

7. Primary vitrectomy at the Charité, Campus Benjamin Franklin

PPPV for the treatment of RRD was introduced in the Department of Ophthalmology, CCBF in 1992. The results of the first series of patients operated at the CCBF, combined with the initial results of our surgeons performed in the Universitäts-Augenklinik Essen, Germany, was published by the applicant in 1996 (series 1) [39]. In a second series, we reviewed 512 cases of PPPV and performed a statistical analysis of per- and intraoperative risk factors with an unfavourable outcome (series 2) [44]. In addition, we studied the influence of vitreoretinal surgery on the severity of postoperative dry eye symptoms in a morphological [40] and a clinical study [42].

7.1. PPPV at the CCBF 1992-1994 (series 1)

7.1.1. Patients and methods

A retrospective analysis of 53 cases undergoing primary vitrectomy without additional scleral buckling was performed. Final follow-up examinations were performed between 6 and 45 months postoperatively (median 13.8 months, mean 17.8 months). 68% (36/53) of the patients were males and 32% (17/53) were females. The age of the patients ranged from 25 to 82 years of age (median 58.3 years, mean 55.8). In all cases the diagnosis of RRD was confirmed before or during surgery. Excluded from this series were patients with retinal detachment secondary to trauma, redetachments, cases in which no retinal hole could be found before or during surgery, patients with diabetes mellitus or a history of uveitis, and patients with a follow-up period of less than 6 months.

Preoperative refraction ranged from -16.0 to +0.5 diopters (dpt; median -2.75 dpt, one case of aphakia-correction of +3.0 dpt). In 24% (13/53) of all patients, myopia exceeded -6.0 dpt. Visual acuity was between light perception and 1.0 with 81% (43/53) of patients with 0.1 or better and 30% (16/53) with 0.4 or better. A single retinal hole could be found in 57% (30/53), 2 or more holes in 43% (23/53). The locations of the holes were as follows: 67% in the upper temporal quadrant, 17% in the upper nasal, 8% in the lower temporal and 8% in the lower nasal. In 11% (6/53), retinal holes could be detected below

the 4 and 8 o'clock positions. The macula was attached in 55% of cases (29/53); in the remaining 45% (24/53), the macula was detached or partially detached. In 81% (43/53) of all patients, a clear lens was noted preoperatively. Preoperative cataract formation could be observed in 13% (7/53). Two patients had undergone cataract surgery with implantation of a posterior chamber lens; in one case of Marfan's syndrome, a lensectomy without implantation of an intraocular lens had been performed due to subluxation of the clear lens.

In two cases, SBS was interrupted and PPPV was performed due to insufficient intraoperative reattachment. In one patient, photocoagulation of a retinal break had been performed before retinal detachment. Not included in this series were 36 cases of vitrectomy without additional buckling and a follow-up of less than 6 months, 21 cases in which vitrectomy was combined with scleral buckling surgery and 12 cases in which silicone oil was used for internal tamponade.

7.1.2. Indications and techniques of PPPV

The decision for primary vitrectomy without scleral buckling was based on the surgeon's individual preferences. Preoperative findings included large retinal breaks, breaks with marked vitreous traction, unusual shape of breaks associated with lattice degeneration or radial extension posterior to the equator, multiple retinal breaks, vitreous haemorrhage, bullous detachment, preoperative PVR and insufficient visibility of the fundus due to dense cataract or secondary cataract and miosis in pseudophakic eyes (Table 8).

In all cases, standard 3-port vitrectomy with cryo- or laser treatment of retinal breaks and fluid-gas exchange was performed under general anaesthesia. In 42% (22/53), the flap of the retinal break was removed. In 21% (11/53) perfluorodecalin or perfluorooctan were used to unfold the detached retina. In one case, a retinotomy for internal drainage of subretinal fluid was necessary. The retinal breaks were treated with exocryo in 57% (30/53), endocryo in 24% (13/53), exo- and endocryo in 15% (8/53), exocryo and endolaser in 2% (1/53) and endolasercoagulation in 2% (1/53). After fluid-air exchange,

a 30%-40% SF₆-air mixture was used for internal tamponade. In 2 cases with dense cataract, a lensectomy was performed.

	All patients (n=53)	Redetachment (n=19)
Unusual break (marked vitreous traction, lattice degeneration)	68% (36/53)	63% (12/19)
Large breaks	60% (32/53)	58% (11/19)
Break extension posterior to the equator	58% (31/53)	63% (12/19)
Single break	57% (30/53)	58% (11/19)
Macula attached	55% (29/53)	58% (11/19)
Macula detached	45% (24/53)	42% (8/19)
Multiple breaks	43% (23/53)	42% (8/19)
Vitreous haemorrhage	24% (13/53)	26% (5/19)
Myopia > -6.0 dpt	24% (13/53)	16% (3/19)
Bullous detachment	17% (9/53)	5% (1/19)
Preoperative PVR	9% (5/53)	21% (4/19)
Breaks below 4 to 8 clock hours	11% (6/53)	16% (3/19)

Table 8: Preoperative characteristics of patients in series 1

7.1.3. Results

After one operation, the retina was reattached at the final follow-up in 64% (34/53) of all patients. The success rate was 89% (47/53) after 2 operations (46 patients) and 92% (49/53) after 3 operations. In a further three cases, the retina was attached at final examination with intraocular silicone oil tamponade; these cases were not included in the calculation of the final success rate. In one case, the retina remained partly detached despite a 4th surgical intervention due to severe PVR.

Redetachment after the first procedure was believed to be due to new or previously undetected retinal breaks in 74% (14/19) of redetachments (see figure 2), to PVR in 16% (3/19) and to insufficiently closed breaks in 10% (2/19). 84% (16/19) of redetachments were diagnosed within the first three postoperative months. The remaining 3 redetachments occurred 4, 12 and 42 months after the initial procedure. Preoperative findings of patients with redetachments are listed in Table 1.

Intraoperative complications included one case of combined pre- and subretinal bleeding, probably due to rupture of a retinal vessel, during exocryo treatment. This complication occurred during scleral buckling surgery and the decision for vitrectomy was made following this complication. In two other cases, an iatrogenic retinal hole was

created during intraocular manipulations. In one case, retinal incarceration in a sclerotomy site was noted. During one vitrectomy-revision, a severe choroidal haemorrhage occurred which made a third intervention necessary.

Postoperative complications included a markedly elevated intraocular pressure necessitating partial drainage of intraocular gas in one case. New retinal holes that were treated with cryo- or lasercoagulation occurred in 9% (5/53) patients; in 2 of these cases, a redetachment developed subsequently. In a further 2 of the 5 patients occurrence of the new break followed redetachment surgery. Macular pucker occurred in 11% (6/53), 3 of which developed after redetachment surgery.

PVR causing retinal redetachment was noted in 6% (3/53). In 1 patient, preretinal membranes with circumscribed wrinkling of the retinal surface could be seen but remained stable and did not lead to a redetachment during the follow-up period.

Of all patients with a clear lens preoperatively, 86% (37/43) developed a significant nuclear cataract during follow-up compared to the fellow eye and/or preoperative staging (see figure 3); in 41% (15/37) of these patients with significant postoperative cataracts additional surgery for retinal redetachment had been performed during follow-up.

The median age of patients with a clear lens preoperatively was 55.3 years. Cataract formation could be noted in 76% (15/ 21) of patients younger than 55 years and in all patients (22/22) older than that. In 28% (12/43) of patients with a clear lens preoperatively, cataract surgery was performed during the follow-up period (7 cases cataract surgery with implantation of an intraocular lens, 5 cases lensectomy during redetachment intervention). All 7 patients with preoperative cataracts underwent cataract surgery during follow-up (2 vitrectomy combined with lensectomy). The mean time interval between vitrectomy and cataract-surgery was 15.4 months.

Operations for redetachment included revision of vitrectomy with SF₆ tamponade in 8 cases; vitrectomy revision, SF₆-tamponade plus encircling band in 7 cases; encircling band or segmental episcleral buckle in 2 cases; and vitrectomy revision, silicone oil tamponade plus encircling band in 2 cases. Of 6 cases with a second redetachment, silicone oil tamponade plus encircling band was performed in 4 cases; gas-tamponade in one case and an encircling band in one case. One retina remained partly detached

despite a fourth intervention due to severe choroidal haemorrhage during the first reoperation and subsequent PVR. Silicone oil removal without further redetachment could be performed in 3 cases during the follow-up period.

Postoperative visual acuity was between light perception and 1.0 with 75% (40/53) of patients with 0.1 or better and 41% (22/53) with 0.4 or better (Table 9). Details of visual acuity according to pre- and postoperative characteristics are listed in Table 2 and Figure 4. Visual acuity of less than 0.1 occurred in 25% (13/53) of all patients. This was thought to be due to a combination of dense cataract and macular dysfunction in 5 cases, to dense cataract in 2 cases, to pre-existent macular degeneration in 2 cases, to macular pucker in one case and to persistent retinal detachment in one case. In 2 cases, no obvious reason for a visual acuity of less than 0.1 could be detected.

In 15 of 18 patients with a visual acuity between 0.1 and 0.4, nuclear cataract was judged to be the main factor responsible for decreased visual acuity; further reasons for a decreased acuity included presumed macular dysfunction in 2 cases with retinal redetachment, one case of macular pucker and one case of amblyopia.

	n	Postoperative visual acuity	
		≥0.1	≥0.4
All patients	53	75% (40/53)	41% (22/53)
Phakic at final examination	31	71% (22/31)	29% (9/31)
Cataract surgery	22	77% (17/22)	59% (13/22)
Macula attached	29	83% (24/29)	38% (11/29)
Macula detached	24	67% (16/24)	46% (11/24)
No redetachment	34	91% (31/34)	56% (19/34)
Redetachment	19	47% (9/19)	16% (3/19)

Table 9: Postoperative visual acuity in series 1

7.2. PPPV at the CCBF 1994-2004 (series 2)

7.2.1. Patients and methods

Surgical protocols of all patients with a RRD treated at the Department of Ophthalmology, Charité Campus Benjamin Franklin, between July 1994 and June 2003 were identified in the hospital database (FileMaker Pro 4.1). Patients with retinal

redetachments, proliferative diabetic retinopathy, previous vitreoretinal surgery (except laser-photocoagulation or cryopexy for retinal breaks), history of ocular trauma or recurrent uveitis were excluded from analysis. None of the patients of series 1 was included in series 2.

A retrospective chart review of all identified patients treated with PPPV was conducted. If the documented follow-up period within the hospital charts was less than 3 months, the patient and the treating ophthalmologist were contacted and a standardized questionnaire was sent to the ophthalmologist. The questionnaire included questions about all relevant data (e.g. re-operations, visual acuity, retinal situation) that was extracted from the patients' files with a follow-up of 3 months or more within the hospital charts. If no information about the follow-up beyond 3 months could be obtained either by chart review or questionnaire, the patient was not included into the analysis.

In all cases, a standard three-port system pars plana vitrectomy was performed under general anaesthesia. The surgical technique consisted of a central and peripheral vitrectomy that released the vitreous traction around the breaks, and removal of the flap of the retinal tear to reduce persistent traction on the break in some cases. The vitreous base was removed as far as possible using external indentation. Drainage types of subretinal fluid were internal, external drainage and combination of both, or a retinotomy for internal drainage of subretinal fluid if necessary; a 20% -40% SF₆-air mixture or silicone oil were used for internal tamponade. Exo-, endocryopexy or endolaserphotocoagulation were used to create chorioretinal adhesions. An encircling band or local buckle were used in some cases. Perfluorodecalin or perfluorocetan could be applied to unfold the detached retina. In addition to the basic vitrectomy technique, combined cataract surgery was also performed in the patients with significant cataract. The indication for primary vitrectomy, the choice of tamponade, the use of additional scleral buckling and the type of coagulation method were based on the surgeons' individual preferences.

The study was carried out during the transition from conventional contact lenses [47] to wide-angle viewing systems [90] in our department. From 1994 to 1997, all cases were operated on with the conventional lenses. Three out of ten surgeons left the department

in 1997 and 1998 and started using wide-angle viewing systems only in their new departments (cases not included). Three surgeons continued to use contact lenses throughout the study. The remaining four surgeons started their surgery using contact lenses but almost immediately switched to wide-angle viewing systems during the study. However, it was not recorded in the surgical protocol which system was used for intraoperative visualization of the retina.

7.2.2. Pre-, intra- and postoperative assessment and outcome measures

The preoperative variables which were recorded included age, sex, symptoms, best-corrected visual acuity (VA), refractive error, intraocular pressure (IOP), lens status (phakia, aphakia/pseudophakia), extent location of retinal detachment (4 quadrants), macular status (macular on/off), macular diseases (macular pucker, hole /degeneration and submacular blood), retinal breaks (location, number and size, breaks not seen), proliferative vitreoretinopathy (PVR), vitreous haemorrhage (VH), retinal tear, a history of laser photocoagulation or cryocoagulation and other eye diseases.

Intraoperative variables recorded included vitreoretinal surgeon, intravitreal tamponade (20% ~40% SF6-air mixture or silicone oil), placement of an encircling buckle or local buckle, situation of retinal breaks, use of endo-/exocryopexy, endolaserphotocoagulation and perfluorodecalin, removal of the flap of the retinal break, drainage of subretinal fluid (internal, external or both), retinotomy, combined lens surgery, complications (iatrogenic holes, lens touch, subretinal, vitreous or choroidal bleeding), change of operating method and reasons for it.

The postoperative variables were follow-up time, initial and final anatomic success rate, best-corrected visual acuity, changes in refractive errors, causes of postoperative visual acuity below 0.4, IOP, complications (cataract progression, macular pucker, PVR, vitreous haemorrhage), number and causes of retinal redetachment and subsequent surgical interventions for recurrence of retinal detachment or retinal breaks, additional cataract surgery, and other ocular surgery.

The outcomes of rhegmatogenous retinal detachment surgery were evaluated using six main points: (1) best visual acuity during the follow-up period; (2) final visual acuity, best-corrected visual acuity at the last follow-up time, both of them irrespective of any intermediate cataract surgery; (3) initial anatomic success rate, irrespective of any prophylactic manipulation that reattaches the retina or ensures its attachment e. g. laser- or cryocoagulation for retinal break; (4) final anatomic success rate, any kind of reoperation permitted; (5) postoperative occurrence of PVR, irrespective of any reoperation; and (6) postoperative occurrence of macular pucker.

7.2.3. Statistical analysis

Statistical analysis was performed using the SPSS software 10.0 (SPSS Inc, USA). Data relating to 46 pre-, per-, and postoperative variables were studied. Descriptive statistics are given as mean and standard deviation, median and range for continuous data. All items were analysed as categorical variables. Survival time of retina was calculated from the date of the operation to the date of retinal re-detachment or last follow-up, and survival curves were constructed using Kaplan-Meier method. The risk factors initial and final retinal reattachment, best and final visual acuity, macular pucker and postoperative PVR were analysed with univariate by Pearson chi-square test or Fisher exact test and multivariate using a logistic regression model. A forward stepwise fashion was used, with variables being added to the model according to a partial likelihood ratio test using an entry criterion of $p < 0.10$. A p -value of ≤ 0.05 was considered to be significant.

Statistical analysis of visual functional outcome, retinal reattachment status, macular pucker and postoperative PVR was carried based on the data obtained from patients with clinical visits up to the last follow-up examination (from 3 to 108 months).

Visual acuity was measured with a Snellen visual acuity chart. For purposes of statistical analysis, visual acuity were divided into three groups: Group 1: VA range from no light perception (NLP) to 0.05 were grouped into group 1, Group 2: VA from 0.1 to 0.3 into group 2, Group 3: VA from 0.4 to 1.0 into group 3. IOP was most often measured with the Goldmann applanation tonometer, or occasionally with the Schiøtz tonometer. IOPs were divided into 5 groups. Unusual breaks were defined as any break other than round

holes or horseshoe tears. Retinal tears referred to retinal breaks of three or more clock hours. The presence of PVR was defined as PVR grade B or greater [65]. Macular diseases included macular hole, macular pucker, macular degeneration and submacular haemorrhage. Cataract surgery included phakoemulsification and intraocular lens implantation, lensectomy, posterior capsulotomy, intraocular lens removal and intraocular reposition.

To analyse if the surgical experience of the performing surgeons was a significant factor influencing the outcome, surgeons were firstly divided into two groups depending on their experience: Specialist (more than 100 par plana vitrectomies before entry into this study) and non-specialist. All surgeries of non-specialists were further divided into two groups: “beginners’ surgeries” were defined as the first 30 cases of PPPV of the individual surgeon; “non-beginners’ surgeries” were coded from the 31st PPPV onwards.

7.2.4. Results

Case notes were identified and clinical and surgical data were recorded into a computer database (Filemaker Pro 4.1). A total of 591 eyes of patients with PPPV for RRD were documented. Of these cases, clinical information about a follow-up period of 3 months or more could be extracted from the hospital charts in 410 cases. Through questionnaires, additional information could be retrieved in 112 cases. In total, a follow-up period of 3 months or more could be accomplished in 86.6% (512/591) of all cases treated with PPPV for RRD. The 512 cases included 24 patients with bilateral detachments. Therefore, a total of 488 patients were included, 174 (36%) were female, 314 (64%) were male. The median age was 60 years (range, 12-94).

At study entry, 67 (13%) eyes had a history of peripheral retinal breaks, which were treated with laser- or cryo-coagulation prior to PPPV. Fourty (7.8%) eyes had amblyopia, 28 (5.5%) glaucoma, 11 (2.1%) strabismus. Nine (0.8%) and 127 (24.8%) eyes were aphakic and pseudophakic; 84 (16.4%) eyes were myopic higher than -10 dpt; 75 (14.6%) eyes were found to have vitreous haemorrhage, 298 (58.2%) eyes were operated with a macular detached; 89 (17.4%) eyes had a total retinal detachment.

Sixty-three (12.3%) eyes had a retinal hole posterior to the equator; 118 (23%) eyes had 4 or more breaks; a further 117 (22.8%) had a break 2 clock hours or larger and/or an unusual break (break with irregular edges, not corresponding to a typical horseshoe configuration or round holes); 35 (6.8%) had a retinal tear. Of 77 (15%) eyes without breaks detected before operation, in 54 (70.1%) eyes the breaks were found during operation.

A segmental scleral buckling procedure was performed in 8 (1.6%) eyes, and an encircling band in 133 (26%) eyes. Silicone tamponade was used in 81 (15.8%) eyes. PFCL was used in 355 (69.3%) eyes. A flap of break was removed in 363 (70.9%). A drainage or relaxing retinotomy was performed in 41 (8.0%) eyes. Iatrogenic retinal breaks occurred in 41/512 operations (8%). A lens touch was noted in 42/376 phakic patients (9%) Cataract operation was simultaneously performed in 49 (9.6%) eyes.

The postoperative follow-up period ranged from 3 to 108 months (median, 14.8 months). More than 1 and 2 years follow-up were obtained for 312(60.9%) and 148(28.9%) eyes. At the last follow-up time, silicone remained in 42 (8.2%) of 153 eyes. The relationship between follow-up period and various postoperative outcomes was evaluated. No statistically significant associations were found among any of the anatomic and functional outcomes, PVR and macular pucker analysed. However, initial success rate and percentage of eyes with visual acuity of 0.4 or more gradually increased by follow-up period (Table 10)

The retina was reattached in 362/512 (70.7%) eyes at three or more months follow-up after single operation and 499/512 (97.5%) after one or more operations (Table 10, Figure 5). In 150 (29.3%) eyes the retina re-detached after one procedure, in 126 of them (84%) the re-detachment occurred during three or less months after the initial operation. New breaks were the most important causes of initial retinal re-detachment in 32% (48/150) of patients with re-detachments, followed by a combination of new break and PVR (28.7%), PVR without new breaks (16%), and reopened breaks (11.3%).

Variable	≥3months n=512	>6months n=461	>12months n=312	>24months n=148
Anatomic outcomes				
Initial success rate	362(70.7%)	329(71.4%)	222(71.2%)	110(74.3%)
Final success rate	499(97.5%)	451(97.8%)	305(97.8%)	143(96.6%)
Functional outcomes				
Best VA (median=0.4)				
NLP ↔ 0.05	53(10.4%)	42(9.1%)	30(9.7%)	11(8.5%)
0.1 ↔ 0.3	149(29.1%)	130(28.2%)	75(24%)	31(20.9%)
0.4 ↔ 1.0	310(60.5%)	289(62.7%)	207(66.3%)	106(71.6%)
Final VA (median=0.3)				
NLP ↔ 0.05	88(17.2%)	76(16.5%)	54(17.4%)	24(16.2%)
0.1 ↔ 0.3	177(34.6%)	153(33.2%)	90(28.8%)	36(24.3%)
0.4 ↔ 1.0	247(48.2%)	232(50.3%)	168(53.8%)	88(59.5%)
PVR	86(16.8%)	76(16.5%)	57(18.3%)	20(13.5%)
Macular pucker	113(22.1%)	103(22.3%)	72(23.1%)	32(21.6%)
Cataract surgery	218(42.8%)	210(45.6%)	158(50.6%)	77(51.7%)

Table 10: Anatomical and functional results of series 2

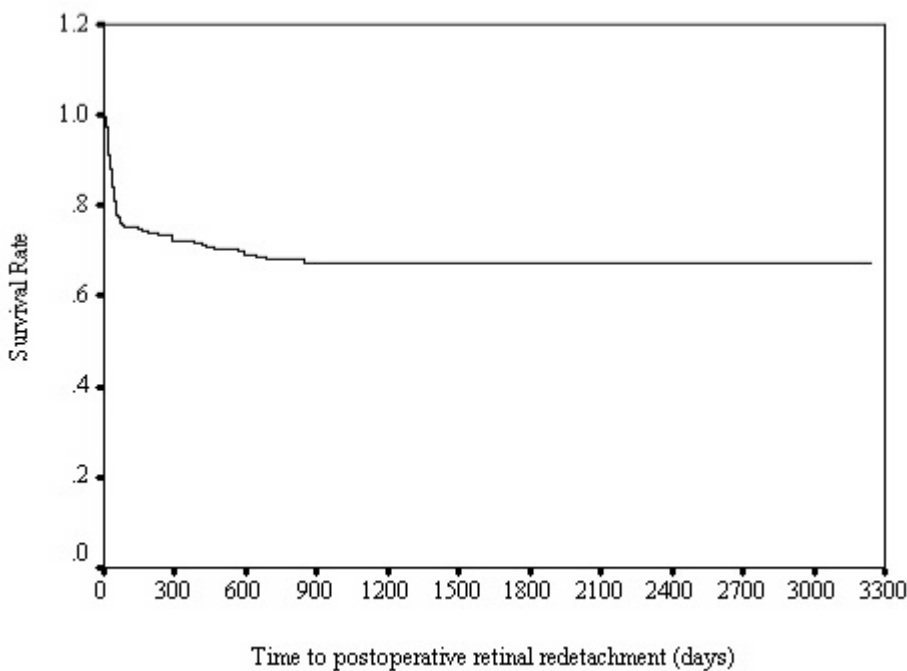


Figure 5: Kaplan-Meier analysis of retinal redetachment (series 2)

Macular pucker was present in 11 eyes (2.1%) preoperatively and 113 (22.1%) postoperatively. PVR was noted in 102 (19.9%) and 86 (16.8%) eyes pre-operatively and postoperatively respectively. Of 102 eyes with PVR pre-operatively, 25 (24.5%)

developed PVR postoperatively. This percentage was significantly higher ($p = 0.026$) compared to eyes without PVR preoperatively.

Of the 376 phakic eyes preoperatively, 22(5.9%) and 10(2.7%) eyes underwent phacoemulsification and IOL implantation and lensectomy during operation, 218 (58%) eyes underwent cataract surgery during the study follow-up interval postoperatively, 126(33.5%) eyes were phakic at the final visit. A retinal redetachment occurred in 80 (36.7%) of 218 eyes, 58 eyes (72.5%) before the cataract surgery, 9 (11.3%) after it and 13 (16.3%) both of it respectively

Postoperative visual acuity was between no light perception and 1.0. A visual acuity of 0.1 or better was measured in 260 (50.8%) eyes pre-operatively, 459 (89.6%) and 424 (82.8%) eyes at any and final visit postoperatively; 0.4 or better in 158 (30.9%) eyes preoperatively, 310 (60.5%) and 247 (48.2%) eyes at any and final visit postoperatively. Compared with preoperatively, postoperative best visual acuity improved in 271 (52.9%) eyes, remained in 211 (41.2%), and worsened in 30 (5.9%) eyes; final visual acuity in 236 (46.1%), 211 (41.2%) and 65 (12.7%) eyes respectively. Of the 252 (49.2%) eyes with visual acuity of 0.05 or less preoperatively, 203 (80.6%) and 182 (72.2%), 110 (43.7%) and 87 (34.5%) improved to 0.1 or better and 0.4 or better at any and final visit post-operatively. Final visual acuity of less than 0.1 occurred in 88 (17.2%) of all eyes. Presumed macular dysfunction in an attached retina and clear media, occurring in 28 (31.8%) of 88 eyes, was the most common reason. Postoperative optic nerve head atrophy was noted in 10 (11.4%) of 88 eyes

A retinal redetachment was detected 4 days to 28.1 months (mean \pm SD, 2.8 \pm 4.8 months, median, 36 days). A retinal survival time was 4 days to 108 months (mean \pm SD, 74.2 \pm 2.4 months, 95% CI, 69.5~78.9).

All recorded pre- and intraoperative factors were entered into statistical analysis regarding primary and final anatomical success and postoperative visual acuity. The factors that were defined to be significant ($p < 0.05$) are displayed in Table 11.

Variable	Redetachment after 1 st operation	Redetachment at final visit	Final visual acuity < 0.1
Duration of symptoms			0.001 †
Lower level of initial visual acuity			< 0.001 † < 0.001 *
Higher level of myopia		0.015 *	0.003 † 0.034 *
Amblyopia		< 0.001 † 0.001 *	< 0.001 † < 0.001 *
IOP < 22mmHg	0.028 †		0.046 †
Macula detached			< 0.001 †
Preoperative PVR ≥ Grade B			< 0.001 †
Number of quadrants detached		0.004 †	< 0.001 †
Inferotemporal quadrant detached	0.033 † 0.027 *	0.038 †	< 0.001 †
Inferonasal quadrant detached		0.021 †	< 0.001 †
No break seen preoperatively		0.004 †	
Breaks larger > 1 clock hour	0.009 *		
Breaks posterior to the equator		0.018 †	< 0.001 † < 0.006 *
Surgeon			0.002 †
Specialist surgeon	0.033 *		0.003 †
Endocryotherapy	0.007 †	0.031 †	
Combined scleral buckle		0.011 *	< 0.001 † < 0.001 *
Combined cataract surgery		0.016 †	0.001 †
Retinotomy			< 0.001 †

Table 11: Statistical analysis of series 2

7.3. Dry eye symptoms following vitreoretinal surgery

Dry eye symptoms commonly occur following vitreoretinal surgery. Although this fact has been known to vitreoretinal surgeons since the introduction of PPV, no scientific studies have analysed their occurrence and the morphological changes responsible for these changes. Regarding PPPV, postoperative dry eye symptoms are of practical meaning in many different ways: Firstly, a regular tear film is necessary for a clear optical image. Irritations of this layer will result in decreased visual acuity and visual disturbances. Secondly, moderate to severe dry eye symptoms cause medical problems such as chronic inflammation of the ocular surface, defects of the conjunctival and corneal epithelial layers and pain. Thirdly, the increase in postoperative medications,

ophthalmological examinations and days off work due to severe forms of the disease have a great impact on the financial calculations regarding the overall costs of the surgery performed. In two different studies, we examined the changes of the ocular surface [40] and the overall occurrence of dry eye symptoms following vitreoretinal surgery [42] and compared them to a cohort of patients following ocular tumour therapy.

7.4. Morphological examination of conjunctival specimen

7.4.1. Patients and methods

Biopsies of the superior bulbar conjunctiva were obtained from 141 patients during cataract surgery between 2 weeks and 2 years following retinal surgery (n = 92), radiotherapy for uveal melanoma (n = 20) and from control subjects without previous ocular surgery (n = 29). In all cases of retinal surgery or radiotherapy, the conjunctiva was dissected at the corneal limbus with relaxing incisions parallel to the lid margins and re-sutured with 7-0 vicryl sutures (Johnson & Johnson, Brussels, Belgium).

In the retinal surgery group (n=92), the initial surgery consisted of 75 pars plana vitrectomies, 10 pars plana vitrectomies combined with scleral buckling surgery and 7 scleral buckling surgeries. Indications for retinal surgery were retinal detachment (51/92), macular hole (12/92), macular degeneration (8/92), proliferative diabetic retinopathy (11/92), idiopathic epiretinal gliosis (8/92) and endogenous fungal endophthalmitis (2/92). Additional surgeries consisted of either pars plana vitrectomies or surgical revisions of pars plana vitrectomies. A total of one surgical intervention was performed before biopsy in 62 of these 92 patients, two surgeries in 19 of 92, three surgeries in 8 of 92, and four surgeries in the remaining 4 of 92 patients.

In the tumour therapy group (n=20), patients with choroidal melanomas were treated either with ruthenium106- or iodine125-brachytherapy. The surgical manipulations involved fixation of the plaque on the scleral surface and plaque removal in a second operation in all patients. In two patients, additional photocoagulations of the ciliary body with a diode-laser were performed. In another patient, a pars plana vitrectomy was performed for retinal detachment following treatment of the choroidal melanoma. The

radiation applied varied between 200 and 1300 Gy (median 455) at the sclera, and 51 and 129 Gy (median 100) at the tumour apex (Table 12).

	N	Gender: male/female	Age range / median (years)	Number of previous surgeries range / median	Time interval 1st surgery-biopsy / median (months)	Time interval last surgery-biopsy / median (months)
All patients	141	64 / 77	22-85 / 64	0 – 4 / 1	0 – 248 / 9	0 – 96 / 8
Controls	29	14 / 15	23-84 / 69	0	0	0
All operated patients	112	50 / 62	22-85 / 63	1 – 4 / 1	0.5 – 248 / 12	0.5 – 96 / 10
Retinal surgery	92	39 / 53	22-85 / 63	1 – 4 / 1	0.5 – 248 / 11	0.5 – 96 / 8
Tumour therapy	20	11 / 9	29-80 / 56	2 – 4 / 2	1 – 69 / 21	0.5 – 69 / 18

Table 12: Patient characteristics, morphological examination

In all 141 patients, specimens of superior bulbar conjunctiva were obtained with minimal trauma from the edge of the conjunctival flap during cataract surgery. Specimens were, therefore, obtained from the same conjunctival region, eliminating the risk of regional differences in cellularity, particularly important for goblet cells. Specimen size varied from 3-5mm². The biopsy specimens were fixed immediately in 4% buffered formalin and embedded in paraffin. Conventional histological stains included hematoxylin and eosin (HE), periodic-acid Schiff (PAS) and Van-Giesson for elastin fibres (ELA). Additional slides were stained for immunohistochemical studies using several monoclonal antibodies that are reactive in paraffin sections. An antigen retrieval method using a pressure cooker was performed before immunohistochemical staining [71]. The staining consisted of a first-stage incubation with the following primary monoclonal antibodies: MUC1 (E29, DAKO), MUC5AC (Chemicon), Tenascin-C and syndecan-1 (CD138, MI15, Pharmingen). The antibodies were made visible with an indirect immunoperoxidase method for MUC1, whereas the alkaline phosphatase anti-alkaline phosphatase (APAAP) method was used to demonstrate the binding of the remaining antibodies [20].

For each specimen, the degree of stratification of the epithelium was graded as follows: 0 = none (4-6 epithelial layers); 1 = mild (7-8 epithelial layers); 2 = moderate (9-10 epithelial layers); and 3 = severe (>10 layers with or without associated acanthosis). The number of goblet cells were counted, using both the PAS and MUC5AC stains, per 3-5

250x power fields (depending on the size of the specimen), and the average obtained. In addition, the intensity of the MUC5AC stain was graded: 0= none; 1 = mild; 2 = moderate; and 3 = strong. The presence of inflammatory cells within the conjunctival stroma was graded using the HE and PAS stains: 0 = none; 1 = mild; 2 = moderate; and 3 = severe. The degree of fibrosis was evaluated using the ELA stain as follows: 0= none; 1 = mild; 2 = moderate; and 3 = severe. As MUC1 is not positive in the basal layer of the conjunctival epithelium using the E29 antibody, the intensity of the MUC1 stain was graded as follows: 0 = none; 1 = weak in all layers except the basal layer; 2 = moderate in all layers except the basal layer; 3 = strong in all layers except the basal layer; 4 = weak patchy (i.e. weak only in the upper layers); and 5 = moderate patchy (i.e. weak only in the upper layers). The degree of syndecan-1 expression was graded as follows: 0 = none; 1 = mild in all layers; 2 = moderate in all layers; 3 = strong in all layers; 4 = weak patchy; and 5 = moderate patchy. The presence or absence of TN-C staining in the conjunctival epithelium, in the subepithelial collagen layer, in the conjunctival stroma and/or in the conjunctival blood vessels was noted.

Regarding the statistical analysis, univariate hypotheses about distributional differences in ordinal-scaled outcome variables over treatment groups (retinal surgery, radiotherapy, control) were tested by means of Kruskal-Wallis and Wilcoxon rank sum tests. Pairwise association of categorical variables was assessed by Fisher's exact test. Multivariate association of outcome variables (dichotomised, if required) with treatment group, gender, age, number of previous surgeries, time interval 1st surgery-biopsy and time interval last surgery-biopsy were investigated by means of stepwise (forward) multiple logistic regression analysis or stepwise multiple linear regression analysis (for number of Becher-cells only). All statistical analyses were performed using the statistical software SPSS for Windows, Release 9.0.1. Only statistical significant (i.e. $p < 0.05$) results are presented. Exact p-values are given if available. Results are not adjusted for multiple testing.

7.4.2. Results

The conjunctival specimens from the control patients demonstrated either no or mild stratification of the conjunctival epithelium. The mean number of goblet cells per 250x power field was 21.4. The degree of fibrosis in the control specimens was at the most mild. Occasional lymphocytes, mast cells and plasma cells were seen in the conjunctival stroma. TN-C expression was limited to the subepithelial collagen layer and to the conjunctival blood vessels when present in the specimen. Syndecan-1 expression was seen in all layers of the conjunctival epithelium, however, the basal layers demonstrated the strongest staining. Moderate to strong MUC1 staining was observed in all epithelial layers except for the basal cell layer; it was not observed in goblet cells. MUC5AC, in contrast, was observed only in the goblet cells with moderate to strong intensity.

The conjunctival specimens from the patients who had previously undergone vitrectomy demonstrated moderate stratification of the conjunctival epithelium, with an increase in the number of basal cells. The mean number of goblet cells was reduced to 10.1 per 250x power field, varying between 0 and 28 cells. Moderate fibrosis was seen in the conjunctival stroma. The inflammatory cells within the conjunctival stroma were not significantly increased compared to normal specimens. Alterations in the distribution of TN-C staining were observed: in the majority of the specimens, the subepithelial collagen layer was present but was accompanied by faint “speckled” or granular cytoplasmic staining within the stratified conjunctival epithelial layers. In some specimens, the subepithelial collagen layer was negative for TN-C despite repetition of staining. Further, syndecan-1 expression in the conjunctival epithelium altered slightly with increased positivity being observed in all epithelial layers, without a graduation from the basal to the upper layers as seen in the control specimens. Subsequent changes in MUC1 expression were also observed, with only the upper layers of the epithelium being positive for this marker. The intensity of the MUC5AC expression in the goblet cells did not differ significantly from the control specimens.

The conjunctival specimens from the patients who had undergone brachytherapy for uveal melanoma demonstrated a moderate to severe degree of stratification with, in some patients, obvious acanthosis. An increase in inflammatory cells in the conjunctival stroma was not present. Similar re-distributions in MUC1, syndecan-1 and TN-C

stainings as those seen in the conjunctival specimens following retinal surgery were observed in those conjunctival specimens following brachytherapy. The number of goblet cells varied between 0 and 18 per 250x power field, with an average of 3.1.

Analysis of variance based on ranks				
	Any difference between groups*	Retinal surgery vs. Control**	Radiotherapy vs. Control**	Retinal surgery vs. Radiotherapy**
Stratification	< 0.001	< 0.001 (rs > c)	< 0.001 (rt > c)	ns
Degree of GC loss	< 0.001	< 0.001 (rs > c)	< 0.001 (rt > c)	< 0.001 (rs < rt)
GC number	< 0.001	< 0.001 (rs < c)	< 0.001 (rt < c)	< 0.001 (rs > rt)
Fibrosis	< 0.001	< 0.001 (rs > c)	< 0.001 (rt > c)	0.030 (rs < rt)
Syndecan-1	0.041	0.013 (rs > c)	ns	ns
MUC1	< 0.001	< 0.001 (rs > c)	< 0.001 (rt > c)	ns
MUC5AC	< 0.001	< 0.001 (rs < c)	< 0.001 (rt < c)	0.003 (rs > rt)
Statistical association				
	p-value from exact Fisher test			
TN-C control vs. treatment group	0.019			

Table 13: Statistical analysis, morphological examination

Multiple logistic regression				
		Coefficient	Standard error	p-value (Wald)
Degree of GC loss (dichotomisiert: Value 0, 1 vs. 2, 3)	Constant term	0.228	1.116	ns
	rs vs. C	2.517	0.598	< 0.001
	rt vs. C	4.706	1.171	< 0.001
	Age	- 0.034	0.017	0.043
MUC1 (dichotomisiert: Value 0-3 vs. 4, 5)	Constant term	- 1.283	0.491	0.009
	rs vs. C	4.046	0.797	< 0.001
	rt vs. C	6.091	1.365	< 0.001
	n_ops	- 0.824	0.287	0.004
	Gender	0.921	0.472	ns (0.051)
	Postoperative period	- 0.038	0.019	0.043
MUC 5AC (dichotomisiert: Value 0-2 vs. 3)	Constant term	- 0.369	0.993	ns
	rs vs. C	- 1.715	0.546	0.002
	rt vs. C	- 2.832	0.759	< 0.001
	Age	0.031	0.014	0.029

Table 14: Multivariate logistic regression, morphological examination

All statistical significant results found and details of significant models investigated are presented in Table 13 and Table 14. It can be seen from the first column in Table 13 that there were statistically significant differences for the parameters evaluated according to the Kruskal-Wallis test. Further, comparison between conjunctival specimens following retinal surgery and control specimens, between those following radiotherapy and controls, as well as between the two post-therapeutic groups demonstrated statistically

significant differences using the Wilcoxon test. In particular, both retinal surgery and radiotherapy lead to a significant increase in stratification of the conjunctival epithelium, goblet cell loss, fibrosis of the conjunctival stroma and alterations in both MUC1 and MUC5AC staining distribution. Comparison between conjunctival specimens following radiotherapy and retinal surgery demonstrated that the former therapeutic measure resulted in the greatest goblet cell reduction (evaluating both PAS and MUC5AC stains) and stromal fibrosis. There was no significant difference in MUC1 staining between the two post-therapeutic groups. Only retinal surgery lead to significant changes in syndecan-1 staining patterns. A statistical association in TN-C alterations was observed in the radiotherapy group compared to the control group using the exact Fisher test. Using multiple logistic regression the statistical significance of the parameters “degree of GC loss”, “MUC1-staining” and “MUC5AC-staining” between the post-therapeutic groups and controls were confirmed (Table 14). It can also be seen that both GC loss and MUC5AC staining was age dependent, whereas MUC1 staining was dependent on the number of operations performed as well as on the length of the post-therapeutic period.

7.5. Dry eye symptoms following vitreoretinal surgery

7.5.1. Patients and methods

A total of 334 eyes (194 patients) were included into this study. Patients were divided into 3 groups: Group 1: eyes following vitreoretinal surgery or ocular tumour therapy (n=140). Between one and six operations were performed in these patients (median 2). The timer interval between the last operation and the examination was between 6 and 92 months (median 16 months). Patients were divided into two age groups according to the questionnaire; 17% (24/141) were ≤ 45 years and 83% (117/141) > 45 years. There were 54% (76/140) females and 46% (64/140) males. Vitreoretinal surgeries included PPPV and SBS for RRD as well as PPV for macular hole and diabetic retinopathy (subgroup 1a, n=31). Patients treated with Ruthenium¹⁰⁶-brachytherapy (subgroup 1b, n=76) rereceived a radiation dose between 200 und 1300 Gy at the sclera. Patients receiving proton beam radiation had an initial operation to mark the tumour edges with

clips sutured onto the sclera and then received proton beam radiation with an energy of 60Gy (subgroup 1c, n=33). Group 2: Fellow eyes of eyes in group 1 (n=140). Only patients without previous surgeries of the fellow eyes were included into the study. Group 2 was further divided into subgroups according to group 1. Group 3: Control patients presenting with retinal or ocular tumour diseases but without previous surgeries. In this group, one eye was chosen by randomisation (n=54).

All patients were interviewed with a standardized dry-eye questionnaire of the German Association of Ophthalmologists. In addition, a Schirmer-test following local anaesthesia, measurement of the tear break-up time and a slit-lamp examination were performed. Statistical analysis was performed using SPSS software, version 11.0.1.

7.6. Results

Sixtythree percent of all treated patients versus 40% of the controls complained of dry eye symptoms ($p=0.004$). The tear break-up time was decreased in treated patients ($p<0.001$, medians: 15 vs 20 s). No significant difference was seen on the Schirmer test ($p=0.825$; medians: 12 vs 12 mm). The results are summarized in Figure 6, Figure 7 and Table 15.

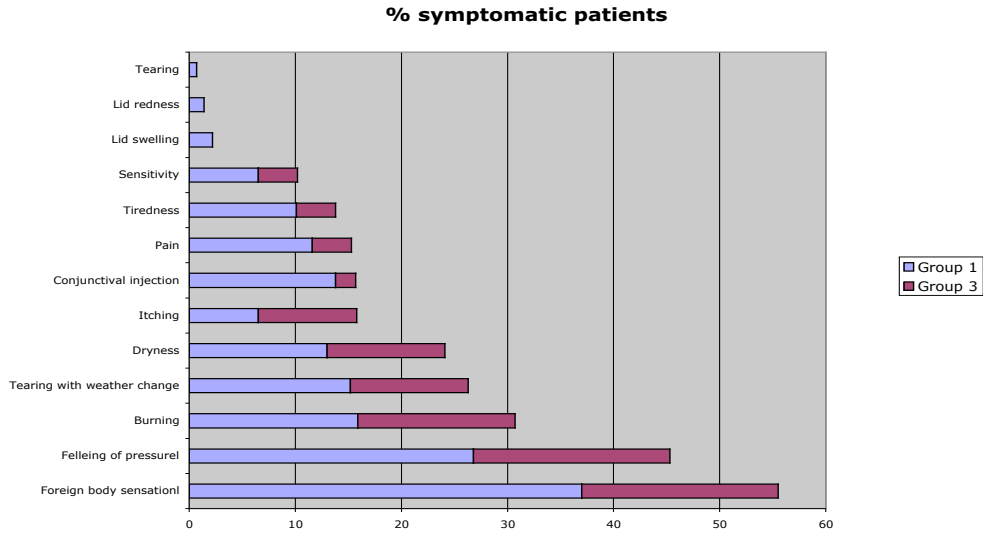


Figure 6: Symptoms and percentage of symptomatic patients

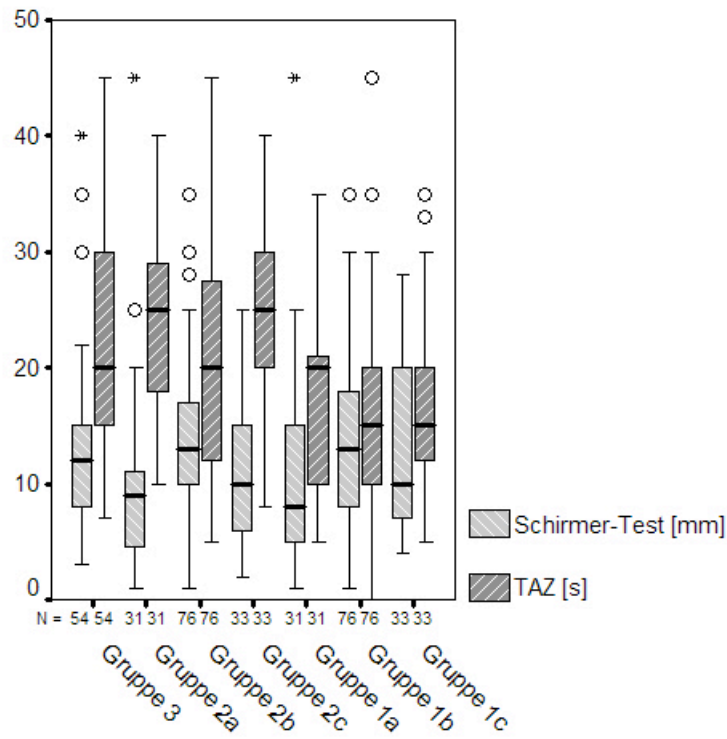


Figure 7: Schirmer-Test and BUT (TAZ) in groups and subgroups (Gruppe=group).

	Group 1 (surgery)	Group 2 (fellow eyes)	Group 3 (controls)	Group 1a (retinal surgery)	Group 1b (plaque)	Group 1c (proton)
n	140	140	54	31	76	33
Symptomatic patients	89 (63,6%)	19 (13,6%)	22 (40,7%)	18 (58,1%)	50 (65,8%)	21 (63,6%)
marked	3 (2,1%)		1 (1,9%)	1 (3,2%)	1 (1,3%)	1 (3,0%)
moderate	14 (10,0%)	5 (3,6%)	2 (3,7%)	1 (3,2%)	11 (14,5%)	2 (6,1%)
mild	72 (51,4%)	14 (10,0%)	19 (35,2%)	16 (51,6%)	38 (50,0%)	18 (54,4%)
never	51 (36,4%)	121 (86,4%)	32 (59,3%)	13 (41,9%)	26 (34,2%)	12 (36,4%)
p* (controls vs treatment)	0,004	<0,001		0,147	0,003	0,044
Conjunctival injection	76 (54,3%)	72 (51,4%)	22 (40,7%)	22 (71,0%)	37 (48,7%)	17 (51,5%)
p** (controls vs treatment)	0,091	0,182		0,007	0,370	0,327

Table 15: Symptoms and conjunctival injection in treated patients vs. controls.
*Mann-Whitney-U, **Chi-Quadrat (2-sided)

7.7. Summary

In two consecutive series of 53 and 512 patients, we examined the results of PPPV at the CCBF. In addition, we studied dry eye symptoms following vitreoretinal surgery in a morphological as well as an additional clinical study. The results can be summarised as follows:

- With PPPV for RRD, primary and final reattachment rates of 64% (34/53) and 92% (49/53) were achieved in series 1 and of 71% (362/512) and 97% (499/512) were achieved; regarding the different inclusion criteria of both series with more complicated situations being included in the second series, this means an improvement of the surgical outcome over the past 10 years
- The vast majority of redetachments (84%) occurred during the first 3 months of follow-up
- Keeping in mind that more complicated situations of RRD were included in these series compared to most published series of PPPV, the functional success rates with 0.4 or better 48% (247/512) are comparable to those of other series of PPPV and compare favourably to the results of SBS

- The most common intraoperative complications were iatrogenic breaks in 8% and lens touch in 9%
- The most common postoperative complications other than redetachment were macular pucker in 22% (113/512) and cataract progression, leading to cataract surgery in 58% (218/512) of initially phakic patients
- The major reasons for anatomical failure in both series were the development of new retinal breaks and PVR associated with new breaks; this finding is in contrast to most series of conventional RRD surgery in which PVR is believed to be the most common reason for failure
- The majority of risk factors identified for postoperative anatomical and functional failure matched those published in the literature of conventional surgery
- The use of endocryotherapy was for the first time identified as a risk factor for postoperative failure
- Regarding the level of surgical training, beginning surgeons achieved results at least results comparable to those of more experienced surgeons
- Dry eye symptoms were identified as a significant postoperative complication following vitreoretinal surgery; one of the reasons for this complication is the loss of goblet cells in the conjunctiva following vitreoretinal surgery and a weakening of the mucin layer of the tear film