Treatment of Retinoblastoma: The Role of External Beam Radiotherapy

Joo-Young Kim and Younghee Park*

Proton Therapy Center, National Cancer Center, Goyang, Korea.

The risk of radiotherapy-related secondary cancers in children with constitutional retinoblastoma 1 (RB1) mutations has led to reduced use of external beam radiotherapy (EBRT) for RB. Presently, tumor reduction with chemotherapy with or without focal surgery (chemosurgery) is most commonly undertaken; EBRT is avoided as much as possible and is considered only as the last treatment option prior to enucleation. Nevertheless, approximately 80% of patients are diagnosed at a locally advanced stage, and only 20−25% of early stage RB patients can be cured with a chemosurgery strategy. As a whole, chemotherapy fails in more than two-thirds of eyes with advanced stage disease, requiring EBRT or enucleation. Radiotherapy is still considered necessary for patients with large tumor(s) who are not candidates for chemosurgery but who have visual potential. When radiation therapy is indicated, the lowest possible radiation dose combined with systemic or local chemotherapy and focal surgery may yield the best clinical outcomes in terms of local control and treatment-related toxicity. Proton beam therapy is one EBRT method that can be used for treatment of RB and reduces the radiation dose delivered to the adjacent orbital bone while maintaining an adequate dose to the tumor. To maximize the therapeutic success of treatment of advanced RB, the possibility of integrating radiotherapy at early stages of treatment may need to be discussed by a multidisciplinary team, rather than considering EBRT as only a last treatment option.

Key Words: Retinoblastoma, treatment, external beam radiotherapy

INTRODUCTION

Radiation oncologists face difficulties with using radiotherapy to treat children with retinoblastoma (RB). External beam radiotherapy (EBRT), which was long used with great success to completely control these tumors, was found to also save globes and vision. However, radiation was found to increase the lifelong risk of secondary cancers in children with constitutive RB1 mutations. Radiation was also found to affect the growth of the soft tissue and bone around the eye. At present, radiotherapy is usually performed when all other treatments have failed or when tumors are large and cannot be controlled by focal surgery.

The ultimate goals of RB treatment are to save life and vision, as well as the eye itself. Every effort must be made to preserve vision, regardless of whether RB is unilateral or bilateral. Focal surgical treatment, such as cryotherapy, thermotherapy, or laser therapy, can control the tumor, save vision, and preserve cosmesis when tumors are at an early stage. The selection of a treatment modality for RB patients depends on several factors, including age at diagnosis, the risk of secondary malignancy after treatment, the site of the tumor within the globe, the clinical stage of the tumor, and the visual potential of the involved eye after treatment.

Since only 20% of RB patients have a family history of this disease,[1] most patients with RB cannot be diagnosed via a screening examination. Therefore, most RBs are detected only when there are symptoms and signs, and the majority of patients are diagnosed at advanced intraocular stages. About 80% of patients seen at ophthalmology clinics present with

large tumors or with subretinal and/or vitreous seeding.[2] Radiotherapy is still an important treatment option in these patients when there is a possibility of saving the eyeball and vision. The risk of metastasis increases, while the likelihood of saving useful vision decreases, when the tumor invades the optic nerve, choroid, or orbit. In such cases, timely enucleation reduces the risk of metastatic spread, the side-effects of chemotherapy and radiotherapy, and the need for repeat examinations under anesthesia.[2,3] In general, secondary glaucoma, pars plana seeding, and anterior chamber invasion are also best managed by enucleation.[1]

There are great disparities in the survival rates of children with RB among different regions of the world. Patient mortality rates range from 3–5% in Europe, Canada, and the US and 40–70% in certain parts of Asia and Africa.[4] These differences are largely due to delayed diagnosis and the lower priority of

health care for rare diseases such as RB in less developed countries.[5] The Reese-Ellsworth (RE) classification (Table 1) and the International Classification of RB (ICRB) (Table 2) are the most commonly used methods of classifying RB limited to the orbit, and are frequently utilized in developed countries where extraocular disease is relatively rare. In contrast, American Joint Committee on Cancer TNM staging takes into account systemic disease and includes the statuses of both extraocular and intraocular involvement (Table 3). The RE classification system was created in 1963 to predict rates of tumor control and globe preservation following photon radiation therapy using lateral beams. Peripheral tumors were given a higher stage due to technical difficulties in preserving vision using lateral beam EBRT. The RE classification divides tumors into five groups and 10 subgroups, based on the size, location, and number of tumors (Table 1). Due to the more frequent use of

Table 1. Reese-Ellsworth Classification of Intraocular Retinoblastoma

Group likelihood of globe salvage	Subgroup	Description
I: very favorable	1A	Solitary tumor <4 DD at or behind the equator
	1B	Multiple tumors, none >4 DD, all at or behind the equator
II: favorable	IIA	Solitary tumor, 4–10 DD, at or behind the equator
	IIB	Multiple tumors, 4–10 DD, at or behind the equator
III: doubtful	IIIA	Any lesion anterior to the equator
	IIIB	Solitary tumor >10 DD behind the equator
IV: unfavorable	IVA	Multiple tumors >10 DD behind the equator
	IVB	Any lesion extending anteriorly to the ora serrata
V: very unfavorable	VA	Massive tumors involving more than half the retina
	VB	Vitreous seeding

DD, disc diameter.

Table 2. International Classification for Retinoblastoma

Group A: small intraretinal tumors away from the foveola and disc	All tumors ≤3 mm in greatest dimension, confined to the retina, and located >3 mm from the foveola and >1.5 mm from the optic disc
Group B: all remaining discrete tumors confined to the retina	All other tumors confined to the retina not in group A
	Tumor-associated subretinal fluid <3 mm from the tumor with no subretinal seeding
Group C: discrete local disease with minimal subretinal or vitreous seeding	Tumor(s) are discrete
	Subretinal fluid, present or past, without seeding, involving up to one-quarter of the retina
	Local fine vitreous seeding may be present close to discrete tumor
	Local subretinal seeding <3 mm (2 DD) from the tumor
Group D: diffuse disease with significant vitreous or subretinal seeding	Tumor(s) may be massive or diffuse
	Subretinal fluid present or past without seeding, involving up to total detachment
	Diffuse or massive vitreous disease may include "greasy" seeds or avascular tumor masses
	Diffuse subretinal seeding may include subretinal plaques or tumor nodules
Group E: presence of any one or more of these poor prognosis features	Tumor touching the lens
	Tumor anterior to anterior vitreous face involving the ciliary body or anterior segment
	Diffuse infiltrating retinoblastoma
	Neovascular glaucoma
	Opaque media from hemorrhage
	Tumor necrosis with aseptic orbital cellulitis
	Phthisis bulbi

DD, disc diameter.

chemotherapy in the 1990s, the ICRB system was designed to better predict responses to chemotherapy. Although the ICRB system is based on tumor size and location, it also classifies tumors by the presence or absence of subretinal and vitreous seeds, as well as by the extent of retinal involvement, indicated as the percentage of the total retinal area (Table 2). Tumors staged in the high ICRB group are regarded as involving a high risk of chemotherapy failure and thus potentially requiring EBRT or enucleation. Therefore, the ICRB system can predict globe, but not systemic, prognosis.

RB MUTATIONS, GENETIC TESTING, AND SCREENING

Ninety-five percent of RB gene mutations can be detected by

clinically available methods. Bilaterality is considered a surrogate marker of heritability, and age less than 12 months at the time of diagnosis is likely to be associated with heritability. About 15% of patients with unilateral RB, whose parents have no ophthalmologic abnormality, exhibit genetic mutations. Family history is absent in 80% of children with RB, with the mutation occurring *de novo*. Hence, genetic testing is recommended for all patients with RB, as it enables prenatal diagnosis of RB 1 mutations for the children of RB survivors. If an RB 1 gene mutation is detected, the fetus can be screened for genetic mutations during gestation. Fetuses with RB gene mutations are recommended to undergo post-natal ophthalmologic examinations every three months, enabling early detection. Second and subsequent children should also be tested if an older sibling was diagnosed with RB.[1,6] Early treatment of small tumors found by regular screening after birth enables both

Table 3. TNM Classification of Retinoblastoma

Category	Subcategory	Description
TX		Primary tumor cannot be assessed
T0		No evidence of primary tumor
T1		Tumor <2/3 of eye, with no vitreous or subretinal seeding
	T1a	Tumor <3 mm or <1.5 mm from the optic nerve or fovea
	T1b	Tumor >3 mm or >1.5 mm from the optic nerve or fovea Subretinal fluid <5 mm from the base of the tumor
	T1c	Tumor >3 mm or <1.5 mm from the optic nerve or fovea Subretinal fluid >5 mm from the base of the tumor
T2		Tumor <2/3 of eye with vitreous or subretinal seeding
	T2a	Focal vitreous and/or subretinal seeding
	T2b	Massive vitreous and/or subretinal seeding
T3		Severe intraocular disease
	T3a	Tumor >2/3 of the eye
	T3b	Presence of neovascular glaucoma, anterior segment extension, hyphema, vitreous hyphema, vitreous hemorrhage or orbital cellulitis
T4		Extra-ocular disease detected by imaging studies
	T4a	Invasion of the optic nerve
	T4b	Invasion into the orbit
	T4c	Intracranial extension not past the chiasm
	T4d	Intracranial extension past the chiasm
NX		Regional lymph nodes cannot be assessed
N0		No regional lymph node metastasis
N1		Regional lymph node involvement
N2		Distant lymph node involvement
MX		Presence of distant metastasis cannot be assessed
M0		No distant metastasis
M1		Systemic metastasis
	M1a	Single lesion at sites other than the CNS
	M1b	Multiple lesions at sites to other than the CNS
	M1c	Prechiasmatic CNS lesion(s)
	M1d	Postchiasmatic CNS lesion(s)
	M1e	Leptomeningeal or CSF involvement

CNS, central nervous system; CSF, cerebrospinal fluid.

complete tumor removal and preservation of vision. Genetic testing of pediatric patients with unilateral RB is also recommended, as awareness of mutation status can assist in predicting the risk of secondary malignancies. If a mutation test is negative, the patient's parents can be advised that radiotherapy is not a hazardous treatment option and that the risk of having another affected child is negligible.[1] Moreover, information about the absence of a gene mutation can obviate the need for the patients' siblings and relatives to undergo repeated invasive surveillance procedures under anesthesia.

RB MUTATIONS AND RADIOSENSITIVITY

Tumors with RB gene mutations appear to be more sensitive to radiation. Previously, control of RB tended to be more successful in patients with bilateral rather than unilateral RB; this was attributed to the fact that patients with bilateral disease are more likely to have RB gene mutations. Of 110 eyes with vitreous seeds treated with high dose chemotherapy and periocular carboplatin, 33 failed treatment and required EBRT, whereas 77 were salvaged. A multivariate analysis of factors prognostic for tumor regression showed that bilateral RB and the absence of subretinal fluid were predictive of salvage, suggesting that RB-mutated cells are more sensitive to chemotherapy and/or radiotherapy.[7] In support of this clinical observation, RB pathway inactivation in breast cancer was shown to be associated with an improved response to neoadjuvant chemotherapy.[8] A genomic study of drug sensitivity in cancer showed that cells with RB gene alterations were more sensitive to mitotic inhibitors such as paclitaxel.[9] *In vitro* assessments of RB cell lines showed that they were extremely sensitive to ionizing radiation.[10] Animal RB tumors also showed significantly greater radiosensitivity than control tumors at doses of 17.5 proton Gray (cobalt gray equivalent, CGE) or above.[11] Moreover, successful treatment outcomes were observed when low dose radiotherapy, ranging from 24–36 Gy, was administered as the primary treatment[12-14] or as salvage treatment after chemotherapy,[15,16] suggesting that there is a subset of RBs that are exceptionally sensitive to radiation.

TREATMENT OF LOCALLY ADVANCED INTRAOCULAR RETINOBLASTOMA: FOCAL THERAPIES AND PLAQUE THERAPY

Focal therapies, including laser therapy, thermotherapy, cryotherapy, and plaque radiotherapy, are used to treat patients initially diagnosed with group A RB, according to the ICRB. Plaque radiotherapy using radioisotopes, such as iodine 125 and ruthenium 106, can be considered for the treatment of groups B or C RBs when the tumor diameter is <16 mm, tumor thickness is 4–9 mm, and vitreous seeding is limited.[17]

Plaque radiotherapy is an excellent treatment for small isolated tumors located far from the optic nerve or macula, as well as for tumors recurring focally after chemotherapy or EBRT.

CHEMOREDUCTION STRATEGY

Chemotherapy used to be the main modality for tumors with extraocular extension invading the choroid, optic nerve, and orbit, as well as for tumors with systemic metastasis. Since the 1990s, however, chemotherapy has been widely used as a primary treatment for locally advanced RB to reduce tumor size prior to focal therapies. Since even long-term systemic chemotherapy is ineffective at controlling intraocular RB when used on its own, good initial responses to chemotherapy in most patients must be consolidated with laser photocoagulation, cryotherapy, and thermotherapy.[4] This strategy, called chemoreduction or chemosurgery, has become the standard approach for intraocular tumors of all stages. Chemosurgery on locally advanced RB is performed to avoid EBRT, control the tumor, and save vision in that eye. However, over 80% of tumors are either too large at presentation or have subretinal and/or vitreous seeding, preventing the application of this strategy.[2] Fewer than 25% of RBs are cured by chemotherapy with or without focal techniques,[2] with most cured patients classified as having ICRB groups A and B tumors. Moreover, this treatment fails in 40% of group C eyes and the majority of groups D and E eyes, necessitating enucleation or radiation. Overall, approximately 47% of patients with advanced disease still require EBRT.[18,19]

The effect of chemoreduction on 14 patients with RE group V RB found that chemotherapy coupled with EBRT of 40–44 Gy over 20–22 fractions salvaged 67% of eyes with vitreous seeding.[20,21] However, the functional outcomes of the salvaged eyes were not good.

Systemic chemotherapy, however, is often associated with toxicities. Permanent hearing loss has been reported in 5–33% of children, which is especially detrimental for those who have problems with vision. The RB database of the National Institutes of Health of the USA and Memorial Sloan-Kettering Cancer Center reported that 15 patients developed a secondary malignancy, particularly acute myelogenous leukemia, which was fatal in 10 of these 15 patients.[2,22] Chemotherapy administered via the ophthalmic artery [intra-arterial chemotherapy (IAC)] has become the most widely used type of local chemotherapy. IAC was developed to reduce the toxicity of systemic chemotherapy and to avoid EBRT. IAC has been shown to be effective in locally controlling 80–100% of patients with groups D and E RB when used in combination with systemic chemotherapy.[20] Systemic chemotherapy is required as the primary therapy in higher risk RB, which includes bilateral groups D and/or E. It could provide prevention of metastatic disease as well as control of intraocular tumors. IAC could be a new op-

tion for unilateral RB and possesses little risk of systemic complication and mostly associates with local ocular toxicities such as ptosis, choroidal vascular attenuation, and optic neuropathy.[20] Periocular injection of carboplatin via the subconjuctival or sub-Tenon's space is being attempted, although its long-term toxicity has not yet been determined. Also, intravitreal chemotherapy using melphalan or methotrexate has been used for recurrent RB with vitreous seeding; however, its long-term complications have not been assessed.

CONVENTIONAL EXTERNAL BEAM RADIOTHERAPY

The use of EBRT to treat RB has decreased dramatically over the past four decades, more than for other types of pediatric cancer. According to the National Cancer Institute's Surveillance, Epidemiology, and End Results database of the nine original tumor registries (SEER-9), the use of EBRT for RB has declined from 30% of treatments in the period from 1973 to 1976 to 2% in the period from 2005 to 2008.[23] An evaluation of 595 patients who were treated between 1973 and 2009 showed that enucleation rates remained stable from 1990 to 2000,[24] suggesting that the eye preservation rates in the chemoreduction era were not improved, compared with the EBRT era. According to that report, EBRT was delivered as part of initial treatment to 21.5% of all RB patients, including 51.6% of patients with bilateral disease and 10.7% of those with unilateral disease.[24] Enucleation of the more severely affected eye and irradiation of the other eye is still a common practice in treating patients with bilateral RB. EBRT rather than local therapy

is also used to treat patients with multifocal RB and those with tumors close to the macular or optic nerve with preserved vision. EBRT is also used to treat large tumors and those with vitreous seeding that do not respond to systemic chemotherapy. Tumors too large or difficult to treat with radiotherapy alone may be treated with combinations of radiotherapy and focal surgical procedures to optimize cure rates and reduce the risks of treatment-related complications that may result from moderate to high dose radiotherapy. EBRT was most frequently used in the 1980s, when about 30% of patients with RB were treated with this modality.[24]

Conventional EBRT in the megavoltage era showed local control rates of 41–56%, with eye survival rates of 60–100%.[13,25-28] Local control rates were reported to be 78.5% for RE groups I–II eyes and 20% for RE groups III–V eyes.[28] Failure may occur in 40–60% of patients, with salvage with other focal modalities, resulting in long-term eye survival rates of around 80%. Eye survival was also found to be correlated with clinical stage, ranging from 80–90% for RE groups I–III to 60% for RE groups IV–V.[26] The correlation between tumor stage and local control rate is consistent among studies; however, the relationship between tumor size and local control rate remains unclear. One study reported that failure rates at the primary site differed for tumors <15 mm and >15 mm in diameter (50% vs. 21%),[28] whereas other studies did not observe clear differences in the dose-response relationships for varying tumor sizes.[25,27] Complications of EBRT include dryness of the eye, cataract, and orbital hypoplasia. During the megavoltage EBRT era, cataract developed in about 20–30% of eyes[25,28,29] about 2–3 years after radiotherapy. The incidence of post-radiotherapy cataract is higher in patients treated with orthovoltage X-rays.[30] Glauco-

Table 4. Treatment Outcomes of Chemoreduction

Authors	Patients	Chemotherapy	Focal treatment	Outcome*
Shields, et al.[18]	158 eyes of 103 patients (364 tumors)	6 cycles (vincristine, etoposide, and carboplatin)	Cryotherapy, thermotherapy, or plaque radiotherapy	Treatment failure rate at 5 yrs RE groups I–IV: EBRT required in 10% Enucleation required in 15% RE group V: EBRT required in 47% Enucleation required in 53%
Shield, et al.[32]	249 eyes of 163 patients	6 cycles (vincristine, etoposide, and carboplatin)	Thermotherapy or cryotherapy	Treatment success rate ICRB group A: 100% ICRB group B: 93% ICRB group C: 90% ICRB group D: 47%
Künkele, et al.[33]	56 eyes of 40 patients	6 cycles (vincristine, etoposide, carboplatin, and cyclophosphamide)	Thermotherapy, laser coagulation, cryotherapy, or brachytherapy	Treatment failure rates ICRB group A: 25% ICRB group B: 15% ICRB group C: 33.3% ICRB group D: 83.3%

RE, Reese-Ellsworth; ICRB, International Classification of retinoblastoma.
*Failure defined as progression requiring enucleation or external beam radiotherapy (EBRT).

ma, neovascularization, and hemorrhage sometimes require enucleation after EBRT. Today, in the chemoreduction era, where radiotherapy is used as a last resort after all other treatments have failed, the complication rate after EBRT is likely to be much higher than that for previous eras,[2] since patients referred for radiotherapy have already undergone multi-agent systemic and regional chemotherapy and multiple sessions of focal surgery. Chemotherapy and EBRT may synergize in producing long-term complications, such as retinal and optic disc ischemia, similar to findings in patients with central nervous system tumors.[31]

Results of chemoreduction and radiotherapy as salvage treatment

At present, the clinical endpoints for RB treatment include the rates of avoidance of EBRT, as well as rates of local control and eye preservation. The results of chemoreduction are summarized in Table 4. Although chemoreduction achieved considerable tumor control in early stage RB, treatment outcomes for patients with RE group VB and ICRB group E RB remain poor. A study of 101 eyes in 101 patients with unilateral RB (21 group C, 40 group D, 40 group E by ICRB) reported that intensified chemotherapy with periocular carboplatin resulted in eye salvage in 20 (95%) group C, 34 (85%) group D, and 23 (57.5%) group E eyes. They also found that 96% of salvaged eyes achieved visual acuity of 20/200 or better, with 33 patients requiring EBRT.[7] An earlier study of EBRT alone found that the long-term globe salvage rate using doses of 42−45 Gy was 53%, with local control in 50% of patients with ICB group E and RE group VB RB.[25] Salvage EBRT after chemotherapy and focal surgical therapies showed relatively good salvage rates, especially for patients with bilateral RB. For example, among 90 patients with bilateral RB who received primary chemotherapy and focal treatments, 36 eyes of 22 patients failed and required salvage EBRT. Of the 36 eyes, 24 eyes (66.7%) were controlled by EBRT of 40−44 Gy over 20−22 fractions and required no further treatment. Overall, 30 out of 36 eyes (83.3%)[34] were preserved at 40 months. The likelihood of salvage was better in eyes with early stage RB, although salvage was observed in 28.6−62.5% of RE groups IV–V patients. Visual acuity was preserved in 19 eyes, although 31.6% read 6/60 or worse.[34] Another study reported the treatment outcomes in 30 eyes of 15 patients with bilateral RB who had group D (RE group V) in at least one eye. Of the 18 group D eyes in patients treated with primary chemotherapy alone, two (11%) showed complete tumor control, seven (39%) underwent enucleation, and nine underwent successful salvage treatment. EBRT was a successful salvage treatment in five of these 9 patients, resulting in an event-free survival rate of 34% two years after treatment.[35]

In summary, globe salvage was successful in 85% of RE groups I−IV and 36% of RE group V eyes. EBRT was required for 10−22% of patients with RE groups I−IV and 36−75% of those with RE group V RB.[18,36,37]

Radiotherapy dose

The traditional therapeutic dose of EBRT is 40−50 Gy; however, successful tumor control has been reported with doses less than 36 Gy.[12,13] Patients treated with EBRT after cytoreduction with chemotherapy and repeated focal surgical therapies may be at greater risk for eye complications, while cytoreduction modalities may place patients at greater risks of vascular complications and drug toxicity.[20] A lower dose of radiation may be considered when radiotherapy is used as a consolidation treatment followed by other treatment modalities. The rates of enucleation and therapeutic radiotherapy were reported to be significantly lower in patients treated with chemotherapy plus low-dose prophylactic planned EBRT than chemotherapy alone.[16] In that study, patients who previously underwent enucleation of the contralateral eye and those with group E RB with no clinically visible recurrent tumors were offered EBRT 2600 cGy over 13 days, starting two months after chemotherapy. In contrast, patients with a normal contralateral eye and those with groups A−D RB were treated with chemoreduction with or without therapeutic EBRT of 4000 cGy over 20 days. Among the patients with group E RB, those managed with chemotherapy and prophylactic low-dose EBRT had a significantly lower recurrence rate, a lower likelihood of enucleation, and less of a need for high-dose therapeutic radiotherapy than patients managed with chemotherapy alone. The globe salvage rates of eyes managed with chemotherapy alone, chemotherapy plus therapeutic EBRT, and chemotherapy plus lower-dose prophylactic RT were 25%, 50%, and 83%, respectively. In another study, 18 patients (24 eyes) with group D RB were treated with chemoreduction, local treatment including plaque radiotherapy, sub-Tenon carboplatin injection, and 2400−3600 cGy intensity modulated radiotherapy (IMRT). All patients showed persistent or recurrent disease after treatment. At a mean follow-up of 63 months, 19 eyes (79%) were salvaged, four were enucleated due to tumor recurrence at 9−31 months following radiotherapy, and one underwent enucleation for a painful eye and optic nerve atrophy 53 months after radiotherapy. The overall one- and five-year eye survival rates were 82% and 68%, respectively, with salvage radiotherapy with low dose IMRT, accounting for the preservation of an additional 35% of eyes. However, 12 eyes (50%) developed cataracts, which required extraction; four (17%) developed radiation retinopathy; and three (13%) developed retinal detachment requiring a scleral buckling procedure.[15] Of the 36 patients who received salvage radiotherapy with 4000−4400 cGy/20−22 fractions after chemoreduction and focal therapies, 12 experienced tumor recurrence and six required enucleation. Twenty-four patients (66.7%) showed local control, with 30 eyes (83.3%) preserved after 40 months. Complications included keratoconjunctivitis sicca and cataract in four patients with no retinopathy.[34] Taken together, these reports indicate that salvage EBRT with low dose radiotherapy may result in less orbital hypoplasia and better functionally pre-

served eyes. However, the local control rate was lower when compared with the same dose of EBRT as that of consolidation treatment.[16] The comparison of chemoreduction, chemoreduction combined with EBRT, and chemoreduction combined with prophylactic lower dose RT is summarized in Table 5.

RADIATION TECHNIQUES

Modern precision radiotherapy techniques, such as IMRT and stereotactic radiotherapy using a hypofractionated dose schedule, aim to achieve conformal dose distribution to the eye tumor. However, IMRT results in a high integral dose by delivering low doses to surrounding tissues, which may increase the risk of secondary tumors. The volume of the bony orbit receiving >5 Gy was found to be 69% for IMRT, 25% for three-dimensional (3D) conformal electrons, and 10% for proton radiotherapy.[38] A dosimetric study using 10 modern radiotherapy techniques showed that the volume of the ipsilateral bony orbit receiving at least 20 Gy (V20 GY) was much lower for arc-based IMRT than for 3D-conformal radiotherapy (56% vs. 90%).[39]

PROTON BEAM THERAPY

By reducing the radiation dose to the bone surrounding the eye, proton beam therapy (PBT) is expected to reduce the incidence of secondary sarcoma. A retrospective analysis of patients with RB treated with PBT at Massachusetts General Hospital or photon RT at Boston Children's Hospital showed that the former significantly reduced the rate of secondary malignancy [0/55 (0%) vs. 4/31 (13%)][40] (Fig. 1). However, since the median follow-up period was shorter for PBT than for photon RT (6.9 years vs. 13.1 years) and the number of RB patients treated with PBT was relatively small,[40] this finding requires confirmation in larger patient cohorts.

Table 5. Comparison of Chemoreduction, Chemoreduction Plus Radiotherapy (RT) and Chemoreduction Plus Lower Dose Prophylactic RT in Advanced Retinoblastoma

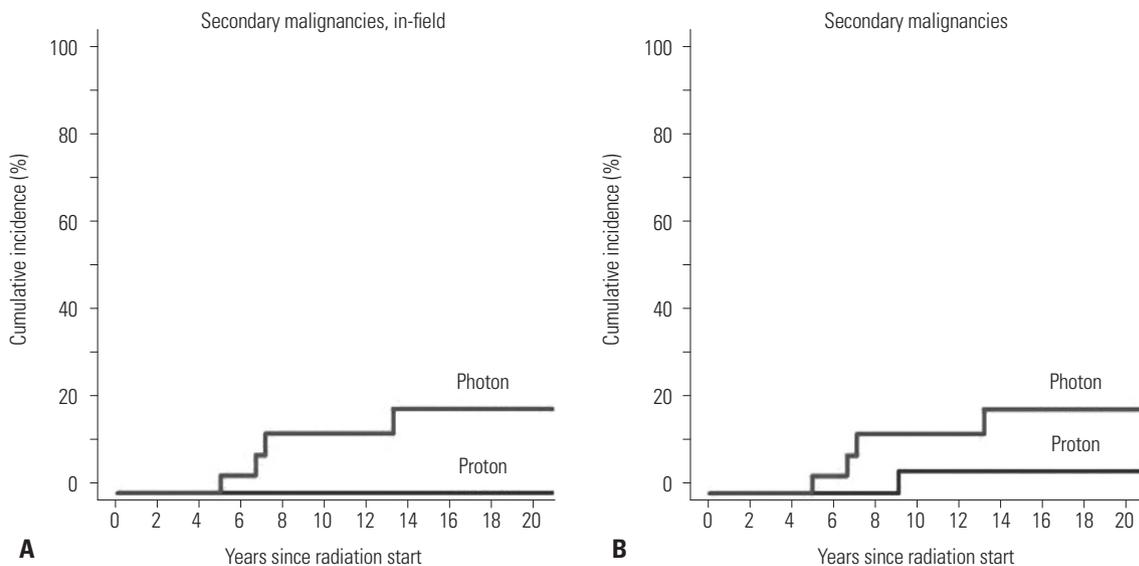| Treatment modality	Chemoreduction alone	Chemoreduction+RT	Chemoreduction+lower dose prophylactic RT
Pros	Avoid or delay enucleation or RT	Higher tumor control than chemoreduction alone or lower dose RT	Less recurrence than chemoreduction alone Lower risk of RT related toxicity is expected than therapeutic RT
Cons	30–50% eventually required RT for globe salvage[18,28]	Late complication of radiation such as orbital bone hypoplasia or secondary malignancy	Exact risk of lower dose of RT is not known Prospective study may needed
Globe salvage rate	Group D: 11–47%[15,35] Group E: 53% at 2 yrs, 48% at 5 yrs[16]	RE groups IV–V: 28.6–62.5% at median F/U of 40 months[34]	Group D: 82% at 1 yr, 68% at 5 yrs[15] Group E: 91% at 2 yrs, 80% at 5 yrs[16]

RE, Reese-Ellsworth.

Fig. 1. Cumulative rates of (A) "in-field" or "radiation-induced" secondary malignancies and (B) all secondary malignancies in patients treated with proton beam therapy and photon radiotherapy.

Treatment volume and radiation dose

Treating the entire retina due to concerns about new retinal lesions after EBRT was conventional practice.[41] However, the rates of new lesions in the uninvolved retina were similar in patients who received focal and whole retinal treatment. Therefore, avoiding irradiation of the uninvolved retina may
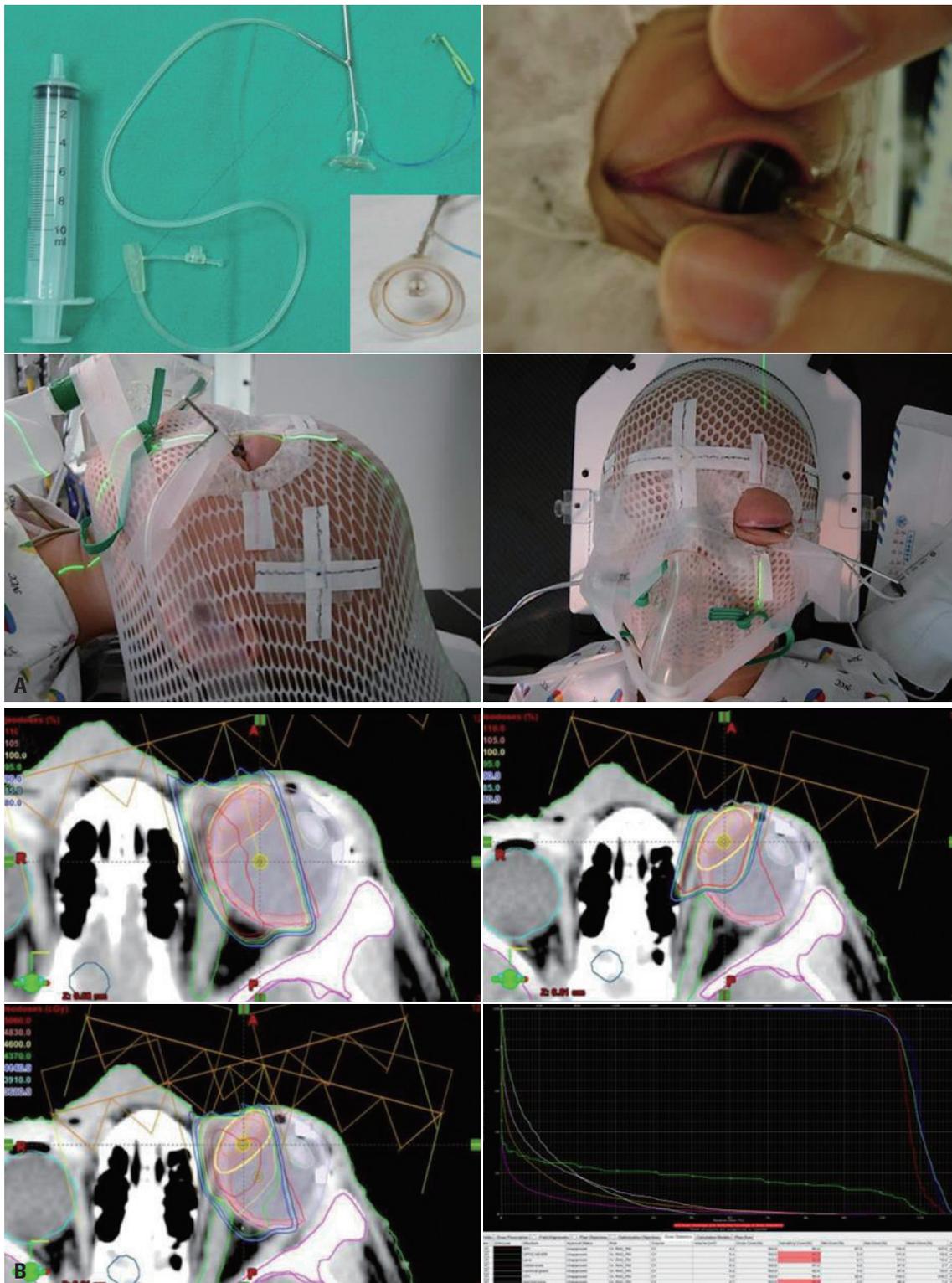

Fig. 2. Practices at National Cancer Center, Korea. (A) Under anesthesia, a small suction cup is placed on the cornea and the eyeball is rotated so that the proton beam can maximally avoid the orbital bone while covering the retinal target. (B) Dose distribution in proton beam therapy–initial field (left upper), boost field (right upper), summation of both fields (left lower) and corresponding dose volume histogram for the entire plan (right lower).

Fig. 3. Cosmetic outcomes in a patient treated with the radiotherapy plan described in Fig. 2. The patient's right eye was enucleated and the left eye was treated with PBT. Left to right: photos taken prior to PBT, 3 months after completion of PBT, and 6 years after PBT. PBT, proton beam therapy.

reduce the rates of eye complications.[28] Whole retina treatment may be required for group D eyes as well as salvage therapy in eyes with vitreous or subretinal seeding unresponsive to chemotherapy. However, the anterior chamber can be excluded from the radiation field when the tumors are located in the posterior part of the globe, because small lesions occurring after PBT can be controlled with cryotherapy or laser therapy.[40]

Proton therapy planning

Several proton beam delivery techniques are used to treat RB,[3,38] the most frequent being the use of a single lateral beam or anterior oblique beam.[38] The latter has the advantage of sparing the orbital bone while fully covering the retina. It may be difficult to save the posterior surface of the lens when the tumor is located anterior to the equator and when the retina at the level of the ora serrata requires irradiation. At the National Cancer Center, Korea, a silicon suction contact lens with a radio-opaque ring marker is placed on the cornea, and the eyeball is rotated to the nasal or temporal side, depending on the location of the tumor, so that the bone surrounding the orbit is not in the path of the proton beam (Fig. 2). Since the radiation dose to the surrounding bone and soft tissue is lower, PBT may reduce secondary cancer rates. This technique is generally associated with improved cosmetic results and good eye function (Fig. 3). Our institute uses a single scattering mode rather than a double scattering mode to treat the retina, as the former results in a reduced lateral penumbra and a smaller distal range than the latter. Although the Paul Sherrer Institute uses scanned beams to treat the entire orbit in patients with advanced RB,[3] it may be difficult to treat a small volume and at a shallow depth with pencil beam scanning (PBS) when only the retina requires irradiation. The status of eye fixation can be viewed in real-time on the computer monitor in the treatment control room so that any deviation from the initial set-up can be immediately corrected (Fig. 4). The video image is transferred from a small closed-circuit camera attached to the periphery of the aperture attached to the snout. Examples of tumor regression after PBT are shown in Figs. 5 and 6.

Suggested indications for PBT

Expert consensus recommends that radiotherapy is indicated when other means of saving the eye, such as chemotherapy

Fig. 4. Treatment monitoring system used at National Cancer Center, Korea. The position of the eye is monitored in the control room through a CC camera attached to the aperture during treatment. CC, closed-circuit.

and focal therapy, have failed.[6] When radiotherapy is used, modern high-precision radiotherapy is recommended to minimize the dose to the orbital bones,[6] and PBT could be an excellent treatment option. PBT can be used in combination with chemotherapy as a local treatment modality, consolidating the effect of chemoreduction, or as salvage treatment after other therapeutic modalities. Depending on the location of the tumor within the eye, proton beam dosimetry can minimize the dose to the orbital bone. Careful selection of patients may contribute to high cure rates with good vision and good cosmesis without the need for long-term chemotherapy and may reduce chemotherapy- and radiotherapy-associated complications. Patient selection should be based on careful examination to assess whether PBT can save the vision and eyes of patients with ICRB groups C−E RBs. Currently, there is no active multinational protocol for PBT of RB. The primary goals of PBT should be to save the patient's vision and eyeball, to prevent recurrence, and to increase overall survival rates. Secondary goals should include minimizing rates of secondary malignancy, avoiding eye complications, and improving cosmesis.

CLINICAL TRIALS IN RETINOBLASTOMA

Although the gold standard in pediatric cancer care is to treat
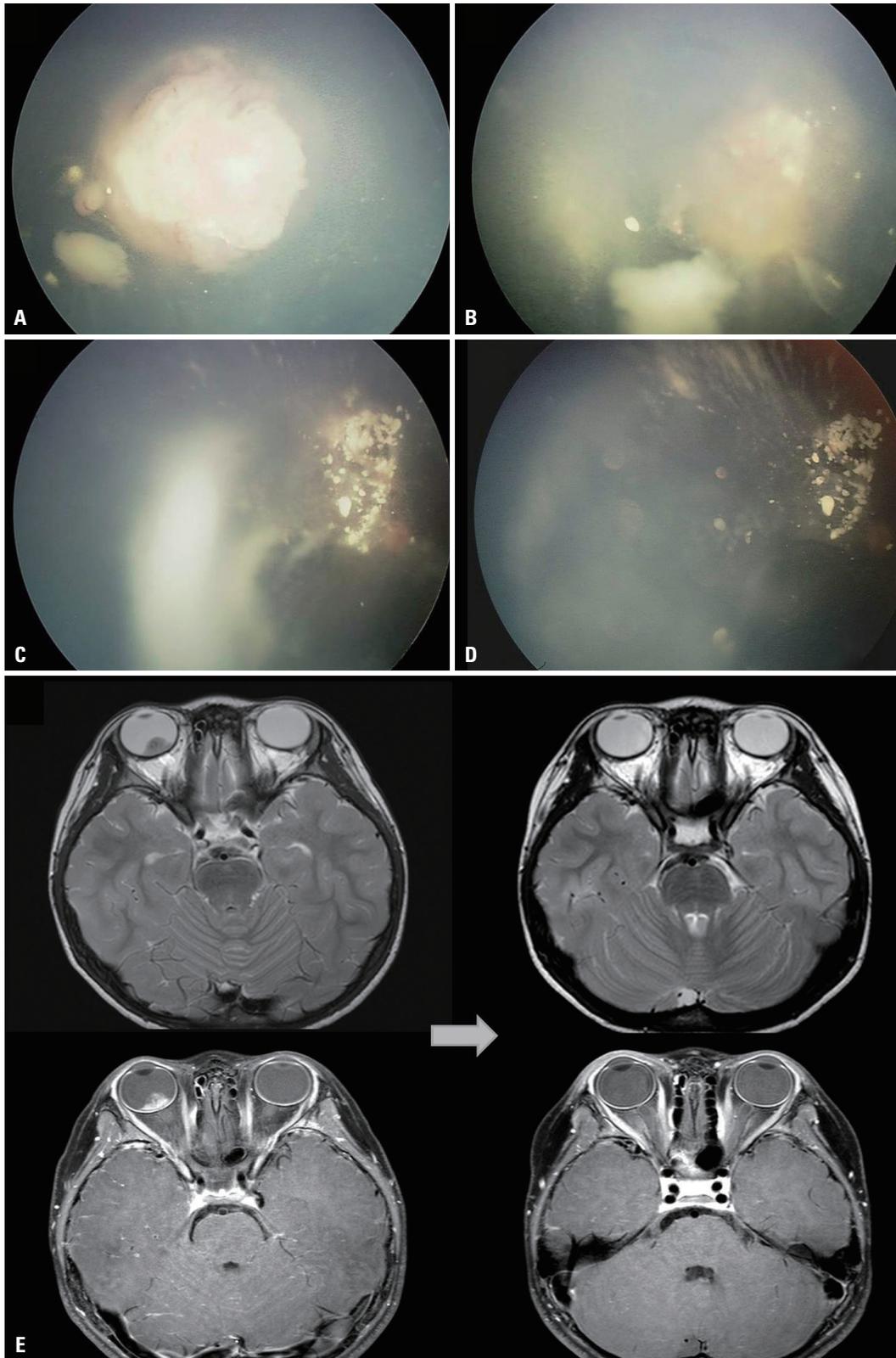
Fig. 5. Treatment outcome of unilateral RB after PBT. Fundoscopic examination of a 5-year-old boy diagnosed with RB in the right eye. (A) Pre-PBT: endophytic mass obscuring the posterior pole with two satellite masses. (B) During PBT: following the delivery of 2340 cGy, the main mass at the posterior pole has partially regressed, whereas the smaller seeding masses have slightly increased in size. (C) Two weeks after PBT: the main mass has regressed while the seeding masses have remained stable. (D) Three months after PBT: masses have overall remained stable. (E) MRI findings before (left) and after (right) PBT: a lobulated contoured intraocular mass of the right orbit, present before PBT, absent after PBT. RB, retinoblastoma; PBT, proton beam therapy.
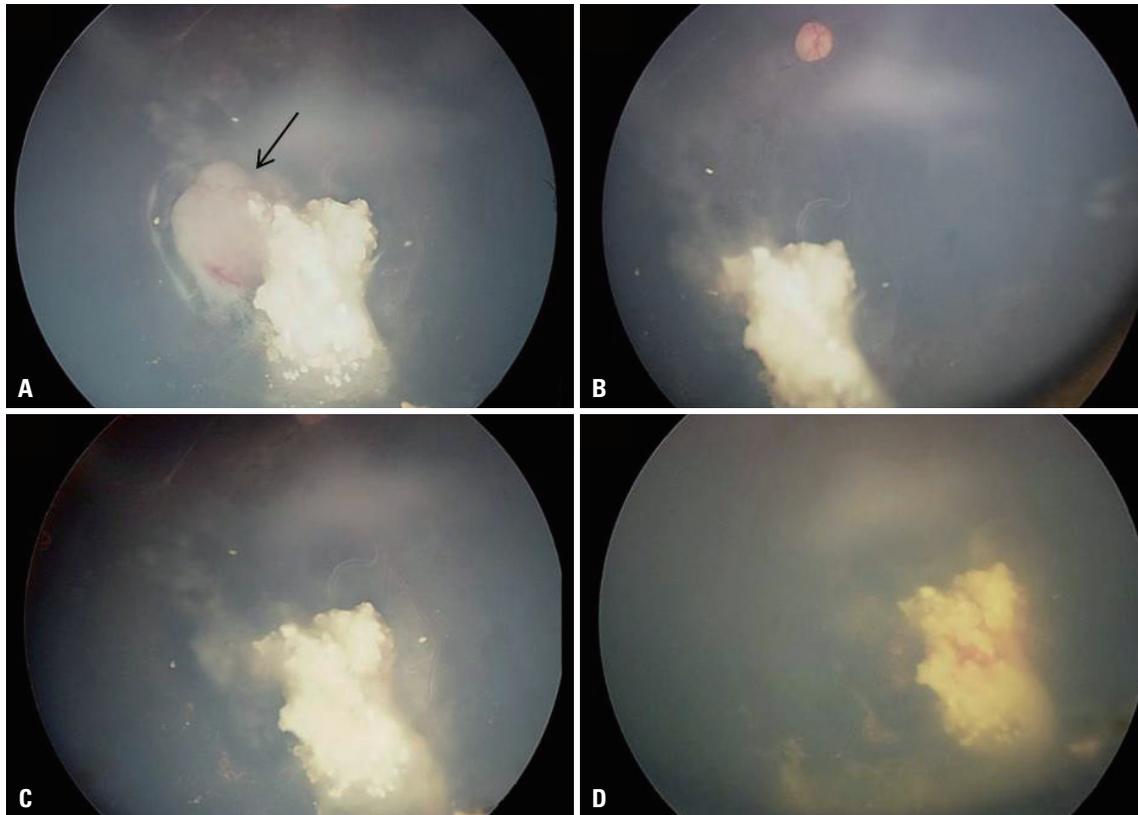
Fig. 6. Treatment outcome of PBT in a patient with bilateral RB. The patient was diagnosed with bilateral RB and received chemotherapy and transpupillary thermotherapy (TTT) for 1 year. After treatment, the masses regressed and have remained stable for 1.5 years. However, new masses developed in the right eye. PBT was delivered to the mass refractory to TTT. (A) Pre-PBT, showing the re-growth of a solid mass (arrow) at the temporal margin of a previous mass that had regressed. (B, C, and D) Views 1 (B), 2.5 (C), and 8 (D) months after PBT, showing that the main mass had regressed and remained stable for 8 months. Five months after PBT, a hemorrhage developed at the site of the previously regressed mass treated with TTT, and persisted until 8 months after PBT. There has been no evidence of disease to date, but glaucoma developed as a result of hemorrhage. RB, retinoblastoma; PBT, proton beam therapy.

the patient within the context of a clinical trial, few clinical trials have been performed for RB due to the rarity of the disease and the varying clinical factors among individuals with RB. Hence, there is no class A evidence from randomized clinical trials to guide treatment. Current guidelines are available from the Canadian RB Society and the International Society of Paediatric Oncology for Developing Countries (SIOP-PODC), depending on socioeconomic setting.[6,42] Short-course chemotherapy is currently being tested in an international, multicenter clinical trial to reduce the risk for short-term and long-term toxic effects. Current ongoing clinical trials are summarized in Table 6.

CONCLUSIONS

In an effort to avoid radiotherapy-related toxicity, including secondary malignancy, chemotherapy, which was formerly used only for RBs with extraocular extension or systemic metastasis, is now regarded as a primary treatment modality, even in patients with locally advanced intraocular RB, to reduce tu-

mor size prior to focal therapies. However, over 80% of tumors are too large or too advanced at presentation for this strategy. Thus, EBRT remains the primary treatment option to preserve the eye and vision in these patients. The use of EBRT in RB patients previously treated with multiple rounds of systemic and local chemotherapy, with or without focal surgery, may yield poorer treatment outcomes than its previous *de novo* use, as evaluated by cure and eye complication rates. With recent advances in RT techniques, such as IMRT and PBT, radiation could be delivered more safely with a reduced dose to adjacent normal organs, resulting in a dramatic reduction of late complications. Meticulous planning by a multidisciplinary team of EBRT, beginning at the initial stage of treatment, can optimize therapeutic outcomes in patients with RB.

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Table 6. Currently Active Protocols for Retinoblastoma (Modified from clinicaltrials.gov, as of Apr 2014)

Title	Study summary

Protocol for the study and treatment of participants with intraocular retinoblastoma (phase 2)	To evaluate the response rate of RB patients treated with different combinations of systemic chemotherapy, subconjunctival chemotherapy, focal treatment, and enucleation, depending on patient age, disease status, and risk group.
	*Chemotherapy agent
	 - Systemic:
	  Vincristine and carboplatin (VC)
	  Vincristine and topotecan (VT)
	  VC alternating with VT
	  Vincristine-carboplatin-etoposide (VCE)
	  Vincristine-carboplatin-doxorubicin (VCD)
	 - Subconjunctival: carboplatin
	*Focal treatment
	 Cryotherapy
	 Laser-photocoagulation
	 Thermotherapy
	 Radiation therapy

Intra-arterial chemotherapy for the treatment of intraocular retinoblastoma (phase 2)	To show that chemotherapy delivered directly through the ophthalmic artery to patients with RB is a safe and effective treatment alternative to conventional systemic chemotherapy, external beam radiation, and surgical removal of the eye. *Chemotherapy agent: mephalan
A study of the effectiveness of a local injection of chemotherapy for retinoblastoma	To evaluate the safety and efficacy of intra-arterial (ophthalmic artery) chemotherapy for retinoblastoma. *Chemotherapy agent: mephalan and carboplatin
Combination chemotherapy and cyclosporine followed by focal therapy for bilateral retinoblastoma (phase 2, multicenter)	To compare the efficacy of high dose combination chemotherapy with cyclosporine followed by focal therapy to historical world data of chemotherapy treatment without cyclosporine in newly diagnosed bilateral RB patients. *Chemotherapy agent: VCE+cyclosporine *Focal therapy: cryotherapy and/or laser therapy
Efficacy study of lucentis in the treatment of retinoblastoma (phase 2, randomized)	To evaluate the clinical efficacy of intravitreal injections of ranibizumab (Lucentis) together with chemotherapy compared with chemotherapy alone. *Chemotherapy agent: - Systemic: VCE - Intravitreal: Ranibizumab (Lucentis)
Pilot study of topotecan/vincristine with subconjunctival carboplatin for patients with bilateral retinoblastoma	To evaluate the safety and efficacy of sub-Tenon carboplatin in combination with systemic chemotherapy in refractory or recurrent intraocular RB. *Chemotherapy agent: - Systemic: VT - Sub-Tenon: Carboplatin
Adjuvant chemotherapy for high-risk retinoblastoma after enucleation (phase II randomized)	To determine whether 3 cycles of chemotherapy are as effective as 6 cycles of chemotherapy in the treatment of stage I enucleated retinoblastoma. *Chemotherapy agent: VCE
Combination chemotherapy, autologous stem cell transplant, and/or radiation therapy in treating young patients with extraocular retinoblastoma (phase 3)	To determine the side effects and efficacy of combination chemotherapy with autologous stem cell transplantation and/or radiation therapy in young patients with extraocular RB. *Chemotherapy: - Induction: vincristine, cisplatin, cyclophosphamide - Consolidation: carboplatin, thiotepa, etoposide *Radiation therapy: to the initial involved site beginning within 42 days after the start of cycle 4 of induction chemotherapy or 42 days after autologous stem cell infusion.

RB, retinoblastoma.

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