Strahlentherapie
und Onkologie

**Original Article**

# Prospective Study of Exclusive Strontium-/Yttrium-90 β-Irradiation of Primary and Recurrent Pterygia with No Prior Surgical Excision

## Clinical Outcome of Long-Term Follow-Up

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**Purpose:** To evaluate the consecutive treatment results regarding pterygium recurrence and the efficacy of exclusive strontium-/yttrium-90 β-irradiation for primary and recurrent pterygia and to analyze the functional outcome.

**Patients and Methods:** Between October 1974 and December 2005, 58 primary and 21 recurrent pterygia were exclusively treated with strontium-/yttrium-90 β-irradiation with doses ranging from 3,600 to 5,500 cGy. The follow-up time was 46.6 ± 26.7 months, with a median of 46.5 months.

**Results:** The treatment led to a size reduction in all pterygia ($p < 0.0001$). Neither recurrences nor side effects were observed during therapy and follow-up in this study. Best-corrected visual acuity increased ($p = 0.0064$). Corneal astigmatism was reduced in recurrent pterygia ($p = 0.009$).

**Conclusion:** Exclusive strontium-/yttrium-90 β-irradiation of pterygia is a very efficient and well-tolerated treatment, with remarkable aesthetic and rehabilitative results in comparison to conventional treatments, especially for recurrent lesions which have undergone prior surgical excision.

**Key Words:** Pterygium · Strontium-/yttrium-90 β-irradiation · Astigmatism

**Strahlenther Onkol 2009;185:808–14**
DOI 10.1007/s00066-009-2000-1

**Prospektive Studie zur Behandlung des primären und rezidivierenden Pterygiums nach ausschließlicher Strontium-/Yttrium-90-Bestrahlung. Klinisches Ergebnis im Langzeitverlauf**

**Ziel:** Evaluation der Behandlungsergebnisse in Bezug auf Rezidivrate, Effizienz und Funktion der ausschließlichen Strontium-/Yttrium-90-β-Bestrahlung von primären und rezidierenden Pterygien. Analyse des kornealen und des refraktiven Astigmatismus im Vergleich zu den postoperativen Ergebnissen konventioneller Behandlungsmethoden.

**Patienten und Methodik:** Zwischen Oktober 1974 und Dezember 2005 wurden 58 primäre und 21 rezidivierende Pterygien mit ausschließlicher Strontium-/Yttrium-90-β-Bestrahlung mit Dosen von 3 600–5 500 cGy behandelt. Die mittlere Nachbeobachtungszeit betrug 46,6 ± 26,7 Monate, median 46,5 Monate.

**Ergebnisse:** Die Behandlung führte bei allen Pterygien zu einer Größenabnahme ($p < 0{,}0001$). Es wurden keine Rezidive und keine unerwünschten Nebenwirkungen beobachtet. Die bestkorrigierte Sehschärfe stieg signifikant an ($p = 0{,}0064$), der korneale Astigmatismus verkleinerte sich signifikant bei den rezidivierenden Pterygien ($p = 0{,}009$).

**Schlussfolgerung:** Die ausschließliche Strontium-/Yttrium-90-β-Bestrahlung des Pterygiums ist eine sehr effiziente und gut tolerierte Behandlungsmethode mit einem bemerkenswerten ästhetischen und rehabilitativen Resultat in Vergleich zu den konventionellen Behandlungskonzepten, vor allem bei rezidivierenden Pterygien nach primärer operativer Exzision.

**Schlüsselwörter:** Pterygium · Strontium-/Yttrium-90-β-Bestrahlung · Astigmatismus

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**Received: February 5, 2009; accepted: September 30, 2009**

## Introduction

The medical term *pterygium*, a bulking, vascular tissue, which expands toward the center of the cornea, is derived from the Greek word *pteron* meaning wing. According to a hypothesis made by Dushku et al. regarding the pterygium pathogenesis, the limbal epithelial stem cells are proliferating, using Bowman's membrane as a leading structure and destroying it during its advancement [16]. The pterygium consists of a cup, body and head, and it appears predominantly in the nasal site and less often in temporal site [12]; bilateral lesions have also been documented [14, 32]. The incidence and prevalence vary according to the geographic region, favoring southern climate regions, since studies have correlated its frequency with chronic exposure to UV radiation (290–400 nm), hence affecting predominantly population near the equator, the Mediterranean, Australia, and in the Middle East [13, 44]. However, pathogenesis of pterygium is considered to be a multifactorial process involving other pathologic factors and mechanisms [13].

Mutations in the TP53 gene or TP53 family in the parental limbal basal cells caused by UV light exposure, abnormal elastotic material production and various matrix metalloproteinase proteins invading the cornea, the overproduction of the transforming growth factor (TGF-β) via the p53-Rb-TGF-β pathway [16] and fibroblast growth factors combined with vascular endothelial growth factors responsible for the angiogenesis [16, 25, 45] are part of this complex process, placing pterygia close to invasive tumors [11, 16].

Clinically, the progression of this lesion demonstrates a great impact on the cornea morphology and shape inducing corneal and refractive astigmatism by flattening localized areas central to their apex [13, 14, 26, 35, 42]. The pterygium was also found to induce significant amount of regular and irregular astigmatism according to its size [5, 24, 26, 29, 31, 32, 41, 43] and various complications like tear pooling, a feature found also in cases of limbal conjunctival carcinomas [14, 26], were also correlated to pterygium proliferation.

In general practice, pterygia are treated surgically, and over the years, various techniques like bare sclera surgical excision, conjunctiva flaps and autografts [22] surfaced. Such techniques showed rather unsatisfactory results since recurrence of the lesion with a more aggressive pattern occurred frequently [16]. The post- and/or intraoperative use of antimetabolite drugs like mitomycin C and thiotepa improved results with low recurrence rates, but still reports of severe complication due to high toxicity like cataract formation and scleral calcifications or necrosis were documented [21].

The therapy approach through postoperative strontium-/yttrium-90 β-irradiation is not so propagated among fellow ophthalmologists. Although radiation therapy is widely regarded as beneficial in ophthalmology as well [9], standard methods like surgical excision with or without the use of antimetabolite drugs [22] are commonly used even nowadays.

This study provides evidence, that the moderately advanced primary and recurrent pterygia are responding remarkably well to radiotherapy – in line with the efficacy of radiotherapy in other benign diseases [20, 27, 36, 37, 47, 50] –, with neither recurrence nor late complications observed after therapy and during follow-ups in any patient in this study.

## Patients and Methods

Between October 1974 and December 2005, 70 patients (38 females), with age varying from 28 to 95 years (median, 65 ± 14.03 years), were recruited to this study earlier from the Swiss Eye Research Foundation – ORASIS Eye Clinic, Reinach, and later from the Ophthalmology Clinic Pallas, Olten, both Switzerland. The study protocol was formed initially in 1974 in which all patients with signs of pterygium activity were included. Inclusion criteria were pterygium activity (vascular growth and length growth), chronic irritation (sicca syndrome) and red-eye syndrome with visual acuity disturbances escorted with astigmatism's increase. Exclusion criteria were predominantly signs of inactive pterygium or pseudopterygium. The number of scheduled protocol ophthalmologic sessions was five (1st, 3rd, 6th, 12th, and 18th month with the 18th month being the early endpoint). Postprotocol sessions up to 46.5 months were also included as late endpoint result to evaluate recurrence or late complications (radiogenic cataract) over a long period of time. All late endpoints were assessed by two ophthalmologists (B.P. and I.V.) with identical assessment criteria. Prior to treatment, all patients were informed about possible complications of the irradiation including iatrogenic-radiogenic cataract formation, possible recurrence of the lesion, chronic scleral calcifications, and scleral necrosis.

A total of 79 pterygia (58 primary and 21 recurrent pterygia after former excision and mitomycin C 0.02% instillation), all located nasally, were treated with exclusive strontium-/yttrium-90 irradiation. 14% of pterygia were found in people with Mediterranean origin and in people with origin from the Balkan and Asia Minor region respectively, while the remaining percentage was found in patients from the region of the institutions. The pterygia had a progressive proliferation with signs of activity, ocular irritation and astigmatism (–1.0 ± 1.5 D), with the lowest value being –5.75 D. Pictures of each pterygium were taken at the beginning of treatment

**Table 1.** Summary of irradiation dose and fractions.

**Tabelle 1.** Dosis per Fraktion und Anzahl der Fraktionen.

| Total dose (cGy) | 5,500 | 5,000 | 4,800 | 4,200 | 3,600 |
|---|---|---|---|---|---|
| Fractions (n) | 5 | 4 | 8 | 7 | 6 |
| Single dose (cGy) | 1,100 | 1,250 | 600 | 600 | 600 |
| Primary (n) | 0 | 29 | 0 | 6 | 23 |
| Recurrent (n) | 1 | 7 | 9 | 1 | 3 |

using a fundus camera (FF 450/FF 450 IR Zeiss) for digitized photo measuring process of the eye's surface. In earlier and later times, slit-lamp measurements of each pterygium's length, size and distance of the head to the corneal limbus were made in order to control the proliferation. In earlier times, manual keratometry was used for corneal astigmatism record, while later corneal topography was performed with a video keratoscope (orbscan II version 3.0, Bausch & Lomb Zyoptix), which served for the same purpose. Astigmatism analysis is quite complex [51] due to its direction and magnitude. We analyzed corneal and refractive astigmatism using the surgically induced vector analysis and the simple subtraction analysis [2].

The total irradiation dose, the single irradiation dose and fractionation for the primary and recurrent pterygia varied (Table 1). The irradiation was applied using the strontium-/yttrium-90 applicator, a convex plate of 12 mm diameter with the radioactive material in the inner surface of the plate. This plate is then attached to a pen-like hold, which facilitates its use (Figure 1).

The patients received local anesthesia (oxybuprocaine), eyelids were spread, and the patients were instructed to fix on a spot on the ceiling and to hold this fixation while the physician targeted the affected area [32].

The opening of the applicator is coated with layers of stainless steel and aluminum, which acts as a filter decreasing the strontium-90 irradiation to 3% and the yttrium to 60% of their initial values [32]. The dose at 1 mm distance from the applicator surface decreases down to 50% of the surface dose. This value is < 25% of the initial dose at 2 mm and about 1% of the dose at 5 mm distance. The distance between the lens equator and the limbus is 4 mm. Therefore, the lens reaches < 4% of the calculated treatment dose (Figure 2) [32]. The duration of the application is determined by the age of the strontium plate and the level of the fraction dose. The dose was prescribed on the surface. All applications were performed twice a week. A complete ophthalmologic examination was performed in all patients prior to irradiation and during the 1st week. The mean follow-up time was 46.6 ± 26.7 months, with a median of 46.5 months. The treatment results are presented according to our study protocol in the previously mentioned time periods. However, as stated before, data of postprotocol sessions were also recorded and analyzed to assess recurrence and cataract formation after the early endpoint (18th month). None of the patients had undergone cataract or refractive surgery prior to or after this treatment.

For statistical analysis, MedCalc® version 9.3.0.0 was used. Wilcoxon's, Kruskal-Wallis and rank correlation tests were used where rejection of normal distribution existed (Kolmogorov-Smirnov test and Chi-square test). Where distribution was normal, Student's paired t-test, one way-analysis of variance (ANOVA) or other parametric tests were used. Significance was given at $p \leq 0.05$.

**Figure 1.** Strontrium-/yttrium-90 applicator.
**Abbildung 1.** Strontium-/Yttrium-90-Applikator.

### Results

All pterygia showed a significant decrease in size even after the 1st month of treatment. The initial mean horizontal diameter of all pterygia was 2.05 ± 1.1 mm with size ranging from 0.3 to 5 mm and, until the last frame of record for every patient, diminished to 1.03 ± 0.8 mm with the highest value being 4.2 mm and the lowest 0 mm, which was recorded in eleven cases ($p < 0.0001$). Primary lesions shrunk from 2.12 ± 1.01 mm to 1.07 ± 0.78 mm, and the recurrent ones from 1.85 ± 0.98 mm to 1.02 ± 0.74 mm. This difference in size was highly statistically important on the whole, as well as individually for primary and recurrent pterygium ($p < 0.0001$ and $p < 0.0001$, respectively). The percentage in size reduction for all lesions was also highly statistically important ($p < 0.0001$). The steepest decrease, 16% ± 22%, took place between the 3rd and 6th month. The results regarding the decrease in size and the percentage in size reduction through time are analytically displayed in Table 2.

The mean of best-corrected visual acuity (BCVA) prior to this treatment was 0.9 ± 0.29, with values ranging from 0.25 to 1.0, and increased to 1 ± 0.15, with values ranging from 0.3 to 1.20, as measured in Snellen optotypes. The BCVA prior to treatment differed statistically significantly regarding the kind of lesions ($p = 0.0228$; means 0.94 ± 0.26 and 0.75 ± 0.33). The improvement of BCVA showed to be statistically significant for all treated eyes in this study and differed regarding the pterygia ($p = 0.0027$; means 4.33 ± 17.10 and 63.7 ± 91.86). More analytic results are demonstrated in Table 3.

The corneal astigmatism for all pterygia was –2.29 ± 2.27 D × 76.92° ± 71.34° and was reduced to –1.80 ± 2.28 D × 81.76° ± 74.34°. The difference of corneal astigmatic magnitude was statistically significant regarding the kind (primary, recurrent) of pterygia ($p = 0.0035$, mean

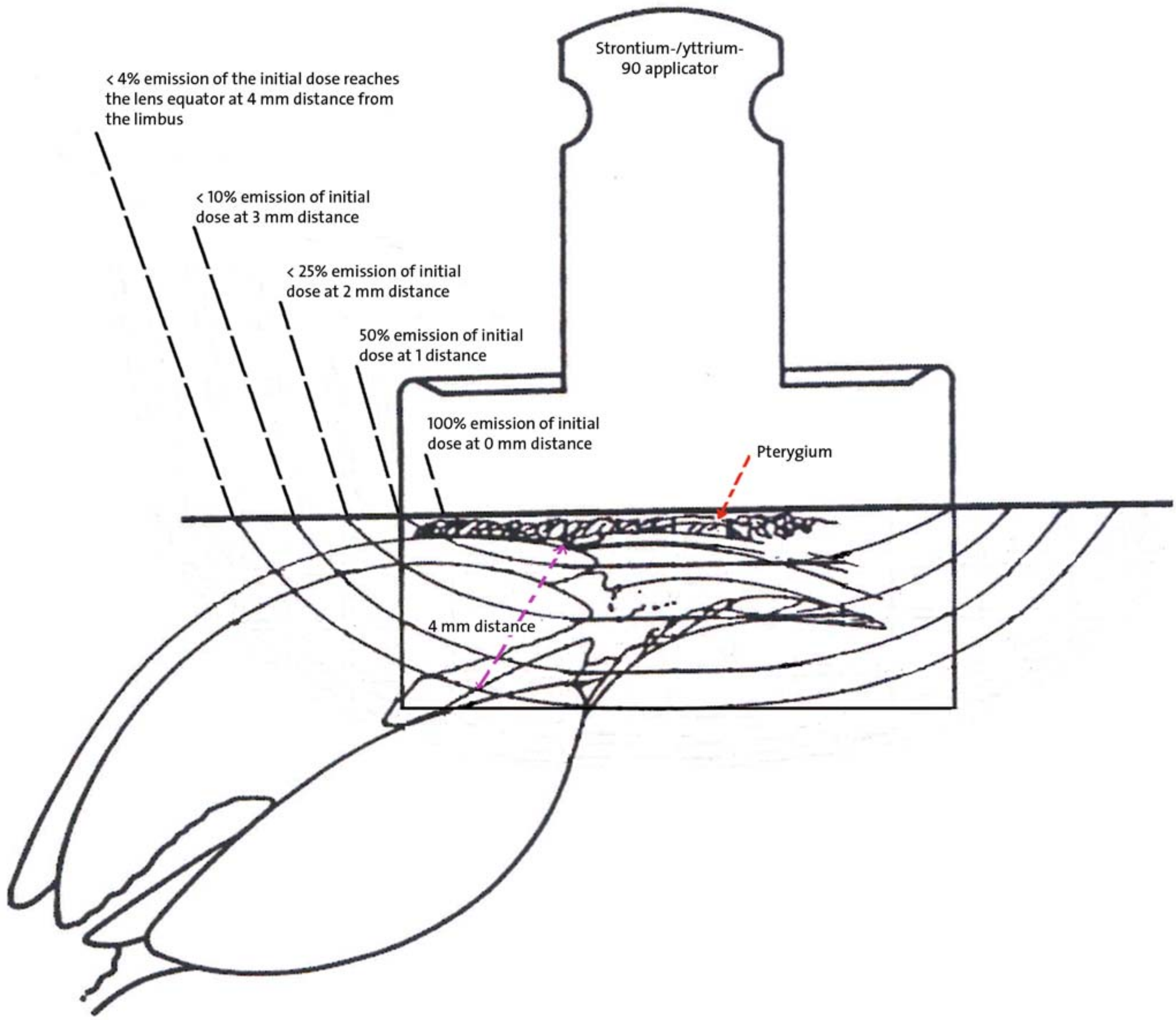



**Figure 2.** Schematic representation of the depth-dose exponential decrease of strontium-/yttrium-90 irradiation emission through the anatomic parts of the eye.

**Abbildung 2.** Darstellung der Tiefendosiskurve der Strontium-/Yttrium-90-Bestrahlung in Relation zu den anatomischen Strukturen des Auges.

**Table 2.** Analytic display regarding means of size and percentage reduction.

**Tabelle 2.** Größenreduktion der Pterygien (Mittelwerte und Prozente).

| | Primary pterygia | | | | Recurrent pterygia | | | |
|---|---|---|---|---|---|---|---|---|
| | Size (mm) | p-value | Percentage (%) | p-value | Size (mm) | p-value | Percentage (%) | p-value |
| Baseline | 2.12 ± 1.01 | | 0 | | 1.85 ± 0.98 | | 0 | |
| 1st month | 1.84 ± 0.97 | < 0.0001 | 12 ± 16 | < 0.0001 | 1.75 ± 0.89 | 0.0013 | 9 ± 11 | 0.0010 |
| 3rd month | 1.56 ± 0.90 | < 0.0001 | 26 ± 26 | < 0.0001 | 1.53 ± 0.79 | 0.0068 | 22 ± 25 | 0.0010 |
| 6th month | 1.34 ± 0.84 | < 0.0001 | 38 ± 25 | < 0.0001 | 1.25 ± 0.82 | 0.0063 | 37 ± 27 | 0.007 |
| 12th month | 1.228 ± 0.84 | 0.0001 | 45 ± 25 | < 0.0001 | 1.03 ± 0.80 | 0.0005 | 49 ± 32 | 0.0013 |
| 18th month | 1.22 ± 0.81 | 0.0150 | 45 ± 26 | 0.0127 | 1.02 ± 0.80 | 0.0823 | 43 ± 31 | 0.1063 |
| Last frame of record | 1.07 ± 0.78 | 0.0005 | 49 ± 25 | 0.003 | 1.02 ± 0.74 | 0.0893 | 47 ± 32 | 0.29 |

**Table 3.** Summary of results. BCVA: best-corrected visual acuity.

**Tabelle 3.** Resultate in der Übersicht. BCVA: bestkorrigierte Sehschärfe.

| | Primary pterygia (n = 58) | | | Recurrent pterygia (n = 21) | | |
|---|---|---|---|---|---|---|
| | Baseline | Postirradiation | p-value | Baseline | Postirradiation | p-value |
| Size (mm) | 2.12 ± 1.01 | 1.07 ± 0.78 | 0.0001 | 1.85 ± 1.0 | 0.93 ± 0.72 | 0.0002 |
| Reduction (%) | 0 | 49 ± 25 | 0.0001 | 0 | 47 ± 32 | 0.0005 |
| BCVA | 0.9 ± 0.25 | 1.0 ± 0.25 | 0.35 | 0.75 ± 0.3 | 1.0 ± 0.21 | 0.003 |
| Refractive astigmatism (D) | –0.75 ± 1.20 | –0.75 ± 1.23 | 0.25 | –1.30 ± 2.25 | –0.86 ± 1.61 | 0.18 |
| Corneal astigmatism (D) | –2.16 ± 2.51 | –2.01 ± 2.46 | 0.40 | –2.73 ± 1.29 | –1.1 ± 1.5 | 0.009 |

**Table 4.** Importance of single irradiation dose for best-corrected visual acuity (BCVA) differences and size reductions (comparison of means of baseline and endpoint results).

**Tabelle 4.** Bedeutung der Einzeldosis in Bezug auf Unterschiede in der bestkorrigierten Sehschärfe („best-corrected visual acuity" [BCVA]) und Größenreduktion der Pterygien (Vergleich der Mittelwerte von Ausgangsbefunden und Ergebnissen am Ende des Nachbeobachtungszeitraums.

| | All pterygia | | | Primary pterygia | | | Recurrent | | |
|---|---|---|---|---|---|---|---|---|---|
| Irradiation (cGy) | 1,250 | 600 | | 1,250 | 600 | | 1,250 | 600 | |
| | Means | | $p \leq 0.05$ | Means | | $p \leq 0.05$ | Means | | $p \leq 0.05$ |
| BCVA difference | 0.09 ± 0.20 | 0.08 ± 0.23 | 0.99 | 0.03 ± 0.15 | 0.07 ± 0.13 | 0.91 | 0.29 ± 0.22 | 0.38 ± 0.30 | 0.33 |
| Size reduction (%) | 46 ± 35 | 50 ± 16 | 0.85 | 49 ± 32 | 49 ± 16 | 0.81 | 36 ± 46 | 56 ± 20 | 0.43 |

0.15 ± 0.77 and 1.62 ± 0.97, Kruskal-Wallis test). The extent of the reduction was of high statistical importance in Student's t-test for the recurrent pterygia (Table 3). The astigmatic magnitude postoperatively was highly correlated with the final size of all pterygia accounted at the last frame of record for every patient ($p = 0.0046$, $r = –0.53$, correlation coefficient test). The induced refractive astigmatism due to irradiation was 0.37 ± 0.83 D × 43.26° ± 60.91° and the induced corneal astigmatism due to irradiation was 0.97 ± 0.54 D × 84.54° ± 60.35°. Induced corneal and refractive astigmatism differed statistically significantly between them ($p = 0.0214$; means 0.97 ± 0.54 and 0.53 ± 1.11, Wilcoxon's paired-sample test).

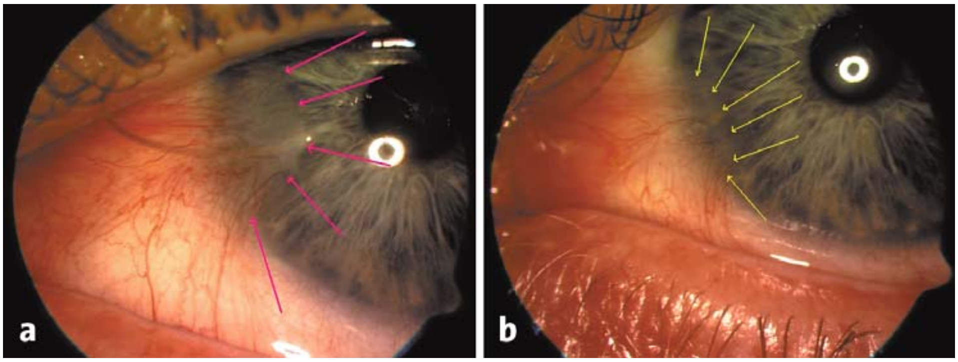
Regarding the kind of pterygium and the single irradiation doses (6 and 12.5 cGy) mostly used in this study, no statistically important results in means of size reduction percentage or BCVA were found (Table 4). In none of 79 pterygia a recurrence developed. No scleral thinning, necrosis or scleral calcification as well as iatrogenic (radiogenic) cataract was induced during or after the treatment and follow-up sessions. Minor ocular irritations (red eye, telangiectasia, and sicca) were properly handled.

## Discussion

Exclusive irradiation of pterygium without prior surgical excision is still an option of treatment not so common among fellow ophthalmologists [40]. In the major review by Hirst [22], radiotherapy is not mentioned and was only recently added as a therapeutic approach [4]. Commonly, β-irradiation was familiar among ophthalmologists as an option of treatment only after an excision had been made in order to prevent further recurrence of the lesion [10].

This study presents, for the first time, long-term results using exclusive strontium-/yttrium-90 irradiation, not only concerning size reduction, as we demonstrated in previous publications [32], but also regarding the way pterygia responded to this treatment divided in groups, the assessment of recurrence rate, the improvement of BCVA, and the extent corneal astigmatism changed in favor of the patient.

Recurrences are well known to occur after excision of pterygia using common surgery techniques like the bare sclera excision or conjunctiva flaps and autografts, or after β-irradiation using predominantly a single-dose (> 2,000 cGy) treatment [8, 10]. In a study by Anduze & Merritt, out of 300 pterygia recruited, 270 primary pterygia were treated surgically of which 247 lesions showed recurrence after 12 months (91%). Out of 17 recurrent pterygia, six lesions showed a second recurrence (35%) [3]. The post- and/or intraoperative use of antimetabolite drugs like mitomycin C or thiotepa [19, 33, 38] improved results with low recurrence rates, but still reports of severe complication due to high toxicity like cataract formation and scleral calcifications or necrosis are well documented [15, 18, 39]. However, recent publications on primary pterygium surgical treatment followed by extended conjuctival transplantation, showed remarkable results in 250 primary pterygia concerning the recurrence rate, achieving a recurrence rate of 0.4% and no change in BCVA during 462 ± 172 days of follow-up [23].




**Figures 3a and 3b.** A patient's eye prior to (a) and after treatment (b) at 6-month follow-up.

**Abbildungen 3a und 3b.** Pterygium vor (a) und 6 Monate nach Behandlung (b) mit dem Strontium-/Yttrium-90-Applikator.

The use of β-irradiation was more common postoperatively in the treatment of pterygia. Paryani et al. treated 690 pterygia, using a total dose of 6,000 cGy divided in six fractions and achieved a recurrence rate of 1.7% [34]. Van den Brenk treated 349 lesions using a total dose of 2,400 cGy divided in three fractions and reported 1.4% of recurrences [48]. Alaniz-Camino treated 483 lesions using a total dose of 2,800 cGy divided in four fractions and achieved a 4.32% recurrence rate [1]. Many fellow colleagues anticipated less recurrences by increasing the total dose and dividing it into more fractions. Hilgers, by increasing the total dose by 1,000 cGy (from 2,790 to 3,750 cGy), reduced the recurrence rate from 43% to 3% [21]. Van den Brenk increased the total dose from 1,750 cGy to 3,000 cGy and reduced the recurrence rate from 43% to 1.4% [48]. Brenner & Merriam calculated the linear-quadratic parameter $\alpha/\beta$ (~ 25 Gy) and suggested that fractionation should give an increased therapeutic ratio between nonrecurrence and late sequelae. Recurrence over late complications is demonstrated by the isoeffect curves [10]. However, Viani et al., in a series of 623 patients, applied brachytherapy after surgical excision with a median of 60 months follow-up and using a total of 3,500 cGy with a five-to-seven-fractionation scheme; he reported > 9% of recurrences in 73 cases and 0.8% of cataract formation in the context of other late complications due to the treatment [49]. According to Nowell the dose of 500 cGy at the level of the lens is thought to be caractogenic [30]. In his series of treatment in 205 eyes a recurrence of only two eyes (1.46%) occurred, implying that recurrence may occur when the output of the strontium applicator diminishes as the isotope decays in time. Van den Brenk [48], in the total series of 1,300 treated cases using various fractionations, reported no cataract formation due to irradiation, as he postulated that between 3 and 6 mm distance from the lens equator, only 20% to 1% of the total dose can reach the lens.

In our study, neither recurrence nor late complications including radiogenic cataract formation were documented during the follow-up sessions and until the last frame of record for every patient treated with the respective dose and fractionation. We present, however, our recurrence results with caution, since the number of cases treated was small. Regarding the single irradiation dose or the fractions of the irradiation, we found no statistically significant results that made a difference in size percentage reduction and BCVA of the pterygia treated. Still we feel that a total dose of 3,600 cGy, divided in six fractions, is safer for the patient [6, 9, 32, 36, 37, 47] and is associated with the same benefits in all aspects tested in this study. Concerning the astigmatism and the BCVA final outcome after surgical excision, mostly of the primary pterygium, various studies habe been published with very good results (e.g. [28, 46]). Errais et al. recently demonstrated that the astigmatism in 20 eyes with pterygium, treated with surgical excision, was reduced from 5.47 ± 3.45 D to 1.79 ± 1.52 D and BCVA increased from 0.73 ± 0.20 to 0.89 ± 0.16 [17]. Bahar et al., in a similar study of 55 eyes with primary pterygium, came with almost the same results. Astigmatism was reduced from 3.12 ± 2.43 D to 2.51 ± 2.5 D and BCVA increased from 20/40 to 20/25 (0.5–0.8 in Snellen) [7]. In our study, the corneal astigmatism of all pterygia was –2.29 ± 2.27 D × 76.92° ± 71.34° and was reduced to –1.80 ± 2.28 D × 81.76° ± 74.34°. The difference of corneal astigmatic magnitude was statistically significant regarding the kind of pterygia and in recurrent lesions diminished from –2.73 ± 1.29 D to –1.1 ± 1.5 D. The BCVA prior to irradiation was 0.90 ± 0.28 and increased to 1 ± 0.15 for all lesions accounted. In recurrent pterygia, it increased from 0.75 ± 0.3 to 1.0 ± 0.21, and in primary pterygia, it improved, but no statistically important difference was found.

## Conclusion

The very favorable aesthetic and functional results presented in this study (Figures 3a and 3b) suggests that nonsurgical, exclusive strontium-/yttrium-90 β-irradiation is a noninvasive and well-tolerated procedure that should be administered to patients and should be taken into consideration by fellow colleagues as a reliable treatment option.

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