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≤0.05) loss of transparency of layers 5 and 7 of the nuclear region. In layer 1 (capsulopithelial 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 capsulopithelial region and the nuclear layers showed precataractous 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 carcinogenesis, and if so, after what time interval and to what extent cataract occurs.

External beam radiotherapy has been evaluated for treatment of patients with age related macular degeneration (AMD), accompanied by subfoveal choroidal neovascularisation. 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 applied, which were divided into 6–10 fractions. 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 episora and transient conjunctival irritation. 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. 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. 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.

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. Martin et al found cataract formation in one eye treated with 20 Gy in five fractions. Sasai et al described cataract formation in one eye 1 year after the patient had received a fractionated dose of 20 Gy.

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. The suitability of this method for documenting radiation cataract in particular has been evaluated experimentally. The study reported here is the first clinical study invol-
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 acceler-
After 6 and 12 months

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

<table>
<thead>
<tr>
<th>Layer</th>
<th>6 months (MV, SD)</th>
<th>12 months (MV, SD)</th>
<th>p Value</th>
<th>6 months (MV, SD)</th>
<th>12 months (MV, SD)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 radiation</td>
<td>1.014 0.035</td>
<td>1.016 0.026</td>
<td></td>
<td>1.018 0.030</td>
<td>1.012 0.026</td>
<td>0.756</td>
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<tr>
<td>2 control</td>
<td>1.034 0.033</td>
<td>1.018 0.030</td>
<td></td>
<td>0.992 0.070</td>
<td>0.982 0.036</td>
<td>0.715</td>
</tr>
<tr>
<td>3 radiation</td>
<td>0.969 0.050</td>
<td>1.001 0.010</td>
<td></td>
<td>1.021 0.036</td>
<td>0.998 0.049</td>
<td>0.237</td>
</tr>
<tr>
<td>4 control</td>
<td>1.011 0.069</td>
<td>0.982 0.070</td>
<td></td>
<td>0.992 0.026</td>
<td>0.982 0.036</td>
<td>0.811</td>
</tr>
<tr>
<td>5 radiation</td>
<td>0.986 0.047</td>
<td>1.012 0.029</td>
<td></td>
<td>1.024 0.026</td>
<td>0.998 0.049</td>
<td>0.237</td>
</tr>
<tr>
<td>6 control</td>
<td>1.005 0.043</td>
<td>1.012 0.029</td>
<td></td>
<td>1.021 0.036</td>
<td>0.998 0.049</td>
<td>0.237</td>
</tr>
<tr>
<td>7 radiation</td>
<td>0.993 0.033</td>
<td>1.015 0.034</td>
<td></td>
<td>0.992 0.026</td>
<td>0.982 0.036</td>
<td>0.811</td>
</tr>
<tr>
<td>8 control</td>
<td>1.022 0.035</td>
<td>1.015 0.034</td>
<td></td>
<td>1.024 0.026</td>
<td>0.998 0.049</td>
<td>0.237</td>
</tr>
<tr>
<td>8 radiation</td>
<td>1.017 0.031</td>
<td>1.027 0.038</td>
<td></td>
<td>1.022 0.036</td>
<td>1.001 0.031</td>
<td>0.655</td>
</tr>
<tr>
<td>8 control</td>
<td>0.997 0.048</td>
<td>0.982 0.036</td>
<td></td>
<td>1.022 0.036</td>
<td>1.001 0.031</td>
<td>0.655</td>
</tr>
</tbody>
</table>

In general, the most frequent type of radiation cataract is posterior subcapsular opacity. 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.

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, but only four cases of permanent cataract formation have been described in these studies so far.

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

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 (capsulopatellar 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 precataractous 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.