

External beam radiotherapy for retinoblastoma: II Lens sparing technique

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Abstract

A retrospective analysis is presented of the results of external beam radiotherapy for retinoblastoma utilising an accurate lens sparing technique. Local tumour control has been assessed in a consecutive series of 67 eyes in 53 children all of whom received external beam radiotherapy as the primary treatment of retinoblastoma. Follow up ranged from 12 to 82 months (median 35 months) with 76% of the children followed for more than 2 years. Tumour control rates have been analysed with respect to the Reese-Ellsworth classification. The role of adjuvant and salvage focal therapy is emphasised. Following lens sparing radiotherapy with prior adjuvant treatment of anterior tumours, where appropriate, the overall ocular cure rate was 72%. With salvage therapy of persistent, recurrent, or new tumours, 93% of eyes could be preserved in this series which includes mainly eyes classified in Reese-Ellsworth groups I-III. These results compare favourably with those of whole eye external beam radiotherapy for comparable tumours, and with those of lens and anterior segment sparing using other techniques. They were achieved without the ocular morbidity associated with whole eye external beam radiotherapy.

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Whole eye external beam radiotherapy for retinoblastoma is associated with severe ocular morbidity which often leads to substantial loss of vision and produces painful, photophobic, and unsightly eyes which are difficult to treat.¹⁻⁵ Although radiation chorioretinopathy and optic neuropathy have been minimised by reducing the total dose of radiation delivered to the eye and by increasing the fractionation,^{3 4 6-10} the harmful effects of radiation on the ocular adnexa and on the anterior segment of the eye have proved more difficult to eliminate.

Several methods have been devised for sparing the lids and anterior segment while delivering a homogeneous dose of radiation to

the entire retina, but most have lacked the necessary precision and set up reproducibility.⁵

Since 1986, Harnett's modification of Schipper's technique of lateral field, lens sparing external beam radiotherapy, has been employed at St Bartholomew's Hospital to treat selected cases of retinoblastoma.^{5 11 12} This study compares the results of the new technique with those of treating the whole globe¹³ in eyes with comparable tumours to establish whether or not lens sparing external beam radiotherapy is a safe alternative to the whole eye method.

Patients and methods

The case records of all the children treated for retinoblastoma at St Bartholomew's Hospital by the modified Schipper technique between 1986 and 1992 were reviewed retrospectively. The indications and contraindications for lens sparing external beam radiotherapy during the period of the study are summarised in Tables 1 and 2.

To make the series as compatible as possible with the whole eye study, eyes were included only when lens sparing radiotherapy had been the primary form of treatment of their disease. In order to take advantage of the benefits of sparing the lens and anterior segment, some eyes were selected for the lens sparing technique despite having additional small tumours located anterior to the equator and therefore outside the collimated beam. These eyes were first treated focally, usually by triple freeze cryotherapy though occasionally by a radioactive scleral plaque. Eyes which received focal pretreatment of anterior tumours were not excluded from the present study. However, those eyes which received lens sparing radiotherapy because of failure of prior focal treatment were not included in the present analysis. Additional criteria for inclusion were: the availability of complete follow up data and a minimum follow up period of 12 months.

Each case underwent examination under anaesthesia. Indirect ophthalmoscopy with scleral indentation, retinal drawings, fundus photography, diagnostic computed tomography (CT) scanning and B scan ultrasonography were performed. Each affected eye was then graded according to the Reese-Ellsworth

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Table 1 Indications for lens sparing external beam radiotherapy

Tumour at or behind the equator and unsuitable for focal treatment because
Too close (<5 mm) to optic disc or macula
Too large (>10 mm diameter) for plaque therapy
Too numerous (>2 tumours) for plaque therapy

Table 2 Contraindications to lens sparing external beam radiotherapy

Untreated tumour anterior to equator
Retinal detachment extending to ora serrata
Vitreous seeding

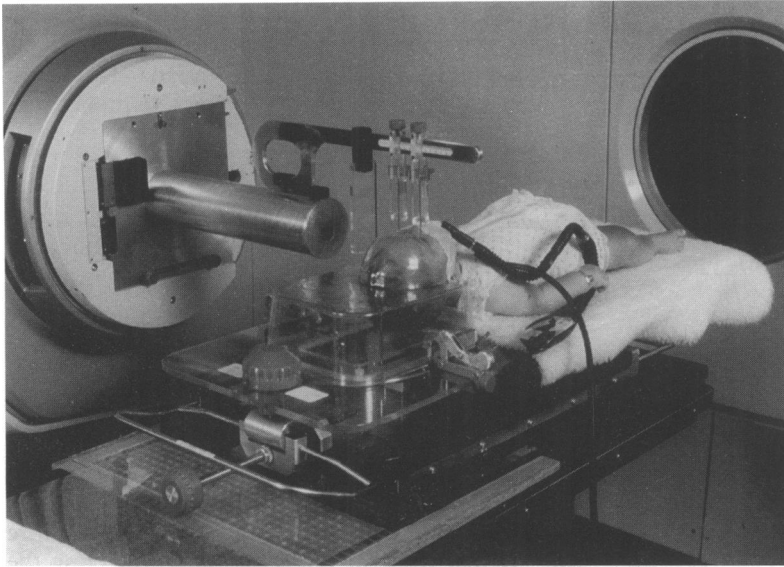


Fig 1A

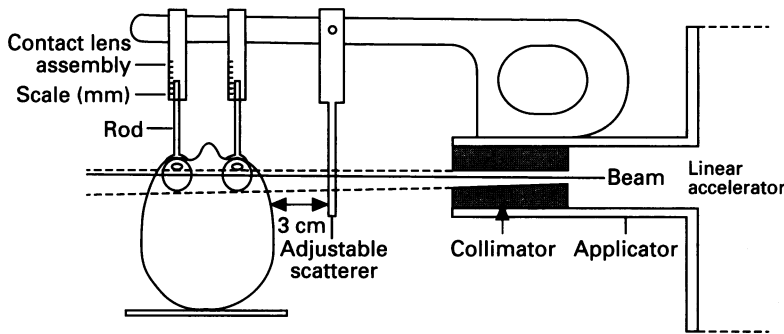


Fig 1B

Figure 1 (A) Set up for lens sparing external beam radiotherapy for retinoblastoma. (B) Schematic illustration of lens sparing technique.

classification.¹⁴ A scan ultrasonography was utilised to determine the distance from the anterior corneal surface to the posterior surface of the lens.

The technique has been described in full elsewhere.⁵ In brief, a standard 6 MV linear accelerator beam has been modified to produce a non-divergent and almost penumbra free anterior beam edge by a beam splitting and extended collimation system (Fig 1). Using a contact lens to provide a reference point on the surface of the eye and an attached rod and scale measuring system directly linked to the collimator it has been shown that, based on the A scan measurements, the anterior border of the radiation field can be placed behind the lens of the eye with 0.5 mm accuracy in a supine, immobilised, and anaesthetised infant. If the contralateral eye has been enucleated, a direct lateral field is used. When both eyes require lens sparing external beam radiotherapy, horizontally opposed lateral fields are employed (Fig 2). If the contralateral eye is healthy, the radiation portal is angled 40° in a superoinferior direction, exiting through the contralateral maxilla (Fig 3). Throughout the period of the study the dose employed was 40 Gy administered in 20 fractions over 28 days.⁵

The results of treatment were first assessed 1 month after completion of radiotherapy and thereafter at 3 monthly intervals for the first post-treatment year followed by longer intervals according to the response. Patients who had focal treatment of pre-equatorial tumours were re-examined approximately half way through radiotherapy to ensure that their anterior tumours were controlled. Additional focal treatment was given to these children when necessary. Eyes which developed recurrences and new tumours after lens sparing external beam radiotherapy could often be salvaged by focal therapy. Cryotherapy was the method of choice for single or multiple tumours 6 mm or less in diameter and radioactive scleral plaque therapy with an iodine-125 or ruthenium-106/rhodium-106 applicator for single lesions more than 6 mm and up to 13 mm in diameter.

In the statistical analysis, comparison of proportions was by χ^2 test with continuity correction or by Fisher's exact test if any expected counts were less than 5. Pooled comparison of success rates across Reese-Ellsworth groups was by the Mantel-Haenzel test.

Results

A total of 55 children had been treated by lens sparing external beam radiotherapy. Follow up data were incomplete on two children from abroad who were excluded from the present study. In the 53 children who fulfilled the criteria for inclusion, 67 eyes had been treated by the lens sparing method. Follow up ranged from 12 to 82 months (median 35 months). Seventy six per cent of the treated children have been followed for more than 2 years.

Fourteen (21%) of the 67 eyes receiving lens sparing external beam radiotherapy as the primary treatment of post-equatorial retinoblastomas required prior focal treatment to anterior tumours.

Figure 4 summarises the initial results of lens sparing external beam radiotherapy. Treatment was successful in 48 eyes (72%). Treatment failure (failure to control tumour growth or local recurrence) occurred in six eyes (9%). New tumours developed in 13 eyes (19%). Ninety three per cent of the new tumours arose anterior to the equator. Time to diagnosis of treatment failure or new tumour development ranged from 2 to 25 months (mean 10 months).

Table 3 lists the initial success rate following lens sparing radiotherapy, the salvage rate among those eyes requiring further treatment and the overall success rate by Reese-Ellsworth group. Three of the treatment failure eyes required enucleation. Salvage therapy (cryotherapy/plaque therapy) was attempted for the other three failed eyes and for all 13 eyes with new tumours. This was successful in 14/16 eyes (88%).

Overall five eyes (7%) required enucleation, all for failure to control tumour growth. Two eyes were enucleated for persistent tumour growth anterior to the equator, two for tumours posterior to the equator, and one for

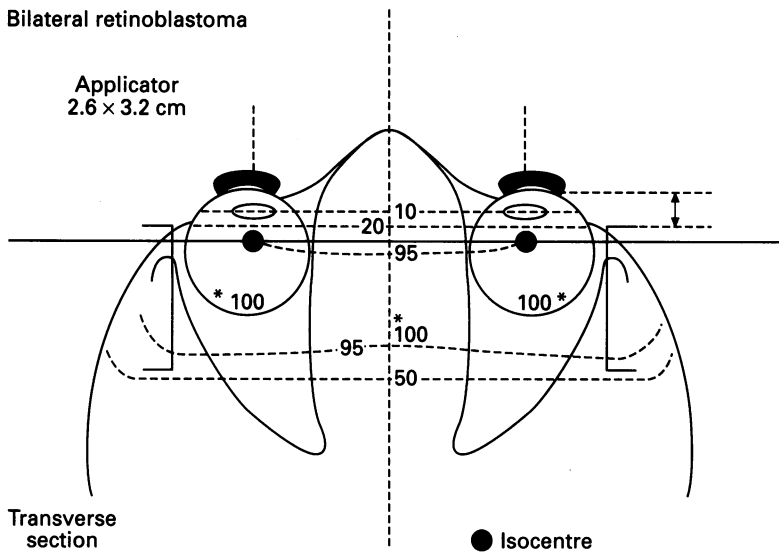


Figure 2 Treatment plan for horizontally opposed lateral fields.

uncontrolled tumour growth at both sites. All the anteriorly located tumours in eyes which subsequently required enucleation developed after completion of lens sparing external beam radiotherapy. No eyes were enucleated for complications of radiotherapy.

Immediate side effects of lens sparing radiotherapy were confined to mild erythema at the entry site which resolved within a few days of completion of treatment. In the longer term, middle facial growth retardation has been observed, and is more evident the younger the age of the patient at the time of radiotherapy. No cataracts have developed to date in children who received lens sparing radiotherapy with or without additional cryotherapy. One patient who received radioactive scleral plaque therapy for an anterior recurrence has developed a slight posterior subcapsular cataract though this has not yet required surgical treatment. A

Unilateral retinoblastoma

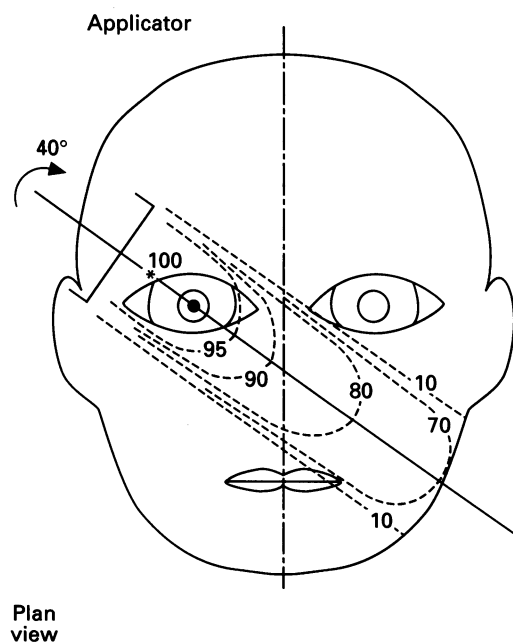


Figure 3 Treatment plan for oblique lateral field.

second patient has developed a vitreous haemorrhage stemming from the site of radioactive plaque application. No other anterior or posterior segment complications have been noted so far.

Discussion

The anterior segment complications associated with whole eye radiotherapy including eyelid damage, impairment of tear production, corneal toxicity, and the high incidence of cataract formation have been well documented.^{2 4 5 15-17}

In order to avoid these complications, various forms of radiotherapy aimed at sparing the lens/anterior segment have been developed. To achieve accurate and reproducible irradiation of an eye with the aim of treating the entire retina, while at the same time protecting the lens/anterior segment, makes considerable demands on the technique employed. This is attributable to the close anatomical proximity of the structures involved, in addition to the radiosensitivity of the lens.

The minimum total cataractogenic dose following radiotherapy in single or fractionated applications has been reported to be as low as 200 cGy and as high as 1000 cGy.^{12 18 19} Although the total dose of radiation for the treatment of retinoblastoma has been reduced over the years, a dose of 3500-5000 cGy fractionated over 3-6 weeks is recommended by most centres.

Several authors have reported on the incidence of cataract formation utilising various techniques of lens sparing radiotherapy. Egbert utilising a lateral photon beam which was positioned with the aid of a Comberg contact lens delineating the limbus,²⁰ reported a 66% incidence of cataract.⁹

McCormick reported on the results of two further methods.²¹ First, the anterior edge of a lateral photon beam was placed at the bony lateral canthus and used in conjunction with an anterior electron beam. The lens of the eye was protected by a contact lens mounted lead shield. In this series, 12% of eyes developed cataracts. This technique was superseded by a method which employed a lateral photon beam with its anterior edge placed 2-3 mm posterior to the limbus together with superadded

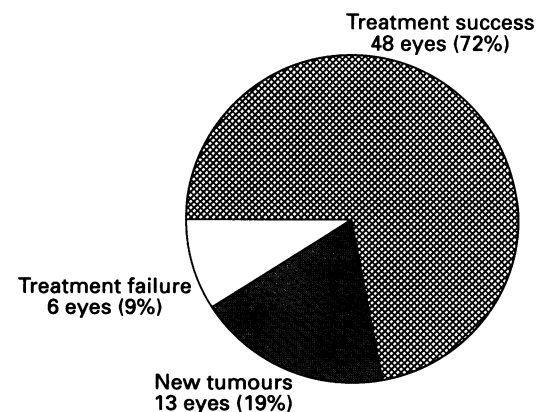


Figure 4 Initial results of lens sparing external beam radiotherapy.

Table 3 Results of lens sparing radiotherapy alone and in combination with salvage focal therapy

Reese-Ellsworth group	Success rate of primary radiotherapy*	Salvage rate of failures and new tumours by focal therapy	Overall success rate including salvage by focal therapy
I	14/18 (78%)	4/4 (100%)	18/18 (100%)
II	22/33 (67%)	7/11 (64%)	29/33 (88%)
III	7/11 (64%)	3/4 (75%)	10/11 (91%)
IV	5/5 (100%)	0	5/5 (100%)
Total	48/67 (72%)	14/19 (74%)	62/67 (93%)

*Includes patients treated by adjuvant focal methods.

oblique electron beams. Although no cataracts were reported following this modification, the follow up period was short and development of late lens opacities was anticipated.

Schipper described a technique utilising a lateral beam with a highly accurate method of positioning the treatment field.^{11 12} Initially the anterior margin of the beam was positioned 2 mm posterior to the lens. Following the development of several recurrences and new tumours in the peripheral retina, the technique was modified so as to place the anterior margin of the beam tangential to the posterior surface of the lens for tumours posterior to the equator and 1–3 mm into the lens in the presence of anterior tumours or vitreous seeds. Thirty three per cent of treated eyes developed cataracts after treatment. It was found that a cataract developed when more than 1 mm of the lens thickness was included in the radiation field.

Foote *et al*²² utilising a lateral D-shaped beam with the anterior beam edge positioned at the limbus, or between the limbus and the caruncle for posterior tumours, with or without posterior angulation of the beam, reported the development of cataracts in 29% of cases.

In our series, using the modified Schipper technique, only one patient (1.5%) developed lens opacities. This occurred in an eye which required additional plaque therapy for an anterior recurrence outside the radiation field. The lens opacities have not advanced since detection 82 months previously and have not required surgical treatment. The development of lens opacities in this patient is probably due to the adjuvant plaque therapy she received. We attribute the fact that no cataract has developed in any other patient to the accurate and reproducible localisation of the radiation field achieved by the modified Schipper technique. By contrast, cataract requiring lens aspiration developed usually within 2 years in all 140 retained eyes of a series of 175 eyes

Table 4 Comparison of overall results of lens sparing and whole eye external beam radiotherapy including salvage focal treatment

Reese-Ellsworth group	Eye preservation rate		
	Lens sparing external beam radiotherapy	Whole eye external beam radiotherapy	p Value
I	18/18 (100%)	16/16 (100%)	1
II	29/33 (88%)	46/55 (84%)	0.76
III	10/11 (91%)	56/68 (82%)	0.68
IV	5/5 (100%)	3/7 (43%)	0.08
V	–	19/29 (66%)	
Total	62/67 (93%)	140/175 (80%)	0.18

which received whole eye external beam radiotherapy¹³ ($\chi^2=232$, $p<0.0001$). The development of cataract after whole eye external beam radiotherapy in eyes which are also dry and intolerant to aphakic contact lenses results in amblyopia in many eyes with extrafoveal tumours which would otherwise have good vision. This is particularly a problem when only one eye is irradiated.

No other anterior segment complications have been encountered so far and, although longer follow up is required, none is foreseen in the future. In particular there has been no evidence of eyelash loss, lid shrinkage, lagophthalmos, dryness, corneal vascularisation and opacification, or conjunctival telangiectasia in any of the patients treated. A slight impairment of middle facial growth has been noted, particularly in children treated before the age of 1 year. When only one eye was treated this led to facial asymmetry in some instances, however, this has generally been less marked than that observed after whole eye treatment, presumably because the treated volume of bone is significantly less when the lens and anterior segment are spared. The opportunity to avoid dry, vascularised, painful, and photophobic eyes in carefully selected children has substantially improved comfort and cosmesis compared with similar patients treated by whole eye external beam radiotherapy.

To capitalise fully on the advantages of sparing the lens and anterior segment, the eye preservation rate should be at least as good as that achieved employing a whole eye approach. In a study comparing the results of whole eye and lens sparing radiotherapy, Foote and co-workers noted a higher tumour control rate following primary whole eye radiotherapy in comparison with lens sparing radiotherapy (64% cf 29%). They concluded that whole eye irradiation was the preferable mode of treatment. However, when their data on ocular survival are analysed, there appears to be a comparable success rate between the two methods (whole eye 82% cf lens sparing 79%).²²

Table 4 compares the overall success rates of lens sparing and whole eye external beam radiotherapy including salvage focal treatment in our series. Most of the lens sparing patients were in Reese-Ellsworth groups I to III though a few group IV patients fulfilled the selection criteria. Because sparing the lens was considered inappropriate for some group IV patients it is only possible to make direct comparisons with the whole eye approach in groups I to III. External beam radiotherapy was universally successful following both methods for group I tumours which were small lesions irradiated externally because of their location close to the optic disc or macula ($p=1$). An improvement in overall success rate following lens sparing compared with whole eye treatment was observed in groups II ($p=0.76$) and III ($p=0.68$) although the difference is not statistically significant.

When the results of treatment for groups I–III are considered collectively, a success rate of 85% was achieved following whole eye and 92% after lens sparing radiotherapy ($\chi^2=0.36$,

Table 5 Comparison between reported eye preservation rates following lens sparing radiotherapy and those of the present study (%)

	Groups I-V		Groups I-III	
	RT	RT+ salvage	RT	RT+ salvage
Cassady <i>et al</i> ⁸	49	69		73
Egbert <i>et al</i> ⁹		58		80
Schipper <i>et al</i> ¹²	41	81	54	94
McCormick ²¹				
ALSRT			33	73
MLB			83	100
Foote <i>et al</i> ²²	29	79	40	80
Toma <i>et al</i> (1994)	72	93	69	92

RT=radiotherapy, ALSRT=anterior lens sparing radiotherapy. MLB=modified lateral beam.

p=0.55). Only 76% of the lens sparing group have been followed for more than 2 years compared with 100% of the whole eye group. However, as 78% of treatment failures and new tumour development following primary whole eye radiotherapy occurred within the first year and 95% within the first 2 years,¹³ we would not expect to see many further relapses in the lens sparing patients. The radiation dose was better fractionated in the lens sparing group of children than in the early patients treated by the whole eye technique, three of whom lost an eye from side effects of insufficiently fractionated radiotherapy.

Our results also compare favourably with those achieved by other methods of sparing the lens (Table 5),^{8 9 12 21} although a direct comparison between these various studies is difficult because of differences in patient selection, radiotherapy technique, follow up and presentation of data.

In our series, new tumours developed in 13 eyes (19%) and the majority (93%) were located anterior to the equator. The high incidence of new tumours in the unirradiated anterior retina concurs with other studies in which the incidence of new tumours was 6-27%, of which 67-90% developed anterior to the equator.^{12 22-24}

Our experience suggests that, when sparing the lens, new anterior tumours arising in the unirradiated field lead to a substantial increase in the overall incidence of new lesions. In an analysis of 175 eyes treated by whole eye radiotherapy, the incidence of new tumours was significantly lower at 5% ($\chi^2=10.8$, $p=0.001$) with only 22% ($\chi^2=8.5$, $p=0.004$) of these developing anterior to the equator.¹³ Several authors have referred to the prophylactic effect of radiotherapy on the development of new tumours.^{2 6 12} This effect probably results from destruction of tumours which are too small to visualise ophthalmoscopically. The results of various series^{12 13 23 24} lend support to this concept. Even when very accurate placement of the anterior beam edge is achieved, it is impossible to avoid a fall off of dose to the anterior retina when sparing the lens. Loss of the prophylactic effect probably explains the higher incidence of new tumours,⁴ though some new retinoblastomas occur anterior to the equator even when the whole retina is irradiated. New retinoblastomas may develop in irradiated retina as a result either of

undetected implantation of tumour cells from the vitreous or from malignant transformation of undifferentiated retinal cells harbouring the germinal mutation. The maturation process of retinal cells proceeds centrifugally and there is some evidence to suggest that late in the disease undifferentiated cells are more common anteriorly.¹²

The higher incidence of new anterior tumours did not reduce the overall ocular cure rate of lens sparing compared with whole eye radiotherapy (Table 4). This is due to careful monitoring post radiotherapy thus allowing early detection and treatment of these tumours by judicious use of focal salvage techniques.

This preliminary study suggests that, unless, with longer follow up, a significant number of unsalvageable late relapses are seen in the lens sparing group, the modified Schipper technique is appropriate for all eyes in Reese-Ellsworth groups I to III. Furthermore, the lens may be spared in group IV eyes provided that any tumours anterior to the equator are amenable to focal adjuvant therapy. In the presence of anterior tumours too large for focal therapy or of a retinal detachment extending forwards to the ora serrata we would advocate including the whole retina and therefore the posterior part of the lens in the treatment field. In our view, the potential for anterior chamber extension in vitreous seeding is sufficient to justify applying a whole eye radiation field in eyes with this finding, and for which a conservative approach can be justified. In carefully selected cases, the modified Schipper technique together with adjuvant and salvage focal therapy has so far produced a local ocular cure rate at least as good as whole eye external beam radiotherapy but without the associated anterior segment morbidity.

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