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A 10-Year Review of Penetrating Keratoplasty

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Purpose: To survey the changes in indications for penetrating keratoplasty (PKP) and re-evaluate the risk factors for allograft rejection and graft failure.

Methods: We evaluated the records of 396 eyes of 335 patients who had undergone PKP at the Tokyo University Hospital between 1987 and 1997. Clinical results were analyzed by the Kaplan-Meier life table method and the log-rank test.

Results: The overall rates of graft survival and rejection-free graft survival at 10 years were 72.2% and 76.8%, respectively. The rates of graft survival and rejection-free graft survival were 98.8% and 86.6% in keratoconus, 87.0% and 56.5% in herpetic keratitis, 76.9% and 73.1% in corneal dystrophy and degeneration, 69.4% and 80.6% in nonherpetic keratitis, 62.5% and 75.0% in chemical burns, 61.8% and 72.1% in regrafting, and 51.1% and 79.8% in bullous keratopathy, respectively. The graft survival rates were statistically higher in the PKP alone group than in the combined operation group. The graft survival and rejection-free graft survival rates were statistically higher in the first operation group than in the re-grafted group, and in the avascular cornea group than in the vascular cornea group.

Conclusions: We recognized changes in indications for PKP. Combined operation, reoperation, and vascularization of recipient cornea were risk factors for graft failure. **Jpn J Ophthalmol 2000;44:139–145**

Key Words: Graft survival, penetrating keratoplasty, rejection, 10-year evaluation.

Introduction

Penetrating keratoplasty (PKP) is a very common and successful form of organ transplantation.[1] Owing to recent developments in surgical techniques and materials and postoperative management, indications for PKP have been extended to high-risk patients with conditions such as corneal vascularization or regrafting. One of the most important factors that affects the clinical outcome of PKP is still allograft rejection.[2] As high-risk patients are more likely to suffer from allograft rejection than low-risk ones, their PKP outcomes have not been good. Risk factors for graft failure and rejection in PKP were reported to be corneal vascularization, previous transplant number, suture, and endothelial cell function.[3–6] There was no statistically significant association between graft failure and surgery type, recipient age, and preoperative donor endothelial cell density.[3]

We evaluated the long-term outcomes of PKP at the Tokyo University Hospital during the 10 years from 1987 to 1997 in terms of rejection-free graft survival rate and graft survival rate. We also evaluated operation type, operation number and vascularization as risk factors for allograft rejection and graft failure.

Materials and Methods

We made a retrospective study of 396 consecutive PKPs performed at the Tokyo University Hospital

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Table 1. Preoperative Diagnosis

	Oct. 1987–Sept. 1992 (n = 170)	Oct. 1992–Sept. 1997 (n = 226)	Overall (n = 396)
Bullous keratopathy	35 (20.5)	59 (26.2)	94 (23.7)
Keratoconus	39 (22.8)	43 (19.1)	82 (20.7)
Nonherpetic keratitis	31 (18.1)	41 (18.2)	72 (18.2)
Graft failure	18 (10.5)	50 (22.2)	68 (17.2)
Herpes keratitis	29 (17.0)	17 (7.6)	46 (11.6)
Corneal dystrophy and degeneration	15 (8.8)	11 (4.9)	26 (6.6)
Chemical burns	4 (2.3)	4 (1.8)	8 (2.0)

Values in parentheses are percent of total.

between October 1987 and September 1997. These 396 transplants were performed on 335 patients (203 male and 132 female patients). The mean age of patients was 51.6 years (SD, 18.4 years; range, 6–84 years).

The preoperative diagnoses were divided into 7 categories (Table 1). The overall indications were mainly bullous keratopathy (23.7%), keratoconus (20.7%), and nonherpetic keratitis (18.2%). A marked change was noted over the study period with respect to the percentage of PKP cases performed for graft failure. This association showed an increase in frequency from 18 of the 170 cases (10.5%) in the first 5 years (October 1987 to September 1992) to 50 of the 226 cases (22.2%) in the last 5 years (October 1992 to September 1997). Bullous keratopathy as an indication for PKP showed a tendency to increase in frequency from 35 of the 170 cases (20.5%) in the first 5 years to 59 of the 226 cases (26.2%) in the last 5 years.

Herpetic keratitis as an indication for PKP, however, showed a tendency to decrease in frequency from 29 of the 170 cases (17.0%) in the first 5 years to 17 of the 226 cases (7.6%) in the last 5 years.

The surgical methods are shown in Table 2. PKP without cataract extraction or anterior vitrectomy was 295 eyes (74.5%). Penetrating keratoplasty was combined with cataract extraction in 45 eyes (11.4%), and with anterior vitrectomy in 38 eyes (9.6%).

The number of PKP operations per case is shown in Table 3. Three hundred of the 396 cases were first operations (75.7%) and 94 of the 396 cases (23.8%) were regrafts.

The extent of preoperative corneal vascularization is shown in Table 4. The percentage of patients with vascular cornea (49.7%) is similar to the percentage with avascular cornea (50.3%).

Donor eyes, enucleated aseptically, were maintained in preservation media (EP-II; Kaken Pharmaceuticals, Osaka) at 4°C. Almost all transplantations were done within 72 hours of enucleation. Sclerocorneal rims were made at the time of surgery, the donor buttons being punched out of the endothelial side with Weck's disposable trephines. The mean diameter of the corneal graft was 7.70 mm (SD, 0.60 mm; range, 5.00–12.00 mm). The diameter of the corneal graft was 0.25–0.50 mm larger than that of the recipient cornea. The grafts were sutured to the recipient corneas with eight interrupted 10-0 nylon preplaced sutures followed by running or interrupted 10-0 nylon sutures. Lensectomy, anterior vitrectomy, intraocular lens implantation, or intraocular lens removal were done as necessary. The patients received a subconjunctival injection of dexamethasone (2 mg) and ofloxacin ointment at the end of surgery. Systemic prednisolone (30–60 mg/day) and topical betamethasone (1 mg/mL), ofloxacin, and tropic amide as a postoperative treatment were prescribed. Topical treatment was tapered over several months; from 6 times a day postoperatively to 4 times a day at 3 months, 3 times daily at 6 months, and twice daily at 12 months. The corneal sutures were usually removed 12 to 18 months after surgery. The mean postoperative follow-up period was 46.6 months (SD = 30.4 months).

The patients were classified into two groups: high-risk and low-risk.[7] High-risk patients were those who had corneal vascularization in two or more quad-

Table 2. Methods of Operation for 396 Penetrating Keratoplasties

	Overall (n = 396)
PKP	295 (74.5)
PKP + cataract surgery	45 (11.4)
PKP + anterior vitrectomy	38 (9.6)
Others	18 (4.5)

Values in parentheses are percent of total.
PKP: penetrating keratoplasty.

Table 3. Number of PKP Operations Per Case for 396 Penetrating Keratoplasties

No. of PKP	Overall (n = 396)
1	300 (75.7)
2	72 (18.2)
3	15 (3.8)
4	2 (0.5)
5	4 (1.0)
6	1 (0.3)
Unknown	2 (0.5)

Values in parentheses are percent of total.
PKP: penetrating keratoplasty.

rants of the cornea preoperatively or who had a history of graft failure. Of the 396 PKPs, 168 were high-risk and 228 were low-risk transplantations.

A corneal graft was defined as rejected when it became edematous and showed such signs of immunological rejection as a rejection line, infiltrative keratic precipitates, or anterior segment inflammation.[8] The diagnosis of rejection was made only if the transplant had remained clear for at least 2 weeks after surgery. Graft failure was defined as an irreversible loss of central graft clarity and determined clinically using a slit-lamp biomicroscope.

Patients who developed immunological rejection were treated intensively with topical and systemic steroids. The usual treatment for allograft rejection included the instillation of steroid eye drops every 1 or 2 hours, and subconjunctival injection of 1.2–2.0 mg dexamethasone and systemic administration of prednisolone (30–60 mg/day) for 1–2 weeks with tapering off.

Statistical Analysis

Data are presented in graph and table forms. The comparability of patients, eyes, and donor covariates between subgroups were analyzed using the χ^2 test for categoric covariates and the independent *t*-test for continuous covariates. Relative risks and adjusted survival probabilities were estimated by Cox's proportional hazards model.[9] The graphical graft survival and rejection-free graft survival curves were made by the Kaplan-Meier method,[10] and compared with the data of the log-rank test.

Table 4. Frequency of Preoperative Corneal Vascularization in 396 Penetrating Keratoplasties

Recipient Vascularization	Overall (n = 271)
No vascularization	131
Within one quadrant	59
Two quadrants	38
Three quadrants	26
Four quadrants	15
Unknown	2

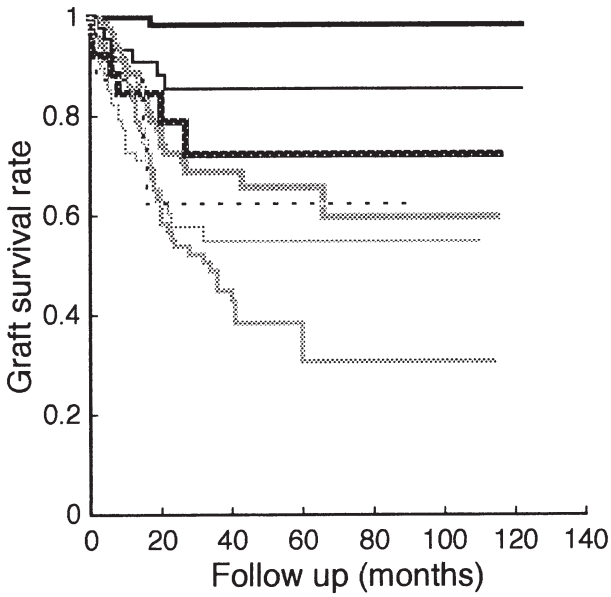

Figure 1. Graft survival in keratoconus, herpes keratitis, corneal dystrophy and degeneration, nonherpetic keratitis, chemical burn, graft failure, and bullous keratopathy, estimated by Kaplan-Meier method.

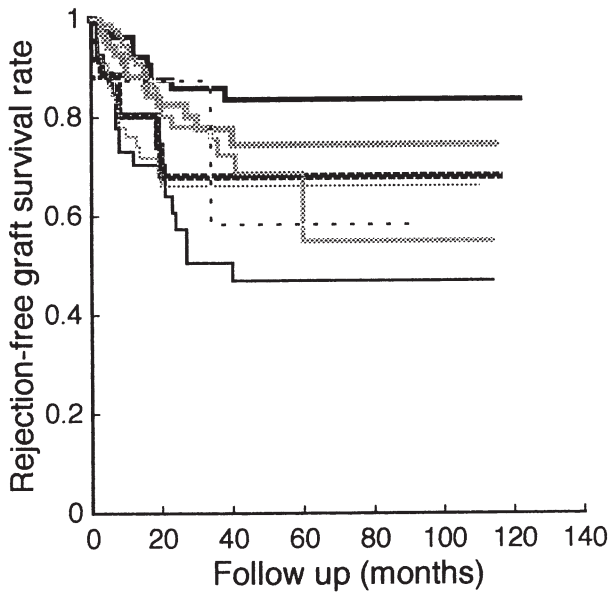

Figure 2. Rejection-free graft survival in keratoconus, nonherpetic keratitis, bullous keratopathy, chemical burn, corneal dystrophy and degeneration, graft failure, and herpes keratitis, estimated by Kaplan-Meier method.

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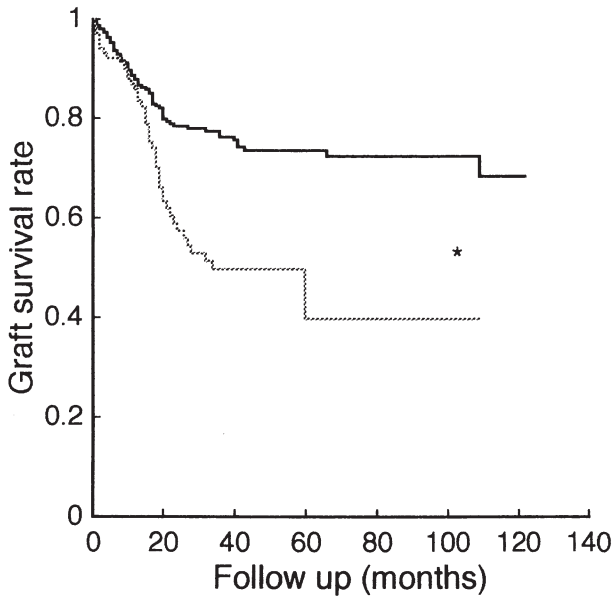

Figure 3. Graft survival in penetrating keratoplasty (PKP) alone (solid line) and combined operation (broken line) groups estimated by Kaplan-Meier method. *Log-rank test: $P < .0001$.

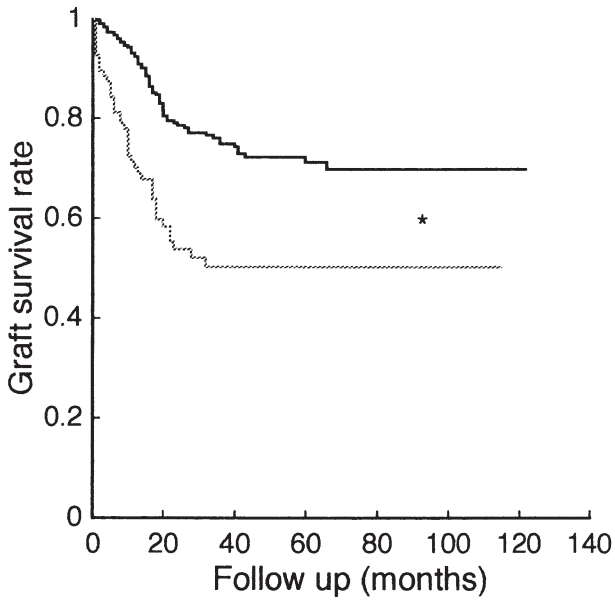

Figure 5. Graft survival in the first penetrating keratoplasty (PKP) (solid line) and regraft (broken line) groups estimated by Kaplan-Meier method. *Log-rank test: $P < .0001$.

Results

The final overall graft survival rate at 10 years after PKP was 72.2%, with a rate of 98.8% in keratoconus, 87.0% in herpetic keratitis, 76.9% in corneal dystrophy and degeneration, 69.4% in nonherpetic keratitis, 62.5% in chemical burns, 61.8% in graft failure and 51.1% in bullous keratopathy (Figure 1). The final overall rejection-free graft survival rate was 76.8%, with a rate of 86.6% in keratoconus,

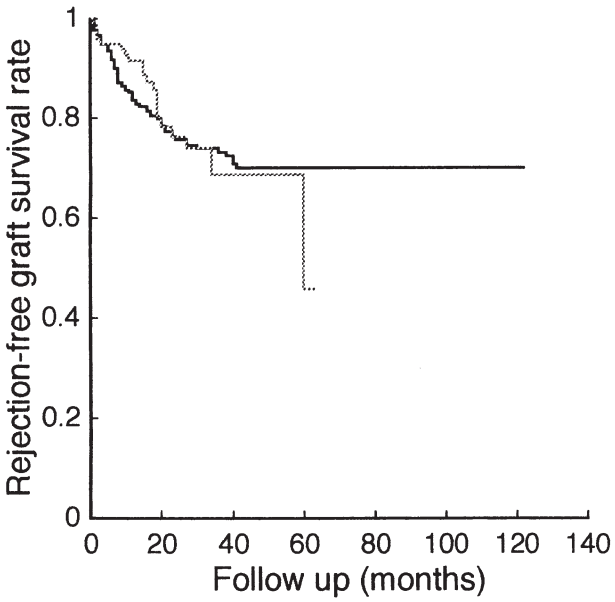

Figure 4. Rejection-free graft survival in penetrating keratoplasty (PKP) alone (solid line) and combined operation (broken line) groups estimated by Kaplan-Meier method. *Log-rank test: $P = .81$.

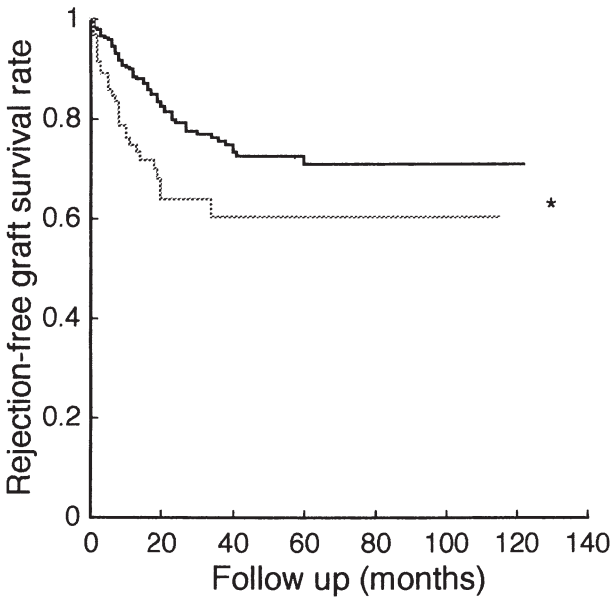

Figure 6. Rejection-free graft survival in the first penetrating keratoplasty (PKP) (solid line) and regraft (broken line) groups estimated by Kaplan-Meier method. *Log-rank test: $P = .003$.

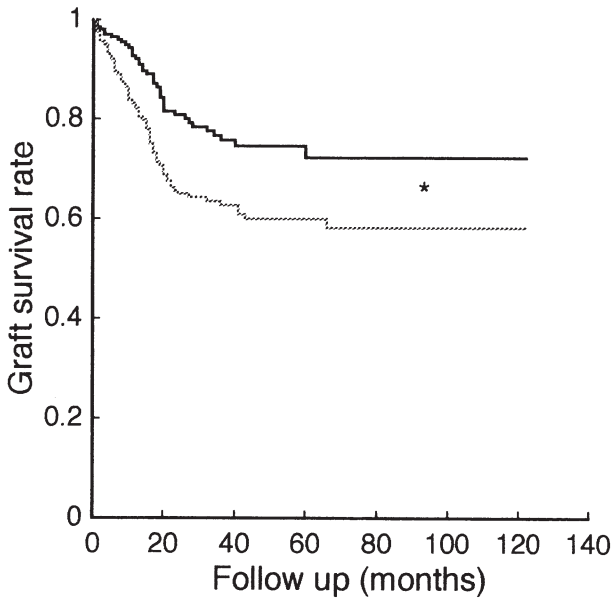

Figure 7. Graft survival in avascular cornea (solid line) and vascular cornea (broken line) groups estimated by Kaplan-Meier method. *Log-rank test: $P = .002$.

80.6% in nonherpetic keratitis, 79.8% in bullous keratopathy, 75.0% in chemical burns, 73.1% in corneal dystrophy and degeneration, 72.1% in graft failure and 56.5% in herpetic keratitis (Figure 2).

The graft survival rates were statistically higher in the PKP alone than in the combined operation group (Figure 3, $P < .001$). The rejection-free graft survival rates were similar for the PKP alone and the combined operation groups (Figure 4, $P = .806$). The graft survival (Figure 5, $P < .001$) and rejection-free graft survival (Figure 6, $P = .003$) rates were statistically higher in the first operation group than in the regraft group. The graft survival (Figure 7, $P = .002$) and rejection-free graft survival (Figure 8, $P < .001$) rates were statistically higher in the avascular cornea group than in the vascular cornea group.

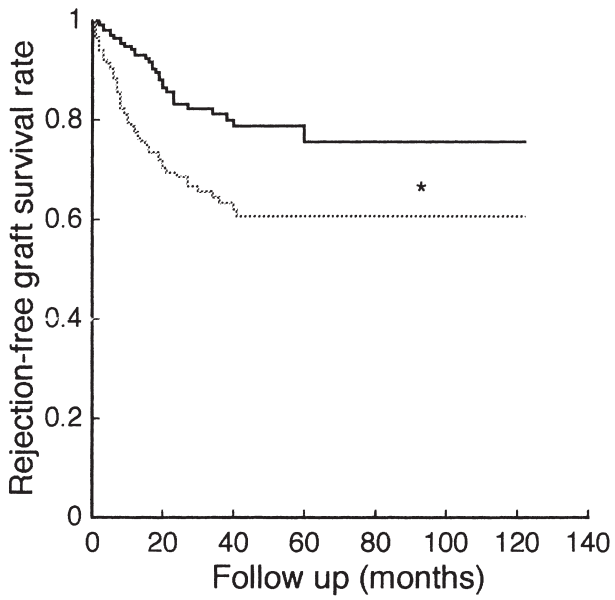

Figure 8. Rejection-free graft survival in avascular cornea (solid line) and vascular cornea (broken line) groups estimated by Kaplan-Meier method. *Log-rank test: $P < .0001$.

In the combined surgery group increased the estimated risk of graft failure (1.88), but not that of rejection ($P = .81$) (Table 5). In the regraft group the estimated relative risk of graft failure (1.93) and that of rejection (1.44) increased. The estimated relative risks of graft failure and rejection in the vascular recipient cornea were 1.72 and 1.93, respectively.

Discussion

The cornea is commonly thought to be immunologically privileged because blood vessels and lymphatics are absent. The immune privilege of the cornea is a relative concept of allograft rejection compared with the transplantation of other organs.[1] Although the cornea is an immune privileged site, the incidence of allograft rejection after PKP is about 30%,[7,11] and the main cause of graft failure is allograft rejection.[4]

In Japan, overall corneal graft survival rates are reported as ranging from 61%–94.5%,[4,12–21] and overall rejection-free graft survival rates from 55%–86%.[5,12–21] In our institution, the overall corneal graft survival rate was 72.2%, and the overall rejection-free graft survival rate, 76.8%. These results are comparable to those of previous reports.[12–21] The graft survival rate was reported 86%–100% in keratoconus,[13,17,19–21] 66.7%[17] and 74.3%[20] in herpetic keratitis, 67%–87% in corneal dystrophy and degeneration,[13,20,21] 58.3%[17] and 100%[13] in nonherpetic keratitis, 45% in transplant rejection,[20] 12%–70% in bullous keratopathy,[13,17,19–21] and 0%–37%[6,19,21] in chemical burns. Recently, PKP was thought to be contraindicated for cases of chemical burns. We believe PKP can be indicated in mild cases of chemical burns, in which corneal epithelium is not completely destroyed, and we performed PKP in those cases. According to previous reports in Japan, the rejection-free graft survival rate was reported as 80%,[18] 92%,[20] and 98%[4] in keratoconus; 77.1%,[20] 77.8%,[18] and 83%[4] in herpetic keratitis; 61.5%,[18] 100%,[20] and 59%[4] in corneal dystrophy and degeneration; 70.6%[18] in nonherpetic keratitis; 30%[4] and 55%[20] in

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Table 5. Estimated Graft Survival Rate and Risk of Graft Failure

	Estimated Graft Survival (%)	Log-Rank Value	*P* Value	Estimated Relative Risk of Graft Failure
Graft survival group				
PKP	68.3			
Combined surgery	39.7	17.7	<.0001	1.88
First PKP	69.9			
Regraft	50.2	24.0	<.0001	1.93
Recipient-avascularization	72.2			
Recipient-vascularization	58.2	9.69	.002	1.72
	Estimated Rejection Free Graft Survival (%)	**Log-Rank Value**	***P* Value**	**Estimated Relative Risk of Rejection**
Rejection-free graft survival group				
PKP	70.1			
Combined surgery	45.8	0.06	.81*	–
First PKP	70.9			
Regraft	60.4	8.96	.003	1.44
Recipient-avascularization	75.6			
Recipient-vascularization	60.6	15.3	<.0001	1.93

PKP: Penetrating keratoplasty.
*Not significant.

graft failure; and 28%[4] and 33%[20] in bullous keratopathy. The graft survival rate in Japan was reported higher in PKP alone (51%[16] and 86%[13]) than in PKP with cataract surgery (43%[16] and 67%[13]). The graft survival rate was higher in the first operation group (83%,[13] 76%,[19] and 52%[16]) than in the regraft group (50%,[13] 23%,[19] and 30%[16]). The graft survival rate was higher in avascular cornea (97%[19] and 83%[20]) than in vascular cornea (20%[19] and 68%[20]). Chikama et al,[17] however, reported the graft survival rate was similar for avascular and vascular cornea patients. The rejection-free graft survival rate was reported higher in avascular cornea (94%,[20] 88%,[14] and 83.3%[18]) than in vascular cornea (79%,[20] 75%,[14] and 66.7%[18]). Our results are comparable with those of previous reports.[11–16]

The indications for PKP have changed throughout the years, reflecting changes in the incidence and treatment of various corneal diseases. Smith et al[22] reported clinical indications of 710 PKP patients from 1947 to 1978. The leading indications were aphakic bullous keratopathy (18.4%), regrafts (15.4%), keratoconus (12.7%), and Fuchs' endothelial dystrophy (9.8%). The indication of aphakic bullous keratopathy gradually increased from 1962. That of scarring or active keratitis secondary to virus (herpetic keratitis) gradually decreased from 1962. Robin et al[23] reported clinical indications for 497 PKP cases from 1979 to 1983. The five most commonly encountered diagnoses were pseudophaxkic bullous keratopathy (17.5%), regraft (15.1%), aphakic bullous keratopathy (10.9%), corneal trauma (9.3%), and Fuchs' endothelial dystrophy (9.1%). The emergence of pseudophakic bullous keratopathy as the most common cause for PKP correlates well with the dramatic increase in the number of cataract extractions with intraocular lens implantations performed since the mid-1970s. Ing et al[3] reported clinical indications for 394 PKP cases from 1947–1978. Preoperative recipient diagnoses were Fuchs' dystrophy (27%), keratoconus (21%), pseudphakic corneal edema (19%), and aphakic corneal edema (17%). Brady et al[24] reported clinical indications of 150 PKP cases from 1983–1988. The incidence of PKP for graft failure was 10.1% overall and no significant change was noted in this percentage over the 6 years of the survey. Bullous keratopathy was the most common indication for PKP, accounting for 22.9% overall and this percentage has shown a marked increase year by year. The percentage of viral disease, including herpes simplex keratitis, was 4.4% overall and decreased over 6 years. In our study, graft failure accounted for 68 (17.2%) cases overall and increased in frequency from 18 of 170 cases (10.5%) between October 1987 and September 1992 to 50 of 226 cases (22.2%) between October 1992 and September 1997. Bullous keratopathy accounted for 94 (23.7%) cases overall and increased

in frequency from 35 of 170 cases (20.5%) to 59 of 226 cases (26.2%). This is probably because the indication of PKP has been gradually extended to high-risk patients. Herpetic keratitis accounted for 46 (11.6%) cases overall and demonstrated a tendency to decrease in frequency from 29 of 170 (17.0%) cases to 17 of 226 (7.6%) cases, consistent with marked improvement in the recognition and medical treatment of herpetic keratitis. Corneal dystrophy and degeneration accounted for 26 (6.6%) cases overall and demonstrated a tendency to decrease in frequency from 15 of 170 (8.8%) cases to 11 of 226 (4.9%) cases, because for cases of corneal dystrophy and degeneration, lamellar keratoplasty (LKP) has been performed recently.

Williams et al[2] reported that the respective estimated relative risks of graft failure in vascular cornea were 2.74 and in second graft 3.80. Yamagami et al[5] reported that the respective estimated relative risks of rejection in vascular cornea were 1.65 (within one quadrant), 2.74 (two quadrants), 4.53 (three or more quadrants), and in repeat graft, 2.39. We found that the estimated relative risk of graft failure and rejection increased in both the re-graft and the vascular cornea groups.

The estimated relative risks of rejection are similar between PKP and combined surgery in our survey. We considered in the combined surgery group that graft failure occurred before allograft rejection.

We conclude that transplantation rejection and bullous keratopathy as an indication for PKP have shown a gradual increase in frequency over the past 10 years, whereas herpetic keratitis has shown a gradual decrease. The rate of allograft transparency is high and the risk of allograft rejection is low in keratoconus. However, the rate of allograft transparency is low and the risk of allograft rejection is high in bullous keratopathy. The rate of allograft transparency is high in PKP without cataract or vitreous surgery, first operation, and PKP with a significant avascularization of recipient cornea. Allograft rejection is less in first operations and in those PKP cases with a significant avascularization of the recipient cornea.

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