Veterinary Ophthalmology (2010) **13**, 1, 20–25

Radiotherapy for canine chronic superficial keratitis using soft X-rays (15 kV)

Ingrid Allgoewer* and Stefan Hoecht†

**Animal Eye Practice, Lindenthaler Allee 9, 14163 Berlin, Germany, †Clinic for Radiooncology and Radiotherapy, Charité Campus Benjamin Franklin, Hindenburgdamm 30, 12200 Berlin, Germany*

Address communications to:

I. Allgoewer

Tel.: +49 30 80589868
Fax: +49 30 80589579
e-mail: ia@tieraugen.com

The results of this study were presented at the 2005 ECVO meeting in Oporto, Portugal.

Abstract

Objective To evaluate the effect of soft X-ray therapy in the treatment of refractory chronic superficial keratitis (CSK).

Animals studied Thirteen dogs with severe CSK, that had been refractory to prior medical and/or surgical therapy were treated with soft X-ray therapy.

Procedures Both corneas of each dog were irradiated with soft X-rays (15 kV), to a total dose of 30 Gy, administered as two fractions over 48–96 h. Treatment was carried out under deep sedation in all dogs. Three dogs were treated by superficial lamellar keratectomy 48 h prior to radiotherapy. Changes in the extent of corneal pigmentation, pigment density and corneal vascularization were documented using a semi-quantitative grading scheme, schematic drawings and clinical photographs.

Results Only minor, transient adverse effects of treatment, such as photophobia, epiphora and blepharitis were noted. Overall the effect of soft X-rays on the course of the keratitis was superior when compared to the effect of Sr-90 irradiation that had been determined in a previous study.

Conclusion Soft X-ray irradiation combined with keratectomy is a safe and effective new treatment option for severe and advanced CSK with significant visual impairment due to corneal pathology.

Key Words: chronic superficial keratitis, cornea, dog, pannus, radiotherapy, soft X-rays

INTRODUCTION

Chronic superficial keratitis (CSK), also called pannus or Überreiter keratitis, is a chronic progressive disease that may lead to visual compromise or blindness in dogs due to corneal vascularization and pigmentation.[1] German Shepherds and Shepherd crosses are most commonly affected and usually present with conjunctivitis and temporal corneal vascularization.[2] In the acute phase superficial vascularization is followed by centripetally progressing fibrovascular granulation tissue (pannus). The chronic phase is characterized by epithelial and stromal pigmentation,[1] associated with infiltrates of histiocytes, plasma cells and degranulated mast cells. An immune-mediated etiology is assumed.[3,4] Sunlight seems to play an important role, as ultraviolet rays may modify cornea specific antigens which initiate the auto-immune processes.[5] Since the first description of the disease by Überreiter,[2] several different therapies have been described. However, a standard treatment has not been determined and there is currently no cure for CSK. The goal of all described therapies is to delay progression. In mildly affected cases this can be achieved by topical treatment with corticosteroids and ciclosporine.[5] In patients that are nonresponsive to therapy, progressive corneal vascularization and pigmentation will eventually result in blindness. In such cases, superficial keratectomy is recommended and can be combined with adjuvant radiotherapy. Beta irradiation has been suggested without keratectomy in severe cases.[1,6] Controlled studies of radiotherapy for CSK are sparse and specific detailed information regarding dose, dose specification and side effects are rarely mentioned. Given the steep dose fall-off of either superficial X-rays or Sr-90, which are the two major sources of radiation in use for CSK, doses applied have to be specified in detail. In a typical treatment situation, the dose of a 15 kV X-ray beam is reduced to approximately half of the surface-dose within just 1 mm of tissue, or within 2 mm for Sr-90. Hence just providing doses without specifying the precise point at which the radiation dose is delivered (i.e. at the surface or in the depth in tissue, in mm) is simply misleading. This probably leads to the large disparities between some of the publications. As the tissue penetration capability of radiation delivered by different X-ray machines is not the

same, details of tissue penetration or radiation delivered are often provided in the form of 'half volume layers'.

The positive effect of radiotherapy on CSK was shown in a previous study in which Sr-90 was used as source of beta-rays.[7,8] There are only a few Sr-90 applicators in use in human ophthalmology in Germany and these are not easily accessible for the treatment of dogs.

Willner and others had presented positive results of 20 kV irradiation on pterygium in people as an alternative to Sr-90 applicators.[9] According to the dose penetration in depth of water, 15 kV X-rays seemed to be appropriate for the therapy of CSK and were chosen as an alternative source of irradiation in this series of cases.

The aim of this study was to evaluate the effect of soft X-rays (15 kV) for treatment of refractory CSK and to compare results to a previous study using Sr-90. Soft X-ray units are widely available and may offer successful treatment for canine CSK.

MATERIALS AND METHODS

Thirteen dogs with confirmed CSK were included in this prospective study. All dogs showed progressive corneal pigmentation despite long term topical anti-inflammatory treatment with dexamethasone 0.1% and ciclosporine 2% BID. Eleven dogs were included in the subsequent analysis, as their follow-up and documentation were complete.

Breeds represented were seven German Shepherds, three Shepherd-crosses and one Labrador-cross. Seven of the dogs were female, five intact and two neutered, and four dogs were intact males. Mean age of the dogs at the onset of clinical signs of CSK was 5.6 years, mean age at the time of the radiotherapy was 7 years (range 3–9 years). Medical treatment protocol, follow-up and documentation was performed as described in a previous study regarding the effects of Sr-90 on CSK.[7,8] A separate control group was considered unnecessary as the results are compared to a previous study undertaken under the same conditions.[7,8] All dogs received bilateral irradiation with 15 kV soft X-rays (Darpac 150 MC/TH150, RayTech®, Swindon, UK; 1.5 cm round tube, focus-surface-distance [FSD] 15 cm, filtering of tube equals 0.8 mm Be at 15 kV and 5.2 mA) (Fig. 1). The lids were kept open with a lid speculum. The globes were rotated and stabilized by grasping the conjunctiva with a fine hemostat (Fig. 1). The tube was placed over the eye adapting and aligning it to the limbus. Both eyes were treated with a superficial dosage of 15 Gy twice within 48–96 h (total dose 30 Gy). The time interval between treatments was 48 h except for two dogs that could only receive the second treatment after 96 h for logistical reasons. The treatment time was approximately 1.5 min. The radiotherapy was applied under deep sedation (ketamine, xylazine, diazepam intravenously).

Due to the advanced stage of keratitis and extensive corneal pigmentation, three dogs showed severe visual impairment. These three dogs underwent a superficial lamellar keratectomy 48 h prior to irradiation. In two dogs, the keratectomy was performed bilaterally, in one dog unilaterally. After the irradiation topical dexamethasone was discontinued for 5 days and after keratectomy, triple antibiotic ointment (polymyxin-neomycin-bacitracin, Polyspectran®, Alcon, Germany) was applied BID for 5 days. All dogs continued on topical therapy (dexamethasone, 0.1% and ciclosporine, 2% BID) indefinitely thereafter. Complete ophthalmologic examinations including Schirmer tear test (STT), fluorescein stain, slit-lamp examination, tonometry and indirect ophthalmoscopy were performed prior to radiotherapy as well as 3, 6, 12 and 24 weeks after irradiation. Clinical findings were documented using a grading system for clinical signs (0 = no signs, 1 = mild, 2 = moderate, 3 = severe signs), schematic drawings and photographs. As in the previous study,[7] the cornea was schematically divided into 24 sectors for documentation (Fig. 2). The division of the cornea into sectors compensated for the greater clinical importance for vision of the central vs. the peripheral sectors, by making the former smaller than the latter. The parameters evaluated were corneal pigmen-

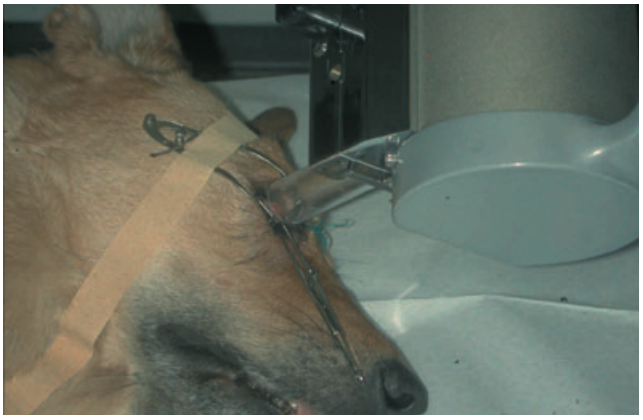

Figure 1. Patient positioned for soft X-ray irradiation using a Darpac 150 MC/TH150, RayTech®, UK.

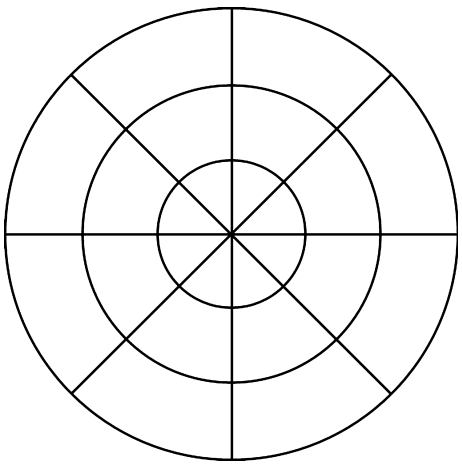

Figure 2. Schematic division of the cornea into sectors for documentation of extent and density of corneal pigmentation, as well as corneal vascularization.

tation, with regard to both pigment density and pigment extent, as well as corneal vascularization. Each corneal sector was evaluated for corneal pigment extent (yes/no) and corneal vascularization (yes/no) as well as for corneal pigment density. Corneal pigment density was graded within the sectors from 0 to 3 (0 = none, 1 = fundus visible, 2: = iris visible, 3 = cornea opaque). The mean corneal pigment density was calculated by adding the products of the numbers of sectors and grade of pigmentation divided by the total number of pigmented sectors. The course of the disease process in each eye was documented over a follow-up period of 24 weeks. Given the relatively small number of subjects involved in the study, results were presented and evaluated by descriptive statistics.

RESULTS

Immediately after radiation treatment all dogs showed blepharospasm, photophobia and epiphora. Those signs ceased within 3–5 days without special treatment. No signs of infection were noted. Three dogs showed a mild blepharitis bilaterally that resolved without treatment after 7 days. One dog which had received irradiation only developed a superficial corneal ulcer unilaterally, 16 weeks after irradiation. The ulcer healed within 10 days with additional topical application of triple antibiotic ointment (polymyxin-neomycin-bacitracin, Polyspectran®) discontinuing dexamethasone for that perior of time.

During the observation period (24 weeks) the extent of corneal pigmentation was reduced in all eyes (Fig. 3). The pigment density was diminished in all eyes within the first months after treatment but increased in 6/22 eyes by the end of the observation period, mostly to a minor degree (Fig. 4). The extent of corneal vascularization decreased in all eyes initially and this reduction was maintained in 19/22 eyes over the evaluation period (Fig. 5). The dogs that received keratectomy prior to irradiation regained vision in the treated eyes and remained visual during the observation

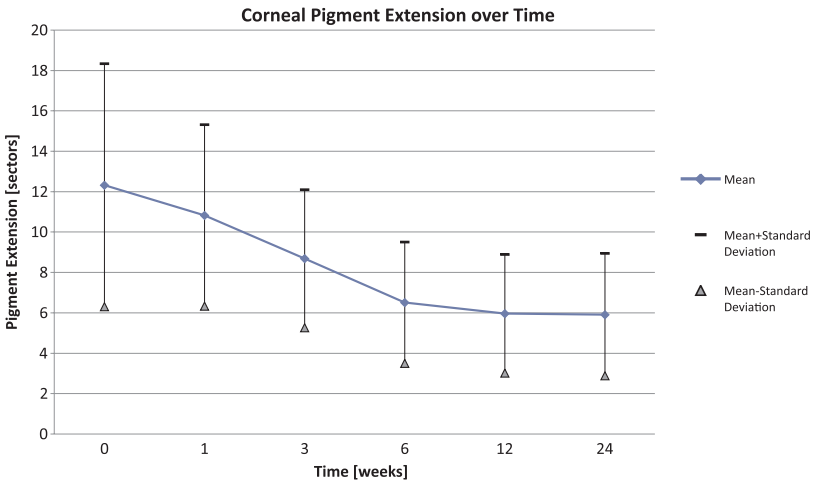

Figure 3. Extent of corneal pigmentation in the irradiated eyes over 24 weeks.

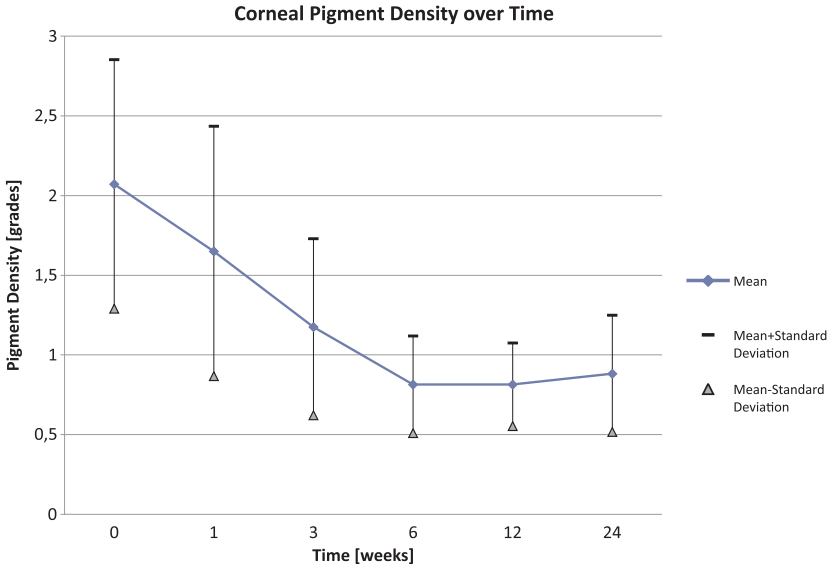

Figure 4. Corneal pigment density in the irradiated eyes over 24 weeks.

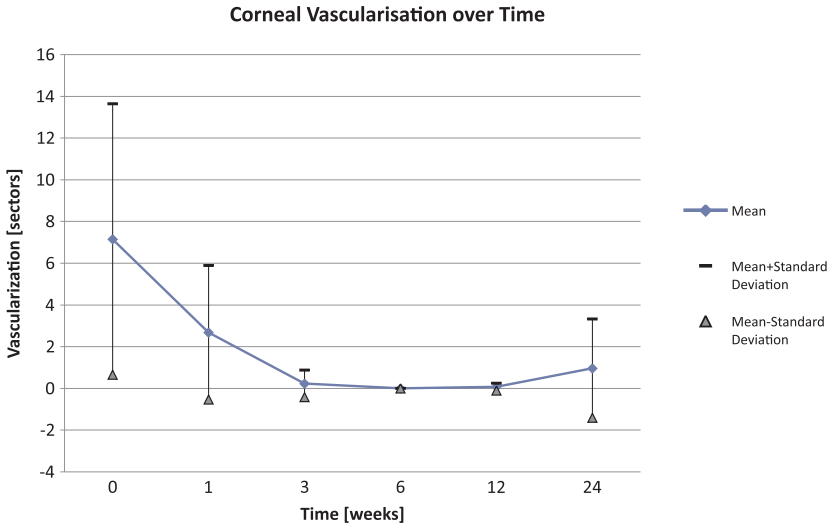

Figure 5. Extent of corneal vascularization in the irradiated eyes over 24 weeks.

period. Two of those dogs were followed for 36 months after keratectomy and irradiation while receiving ongoing topical dexamethasone, 0.1%, treatment BID. They remained visual and showed sparse pigmentation peripherally that did not interfere with vision 36 months after keratectomy and irradiation (Figs. 6 and 7).

DISCUSSION

The effect of radiotherapy treatment with soft X-rays (15 kV) on canine CSK was documented for the first time in this study. Despite all selected cases of this study demonstrating a poor response to medical therapy alone, all responded well to treatment with soft X-rays. Variable response of CSK cases to medical treatment alone has been described previously.[10,11] Generally the outcome of medical treatment is good. However, there are cases that demonstrate severe relapses and rapid progression of pigmentation despite medical therapy.

Previous studies have provided documented evidence of a positive effect of Sr-90 irradiation on CSK.[1,7,8,12] As Willner *et al.* showed positive results of 20 kV irradiation on pterygium in people as an alternative to Sr-90 therapy,[9,13] and Sr-90 applicators are not widely available compared to soft X-ray units, we chose the latter treatment modality for this study.

Technically, the 15 kV treatment with a round tube is superior to the Sr-90 therapy. With the 15 kV tube there is complete and homogenous irradiation effect on the entire cornea as well as the limbus with only one treatment (Fig. 8). With the Sr-90 applicator several applications are necessary to cover the affected corneal area. This results in several over- and under-dosed areas as well as untreated parts of limbus and cornea. The untreated and under-dosed areas may subsequently represent sites for initiation of subsequent relapses. Furthermore, the use of Sr-90 applicators exposes the radiotherapist to irradiation, whereas 15 kV irradiation does not require a radiotherapist to be present in the room for treatment. This is important in terms of radiation protection of personnel.

The effect of irradiation on the disease process is not completely understood. A direct effect of ionizing rays on the corneal pigmentation can be explained by an inhibition of RNA synthesis and thereby inhibition of tyrosinase activity within the cornea.[1,14] An indirect effect of irradiation on corneal pigmentation is through reduction of the corneal vascularization which impedes the migration of limbal melanocytes into the stroma.[15] The effect of irradiation on vascularization seems to be due to an inhibition of mitosis of the actively dividing vascular endothelial cells.[16] Apart from this primary effect,[17] there is a long term anti-inflammatory effect on the irradiated eye. With regression of the vascularization the cornea loses its biochemically active inflammatory state and returns to the normal, quiescent state. [18]

The prescriptions for radiation therapy of CSK given in the literature are inconsistent, ranging from single doses that vary between 5 and 100 Gy and total doses between 10 and 585 Gy and no information has been provided about the depth of the dose distribution.[1] Therefore, we chose to follow the reference dose for irradiation of human pterygium.[13,19] Considering the dose distribution according to the depth of penetration in water (Fig. 9), we selected 15 kV rays as an appropriate source of irradiation. A total of 15 kV rays penetrate even less than Sr-90 while having full effect on the superficial cornea, thereby causing less potential side effects. Obviously much higher dosages of 60–90 Gy are tolerated, as seen in overlapping areas with the Sr-90 applicator. Serious side effects were not noted in either study.

Chronic superficial keratitis is a progressive disease. Therefore arrest in, or even delay of, progression may be regarded as treatment success. This was achieved in almost all cases after irradiation. The chosen superficial dosage of 2×15 Gy irradiation was effective and safe in both 15 kV treated dogs in the current study, and in Sr-90 treated dogs

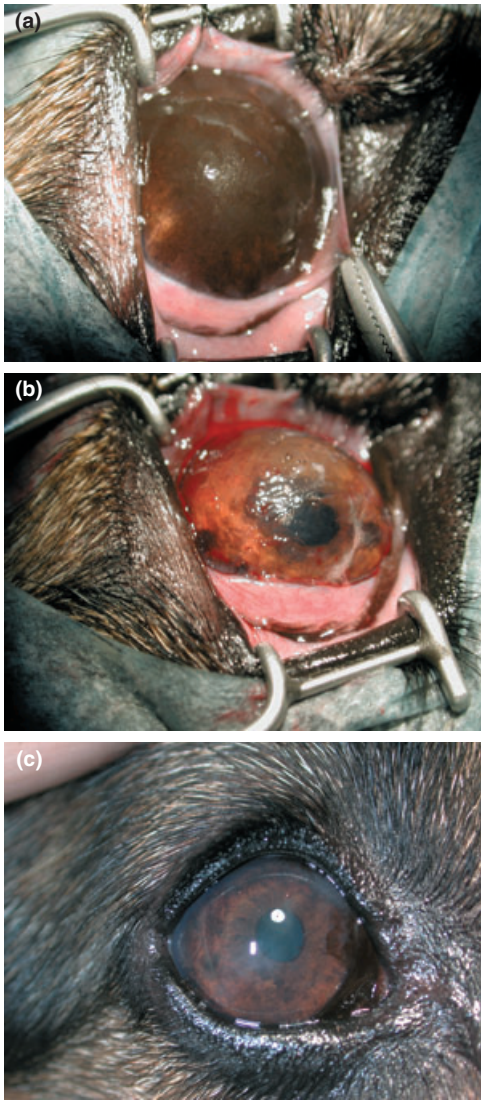

Figure 6. Course of one case of severe CSK treated by keratectomy and soft X-rays. (a) Clinical appearance of a severe case of CSK prior to keratectomy. Pigment extent: 24 sectors, vascularization: 4 sectors, pigment density: grade 2.75. (b) Presentation of the same eye as in (a) immediately after keratectomy. (c) Presentation of the same eye as in (a + b), 36 months after irradiation, under continuing treatment with topical dexamethasone, 0.1%, BID. Pigment extent: 3 sectors, vascularization: 0 sectors, pigment density: grade 1.

in our previous report.[7] The overall effect of soft X-rays on the course of the keratitis seemed to be superior. Extent of pigmentation was reduced in all eyes (22/22) after 15 kV irradiation, whereas in the Sr-90 group it was only reduced in 77% of dogs. Pigment density diminished in 18/22 eyes (82%) in the 15 kV group, while it only diminished in 31% of the eyes and remained unchanged in 69% of the Sr-90 group in our previous study.[7] Corneal vascularization was reduced in 19/22 eyes (87%) in the 15 kV group compared to only 54% of the Sr-90 group. When comparing the results of the 15 kV-treated group to the Sr-90-treated group, two important points have to be taken into account:

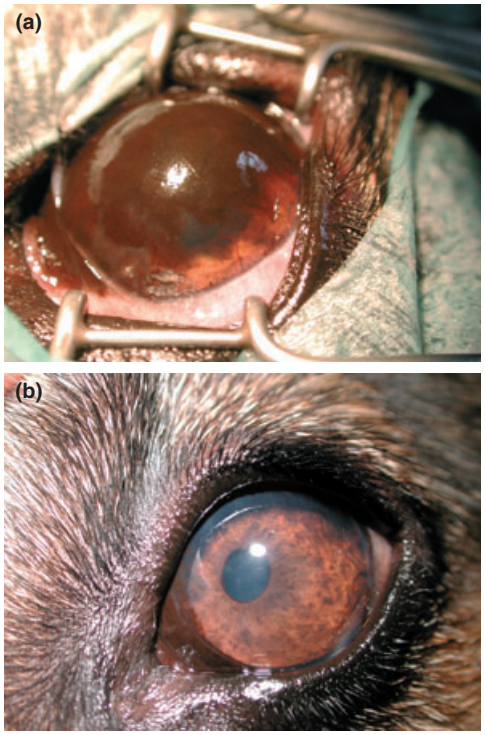

Figure 7. Severe CSK treated by keratectomy and soft X-rays before treatment and after 3 years. (a) Clinical presentation of a severe case of CSK prior to keratectomy. Pigment extent: 24 sectors, vascularization: 5 sectors, pigment density: grade 2.75. (b) Presentation of the same eye as in (a) 36 months postirradiation under continuing treatment with topical dexamethasone, 0.1%, BID. Pigment extent: 2 sectors, vascularization: 0 sectors, pigment density: grade 1.

the mean age of onset of clinical signs was lower in the Sr-90 group (4.4 years) than in the 15 kV group (5.6 years). In younger dogs CSK tends to be more severe and progresses faster than in older dogs.[20]

Radiotherapy reduces corneal pigmentation and vascularization in CSK. When combined with keratectomy in eyes with totally pigmented corneas, with visual impairment, the results are impressive. We advocate keratectomy and irradiation combined with lifelong topical anti-inflammatory therapy as the treatment of choice for advanced cases of CSK with vision loss. Based on the positive effect of 15 kV soft X-rays on CSK in our study, this therapy shows promise as a more widespread clinical application, particularly as soft X-ray-machines are widely distributed in radiotherapy departments and practises.

This study may serve as a pilot study for larger, future studies, incorporating strict control groups and providing more rigorous evidence for the use of this technique by future contolled clinical trials. However, enrolling clinical patients will always limit the number of comparable cases meeting the requirements for eligibility.

In conclusion, soft X-ray irradiation offers a new and effective treatment alternative, especially in combination with keratectomy, for advanced and progressive cases of CSK in dogs.

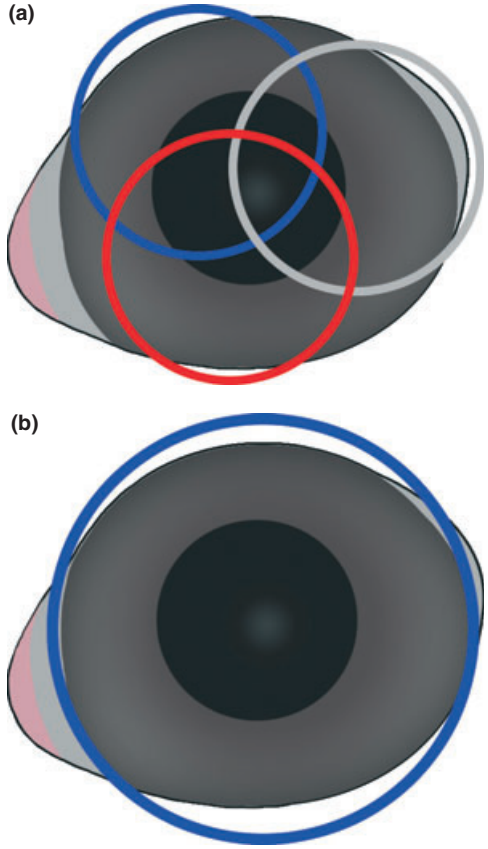

Figure 8. Corneal coverage of the Sr-90 applicator and the 15 Kv tube: Schematic comparison of the irradiation with a Sr-90 applicator (a) and soft X-ray round tube (b). Overlapping zones and untreated areas are present with the Sr-90 applicator. The entire cornea as well as the limbus are covered by the soft X-ray tube.

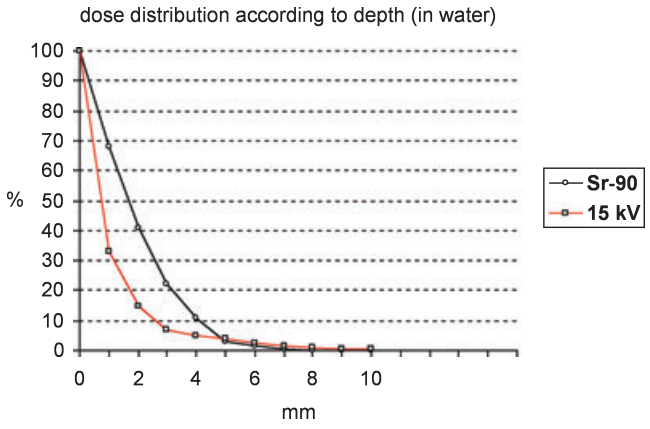

Figure 9. Dose distribution according to depth of penetration in water of Sr-90 and soft X-rays.

ACKNOWLEDGMENTS

We gratefully acknowledge the help of Prof. Dr. Klaus Hartung in designing our study and discussing the results achieved. The paper profited from Gill McLellan's linguistic proficiency. We thank her for her proof-reading and suggestions and Matthias Zörner for his assistance with the graphs.

REFERENCES

1. Slatter DH, Lavach JD, Severin GA *et al.* Überreiter's syndrome (chronic superficial keratitis) in dogs in the Rocky Mountain area (463 cases). *Journal of Small Animal Practice* 1977; **18**: 757–772.
2. Überreiter O. Eine besondere Keratitisform (Keratitis superficialis chronica) beim Hunde. *Wien Tieraerztl Monatsschr* 1961; **2**: 65–77.
3. Eichenbaum J, Lavach D, severin G *et al.* Immunohistochemical staining patterns of canine eyes affected with chronic superficial keratitis. *American Journal of Veterinary Research* 1986; **47**: 1952–1955.
4. Williams DL. Histological and immunohistochemical evaluation of canine chronic superficial keratitis. *Research in Veterinary Science* 1999; **67**: 191–195.
5. Williams DL, Hoey AJ, Smitherman P. Comparison of topical cyclosporin and dexamethasone for the treatment of chronic superficial keratitis. *Veterinary Record* 1995; **137**: 635–637.
6. Bedford P, Longstaffe JA. Corneal pannus (chronic superficial keratitis) in the German Shepherd dog. *Journal of Small Animal Practice* 1979; **20**: 41–56.
7. Grüning G, Allgoewer I, Höcht S *et al.* Zur Strahlentherapie der Keratitis superficialis chronica mit Strontium 90. *Kleintierpraxis* 2001; **46**: 389–399.
8. Höcht S, Grüning G, Allgoewer I *et al.* Die Behandlung der Keratitis chronica superficialis des Hundes mit Strontium-90. *Strahlentherapie und Onkologie* 2002; **178**: 99–104.
9. Willner J, Flentje M, Lieb W. Soft X-ray therapy of recurrent pterygium – an alternative to 90 Sr eye applicators. *Strahlentherapie und Onkologie* 2001; **177**: 404–409.
10. Jackson P, Kaswan R, Merideth R *et al.* Chronic superficial keratitis in dogs, a placebo controlled trial of topical cyclosporine treatment. *Progress in Veterinary and Comparative Ophthalmology* 1991; **1**: 269–275.
11. Bigelbach A. Die lokale Behandlung kortikoresistenter Fälle von Keratitis superficialis chronica (Überreiter) und plasmazellulärer Nickhautinfiltration mit cyclosporin. *Kleintierpraxis* 1993; **38**: 271–280.
12. Stanley RG. Superficial stromal keratitis in the dog. *Australian Veterinary Journal* 1988; **65**: 321–323.
13. Fukushima S, Inoue TO, Inoue TA *et al.* Postoperative irridation of pterygium with Sr 90 eye applicator. *International Journal of Radiation Oncology, Biology, Physics* 1999; **43**: 597–600.
14. Hanna C, Combs S, Barnhard H. Effects of beta-rays on DNA synthesis during corneal wound healing. *American Journal of Ophthalmology* 1969; **68**: 291–295.
15. Bellhorn R, Henkind P. Superficial pigmentary keratitis in the dog. *Journal of the American Veterinary Medical Association* 1966; **149**: 173–17.
16. Catcott EJ, Tharp L, Johnson E. Beta ray therapy in ocular diseases of animals. *Journal of the American Veterinary Medical Association* 1953; **122**: 172–175.
17. Friedell H, Thomas M, Krohmer M. Description of a Sr 90 beta ray applicator and its use to the eye. *American Journal of Roentgenology* 1951; **65**: 232–243.
18. Mailath L, Peter M. Die ß-Strahlen-Behandlung der Hornhautvaskularisation nach Keratoplastik. *Klin Mbl Augenheilk* 1972; **160**: 554–559.
19. Schultze H, Hinrichs K, Kimmig B. Strahlentherapie des Pterygiums. *Strahlentherapie und Onkologie* 1996; **172**: 417–421.
20. Farmer AMT. Corneal pannus in the dog. *Veterinary Annual* 1984; **24**: 315–324.