REVIEW ARTICLE

Drugs 2007; 67 (15): 2173-2185
0012-6667/07/0015-2173/$49.95/0

Current Management Strategies for Intraocular Retinoblastoma

Jonathan W. Kim,[1] *David H. Abramson*[1] and *Ira J. Dunkel*[2]

1 Department of Ophthalmic Oncology, Memorial Sloan-Kettering Cancer Center, New York, USA
2 Department of Pediatric Neuro-Oncology, Memorial Sloan-Kettering Cancer Center, New York, USA

Contents

Abstract

Survival rates for retinoblastoma patients have increased dramatically over the last century, with documented 5-year survival figures reaching 87–99% in developed countries. During the last decade, there has been a dramatic paradigm shift in the treatment approach for intraocular retinoblastoma, emphasising chemoreduction protocols and minimising the use of external beam radiation. The recognition of the increased risk for second non-ocular cancers with external beam radiation contributed to the growing emergence of chemotherapy. Although chemoreduction protocols vary slightly between institutions, many centres are currently treating intraocular retinoblastoma with carboplatin, vincristine and etoposide as a three-drug regimen given in two to six cycles. Clinical studies have demonstrated that systemic chemotherapy must be combined with other modalities, such as laser treatment and cryotherapy, for adequate tumour control and many eyes with advanced intraocular disease require salvage therapy with radiation or enucleation. Therefore, modern centres treating retinoblastoma continue to manage patients with a variety of modalities, individualising the therapy according to the patient's presentation and clinical course.

Retinoblastoma is the most common primary intraocular tumour in children and the tenth most common paediatric cancer in the US.[1] The cumulative lifetime incidence of retinoblastoma is between 56.5 and 62.5 cases per million persons or approximately 1 in 15 000 to 1 in 18 000 individuals in the US.[2] Survival rates for retinoblastoma patients in developed countries have increased dramatically over the last century. The mortality of retinoblastoma was reported to be almost 100% prior to 1900, but recent cancer registry data from Europe and the US have documented 5-year survival rates between 87% and 99%.[1,3,4] Unfortunately, developing nations continue to report higher mortality figures, as

many patients in poorer countries present with extraocular or metastatic retinoblastoma.[5,6] In modern centres, intraocular retinoblastoma is managed with a variety of treatment modalities including: enucleation, external beam radiation (EBR), transpupillary thermotherapy (laser), cryotherapy, brachytherapy and chemotherapy (systemic and periocular). Over the last decade, there has been an effort to increase the use of chemotherapy and focal treatments, and to avoid the use of EBR therapy, mainly because of the growing awareness of second tumours in retinoblastoma patients with germinal disease. Retinoblastoma typically responds, at least partially, to all eye-conserving treatment modalities. However, tumour regrowth is a common cause of treatment failure, necessitating constant surveillance and monitoring. When all conservative strategies have failed, enucleation is typically curative unless the tumour extends to the optic nerve margin or invades the sclera.

This review article summarises current management approaches for intraocular retinoblastoma, emphasising the clinical indications for systemic and periocular chemotherapy, EBR, brachytherapy and enucleation.

1. Classification and Staging

The staging of retinoblastoma is currently an area of much heated debate among ophthalmic oncologists. The Reese-Ellsworth (R-E) classification scheme, developed by Algernon Reese and Robert Ellsworth at the Columbia Presbyterian Medical Center in the 1960s, is the most commonly used nomenclature system for describing intraocular retinoblastoma.[7] The R-E scheme is better characterised as a classification system and not a true staging scheme, since the groupings are based on intraocular findings and not the disease state of the patient. Patients also do not typically progress from lower groups to higher groups. It was originally developed to predict prognosis in eyes that were treated with lateral port EBR. The R-E system divides eyes according to the extent and location of disease as determined by ophthalmoscopy into five groups (I–V) and ten subgroups ('a' and 'b' for each group) [table I]. Anterior tumours of any size, even small tumours, were placed in higher risk groups III and IV, presumably because they were more difficult to cure with lateral port techniques. Subgroup Vb contains eyes with vitreous seeding, a common finding at initial diagnosis and a feature widely recognised as being a poor prognostic sign for globe survival. Despite its limitations, the R-E classification has served as an excellent ocular reference for comparing different series and treatment schemes, as nearly all scientific papers published on retinoblastoma during the past 40 years have used this system to classify patients.

In recent years, the utility of the R-E scheme has been questioned by many ophthalmic oncologists who feel it is an antiquated system, particularly with the recent trend away from the use of external beam radiotherapy and toward the use of chemoreduction. Recent papers reporting clinical outcomes no longer use the R-E classification consistently,[8] and this has hampered comparisons of results between centres and the interpretation of outcomes data. Murphree[9] has written that with the advent of chemotherapy, tumour size, number and location are less important than the presence of seeding in the vitreous or sub-retinal space, which has limited representation in the R-E classification. To rectify this, sev-

Table I. Reese-Ellsworth classification for intraocular retinoblastoma

Group	Prognosis	Features
I	Very favourable	(a) Solitary tumour, <4 disc diameters in size, at or behind the equator
		(b) Multiple tumours, none >4 disc diameters in size, all at or behind the equator
II	Favourable	(a) Solitary tumour, 4–10 disc diameters in size, at or behind the equator
		(b) Multiple tumours, 4–10 disc diameters in size, behind the equator
III	Doubtful	(a) Any lesion anterior to the equator
		(b) Solitary tumours >10 disc diameters behind the equator
IV	Unfavourable	(a) Multiple tumours, some >10 disc diameters
		(b) Any lesion extending anteriorly to the ora serrata
V	Very unfavourable	(a) Massive tumours involving over half the retina
		(b) Vitreous seeding

Table II. International Classification of Retinoblastoma (ICRB)

Group	Subgroup	Quick reference	Specific features
A	A	Small tumour	Retinoblastoma ≤3mm in size
B	B	Larger tumour	Retinoblastoma >3mm in size or
		Macula	Macular retinoblastoma location (≤3mm to foveola)
		Juxtapapillary	Juxtapapillary retinoblastoma location (≤1.5mm to disc)
		Subretinal fluid	Clear subretinal fluid ≤3mm from margin
C		Focal seeds	Retinoblastoma with
	C1		subretinal seeds ≤3mm from retinoblastoma
	C2		vitreous seeds ≤3mm from retinoblastoma
	C3		both subretinal and vitreous seeds ≤3mm from retinoblastoma
D		Diffuse seeds	Retinoblastoma with
	D1		subretinal seeds >3mm from retinoblastoma
	D2		vitreous seeds >3mm from retinoblastoma
	D3		both subretinal and vitreous seeds >3mm from retinoblastoma
E	E	Extensive retinoblastoma	Extensive retinoblastoma occupying >50% globe or
			Neovascular glaucoma
			Opaque media from haemorrhage in anterior chamber, vitreous or subretinal space
			Invasion of postlaminar optic nerve, choroid (>2mm), sclera, orbit or anterior chamber

eral authors have proposed new classification systems designed to predict prognosis in eyes treated with chemotherapy as the primary modality. With the support of the newly formed Children's Oncology Group, a new classification scheme was published by Murphree[9] in 2005. This system classified tumours based on specific morphological features that are thought to correlate with the risk for treatment failure, particularly the presence of intraocular tumour dissemination. The Shields group[8] has also published a similar grouping system based on the presence of subretinal fluid, and subretinal and vitreous seeds. These newer schemes do not classify tumours based on location or multifocality, but rather assign eyes with vitreous seeds and sub-retinal seeds to the higher risk groups, reflecting the difficulty in treating these eyes with chemotherapy and focal modalities.

The International Classification of Retinoblastoma (ICRB) is now becoming adopted by many ocular oncology centres that utilise chemoreduction (table II). The ICRB system has specific criteria for quantifying the distance of subretinal and vitreous seeds from the originating tumour, with minor considerations for tumour size and location.[10] Finalised by a group of experts at an international meeting in Paris, the ICRB was designed to standardise the classification of intraocular retinoblastoma in the modern era with a scheme that predicted treatment success with chemoreduction protocols. In 2006, Shields and colleagues[10] published an analysis of the R-E scheme and the ICRB scheme in predicting success in eyes treated with chemotherapy (defined as tumour control without EBR or enucleation). They found that, although both classification schemes demonstrated reliability in predicting treatment success between the major categories, the ICRB was the only system that showed fairly consistent reliability within the subcategories. For example, their series showed that eyes with R-E group IVa disease had only a 50% success rate with chemoreduction, while the higher group IVb eyes had an even higher success rate of 80%.[10] Despite the enthusiasm regarding these new classification schemes, it should be kept in mind that, to date, the R-E scheme is the only one that has been widely accepted among all ocular oncology centres. Furthermore, many of the intraocular findings included in the newer schemes, such as subretinal seeds, are difficult to quantify even for experienced examiners. Finally, Abramson and Schefler[11] have pointed out that any classification system designed to predict prognosis on the basis of one treatment modality, such as chemoreduction, may become less useful once the treatment modality on which the system is based becomes outdated.

2. Chemoreduction

Before 1990, most centres reserved chemotherapy for patients requiring adjunctive treatment after enucleation, or rescue therapy for extraorbital or metastatic disease. The recognition of the increased risk for second tumours in patients treated with EBR stimulated many groups in the 1990s to use chemotherapy to treat intraocular retinoblastoma. Over the last decade, chemoreduction has emerged as the most important conservative (eye-sparing) treatment approach for intraocular retinoblastoma. Chemotherapy is currently used to treat tumours that are too large or widespread to treat with focal modalities such as cryotherapy, thermotherapy or brachytherapy, particularly for younger patients (aged <12 months). It has been recognised that children aged <12 months who receive EBR are at an increased risk for developing second non-ocular cancers, as well as other complications such as orbital and midfacial hypoplasia. Although EBR remains an excellent option for preserving vision in patients with retinoblastoma, most clinicians believe that current chemotherapy regimens offer a better safety profile than radiotherapy. The visual outcomes of chemoreduction also appear to be comparable with EBR for patients with bilateral disease and visual potential in one or both eyes.[12] Often, extensive tumours in the posterior pole will shrink enough with chemotherapy to allow treatment with focal modalities in an attempt to preserve at least a portion of central vision. Patients with advanced unilateral disease (group V) without visual potential in the involved eye are often encouraged to undergo enucleation to spare the child the potential toxicities of systemic chemotherapy or EBR.

Published clinical studies on chemoreduction from major treatment centres are summarised in table III. Since 1996, the majority of published chemoreduction protocols for intraocular retinoblastoma have utilised vincristine, carboplatin and an epipodophyllotoxin (either etoposide or teniposide).[13-23] Carboplatin, an analogue of cisplatin with less nephrotoxicity and ototoxicity, is an active agent against many brain tumours and is known to cross the blood-brain barrier.[14] The regimen of carboplatin, etoposide and vincristine has been used successfully against extraocular retinoblastoma,[24,25] as well as other primitive neuroectodermal tumours such as neuroblastoma. The addition of ciclosporin (cyclosporine) as a P-glycoprotein inhibitor was suggested by Chan et al.[26,27] to increase chemosensitivity. Their group has demonstrated that some patients who became resistant to multiple cycles of chemotherapy responded to the same regimen given with ciclosporin.[28] The success rate in their series of patients also seemed to correlate with higher doses of ciclosporin. The choice of agents used in chemoreduction regimens as well as number of cycles varies at different institutions. Many centres have utilised a two-agent regimen of carboplatin with either etoposide or vincristine, with similar outcomes as the three-drug regimen.[17,29-32] Single-agent chemotherapy with carboplatin has also been used with success by Abramson's group.[33,34]

Although the ideal regimen for chemoreduction has not been determined, most authors agree that chemotherapy must be combined with other modalities for adequate tumour control. Although almost all eyes respond initially to chemotherapy,[18,34] it is rare for a tumour to be cured with chemotherapy alone, even after six cycles.[16] Without laser treatment or cryotherapy, Wilson et al.[31] found that in 92% of eyes the tumour progressed after completion of chemotherapy. Abramson et al.[34] suggested that focal treatments can usually be delivered after two to three cycles, since cumulative reduction in tumour area was near maximal after two cycles and the mean reduction in tumour area for the third treatment alone was only 5.4%. Gallie et al.[28] also suggested treatment after two cycles if the clinical examination confirmed adequate tumour reduction and resolution of subretinal fluid. Conversely, Shields and colleagues[16] have reported that patients undergoing a minimum of six cycles of chemotherapy achieved better long-term tumour control when compared with two cycle regimens, particularly for eyes with advanced disease. Although there is no consensus on the timing of focal treatments and the number of cycles of chemotherapy for each patient, the treatment should be individualised to the clinical response. Focal modalities can be used to treat tumours that have responded to chemoreduction when clinical judgment indicates that tumours can be cured with laser treatment, cryotherapy or

Table III. Summary of clinical studies on chemoreduction in children with retinoblastoma

Study (year)	No. of eyes	Regimen	Cycles	Group V eyes[a]	Further treatment			F/U (mo)
					EBR	enuc	none	
Gallie et al.[28] (1996)	40	VRES		18	4	1	13	3
Kingston et al.[18] (1996)	24	VRE	2–4	24	20	6	18	60
Murphree et al.[14] (1996)	35	VRE	3	21	7	17	0	?
Shields et al.[15] (1996)	31	VRE	2	22	9	0	13	6
Greenwald et al.[17] (1998)	11	RE	6–7	6	5	3	1	23
Bornfeld et al.[20] (1997)	12	VRES	3	7	2	1	4	7
Shields et al.[16] (1997)	52	VRE	6	36	19	8	9	17
Gunduz et al.[19] (1998)	27	VRE	6	27	16	10	5	25
Friedman et al.[22] (2000)	75	VRE	6	30	13	9	14	13
Beck et al.[29] (2000)	33	RE	2–5	13	7	5	2	31
Wilson et al.[31] (2001)	36	VR	6	14	8	5	5	19
Shields et al.[35] (2002)	158	VRE	6	75	32	32	27	28
Brichard et al.[21] (2002)	24	VRE	2–6	12	0	2	10	21
Rodriguez-Galindo et al.[32] (2003)	43	VR	8	15	8	6	4	32
Schiavetti et al.[30] (2005)	58	RE	4–8	17	4	11	1	53
Antoneli et al.[23] (2006)	145	VRE	2–6	74	?	?	30	?
Total	**804**			**411**			**156**	

a Eyes with Reese-Ellsworth group V disease.

E = etoposide; **EBR** = external beam radiation; **Enuc** = enucleated eyes; **F/U** = mean follow-up; **None** = eyes avoiding enucleation and EBR; **R** = carboplatin; **S** = ciclosporin; **V** = vincristine; **V eyes** = eyes with Reese-Ellsworth group V disease; **?** indicates unknown.

brachytherapy, keeping in mind the importance of preserving central vision in one or both eyes.

Similar to other treatment modalities, clinical studies examining the efficacy of chemoreduction demonstrate a correlation with the stage of intraocular disease. The strategy of combining chemoreduction with focal therapy has been associated with a 90–100% chance of radiation and enucleation-free survival for eyes in R-E groups I–III.[8,16] Shields et al.[16] reported that all 39 eyes in groups I–III treated with six cycles of vincristine, carboplatin and etoposide, and focal therapies were cured without EBR.[16] Results for patients with R-E groups IV and V disease have been less encouraging. Although there is a wide range of globe salvage rates between different series for eyes with R-E group V disease, overall only 38% of such eyes avoided both EBR and enucleation (table III). Clearly, the strategy of using chemoreduction alone is only successful in avoiding radiation in a minority of eyes with advanced disease. However, when combined with EBR, chemoreduction can contribute to a high globe salvage rate for these advanced eyes. Kingston et al.[18] reported an eye preservation rate of 70% for patients with group V disease treated with both chemoreduction and EBR. Shields et al.[16] in 1997 reported the eye preservation rate for eyes with group V disease as 78%, with 75% of these eyes receiving EBR.[16] Although Greenwald et al.[17] have suggested that chemotherapy plus radiation may have a synergistic effect in eyes with group IV and V disease, chemotherapy does not appear to lead to a notable improvement in globe salvage rates when compared with historical controls where radiation alone was utilised.[18,36] However, an important benefit for these patients is that chemoreduction protocols can delay the onset of EBR in young children by ≥6 months.[31] Therefore, when attempting to salvage eyes with advanced intraocular disease, chemoreduction plays an important role in the treatment algorithm, recognising that EBR may become necessary in a significant percentage of patients with group V disease.

Tumour regression following chemoreduction has been described and quantitated by several authors. An early report by Shields et al.[13] showed that tumours decreased in size an average of 35% in basal diameter and 50% in tumour thickness after only two cycles of chemotherapy. Greenwald et al.[17] reported similar responses, with a mean reduction of 32% in the initial base area and 55% of the initial base diameter. Abramson et al.[34] in 2005 reported a 37.1% reduction in tumour area and a 21.3% reduction in basal diameter following only one cycle of carboplatin; the serous retinal detachment also appeared to improve or resolve in the majority of eyes.[17,18,37] The reduction in tumour volume seen often resulted in an increased distance of the tumour margin from visually vital structures.[13] Another important observation was that tumour regression patterns after chemoreduction were not as reliable in predicting the risk of tumour reactivation as those following EBR.[31] Murphree et al.[14] pointed out that anything other than a type IV regression (flat scars) or type I regression (calcified tumours) was inadequate following chemoreduction. Although larger tumours often demonstrate a more dramatic clinical response than smaller tumours, the percentage reduction in tumour base does not appear to correlate with initial size.[13,34] Several authors have suggested that a subset of smaller tumours (<2mm) are at greater risk for recurrence following treatment.[15,38] Gombos et al.[38] have postulated that tumours in this size category may be less responsive to intravenous chemotherapy because of more differentiated cells or because of a lack of feeder vessels. A histopathological study of eyes treated solely with chemotherapy showed that tumours with well differentiated components showed less shrinkage from chemoreduction.[12]

The presence of subretinal or vitreous seeds is a common cause of treatment failure in eyes undergoing chemoreduction. Earlier studies suggested that chemotherapy had a favourable effect on tumour seeds in the vitreous cavity and subretinal space.[13,17] In 1996, Shields et al.[13] reported that calcification occurred in 50% of vitreous seeds and 78% of subretinal seeds following two cycles of chemotherapy, similar to the findings after EBR. Despite this initial favourable report, it soon became apparent that the presence of vitreous seeds imparted a poor prognosis to eyes undergoing chemoreduction. In follow-up studies by the same group, subretinal seeds present at the initial examination was the only factor predictive of retinal tumour recurrence,[35] and the globe preservation rate was

worse when vitreous or subretinal seeds recurred.[16] Overall, eyes with vitreous and subretinal seeds developed tumour recurrence at a rate of approximately 46% and 62% at 3 and 5 years of follow-up, respectively.[35] Recurrence of vitreous or subretinal seeds may not necessarily reflect resistance of the tumour to chemotherapy. Wilson et al.[31] have pointed out that seed dispersion can be induced or worsened by chemotherapy: as tumours regress during the initial cycles of chemotherapy, tumours can fragment and release seeds into the vitreous cavity. Persistence of seeds may also represent inadequate penetration of the chemotherapy to the avascular sites in the vitreous cavity and subretinal space. Another possible cause of treatment failure with chemoreduction is the development of new tumours. In the study by Lee and colleagues[33] of single-agent carboplatin, 47% of eyes developed additional tumours during the period of follow-up and 37% of eyes had new tumours only 1 month after the initial cycle of chemotherapy. The risk of new tumour formation was more than twice as likely if the child was treated before the age of 6 months and nearly all new tumours occurred in the first 2 years of life. These figures can be compared with the rate of new tumour formation of 6% of unilateral retinoblastoma[39] and 25% of bilateral cases[40] in the era prior to the advent of chemoreduction. The development of these new tumours could represent primary tumour resistance, selection of a resistant tumour cell line, or inadequate chemotherapeutic concentrations within small, minimally vascularised tumour foci. These findings confirmed that systemic chemotherapy does not appear to have a protective or prophylactic effect against the development of new tumours, even in the immediate post-treatment period.

Short-term systemic adverse effects of chemotherapy are common, including fatigue, nausea and vomiting, and haematological effects such as leukopenia, thrombocytopenia and anaemia. Occasionally, patients require transfusions or admissions for neutropenic fevers, but haematological suppression rarely requires a delay of chemotherapy doses.[28] No confirmed cases of ototoxicity have been reported in the literature with therapeutic doses of carboplatin; however, baseline hearing testing is encouraged in all patients.[41] Several ophthalmic complications have been reported in patients undergoing chemoreduction and focal therapy for retinoblastoma. Anagnoste et al.[42] reported three cases of rhegmatogenous retinal detachments and Gombos et al.[43] reported a case of intraocular cholesterosis following chemoreduction.

A rare but potentially life-threatening complication of chemoreduction is the development of second nonocular cancers, particularly haematological malignancies such as leukaemia. Acute myelogenous leukaemia (AML) has been reported following the use of etoposide with relatively short latency periods of 1–7 years.[44] In lymphoblastic leukaemia patients undergoing chemotherapy, the long-term risk of AML has been reported to be 2–3% for intensive weekly or twice weekly schedules of teniposide or etoposide.[44] A recent survey by Gombos et al.[45] identified 12 cases of AML in retinoblastoma patients undergoing chemoreduction. This survey included a questionnaire of retinoblastoma specialists practicing throughout the Americas and Europe, as well as a database of 1601 patients from the National Institutes of Health, Department of Health and Human Services, and the Ophthalmic Oncology Service at the Memorial Sloan-Kettering Cancer Center. Among the 12 identified cases, nine patients had bilateral or multifocal retinoblastoma, and eight patients had received an epipodophyllotoxin (etoposide or teniposide). Although a causative link between AML and epipodophyllotoxin therapy in retinoblastoma patients has not been established, it is concerning that prior to the chemoreduction era, the development of leukaemia was thought to be a rare event. In a study published in 1984, Abramson et al.[46] found only one case of leukaemia among 1900 survivors of retinoblastoma. Without knowing the total number of retinoblastoma patients treated with chemoreduction in the modern era, it is not possible to calculate the risk of developing AML in this population of patients or even to conclude that a definite association exists. However, this recent report by Gombos et al.[45] suggests that further investigation will be required to fully assess the validity of this risk, particularly since patients with intraocular retinoblastoma are receiving chemotherapy for non-life-threatening indications.

2.1 Periocular Chemotherapy

The ideal delivery method for chemoreduction would achieve high concentrations in the intraocular space with no systemic exposure to the drug. Because of the theoretical risk of tumour spread with intraocular injection, several groups have explored the local delivery of chemotherapeutic agents through periocular administration. In 1998, Mendelsohn and Abramson[47] showed that peribulbar and episcleral injection of carboplatin could achieve higher vitreous concentrations than intravenous administration in primates. Murray and colleagues[48] showed a dose-dependent inhibition of tumour growth with subconjunctivally delivered carboplatin in transgenic retinoblastoma mice. In the same study, no histopathological toxicity was detected 11 weeks after periocular carboplatin injections. The first clinical trial was performed by Abramson et al.[49] on 11 children with bilateral retinoblastoma, using a median of three injections per eye with an interval of 21 days between injections. In that trial, a major clinical response was observed in three of five eyes with vitreous seeds and two of five eyes with retinal tumours. Periorbital oedema and redness after injection were observed in 4 of 13 eyes and one patient developed optic neuropathy.[49]

Although the early clinical experience with periocular injection has been encouraging, there have also been several reports of local complications with this delivery method. In a recent histological study, Schmack and colleagues[50] reported four cases of optic nerve atrophy in eyes that had been enucleated following periocular carboplatin injection. The enucleated eyes had received between three and seven periocular carboplatin injections, but they had also been treated with systemic chemotherapy, transpupillary thermotherapy, transscleral cryotherapy and EBR. Histopathological examination showed focal areas of ischaemic necrosis and atrophy in the retrobulbar optic nerve along with dystrophic calcification and inflammation in the surrounding fibrovascular tissue. Optic neuropathy with systemic chemotherapy has been reported with cisplatin, but not with carboplatin alone.[51,52] Mulvihill and colleagues[53] reported ten patients with ocular motility restriction following subtenons carboplatin injection, diagnosed by forced duction testing. They reported that subtenon carboplatin injection performed through a conjunctival incision was associated with significant fibrosis of orbital soft tissues, restricting eye movement and making subsequent enucleation difficult. Restriction of eye movement was detected after only one subtenon injection and the degree of restriction correlated with the greater number of injections. Other groups performing periocular injections have not reported similar problems with ocular motility and the technique of creating a conjunctival incision for each injection may be a contributing factor.

Because of the potential for local toxicity, most centres reserve periocular injection for advanced intraocular disease that has not responded to multiple cycles of systemic chemotherapy. Local delivery of chemotherapeutic agents has the potential to increase globe salvage rates, particularly for eyes with vitreous and subretinal seeds, but further study and longer follow-up periods are needed to determine the safety and applicability of this new modality.

3. External Beam Radiotherapy

Over the past two decades, retrospective studies have documented an increased risk of second cancers in patients with germinal retinoblastoma treated with EBR.[54-57] A recent long-term study showed that patients with germinal retinoblastoma who undergo radiotherapy have a 38% cumulative incidence of second cancers by 50 years of age versus an incidence of 21% in children who have not been treated with EBR.[56,58] Age at the time of radiation therapy appears to be critical; children irradiated during the first year of life are two to eight times as likely to develop second cancers as those irradiated after the age of 1 year.[11,58,59] Non-ocular cancers observed in survivors of germinal retinoblastoma include, in order of most common to least common: soft tissue sarcomas, osteogenic sarcomas of the skull and long bones, pineoblastomas, cutaneous melanomas, other brain tumours, Hodgkin's disease, lung cancer, breast cancer and other epithelial neoplasms. When considering second cancers, patients treated with radiation tend to develop brain tumours and sarcomas of the head and neck within the radiation field in the first 10 years of life, whereas germinal retinoblastoma survivors who do not undergo radiation develop epithelial cancers (lung,

bladder, melanomas) out of the radiation field in adulthood.[60]

Retinoblastoma is a radiosensitive tumour and one of the few solid cancers that can be routinely cured by radiotherapy. Despite the recent paradigm shift toward chemoreduction in virtually all modern centres treating retinoblastoma, EBR remains an excellent method for preserving vision in children with retinoblastoma aged >1 year. Unlike focal therapies, EBR can treat tumours in the posterior pole without destroying central vision. EBR is also commonly used as salvage therapy following unsuccessful chemoreduction. Diffuse vitreous and retinal seeds cannot be treated with focal methods and typically are not cured with systemic chemotherapy, and therefore EBR is often considered for eyes with these seeds, although the salvage rate is only ≈ 50% with radiotherapy.[36] In cases of bilateral advanced intraocular disease in which clinical judgment cannot predict which eye is more likely to have useful vision, EBR can be used bilaterally. Other than the recently adopted clinical dictum to avoid radiation in children with retinoblastoma younger than 1 year of age, the decision to treat with EBR must be made on a case by case basis, and treatment algorithms are not always useful because of the various factors that must be considered.

Over the last 50 years, the optimal dose, dose rate, portals, fraction scheme and energy to treat retinoblastoma have been determined through the collaborative work of ocular oncologists and radiation oncologists. Radiation therapy for retinoblastoma is designed to encompass the entire tumour-bearing portion of the globe and at least 1cm of optic nerve. The fields are designed so that the radiosensitive lens receives a significantly lower dose than the tumour. For children with bilateral disease, parallel opposing lateral D-shaped fields are used to avoid radiation-induced cataracts, which are more common when anterior fields are used.[61] For patients with unilateral disease, a pair of superior and anterior wedged oblique 'D' fields are employed, with more radiation supplied to the superior oblique field to avoid a significant exit dose to the frontal lobe.[62] The dose prescribed to the retinal target typically ranges between 4200–4600 cGy in most centres, administered in 180–200 cGy per day fractions, five times per week. As would be predicted by the R-E classification, the location and size of the tumour determines the likelihood that it will respond to EBR. Small tumours in the posterior pole tend to respond well to EBR, with excellent visual results.[14] Large anterior tumours and those with vitreous seeds respond poorly to therapeutic doses of EBR. Overall rates of local control in the radiated eye, defined as preservation of the globe, vary in different series from 58% to 88%.[63-65] The probability of salvaging an eye with retinoblastoma treated with radiation varies with the R-E group: the globe preservation rate is 95% for eyes with group I–III disease that are treated with the lateral beam technique, but only 50% for eyes with group IV or V disease.[61] Studies of radiotherapy for eyes with group V disease report ocular salvage rates of 10–66%.[65-69] A follow-up study published in 2004 with the most severely affected eyes, eyes with vitreous seeding (group Vb), showed a tumour control rate of only 53.4% at 10 years.[36]

Although the development of additional nonocular cancers is the most serious long-term complication of EBR, other adverse effects do occur, particularly with higher doses in younger children.[66] For patients with lesions between the equator and the ora serrata, the anterior edge of the field is brought forward to include the lens, increasing the risk for a cataract. In one study of children treated with EBR before 1 year of age with anterior fields, clinically significant cataracts occurred in 85% of eyes over 12–49 months of follow-up.[70] Conversely, lens-sparing techniques have much lower rates of cataracts of 28%,[65] but also higher rates of anterior retinal recurrence. Another potential complication of EBR is damage to the vascular endothelium, with manifestations ranging from optic neuropathy, retinal vascular occlusion, vitreous haemorrhage and neovascular glaucoma. At the doses currently employed, the incidence of vascular complications is ≈ 5%.[71] Facial and temporal bone hypoplasia can also occur following radiation in very young children. This deformity is most marked when both eyes are treated with parallel opposing fields and when the children treated are under the age of 6 months. Fontanesi et al.[70] has reported that all children aged <1 year who received >30Gy using lens-sparing techniques experienced some facial asymmetry. Less serious complications that have been asso-

ciated with EBR include keratitis sicca, corneal ulceration, keratinisation of the conjunctiva and sclera, lacrimal gland atrophy/fibrosis, loss of lashes, hyphaema, iritis/uveitis, cataract, fat atrophy in the orbit and skin erythema within the area of the radiation portal.

4. Brachytherapy

In current treatment regimens for intraocular retinoblastoma, episcleral brachytherapy is the preferred modality for focal tumours that are too large for cryotherapy or laser treatment. Unlike EBR, radiation exposure is limited to the ocular structures and there is no increased risk of second non-ocular cancers or orbital hypoplasia. As is the case with other modalities, proper selection of patients is critical for success with brachytherapy. The ideal candidate for a radioactive plaque is a patient with a focal tumour between 4 and 10 disc diameters in size (≤8mm in thickness), without vitreous or subretinal seeds, and >2 disc diameters away from the macula or optic nerve. A large retinoblastoma tumour in the posterior pole treated with brachytherapy is likely to have a poor visual outcome, although in most cases the tumour has already destroyed central vision. Brachytherapy is also effective as a salvage technique in eyes in which other types of therapy, including external beam radiation, photocoagulation or cryotherapy, have failed. Diffuse vitreous or subretinal seeding will not respond to brachytherapy, although focal areas of vitreous seeding over the tumour can be treated.

When used as the primary modality in retinoblastoma patients, Shields and colleagues[72] reported a tumour recurrence rate of only 12% at 1 year of follow-up and an overall tumour control rate of 79% at 5 years. Schueler and colleagues[73] in Germany reported a 5-year tumour control rate of 94.4% and a 5-year eye preservation rate of 86.5% using ruthenium plaques, with a very high radiation dose to the tumour apex (>100Gy). Used as salvage therapy for eyes that have failed other treatment methods, Abramson and colleagues[74] reported an overall success rate for brachytherapy of 50%, utilising cobalt plaques. Merchant and colleagues[75] recently reported a salvage rate of 60% in eyes that had failed chemotherapy or external beam radiotherapy. Risks for tumour recurrence following brachytherapy include the presence of tumour seeds in the vitreous and subretinal space, large tumour size, prior failure of external beam radiation, lower dose of radiation (<38Gy) and increasing patient age.[72,73,75]

Iodine-125 is currently the most commonly used isotope for brachytherapy in the US. As described in the previous paragraph, other source materials, such as ruthenium, have been used successfully in Europe.[73] When creating an iodine-125 plaque for a child with retinoblastoma, radioactive seeds are placed into a custom-built plaque designed to treat the specific shape and size of the tumour. Plaque placement is confirmed with an indirect ophthalmoscope and the active plaque is inserted in the operating room. The regression response most commonly seen after removal is a type IV pattern (flat scar). With iodine plaques, the radiation dose is 4000–4500 cGy to the apex of the tumour at a rate of 1000 cGy/day. The plaque is removed in a second operation 3–5 days later, depending on the isotope used and the size of the tumour.

Although the radiation dose for retinoblastoma is lower than the doses typically used for uveal melanoma, ocular complications should be anticipated. In their series of 208 tumours managed with plaque radiotherapy, Shields et al.[72] reported retinopathy in 27%, papillopathy in 26%, cataract in 31% and glaucoma in 11% of treated eyes. Schueler et al.[73] reported a high incidence of intraocular haemorrhage of 29.1% in their series of patients treated with ruthenium-106 plaques, with almost half of these patients developing vitreous haemorrhage. The authors did not comment on the possible cause for this high rate of intraocular haemorrhage in their series, although the radiation doses used in this study may have contributed (mean 138Gy to tumour apex).[73] Eyes that have previously received EBR may be at higher risk for these ocular complications.

5. Enucleation

Despite the progress of conservative modalities, enucleation remains the most commonly employed technique for treating retinoblastoma worldwide. The vast majority of retinoblastoma cases are sporadic (non-familial), and many children do not present for medical care until the eye is filled with tumour, causing leukocoria, strabismus or glaucoma. Typically these eyes have very limited visual

potential, even with aggressive treatment. If the other eye is not involved or can be treated with focal therapies, there is little reason to subject the patient to the toxicities of systemic chemotherapy or EBR. Patients considered for enucleation are those with unilateral or bilateral R-E group V disease, patients with active tumour in a blind eye, and patients who develop glaucoma from tumour invasion of the anterior segment. Patients are also considered for enucleation if all other forms of treatment have failed, or if they have active tumour and cannot be followed. More than 99% of patients with unilateral retinoblastoma without extraocular disease are cured by enucleation, a rare situation in surgical oncology.[76]

The decision to enucleate an eye with retinoblastoma should be made in consultation with the family and several key issues should be discussed. First, it should be emphasised that the eye has not had useful vision for a prolonged period and the child will not experience any functional limitations from enucleation. Secondly, the operation is not typically painful and can usually be performed on an outpatient basis. Finally, the family should understand that enucleation is being considered because tumour control cannot be accomplished with any of the available modalities, and that the risk of keeping a blind eye cannot be justified when there is a risk for tumour spread and metastasis.

Critical elements of the surgery include avoiding any perforations of the globe and obtaining a long section of optic nerve of at least 15mm. Different techniques have been described for obtaining a long section of optic nerve during enucleation. Although most experienced ocular oncologists routinely obtain 15–20mm of optic nerve with enucleation, one of the newer techniques is to sever the optic nerve under direct visualisation through a superior orbital approach, utilising a small upper lid incision.[77] Shrinkage of the optic nerve segment typically occurs with processing and this should be kept in mind when evaluating the results of different surgical techniques.[78]

A variety of orbital implants are available to re-establish the orbital volume, including silicone, hydroxyapatite, Medpor® [1] and dermis fat graft. When considering implant choices, the silicone sphere is widely available, has the lowest incidence of complications and provides acceptable motility. Porous implants, such as hydroxyapatite and high-density polyethylene (Medpor®), have gained in popularity because of the low rates of implant migration and the potential for better motility if the implant is pegged to allow coupling with the prosthesis. No study has demonstrated a motility advantage for non-pegged porous implants (hydroxyapatite, Medpor®) when compared with non-porous implants (silicone). In addition, porous orbital implants have higher rates of implant exposure and infection compared with silicone spheres, as well as higher costs.[79] No matter which implant is chosen, the largest implant that can be fit into the orbit should be selected (16–18mm), both to encourage orbital growth and to obviate the need to place a secondary implant when the child grows.

Postoperative infections and other complications are extremely rare with modern surgical techniques. After 4 weeks, patients can be fitted with a prosthesis by the ocularist. Continued monitoring of the child will be necessary in the postoperative period to detect orbital recurrence in the socket, which is a poor prognostic sign for metastatic disease.[80,81]

6. Conclusion

Strategies for treating intraocular retinoblastoma continue to evolve as new therapies are developed and others fall out of favour. Currently, intraocular retinoblastoma is managed by a variety of treatment modalities, including chemoreduction, EBR, brachytherapy, transpupillary thermotherapy, cryotherapy and enucleation. The emergence of chemoreduction over the past decade has spared many young children with retinoblastoma the potential adverse effects of EBR. Despite this success, there continue to be significant challenges in improving visual outcomes and globe salvage rates in patients with retinoblastoma.

Acknowledgements

No sources of funding were used to assist in the preparation of this article. The authors have no conflicts of interest that are directly relevant to the content of this review.

1 The use of trade names is for product identification purposes only and does not imply endorsement.

References

1. Gatta G, Capocaccia R, Coleman MP, et al. Childhood cancer survival in Europe and the United States. Cancer 2002; 95 (8): 1767-72
2. Augsburger JJ, editor. Epidemiology of retinoblastoma. New York: Marcel Dekker, 2003: 49
3. Novakovic B. U.S. childhood cancer survival, 1973-1987. Med Pediatr Oncol 1994; 23 (6): 480-6
4. Sant M, Capocaccia R, Badioni V. Survival for retinoblastoma in Europe. Eur J Cancer 2001; 37 (6): 730-5
5. Mouratova T. Retinoblastoma in Uzbekistan. Bull Soc Belge Ophtalmol 2003; 289: 63-9
6. Freedman J, Goldberg L. Incidence of retinoblastoma in the Bantu of South Africa. Br J Ophthalmol 1976; 60 (9): 655-6
7. Reese AB, Ellsworth RM. The evaluation and current concept of retinoblastoma therapy. Trans Am Acad Ophthalmol Otolaryngol 1963; 67: 164-72
8. Shields CL, Mashayekhi A, Cater J, et al. Chemoreduction for retinoblastoma: analysis of tumor control and risks for recurrence in 457 tumors. Trans Am Ophthalmol Soc 2004; 102: 35-44
9. Murphree AL. Intraocular retinoblastoma: a case for a new group classification. Ophthalmol Clin North Am 2005; 18: 41-53
10. Shields CL, Mashayekhi A, Au AK, et al. The International Classification of Retinoblastoma predicts chemoreduction success. Ophthalmology 2006; 113 (12): 2276-80
11. Abramson DH, Schefler AC. Update on retinoblastoma. Retina 2004; 24 (6): 828-48
12. Demirci H, Shields CL, Meadows AT, et al. Long-term visual outcome following chemoreduction for retinoblastoma. Arch Ophthalmol 2005; 123 (11): 1525-30
13. Shields CL, De Potter P, Himelstein BP, et al. Chemoreduction in the initial management of intraocular retinoblastoma. Arch Ophthalmol 1996; 114 (11): 1330-8
14. Murphree AL, Villablanca JG, Deegan III WF, et al. Chemotherapy plus local treatment in the management of intraocular retinoblastoma. Arch Ophthalmol 1996; 114 (11): 1348-56
15. Shields JA, Shields CL, De Potter P, et al. Bilateral macular retinoblastoma managed by chemoreduction and chemothermotherapy. Arch Ophthalmol 1996; 114 (11): 1426-7
16. Shields CL, Shields JA, Needle M, et al. Combined chemoreduction and adjuvant treatment for intraocular retinoblastoma. Ophthalmology 1997; 104 (12): 2101-11
17. Greenwald MJ, Goldman S, Strauss LC. Combined chemoreduction and adjuvant treatment for intraocular retinoblastoma. Ophthalmology 1998; 105 (9): 1579-81
18. Kingston JE, Hungerford JL, Madreperla SA, et al. Results of combined chemotherapy and radiotherapy for advanced intraocular retinoblastoma. Arch Ophthalmol 1996; 114 (11): 1339-43
19. Gunduz K, Shields CL, Shields JA, et al. The outcome of chemoreduction treatment in patients with Reese-Ellsworth group V retinoblastoma. Arch Ophthalmol 1998; 116 (12): 1613-7
20. Bornfeld N, Schuler A, Bechrakis N, et al. Preliminary results of primary chemotherapy in retinoblastoma. Klin Padiatr 1997; 209 (4): 216-21
21. Brichard B, De Bruycker JJ, De Potter P, et al. Combined chemotherapy and local treatment in the management of intraocular retinoblastoma. Med Pediatr Oncol 2002; 38 (6): 411-5
22. Friedman DL, Himelstein B, Shields CL, et al. Chemoreduction and local ophthalmic therapy for intraocular retinoblastoma. J Clin Oncol 2000; 18 (1): 12-7
23. Antoneli CB, Ribeiro KC, Steinhorst F, et al. Treatment of retinoblastoma patients with chemoreduction plus local therapy: experience of the AC Camargo Hospital, Brazil. J Pediatr Hematol Oncol 2006; 28 (6): 342-5
24. Doz F, Khelfaoui F, Mosseri V, et al. The role of chemotherapy in orbital involvement of retinoblastoma: the experience of a single institution with 33 patients. Cancer 1994; 74 (2): 722-32
25. Goble RR, McKenzie J, Kingston JE, et al. Orbital recurrence of retinoblastoma successfully treated by combined therapy. Br J Ophthalmol 1990; 74 (2): 97-8
26. Chan HS, DeBoer G, Thiessen JJ, et al. Combining cyclosporin with chemotherapy controls intraocular retinoblastoma without requiring radiation. Clin Cancer Res 1996; 2 (9): 1499-508
27. Chan HS, Canton MD, Gallie BL. Chemosensitivity and multidrug resistance to antineoplastic drugs in retinoblastoma cell lines. Anticancer Res 1989; 9 (2): 469-74
28. Gallie BL, Budning A, DeBoer G, et al. Chemotherapy with focal therapy can cure intraocular retinoblastoma without radiotherapy. Arch Ophthalmol 1996; 114 (11): 1321-8
29. Beck MN, Balmer A, Dessing C, et al. First-line chemotherapy with local treatment can prevent external-beam irradiation and enucleation in low-stage intraocular retinoblastoma. J Clin Oncol 2000; 18 (15): 2881-7
30. Schiavetti A, Hadjistilianou T, Clerico A, et al. Conservative therapy in intraocular retinoblastoma: response/recurrence rate. J Pediatr Hematol Oncol 2005; 27 (1): 3-6
31. Wilson MW, Rodriguez-Galindo C, Haik BG, et al. Multiagent chemotherapy as neoadjuvant treatment for multifocal intraocular retinoblastoma. Ophthalmology 2001; 108 (11): 2106-14
32. Rodriguez-Galindo C, Wilson MW, Haik BG, et al. Treatment of intraocular retinoblastoma with vincristine and carboplatin. J Clin Oncol 2003; 21 (10): 2019-25
33. Lee TC, Hayashi NI, Dunkel IJ, et al. New retinoblastoma tumor formation in children initially treated with systemic carboplatin. Ophthalmology 2003; 110 (10): 1989-94; discussion 94-5
34. Abramson DH, Lawrence SD, Beaverson KL, et al. Systemic carboplatin for retinoblastoma: change in tumour size over time. Br J Ophthalmol 2005; 89 (12): 1616-9
35. Shields CL, Honavar SG, Shields JA, et al. Factors predictive of recurrence of retinal tumors, vitreous seeds, and subretinal seeds following chemoreduction for retinoblastoma. Arch Ophthalmol 2002; 120 (4): 460-4
36. Abramson DH, Beaverson KL, Chang ST, et al. Outcome following initial external beam radiotherapy in patients with Reese-Ellsworth group Vb retinoblastoma. Arch Ophthalmol 2004; 122 (9): 1316-23
37. Shields CL, Shields JA, DePotter P, et al. The effect of chemoreduction on retinoblastoma-induced retinal detachment. J Pediatr Ophthalmol Strabismus 1997; 34 (3): 165-9
38. Gombos DS, Kelly A, Coen PG, et al. Retinoblastoma treated with primary chemotherapy alone: the significance of tumour size, location, and age. Br J Ophthalmol 2002; 86 (1): 80-3
39. Abramson DH, Gamell LS, Ellsworth RM, et al. Unilateral retinoblastoma: new intraocular tumours after treatment. Br J Ophthalmol 1994; 78 (9): 698-701
40. Abramson DH, Greenfield DS, Ellsworth RM. Bilateral retinoblastoma: correlations between age at diagnosis and time course for new intraocular tumors. Ophthalmic Paediatr Genet 1992; 13 (1): 1-7
41. Smits C, Swen SJ, Theo Goverts S, et al. Assessment of hearing in very young children receiving carboplatin for retinoblastoma. Eur J Cancer 2006; 42 (4): 492-500
42. Anagnoste SR, Scott IU, Murray TG, et al. Rhegmatogenous retinal detachment in retinoblastoma patients undergoing chemoreduction and cryotherapy. Am J Ophthalmol 2000; 129 (6): 817-9
43. Gombos DS, Howes E, O'Brien JM. Cholesterosis following chemoreduction for advanced retinoblastoma. Arch Ophthalmol 2000; 118 (3): 440-1

44. Pui CH, Ribeiro RC, Hancock ML, et al. Acute myeloid leukemia in children treated with epipodophyllotoxins for acute lymphoblastic leukemia. N Engl J Med 1991; 325 (24): 1682-7
45. Gombos DS, Hungerford J, Abramson DH, et al. Secondary acute myelogenous leukemia in patients with retinoblastoma: is chemotherapy a factor? Ophthalmology 2007 Jul; 114 (7): 1378-83
46. Abramson DH, Ellsworth RM, Kitchin FD, et al. Second nonocular tumors in retinoblastoma survivors: are they radiation-induced? Ophthalmology 1984; 91 (11): 1351-5
47. Mendelsohn ME, Abramson DH, Madden T, et al. Intraocular concentrations of chemotherapeutic agents after systemic or local administration. Arch Ophthalmol 1998; 116 (9): 1209-12
48. Murray TG, Cicciarelli N, O'Brien JM, et al. Subconjunctival carboplatin therapy and cryotherapy in the treatment of transgenic murine retinoblastoma. Arch Ophthalmol 1997; 115 (10): 1286-90
49. Abramson DH, Frank CM, Dunkel IJ. A phase I/II study of subconjunctival carboplatin for intraocular retinoblastoma. Ophthalmology 1999; 106 (10): 1947-50
50. Schmack I, Hubbard GB, Kang SJ, et al. Ischemic necrosis and atrophy of the optic nerve after periocular carboplatin injection for intraocular retinoblastoma. Am J Ophthalmol 2006; 142 (2): 310-5
51. Caraceni A, Martini C, Spatti G, et al. Recovering optic neuritis during systemic cisplatin and carboplatin chemotherapy. Acta Neurol Scand 1997; 96 (4): 260-1
52. Wang MY, Arnold AC, Vinters HV, et al. Bilateral blindness and lumbosacral myelopathy associated with high-dose carmustine and cisplatin therapy. Am J Ophthalmol 2000; 130 (3): 367-8
53. Mulvihill A, Budning A, Jay V, et al. Ocular motility changes after subtenon carboplatin chemotherapy for retinoblastoma. Arch Ophthalmol 2003; 121 (8): 1120-4
54. Moll AC, Imhof SM, Schouten-Van Meeteren AY, et al. Second primary tumors in hereditary retinoblastoma: a register-based study, 1945-1997. Is there an age effect on radiation-related risk? Ophthalmology 2001; 108 (6): 1109-14
55. Eng C, Li FP, Abramson DH, et al. Mortality from second tumors among long-term survivors of retinoblastoma. J Natl Cancer Inst 1993; 85 (14): 1121-8
56. Wong FL, Boice Jr JD, Abramson DH, et al. Cancer incidence after retinoblastoma. Radiation dose and sarcoma risk. JAMA 1997; 278 (15): 1262-7
57. Aerts I, Pacquement H, Doz F, et al. Outcome of second malignancies after retinoblastoma: a retrospective analysis of 25 patients treated at the Institut Curie. Eur J Cancer 2004; 40 (10): 1522-9
58. Kleinerman RA, Tucker MA, Tarone RE, et al. Risk of new cancers after radiotherapy in long-term survivors of retinoblastoma: an extended follow-up. J Clin Oncol 2005; 23 (10): 2272-9
59. Abramson DH, Frank CM. Second nonocular tumors in survivors of bilateral retinoblastoma: a possible age effect on radiation-related risk. Ophthalmology 1998; 105 (4): 573-9
60. Fletcher O, Easton D, Anderson K, et al. Lifetime risks of common cancers among retinoblastoma survivors. J Natl Cancer Inst 2004; 96 (5): 357-63
61. McCormick B, Ellsworth R, Abramson D, et al. Radiation therapy for retinoblastoma: comparison of results with lens-sparing versus lateral beam techniques. Int J Radiat Oncol Biol Phys 1988; 15 (3): 567-74
62. McCormick B, Ellsworth R, Abramson D, et al. Results of external beam radiation for children with retinoblastoma: a comparison of two techniques. J Pediatr Ophthalmol Strabismus 1989; 26 (5): 239-43
63. Zelter M, Damel A, Gonzalez G, et al. A prospective study on the treatment of retinoblastoma in 72 patients. Cancer 1991; 68 (8): 1685-90
64. Shidnia H, Hornback NB, Helveston EM, et al. Treatment results of retinoblastoma at Indiana University Hospitals. Cancer 1977; 40 (6): 2917-22
65. Foote RL, Garretson BR, Schomberg PJ, et al. External beam irradiation for retinoblastoma: patterns of failure and dose-response analysis. Int J Radiat Oncol Biol Phys 1989; 16 (3): 823-30
66. Abramson DH, Jereb B, Ellsworth RM. External beam radiation for retinoblastoma. Bull N Y Acad Med 1981; 57 (9): 787-803
67. Abramson DH, Ellsworth RM, Tretter P, et al. Treatment of bilateral groups I through III retinoblastoma with bilateral radiation. Arch Ophthalmol 1981; 99 (10): 1761-2
68. Ellsworth RM. Retinoblastoma. Mod Probl Ophthalmol 1977; 18: 94-100
69. Hungerford JL, Toma NM, Plowman PN, et al. Whole-eye versus lens-sparing megavoltage therapy for retinoblastoma. Front Radiat Ther Oncol 1997; 30: 81-7
70. Fontanesi J, Pratt CB, Kun LE, et al. Treatment outcome and dose-response relationship in infants younger than 1 year treated for retinoblastoma with primary irradiation. Med Pediatr Oncol 1996; 26 (5): 297-304
71. Abramson DH, editor. Treatment of retinoblastoma. New York: Churchill Livingston, 1985: 3-93
72. Shields CL, Shields JA, Cater J, et al. Plaque radiotherapy for retinoblastoma: long-term tumor control and treatment complications in 208 tumors. Ophthalmology 2001; 108 (11): 2116-21
73. Schueler AO, Fluhs D, Anastassiou G, et al. Beta-ray brachytherapy with 106Ru plaques for retinoblastoma. Int J Radiat Oncol Biol Phys 2006; 65 (4): 1212-21
74. Buys RJ, Abramson DH, Ellsworth RM, et al. Radiation regression patterns after cobalt plaque insertion for retinoblastoma. Arch Ophthalmol 1983; 101 (8): 1206-8
75. Merchant TE, Gould CJ, Wilson MW, et al. Episcleral plaque brachytherapy for retinoblastoma. Pediatr Blood Cancer 2004; 43 (2): 134-9
76. Abramson DH, Ellsworth RM. The surgical management of retinoblastoma. Ophthalmic Surg 1980; 11 (9): 596-8
77. Tawfik HA. Superomedial lid crease approach to the medial intraconal space. Ophthal Plast Reconstr Surg 2002; 18 (2): 164-5
78. Abramson DH, Schefler AC, Almeida D, et al. Optic nerve tissue shrinkage during pathologic processing after enucleation for retinoblastoma. Arch Ophthalmol 2003; 121 (1): 73-5
79. Kim JW, Kikkawa DO, Aboy A, et al. Chronic exposure of hydroxyapatite orbital implants: cilia implantation and epithelial downgrowth. Ophthal Plast Reconstr Surg 2000; 16 (3): 216-22
80. Hungerford J, Kingston J, Plowman N. Orbital recurrence of retinoblastoma. Ophthalmic Paediatr Genet 1987; 8 (1): 63-8
81. Hungerford J. Factors influencing metastasis in retinoblastoma [comment]. Br J Ophthalmol 1993; 77 (9): 541

Correspondence: Dr *Jonathan W. Kim,* Department of Ophthalmic Oncology, Memorial Sloan-Kettering Cancer Center, 1275 York Ave, A-330, New York, NY 10021, USA. E-mail: Kimj12@mskcc.org