Mean Pachymetry Decrease (±SD), (%) *		20 ±8 (n=79)	19 ±7 (n=74)	18 ±7 (n=53)	16 ±9 (n=40)

*: Decrease as compared to preoperative values
FU: Follow-up
BCVA: Best corrected visual acuity
SD: standard deviation
ECD: Endothelial cell density
m: months
y: years
n: number of eyes

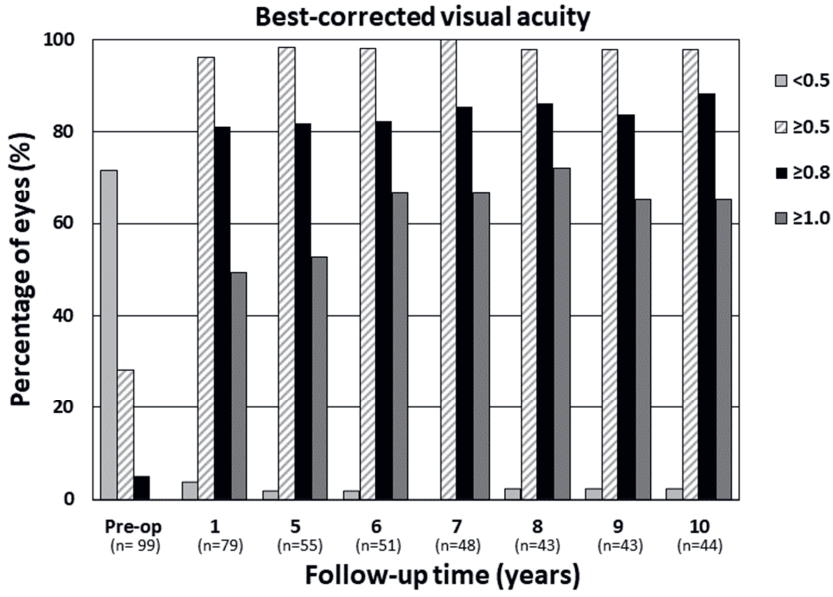


Figure 1. Best-corrected visual acuity outcome after Descemet membrane endothelial keratoplasty.

Best-corrected visual acuity (BCVA) outcomes 10 years after Descemet membrane endothelial keratoplasty (DMEK). Bar graphs display the percentage of eyes reaching the BCVA levels given in decimals (Snellen). Number of eyes available per follow-up is given underneath the follow-up time-points

Endothelial cell density

Average preoperative donor ECD was 2593 (±178) cells/mm^2 and decreased to 1605 (±530) cells/mm^2 at 1 year, 1083 (±432) cells/mm^2 at 5 years, and 845 (±342) cells/mm^2 at 10 years postoperatively, corresponding to an ECD decline of 34%, 59% and 68%, respectively when compared to preoperative ECD values (**Table 2, Figure 2**). The average annual rate of endothelial cell loss between the 1-year and 10-year follow-up was -8% (range, -10.7% to -5.7%) (*P*<0.01 between all consecutive annual follow-up time-points). The 10-year ECD was 903 (±356) cells/mm^2 (-66%) (n=32) in eyes with a completely attached graft and 721 (±262) (n=11) cells/mm^2 (-72%) in eyes with minor graft detachment (*P*=0.128).

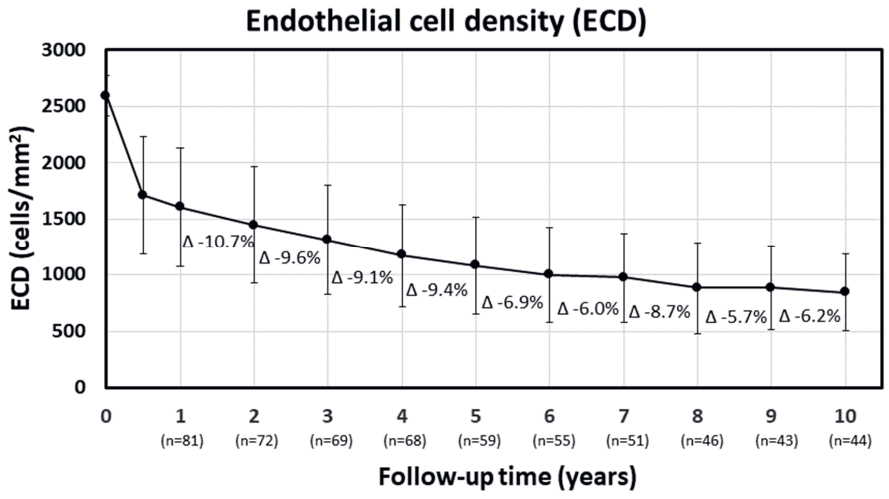
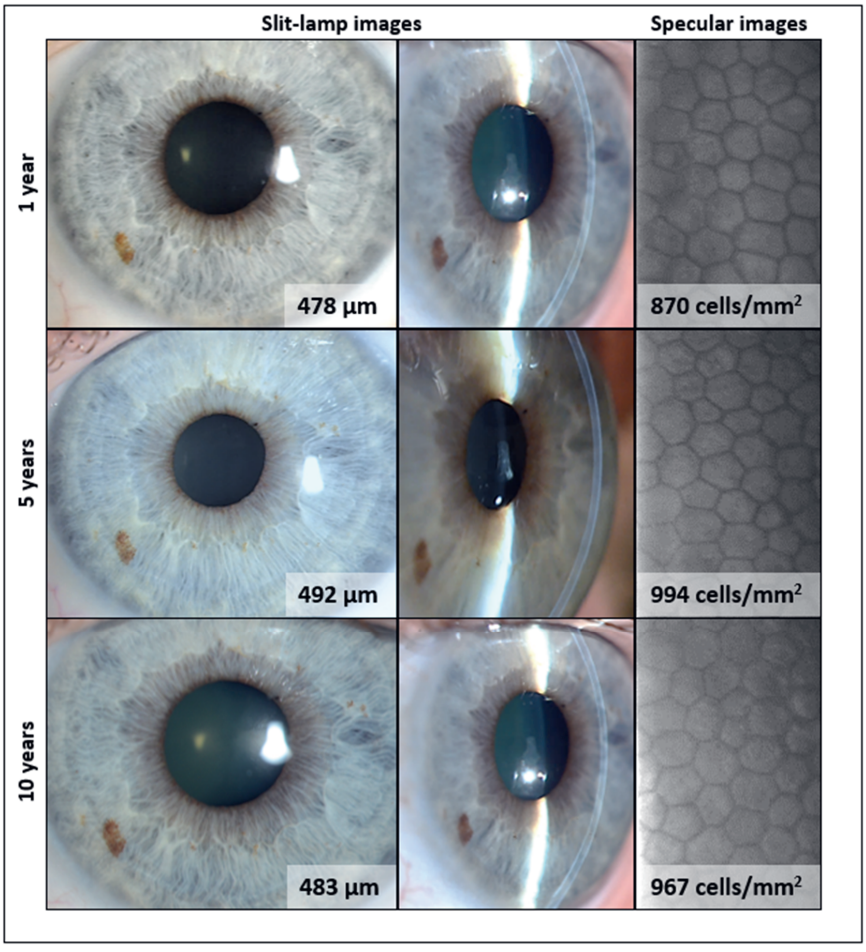


Figure 2. Endothelial cell density up to ten years after Descemet membrane endothelial keratoplasty. Mean endothelial cell density (ECD) values are displayed, vertical bars represent standard deviation and delta represent the percentage of ECD decrease between time-points. Number of eyes available per follow-up is given underneath the follow-up time-points.

Of 15 eyes that had an ECD of <1000 cells/mm^2 (mean ECD 807 (±138) cells/mm^2, median 840 cell/mm^2) at 1 year postoperatively, 6 eyes were still available at the 10-year follow-up (mean ECD 707 (±135) cells/mm^2, median 703 cells/mm^2) (**Supplemental Figure**), while 3 had received repeat DMEK at 30, 33, and 115 months after primary DMEK.

The other 6 eyes, that were unavailable or lost-to-follow-up, had an average ECD of 812 (±170) cells/mm^2 (median 796 cells/mm^2) at the last available follow-up at an average of 63 (±27) months (range, 24-108 months). None of those 6 eyes showed signs of corneal decompensation at the last available follow-up.



Supplemental Figure. Slit-lamp and specular microscopy images of an eye after Descemet membrane endothelial keratoplasty. Slit-lamp (left and center column) and specular microscopy images (right column) of an eye with an endothelial cell density (ECD) of <1000 cells/mm2 at 1 year after Descemet membrane endothelial keratoplasty (DMEK) (top row). The eye remained clear with no increase in pachymetry and a stable ECD up to the 5- and 10-year follow-up (middle and bottom row). Central corneal thickness values are given in left column and ECD values in the right column.

Pachymetry

Average preoperative CCT was 688 (±74) µm and decreased to 536 (±37) µm, 540 (±33) µm and 553 (±43) µm at 1 year, 5 years and 10 years after DMEK, respectively. Overall, CCT had decreased by 16% at 10 years as compared to preoperative CCT **(Table 2)**, but CCT values showed a significant increase between the 5 and 10- year follow-up of 2 (±6) % (P<0.023).

Postoperative complications and re-transplantations

At 6 months postoperatively, a minor graft detachment was visible in 18 cases (18%) and a major detachment in 11 eyes (11%). Seven eyes (7%) underwent a re-bubbling procedure (on average 7 (±7) weeks after DMEK).

Allograft rejection was diagnosed in 4 eyes at 4, 30, 42, and 84 months after DMEK and could be reversed by intensified topical steroid treatment in all but one eye, that resulted in SGF. In total, 6 eyes (6%) developed SGF on average 60 (±33) months (median 60 months) after DMEK (**Table 3**). No primary graft failures occurred within this study group.

Of the entire cohort, 19 eyes (19%) required a re-transplantation on average 29 (±34) months (median 11 months) after DMEK (**Table 3**). Indications for re-transplantation were 'technical failures', i.e. graft detachment (n=13) or SGF (n=6). About half of all re-transplantations were performed within the first year after surgery (10/19, 52.6%), 31.6% between the 1 and 5-year follow-up (6/19), and the remaining (3/19, 15.8%) after the 5-year follow-up.

Table 3. Postoperative complications and secondary procedures after Descemet membrane endothelial keratoplasty.

	Total group (n=100)
Graft detachment* (n)	
Minor (≤1/3 of graft surface area)	18
Major (>1/3 of graft surface area)	11
Allograft rejection+ (n)	4
Graft failure (n)	
Primary^	-
Secondary#	6
Mean time ±SD (range) in months	60 ±33
Median time in months	60 (21-101)
Technical°	13
Mean time ±SD (range) in months	10 ±9
Median time in months	7 (1-31)
Secondary procedures (n)	
Re-bubbling	7
Mean time ±SD (range) in weeks	7 ±7
Median time in weeks	8 (1d – 13w)
Re-transplantation	19
Mean time ±SD (range) in months	29 ±34
Median time in months	11 (1-115)

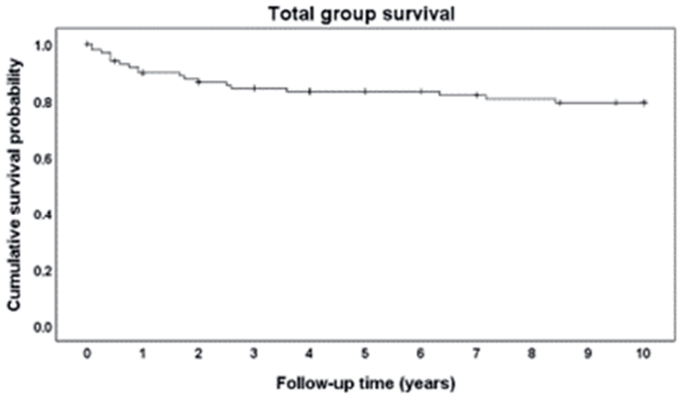
*: Includes all graft detachments as observed at the six months follow-up
+: Allograft rejection diagnosed at 4, 3, 42, and 84 months after DMEK, respectively
^: Primary graft failure refers to an attached graft, but cornea fails to clear
#: Secondary graft failure refers to an attached graft with (signs of) corneal clearance, followed by corneal decompensation
°: Technical failure refers to grafts with persistent graft detachment
n: number of eyes
SD: standard deviation
d: days
w: weeks

Graft Survival

The overall graft survival probability was 0.83 [95% Confidence Interval (CI), 0.75-0.92] at 5 years and 0.79 [95% CI, 0.70 -0.88] at 10 years after DMEK (**Figure 3**).

When looking at graft survival in eyes with either completely attached or with minor detachment, graft survival probability was 0.92 [95% CI, 0.86 -0.98] at 5 years and 0.87 [95% CI, 0.79 -0.95] at 10 years after DMEK (versus 0.2 [95% CI, 0.06-0.69] at both 5 and 10 years for eyes with a major graft detachment (*P*=0.001)). No difference in 10-year graft survival was observed between the first 50 cases (0.77 [95% CI, 0.65-0.89]) and the second 50 cases (0.81 [95% CI, 0.68-0.96]) of the

cohort (*P*=0.5). No subgroup analysis based on surgery indication was performed as only 6 eyes (6%) underwent DMEK for indications other than FECD. Of those 6 eyes, 2 were still clear at the 10-year follow-up, 1 underwent re-transplantation 11 months after DMEK and 3 were lost-to-follow-up.



Follow-up time (years)		0	1	2	3	4	5	6	7	8	9	10
Cumulative survival probability at FU	Estimate	-	0.88	0.86	0.85	0.83	0.83	0.83	0.82	0.80	0.79	0.79
	SE	-	0.04	0.04	0.04	0.04	0.04	0.04	0.04	0.05	0.05	0.05
Cumulative events		0	10	12	13	14	14	14	15	16	17	17
Remaining cases		88	75	70	66	63	59	55	53	51	49	48

Figure 3. Kaplan-Meier curve of cumulative graft survival probabilities after Descemet membrane endothelial keratoplasty. Survival probabilities and number of eyes at risk per follow-up moments are presented in the table below the graph. At the 1-, 5-, and 10-year follow-up, in total 87, 68, and 57 eyes, respectively were available for analysis of which 12, 9, and 9 second operated eyes, respectively, of patients undergoing bilateral DMEK were excluded from the survival analysis.

DISCUSSION

In this study we evaluated the 10-year DMEK graft survival probability and clinical outcomes of 100 eyes of the first DMEK cohort. Overall, the outcomes are satisfactory in terms of graft survival and excellent in terms of visual outcomes when considering that the cohort has been operated within an early phase of technique development.

The overall 10-year graft survival probability was 79%, which is comparable to results reported for the established penetrating keratoplasty (PK) technique (78%).[21] We recently reported a 5-year survival probability of 90% for a cohort of 500 DMEK eyes (comprising all 100 eyes included in this study),[16] whereas the 5-year survival probability of the current cohort was only 83%. For the previous larger cohort, it was remarkable, that the first 250 eyes had a lower survival probability than the second 250 eyes (88% versus 94%).[16] This may indicate that the DMEK learning curve extends beyond the first 25 cases (that have been excluded) and may still have an influence on graft survival after performing more than 100 DMEK cases. Hence, for future studies higher 10-year survival rates may be expected for larger cohorts (predominantly operated on for Fuchs endothelial corneal dystrophy as reported for this study) after longer DMEK experience.[13-16]

Another influencing factor on survival, that is also related to the learning curve, is graft detachment (technical failure). In the current DMEK study group, the rate of eyes with a major detachment at 6 months postoperatively was relatively high with 11% (compared to 5% for the second 250 eyes of the cohort of 500 DMEK eyes). We had previously shown that graft survival is negatively affected by graft detachment,[16] and in this study we also observed significantly higher 10-year graft survival rates for eyes without major detachment, namely 87% versus 20% for eyes with major detachments. Hence, the 10-year survival rate of 87% might reflect the actual survival probability after longer DMEK experience. While in the first years after introducing DMEK, our group, unlike other groups, often avoided a secondary air-injection in eyes with significant graft detachment, as some corneas showed spontaneous clearance or re-attachment,[22], nowadays hardly any eye with a major detachment after the first postoperative week is left untreated and graft attachment is attempted by a re-bubbling procedure.

Clinical outcomes in terms of BCVA remained excellent up to 10 years after DMEK with 89% of the eyes achieving a BCVA of 20/25 or better. These results corroborate findings of previous mid-term studies that the high visual acuity outcomes achieved within the first months after DMEK are maintained also on the longer term, i.e. up to 10 years after DMEK.[12,13,16] Like previously reported 5-year results,[16] no differences in BCVA outcomes at 10 years were observed for eyes with attached grafts and eyes with minor graft detachments, which may indicate that minor graft detachments do not lead to a deterioration of visual acuity on the longer-term.

Interestingly, the observed ECD decrease rate of 68% at 10 years postoperatively corresponds to the ECD decrease observed after Descemet stripping endothelial keratoplasty (67%) and PK (67% to 76%)[21,23,24] even though the observed ECD decline patterns of DMEK and DSEK differ from the one after PK. Of the eyes with an ECD of less than 1000 cells/mm^2 at 1-year postoperatively (average ECD 807 cells/mm^2), 6 eyes remained clear with an average ECD of 707 cells/mm^2, suggesting that these eyes hardly lose any cells after the initial high cell loss and that cells in those eyes are still able to maintain the homeostasis regardless of the low cell count. In contrast to earlier studies,[14,16] that showed higher ECD in eyes with attached grafts than in eyes with minor detachment, for the current cohort this difference did not reach statistical significance at 10-years after DMEK. This may, like for the BCVA outcomes, be due to the small sample size of eyes with a detachment at the 10-year follow-up.

Allograft rejection and secondary graft failure were shown to be the most severe mid-term complications up to 5 years after DMEK.[12,15,16,25] The same holds for the second half of the first decade after DMEK. Until 10 years postoperatively the cumulative allograft rejection rate increased slightly to 4%,[12,15,16] but was still lower than the 5-year rejection rates for Descemet stripping (automated) endothelial keratoplasty and PK (5.0%-7.9% and 14%, respectively). The rate of SGF was 6% and it may be expected that it will become the dominant complication with longer follow-up times and decreasing ECD.

Limitations of this study may be the retrospective design and the increasing number of patient drop-out which could potentially induce selection bias.

Specifically, self-selection bias occurs as the patients decide to drop-out non-randomly due to restricted mobility caused by age and/or health issues. In our study, all drop-outs were due to patients own choice to do the follow-ups at their own ophthalmologist (see **Supplementary Data Table**). Nevertheless, this is the first larger study to report 10-year follow-up after DMEK. It should be noted, however, that survival rates reported by high-volume DMEK centers may not entirely reflect survival rates achieved by lower-volume DMEK centers as survival rates tend to increase with surgical experience.

In conclusion, DMEK provides excellent long-term clinical outcomes with low complication rates suggesting that DMEK is a safe treatment option for corneal endothelial diseases. Since these outcomes are based on the first DMEK surgeries worldwide, the long-term prognosis for DMEK eyes operated on nowadays may be even better and should encourage novel DMEK surgeons in their learning curve.

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