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Corneal Thickness as a Predictor of Corneal Transplant Outcome

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Abstract

Purpose—Assess corneal thickness (CT) and correlation with graft outcome after penetrating keratoplasty in the Cornea Donor Study.

Methods—887 subjects with a corneal transplant for a moderate risk condition (principally Fuchs or pseudophakic corneal edema) had post-operative CT measurements throughout a 5 year follow up time. Relationships between baseline (recipient, donor, and operative) factors and CT were explored. Proportional hazards models were used to assess association between CT and graft failure. Relationship between CT and cell density was assessed with a longitudinal repeated measures model and Spearman correlation estimates.

Results—Higher longitudinal CT measurements were associated with diagnosis of pseudophakic or aphakic corneal edema ($P < 0.001$), intraocular pressure > 25 mmHg during the first post-operative month ($P = 0.003$), white (non-Hispanic) donor race ($P = 0.002$) and respiratory causes of donor death ($P < 0.001$). Among those without graft failure within the first post-operative year, the 5-year cumulative incidence ($\pm 95\%$ CI) of graft failure was $5\% \pm 5\%$ in those with a 1-year CT $500\mu\text{m}$, $5\% \pm 3\%$ for CT $501 - 550\mu\text{m}$, $7\% \pm 4\%$ for CT $551 - 600\mu\text{m}$ and $20\% \pm 11\%$ for CT $> 600\mu\text{m}$. In multivariate analysis, both 1 year CT and cell density were associated with

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subsequent graft failure ($P=0.002$ and 0.009). CT increase was modestly associated with endothelial cell loss during follow up ($r=-0.29$).

Conclusion—During the first 5 years following penetrating keratoplasty, CT can serve as a predictor of graft survival. However, CT is not a substitute for cell density measurement as both measures were independently predictive of graft failure.

Keywords

cornea transplantation; cornea thickness; graft survival

Introduction

The Cornea Donor Study (CDS) was designed to determine whether graft survival over a 5-year period following penetrating keratoplasty is similar using older donor tissue (age 66-75) versus younger tissue (age 10-65). Donor age was found to have no effect on graft survival.¹ The CDS was designed to track other penetrating keratoplasty related parameters. This randomized, prospective, large multi-center trial with tight adherence to 5-year follow-up (since expanded to ten years) has generated data that advance our knowledge of graft longevity, endothelial cell loss, graft rejection, and donor and recipient risk factors for graft failure.¹⁻⁶ In this report based on the 5-year data, we analyze the course of post-keratoplasty corneal thickness (CT) and its correlation with outcomes.

Materials and Methods

Study Protocol

Previous publications provide details on the CDS and the Specular Microscopy Ancillary Study (SMAS) protocols^{1, 2}; pertinent aspects are described here. Eligibility criteria for study recipients included age between 40 and 80 years and corneal disease associated with moderate risk of failure, principally Fuchs dystrophy and pseudophakic or aphakic corneal edema. Corneas eligible for transplantation were from donors aged 10 to 75 years with a preoperative, baseline eye-bank-determined endothelial cell density (ECD) between 2300 and 3300 cells/mm².

Preoperative care, surgical technique, and postoperative care (including prescription of medications) were provided according to each clinical investigator's customary routine. Annual follow-up continued through 5 years after surgery unless a regrant occurred before that time. In addition to a regrant, a graft was considered to have failed if there was loss of central graft clarity sufficient to compromise vision for a minimum of 3 consecutive months.

CT measurements were optional at post-keratoplasty follow-up visits at month 6, year 1 and annually through year 5. Central CT was measured using an ultrasonic pachymeter by the investigator's usual routine. Measurements of central CT were recorded to the nearest micrometer (μm). If a CT measurement was not possible because the cornea was too thick, this was noted on the data collection form.

A subset of the CDS participants also consented to participation in the SMAS. Preoperative specular microscopic images of the central donor corneal endothelium were provided by the eye banks. Postoperative specular microscopic images of the central corneal endothelium of the graft were obtained at the 6-month and annual follow-up visits. The preoperative donor images and postoperative recipient images were evaluated for quality and endothelial cell density by a central reading center, the Cornea Image Analysis Reading Center (formerly the Specular Microscopy Reading Center) at Case Western Reserve University and University Hospitals Eye Institute, using a previously described variable frame analysis method.⁷

To be included in this analysis cohort, a participant needed to have had a condition associated with endothelial dysfunction as the indication for the initial penetrating keratoplasty, and if graft failure occurred, the failure needed to be due to endothelial dysfunction with or without graft rejection. With these restrictions, the analysis cohort included 887 of the 1,090 CDS participants, 65 of whom experienced graft failure (28 associated with graft rejection and 37 without rejection) and 822 who did not experience graft failure by the conclusion of the 5-year follow-up. Among participants who experienced graft failure, only CT measurements obtained prior to graft failure were included and the analysis was therefore conditional on graft survival.

Because CT measurements were optional, thickness data were not available for all participants. Of the 4,663 completed visits from 887 participants, a CT measurement was available for 3376 (72%). Eighty-seven percent of the 887 participants had two or more CT measurements and 73% had 3 or more CT measurements. The CT availability varied by study site ranging from 0% to 100%. A sensitivity analysis was performed to assess whether the missing data might have impacted these results. When restricting this dataset to 20 of the 78 sites (26%), where 85% of visits included a CT measurement (a total of 1620 CT measurements from 1745 visits) results were similar to those from the entire cohort (data not shown).

Statistical Methods

The CT measurements obtained during the study follow up were verified to have an approximately normal distribution by assessment of histograms, q-q plots and regression residuals. Means $\pm$ standard deviations were therefore used to characterize the distribution of the CT values. The relationships between baseline (recipient, donor, and operative) factors and CT were explored in analyses that paralleled the previously published analyses of ECD⁸. Longitudinal repeated measures models were used to evaluate CT changes throughout follow up. The final multivariate model was generated through stepwise selection of covariates at a significance level of 0.01. The large number of statistical comparisons increases the likelihood of a false-positive, and no attempt was made to control the overall type I error in these exploratory analyses.

Five-year rates of graft failure were calculated using cumulative incidence. The cut points for CT categories were specified prior to data analysis. The proportional hazards model was used to assess the association of graft failure and CT at 6 months and 1 year postoperatively. Significant departure from linearity was detected by adding a quadratic term to the model. CT was therefore analyzed as a discrete variable in all proportional hazards models. The models, adjusted with the ECD, were limited to participants with both CT and ECD values at the corresponding follow up time. Models also were fit with the most recent CT value as a time-dependent variable. For the models with CT as a time-dependent covariate, similar results were obtained when missing values were imputed using the Rubin method of multiple imputation (data not shown). Proportional hazards assumptions were verified using time-dependent variables with logarithmic transformation of time. No significant deviation from the proportional hazards assumption was detected for these models.

The relationship between the CT and ECD was assessed with a longitudinal repeated measures model and with Spearman correlation estimates at each follow up time.

All reported *P*-values are 2-sided. Statistical analyses were conducted using SAS version 9.2 statistical software (SAS Institute, Inc, Cary, North Carolina).

Results

The mean ($\pm$ SD) age of the 887 participants included in the analysis was 70 ± 8 years; 562 (63%) were female and 830 (94%) were white, non-Hispanic individuals. At the beginning of the study, these participants underwent penetrating keratoplasty for the following indications: Fuchs dystrophy (65%), pseudophakic or aphakic corneal edema (31%) and a variety of other diagnoses (4%). Other baseline recipient, donor and operative characteristics were comparable to those in previous CDS analyses cohorts.

Corneal Thickness Measurements Over Time

The mean central CT among participants without graft failure increased steadily during the study follow up (Figure 1). At 6 months, the mean ($\pm$ SD) CT was $535 \pm 45\mu\text{m}$ and increased to $580 \pm 59\mu\text{m}$ at 5 years, which represented a relative change of $9\% \pm 11\%$. Between 6 months and 5 years, CT decreased for 18% of the 378 participants without failure.

At 6 months, the median ECD (interquartile range) was 2519 cells/ mm^2 (2152, 2912) and decreased to 792 cells/ mm^2 (580, 1296) at 5 years, which represented a median cell loss of 65% (48%, 74%). The increase in CT was modestly associated with the loss of endothelial cells during the study follow up ($P < 0.001$, Figure 2). At 6 months, the Spearman correlation between CT and ECD values was -0.09 (95% CI: $-0.21, +0.03$, $P = 0.15$, $n = 261$), and was -0.30 (95% CI: $-0.40, -0.20$, $P < 0.001$, $n = 304$) at 5 years. The correlation between the change in CT and the change in ECD at 5 years (Spearman correlation coefficient = -0.29 , 95% CI: $-0.43, -0.14$, $P < 0.001$, $n = 146$) was similar to the correlation between CT and ECD values at 5 years.

Corneal Thickness and Baseline Factors

In longitudinal multivariate analysis, higher CT measurements during follow up were associated with a baseline diagnosis of pseudophakic or aphakic corneal edema ($P < 0.001$), intraocular pressure (IOP) higher than 25mmHg during the first post-operative month ($P = 0.003$), white (non-Hispanic) donor race ($P = 0.002$, Table 1) and respiratory causes of donor death, which included respiratory failures and other respiratory diseases ($P < 0.001$, Table 1). Non-white (including Hispanic) recipient race was significantly associated with CT in univariate analysis, but it did not reach the significance level of < 0.01 in the multivariate analysis due to confounding with baseline diagnosis. The number of non-white or Hispanic donors and recipients was too small to evaluate any interaction between recipient and donor race. Other baseline factors associated with CT that demonstrated a P -value of less than 0.01 in univariate analyses, but were no longer significant at this level in multivariate analyses included recipient gender, recipient glaucoma history, pre-operative lens status, donor tissue size, vitrectomy, and donor history of diabetes. The principal confounding factor accounting for the differences between the univariate and multivariate analyses was corneal diagnosis for the recipient and operative factors and cause of death for the donor diabetes history. Donor age was not significantly associated with CT values in univariate ($P = 0.35$) or multivariate analyses ($P = 0.31$). No other recipient (age, history of diabetes, smoking status), operative (recipient bed size, post-operative lens status) or donor factors (baseline ECD, gender, type of tissue retrieval, tissue refrigeration, time from death to preservation and time from death to surgery) demonstrated significant association with changes in CT over time.

The association between corneal diagnosis, IOP, donor race, cause of death and CT over time remained significant after adjusting the multivariate model for the potential effect of

site in order to control for any influence of the individual surgeon's technique and post-operative care.

Corneal Thickness and Graft Failure

Figure 3 illustrates that CT was predictive of graft failure with larger CT values among the 65 cases whose graft subsequently failed compared with 822 non-failure cases. Among those whose graft did not fail within the first year after penetrating keratoplasty, the 5-year cumulative incidence ($\pm 95\%$ CI) of graft failure was $5\% \pm 5\%$ in the participants with a 1-year CT $< 500\mu\text{m}$, $5\% \pm 3\%$ in the participants with a 1-year CT $501 - 550\mu\text{m}$, $7\% \pm 4\%$ in the participants with a 1-year CT $551 - 600\mu\text{m}$, and $20\% \pm 11\%$ in the participants with a 1-year CT $> 600\mu\text{m}$ (Figure 4). In univariate analysis, the 1-year CT was associated with subsequent graft failure ($P=0.002$, Table 2). In multivariate analysis, a CT $> 600\mu\text{m}$ was still associated with graft failure after adjusting for ECD (Table 2). In an analysis of CT as a time-dependent variable, the most recent CT value was predictive of graft failure (Table 2). A trend toward more subsequent graft failures with higher change in CT from 6 months to 1 year was demonstrated when the change in CT was added to the model with the 1 year CT; however this association was not statistically significant (data not shown).

Discussion

Increased or progressive CT measurements may offer an early warning of rejection, endothelial cell loss, inflammation, or other causes of endothelial cell dysfunction. However, CT measurements alone are not a reliable indicator of corneal health or decompensation. There is a large range of CT found in normal eyes. In a meta-analysis of healthy unoperated eyes, mean CT was $534\mu\text{m}$ ($472 - 596 \pm 2$ SD).⁹ Mean CT was $544\mu\text{m}$ when the analysis was narrowed to studies based on ultrasound technology. Corneal decompensation and associated vision loss usually occur once CT exceeds a threshold beyond 600 to $650\mu\text{m}$.^{10, 11}

A decrease in CT within the first 6 months after penetrating keratoplasty has been attributed to recovery of the donor endothelium after the initial insult of surgery.¹²⁻¹⁴ Borderie et al documented a decrease in CT from an average of $655\mu\text{m}$ at 1 week to $558\mu\text{m}$ at 1 month, and $533\mu\text{m}$ at six months, prior to increases beginning at one year ($538\mu\text{m}$).¹⁵ Lass et al reported a decrease in average graft thickness following penetrating keratoplasty from $595\mu\text{m}$ at 1 week to $520\mu\text{m}$ at three months.¹³ CT measurements were not obtained during the first 6 postoperative months for the CDS.

In the CDS, mean CT increased steadily from 6 months post-operatively throughout the remaining 5 year follow-up period. Previous studies have shown similar results (Table 3). In a retrospective study of 856 consecutive penetrating keratoplasty patients, Borderie et al obtained ultrasonic CT measurements with mean CT $533\mu\text{m}$ at 6 months, $538\mu\text{m}$ at 1 year, $558\mu\text{m}$ at 2 years, $561\mu\text{m}$ at 3 years, and $568\mu\text{m}$ at 4 and 5 years.¹⁵ Patel et al followed 500 consecutive penetrating keratoplasty eyes with CT measured by contact specular microscopy, with mean CT $540\mu\text{m}$ at 1 year, $560\mu\text{m}$ at 3 years, $570\mu\text{m}$ at 5 years, $580\mu\text{m}$ at 10 years, and $590\mu\text{m}$ at 15 years.¹⁶ In each of these series, CT was measured in clear grafts.

Given the role of corneal endothelium in maintaining corneal hydration, and the 70% endothelial cell loss over five years in successful grafts,² the finding of increasing CT over time following PK is expected. Kopplin et al have shown that in eyes with Fuchs dystrophy without slit lamp evidence of corneal edema, increasing CT is associated with increasing guttae.¹⁷

In the CDS, we observed an almost linear relationship between increasing CT and decreasing ECD from 6 months postoperatively to 5 years following PK. The correlation, however, was relatively small, accounting for less than 10% of the variance in thickness. Both CT and ECD were independently predictive of graft failure. Borderie reported a similar relationship between CT and graft failure, documenting that at time points up to 5 years, subsequent graft survival was lower in patients with increased CT compared to normal CT.¹⁵ In penetrating keratoplasty eyes at high risk for immunologic graft failure followed for 3 years in the Collaborative Corneal Transplantation Studies, increased CT at 1, 3, and 6 months post-operative and change in CT between visits were predictive of graft failure.¹⁸

In the CDS, penetrating keratoplasty recipients with a pre-operative diagnosis of pseudophakic or aphakic corneal edema were more likely to have increased CT during the 5 year follow-up period than recipients with Fuchs dystrophy ($P<0.001$). Previous CDS univariate and multivariate analysis showed a 4-fold increased risk of graft failure in recipients with aphakic or pseudophakic edema compared to Fuchs (27% versus 7%).⁴ Factors contributing to an increased rate of graft failure in aphakic or pseudophakic eyes are not well defined, but are likely related to both endothelial cell dysfunction and associated corneal thickening.

Postoperative CT was higher in eyes with an elevated intraocular pressure within the first postoperative month. While the association between increased intraocular pressure and increased corneal thickness has been well documented^{17, 19}, the causal relationship appears to be complex, with mechanisms not well understood. Patients with ocular hypertension are more likely to have increased CT²⁰, in contrast to normal tension glaucoma or primary open angle glaucoma patients who are more likely to have average or lower than average CT.²¹ It is unclear which of our patients with elevated intraocular pressure readings within the first postoperative month may have had ocular hypertension, primary open angle glaucoma, angle closure, or were steroid responders. Measuring artifact from applanation tonometry, which causes overestimation of intraocular pressure in thicker corneas, may in part account for our results.^{9, 22}

A relationship between respiratory cause of donor death and increased postoperative CT has not been previously observed. A possible mechanism is reduced endothelial cell function following prolonged hypoxia. Donor death from respiratory causes was not a risk factor for graft failure in the CDS.³ It is possible that this finding is a false positive result from Type I error due to inclusion of a large number of variables in our analyses.

White (non-Hispanic) donor race was associated with increased recipient CT compared to Nonwhite or Hispanic donor race at 6 months to 5 years post-op penetrating keratoplasty. This finding may be due to racial differences in corneal thickness. African Americans have lower mean CT measurements than whites, with Hispanics similar to whites.^{20, 21, 23, 24}

While our study had the benefit of data acquired in a prospective, randomized, large clinical trial with excellent patient follow up, there are several limitations. Our study results were limited by the fact that CT measurements during follow up were obtained at the discretion of the surgeon. 87% of participants had 2 measurements, 73% had 3 measurements, and 40% had 5 measurements.

The CDS cohort was restricted to eyes at low to mid risk of graft failure following penetrating keratoplasty for endothelial disease. Eyes with corneal decompensation due to other causes, especially those at high risk of graft failure due to stromal neovascularization or past graft failure, might yield different results. Most of the eyes on which we performed penetrating keratoplasty would today likely undergo an endothelial replacement procedure

such as Descemet stripping endothelial keratoplasty or Descemet membrane endothelial keratoplasty, with possibly different CT findings and correlations.

Our major findings include establishing normative values for CT following penetrating keratoplasty in eyes at low to mid risk for graft failure. We have established that, at least during the first 5 years following penetrating keratoplasty, CT can serve as a predictor of graft survival. Considering the advantages of obtaining CT versus ECD measurements in terms of ease, expense, and availability, it is tempting but incorrect to consider CT as a proxy for ECD. Each serves as an independent predictor of graft failure and measures different parameters of corneal health. We are hopeful that future research will allow better utilization of CT as a way of assessing prophylaxis or treatment options for graft failure and corneal disease. For example, if low-grade rejection or inflammation exists as a cause of graft failure, might long-term or more aggressive steroid treatment be evaluated with CT and/or ECD measurements?

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Appendix

A listing of the Cornea Donor Study Investigator Group, including clinical site investigators, eye bank staff, coordinating center staff, specular microscopy reading center staff, and committees, has been previously published online.

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Figure 1.

Box Plot of Corneal Thickness Measurements (μm) over Study Follow up (N=887).

Description: In the box plot, black dots indicate mean values; horizontal lines in the boxes, medians; and the bottom and top of the boxes, the 25th and 75th percentiles.

Figure 2.
Median ECD and CT Values Over Time.

Figure 3. Boxplot of Corneal Thickness (μm) Over Time According to Graft Failure Status (N=887). Description: The decreasing trend over time in the graft failure group is likely a result of selective removal of failed grafts which tend to have higher CT values.

Figure 4.

Kaplan-Meier Plot of Graft Failure According to 1 Year CT (N=621). Description: Kaplan-Meier plots and 5-year failure rates are calculated conditional on graft survival by year 1.

Among 640 participants with 1 year CT measurement, 13 were censored and 6 experienced graft failure prior to year 1.

Table 1
Corneal Thickness over Time According to Baseline Recipient and Donor Factors

Baseline Factors	Corneal Thickness (µm) at:										5Yr Corneal Thickness Change from 6 months		
	6 Months		1 Year		2 Years		3 Years		4 Years		5 Years		Change* (% Change**)
	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean	Mean
Overall	637	536	640	544	596	557	532	562	463	566	508	580	+ 46 (+9%)
RECIPIENT FACTORS													
Age (years)													
40 – < 60	95	531	87	544	83	560	75	560	70	571	88	587	+ 61 (+12%)
60 – < 70	179	538	172	548	174	554	149	561	144	567	144	577	+ 47 (+9%)
70 – 86	363	537	381	542	339	557	308	563	249	564	276	580	+ 40 (+8%)
Race													
White (non-Hispanic)	595	535	603	542	568	555	511	561	441	565	484	579	+ 46 (+9%)
Nonwhite (or Hispanic)	42	555	37	570	28	594	21	585	22	584	24	603	+ 49 (+9%)
Gender													
Male	233	539	236	551	224	562	189	566	163	572	180	589	+ 48 (+9%)
Female	404	535	404	540	372	553	343	559	300	562	328	576	+ 45 (+9%)
Baseline Diagnosis and Lens Status													
Fuchs: pre/post phakic	98	526	101	538	93	546	92	556	84	563	97	572	+ 49 (+10%)
Fuchs: pre phakic/post PA	189	532	190	537	183	549	154	553	149	556	169	577	+ 45 (+9%)
Fuchs: pre/post PA	145	534	141	538	137	550	125	555	109	565	111	579	+ 43 (+8%)
PACE: post PA	179	549	182	559	161	579	143	583	103	584	114	590	+ 44 (+8%)
Other diagnoses /	26	530	26	543	22	547	18	548	18	562	17	607	+ 66 (+12%)
Prior use of glaucoma medications/surgery													
No meds and no surgery	548	535	550	542	515	555	461	560	413	566	458	581	+ 48 (+9%)
Meds and/or surgery	89	546	90	557	81	567	71	571	50	568	50	574	+ 28 (+5%)
OPERATIVE FACTORS													

Baseline Factors	Corneal Thickness (µm) at:												5Yr Corneal Thickness Change from 6 months	
	6 Months		1 Year		2 Years		3 Years		4 Years		5 Years		Change* (% Change**)	
	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean
Donor tissue size (mm)														
<8.0	157	540	158	544	136	567	121	570	111	575	105	585	85	+ 48 (+ 9%)
=8.0	146	539	147	548	135	558	126	571	101	575	116	595	84	+ 63 (+ 12%)
>8.0	334	533	335	542	325	552	285	554	251	558	287	573	209	+ 38 (+ 7%)
Vitrectomy														
No	556	533	556	542	519	554	468	559	417	563	454	580	341	+ 49 (+ 10%)
Yes	81	558	84	556	77	576	64	579	46	587	54	581	37	+ 14 (+ 3%)
Post-operative Intraocular Pressure ² (mmHg)														
≤25	568	535	571	542	531	555	477	559	416	564	455	579	340	+ 46 (+ 9%)
>25	67	548	67	561	64	570	52	589	46	580	50	592	36	+ 40 (+8%)
DONOR FACTORS														
Age (years)														
12 – < 40	84	528	71	538	70	545	62	555	60	554	57	554	49	+ 29 (+ 6%)
40 – < 50	78	545	75	549	69	565	66	567	54	563	61	583	51	+ 45 (+ 9%)
50 – < 60	154	548	157	547	150	557	130	567	112	571	140	585	88	+ 34 (+ 6%)
60 – < 70	196	531	216	540	194	556	180	560	154	569	161	585	118	+ 54 (+ 11%)
70 – 76	125	531	121	546	113	559	94	558	83	564	89	579	72	+ 58 (+ 12%)
Race														
White (non-Hispanic)	607	537	610	545	561	557	510	563	435	567	481	581	360	+ 45 (+ 9%)
Non-white (or Hispanic)	30	518	30	515	35	544	22	537	28	549	27	569	18	+ 55 (+ 11%)
Gender														
Male	425	536	428	546	406	556	355	560	311	564	339	579	255	+ 43 (+ 9%)
Female	212	536	212	539	190	557	177	565	152	570	169	584	123	+ 50 (+ 10%)

Baseline Factors	Corneal Thickness (µm) at:										5Yr Corneal Thickness Change from 6 months		
	6 Months		1 Year		2 Years		3 Years		4 Years		5 Years		Change* (% Change**)
	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean	
Cardio/Stroke	384	536	388	545	373	558	325	560	283	565	315	580	+ 47 (+ 9%)
Cancer	107	533	114	536	98	555	96	565	80	565	86	588	+ 54 (+ 11%)
Trauma	69	530	62	539	55	543	48	559	40	557	43	565	+ 40 (+ 8%)
Respiratory	44	562	45	565	39	580	35	584	36	592	40	599	+ 35 (+ 7%)
Other	33	524	31	538	31	537	28	541	24	553	24	555	+ 35 (+ 7%)
History of diabetes													
No	515	534	514	542	478	554	435	559	380	564	412	578	+ 45 (+ 9%)
Yes	122	545	126	552	118	566	97	573	83	576	96	589	+ 48 (+ 9%)
Baseline ECD (cells/mm²)													
2500	191	535	188	542	168	560	170	567	132	573	151	593	+ 63 (+ 12%)
2501 - 2750	194	539	201	542	177	557	154	559	140	563	158	579	+ 41 (+ 8%)
>2750	252	535	251	547	251	554	208	559	191	563	199	571	+ 37 (+ 7%)
Time from death to preservation													
0- $<$ 5 hrs	105	535	91	544	93	557	79	556	74	560	81	574	+ 39 (+ 8%)
5- $<$ 9 hrs	339	534	353	543	313	558	290	562	249	565	280	582	+ 46 (+ 9%)
9- $<$ 11 hrs	106	545	108	543	101	552	89	561	73	574	82	580	+ 48 (+ 9%)
11- 12 hrs	71	536	74	549	72	557	59	570	55	571	56	582	+ 50 (+ 9%)
>12 hrs	16	536	14	553	17	549	15	564	12	555	9	581	+ 39 (+ 7%)
Time from death to surgery													
0-2 days	78	542	85	551	74	573	65	572	63	572	73	581	+ 32 (+ 7%)
3-4 days	350	536	334	544	326	552	282	558	246	561	263	580	+ 47 (+ 9%)
5-8 days	209	534	221	541	196	558	185	564	154	570	172	581	+ 49 (+ 9%)

PACE = Pseudophakic or aphakic corneal edema; PA = Pseudophakic or aphakic lens

* Change is calculated as the difference between the follow up and the 6 month CT value and the 6 month CT value

** Percent change is calculated as the difference between the follow up and the 6 month CT value divided by the 6 month CT value and expressed as percentage.

† Includes 33 participants with variety of diagnosis: 11 with interstitial keratitis, 5 with posterior polymorphous dystrophy, 2 with perforating corneal injury and 15 with other causes of endothelial failure.

²The maximum intraocular pressure during the first month after surgery. Four participants with missing value for post-operative intraocular pressure

Table 2
Proportional Hazards Regression Analyses for Corneal Thickness and Graft Failure

Covariate	N	Hazard Ratio (95% Confidence Interval)	P-Value
Univariate Models			
Model 1 ^a : CT at 6 months	625		0.15
500 µm	132	1.00	
501 to 550 µm	275	1.63 (0.65 - 4.06)	
551 to 600 µm	162	1.93 (0.74 - 5.02)	
>600 µm	56	3.31 (1.15 - 9.54)	
Model 2 ^a : CT at 1 year	621		0.002
500 µm	103	1.00	
501 to 550 µm	263	0.97 (0.35 - 2.72)	
551 to 600 µm	193	1.26 (0.44 - 3.56)	
>600 µm	62	4.09 (1.42 - 11.76)	
Multivariate model			
Model 3 ^b : CT and ECD at 1 year	320		0.002
CT at 1 year :			
550 µm	198	1.00	
551 to 600 µm	86	2.07 (0.60 - 7.17)	
>600 µm	36	7.42 (2.39 - 23.04)	
ECD at 1 year:			0.009
<1700 cells/mm ²	74	1.00	
1700 to <2200 cells/mm ²	83	0.26 (0.07 - 0.93)	
2200 to <2700 cells/mm ²	92	0.16 (0.04 - 0.72)	
2700 cells/mm ²	71	0.10 (0.01 - 0.77)	
Model with time-dependent variables			
Model 4 ^c : Most recent CT	887		<0.001
500 µm		1.00	
501 to 550 µm		2.83 (0.80 - 10.07)	
551 to 600 µm		4.11 (1.17 - 14.40)	
>600 µm		19.58 (5.93 - 64.61)	

CT = Corneal Thickness (µm); ECD = Endothelial Cell Density (cells/mm²)

^aThe Cox model is conditional on graft survival by the specified time. Results were similar using the Rubin method of multiple imputation for the missing CT values (data not shown).

^bThe Cox model includes 320 participants with both CT and ECD values at 1 year. There were no events among the 54 subjects with 1 year CT 500 µm and the categories 500 µm and 501 – 550 µm were combined into one for this model.

^cCox model includes entire analysis cohort (subjects with 1 or more follow up CT measurements).

Table 3
Mean Corneal Thickness Results Following Penetrating Keratoplasty

Postoperative Time Point:	Mean Corneal Thickness (μm)		
	CDS	Borderie ¹⁵	Patel ¹⁶
6 months	536	533	
1 year	544	538	540
2 years	557	558	
3 years	562	561	560
4 years	566	568	
5 years	580	568	570
10 years			580
15 years			590