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Findings in Human Lenses 40 Years after Injection of Ra-224

Key Words
Radiation · Radium-224 · Eye · Lense · Cataract · Scheimpflug camera

Abstract
Shortly before and after the end of World War II, about 900 patients in Germany were injected with known dosages of Ra-224 for the intended treatment of ankylosing spondylitis and tuberculosis. The present study concerns patients, treated as children or juveniles.

With a Topcon SL-45B Scheimpflug camera system, photographs of the lenses were obtained for 35 of the 121 surviving patients of the juvenile subgroup. Microdensitometry was used to evaluate the photographic negatives, and the densitograms were then quantified in terms of the height of their various peaks. Sixteen patients had lens opacities of various degree in both eyes, in 10 patients there were cataracts classified as age-related, in 11 patients there were bilateral, stationary, posterior subcapsular cataracts (PSC) showing clear subcapsular zones. The densitometry profiles showed, both in PSC and in non-PSC patients, a trend of higher than normal densities in the anterior deep cortex and the posterior cortex. The value for the anterior deep cortex exceeds that for the anterior superficial cortex by about 50%.

The lens is particularly sensitive to various types of radiation. Nonionizing radiations and energetic ionizing radiations penetrate ocular tissues and may injure lens epithelial cells. This can result in the formation of lens opacities.

The classical radiation effect in the lens is a posterior subcapsular opaque plaque which was first described in 1905 by Treutler [1]. Similar disc-shaped posterior cataracts were observed after local radium treatment [2], in survivors of the atomic bomb explosions in Hiroshima and Nagasaki [3], after radiotherapy [4] – including total body irradiation in leukaemia patients [5–8], in cyclotron workers [9,

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Table 1. Half-lives of Ra-224 and daughters

	Ra-224	Rn-220	Po-216	Pb-212	Bi-212	Po-212	Tl-208	Pb-208
Half-life	3.62 days	55.6 s	0.15 s	10.6 h	60.5 min	0.3 μs	3.1 min	stable

10], in Ra-226 dial painters [11], and in one plutonium worker [12].

From 1943 to about 1952, numerous adults and children were given repeated injections of Peteosthor for intended treatment of ankylosing spondylitis, tuberculosis, and some other diseases. Peteosthor is a solution of Ra-224, colloidal platinum, and the red dye eosin. Ra-224 is a member of the thorium decay chain. It is a short-lived α-particle emitter which deposits in melanocytes of the eye. The decay of one atom Ra-224 results in the ultimate emission of four α-particles that release about 26.5 MeV within a short distance of less than 50 μm in soft tissue. The descendants of Ra-224 comprise isotopes of radon, polonium, lead, bismuth, and thallium [13, 14] (table 1).

The Ra-224 activities that were administered in the years before 1960 were substantially higher than those utilized later, and, up to recent years, in the treatment of ankylosing spondylitis. The treatment was ineffective against tuberculosis. The cohort (Spiess series) was subsequently followed by Spiess and later in cooperation with Mays. There was a striking excess of malignancies in this cohort, predominantly of bone tumors, but also of breast, liver, and kidney cancer. For the bone tumors the causation by Ra-224 and its decay products has been clearly established. There was also an excess of various other, deterministic effects, such as growth retardation and tooth breakage.

In the initial phase of the follow-up there had been no expectation of lens damage due to Ra-224, and thus no systematic investigations were performed. In 1967, when some patients had complained of impaired vision, Spiess noted the occurrence of a few cataracts at an early age (for details on cataracts in Spiess' Peteosthor series see Stefani et al. [15]). Then the dosage and time dependence of these cataracts was studied on the basis of clinical reports [16].

A total of 218 patients in the Spiess series were injected with Ra-224 as juveniles. In 1989, slitlamp observations were performed in a subgroup of 25 patients with some degree of lens opacifications. In 11 of these patients there was a stationary bilateral posterior subcapsular cataract; in 8 of them the bilateral dense round plaque showed a clear subcapsular zone of about 0.5–0.6 mm corresponding to lens fibers newly deposited after the original trauma [17–19].

By January 1993, 121 patients of the juvenile subgroup in the Spiess series were alive. Of these, 66 patients were still younger than 55 years (36 males, 30 females). Among these patients 36 were known to have incurred cataracts, 19 of 57 females (12 up to age 54) and 17 of 64 males (9 up to age 54) (fig. 1); part of these cataracts became known through the reports of the patients' ophthalmologists, part were assessed in the investigation that will here be reported.

Material and Methods

The objective of the present study has been anterior eye segment photography with a Topcon SL-45B Scheimpflug camera among a subgroup of juvenile patients within the Spiess series. In order to examine a substantial number of patients in a wider geographic area the Scheimpflug system has been installed in a van.

Photographs of the lens could be obtained from 35 patients of the juvenile subgroup. Eighteen of them were males, their average age was 54 years (range: 46–64); 17 were females (average age: 55 years; range: 48–62). The negatives of one aphakic patient were not used for densitometry.

Scheimpflug slit-image black-and-white photographs were taken at five different camera orientations (0°, 45°, 90°, 135°, and 180°) from the patients' right and left eyes after maximum pupil dilatation. The film negatives underwent linear microdensitometry by a Joyce Loebl 3 CS densitometer in the Department of Ophthalmology of Bonn University [20], and the resulting densitogram profiles were evaluated in terms of the quantification of peak heights according to methods developed by the Bonn group.

Axial linear microdensitometry was performed in the photographs along the anteroposterior axis. In some of them paraaxial linear densitograms were obtained between +3.5 and −3.5 mm from the central axis. Where possible, each densitometry profile was first divided into the corresponding ten lens zones according to Hockwin et al. [20] (1 = anterior capsule; 2 = anterior clear zone; 3 = anterior superficial cortex; 4 = anterior deep cortex; 5 = anterior supranuclear zone; 6 = anterior nucleus; 7 = posterior nucleus; 8 = posterior supranuclear zone; 9 = posterior cortex; 10 = posterior capsule). The peak height above the baseline was then measured für each zone.

Up to five linear axial densitometry profiles along the central axis have been averaged for a comparison to standard densities in the corresponding age group. The individual densitometry profiles were scaled to the value = 1 for the height of the corneal peak. Standard densities for paraaxial linear densitograms were not available.

Results

Clinical Findings

In none of the 35 patients was glaucoma detected. Two patients showed unilateral amblyopia. One patient had marked corneal astigmatism, another suffered from unilateral postinflammatory corneal scars. In 7 of the 35 patients the irides were described as brown, while in the remaining 28 patients the irides were blue to greyish or green. All eyes with posterior subcapsular cataracts (PSC), except one, showed slightly pigmented irides with blue to greyish or greenish color. One patient had had extracapsular cataract extraction (ECCE) with intraocular lens (IOL) implantation in both eyes. No patient had signs of anterior or posterior segmental uveal inflammation. Two patients had used ocular medication regularly, one for chronic conjunctivitis, another one for dry eye syndrome. There were no defects of the iris pigment epithelium. There was one iris nevus, and no lesion indicative of a uveal malignant melanoma. To our knowledge no patient was diabetic. One patient suffered from polyneuropathy. One patient was a chronic alcoholic.

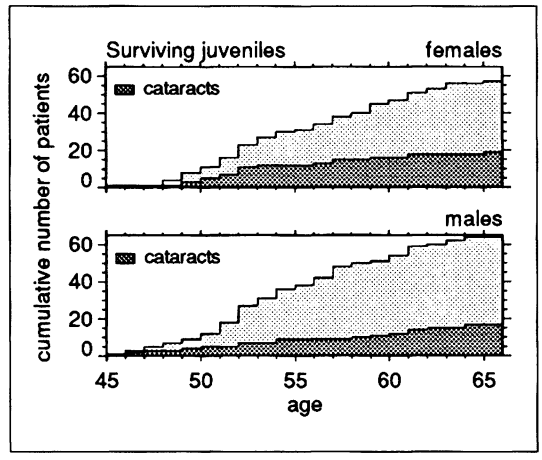

Fig. 1. Age distribution of the survivors (Jan. 1993) among the Ra-224 patients treated as juveniles. The upper curves give the number of all survivors up to the specified ages, the lower curves the number of patients known to have incurred cataracts.

Administered Activities

The average injected dosage of Ra-224 for the group of 218 juvenile patients has earlier been stated to be 1 MBq per kg body weight (1 MBq/kg) (=28 μCi/kg). Of the 35 examined patients, 10 received more, and 25 less than 1 MBq/kg Ra-224, the average dosage was 0.92 MBq/kg.

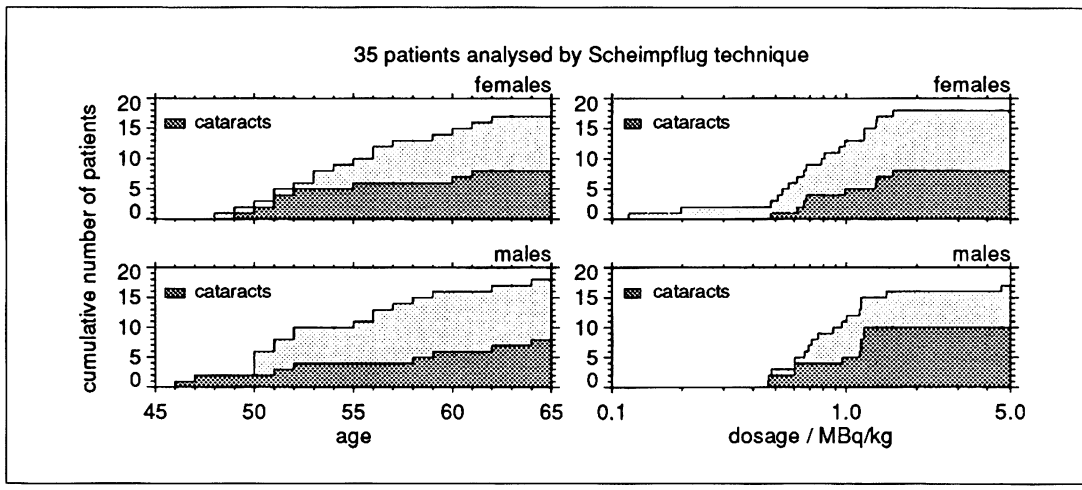

Fig. 2. Distribution in age and in injected activities of Ra-224 of the 35 patients analyzed by the Scheimpflug technique. The upper curves give the numbers of patients up to specified age or dosage, the lower curves the number of patients known to have cataracts.

Cataracts

Of the 35 patients examined by the Scheimpflug technique 16 had some lens opacities of various degree in both eyes. Of the 10 patients above 1 MBq/kg 6 had cataracts, of the 25 below this value 10 had cataracts (8 observed in female patients, 5 of them before age 55, and 8 in male patients, 4 of them before age 55) (fig. 2).

In 10 patients there were cataracts classified on the basis of additional clinical findings, such as cortical spokes, waterclefts, vacuoles, as similar to age-related cataracts. Nuclear sclerosis was classified only in a few patients.

In 11 patients there were PSCs. The average administered Ra-224 activity was 1 MBq/kg (range: 0.46–1.58 MBq/kg), 5 of these patients had less, and 6 more than 1 MBq/kg. The PSC plaque was of variable size, but usually it was fairly small and located outside the central axis (mainly in the paraaxial temporal quadrant).

Evaluation of the Scheimpflug Slit-Image Photographs

The mean axial densitometry profile for each eye in the age groups 45–54 and 55–65 showed, both in PSC and in non-PSC patients, a trend of higher than normal densities in zones 4 (anterior deep cortex) and 9 (posterior cortex).

The peak heights in the averaged profiles can be termed the 'individual mean central densitogram'. They, too, indicate higher densities in zones 4 and 9 compared to normal densitometry profiles for the corresponding age groups. According to norm values of the Bonn Institute the density peak in zone 4 is usually higher than that in zone 3 (anterior superficial cortex). In our data the value for zone 4 exceeds that for zone 3 by about 50% on average. Four of 10 patients who had received more, and 2 of 24 patients who had received less than 1 MBq/kg, showed only little differences between zone 3 and 4. In some others, peak 4 was higher than normal. Zones 6 and 7 were quite equal in both dosage groups, with one unilateral exception.

In zone 9, the posterior lens cortex, radium-induced stationary PSCs with a clear zone between the capsule and opaque fibers were expected. There were no significant differences in

densities of zone 9 between patients with administered Ra-224 activities above or below the average value of 1 MBq/kg. The height of peak 9 varied in a wide range.

Paraaxial densitograms as the level of zone 9 and zone 10 (posterior capsule) did not show evidence of a 'clear zone' between a cortical plaque and the capsule, which was obvious in earlier slitlamp examinations.

Discussion

In the juvenile subgroup of Ra-224 patients followed-up by Spiess, cataracteous lens changes are now, at an age of 50–60, increasingly present. At higher ages the lens changes may largely be age-related.

PSC is, in general, a complicated, nonspecific cataract. It occurs not only in radiation trauma. PSC may be progressive, but it appears that it can also be stationary, if there was limited primary damage of short duration [18, 21, 22], and this may apply to some of the patients of the Spiess series.

PSC is characterized histologically by lens fibre swelling and fibre breakdown [23, 24]. PSC occurs in 2.1% of a population aged 52–85 years [25]. One would, accordingly, expect only few such cataracts in this subgroup of patients of the Spiess series treated as juveniles; others appear as stationary, bilateral, radiation-related, localized PSC.

The mechanisms involved in Ra-224-induced cataracts are not understood. A marked affinity of radium to pigmented cells has been documented experimentally in rabbits [26] and mice [27] and has been taken as an explanation for the clinical observation of post-injectional iritis attacks in ankylosing spondylitis patients. But there is no correlation of PSC to the iris color in the present data, and this agrees with earlier experimental findings in dogs [28].

Radiation-induced stationary PSC has been observed in humans following radiation exposure in Hiroshima [Cogan, pers. commun., 1989]. In our series there was a number of stationary PSCs which had developed a subcapsular clear zone of about 0.5 mm within 40 years [17, 18]. Stationary PSC has also been induced experimentally in bullfrogs *(Rana catesbeiana)* with low-dose X-rays [21]. These experiments substantiated clinical observations [18, 29]; a subcapsular transparent cortex suggested an epithelial healing process with reorganisation of the meridional row [21, 30]. Using Scheimpflug slit-image photography these optically clear fibres, superficial to the opacity, have been shown recently [22].

The present observations are a first set of Scheimpflug slit-image photographs and densitograms in the Ra-224 Spiess series; accordingly we have, at this point, no follow-up with this technique. Axial densitograms do not fully describe an individual lens. Localized 'stationary' small PSC outside the central axis in a paraaxial plane may be missed. The mean axial densitometry profile for each eye of the age groups 45–54 and 55–65 in both PSC and non-PSC patients shows higher than normal density in the cortex zones 4 (deep anterior cortex) and 9 (posterior cortex).

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