Radiation retinopathy following treatment of posterior nasal space carcinoma

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SUMMARY Posterior nasal space carcinoma has a high mortality and most patients are treated with radiotherapy. Radiation retinopathy was encountered in 7 out of 10 survivors included in this study. Five of the affected patients lost vision as a result of the retinopathy. One patient required laser photocoagulation and responded well to this treatment. There was a variation in the severity of the retinopathy among the patients studied despite the fact that all patients received a similar dose of radiotherapy. We suspect that previously unrecognised factors in the planning of radiotherapy fields may explain this difference.

Posterior nasal space carcinoma is a difficult tumour to treat successfully. Because of its situation it is not amenable to surgical resection, and most cases are treated by radiotherapy. The most common pathology encountered at this site is squamous cell carcinoma, the treatment of which requires high-dosage radiation (usually 6000-7000 rads).

The field of irradiation necessary to encompass the nasopharynx includes the base of the skull and adjacent orbits. The posterior parts of the eye are often unavoidably included in the treatment plan.

The ocular effects of ionising radiations are well described following therapy of primary ocular tumours¹⁻⁸ and lesions of adjacent structures.⁹⁻¹³ Improved techniques of radiotherapy have reduced radiation damage to the anterior segment of the globe. However, damage to the posterior segment still occurs when high-dosage radiotherapy is used owing to the difficulty of prophylactic shielding of the area.¹⁰

Radiotherapy of the nasopharynx requires treatment to a well-defined area almost at the centre of the head, preferably with high-energy photons. In patients undergoing treatment for this tumour both eyes are subjected similarly and therefore receive comparable levels of exposure. With our increased understanding of the pathogenesis of retinal vascular lesions⁸ and the possibility of treatment of photocoagulation^{9,14,15} it was considered worthwhile to examine a series of survivors from this treatment. Our

intention was to define the extent of the problem of retinopathy and the feasibility of treatment with photocoagulation.

Material and methods

In this study full ocular assessments were carried out on 24 eyes of 12 patients, all of whom had received a course of cobalt beam radiotherapy for their posterior nasal space carcinoma at least 3 years previously. The overall survival rate following treatment for this tumour at this hospital is approximately 30%. Our patients represent almost all the survivors on record in the Department of Radiotherapy at least 3 years after treatment.

Each patient was treated by the standard technique used at St Bartholomew's Hospital: a course of 6000-7000 rads is administered with daily fractionation over 50-70 days by means of a cobalt teletherapy unit. At the beginning of treatment large lateral fields are used, equal doses of radiation being given on both sides. After 4000 rads the posterior limit of the field is brought anteriorly to spare the spinal cord. The eye is protected during treatment by a rectangular lead shield at least 8 cm thick placed anterior to the outer canthus. The radiation dose to the posterior segment of each eye was calculated by reference to the original simulator films and treatment radiographs (Fig. 1). Cytotoxic therapy in the form of methotrexate and cyclophosphamide was administered concurrently.

Ocular symptoms which developed following treatment were noted. Best corrected vision was

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Fig. 1 Treatment plan for patient 3. The eyes have been added to the plan to show the position of the isodose curves (all figures in rads).

assessed using the Snellen chart. Slit-lamp biomicroscopy was carried out looking specifically for features of radiation damage. The intraocular pressure was measured. After dilation of the pupils the media and fundi were examined by direct and indirect ophthalmoscopy. Colour vision, visual fields, and fundal lens examination were carried out if indicated.

All patients had fundal photography of the central and midperipheral retina, while fluorescein angiography was performed provided there was no medical contraindication. The blood pressure was taken and urine analysis carried out to exclude

concurrent untreated hypertension or diabetes, which might have produced similar fundal changes.

Results

Twelve patients were examined but only 10 fulfilled the criteria for inclusion in the study. One was excluded due to a follow-up of less than 2 years, while a second had retinal lesions compatible with radiation change but was a diabetic.

Table 1 shows details of the patients examined. Of the 10 patients 5 showed a drop in visual acuity of 2 lines attributable to radiation retinopathy. The

Table 1 Clinical details of patients after treatment for posterior nasal space carcinoma

Patient no.	Age	Radiation dose (rads)	Treatment duration (days)	Visual acuity		Other disease	Interval since treatment (yr)	Onset of symptoms (yr)	Radiation retinopathy	
				R	L				R	L
1	68	7000	58	6/18	-6/24	High myopia, open-angle glaucoma	16	-	-	-
2	65	6000	56	6/6	-6/12	Systemic hypertension	13	9	+	+
3	23	6000	50	6/5	-6/5	-	12	-	-	-
4	53	6850	62	6/18	-6/6	-	11	7	+	+
5	42	6500	53	6/6	-6/4	-	11	10	+	+
6	57	6607	51	6/6	-6/12	-	8	6	+	+
7	49	6600	52	6/9	-6/5	Right amblyopia	7	-	+	-
8	35	7000	56	6/5	-6/60	-	5	1	+	+
9	45	6841	62	6/5	-6/5	-	3	-	-	-
10	63	6500	69	6/9	-6/6	-	3	-	+	+

Fig. 2 Patient 8. Fluorescein angiogram. Lower nasal retina left eye showing extensive capillary closure with radiation perivasculitis. Fluorescein leakage is more marked from veins.

Fig. 3 Patient 8. Fluorescein angiogram. Left upper temporal retina showing late leakage from new vessels. Laser photocoagulation above this area.

patients' ages ranged from 23 to 68 years. Eleven of our 12 patients were male.

The dose of radiation received by the posterior part of the eye was estimated by reviewing the original treatment plans for each patient. It was considered that the anterior parts of the eye had been well shielded by the lead protection but the posterior part of the globe was within the radiation field. Very similar doses were given to each patient, the range being 6000–7000 rads.

In only 2 patients were any anterior segment changes seen which may have been related to treatment. These consisted of one patient with conjunctival hyperaemia and telangiectasia and another patient with a small conjunctival haemorrhage related to an area of abnormal vessels. No significant lens opacities were seen. The intraocular pressure

was normal in all patients (one patient was having treatment for chronic simple glaucoma), and there was no sign of rubeosis iridis.

The posterior segment was more commonly affected; 7 out of 10 patients showed some features of radiation retinopathy. Five of these patient had complained of visual symptoms related to retinal problems, and all had retinal changes on funduscopy. The extent of the retinal problem varied from a few microaneurysms only to extensive vessel closure (Fig. 2) with new vessel formation (Fig. 3) and vitreous haemorrhage. The range of retinal abnormality is shown in Table 2. Although the retinal changes were very variable in different patients, those affected tended to have a similar distribution of the retinopathy in each eye. Visual acuity was affected when vascular changes involved the macula area (Figs. 4, 5).

Table 2 Extent of retinal changes noted in 7 patients with retinopathy

Patient no.	Uni-/bilateral	Fundal findings
2	Bilateral	Pigment epithelial pallor, microaneurysms and telangiectasia, slow choroidal filling and breakdown of left macular capillary arcade on angiography
4	Bilateral	Macular microaneurysms and telangiectasia
5	Bilateral	Scattered microaneurysms only
6	Bilateral	Pigment epithelial changes, microaneurysms with fluorescein leakage at maculae
7	Right	Microaneurysms only
8	Bilateral	Extensive pigment epithelial change, microaneurysms and vascular closure, gross left exudative maculopathy, retinal neovascular tissue and left vitreous haemorrhage
10	Bilateral	Pigment epithelial changes

Fig. 4 Patient 8. Left posterior pole, gross macular exudate and oedema.

Fig. 5 Patient 6. Fluorescein angiogram. Left macular showing late leakage from widespread microaneurysms with macular oedema.

There was no correlation between the extent of retinal change and the dose of radiotherapy or time over which treatment was given. Moreover in those patients with symptoms the onset of problems varied between one year and 10 years; our most severely affected patient was the earliest to develop symptoms. Age did not seem to be related to the extent of retinopathy, the average age of affected patients being 52 years and the average of all examined 50 years.

The most vulnerable part of the eye to this level of radiation was the retinal vasculature. In no patient was any abnormality of the optic nerve found indicating a radionecrosis of nerve fibres or involvement of the posterior ciliary artery circulation. On fluorescein angiography one patient had delayed choroidal filling, indicating possible damage to the posterior ciliary circulation, but he was also hypertensive, which may have contributed to the finding.

One patient who developed forward new vessels causing a vitreous haemorrhage was treated with argon laser panphotocoagulation. After that he responded well, with regression of vessels and no recurrence of haemorrhage.

Discussion

Stallard¹ and Foster Moore² first described retinal complications following radon seed implantation for treatment of retinoblastoma in the 1930s. Subsequently other authors confirmed and accurately

documented the features of a vascular retinopathy developing some time after irradiation.^{8,16} The same clinical picture has been reported following irradiation in the region of the globe for carcinoma of the paranasal sinus and nose, skin tumours of the face, pituitary, and intracranial lesions.^{9-13,15}

High-dose irradiation affects all the ocular tissues with the exception of the sclera. Cibis¹⁷ has shown in animals that, while the rods may be damaged by doses of 2000 rads or more, the cones are much more resistant (10 000 rads). He observed vascular congestion, exudate, and oedema a few hours after exposure. These changes have not been noted to occur in man, and nervous tissue has been considered relatively radioresistant. Clinical changes first occur in the retinal vessels after a latent period varying from several months to several years. Histologically these changes have been shown to consist of thickening, hyalinisation, and occlusion of the retinal vessels,¹⁸ shrinkage of choroidal vessels, inner retinal layer atrophy,¹¹ and myointimal proliferation and narrowing of central retinal and ciliary arteries.¹⁹

Clinically these histological changes are reflected in the features of a vascular retinopathy. Commonly seen are microaneurysms and small vessel telangiectasia (Fig. 6), while retinal haemorrhages, exudates, and cotton-wool spots are seen in the severe cases. Rarely the ischaemic changes are sufficient to result in retinal new-vessel formation with vitreous haemorrhage. Seven out of our 10 patients showed some evidence of retinopathy. In only one was it severe enough to cause new vessel formation.

Fig. 6 Patient 2. Fluorescein angiogram. Left posterior pole (arteriovenous phase) showing breakdown of macular capillary arcade with microaneurysm formation.

Hayreh⁸ believes that the vascular changes are confined to the retinal vessels and the posterior ciliary circulation is unaffected, but this view has been challenged by the findings of other authors,¹⁹ who noted histological changes in the posterior ciliary arteries. One of our patients showed delayed choroidal filling on fluorescein angiography, indicating possible posterior ciliary artery damage, but he was also receiving treatment for systemic hypertension, which may have contributed to the pathology.

The special susceptibility of the macula to vascular changes after radiation has been noted by Bedford *et al.*³ following treatment with cobalt plaques away from this region. Patients in this study also showed a tendency to maculopathy.

Fluorescein angiography was useful in more accurately delineating the vascular abnormalities present, but in none of our cases were significant lesions found with fluorescein that could not be seen by careful ophthalmoscopy. We concluded that fluorescein angiography was not essential to screen a patient for early retinopathy, and is necessary only when treatment is being considered.

The frequency of occurrence of radiation retinopathy depends on the dose, photon energy, and radiation field arrangement. Moreover there is a latent period between treatment and the onset of retinopathy which must be taken into account when comparing cases. Because of the variability of these factors it is not possible to make direct comparisons between radiation retinopathy studies. However,

Shukowsky and Fletcher,¹² using a high-dose technique to treat tumours of the ethmoid sinus and nasal cavity, found that 6 of 15 patients lost the vision of one eye and 3 of 15 lost sight in both eyes in 5 years (3 from optic nerve complications, 2 from central retinal artery occlusion). The time of loss of vision was not dose related, no patient receiving less than 7500 rads (2500 rets) lost vision. Perrers-Taylor *et al.*¹¹ examined 119 patients who had had radiation near their eyes and found significant chorioretinal changes in 24. Radiation doses varied between 1000 and 3500 rads. De Schryver *et al.*,¹⁰ reporting on 30 survivors 10 years after treatment for nasopharyngeal carcinoma (estimated eye exposure was 1300–3500 rads), found mild changes in 18 patients, 14 of whom had received over 2500 rads. No patients were reported as having lost vision from retinopathy.

In a number of these case reports retinal changes have been observed to be stationary⁹ or to change very slowly.¹¹ Our findings support these observations. Just as the incidence of retinopathy varies from report to report, so does the latent period before the retinopathy occurs. A range of between one month⁴ and 15 years⁶ has been reported, but most cases occur between one and 3 years.

In our patients 7 out of 10 show signs of retinal damage, the onset of symptoms varying between one and 10 years (mean 6.6 years) following treatment. That the extent of the retinal change is related to the dose of radiation was shown by Howard,¹⁸ who noted a much more severe retinopathy in eyes receiving a second course of radiotherapy for retinoblastoma.

It has been suggested that the effect of ionising radiation on nervous tissue is potentiated by the associated use of chemotherapy,²⁰ following the development of optic atrophy after 2400 rads of cranial radiation in 2 patients with leukaemia. All patients in our series received chemotherapy in addition to radiotherapy when first treated. None developed optic atrophy.

Radiotherapeutic treatment of tumours of the posterior nasal space provides a useful model of the differing effects of radiation in patients whose eyes are exposed to very similar dose levels. Considering that all 10 patients received a very similar dose of radiation to a well-defined area by a standard technique for shielding the eyes, there was a very wide range in the severity of retinopathy. Although only one patient suffered severe damage to the vision from treatment, 5 out of 10 patients had a fall in visual acuity attributable to radiation retinopathy. There was a tendency for both eyes to be similarly affected. The age of the patient was not related to the severity of the retinopathy. This variation in the extent of retinopathy may be due to individual differences in the standard radiotherapy technique for different

patients. For instance, although in our patients the eyes were shielded with lead protection to the side of the orbit, the position of the globes themselves is not recorded on the radiation plan. It is possible that a variation in the position of the globes in relation to the standard calculated radiation fields is a factor in the differing complications after treatment. Planning should be improved by plotting the exact position and length of the globe on radiation plans prior to treatment.

The recognition of the extent and severity of the problem of radiation retinopathy has become more important with the potential for treating the condition. Gass¹⁴ and Chee⁹ reported some success on the treatment of macular exudates due to radiation retinopathy by photocoagulation. Chaudhuri *et al.*¹⁵ described the successful treatment of new vessels by panretinal photocoagulation. One patient in our series with proliferative retinal changes has been treated by argon laser panretinal ablation with regression of new vessels and cessation of recurring vitreous haemorrhage.

CONCLUSION

Radiation retinopathy is more common than previously thought. Changes attributable to radiation were found in 7 out of 10 patients included in this study, while 5 of the affected patients lost vision as a result of the retinopathy. The damage to the neural retina was secondary to retinal vascular changes.

One patient in the series responded well to laser treatment. In view of the possibility of treatment it would appear reasonable to screen all patients receiving radiation near the eye for 12 months following completion of their radiotherapy.

Although the radiotherapeutic techniques remained unchanged throughout the series and an equal dose of radiation was given to each eye, we are unable to explain the large variation in severity of radiation retinopathy encountered. Plotting the exact position of the globe on radiation plans prior to treatment may provide insight into this problem.

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