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Abstract: Purpose: To identify preoperative parameters that may predict flattening of the keratoconus cornea after corneal crosslinking (CXL).
Setting: Institut für Refraktive und Ophthalmo-Chirurgie (IROC), Zurich, Switzerland.
Methods: In a prospective study, 151 eyes of 151 patients with verified progressive primary keratectasia received standard CXL. Preoperatively and 12 months after CXL among others best spectacle-corrected visual acuity (BSCVA) and Scheimpflug tomography (Pentacam) was used to follow the postoperative evolution. Statistical analysis included U-tests and Spearman rank correlation tests to detect risk-factors for flattening of the keratoconus.
Results: More than 80% completed the 12 month follow-up. The flattening rate (flattening of the maximal curvature > 1D) was 37.7%. A preoperative Kmax-reading of more than 54 dioptres was identified as the only significant risk factor for this effect (odds-ratio 1.88, 95%-confidence interval 1.01 to 3.51). A restriction to corneas with Kmax>54D would have resulted in a significant flattening in 51% of the cases.
Conclusions: A statistically significant flattening during 1 year after CXL occurs in more than 50% of the cases if the preoperative maximal K-reading was more than 54D. None of the other preoperative parameters investigated such as age, gender, diagnosis, BSCVA, and shape factors of the cornea had a statistically significant impact on corneal flattening after CXL.

William J. Dupps, MD, PhD

Associate Editor

Journal of Cataract & Refractive Surgery

Ref.: Ms. No. JCRS-10-999, Regression of keratoconus after cross-linking of the cornea (CXL)

Dear Dr. Dupps

Please find enclosed the revised manuscript including a change in title.

We were able to follow all recommendations of reviewer 1, however, had problems with the desires of reviewer 2. For example, it is ok with me to change the nomenclature of Scheimpflug photography into Scheimpflug tomography because this term describes a new type of information from anterior and posterior surface of the cornea. Corneal topography, however, is in the field since more than 20 years and everybody knows what it is about. To change now the name into a rather questionable better one “Placido imaging” does not make sense and I do not see the advantage.

Nevertheless, also here we followed the majority of the recommendations.

We hope that the current version will be accepted for publication.

Yours sincerely,

Theo Seiler

Professor and Chairman

Flattening of the cornea after corneal cross-linking (CXL) for keratoconus

running head: flattening after CXL

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Setting: Institut für Refraktive und Ophthalmo-Chirurgie (IROC), Zurich, Switzerland.

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Conclusions: A statistically significant flattening during 1 year after CXL occurs in more than 50% of the cases if the preoperative maximal K-reading was more than 54D. None of the other preoperative parameters investigated such as age, gender, diagnosis, BSCVA, and shape factors of the cornea had a statistically significant impact on corneal flattening after CXL.

More than ten years ago, corneal cross-linking (CXL) by means of riboflavin and ultraviolet light was proposed as a therapeutic approach to improve the biomechanical and biochemical properties of the cornea[1,2]. Meanwhile, there is clinical evidence that CXL is a clinically useful operation halting the progression of primary as well as secondary keratectasia with a failure rate of approximately 3% and a complication rate of 1% and less[3-8]. As a positive side effect, in a certain percentage of the eyes treated with CXL a regression of the keratectasia documented by significant flattening of the cornea may occur[3,7] which in rare cases amounts up to more than 10 dioptres[9]. It would be of interest for patients and physicians to identify preoperative parameters that may predict such a flattening.

In this prospective study, in eyes with primary keratectasia the 1 year-results after CXL were analyzed to identify preoperative factors that may predetermine a substantial flattening of the keratectasia.

Patients and Methods

1. Study group and protocol

One hundred and ninety-two eyes of 192 patients with progressive keratectasia were enrolled in this study. Progression of the keratectasia was verified by repeated Scheimpflug tomographies (Pentacam 70700, Oculus, Wetzlar, Germany) over at least 6 months and progression was accepted if the increase in maximal K-reading exceeded 1 dioptre which equals 3 standard deviations[8]. Second eyes were treated not earlier than 6 months after the first one and were not included in the study group. Eyes with maximal K-reading <76.0D (only together with contact lens tolerance) and minimal corneal thickness > 350 µm were included whereas eyes with preoperative corneal opacities were not accepted because Scheimpflug photography may give false results. Additional exclusion criteria were: ocular pathology other than keratectasia, in detail cornea guttata or other endothelial irregularities, history of recurrent erosions, actual or intended pregnancy, non-availability for follow-up examinations during 1 year, and connective tissue diseases. The study protocol was approved by the Ethikkommittee des Kantons Zürich. We differentiated between the diagnoses pellucid marginal degeneration (n=32) and keratoconus (n=103) based on the claw-pattern in corneal topography. In 21 cases, the differentiation between the two diagnoses was not possible. Of the 192 patients only 155 completed the 1 year follow-up (drop out-rate: 19.3%). Additionally, 4 eyes were excluded because of massive remodelling due to stromal scars after CXL[9]. The demographic data of study group is listed in Table 1.

The patients were examined preoperatively, early postoperatively (1 to 3 days until epithelial healing), at 1 month, 6 months, and 12 months after CXL. At every follow-up, except the early postoperative, a standard examination was performed consisting of autorefractometry and autokeratometry (Humphrey Model 599, Zeiss, Jena, Germany), corneal topography (Keratograph C, Oculus, Wetzlar, Germany), Scheimpflug imaging (Pentacam 70700, Oculus, Wetzlar, Germany), manifest refraction using the fogging technique, unaided (UVA) and best spectacle-corrected visual acuity (BSCVA), applanation tonometry, and slit lamp inspection of the anterior and posterior segments of the eyes. At the 1 month follow-up examination the depth of the demarcation line was determined by the slitlamp[10] or by OCT[11].

Patients using rigid contact lenses were asked not to use their lenses for at least 3 weeks before the preoperative examination and for one month after treatment. The lenses had to be removed at least 3 weeks before each follow-up examination.

2. Treatment

Topical anaesthesia of the cornea was obtained using oxybuprocaine and tetracaine alternating every 3 minutes for 15 minutes. After insertion of a lid speculum, a corneal abrasion with a diameter of 9mm was performed followed by the instillation of 0.1% riboflavin drops every 3 minutes for 30 minutes. The riboflavin drops were prepared immediately before the treatment mixing 0.5% aqueous riboflavin solution (Streuli&Co, Uznach, Switzerland) with 20% dextrane T-500 solution (Roth, Karlsruhe, Germany). During the imbibition with riboflavin drops, the thickness of the central cornea using ultrasound was performed. In cases with a central thickness (without epithelium) of less than 400 µm additional 0.1% riboflavin drops without dextrane were applied until the thickness exceeded 400 µm. The eyes were then inspected at the slit lamp to ensure that the riboflavin has arrived in the aqueous (blue light). After this, the eye was irradiated for 30 minutes with UVA with an irradiance of 3 mW/cm^2 (UV-X, Peschkemed Meditrade, Huenenberg, Switzerland). During irradiation, the cornea was moistened every 3 minutes with 0.1% riboflavin drops and oxybuprocaine drops at the patient's discretion. At the end of the procedure antibiotic ointment (ofloxacine 0.3%) was applied and the eye was patched. The patient was asked to use the antibiotic ointment five times a day for three days. After epithelial healing the patients used topical flourometholone twice a day for one week.

3. Numerical evaluation

A significant corneal flattening 1 year after CXL was defined by a decrease in maximal K-reading K_{max} of more than 1 dioptre compared to preoperative. The difference $\Delta K_{max} = K_{max,preop} - K_{max,1\ year}$ was, therefore, the main variable, whereas some preoperative parameters that have been shown to influence the outcome of CXL like age, K_{max}, BSCVA, minimal thickness of the cornea d_{min}, eccentricity of the cone (radial distance between apex and point of highest curvature), asphericity of the anterior corneal shape Q_{ant}, index of surface variance ISV, and the keratoconus index KI[8] were considered secondary parameters. The correlation of these variables with ΔK_{max} and its one-sided significance was calculated using the Spearman rank correlation test. The influence of the digital variables gender (f/m), side (OD/OS), and diagnosis (PMD/KC) was studied using the U-test (Mann-Whitney). The group of patients with significant corneal flattening (ΔK_{max}

>1D) was compared with the total group by means of the odds-ratio algorithm. The odds-ratio of a potential risk factor for regression and its confidence interval was calculated by means of the standard algorithm for a 2x2-table. All calculations were performed with WinSTAT® for Excel (R. Finch Software, 2002). Statistical significance was accepted if $p<0.05$.

Results

Of the 151 eyes receiving CXL with an uneventful postoperative healing phase 57 eyes (37.7%) demonstrated significant flattening of ΔK_{max} >1D. In this flattening group the average flattening was 2.24D compared to 0.89D in the total group (Tab. 3). Twenty eyes (13%) showed a flattening of ΔK_{max} >2D, 91eyes (60.3%) remained stable, and 3 eyes (2%) experienced progression of the keratectasia. The maximal flattening of 7.2D occurred in a 34 years old male. The demographic data shown in Table 1 demonstrate a skew towards male patients, left eyes, and keratoconus. Neither the age of patients in the study group did differ significantly from that of the flattening group ($p = 0.49$) nor did the parameters side ($p = 0.976$), gender ($p = 0.811$), and diagnoses ($p = 0.24$).

Table 2 presents the correlation coefficients of the flattening parameter ΔK_{max} and the preoperative variables. A statistically significant correlation with ΔK_{max} exists only regarding K_{max}, Q_{ant}, eccentricity of the cone and BSCVA.

The comparison of the flattening group with the total study group is demonstrated in Table 3. Only the preoperative parameters K_{max} and Q_{ant} differ statistically meaningful between the 2 groups. To illustrate the significant difference in K_{max} in more detail Fig. 1 compares the relative distributions of K_{max} within the two groups: K_{max}-readings >54D occur more frequently in the flattening group compared with the total study group. To substantiate this impression the odds-ratio algorithm was used and, indeed, "K_{max}>54D" represents a real risk factor for flattening (odds-ratio 1.88, 95%-confidence interval 1.01 to 3.51). If only eyes with K_{max}>54D would have been included in the study the percentage of eyes experiencing significant flattening would increase from 38% to 51%. We could not find a significant risk limit regarding Q_{ant}.

Discussion

The major findings of this prospective clinical study are (1) maximal curvature regressed significantly in approximately 40% within the first year after CXL and (2) the only predictive factor for such flattening is the preoperative curvature K_{max}>54.0D.

Both Wollensak et al.[3] and our working group[8] report a reduction in maximal K-readings after CXL which is confirmed in this study. According to the long term follow up presented by the Dresden group [12] this flattening process may, on average, continue for years. Although the reduction in maximal K-reading by 1 or 2 dioptres may be not enough to rehabilitate visual acuity, the accumulative effect during several years can do so. Moreover, in special cases the flattening effect is much stronger: in Fig.2 the evolution of a corneal shape during the first year after CXL is demonstrated with a flattening of more than 6 diopters at the central cornea.

The flattening parameter ΔK_{max} demonstrated a statistical significant correlation with the preoperative variables maximal curvature K_{max}, corneal asphericity Q_{ant}, eccentricity of the cone and spectacle corrected visual acuity BSCVA. Comparing, however, the group with significant flattening with the total group K_{max} remained the only statistical significant factor (Table 3). Figure 1 depicts the relative distributions of K_{max} within the two groups and it is obvious that corneas with stronger curvature have a higher chance of flattening after CXL. We expected to find other predictive parameters such as age, diagnosis and keratoconus indices, however, none of these variables passed the simple significance test. The risk analysis made it even clearer: K_{max}>54D represents the only statistically significant risk factor for significant flattening after CXL and none of the other factors came close to significance.

In a previous study[7] the risk factor for failure of CXL, defined as a 1 dioptre-increase in K_{max} during the first postoperative year, was K_{max}>58D. The combination of this statistical recommendation and the one presented here creates a relatively narrow band of maximal success between 54 and 58 dioptres of K_{max} where a flattening rate of more than 50% is comes along with a failure rate of less than 1%. In the range of 54D and less one can expect less flattening, however, still a good success rate regarding stabilisation of the keratoconus of more than 99%. In contrast, K_{max}-values of more than 58 dioptres predict more flattening but also more failures which may have to be emphasized during patient counselling.

A topic that needs to be addressed in this discussion is the customized surface ablation to regularize the multifocal shape of the keratoconus cornea as proposed by us[13] and others[14]. So far the reasoning for a simultaneous surface ablation and CXL included the erosion pain to happen only once[14]. A flattening of more than 1 dioptre within the first year after CXL in more than 50% of the cases and even more a flattening of 2 dioptres and more in 13% does, however, decrease the predictability of such a simultaneous operation. Targeting on undercorrection or performing the operations in two steps may be considered as solutions.

In summary, we could show that a statistical significant flattening of the cornea (without scarring) during 1 year after CXL occurs in more than 50% of the cases if the preoperative maximal K-reading was more than 54D. None of the other preoperative parameters investigated such as age, gender, diagnosis, BSCVA, and shape factors of the cornea had a statistically significant impact on regression after CXL.

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Legends

Figure 1

Comparison of the relative incidences of K_{max}-values in the flattening group (black columns) and total study group (white columns). K_{max}-readings of more than 54D occur more frequently in the flattening group.

Figure 2

Temporal evolution of a cornea after CXL within the first postoperative year. The maximal flattening is more than 6 diopters as depicted in the difference map. The reduction of K_{max} is, however, only 3.2 dipters.

Table 1: Demographic data of the study and the flattening group

	study group (n=151)	flattening group (n=57)
age in years (at treatment)	29.3 ± 8.6 , range 12 to 53	28.2 ± 8.4 , range 15 to 46
gender (female : male)	54 : 97	21 : 36
side (OD : OS)	66 : 85	25 : 32
diagnosis (KC : PMD)	103 : 32	43 : 8

Table 2: Correlation of preoperative parameters with the flattening parameter ΔK_{max}

	correlation coefficient	p-value
K_{max}	0.214	0.004
Q_{ant}	-0.149	0.045
eccentricity	-0.141	0.05
BSCVA	-0.136	0.048
age	-0.100	0.110
KI	0.079	0.170
ISV	0.078	0.174
d_{min}/µm	-0.051	0.270

Table 3: Comparison of flattening group and total study group

	flattening group		total study group		difference
	average	STD	average	STD	p-value
ΔK_{max}	2.24	1.42	0.89	1.49	<0.001
K_{max}/D	56.2	6.5	54.3	6.4	0.043
Q_{ant}	-0.88	0.53	-0.72	0.64	0.052
Δ eccentricity/mm	-0.08	0.24	-0.07	0.21	0.082
BSCVA	0.49	0.29	0.55	0.28	0.19
KI	1.28	0.13	1.26	0.14	0.22
ISV	100	40	95	43	0.35
age/years	28.2	8.4	29.3	8.6	0.50
d_{min}/µm	447	39	450	37	0.64
diagnosis	-	-	-	-	0.24

Revision notes

Reviewer No 1

1. We agree that the term „regression“ may be misleading in this context and we changed the term to “flattening” throughout the manuscript.

2. Page 8, Results, 1st paragraph: we stated the average flattening of the total group and the flattening group. In addition, we also present the percentage of eyes with a flattening of 2 and more diopters.

3. Page 11, 2nd paragraph: we discussed the narrow band of optimal outcome of CXL between 54 and 58 D.

Reviewer No 2

General: We disagree. In the publication Ref.8. we reviewed more than 15 Pentacam-parameters and found Kmax to be the most sensitive one. In detail, corneal thickness and posterior float showed such high variations that we had to conclude that any information from the back surface of the cornea after CXL is highly biased. Also, the eccentricity of the point of maximal curvature was not sensitive at all and the interpretation of centralization of the cone after CXL is rather speculative and not substantiated by scientific evidence.

2. We agree and used the “tomography” throughout the paper. We disagree regarding the term corneal topography which is a term used since more than 20 years and is well understood in the scene.

3. Page 4, line 10: D`accord. We added a comment about contact lens tolerance.

4. Pregnancy: According to the vote of the Ethikkommittees patients being pregnant and planning to become pregnant must not be included in the study. The argumentation was clear: in case of complications we might have to use potentially teratogenic steroids and antibiotics and in case of a keratoplasty even general anesthesia.

5. Page 6, 1st paragraph: we stated that in cases of too thin corneas riboflavin solution without dextrane was used to swell the stroma to a thickness exceeding 400 microns.

6. We disagree. As long as there is not a generally accepted definition of PMD and, even more, a generally accepted differential diagnosis of KC vs. PMD we will not accept them as different clinical entities. Please provide scientific evidence that the two diseases are clinically different.

7. We agree that BSCVA (and refraction) are poor parameters, however, it is accepted to evaluate safety of procedures. Including the CL-VA would have given more reliable results but only 50% of the cases were CL-tolerant.

8.Page 5, line 10: “at” is replaced by “by”, 9.Figure 2: Agreed, we changed the figure to a case of the series with more than 2 D flattening.

Thanks for the constructive comments.

***Synopsis**

Significant regression of keratoconus after crosslinking is not dependent on age or gender but only on preoperative maximal curvature.

Figure

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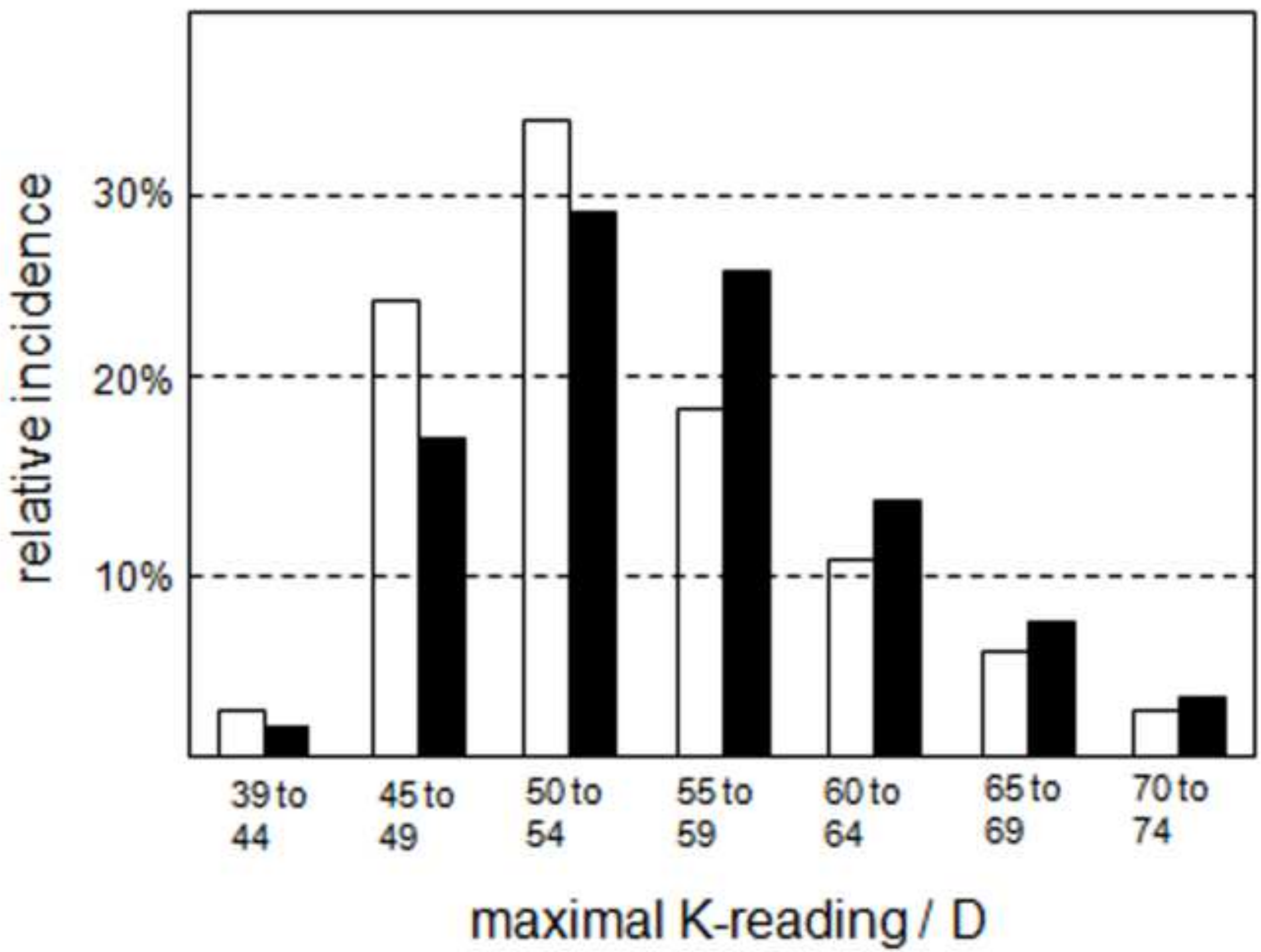

Figure
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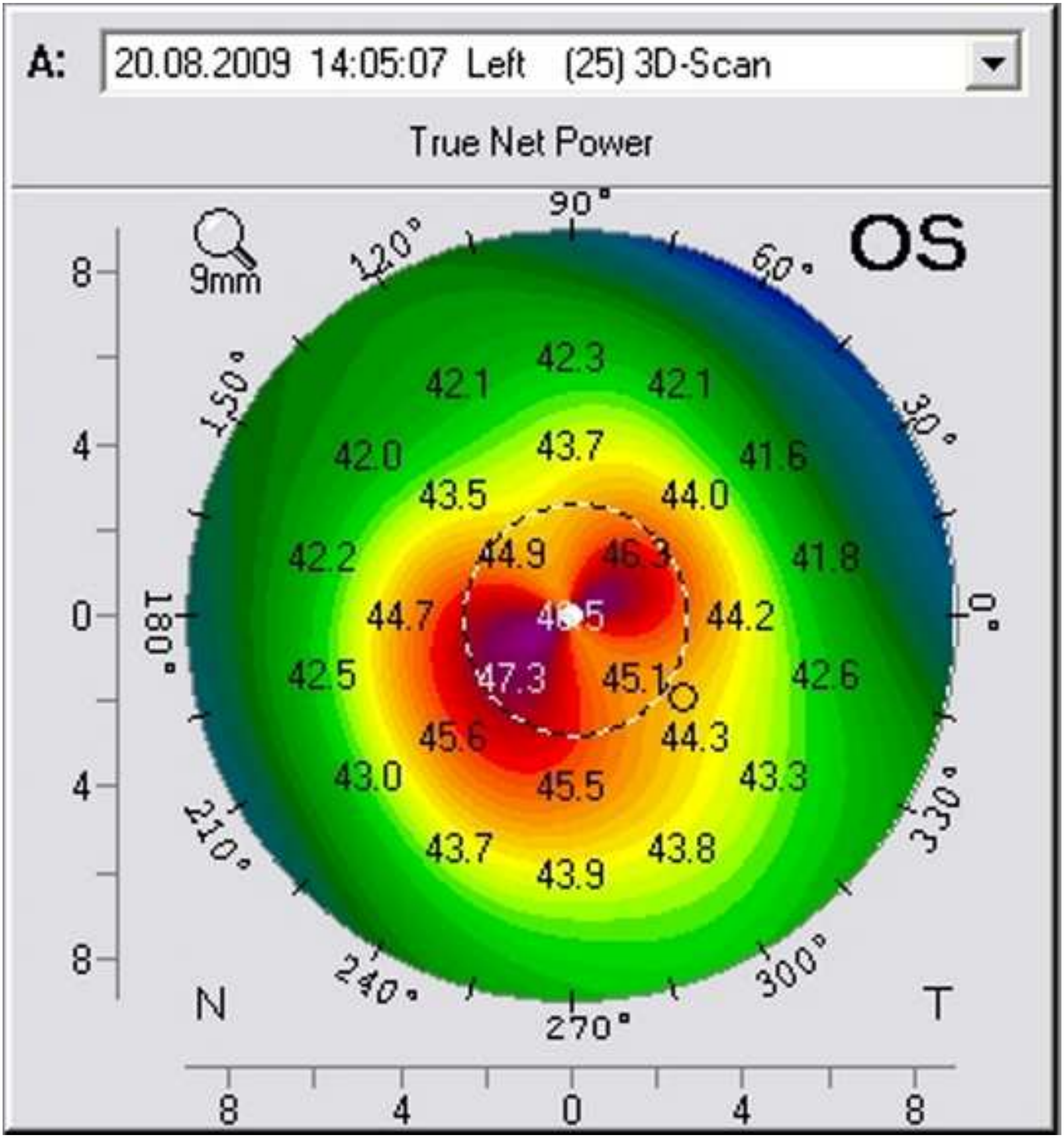

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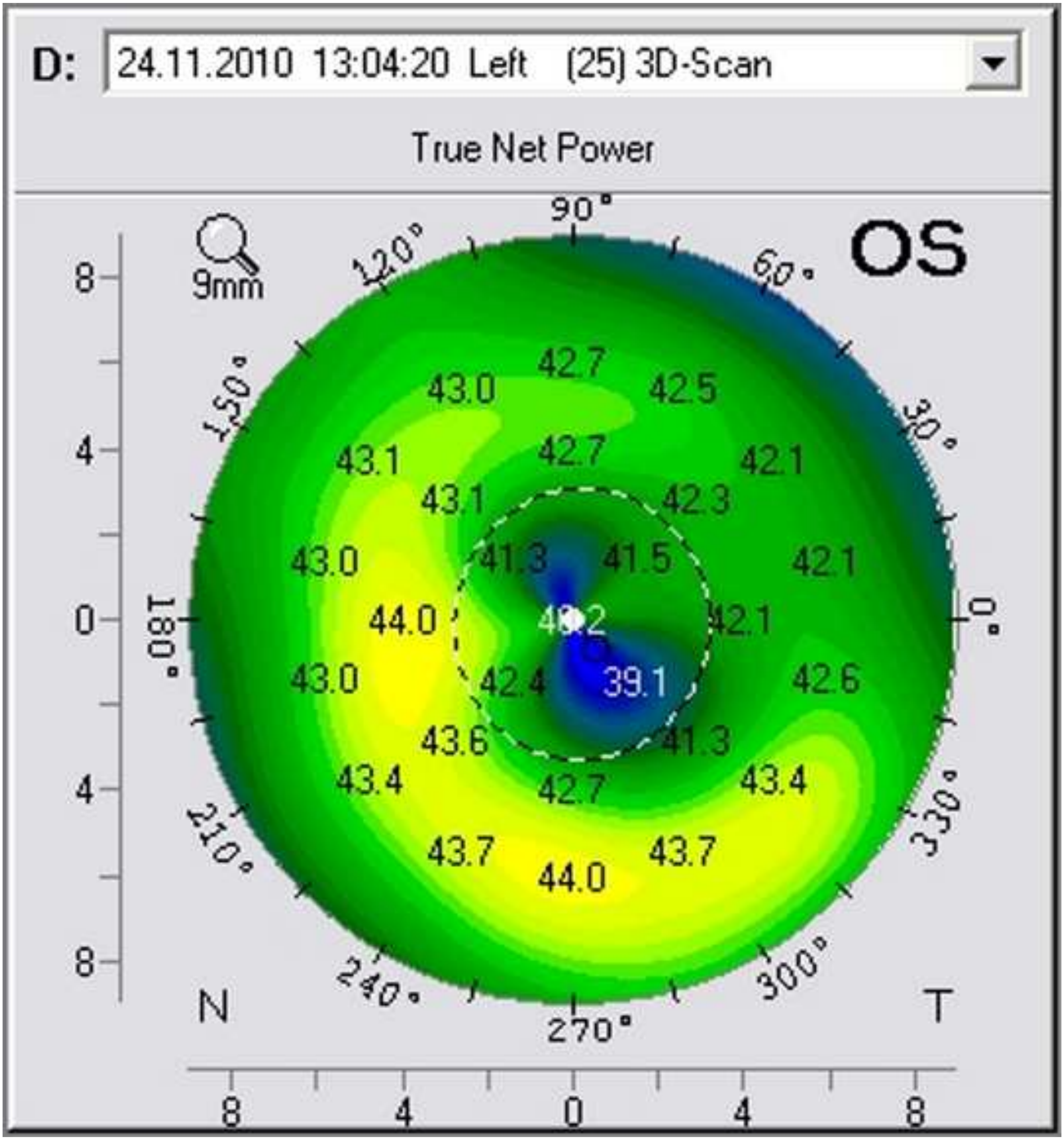

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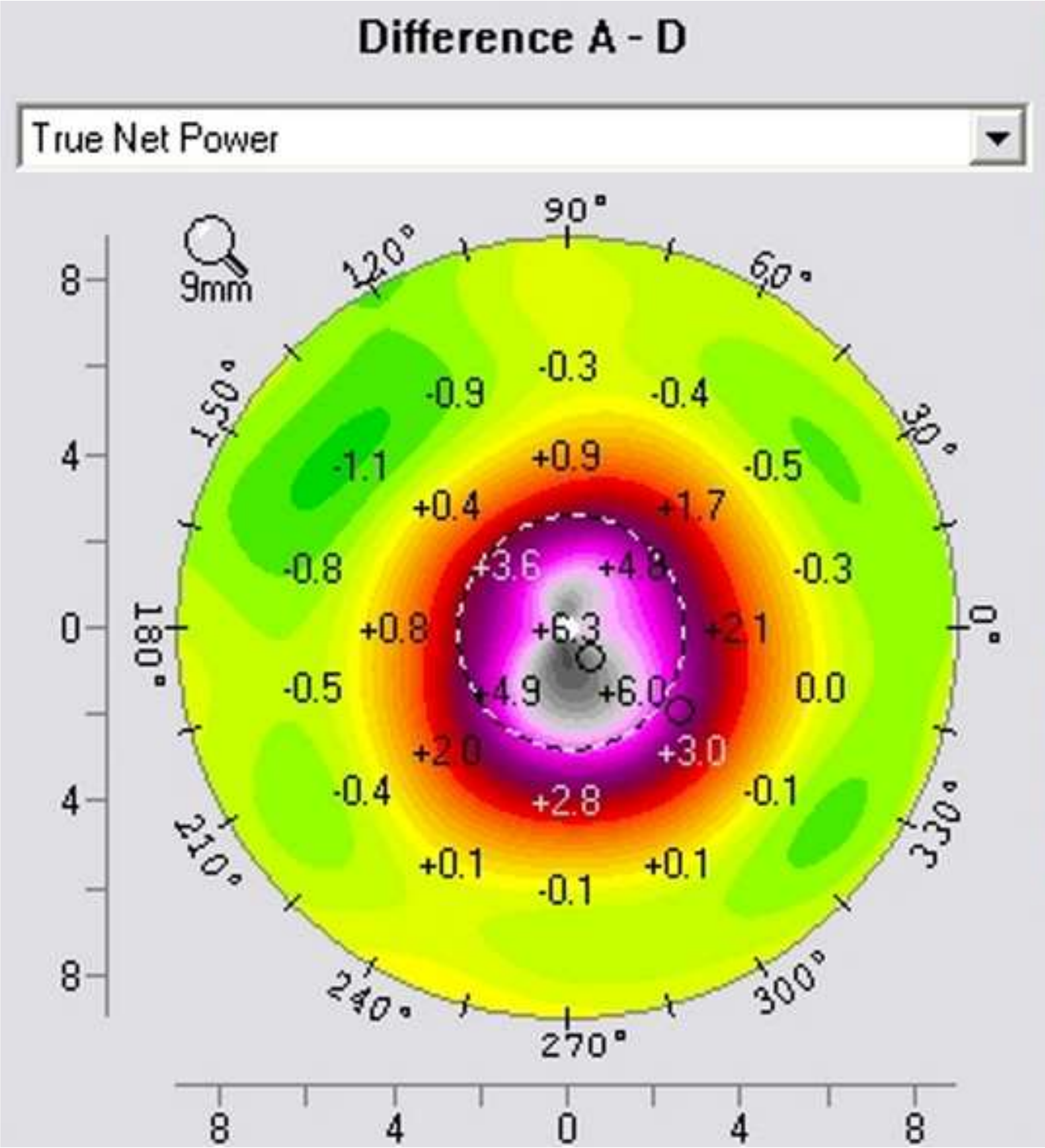

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diagnosis	-	-	-	-	0.24

*Revised Manuscript (changes highlighted)

Style Definition: src1

~~Regression~~Flattening of ~~keratoconus~~ the cornea after corneal cross-linking (CXL) ~~of the cornea (CXL)~~ for keratoconus

running head: ~~regession~~flattening after CXL

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Formatted: English (U.S.)

Abstract

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Setting: Institut für Refraktive und Ophthalmo-Chirurgie (IROC), Zurich, Switzerland.

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Results: More than 80% completed the 12 month follow-up. The ~~regression~~flattening rate (~~regression~~flattening of the maximal curvature > 1D) was 37.7%. A preoperative K_{max}-reading of more than 54 dioptres was identified as the only significant risk factor for this ~~regression~~effect (odds-ratio 1.88, 95%-confidence interval 1.01 to 3.51). A restriction to corneas with K_{max}>54D would have resulted in a significant ~~regression~~flattening in 51% of the cases.

Conclusions: ~~-~~A statistically significant ~~regression~~flattening during 1 year after CXL occurs in more than 50% of the cases if the preoperative maximal K-reading was more than 54D. None of the other preoperative parameters investigated such as age, gender, diagnosis, BSCVA, and shape factors of the cornea had a statistically significant impact on ~~regression~~corneal flattening after CXL.

More than ten years ago, corneal cross-linking (CXL) by means of riboflavin and ultraviolet light was proposed as a therapeutic approach to improve the biomechanical and biochemical properties of the cornea[1,2]. Meanwhile, there is clinical evidence that CXL is a clinically useful operation halting the progression of primary as well as secondary keratectasia with a failure rate of approximately 3% and a complication rate of 1% and less[3-8]. As a positive side effect, in a certain percentage of the eyes treated with CXL a regression of the keratectasia documented by significant flattening of the cornea may occur[3,7] which in rare cases amounts up to more than 10 dioptres[9]. It would be of interest for patients and physicians to identify preoperative parameters that may predict such a ~~regression~~flattening.

In this prospective study, in eyes with primary keratectasia the 1 year-results after CXL were analyzed to identify preoperative factors that may predetermine a ~~regression~~substantial flattening of the keratectasia.

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Patients and Methods

1. Study group and protocol

One hundred and ninety-two eyes of 192 patients with progressive keratectasia were enrolled in this study. Progression of the keratectasia was verified by repeated Scheimpflug ~~images~~tomographies (Pentacam 70700, Oculus, Wetzlar, Germany) over at least 6 months and progression was accepted if the increase in maximal K-reading exceeded 1 dioptre which equals 3 standard deviations[8]. Second eyes were treated not earlier than 6 months after the first one and were not included in the study group~~.~~. Eyes with maximal K-reading <76.0D (only together with contact lens tolerance) and minimal corneal thickness > 350 µm were included whereas eyes with preoperative corneal opacities were not accepted because Scheimpflug photography may give false results. Additional exclusion criteria were: ocular pathology other than keratectasia, in detail cornea guttata or other endothelial irregularities, history of recurrent erosions, actual or intended pregnancy, non-availability for follow-up examinations during 1 year, and connective tissue diseases. The study protocol was approved by the Ethikkommittee des Kantons Zürich. We differentiated between the diagnoses pellucid marginal degeneration (n=32) and keratoconus (n=103) based on the claw-pattern in corneal topography. In 21 cases, the differentiation between the two diagnoses was not possible. Of the 192 patients only 155 completed the 1 year follow-up (drop out-rate: 19.3%). Additionally, 4 eyes were excluded because of massive ~~regression~~remodelling due to stromal scars after CXL[9]. The demographic data of study group is listed in Table 1.

The patients were examined preoperatively, early postoperatively (1 to 3 days until epithelial healing), at 1 month, 6 months, and 12 months after CXL. At every follow-up, except the early postoperative, a standard examination was performed consisting of autorefractometry and autokeratometry (Humphrey Model 599, Zeiss, Jena, Germany), corneal topography (Keratograph C, Oculus, Wetzlar, Germany), Scheimpflug imaging (Pentacam 70700, Oculus, Wetzlar, Germany), manifest refraction using the fogging technique, unaided (UVA) and best spectacle-corrected visual acuity (BSCVA), applanation tonometry, and slit lamp inspection of the anterior and posterior segments of the eyes. At the 1 month follow-up examination the depth of the demarcation line was determined ~~at~~by the slitlamp[10]~~.~~ or by OCT[11].

Patients using rigid contact lenses were asked not to use their lenses for at least 3 weeks before the preoperative examination and for one month after treatment. The lenses had to be removed at least 3 weeks before each follow-up examination.

2. Treatment

Topical anaesthesia of the cornea was obtained using oxybuprocaine and tetracaine alternating every 3 minutes for 15 minutes. After insertion of a lid speculum, a corneal abrasion with a diameter of 9mm was performed followed by the instillation of 0.1% riboflavin drops every 3 minutes for 30 minutes. The riboflavin drops were prepared immediately before the treatment mixing 0.5% aqueous riboflavin solution (Streuli&Co, Uznach, Switzerland) with 20% dextrane T-500 solution (Roth, Karlsruhe, Germany). ~~Thereafter,~~During the imbibition with riboflavin drops, the thickness of the central ~~corneal~~

~~pachymetry~~cornea using ultrasound was performed. In cases with a central thickness (without epithelium) of less than 400 µm additional 0.1% riboflavin drops without dextrane were applied until the thickness exceeded 400 µm. The eyes were then inspected at the slit lamp to ensure that the riboflavin has arrived in the aqueous (blue light). After this, the eye was irradiated for 30 minutes with UVA with an irradiance of 3 mW/cm^2 (UV-X, Peschkemed Meditrade, Huenenberg, Switzerland). During irradiation, the cornea was moistened every 3 minutes with 0.1% riboflavin drops and oxybuprocaine drops at the patient's discretion. At the end of the procedure antibiotic ointment (ofloxacine 0.3%) was applied and the eye was patched. The patient was asked to use the antibiotic ointment five times a day for three days. After epithelial healing the patients used topical flourometholone twice a day for one week.

3. Numerical evaluation

A significant ~~regression of keratectasia~~corneal flattening 1 year after CXL was defined by a decrease in maximal K-reading K_{max} of more than 1 dioptre compared to preoperative. The difference $\Delta K_{max} = K_{max,preop} - K_{max,1\ year}$ was, therefore, the main variable, whereas some preoperative parameters that have been shown to influence the outcome of CXL like age, K_{max}, BSCVA, minimal thickness of the cornea d_{min}, eccentricity of the cone (radial distance between apex and point of highest curvature), asphericity of the anterior corneal shape Q_{ant}, index of surface variance ISV, and the keratoconus index KI[8] were considered secondary parameters. The correlation of these variables with ΔK_{max} and its one-sided significance was calculated using the Spearman rank correlation test. The influence of the digital variables gender (f/m), side (OD/OS), and diagnosis (PMD/KC) was studied using the U-test (Mann-Whitney). The group of patients with ~~regression~~significant corneal flattening (ΔK_{max} >1D) was compared with the total group by means of the odds-ratio algorithm. The odds-ratio of a potential risk factor for regression and its confidence interval was calculated by means of the standard algorithm for a 2x2-table. All calculations were performed with WinSTAT® for Excel (R. Finch Software, 2002). Statistical significance was accepted if $p<0.05$.

Results

Of the 151 eyes receiving CXL with an uneventful postoperative healing phase 57 eyes (37.7%) demonstrated ~~regression~~significant flattening of ΔK_{max} >1D. In this flattening group the average flattening was 2.24D compared to 0.89D in the total group (Tab. 3). Twenty eyes (13%) showed a flattening of ΔK_{max} >2D, 91eyes (60.3%) remained stable, and 3 eyes (2%) experienced progression~~.~~ of the keratectasia. The maximal flattening of 7.2D occurred in a 34 years old male. The demographic data shown in Table 1 demonstrate a skew towards male patients, left eyes, and keratoconus. Neither the age of patients in the study group did differ significantly from that of the ~~regression~~flattening group ($p = 0.49$) nor did the parameters side ($p = 0.976$), gender ($p = 0.811$), and diagnoses ($p = 0.24$).

Table 2 presents the correlation coefficients of the ~~regression~~flattening parameter ΔK_{max} and the preoperative variables. A statistically significant correlation with ΔK_{max} exists only regarding K_{max}, Q_{ant}, eccentricity of the cone and BSCVA.

The comparison of the ~~regression~~flattening group with the total study group is demonstrated in Table 3. Only the preoperative parameters K_{max} and Q_{ant} differ statistically meaningful between the 2 groups. To illustrate the significant difference in K_{max} in more detail Fig. 1 compares the relative distributions of K_{max} within the two groups: K_{max}-readings >~~55D~~54D occur more frequently in the ~~regression~~flattening group compared with the total study group. To substantiate this impression the odds-ratio algorithm was used and, indeed, "K_{max}>54D" represents a real risk factor for ~~regression~~flattening (odds-ratio 1.88, 95%-confidence interval 1.01 to 3.51). If only eyes with K_{max}>54D would have been included in the study the percentage of eyes experiencing significant ~~regression~~flattening would increase from 38% to 51%. We could not find a significant risk limit regarding Q_{ant}.

Discussion

The major findings of this prospective clinical study are (1) maximal curvature regressed significantly in approximately 40% within the first year after CXL and (2) the only predictive factor for such ~~regression~~flattening is the preoperative curvature K_{max}>54.0D.

Both Wollensak et al.[3] and our working group[8] report a reduction in maximal K-readings after CXL which is confirmed in this study. According to the long term follow up presented by the Dresden group [~~11~~12] this flattening process may, on average, continue for years. ~~-~~Although the reduction in maximal K-reading by 1 ~~dioptre~~or 2 dioptres may be not enough to rehabilitate visual acuity, the accumulative effect during several years can do so. ~~In~~Moreover, in special cases the flattening effect is much stronger: in Fig.2 the evolution of a corneal shape during ~~4 years~~the first year after CXL is demonstrated ~~and this went along~~ with ~~an increase in BSCVA from 0.8 to 1.5~~a flattening of more than 6 diopters at the central cornea.

The ~~regression~~flattening parameter ΔK_{max} demonstrated a statistical significant correlation with the preoperative variables maximal curvature K_{max}, corneal asphericity Q_{ant}, eccentricity of the cone and spectacle corrected visual acuity BSCVA. Comparing, however, the ~~regression~~ group with significant flattening with the total group K_{max} remained the only statistical significant ~~difference~~ factor (Table 3). Figure 1 depicts the relative distributions of K_{max} within the two groups and it is obvious that corneas with stronger curvature have a higher chance of ~~regression~~flattening after CXL. We expected to find other predictive parameters such as age, diagnosis and keratoconus indices~~;~~, however, none of these variables passed the simple significance test. The risk analysis made it even clearer: K_{max}>54D represents the only statistically significant risk factor for ~~regression~~significant flattening after CXL and none of the other factors came close to significance.

In a previous study[7] the risk factor for failure of CXL, defined as a 1 dioptre-increase in K_{max} during the first postoperative year, was K_{max}>58D. The combination of ~~the 2~~this statistical ~~recommendations~~recommendation and the one presented here creates a relatively narrow band ~~(~~of maximal success between 54 and 58 dioptres of K_{max} where a ~~regression~~flattening rate of more than 50% ~~and~~ is comes along with a failure rate of less than ~~3%) between 54 and 58 dioptres of K_{max}.~~1%. In the range of 54D and less one can expect less ~~regression~~flattening, however, still a good success rate regarding stabilisation of the keratoconus of more than ~~97~~99%. In contrast, K_{max}-values of more than 58 dioptres predict more ~~regression~~flattening but also more failures which may have to be emphasized during patient counselling.

A topic that needs to be addressed in this discussion is the customized surface ablation to regularize the multifocal shape of the keratoconus cornea as proposed by ~~us[12]~~us[13] and ~~others[13].~~others[14]. So far the reasoning for a simultaneous surface ablation and CXL included the erosion pain to happen only ~~once[13].~~once[14]. A ~~regression~~flattening of more than 1 dioptre within the first year after CXL in more than 50% of the cases ~~has~~and even more a flattening of 2 dioptres and more in 13% does, however, ~~to be taken into account when planning~~decrease the predictability of such a simultaneous operation. Targeting on undercorrection or ~~undertaking~~performing the operations in two steps may be considered as solutions.

In summary, we could show that a statistical significant ~~regression~~flattening of the cornea (without scarring) during 1 year after CXL occurs in more than 50% of the cases if the preoperative maximal K-reading was more than 54D. None of the other preoperative parameters investigated such as age, gender, diagnosis, BSCVA, and shape factors of the cornea had a statistically significant impact on regression after CXL.

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Legends

Figure 1

Comparison of the relative incidences of K_{max}-values in the ~~regression~~flattening group (black columns) and total study group (white columns). K_{max}-readings of more than ~~55D~~54D occur more frequently in the ~~regression~~flattening group.

Figure 2

Temporal evolution of a cornea after CXL ~~(preoperative, 2 years and 4 years post-op).~~within the first postoperative year. The maximal flattening is more than 6 diopters as depicted in the difference map. The reduction ~~in~~ of K_{max} ~~was~~is, however, only 3.~~6 D and uncorrected VA improved during this time from 0.2 to 1.0 and BSCVA from 0.8 to 1.5.~~2 dipters.

Table 1: Demographic data of the study and the ~~regression~~flattening group

	study group (n=151)	~~regression~~flattening group (n=57)
age in years (at treatment)	29.3 ± 8.6 , range 12 to 53	28.2 ± 8.4 , range 15 to 46
gender (female : male)	54 : 97	21 : 36
side (OD : OS)	66 : 85	25 : 32
diagnosis (KC : PMD)	103 : 32	43 : 8

- Table 2: Correlation of preoperative parameters with the ~~regression~~flattening parameter ΔK_{max}

	correlation coefficient	p-value
K_{max}	0.214	0.004
Q_{ant}	-0.149	0.045
~~eccentricity~~	~~-0.141~~	~~0.05~~
BSCVA	-0.136	0.048
age	-0.100	0.110
KI	0.079	0.170
ISV	0.078	0.174
d_{min}/µm	-0.051	0.270

Table 3: Comparison of ~~regression~~flattening group and total study group

	~~regression~~flattening group		total study group		difference
	average	STD	average	STD	p-value
ΔK_{max}	2.24	1.42	0.89	1.49	<0.001
-K_{max}/D	56.2	6.5	54.3	6.4	0.043
Q_{ant}	-0.88	0.53	-0.72	0.64	0.052
Δ eccentricity/mm	-0.08	0.24	-0.07	0.21	0.082
BSCVA	0.49	0.29	0.55	0.28	0.19
KI	1.28	0.13	1.26	0.14	0.22
ISV	100	40	95	43	0.35
age/years	28.2	8.4	29.3	8.6	0.50
d_{min}/µm	447	39	450	37	0.64
diagnosis	-	-	-	-	0.24