CONTRIBUTED PAPERS

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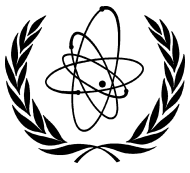
the World Health Organization

Radiological Protection of Patients in Diagnostic and Interventional Radiology, Nuclear Medicine and Radiotherapy



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FOREWORD

An International Conference on the Radiological Protection of Patients in Diagnostic and Interventional Radiology, Nuclear Medicine and Radiotherapy organized by the International Atomic Energy Agency and co-sponsored by the European Commission, the Pan American Health Organization and the World Health Organization was held in Málaga, Spain, from 26 to 30 March 2001. The Government of Spain has hosted this Conference through the Ministerio de Sanidad y Consumo, the Consejo de Seguridad Nuclear, the Junta de Andalucía, the Universidad de Málaga and the Grupo de Investigación en Protección Radiológica de la Universidad de Málaga (PRUMA).

The Conference has been organized in co-operation with the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR), the International Commission on Radiological Protection (ICRP) and the following professional societies: International Organization of Medical Physicists (IOMP), International Radiation Protection Association (IRPA), International Society of Radiation Oncology (ISRO), International Society of Radiology (ISR), International Society of Radiographers and Radiological Technologists (ISRRT) and World Federation of Nuclear Medicine and Biology (WFNMB).

This publication contains contributed papers submitted to the Conference Programme Committee. The papers are in one of the two working languages of this Conference, English and Spanish. The IAEA is planning to issue proceedings of this Conference containing selected presentations.

The topics covered by the Conference are as follows:

- Radiological protection of patients in general diagnostic radiology (radiography)
- Radiological protection of patients in general diagnostic radiology (fluoroscopy)
- Radiological protection issues in specific uses of diagnostic radiology, such as mammography and computed tomography (with special consideration of the impact of digital techniques)
- Radiological protection in interventional radiology, including fluoroscopy not carried out by radiologists
- Radiological protection of patients in nuclear medicine
- Developing and using dose guidance (reference) levels in radiology and nuclear medicine examinations
- Radiological protection of the embryo and foetus in pregnant patients
- Radiological protection of paediatric patients
- Radiological protection of patients in radiotherapy: external beam
- Radiological protection of patients in radiotherapy: brachytherapy
- Radiological protection of patients in biomedical research
- Influence of standardization in the design and development of medical radiological equipment on the radiological protection of patients
- Education, training and continuous professional development in the radiological protection of patients
- Topics for research and development in the radiological protection of patients
- Implementation of regulations on the radiological protection of patients

EDITORIAL NOTE

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RADIOLOGICAL PROTECTION OF PAEDIATRIC PATIENTS (Topical Session 7)

RADIOLOGICAL PROTECTION OF PATIENTS IN RADIOTHERAPY: EXTERNAL BEAM (Topical Session 8a)

TOLERANCE OF THE DIFFERENT STRUCTURES OF THE EYE TO THERAPEUTIC IONIZING RADIATION

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Abstract

Primary tumours of the visual apparatus are rare, although radiation therapy of tumours near the eye is becoming increasingly more common in daily practice. These tumours often incur the incidental irradiation of eye structures, even when the latter are not clinically involved with the tumour. Depending on the dose and irradiated volume some damage to the different structures of the visual apparatus may occur. In addition, the time to expression and severity of injury are dose-dependent. This review analyses the most recent literature and proposes daily practice guidelines.

1. Eyelashes

The eyelashes serve as end organs of touch; their contact with tiny particles initiates a blink that protects the eye. Irradiation epilates the lash, and thus abolishes this protective reflex. This may led to an increased irritation of the conjunctiva and corneal surfaces. Doses of 28 Gy/2 wk with Ortovoltage (100 kVp) may produce permanent depilation. The eyelash may be spared with megavoltage beams, so the eyelash may be at least partially intact even after 50-60 Gy prescribed to a point deep to the lid. But doses in excess of 50 Gy to the eyelids may produce permanent depilation [1].

Like the hair elsewhere, an epilated lash may regrow a different colour, and the new hair may be sparse and short.

2. Eyelids

The eyelids are the thinnest skin of the body, to allow effortless and rapid motion of the lid. Any inflammatory or fibrosing process will decrease the flexibility of the eyelid.
Radiation induced eyelid changes commonly consist of skin erythema, progressing to pallor and teleangiectasia. Chronic structural changes include ectropion, entropion with trichiasis and closure of the eyelid punctae. It must be remembered that deformity of the eyelid margin may lead to corneal irritation, which over time may produce severe damage. Changes in the upper lid are more serious because of the tarsus.

With regard to dosage, permanent alterations are very rare with doses less than 45-50 Gy with conventional fractionation. In Helium therapy 70% of the tumour dose is given to the eyelid (35-56 Gy) and almost always produces the acute changes [2].

3. Lacrimal Apparatus

Tears are composed of secretions from the following glands: Major lachrymal gland, close to the ocular globe, in the upper outer quadrant of the orbit; Accessory lachrymal glands of

Krause: conjunctival fornices (superior mainly); Accessory lachrymal glands of Wolfring: superior aspect of the tarsal plate; Sebaceous Meibomio glands: in both eyelids, mainly in the superior; Accessory sebaceous glands of Moll and Zeiss, near the eyelid margin, and Goblet Cells mucinous; scattered throughout the conjunctiva.

The tear film consist of three layers: Superficial lipid: from Meibomio and Zeiss; It helps to retard evaporation; Middle aqueous: From the accessory (Wolfring and Krause), and major, and Deep mucinous: to wet the relatively hydrophobic corneal and conjunctival epithelia.

Deficiency of any of the three components leads to a loss of the tear film stability and potentially may lead to the *Dry Eye Syndrome*. In this syndrome, patients develop a red scratchy eye, with foreign body sensation and photophobia. The situation may progress to corneal epithelial breakdown, ulceration with bacterial infection, neovascularization, opacification or perforation. Occasionally, phthisis bulbi (Shrinking of the globe) and symblepharon may be observed.

Most of the patients who develop severe dry eye syndrome, become severely symptomatic within 1 month after completion of irradiation, and corneal neovascularization and opacification are often pronounced within 9-10 months after the completion of the X-ray therapy. In the early stages visual acuity is only slightly impaired. If severe dry-eye syndrome develops, the vision deteriorates rapidly, and the entire eye becomes vulnerable to bacterial infection. The lachrymal gland and tissue have a radiation tolerance very similar to that of the salivary gland tissue. If the fractionated dose to the lachrymal glands and eye is in the range of 32-45 Gy slow changes occur over 4-8 yr, with 25% of patients loosing the eye [3]. Since most of the basal secretion of tears comes from the accessory lachrymal glands, which are most plentiful in the upper lid, efforts should be made to shield some of the upper lid, in addition to the major lachrymal gland (eye retractors).

Although additional information is needed, most patients appear to tolerate doses in the range of 30-40 Gy. Parsons recently did a review of the literature [4,5] and plotted the numbers with his own data form University of Florida, shaping a dose response curve: 0% doses <30 Gy; 20% to 40 Gy. Above 40 Gy there is a very steep shape in the curve (50% to 50 Gy; 100% to 57 Gy). There seems to be a lower incidence of these complications when twice a day fractionation (1.2 Gy twice daily) is used. This phenomenon also decreases side effects in salivary glands [6].

4. Nasolacrimal draining system

Doses in excess of 50 Gy to the nasal portion of the eyelids can, in theory, result in blockage of the nasolacrimal system resulting in epiphora, as a result of desquamation of the epithelium of the ducts, with the subsequent inflammation that may lead to fibrosis and stenosis. The literature is very scanty but some authors [7] have not seen any problems of that sort with doses below 60 Gy. This relative ability to preserve the ductal function is an argument in favour of X-ray therapy for patients with malignant lesions near or involving the tissues around the nasolacrimal duct and sac. It is important to remember that in some of these patients prior surgery may have altered the integrity of the nasolacrimal draining system.

4. Cornea

The cornea is the main refractive element of the eye; a decrease in the corneal clarity, in particular when it involves the central axis, results in diminished vision. Radiation induced changes (excluding those caused by a dry eye) do not depend on vascular damage, but only on disruption of the mitotic activity in the epithelial and connective tissue layers. There are five layers in the cornea: epithelium, Bowman's membrane, corneal storm, Descemet's membrane and endothelium. The anterior epithelium thins with X-ray therapy and may develop tiny ulcers (punctuate keratitis), after a dose of 30-50 Gy. Keratitis may happen by the end of treatment of right after, and lasts 4-6 weeks; patients do have anterior segment triad (increased blinking, lacrimation and photophobia). With appropriate ophthalmologic care usually the tiny ulcers do not coalesce, but it may happen, developing a corneal ulcer. With doses of 60 Gy the risk of corneal ulceration is 15-20%, but this number is increased when chemotherapy is added. Edema of the corneal stroma may appear after dose of 30-50 Gy, but it is transient, and subsides within a month, but with high doses 80 Gy, it may be permanent

A recent work present a clinicopathological correlation between corneal perforation and late radiation therapy-induced corneal necrosis in a male adolescent treated for orbital rhabdomyosarcoma[8].

5. Sclera

The sclera is relatively radioresistant. The main effects of X-ray therapy are related to episcleral plaques used for the treatment of coroidal melanoma. The effects are loss of episcleral vessels, scleral thinning and perforation. Treatment of the scleral thinning is aimed to restore or preserve the integrity of the globe. Loss of 50% of the scleral thickness may require a conjunctival graft to cover the defect [1].

6. Uvea

Irradiation of the iris and uveal structures to cancerous doses may lead to vascular changes such as neovascularization, rubeosis iridis and iridociclitis, resulting in an imbalance between aqueous production and absorption ending in glaucoma. Neovascular glaucoma may result in a rapid loss of vision; sever pain (nailing) and headache. It may progress to blindness.

7. Lens

The lens is a biconvex refractive structure located behind the pupil, 1-1.5 mm anterior to the fleshy cantus. Normal lens epithelial cell lie beneath the anterior capsule and equator only. The germinal layer is located at the equator and is the most sensitive layer to radiation, because these are the cells that have active proliferation, as opposed to the anterior epithelial cells that seldom divide). Radiation damage to the germinative zone of the lens epithelial cell DNA is probably responsible for most post-treatment cataracts. In addition to DNA damage, direct cytoplasmic effects, such as disruption of membrane channels protein cross-linking, and ion pump abnormalities are also important in the post radiation cataract progression. Abnormal epithelial cells, termed Wedl cells, migrate posteriorly and form a posterior subcapsular opacity (due to retaining their nuclear detrie). Older patients may develop cataracts sooner because possible pre-existing DNA damage. The proportion of cell damage necessary to cause a cataract is unknown. In Helium treated patients, exposure of less than 25% of the lens in the field can cause cataract.

In general the latency and frequency of lens opacities are a function of radiation dose. In most human studies, fractionated doses less than 5 Gy have not produced visually significant lens opacities. Does of 3 Gy/1 fraction may cause cataract. With fractionated X-ray therapy (1.5-2.0 Gy/fraction) to a dose of 12-14 Gy (fractionated total body irradiation) the risk is 10%. Due to the technical difficulties associated with electron attenuation, some authors have postulated the use of ortovoltage instead of electrons for patients with cutaneous tumours near of the ocular zone. Although paradoxically, there are very recent works that describe preservation techniques of the crystalline lens in patients with retinobastoma, based on electrons treatment [9].

Cataracts in young children may cause significant ambyopia before surgery can be performed.

There is a second mechanism for cataracts but it is usually not in the therapeutic range. It is related to metabolic damage secondary to X-ray therapy-induced to the anterior epithelium (where all the lens nutrients pass throughout).

8. Retina

The neurosensorial retina consists of an extensive network of neural glial and vascular elements.
Radiation induced retinopathy presents a clinical picture similar to that seen in diabetic retinopathy. Retinal injury after high-dose radiation usually is not expressed clinically for 1.5-3.0 years after irradiation during which time visual acuity often remains normal. Some patients with radiation retinopathy develop vasoproliferation of the anterior surface of the iris, and into the angle of the eye (rubeosis iridis). Anterior segment neovascularization is postulated to have the same cause as posterior segment neovascularization, namely, a vasoproliferative factor [5]. Retinal ischemia and hypoxia result in the development of a diffusible vasoproliferative factor, which is presumed to lead to retinal and optic nerve head neovascularization. The findings in fundoscopic exam are: retinal ischemia, edema, microaneurysm formation, capillary dilatation, haemorrhage, cotton-wool spots, teleangiectasis and retinal or optic nerve head neovascularization.

Acute ultrastructural changes have been studied in Rats irradiated and whose eyes were enucleated 1h to 1 month following X-ray therapy (2-20 Gy X-rays, single dose). Acutely, rod photoreceptors (not Rod Givens) were the most sensitive retinal cells. The outer segments developed small membranous whorls 1 h after receiving 2 Gy. These membrane changes were dose dependent. Photoreceptor death occurred at doses over 10 Gy/1fraction. Retinal pigment epithelium cell damage, manifested by mitochondrial swelling, became apparent after doses over 5 Gy/1fraction. Retinal pigment epithelial cell death did not occur following doses of less than 20 Gy/1fraction. In contrast, the inner retinal neurons and vascular cells showed no ultrastructural changes within the time and doses tested. Repair (evidenced by a decrease in the number of whorls), was noted 1 week following XRT with small doses such as 2 Gy.

The University of Florida recently reported their experience on 64 patients (68 retinas) exposed to therapeutic irradiation by techniques that did not produce severe dry-eye complications. Radiation retinopathy was not seen at doses below 45 Gy but increased steadily in incidence at doses of 45 Gy and above, being very steep above 50 Gy. Between 45 and 55 Gy there was a strong dependency on the dose per fraction (>1.9 Gy) and patients who received chemotherapy. The lowest dose associated with retinopathy was 45 Gy in a diabetic

patient. Fraction sizes of 2.25 Gy or more may lead to earlier and more severe changes (at 45 Gy) [5].

Nakissa et al, reported data on patients who received different doses of X-ray therapy to the retina: All patients who received over 45 Gy to the posterior pole had recognizable changes, but most of these did not affect vision. Decreased visual acuity occurred only in patients receiving over 65 Gy. At 60 Gy 50% of the patients displayed some visual changes, and at 80 Gy 85-90% did [10].

Despite the use of 1.8-2.0 Gy/fractions, dose inhomogeneities can be considerable in orbital treatments (up to 20-25%). This can potentially lead to portions of the retina/globe receiving >2.4 Gy/day) despite the fact that much of the treatment volume receives <2 Gy/day) [11].

Panretinal laser photocoagulation is used to treat severely ischemia, irradiated eyes in an attempt to control neovascular glaucoma, although the precise indications and efficacy of this treatment are uncertain. The identification of a vasoproliferative factor may lead to pharmacological interventions

9. Optic Nerve

Radiation optic neuropathy is mainly a vascular ischemic phenomenon, caused by vascular occlusive disease. Patients with pre-existing small vessel disease are at increased risk for this complication. It presents as painless monocular loss of vision that is usually sudden, although it may follow transient episodes of blurring.

The dose per fraction is a very important determinant in the development of optic neuropathy. In stereotactic radiosurgery it has been proven that the tolerance of the optic nerve is unusually lower than that of the other cranial nerves [12]. A single dose of 7 Gy may lead to blindness. Nevertheless, the dose quoted by Cassady and Loeffler for tolerance of the optic nerve and chiasm is 8 Gy [13].

Several institutions have reported their experience in the case of fractionated radiotherapy; With doses below 50 Gy the only optic neuropathies reported are in patients with pituitary tumours (and probably some pre-existing damage to the optic tract), who have received dose per fraction of 2.25 Gy or higher, or chemotherapy. With doses above 60 Gy there is a steep increase in the incidence of optic neuropathy (at least 15-20% and upwards) [4,14].

10. Orbit

The orbit forms a bony cavity in the skull that houses the globe, extraocular muscles, intraorbital portion of the optic nerve and the orbital fat. Late effects of X-ray therapy on the bony orbit are seen primarily when external beam is applied to the growing facial bones of children, as in the treatment of retinoblastoma or rhabdomyosarcoma. Radiation arrests the bone growth of the orbit, leading to bony hypoplasia and atrophic soft tissue changes. The degree of hypoplasia appears to be inversely related to the patient age at the time of the treatment.

In a typical setting, the mid section of the face and involved orbit are hypoplastic. This is manifest by decreased vertical and horizontal orbital diameters, hypoplasia of the nasal bridge zeugmatic bone, and temporal fossa.

The tip of the nose and nasal alae grow normally, despite the flattened nasal bridge, leading to an increased nasal angle. The frontal bone also grows normally and it appears to be disproportionately prominent. Children older than 3 yr are less severely affected. Midfacial hypoplasia is slightly less common following megavoltage as compared with ortovoltage irradiation.

Fat atrophy and fibrosis may result in enophthalmos. Mucous membrane contracture may lead to forthshortening of the fornices and symblepharon formation. (30% after 60 Gy megavoltage irradiation). In cases of enucleation followed by irradiation, the anophthalmic socket is exacerbated; X-ray therapy induced atrophy and contraction of the soft tissues lead to further volume loss, poor prosthetic fitting, and in some cases complete obliteration of the fornices.

Secondary neoplasms

Children with heritable retinoblastoma secondary to a germline cell mutation, have cancer predisposition due the loss of retinoblastoma tumour suppressor gene in every cell in the body.

Tucker did a dose effect study for second tumours. The relative risk was 1.3 with less than 10 Gy; 12.7 between 10-40 Gy, and 19.4 after doses of more than 40 Gy [1]. These investigators did not found a difference in second tumour development when Ortovoltage or megavoltage were used, and chemotherapy (Cyclophosphamide) exerts an additive effect. New papers exist in the fact that patient with retinoblastoma that they received radiotherapy they didn't develop a second tumour [15,16].

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