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Role of external beam radiotherapy in management of retinoblastoma-a review article

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P Vijay Anand Reddy
Department of Radiation Oncology, Apollo Cancer Institute, India

Correspondence: P Vijay Anand Reddy, Professor & Head Department of Radiation Oncology, Apollo Cancer Institute, Apollo Hospitals, Hyderabad, India, Tel +91-40-23607777, Email vijayapreddy@hotmaiol.com, vijayanandpreddy@gmial.com

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Introduction

Retinoblastoma is the most common intraocular malignancy in children, with a reported incidence ranging from 1 in 15,000 to 1 in 18,000 live births.[1] There is no racial or gender predisposition in the incidence of retinoblastoma. Retinoblastoma is bilateral in about 25 to 35% of cases. The average age at diagnosis is 18 months, unilateral cases being diagnosed at around 24 months and bilateral cases before 12 months.[2] Pawius described retinoblastoma as early as in 1597. In 1809, Wardrop referred to the tumor as fungus haematodes and suggested enucleation as the primary mode of management.[3] Initially thought to be derived from the glial cells, it was called a glioma of the retina by Virchow.[3] Flexner (1891) and Wintersteiner (1897) believed it to be a neuroepithelioma because of the presence of rosettes. Later, there was a consensus that the tumor originated from the retinoblasts and the American Ophthalmological Society officially accepted the term retinoblastoma in 1926.[4]

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. Advancements in ophthalmic diagnostics and introduction of ultrasonography, computed tomography, and magnetic resonance imaging contributed to improved diagnostic accuracy and early detection of extraocular retinoblastoma. 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. Early tumor recognition aided by indirect ophthalmoscopy and refined enucleation technique contributed to an improved survival from 5% in 1896 to 81% in 1967. Advances in external beam radiotherapy in the 1960s and 1970s and further progress in planning and delivery provided an excellent alternative to enucleation and resulted in substantial eye salvage.[2]

The recent advances such as identification of genetic mutations,[5,6] replacement of external beam radiotherapy by chemoreduction as the primary management modality, use of chemoreduction to minimize the size of regression scar with consequent optimization of visual potential,[7–11] identification of histopathologic high-risk factors following enucleation[12] and provision of adjuvant therapy to reduce the incidence of systemic metastasis,[13] protocol-based management of retinoblastoma with accidental perforation or intraocular surgery[14–16] and aggressive multimodal therapy in the management of orbital retinoblastoma[17,18] have contributed to improved outcome in terms of better survival, improved eye salvage and potential for optimal visual recovery.

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.

Table 1 Resse-ellsworth classification of intraocular retinoblastoma

Group likelihood of globe salvage	Subgroup	Description
Very favorable	I A	Solitary tumor <4 DD at or behind the equator
	I B	Multiple tumors, none >4 DD, all at or behind the equator
Favorable	II A	Solitary tumor <4-10 DD at or behind the equator
	II B	Multiple tumors, none >4-10 DD, all at or behind the equator
Doubtful	III A	Any lesion anterior to the equator
	III B	Solitary tumor >10 DD at or behind the equator
Unfavorable	IV A	Multiple tumors >10 DD behind the equator
	IV B	Any lesion extending anteriorly to the ora serrata
Very Unfavorable	V A	Massive tumors involving more than half the retina
	V B	Vitreous seeding

Table 2 International classification for retinoblastoma

Group A: Small intraretinal tumors away from the foveola and disc	All tumors <3mm 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	Subretinal fluid, present or past, without seeding, involving up to one-quarter of the retina Local fine vitreous seeding may 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 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

Table 3 TNM classification of retinoblastoma

Category	Subcategory	Description
TX		Primary tumor cannot be assessed
TO		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

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Table Continued...

Category	Subcategory	Description
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

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[19] 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.[19] 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 (Table 4).[19]

Table 4 Indications of External Beam radiotherapy

1	Residual disease after chemotherapy and local therapy
2	Diffuse vitreous seeds
3	Recurrence after chemotherapy4
4	Post enucleation a. Sclera involvement b. Extraocular extension c. optic nerve involvement

Conventional EBRT in the megavoltage era showed local control rates of 41-56%, with eye survival rates of 60-100%.[20–24] Local control rates were reported to be 78.5% for RE groups I-II eyes and 20% for RE groups III–V eyes.[24] 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.[22] 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 in diameter (50% vs. 21%), whereas other studies did not observe clear differences in the dose-response relationships for varying tumor sizes.[21,23] 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.,[21,24,25] about 2-3 years after radiotherapy. The incidence of post-radiotherapy cataract is higher in patients treated with orthovoltage X-rays.[26]

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.[20,27] 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 ERB 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

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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.[28] Taken together, these reports indicate that salvage EBRT with low dose radiotherapy may result in less orbital hypoplasia and better functionally preserved eyes. However, the local control rate was lower when compared with the same dose of EBRT as that of consolidation treatment. The comparison of chemoreduction, chemoreduction combined with EBRT, and chemoreduction combined with prophylactic lower dose RT is summarized in Table 4.

Treatment volume and radiation dose

Treating the entire retina due to concerns about new retinal lesions after EBRT was conventional practice.[29] 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 reduce the rates of eye complications.[24] 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.

Conclusion

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 tumor 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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Conflicts of interest

Author declares that there are no conflicts of interest.

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