Radiotherapy for age related macular degeneration causes transient lens transparency changes

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Abstract

Aim—Evaluation of potential side effects of photon radiotherapy on the transparency of the lens.

Methods—The anterior segments of 14 phakic eyes from patients suffering from subfoveal neovascularisation as a result of age related macular degeneration (AMD) were documented by Scheimpflug photography (Topcon SL-45, Kodak Tmax 400) before the start of radiotherapy as well as 6 and 12 months afterwards. All negatives were evaluated by microdensitometry, and peak heights for distinct layers of the lens were used for statistical comparison. External beam radiotherapy (6 MeV photons) consisted of a total dose of 20 Gy, delivered as 10 fractions of 2 Gy.

Results—Six and 12 months following irradiation statistical comparison of the ratios in density change of lenses from irradiated versus non-irradiated fellow eyes revealed statistically significant ($p \leq 0.05$) loss of transparency of layers 5 and 7 of the nuclear region. In layer 1 (capsuloepithelial complex) the changes were close to significance. At the 12 month examination, however, all of these significant changes had disappeared.

Conclusion—Six months following radiotherapy for AMD, both the anterior capsuloepithelial region and the nuclear layers showed precatactous changes. As most of these significant differences had disappeared after 12 months, it is obvious that these findings reflect acute radiation damage to the lens epithelial cells and an ionising effect on the proteins of the lens nucleus. Long term studies will have to be carried out to demonstrate whether or not this acute radiation damage, which is expressed as a transient increase in light scattering of some layers of the lens, actually does lead to permanent transparency changes, thus reflecting radiation cataractogenesis, and if so, after what time interval and to what extent cataract occurs.

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applied, which were divided into 6-10 fractions.²⁻⁴⁻¹⁵ To minimise radiation effects to the lens and other eye tissues, irradiation techniques with a single lateral port angled several degrees posteriorly have been used in most protocols.

The side effects described are mostly epiphora and transient conjunctival irritation.¹⁶ The eye tissue most sensitive to long term expression of radiation effects, however, is the lens. Sensitivity of the mammalian lens to ionising radiation is triggered by the growth and differentiation characteristics of the lenticular epithelium.¹⁷ Radiation damage to the lens occurs on two levels: (1) acute radical reactions involving lens crystallins or enzymes of the carbohydrate metabolism and the oxidative defence system, leading to transient transparency changes; (2) radiation induced damage to the DNA of the epithelial cells, leading to long term changes that develop together with the ongoing proliferation of lens fibre cells.¹⁸⁻¹⁹ The growth and differentiation potential of the lens declines with age. This leads to a constant decrease in mitotic activity in the germinative zone of the epithelium, causing a permanent increase in the latency period for the expression of radiation induced DNA damage which appears as cataracts.

While this increase in latency may provide a safety margin for the application of ionising radiation as a treatment of AMD, dosage fractionation increases the effectiveness of ionising radiation in damaging the lenticular epithelium, so that the latency period is shortened considerably and the intensity of cataract development can be enhanced.²⁰

Using slit lamp microscopic examination, significant progression of cortical and subcapsular lens opacities with accompanying loss of visual acuity has been described in the eyes of two patients 3 years after receiving a dose of 15 Gy delivered as 5×3 Gy for radiotherapy of AMD.⁸ Martin *et al* found cataract formation in one eye treated with 20 Gy in five fractions.²¹ Sasai *et al* described cataract formation in one eye 1 year after the patient had received a fractionated dose of 20 Gy.²²

Slit lamp microscopy alone, however, only allows detection of fairly obvious visible changes in lens transparency, whereas Scheimpflug photography, with consecutive image analytical evaluation, provides a reproducible and reliable tool for the detection of changes in lens transparency before visible changes occur.²³⁻²⁵ The suitability of this method for documenting radiation cataract in particular has been evaluated experimentally.²⁶ The study reported here is the first clinical study involv-

External beam radiotherapy has been evaluated for treatment of patients with age related macular degeneration (AMD), accompanied by subfoveal choroidal neovascularisation.¹⁻³ In various clinical studies external beam radiotherapy has been applied to the eye using a linear accelerator in an energy range of 6-24 MeV. The doses involved were up to 36 Gy and were delivered in 1-10 fractions. In most studies, however, doses between 12 and 20 Gy were

Figure 1 Computed tomograph with superimposed treatment plan showing isodose distribution for 6 MV photon beam. The green circle shows the 95% isodose. The ipsilateral lens receives 10% of the maximum dose—that is, 2 Gy.

Figure 2 Scheimpflug images of a patient's anterior eye segment at baseline (A) before irradiation, 6 months (B) and 12 months (C) following irradiation. Nos 1, 2, 3 indicate the densitometric scans. The corneal reflex which can be seen in the anterior cortex of (A) has not affected the densitometric reading.

ing Scheimpflug photography as a technique for objective and reproducible control of possible radiotherapy induced side effects in the lens during treatment of AMD.

Methods

Fourteen phakic patients receiving external beam radiotherapy of one eye for AMD with subfoveal choroidal neovascularisation were enrolled in this study. Radiotherapy was performed with a 6 MV photon linear accelera-

Figure 3 (A) Example of a densitometric reading of the human lens with the following identifiable layers: 1 = capsuloeptithelial complex, 2 = anterior zone of fibre cell elongation, 3 = anterior superficial cortex, 4 = anterior deep cortex, 5 = anterior supranuclear layer, 6 = anterior nucleus, 7 = posterior nucleus, 8 = posterior supranuclear layer. (B) Example of three parallel densitometric scans in the areas 1-3 (left, middle, right) at baseline (dotted line) and 12 months later (solid line).

tor using a 2×2 cm target field. A single lateral port tilted 10° posteriorly was chosen to reduce radiation effects in the other eye. A total dose of 20 Gy, fractionated in 10×2 Gy, was applied with a frequency of three sessions per week. The average treatment time was 1.5 minutes. The 95% isodose area was 11 mm. Fixation was monitored as described earlier to prevent radiation misapplication because of eye movement.²⁷ The treatment evaluation plan showed that not more than 10% of the maximum dose reached the posterior pole of the lens—that is, 2 Gy at most (Fig 1).

The anterior eye segments of both eyes of the patients were documented with Scheimpflug photography (Topcon SL-45)²⁸ in mydriasis in three optical sections (0° , 45° , 180°) rotating around the optical axis of the eye. Before the start of treatment, as well as 6 and 12 months after onset of radiotherapy, all eyes were photographed on Kodak Tmax 400 black and white film. The film was processed according to a standard protocol, providing good reproducibility of film contrast and background density.²⁹ Figure 2 shows an example of Scheimpflug images of a patient's anterior eye segment at baseline (A) as well as 6 (B) and 12 (C) months following irradiation. The images were evaluated with microdensitometry with an upgraded Joyce Loebel 3CS microdensitometer in eight defined layers of the lens, reaching from the anterior capsule and epithelium to the posterior supranuclear layer: (L1) the capsuloeptithelial complex, (L2) anterior zone of fibre cell elongation, (L3) anterior superficial cortex, (L4) anterior deep cortex, (L5) anterior supranuclear layer, (L6) anterior nucleus, (L7) posterior nucleus, (L8) posterior supranuclear layer. To facilitate comparison, ratios were used for layers 1-8 of the lenses of both irradiated and non-irradiated eyes.³⁰ Figure 3A shows an example of a densitometric reading of the human lens with clearly identifiable layers as indicated above. Figure 3B shows an exam-

Table 1 Mean values (MV), standard deviations (SD) for right and left lens and results of Wilcoxon signed rank test for each of the lens layers (1–8) investigated in 14 patients after 6 and 12 months

Layer		6 months			12 months		
		MV	SD	p Value	MV	SD	p Value
1	radiation	1.014	0.035		1.016	0.026	
	control	1.034	0.033	0.056	1.018	0.030	0.756
2	radiation	0.969	0.050		1.001	0.010	
	control	1.011	0.069	0.345	0.992	0.070	0.715
3	radiation	0.986	0.047		0.982	0.036	
	control	1.005	0.043	0.209	0.998	0.049	0.237
4	radiation	0.992	0.030		1.012	0.029	
	control	1.002	0.041	0.272	1.021	0.036	0.248
5	radiation	0.993	0.033		1.015	0.034	
	control	1.022	0.035	0.026	1.024	0.040	0.811
6	radiation	1.000	0.040		1.018	0.026	
	control	1.017	0.031	0.124	1.027	0.038	0.508
7	radiation	0.997	0.048		1.014	0.032	
	control	1.044	0.035	0.004	1.022	0.068	0.767
8	radiation	1.001	0.058		1.017	0.012	
	control	1.044	0.054	0.144	1.012	0.031	0.655

ple of three densitometric scans through the above mentioned eight lens layers at baseline and 12 months later. Statistical comparison was carried out by calculating ratios for each lens layer of both the irradiated and non-irradiated lenses before, 6 and 12 months after treatment,³¹ using the Wilcoxon signed rank test. All subjects were treated in accordance with the tenets of the Declaration of Helsinki. Informed consent was obtained from the participants after explanation of the nature and possible consequences of the study, and the approval of the institutional ethics committee was granted.

Results

At the 6 month examination, a density increase was demonstrated for all eight layers, but significant differences could be detected only in layers 5 and 7 (Table 1). In layer 1 the density increase was close to significance. At the 12 month examination, all significant differences had disappeared, which demonstrates that only transient radiation effects have been documented so far.

Discussion

In general, the most frequent type of radiation cataract is posterior subcapsular opacity.¹⁶ However, cortical cataracts, wedge-shaped cataracts, and mature cataracts have also been described as radiation induced. Radiation cataracts can occur after a single dose of 2 Gy or after fractionated radiation dosages of up to 8 Gy. Radiation of the lens with 11 Gy or more will induce radiation cataracts in all patients. A dose of 15 Gy is reported to lead to progressive opacification of the entire posterior lens pole and cortex.³²

External beam radiotherapy for subfoveal choroidal neovascularisation is currently applied in a great number of centres all over the world. Radiation side effects are mostly seen as transient epiphora or conjunctival irritation,^{5,6} but only four cases of permanent cataract formation have been described in these studies so far.^{8,21,22}

In the study regimen of Hart and coworkers, patients were treated with 15 Gy in five fractions over 5 days using a 6 MV linear accel-

erator. The 90% isodose encompassed the macula and optic disc with less than 50% of the maximum dose falling on the posterior lens.⁸ Few other treatment centres found cataract formation on clinical examination, and precatactous transparency changes could not be ruled out by slit lamp examination in a further study.³³

Regarding the isodose scheme of our radiation regimen, the lens of the irradiated eye received less than 10% of the radiation dose—that is, less than 2 Gy. Using Scheimpflug photography, evaluation of transparency changes in up to eight lens layers was possible in this study. We compared the ratio of density changes of the lenses of irradiated versus non-irradiated eyes 6 months after treatment; our results revealed a statistically significant loss of transparency in layers 5 and 7, representing the anterior supranuclear layer and the posterior nucleus of the lens. In layer 1 (capsuloepithelial complex), the difference was close to significant. Transparency loss in the latter layer is consistent with acute radiation damage to the lens epithelial cells, whereas the changes in the nuclear layers reflect an ionising effect on the crystallins. Thus, two metabolically different regions of the lens are being affected: the epithelial complex (L1), which is the metabolically most active region of the lens, and the supranuclear region (L5–L7), which is metabolically inactive. Because of the fairly high mean age of all patients enrolled in this study (74.5 years) before the onset of radiation therapy, all lenses had varying degrees of pre-existing opacities in both eyes. At this time of life, long term expression of radiation damage to the lens may not be relevant for the patient. Nevertheless, 6 months after onset of radiotherapy transient precatactous changes could be detected in both the anterior epithelium and the nucleus. At the 12 month examination, however, these differences in density had disappeared. Long term studies will have to be carried out to determine whether the acute radiation damage will actually lead in the long term to permanent transparency changes, thus reflecting radiation cataractogenesis. Although the mean age of the patients in this study may be too high to permit much long term follow up, we intend to follow up as many as possible.

- 1 Felten G. Über die Behandlung der feuchten Makuladegeneration durch fraktionierte Röntgenbestrahlung des hinteren Augenpols. Medical thesis, University of Hamburg, 1968.
- 2 Chakravarthy U, Houston RF, Archer DB. Treatment of age-related subfoveal neovascular membranes by teletherapy: a pilot study. *Br J Ophthalmol* 1993;77:265–73.
- 3 Bergink GJ, Deutman AF, van den Broek JF, et al. Radiation therapy for subfoveal choroidal neovascular membranes in age-related macular degeneration. A pilot study. *Graefes Arch Clin Exp Ophthalmol* 1994;32:591–8.
- 4 Berson AM, Finger PT, Sherr DL, et al. Radiotherapy for age-related macular degeneration: preliminary results of a potentially new treatment. *Int J Radiat Oncol Biol Phys* 1996;36:861–5.
- 5 Finger PT, Berson A, Sherr D, et al. Radiation therapy for subretinal neovascularization. *Ophthalmology* 1996;103:878–89.
- 6 Freire J, Longton WA, Miyamoto CT, et al. External radiotherapy in macular degeneration: technique and preliminary subjective response. *Int J Radiat Oncol Biol Phys* 1996;36:857–60.
- 7 Haas A, Pakisch B, Langmann G, et al. Fraktionierte Teletherapie bei seniler Makuladegeneration. *Spektrum Augenheilkd* 1997;11:96–9.

- 8 Hart PM, Chakravarthy U, MacKenzie G, et al. Teletherapy for subfoveal choroidal neovascularization of age-related macular degeneration: results of follow up in a non-randomized study. *Br J Ophthalmol* 1996;**80**:1046–50.
- 9 Holz FG, Engenhardt R, Bellmann C, et al. Stereotactic radiation therapy for sub-foveal choroidal neovascularization secondary to age-related macular degeneration. In: Wiegand T, Bornfeld N, Foerster MH, Hinkelbein W, eds. *Radiotherapy of ocular disease. Front Radiat Ther Oncol*. Basel: Karger, 1997;**30**:238–46.
- 10 Schittkowski MP, Schneider H, Ziegler PG, et al. Niedrig dosierte, fraktionierte, perkutane Teletherapie bei subfovealen chorioidalen Neovaskularisationen. *Ophthalmologie* 1998;**95**:466–72.
- 11 Schleicher UM, Adreopoulos D, Wolf S, et al. Radiotherapy of macular degeneration, experience with two fractionation schemes. In: Wiegand T, Bornfeld N, Foerster MH, Hinkelbein W, eds. *Radiotherapy of ocular disease. Front Radiat Ther Oncol*. Basel: Karger, 1997;**30**:253–8.
- 12 Spaide RF, Guyer DR, McCormick B, et al. External beam radiation therapy for choroidal neovascularization. *Ophthalmology* 1997;**105**:24–30.
- 13 Stalmans P, Leys A, van Limbergen E. External beam radiotherapy (20 Gy, 2 Gy fractions) fails to control the growth of choroidal neovascularization in age-related macular degeneration: a review of 111 cases. *Retina* 1997;**17**:481–92.
- 14 Thölen AM, Meister A, Bernasconi P, et al. Radiotherapie von subretinalen Neovaskularisationsmembranen bei altersabhängiger Makuladegeneration (AMD). *Ophthalmologie* 1998;**95**:691–8.
- 15 Valmaggia C, Bischoff P, Ries G. Niedrig dosierte Radiotherapie der subfoveolären Neovaskularisationen bei altersabhängiger Makuladegeneration. Vorläufige Resultate. *Klin Monatsbl Augenheilkd* 1995;**206**:343–6.
- 16 Macfaul PA, Bedford MA. Ocular complications after therapeutic irradiation. *Br J Ophthalmol* 1970;**54**:237–47.
- 17 Worgul BV, Rothstein H. Radiation cataract and mitosis. *Ophthalmic Res* 1975;**7**:21–32.
- 18 Worgul BV, Meriam GR Jr, Medvedovsky C. Cortical cataract development, the expression of primary damage to the lens epithelium. *Lens Eye Toxicol Res* 1989;**6**:557–71.
- 19 Gordon KB, Char DH, Sagerman RH. Late effects of radiation on the eye and ocular adnexa. *Int J Radiat Oncol Biol Phys* 1995;**31**:1123–39.
- 20 Merriam GR Jr, Focht EF. A clinical and experimental study on the effect of single and divided doses of radiation on cataract production. *Trans Am Ophthalmol Soc* 1962;**60**:35–52.
- 21 Martin P, Maugé M, Gérard JP, et al. Radiothérapie des dégénérescences maculaires liées à l'âge (DMLA): résultats préliminaires d'une étude lyonnaise. *Cancer Radiother* 1997;**1**:227–33.
- 22 Sasai K, Murata R, Mandai M, et al. Radiation therapy for ocular choroidal neovascularization (phase I/II study): preliminary report. *Int J Radiat Oncol Biol Phys* 1997;**39**:173–8.
- 23 Hockwin O, Dragomirescu V, Laser H, et al. Measuring lens transparency by Scheimpflug photography of the anterior eye segment: principle, instrumentation, and application to clinical and experimental ophthalmology. *J Toxicol Cut Ocular Toxicol* 1987;**6**:251–71.
- 24 Müller-Breitenkamp U, Hockwin O. Scheimpflug photography in clinical ophthalmology. A review. *Ophthalmic Res* 1992;**24**(suppl 1):47–54.
- 25 Merriam GR, Medvedovsky C, Worgul BV. Scheimpflug image analysis of radiation cataract development. *Invest Ophthalmol Vis Sci* 1988;**29**:427.
- 26 Worgul BV, Medvedovsky C, Wu B. Use of non-subjective analysis of lens transparency in experimental radiation cataract research. *Ophthalmic Res* 1995;**27**(suppl.1):110–15.
- 27 Eter N, Schüller H, Spitznas M, et al. Fixation monitoring during radiation therapy for subfoveal neovascularization. *Graefes Arch Clin Exp Ophthalmol* 1998;**36**:806–10.
- 28 Laser H, Hockwin O, Schieck A, et al. Investigations of the anterior eye segment by Scheimpflug photography using visible or UV light with volunteers of different age and with patients with various types of lens opacification. *Lens Res* 1988;**5**:1–21.
- 29 Hockwin O, Dragomirescu V, Laser H, et al. Scheimpflug photography of the anterior eye segment. Principle, instrumentation and application to clinical and experimental ophthalmology. *J Ophthalmic Photogr* 1986;**9**:104–11.
- 30 Hockwin O, Laser H, Dragomirescu V. Measurements of lens transparency by multilinear densitometry of Scheimpflug photographs. *Ophthalmic Res* 1984;**16**:227–8.
- 31 Chen T, Mayer H, Bates S, et al. Inter- and intra-operator correlation study of SL 45 lens photography. *Lens Res* 1988;**5**:43–54.
- 32 Engenhardt-Cabillic R, Debus H, Holz FG. Strahlentherapie chorioidaler Neovaskularisationen. In: Holz FG und Pauleikoff D eds. *Die altersbedingte Makuladegeneration*, 1997;ch 9:155–68.
- 33 Bergink GJ, Hoyng CB, Van der Maazen RMW, et al. A randomized controlled clinical trial on the efficacy of radiation therapy in the control of subfoveal choroidal neovascularization in age-related macular degeneration: radiation versus observation. *Graefes Arch Clin Exp Ophthalmol* 1998;**36**:321–5.