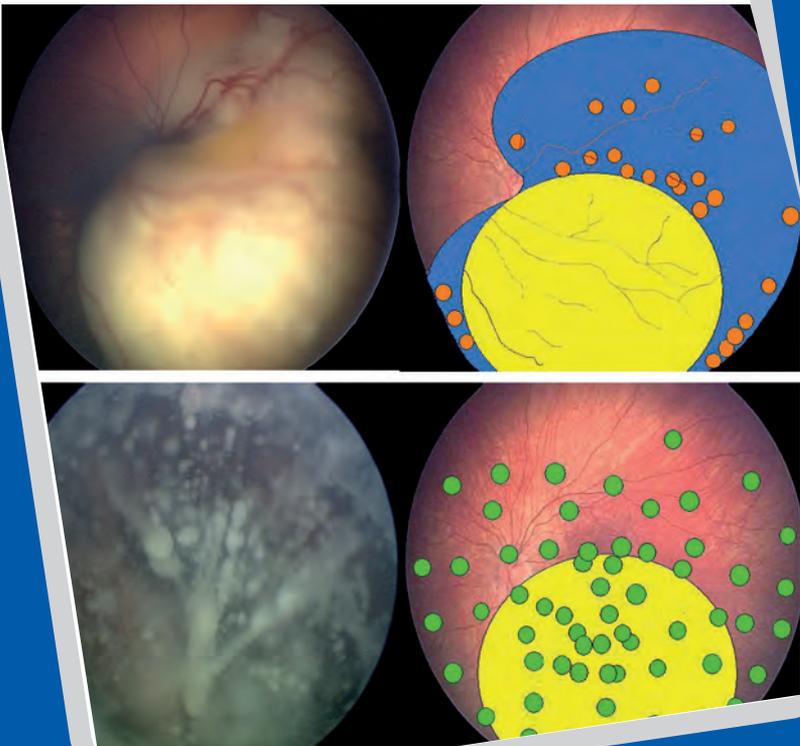




Retinoblastoma

They Live and See!



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Retinoblastoma

They Live and See!



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Foreward

Retinoblastoma is the most common intraocular malignancy of infancy and childhood. Till a century ago Retinoblastoma was uniformly a fatal disease. Thanks to advances in surgical techniques external beam radiation, focal treatment and chemotherapy, the survival rate and preservation of vision have greatly improved.

AIOS is bringing out this CME publication as a comprehensive treatise on Retinoblastoma. It gives an excellent overview on the history of the diseases, its genetic predisposition and epidemiology, clinical features and classification, and the current management strategy. Great emphasis has been placed on the enucleation technique for advanced unilateral retinoblastoma with excellent graphics and photo documentation. The section on radiotherapy encompasses all modern concepts of external beam radiation with or without chemo reduction and all of these has significantly contributed to preservation of vision and increased survival rate. In fact all specifics relating to retinoblastoma have been exhaustively covered in this publication. The authors have done an admirable job by bringing out this outstanding treatise on Retinoblastoma.



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Preface

Among intraocular malignancies of infancy and childhood, retinoblastoma is the most common. Until recently, retinoblastoma outcomes remained uniformly poor unless diagnosed at an early stage. But with the advent of chemo reduction and external beam radiotherapy, in addition to focal treatments like direct photocoagulation, cryotherapy and trans papillary thermo therapy, the survival rates have improved considerably even at advanced stages. However, I would like to emphasize that screening of children for white reflex should be taken up along the lines of a public campaign, and dilated fundus screening for children should become a standard clinical practice. The impact of a child going blind is enormous as it corresponds to the loss of number of man years of productivity.

The Academic and Research committee has brought out a CME on Retinoblastoma with an intention to increase awareness among Ophthalmologists. This CME gives an excellent overview of clinical features, diagnosis and classification of retinoblastoma. It can serve as a good guide to accurately stage the disease and prognosis. In this CME, the authors have demonstrated good outcomes in India, comparable to any series in the world. The outcomes can be even better if the disease is diagnosed at an early stage. The reviewer has done good job in pointing out the relevant lacunae, so that the CME series can aim to be as useful as possible to all Ophthalmologists.

In expect all members of All India Ophthalmological Society go through this CME series, imbibe the knowledge and help in saving lives as well as in preventing blindness in children due to retinoblastoma.



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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 It is second only to uveal melanoma in the frequency of occurrence of malignant intraocular tumors. There is no racial or gender predisposition in the incidence of retinoblastoma. Retinoblastoma is bilateral in about 25 to 35% of cases.² 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 1597.³ In 1809, Wardrop referred to the tumor as fungus haematodes and suggested enucleation as the primary mode of management.³ The discovery of ophthalmoscope in 1851 facilitated recognition of specific clinical features of retinoblastoma. Initially thought to be derived from the glial cells, it was called a glioma of the retina by Virchow (1864).³ Flexner (1891) and Wintersteiner (1897) believed it to be a neuroepithelioma because of the presence of rosettes.³ 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

Retinoblastoma was associated with near certain death just over a century ago. Early tumor recognition aided by indirect ophthalmoscopy and refined enucleation techniques contributed to an improved survival from 5% in 1896 to 81% in 1967.² 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 Focal therapeutic measures such as cryotherapy, photocoagulation and plaque brachytherapy allowed targeted treatment of smaller tumors entailing vision salvage.² Parallel 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.

Despite all the advances that took place between 1960 and 1990, the overall management of retinoblastoma stood at cross roads in the

1990s. The outstanding issues related to identification of a child at risk of developing retinoblastoma by genetic testing, optimization of vision salvage by minimization of the size of the tumor regression scar, reduction in the incidence of second malignant neoplasm following external beam radiotherapy by exploring for alternative therapeutic modalities, reduction in the incidence of systemic metastasis following enucleation, and improvement in the prognosis of orbital retinoblastoma and metastatic retinoblastoma.

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 enucleation¹² and provision of adjuvant therapy to reduce the incidence of systemic metastasis,¹³ protocol-based management of retinoblastoma with accidental perforation or intraocular surgery¹⁴⁻¹⁶ 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.

Genetics of Retinoblastoma

Out of the newly diagnosed cases of retinoblastoma only 6% are familial while 94% are sporadic.^{2,19} Bilateral retinoblastomas involve germinal mutations in all cases. Approximately 15% of unilateral sporadic retinoblastoma is caused by germinal mutations affecting only one eye while the 85% are sporadic.²

In 1971, Knudson proposed the two hit hypothesis.²⁰ He stated that for retinoblastoma to develop, two chromosomal mutations are needed. In hereditary retinoblastoma, the initial hit is a germinal mutation, which is inherited and is found in all the cells. The second hit develops in the somatic retinal cells leading to the development of retinoblastoma. Therefore, hereditary cases are predisposed to the development of nonocular tumors such as osteosarcoma. In unilateral sporadic retinoblastoma, both the hits occur during the development of the retina and are somatic mutations. Therefore, there is no risk of second nonocular tumors.

Genetic counseling is an important aspect in the management of retinoblastoma. In patients with a positive family history, 40% of the siblings would be at risk of developing retinoblastoma and 40% of the offspring of the affected patient may develop retinoblastoma. In patients with no family history of retinoblastoma, if the affected child has unilateral retinoblastoma, 1% of the siblings are at risk and 8% of the offspring may develop retinoblastoma. In cases of bilateral retinoblastoma with no positive family history, 6% of the siblings and 40% of the offspring have a chance of developing retinoblastoma.²

Apart from empiric genetic counseling as described above, the current trend is to identify the mutation and compute specific antenatal risk. We screened twenty-one probands, twelve with bilateral retinoblastoma and 9 with unilateral retinoblastoma, for mutations in the RB1 gene using genomic DNA from peripheral blood leukocytes as well as tumors. Amplification of individual exons and flanking regions of the RB1 gene were carried out, followed by direct sequencing of the amplified products. Sequences of affected individuals were compared with those of controls. Mutations were identified in seven patients, five with bilateral and two with unilateral retinoblastoma. Analysis of the

peripheral blood of seven patients with unilateral disease also showed no mutations.⁵

Subsequently, we carried out mutational screening of the exons and promoter of the RB1 gene in Indian patients with retinoblastoma in order to determine the range of mutations giving rise to the disease. Eight novel mutations were identified, including 4 single base changes, 2 small deletions and 1 duplication. These were g.64365T>G (Tyr325Ter), g.78131G>A (Trp515Ter), g.150061G>T (Glu587Ter), g.170383C>G (S834X), g.41924A>C (IVS3-2A>C), g.150064ins4, g.160792del22, and g.76940del14 (IVS15 del +20-33). All mutations produced nonsense codons or frameshifts. Detectable mutations in exons were found in 46% of patients tested. Knowledge of the full range of mutations can aid in the design of screening tests for individuals at risk.⁶

Histopathology of Retinoblastoma

On low magnification, basophilic areas of tumor are seen along with eosinophilic areas of necrosis and more basophilic areas of calcification within the tumor. Poorly differentiated tumors consist of small to medium sized round cells with large hyperchromatic nuclei and scanty cytoplasm with mitotic figures. Well-differentiated tumors show the presence of rosettes and fleurettes. These can be of various types. Flexner-Wintersteiner rosettes consist of columnar cells arranged around a central lumen. This is highly characteristic of retinoblastoma and is also seen in medulloepithelioma. Homer Wright rosettes consist of cells arranged around a central neuromuscular tangle. This is also found in neuroblastomas, medulloblastomas and medulloepitheliomas. Pseudorosette refers to the arrangement of tumor cells around blood vessels. They are not signs of good differentiation. Fleurettes are eosinophilic structures composed of tumor cells with pear shaped eosinophilic processes projecting through a fenestrated membrane. Rosettes and fleurettes indicate that the tumor cells show photoreceptor differentiation. In addition basophilic deposits, which are, precipitated DNA (released after tumor necrosis) can be found in the walls of the lumen of blood vessels.²

Clinical Manifestations of Retinoblastoma

Leucocoria is the most common presenting feature of retinoblastoma, followed by strabismus, painful blind eye and loss of vision. Table 1 lists the common presenting features of retinoblastoma.²¹

Table 1. Common presenting features of retinoblastoma

1. Leucocoria	56%
2. Strabismus	20%
3. Red painful eye	7%
4. Poor vision	5%
5. Asymptomatic	3%
6. Orbital cellulitis	3%
7. Unilateral mydriasis	2%
8. Heterochromia iridis	1%
9. Hyphema	1%

The clinical presentation of retinoblastoma depends on the stage of the disease.¹⁰ Early lesions are likely to be missed, unless an indirect ophthalmoscopy is performed. The tumor appears as a translucent or white fluffy retinal mass (Figure 1). The child may present with strabismus if the tumor involves the macula, or with reduced visual acuity.

Moderately advanced lesions usually present with leucocoria due to the reflection of light by the white mass in the fundus (Figure 2). As the tumor grows further, three patterns are usually seen:¹⁰

- Endophytic, in which the tumor grows into the vitreous cavity (Figure 3). A yellow white mass progressively fills the entire vitreous cavity and vitreous seeds occur. The retinal vessels are not seen on the tumor surface.
- Exophytic, in which the tumor grows towards the subretinal space (Figure 4). Retinal detachment usually occurs and retinal vessels are seen over the tumor.

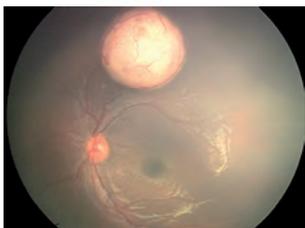


Figure 1



Figure 2

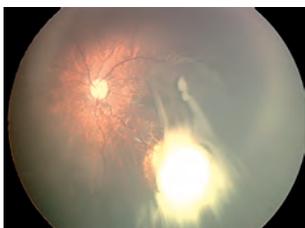


Figure 3

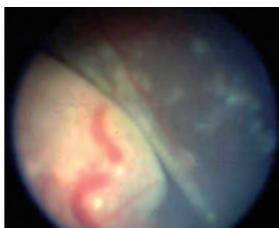


Figure 4

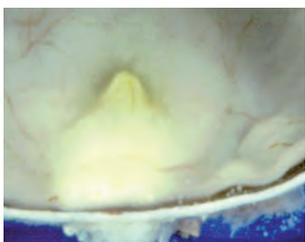


Figure 5



Figure 6



Figure 7



Figure 8

Figure 1. Early manifestation of retinoblastoma with a localized tumor at the posterior pole

Figure 2. Leucocoria is the most common clinical presentation of retinoblastoma.

Figure 3. Endophytic tumor with vitreous seeds.

Figure 4. Exophytic retinal tumor with exudative retinal detachment.

Figure 5. Diffuse infiltrative retinoblastoma with placoid retinal thickening seen on gross examination of the enucleated eye in a 7-year-old child.

Figure 6. Retinoblastoma with orbital extension in a 3-year-old child.

Figure 7. A 5-year-old child with retinoblastoma with anterior segment seeding manifesting with tumor hypopyon.

Figure 8. A 4-year-old with spontaneous hyphema in the left eye. Ultrasonography confirmed the diagnosis of retinoblastoma.

- Diffuse infiltrating tumor, in which the tumor diffusely involves the retina causing just a placoid thickening of the retina and not a mass. This is generally seen in older children and usually there is a delay in the diagnosis (Figure 5).

Advanced tumors manifest with proptosis secondary to optic nerve extension or orbital extension (Figure 6) and systemic metastasis.¹⁰ Retinoblastoma can spread through the optic nerve with relative ease especially once the lamina cribrosa is breached. Orbital extension may present with proptosis and is most likely to occur at the site of the scleral emissary veins. Systemic metastasis occurs to the brain, skull, distant bones and the lymph nodes.

Some of the atypical manifestations of retinoblastoma include pseudohypopyon (Figure 7), spontaneous hyphema (Figure 8), vitreous hemorrhage (Figure 9), phthisis bulbi (Figure 10) and preseptal or orbital cellulites (Figure 11).¹⁰

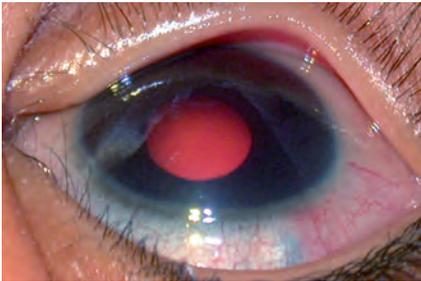


Figure 9



Figure 10



Figure 11

Figure 9. Spontaneous vitreous hemorrhage as the presenting feature of retinoblastoma in a 4-year-old child

Figure 10. An 18-month-old child with bilateral retinoblastoma. The right eye has secondary glaucoma and enlarged cornea while the left eye is phthisical.

Figure 11. A 3-year-old child with retinoblastoma presenting with orbital cellulites

Diagnosis of Retinoblastoma

A thorough clinical evaluation with careful attention to details, aided by ultrasonography B-scan helps in the diagnosis.¹⁰ Computed tomography and magnetic resonance imaging are generally reserved for cases with atypical manifestations and diagnostic dilemma and where extraocular or intracranial tumor extension is suspected.¹⁰

A child with suspected retinoblastoma necessarily needs complete ophthalmic evaluation including a dilated fundus examination under anaesthesia.¹⁰ The intraocular pressure is measured and the anterior segment is examined for neovascularization, pseudohypopyon, hyphema, and signs of inflammation.¹⁰ Bilateral fundus examination with 360 degree scleral depression is mandatory. Direct visualization of the tumor by an indirect ophthalmoscope is diagnostic of retinoblastoma in over 90% of cases.²¹ RetCam is a wide-angle fundus camera, useful in accurately documenting retinoblastoma and monitoring response to therapy (Figure 12).

Ultrasonography B-scan shows a rounded or irregular intraocular mass with high internal reflectivity representing typical intralesional calcification (Figure 13).¹⁰ Computed tomography delineates extraocular extension and can detect an associated pinealoblastoma (Figure 14).¹⁰ Magnetic resonance imaging is specifically indicated if optic nerve invasion or intracranial extension is suspected.¹⁰ On fluorescein angiography, smaller retinoblastoma shows minimally dilated feeding vessels in the arterial phase, blotchy hyperfluorescence in the venous phase and late staining (Figure 15).¹⁰

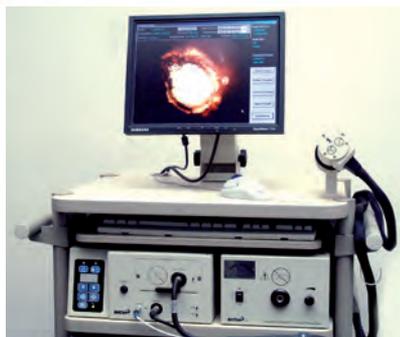


Figure 12



Figure 13



Figure 14



Figure 15

Figure 12. RetCam, a wide-angle digital fundus camera and image archival system helps in documentation and assessment of tumor regression on follow-up

Figure 13. Ultrasonography B-scan showing multifocal retinal tumors

Figure 14. Computed tomography scan shows pinealoblastoma

Figure 15. Fundus fluorescein angiography in retinoblastoma in the early phase shows blotchy hyperfluorescence

Classification of Retinoblastoma

An ideal classification system for retinoblastoma should include two components: grouping and staging. Grouping is a clinical system of prognosticating organ salvage while staging prognosticates survival.

The Reese Ellsworth classification was introduced to prognosticate patients treated with methods other than enucleation.²² This classification was devised prior to the widespread use of indirect ophthalmoscopy and focal measures of management of retinoblastoma and mainly pertained to eye salvage with external beam radiotherapy. Although the Essen classification addressed some of the shortcomings of Reese Ellsworth classification, it is considered too complex. Further, none of the older systems of classification had been designed to prognosticate chemoreduction, the current favored method of retinoblastoma management. The new International Classification of Intraocular Retinoblastoma is a logical flow of sequential tumor grading that linearly correlates with the outcome of newer therapeutic modalities. There are two versions of this classification (Table 2, 3).^{23,24} The recent TNM classification by the American Joint Committee on Cancer and the Union Internationale Contre le Cancer (AJCC/UICC) is comprehensive and includes both clinical and histopathological aspects (Table 4).

The new International Staging system is the first such for retinoblastoma and incorporates five distinct stages (Table 5).²⁵ Staging is based on collective information gathered by the clinical evaluation, imaging, systemic survey and histopathology.

Table 2. International Classification of Intraocular Retinoblastoma (Murphree)

Group A: Small intraretinal tumours away from foveola and disc.

- All tumours are 3 mm or smaller in greatest dimension, confined to the retina
- All tumours are located further than 3 mm from the foveola and 1.5 mm from the optic disc

Group B: All remaining discrete tumours confined to the retina.

- All other tumours confined to the retina not in Group A.
- Tumour-associated subretinal fluid less than 3 mm from the tumour with no subretinal seeding.

Group C: Discrete local disease with minimal subretinal or vitreous seeding.

- Tumour(s) are discrete.
- Subretinal fluid, present or past, without seeding involving up to one-fourth of the retina.
- Local fine vitreous seeding may be present close to discrete tumour.
- Local subretinal seeding less than 3 mm (2 DD) from the tumour.

Group D: Diffuse disease with significant vitreous or subretinal seeding.

- Tumour(s) may be massive or diffuse.
- Subretinal fluid present or past without seeding, involving up to total retinal detachment.
- Diffuse or massive vitreous disease may include "greasy" seeds or avascular tumour masses.
- Diffuse subretinal seeding may include subretinal plaques or tumour nodules.

Group E: Presence of any one or more of these poor prognosis features.

- Tumour touching the lens.
- Tumour anterior to anterior vitreous face involving ciliary body or anterior segment.
- Diffuse infiltrating retinoblastoma.
- Neovascular glaucoma.
- Opaque media from hemorrhage.
- Tumour necrosis with aseptic orbital cellulites.
- Phthisis bulbi.

Table 3. International Classification of Retinoblastoma (Shields)

- Group A Small tumor
- Retinoblastoma ≤ 3 mm in size in basal dimension/thickness
- Group B Larger tumor
- Retinoblastoma > 3 mm in basal dimension/thickness
 - Macular location (≤ 3 mm to foveola)
 - Juxtapapillary location (≤ 1.5 mm to disc)
 - Clear subretinal fluid ≤ 3 mm from margin
- Group C Focal seeds
- C1 Subretinal seeds ≤ 3 mm from retinoblastoma
 - C2 Vitreous seeds ≤ 3 mm from retinoblastoma
 - C3 Both subretinal and vitreous seeds ≤ 3 mm from retinoblastoma
- Group D Diffuse seeds
- D1 Subretinal seeds > 3 mm from retinoblastoma
 - D2 Vitreous seeds > 3 mm from retinoblastoma
 - D3 Both subretinal and vitreous seeds > 3 mm from retinoblastoma
- Group E Extensive retinoblastoma
- Occupying $> 50\%$ globe or
 - Neovascular glaucoma
 - Opaque media from hemorrhage in anterior chamber, vitreous, or subretinal space
 - Invasion of postlaminar optic nerve, choroid (> 2 mm), sclera, orbit, anterior chamber

Table 4. TNM Classification for Retinoblastoma

The TNM (Tumour, Node, Metastasis) classification is developed, monitored and enforced by the American Joint Commission on Cancer and the Union Internationale Control Cancer (AJCC/UICC).

When both eyes are affected, each eye is staged independently. When only one stage is stated in patient reports for a bilateral child, this refers to the stage of the worst eye, as an indicator of risk to the child's life.

Clinical Classification (cTNM)

Primary Tumour (T)

cTX: Primary Tumour cannot be assessed.

cT0: No evidence of primary tumour.

cT1: Tumours no more than 2/3 the volume of the eye, with no vitreous or subretinal seeding:

cT1a: No tumour in either eye is greater than 3mm in largest dimension, or located closer than 1.5mm to the optic nerve or fovea.

cT1b: At least one tumour is greater than 3mm in largest dimension, or located closer than 1.5mm to the optic nerve or fovea. No retinal detachment or subretinal fluid beyond 5mm from the base of the tumour.

cT1c: At least one tumour is greater than 3mm in largest dimension, or located closer than 1.5mm to the optic nerve or fovea, with retinal detachment or subretinal fluid beyond 5mm from the base of the tumour.

cT2: Tumours no more than 2/3 the volume of the eye with vitreous or subretinal seeding. Can have retinal detachment:

cT2a: Focal vitreous and/or subretinal seeding of fine aggregates of tumour is present, but no large clumps or "snowballs" of tumour cells.

cT2b: Massive vitreous and/or subretinal seeding is present, defined as diffuse clumps or "snowballs" of tumour cells.

cT3: Severe Intraocular Disease:

cT3a: Tumour fills more than 2/3 of the eye.

cT3b: One or more complications present which may include tumour-associated neovascular or angle closure glaucoma, tumour extension into the anterior segment, hyphema, vitreous hemorrhage or orbital cellulitis.

cT4: Extra-ocular disease detected by imaging studies:

cT4a: Invasion of optic nerve.

cT4b: Invasion into the orbit.

cT4c: Intracranial extension not past the chiasm.

cT4d: Intracranial extension past chiasm.

Note: The following suffixes may be added to the appropriate T categories:

"m" indicates multiple tumours (eg, T2 [m2]).

"f" indicates cases with a known family history.

"d" indicates diffuse retinal involvement without the formation of discrete masses.

Regional Lymph Nodes (N)

cNX: Regional lymph nodes cannot be assessed.

cN0: No regional lymph node metastasis.

cN1: Regional lymph node metastasis involvement (preauricular, cervical, submandibular).

cN2: Distant lymph node involvement.

Distant Metastasis (M)

cMX: Presence of distant metastasis cannot be assessed

cM0: No distant metastasis

cM1: Systemic metastasis:

cM1a: Single lesion to sites other than Central Nervous System.

cM1b: Multiple lesions to sites other than Central Nervous System.

cM1c: Prechiasmatic Central Nervous System lesion(s).

cM1d: Postchiasmatic Central Nervous System lesion(s).

cM1e: Leptomeningeal or Cerebro Spinal Fluid involvement.

Pathologic Classification (pTNM)

Primary Tumour (pT)

pTX: Primary Tumour cannot be assessed.

pT0: No evidence of primary tumour.

pT1: Tumour confined to the eye with no optic nerve or choroidal invasion.

pT2: Tumour with minimal optic nerve and / or choroidal invasion:

pT2a: Tumour superficially invades optic nerve head but does not extend past lamina cribrosa, or tumour exhibits focal choroidal invasion.

pT2b: Tumour superficially invades optic nerve head but does not extend past lamina cribrosa and tumour exhibits focal choroidal invasion.

pT3: Tumour with significant optic nerve and / or choroidal invasion:

pT3a: Tumour invades optic nerve past lamina cribrosa but not to surgical resection line, or tumour exhibits massive choroidal invasion.

pT3b: Tumour invades optic nerve past lamina cribrosa but not to surgical resection line and exhibits massive choroidal invasion.

pT4: Tumour invades optic nerve to surgical resection line or exhibits extra-ocular extension elsewhere.

pT4a: Tumour invades optic nerve to resection line, but no extra-ocular extension identified.

pT4b: Tumour invades optic nerve to resection line, and extra-ocular extension identified.

Regional Lymph Nodes (pN)

pNX: Regional lymph nodes cannot be assessed.

pN0: No regional lymph node metastasis.

pN1: Regional lymph node involvement (preauricular, cervical).

pN2: Distant lymph node involvement.

Metastasis (pM)

pMX: Presence of metastasis cannot be assessed.

pM0: No distant metastasis.

pM1: Metastasis to sites other than Central Nervous System

pM1a: Single lesion

pM1b: Multiple lesions

pM1c: CNS metastasis

pM1d: Discrete masses without leptomeningeal and/or CSF involvement

pM1e: Leptomeningeal and/or CSF involvement

TNM Descriptors:

For identification of special cases of cTNM or pTNM classifications, the “m” suffix and “y,” “r,” and “a” prefixes are used. Although they do not affect the stage grouping, they indicate cases needing separate analysis.

“m” (suffix) indicates the presence of multiple primary tumours in a single site and is recorded in parentheses: pT(m)NM.

“y” (prefix) indicates those cases in which classification is performed during or following initial multimodality therapy (ie, neoadjuvant chemotherapy, radiation therapy, or both chemotherapy and radiation therapy).

The cTNM (clinical) or pTNM (pathological) category is identified by a “y” prefix. The ycTNM or ypTNM categorizes the extent of tumour actually present at the time of that examination. The “y” categorization is not an estimate of tumour prior to multimodality therapy (ie, before initiation of neoadjuvant therapy).

“r” (prefix) indicates a recurrent tumour when staged after a documented disease-free interval, and is identified by the “r” prefix: rTNM.

“a” (prefix) designates the stage determined at autopsy: aTNM.

Additional Descriptors

Residual Tumour (R)

Tumour remaining in a patient after therapy with curative intent (eg, surgical resection for cure) is categorized by a system known as R classification, shown below.

RX: Presence of residual tumour cannot be assessed.

R0: No residual tumour.

R1: Microscopic residual tumour.

R2: Macroscopic residual tumour.

For the surgeon, the R classification may be useful to indicate the known or assumed status of the completeness of a surgical excision. For the pathologist, the R classification is relevant to the status of the margins of a surgical resection specimen. That is, tumour involving the resection margin on pathologic examination may be assumed to correspond to residual tumour in the patient, and may be classified as macroscopic or microscopic according to the findings at the specimen margin(s).

Vessel Invasion

Vessel invasion (lymphatic or venous) does not affect the T: category indicating local extent of tumour, unless specifically included in the definition of a T category. In all other cases, lymphatic and venous invasion by tumour are coded separately as follows.

Lymphatic Vessel Invasion (L)

- LX: Lymphatic vessel invasion cannot be assessed.
- L0: No lymphatic vessel invasion.
- L1: Lymphatic vessel invasion.

Venous Invasion (V)

- VX: Venous invasion cannot be assessed.
- V0: No venous invasion.
- V1: Microscopic venous invasion.
- V2: Macroscopic venous invasion.

Table 5. International Staging System for Retinoblastoma

Stage 0	No enucleation (one or both eyes may have intraocular disease)
Stage I	Enucleation, tumor completely resected
Stage II	Enucleation with microscopic residual tumor
Stage III	Regional extension <ul style="list-style-type: none"> A. Overt orbital disease B. Preauricular or cervical lymph node extension
Stage IV	Metastatic disease <ul style="list-style-type: none"> A. Hematogenous metastasis <ul style="list-style-type: none"> 1. Single lesion 2. Multiple lesions B. CNS Extension <ul style="list-style-type: none"> 1. Prechiasmatic lesion 2. CNS mass 3. Leptomeningeal disease

Management of Retinoblastoma

The primary goal of management of retinoblastoma is to save life. Salvage of the organ (eye) and function (vision) are the secondary and tertiary goals respectively. The management of retinoblastoma needs a multidisciplinary team approach including an ocular oncologist, pediatric oncologist, radiation oncologist, radiation physicist, and an ophthalmic oncopathologist. The management strategy depends on the stage of the disease – intraocular retinoblastoma, retinoblastoma with high-risk characteristics, orbital retinoblastoma and metastatic retinoblastoma.

Management of retinoblastoma is highly individualized and is based on several considerations - age at presentation, laterality, tumor location, tumor staging, visual prognosis, systemic condition, family and societal perception, and, to a certain extent, the overall prognosis and cost-effectiveness of treatment in a given economic situation (Table 6).

Table 6. Current Suggested Protocol

- A. Intraocular tumor, International Classification Group A to C, Unilateral or Bilateral
 1. Focal therapy (cryotherapy or transpupillary thermotherapy) alone for smaller tumors (≤ 3 mm in diameter and height) located in visually noncrucial areas
 2. Standard 6 cycle chemoreduction and sequential aggressive focal therapy for larger tumors and those located in visually crucial areas
 3. Defer focal therapy until 6 cycles for tumors located in the macular and juxtapapillary areas. Transpupillary thermotherapy or plaque brachytherapy for residual tumor in the macular and juxtapapillary areas >6 cycles.
 4. Focal therapy for small residual tumor, and plaque brachytherapy/ external beam radiotherapy (>12 months age) for large residual tumor if bilateral, and enucleation if unilateral.
- B. Intraocular tumor, International Classification Group D, Unilateral or Bilateral
 1. High dose chemotherapy and sequential aggressive focal therapy
 2. Periocular carboplatin for vitreous seeds

3. Consider primary enucleation if unilateral, specially in eyes with no visual prognosis
- C. Intraocular tumor, International Classification Group E, Unilateral or Bilateral
 1. Primary enucleation
 2. Evaluate histopathology for high risk factors
 - D. High risk factors on histopathology, International Staging, Stage 2
 1. Baseline systemic evaluation for metastasis
 2. Standard 6 cycle adjuvant chemotherapy
 3. High dose adjuvant chemotherapy and orbital external beam radiotherapy in patients with scleral infiltration, extraocular extension, and optic nerve extension to transection.
 - E. Extraocular tumor, International Staging, Stage 3A
 1. Baseline systemic evaluation for metastasis
 2. High dose chemotherapy for 3-6 cycles, followed by enucleation or extended enucleation, external beam radiotherapy, and continued high dose chemotherapy for 12 cycles
 - F. Regional Lymph Node Metastasis, International Staging, Stage 3B
 1. Baseline evaluation for systemic metastasis
 2. Neck dissection, high dose chemotherapy for 6 cycles, followed by external beam radiotherapy, and continued high dose chemotherapy for 12 cycles
 - G. Hematogenous or Central Nervous System Metastasis, International Staging, Stage 4
 1. Palliative therapy in discussion with the family
 2. High dose chemotherapy with bone marrow rescue for hematogenous metastasis
 3. High dose chemotherapy with intrathecal chemotherapy for central nervous system metastasis

1. Management of Intraocular Retinoblastoma

A majority of children with retinoblastoma manifest at a stage when the tumor is confined to the eye. About 90-95% of children in developed countries present with intraocular retinoblastoma while 60-70% present at this stage in the developing world.¹⁰ Diagnosis of retinoblastoma at this stage and appropriate management are crucial in life, eye and possible vision salvage.

There are several methods to manage intraocular retinoblastoma – focal (cryotherapy, laser photocoagulation, transpupillary thermotherapy, transcleral thermotherapy, plaque brachytherapy), local (external beam radiotherapy, enucleation), and systemic (chemotherapy). While primary focal measures are mainly reserved for small tumors, local and systemic modalities are used to treat advanced retinoblastoma.

Cryotherapy

Cryotherapy is performed for small equatorial and peripheral retinal tumors measuring up to 4 mm in basal diameter and 2 mm in thickness.^{2,10} Triple freeze thaw cryotherapy is applied at 4-6 week intervals until complete tumor regression. Cryotherapy produces a scar much larger than the tumor (Figure 16). Complications of cryotherapy include transient serous retinal detachment, retinal tear and rhegmatogenous retinal detachment. Cryotherapy administered 2-3 hours prior to chemotherapy can increase the delivery of chemotherapeutic agents across the blood retinal barrier and thus has synergistic effect.¹⁰

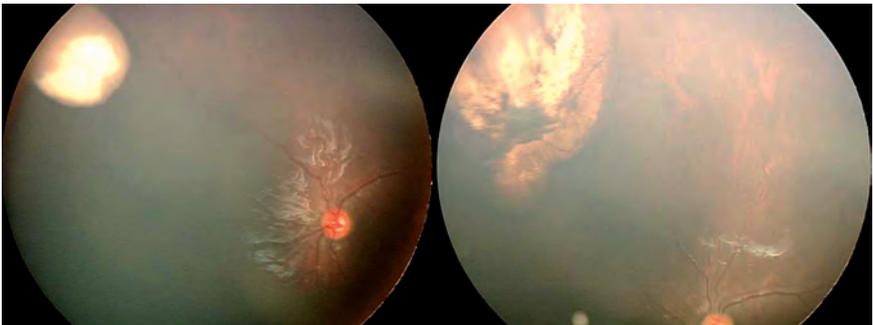


Figure 16. A peripheral retinal tumor that underwent Cryotherapy (left). The tumor has completely regressed but the scar is much larger than the tumor itself (right)

Laser photocoagulation

Laser photocoagulation is used for small posterior tumors 4 mm in basal diameter and 2 mm in thickness.^{2,10} The treatment is directed to delimit the tumor and restrict the blood supply to the tumor by surrounding it with two rows of overlapping laser burns. Complications include transient serous retinal detachment, retinal vascular occlusion, retinal hole, retinal traction, and preretinal fibrosis. A large visual field defect is a major complication of laser photocoagulation if the tumor is located in the juxtapapillary area. It is less often employed now with the advent of thermotherapy. In fact, laser photocoagulation is contraindicated while the patient is on active chemoreduction protocol because it restricts the blood supply to the tumor and consequently reduces the intra-tumor concentration of the chemotherapeutic agent.¹⁰

Thermotherapy

In thermotherapy, focused heat generated by infrared radiation is applied to tissues at subphotocoagulation levels to induce tumor cell apoptosis.²⁶ The goal is to achieve a slow and sustained temperature range of 40 to 60 degree C within the tumor, thus sparing damage to the retinal vessels (Figure 17). Transpupillary thermotherapy using infrared radiation from a semiconductor diode laser delivered with a 1300-micron large spot indirect ophthalmoscope delivery system has become the standard practice. It can also be applied transpupillary through an operating microscope or by the transscleral route with a diopexy probe. The tumor is heated until it turns a subtle gray. Thermotherapy provides satisfactory control for small tumors - 4 mm in basal diameter and 2 mm in thickness. Complete tumor regression can be achieved in over 85% of tumors using 3-4 sessions of thermotherapy.²⁶ The common complications such as focal iris atrophy and focal paraxial lens opacity can be minimized by using 1300-micron indirect ophthalmoscope delivery system and duration of

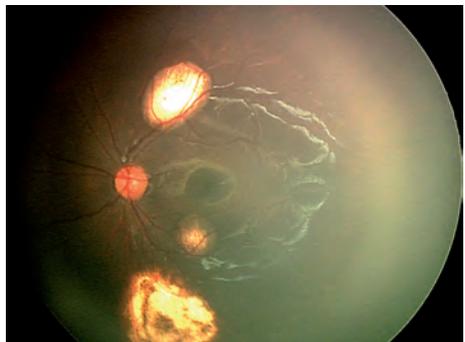


Figure 17. Three focal tumors treated with transpupillary thermotherapy: Note flat scars with patent blood vessels coursing through the scars. Transpupillary thermotherapy classically spares the blood vessels from occlusion and produces a compact scar.

treatment limited to 5 minutes in one session. Retinal traction and serous retinal detachment may occur following heavy thermotherapy. The major application of thermotherapy is as an adjunct to chemoreduction. The application of heat amplifies the cytotoxic effect of platinum analogues. This synergistic combination of thermotherapy with chemoreduction protocol is termed chemothermotherapy or thermochemotherapy depending on the sequence in which the treatments are delivered.



Figure 18. Ruthenium 106 plaque

Plaque Brachytherapy

Plaque brachytherapy involves placement of a radioactive implant on the sclera corresponding to the base of the tumor to transsclerally irradiate the tumor.²⁷ Commonly used radioactive materials include Ruthenium 106 (Figure 18) and Iodine 125. The advantages of plaque brachytherapy are focal delivery of radiation with minimal damage to the

surrounding normal structures, minimal periorbital tissue damage, absence of cosmetic abnormality because of retarded bone growth in the field of irradiation as occurs with external beam radiotherapy, reduced risk of second malignant neoplasm and shorter duration of treatment.

Plaque brachytherapy is indicated in tumors ≤ 16 mm in basal diameter and ≤ 8 mm thickness. It could be the primary or secondary modality of management. Primary plaque brachytherapy is currently performed only in situations where chemotherapy is contraindicated. It is most useful as secondary treatment in eyes that fail to respond to chemoreduction and external beam radiotherapy or for tumor recurrences.

Plaque brachytherapy requires precise tumor localization and measurement of its basal dimensions. The tumor thickness is measured by ultrasonography. The data is used for dosimetry on a three-dimensional computerized tumor modeling system. The plaque design is chosen depending on the basal tumor dimensions, its location, and

configuration – for example, a notched plaque is used to protect the optic nerve when used for tumors which are peripapillary in location. The dose to the tumor apex ranges from 4000-5000 cGy. The plaque is sutured to the sclera after confirming tumor centration and is left in situ for the duration of exposure, generally ranging from 36 to 72 hours. The results of plaque brachytherapy are gratifying, with about 90% tumor control. The common complications are radiation papillopathy and radiation retinopathy.

External Beam Radiotherapy

External beam radiotherapy was the preferred form of management of moderately advanced retinoblastoma in late 1900s.^{28,29} However with the advent of newer chemotherapy protocols, external beam radiotherapy is being used less often. Presently it is indicated in eyes where primary chemotherapy and local therapy has failed, or rarely when chemotherapy is contraindicated.¹⁰

External beam radiotherapy is delivered using Cobalt 60 (gamma rays) or linear accelerator (X-rays). Linear accelerator with multi-beam technique (intensity-modulated radiotherapy), image-guided radiotherapy and stereotactic radiotherapy have better treatment accuracy, minimal damage to normal structures and least complications.

The major problems with external beam radiotherapy are the stunting of the orbital growth, dry eye, cataract, radiation retinopathy and optic neuropathy. External beam radiotherapy can induce second malignant neoplasm especially in patients with the hereditary form of retinoblastoma (Figure 19). There is a high 30% chance of developing another malignancy by the age of 30 years in such patients if they are given external beam radiotherapy, compared to a less than 6% chance in those who do not receive external beam radiotherapy.³⁰ The risk of second malignant neoplasm is greater in children under 12 months of age.³⁰



Figure 19. Osteosarcoma of the frontal bone in a 20-year-old patient with bilateral retinoblastoma who had undergone external beam radiotherapy at 1-year age

Enucleation

Enucleation is a common method of managing advanced retinoblastoma. Just about 3 decades ago, a majority of patients with unilateral retinoblastoma and the worse eye in bilateral retinoblastoma underwent primary enucleation. A substantial reduction in the frequency of enucleation has occurred in the late last century.³¹ Concurrently, there has been an increase in the use of alternative eye- and vision-conserving methods of treatment.^{9,32}

Primary enucleation continues to be the treatment of choice for advanced intraocular retinoblastoma with neovascularization of iris, secondary glaucoma, anterior chamber tumor invasion, tumors occupying >75% of the vitreous volume, necrotic tumors with secondary orbital inflammation, and tumors associated with hyphema or vitreous hemorrhage where the tumor characteristics can not be visualized, especially when only one eye is involved.¹⁰

There are specific considerations while enucleating an eye with retinoblastoma (Table 7). Minimum-manipulation surgical technique should be necessarily practiced.¹¹ It is important to take due precautions not to accidentally perforate the eye. The sclera is thin at the site of muscle insertions and the rectus muscles have to be hooked delicately. It is mandatory to obtain a long optic nerve stump, ideally more than 15 mm, but never less than 10 mm (Figure 20).¹¹ Certain steps can be taken to obtain about 15 mm long optic nerve stump in all cases of advanced retinoblastoma.¹¹ Gentle traction can be applied by the traction sutures applied to recti muscle stumps prior to transecting the optic nerve. As an alternative to the traction sutures, medial or lateral rectus muscle

Table 7. Special considerations for enucleation in retinoblastoma

- a. Minimal manipulation
- b. Avoid perforation of the eye
- c. Harvest long (> 15 mm) optic nerve stump
- d. Inspect the enucleated eye for macroscopic extraocular extension and optic nerve involvement
- e. Harvest fresh tissue for genetic studies
- f. Place a primary implant
- g. Avoid biointegrated implant if postoperative radiotherapy is necessary

stumps may be kept long and traction exerted with an artery clamp. It is best to prolapse the eyeball through the blades of the wire speculum. A 15-degree curved and blunt-tipped tenotomy scissors is introduced from the lateral aspect (or a straight scissors from the medial aspect) and the optic nerve is palpated with the closed tip of the scissors while maintaining gentle anteroposterior traction on the eyeball. The scissors is moved posteriorly to touch the orbital apex while gently “strumming” the optic nerve. The scissors is lifted by 2 or 3 millimeters off the orbital apex (to prevent accidental damage to the contents of the superior orbital fissure), the blades of the scissors are opened to engage the optic nerve, and the nerve is transected with one bold cut. This maneuver easily provides at least 15 mm long optic nerve stump.¹¹ Enucleation spoon and heavy enucleation scissors limit space for maneuverability and may result in a shorter optic nerve stump. In addition, one should be careful not to accidentally perforate the eye during enucleation. The enucleated eyeball is thoroughly inspected for optic nerve (Figure 20) or extraocular extension (Figure 21) of the tumor and suspicious areas (sclera thinning, induration, discoloration, vascularilty, and nodularity and, dilated vortex veins) are marked for histoapthogic examination to evaluate scleral or extrascleral extension of the tumor.

Eyes manifesting tumor necrosis with aseptic orbital cellulitis pose a specific problem. These patients should be imaged to rule out extraocular extension. Enucleation is best performed when the inflammation has resolved.¹¹ A brief course of preoperative oral and topical corticosteroids help control inflammation. Patients with retinoblastoma presenting as phthisis bulbi, specifically phthisical eyes that show disproportionately



Figure 20. Enucleated eyeball showing 18 mm optic nerve stump. Note the proximal portion of the optic nerve is thickened indicating tumor infiltration



Figure 21. Enucleated eyeball showing extraocular tumor extension.

less enophthalmos need imaging to exclude extraocular and optic nerve extension.¹¹ Phthisis generally results following spontaneous tumor necrosis and an episode of aseptic intraocular and orbital inflammation. Enucleation in these cases is often complicated by excessive peribulbar fibrosis and intraoperative bleeding.¹¹

Placement of a primary orbital implant following enucleation for retinoblastoma is the current standard of care. The orbital implant promotes orbital growth, provides better cosmesis and enhances prosthesis motility. The implant could be non-integrated (polymethyl methacrylate or silicon) or bio-integrated (hydroxyapatite or porous polyethylene). Placement of a biointegrated implant is generally avoided if post-operative adjuvant radiotherapy is considered necessary.¹¹ Although most implants structurally tolerate radiotherapy well, implant vascularization may be compromised by radiotherapy thus increasing the risk of implant exposure. Use of myoconjunctival technique and custom ocular prosthesis have optimized prosthesis motility and static cosmesis (Figure 22).



Figure 22. Retinoblastoma in the right eye following enucleation with orbital implant by the myoconjunctival technique (left). Excellent cosmesis following fitting of a custom ocular prosthesis (right).

Systemic Chemotherapy

Chemoreduction, defined as the process of reduction in the tumor volume with chemotherapy, has become an integral part of the current management of retinoblastoma.³² Chemotherapy alone is not curative and must be synergistically combined with sequential and well-timed intensive focal therapy. Chemoreduction coupled with focal therapy can minimize the need for enucleation or external beam radiotherapy without significant systemic toxicity.

Chemoreduction in combination with focal therapy is now extensively used in the primary management of retinoblastoma.³³⁻³⁶ There are different protocols in chemotherapy. The commonly used drugs are vincristine, etoposide and carboplatin in combination, for 6 cycles.⁷⁻¹⁰ (Table 8) Standard dose chemoreduction is provided in Reese Ellsworth groups I-IV (or international classification Group C).¹⁰ In high dose chemoreduction, the dose of etoposide and carboplatin is increased. This is indicated in Reese Ellsworth group V (or international classification Group D or higher) tumors.¹⁰

Table 8. Chemoreduction regimen and doses for intraocular retinoblastoma

Day 1: Vincristine + Etoposide + Carboplatin

Day 2: Etoposide

Standard dose: (3 weekly, 6 cycles): Vincristine 1.5 mg/m² (0.05 mg/kg for children ≤ 36 months of age and maximum dose ≤ 2mg), Etoposide 150 mg/m² (5 mg/kg for children ≤ 36 months of age), Carboplatin 560 mg/m² (18.6 mg/kg for children ≤ 36 months of age)

High-dose (3 weekly, 6-12 cycles): Vincristine 0.025 mg/Kg, Etoposide 12 mg/Kg, Carboplatin 28 mg/Kg

With chemoreduction and sequential local therapy, it is now possible to salvage an eye and maximize residual vision. Chemoreduction is most successful for tumors without associated subretinal fluid or vitreous seeding.^{7,8} Risk factors for tumor, subretinal seed and vitreous seed recurrence, and failure of chemoreduction leading to external beam radiotherapy and/or enucleation have been identified.^{7,8} Chemoreduction offers satisfactory tumor control for Reese Ellsworth groups I-IV eyes, with treatment failure necessitating additional external beam radiotherapy in only 10% and enucleation in 15% at 5-year follow-up. Patients with Reese Ellsworth group V eyes require external beam radiotherapy in 47% and enucleation in 53% at 5 years.^{7,8} Chemoreduction is an option for selected eyes with unilateral retinoblastoma.⁹

Figure 23 shows a tumor involving the macula at presentation. With chemoreduction and transpupillary thermotherapy, there was complete tumor regression. Figures 24, 25 and 26 show that the resulting scar with chemoreduction was much smaller than the original tumor with



Figure 23. Macular retinoblastoma in a 6-month-old child (left), completely regressed with 6 cycles of chemoreduction alone (right).

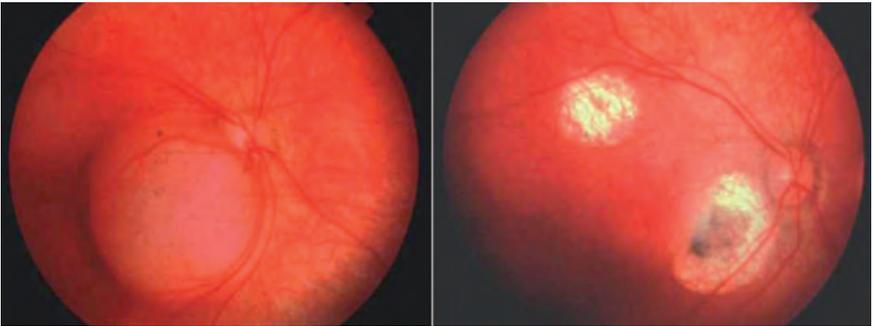


Figure 24. Multifocal retinoblastoma (left) following chemoreduction and transpupillary thermotherapy (right). Note flat scars that are much smaller than the original tumor.

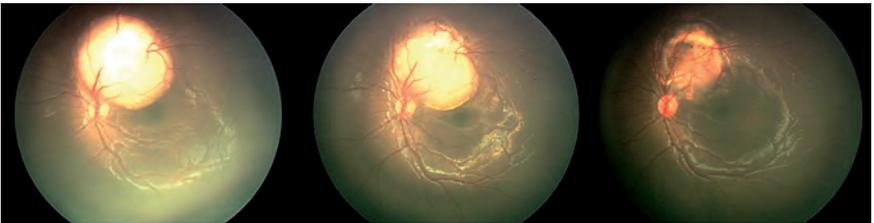


Figure 25. A juxtapapillary retinal tumor in a 9-month-old child (left) partially regressed with 3 cycles of chemoreduction (middle) and completely regressed with 6 cycles of chemoreduction and transpupillary thermotherapy (right). Note the completely exposed fovea following treatment, thus maximizing visual potential.

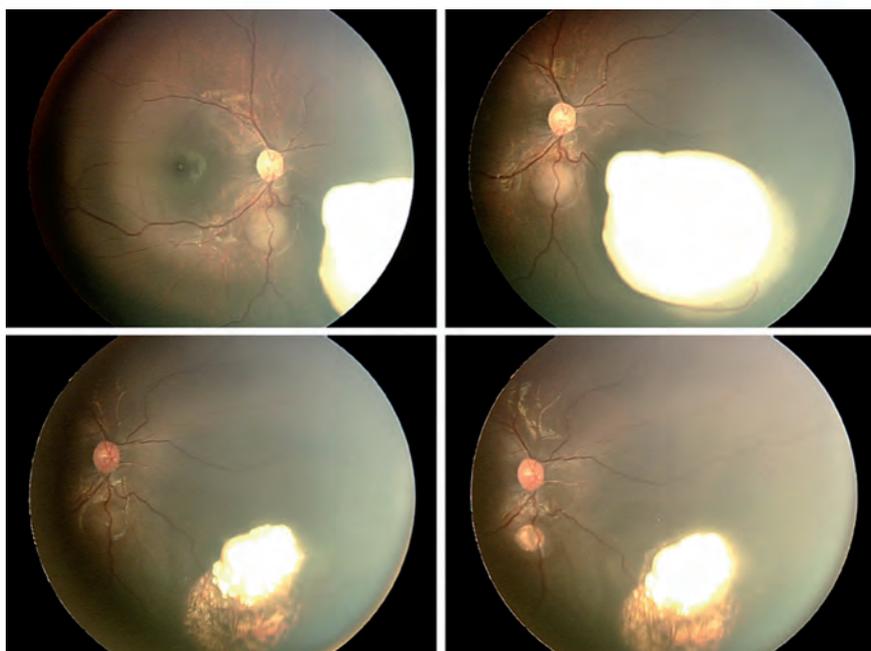


Figure 26. Multifocal retinoblastoma (top) regressed following chemoreduction and transpupillary thermotherapy (bottom).

the foveola fully exposed, thus maximizing visual potential. With the modified protocol that we use specifically for advanced retinoblastoma, our eye salvage rates are 100% for Reese Ellsworth groups 1-3, 90% for group D and 75% for group E (Table 9).

Table 9. Eye Salvage Rates with External Beam Radiotherapy Vs Chemoreduction

Reese Ellsworth Group	Ellsworth, 1977 EBRT	Hungerford, 1995 EBRT	Shields, 2003 Chemoreduction	LVPEI, 2005 Chemoreduction*
I	91%	100%	100%	100%
II	83%	84%	100%	100%
III	82%	82%	100%	100%
IV	62%	43%	75%	90%
V	29%	66%	50%	75%

* High dose chemotherapy for group V, periocular chemotherapy for VB

It is important to be aware of the adverse effects and interactions of chemotherapeutic agents, which include myelosuppression, febrile episodes, neurotoxicity and non-specific gastrointestinal toxicity. Chemotherapy should be given only under the supervision of an experienced pediatric oncologist.

Periocular chemotherapy

Carboplatin delivered deep posterior subtenons has been demonstrated to be efficacious in the management of retinoblastoma with vitreous seeds because it can penetrate the sclera and achieve effective concentrations in the vitreous cavity. This modality is currently under trial. Our early results have shown that periocular chemotherapy achieves 70% eye salvage in patients with Reese Ellsworth group VB retinoblastoma (Figure 27).³⁷

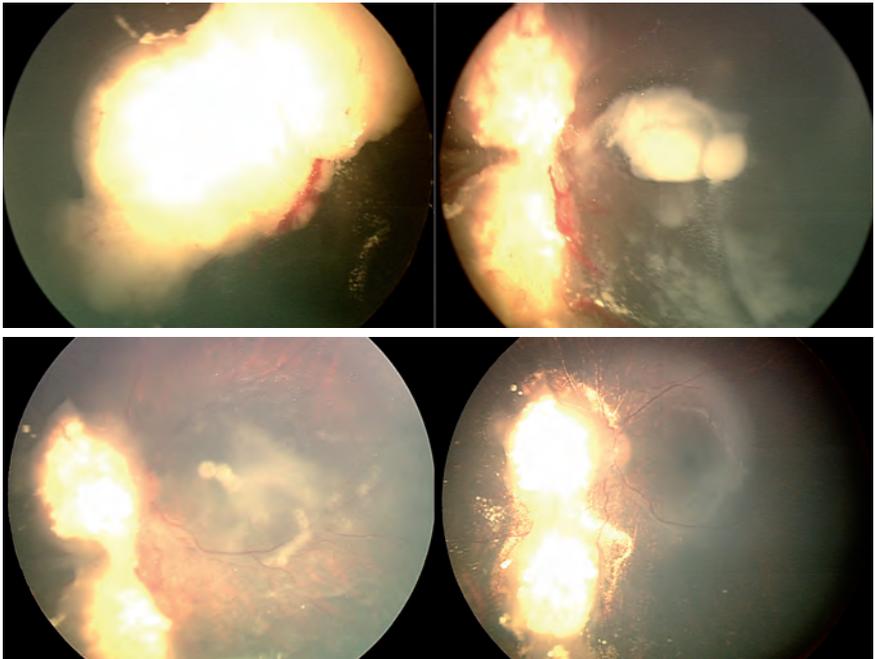


Figure 27. Retinoblastoma with massive vitreous seeds (Figure 27 top left). Following 3 cycles of high-dose chemoreduction (Figure 27 top right) the tumor is partially regressed but the vitreous seeds persist. With periocular carboplatin injection in addition to high dose chemoreduction, the vitreous seeds show complete regression (Figure 27 bottom, left and right).

Intraarterial chemotherapy

Although chemotherapy protocols used in retinoblastoma are generally considered safe, there are concerns about the increased risk of secondary acute myelogenous leukemia. Techniques that offer concentrated delivery of chemotherapy to the eye, while avoiding high systemic concentrations seems ideal. Although there have been few case reports of intravitreal injection of chemotherapy, such approach has not gained wide acceptance because of concerns regarding extraocular dissemination of retinoblastoma. Injection of a chemotherapeutic agent into the carotid artery was first attempted by Reese in 1957. More recently, Japanese investigators have employed interventional radiology to catheterise the carotid artery, and inject melphalan. A balloon catheter was then passed into the internal carotid artery and inflated to occlude the artery and allow the medication to perfuse the eye without reaching the brain. However, this technique was combined with hyperthermia and EBRT, making it difficult to assess the effects of the isolated intraarterial chemotherapy. A Recent phase I/II clinical trial has evaluated intraarterial melphalan in unilateral Reese Ellsworth Group V eyes, which would otherwise have undergone enucleation.⁶²

Nine of 10 patients could be successfully cannulated and a total of 27 injections were given. There was dramatic regression of tumors, vitreous seeds and subretinal seeds in nine patients. None of the nine children had a tumor recurrence. Two children underwent enucleation because of concerns regarding persistent retinal detachment and suspected tumor recurrence; however, histopathological examination found no viable tumor. There were no severe systemic side effects, although one child did develop neutropenia. After a mean follow-up of 8.8 months, the researchers found little toxicity associated with the treatment. Three patients developed conjunctival and lid edema that resolved without treatment. One previously irradiated eye developed retinal ischemia, and another eye developed radiation-like retinopathy after subsequent brachytherapy. Although generally poor, vision did stabilize or improve in all but one patient after treatment. Although the early results seem exciting, the outstanding concerns that need to be addressed are the potential for vascular complications (ischemic events, vascular spasms, vascular stenosis or complete occlusion) and drug toxicity.^{63,64}

Follow-up Schedule

The usual protocol is to schedule the first examination 3–6 weeks after the initial therapy. In cases where chemoreduction has been administered, the examination should be done every 3 weeks along with each cycle of chemotherapy. Patients under focal therapy are evaluated and treated every 4–8 weeks until complete tumor regression. Following tumor regression, subsequent examination should be 3 monthly for the first year, 6 monthly for three years or until the child attains 6 years of age, and yearly thereafter.

2. Management of High Risk Retinoblastoma

Systemic metastasis is the main cause for mortality in patients with retinoblastoma. Although the life prognosis of patients with retinoblastoma has dramatically improved in the last three decades, with a reported survival of more than 90% in developed countries,³⁸ mortality is still as high as 50% in the developing nations.^{39,40} Reduction in the rate of systemic metastasis by identification of high-risk factors and appropriate adjuvant therapy may help improve survival.

High-Risk Factors

None of the clinical high-risk factors seem to strongly correlate with mortality. Recent studies have evaluated the role of histopathologic high-risk factors identified following enucleation. The identification of frequency and significance of high-risk histopathologic factors (Figures 28–31) that can reliably predict metastasis is vital for patient selection for adjuvant therapy. Several studies have addressed this issue.^{39,41–49} It is now generally agreed that massive choroidal infiltration, retrolaminar optic nerve invasion, invasion of the optic nerve to transection, scleral infiltration, and extrascleral extension are the risk factors that are predictive of metastasis (Table 10).^{39,41–49}

The reported occurrence of anterior chamber seeding (7%),⁴⁵ massive choroidal infiltration (12–23%),^{43–49} invasion of optic nerve lamina cribrosa (6–7%),^{43–49} retrolaminar optic nerve invasion (6–12%),^{43–49} invasion of optic nerve transection (1–25%),^{43–49} scleral infiltration (1–8%),^{43–49} and extrascleral extension (2–13%),^{43–49} widely vary even in developed countries. Vemuganti and associates have reported that 21% of the 76 eyes enucleated for advanced retinoblastoma in India had anterior chamber seeding, 54% had massive choroidal infiltration, 46% had optic

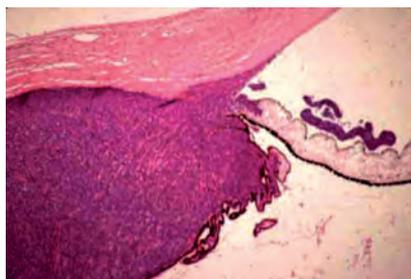


Figure 28

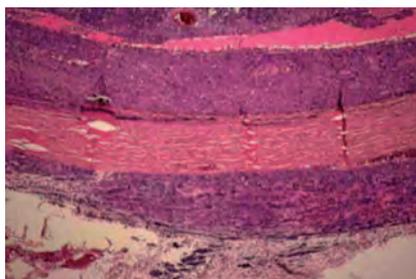


Figure 29

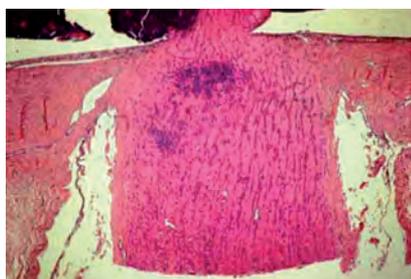


Figure 30



Figure 31

Figure 28. Histopathology of retinoblastoma showing anterior chamber seeding, iris infiltration, trabecular meshwork infiltration and ciliary body invasion.

Figure 29. Histopathology of retinoblastoma showing massive choroidal infiltration, scleral infiltration and extrascleral extension.

Figure 30. Histopathology of retinoblastoma showing infiltration of the optic nerve beyond the lamina cribrosa.

Figure 31. Histopathology of retinoblastoma showing optic nerve infiltration to the level of transection.

Table 10. Histopathologic high-risk factors predictive of metastasis

- Anterior chamber seeding
- Iris infiltration
- Ciliary body infiltration
- Massive choroidal infiltration
- Invasion of the optic nerve lamina cribrosa
- Retrolaminar optic nerve invasion
- Invasion of optic nerve transection
- Scleral infiltration
- Extrascleral extension

nerve invasion at or beyond the lamina cribrosa and 7% had scleral infiltration or extrascleral extension.¹² It is apparent that the incidence of histopathologic risk factors is strikingly high in developing countries compared to the published data from developed countries.

Adjuvant Therapy

Studies on the efficacy of adjuvant therapy to minimize the risk of metastasis initiated in the 1970s were marked by variable results and provided no firm recommendation.¹⁸ A recent study with a long-term follow-up provides useful information.^{13,50} It included a subset of patients with unilateral sporadic retinoblastoma who underwent primary enucleation. The study used specific predetermined histopathologic characteristics for patient selection. A minimum follow-up of 1 year was allowed to include metastatic events that generally occur at a mean of 9 months following enucleation.^{13,50} The incidence of metastasis was 4% in those who received adjuvant therapy compared to 24% in those who did not. The study found that administration of adjuvant therapy significantly reduced the risk of metastasis in patients with high-risk histopathologic characteristics.

Our current practice is to administer 6 cycles of a combination of carboplatin, etoposide and vincristine (identical to the protocol used for chemoreduction of intraocular retinoblastoma) in patients with histopathologic high-risk characteristics. All patients with extension of retinoblastoma up to the level of optic nerve transection, scleral infiltration, and extrascleral extension receive high dose chemotherapy for 12 cycles and fractionated 4500 to 5000 cGy orbital external beam radiotherapy.

3. Orbital Retinoblastoma

Orbital retinoblastoma is rare in developed countries. Ellsworth observed a steady decline in the incidence of orbital retinoblastoma in his large series of 1160 patients collected over 50 years.⁵¹ Orbital retinoblastoma is relatively more common in the developing countries. In a recent large multi-center study from Mexico, 18% of 500 patients presented with an orbital retinoblastoma.⁵² A Taiwanese group reported that 36% (42 of 116) of their patients manifested with orbital retinoblastoma.⁵³ The incidence is higher (40%, 19 of 43) in Nepal, with proptosis being the most common clinical manifestation of retinoblastoma.⁵⁴

Clinical Manifestations

There are several clinical presentations of orbital retinoblastoma.

a. Primary Orbital Retinoblastoma

Primary orbital retinoblastoma refers to clinical or radiologically detected orbital extension of an intraocular retinoblastoma at the initial clinical presentation, with or without proptosis or a fungating mass (Figure 32). Silent proptosis without significant orbital and periorbital inflammation in a patient with manifest intraocular tumor is the characteristic presentation. Proptosis with inflammation generally indicates reactive sterile orbital cellulitis secondary to intraocular tumor necrosis.

b. Secondary Orbital Retinoblastoma

Orbital recurrence following uncomplicated enucleation for intraocular retinoblastoma is termed secondary orbital retinoblastoma (Figure 33). Unexplained displacement, bulge or extrusion of a previously well-fitting conformer or a prosthesis is an ominous finding suggestive of orbital recurrence.

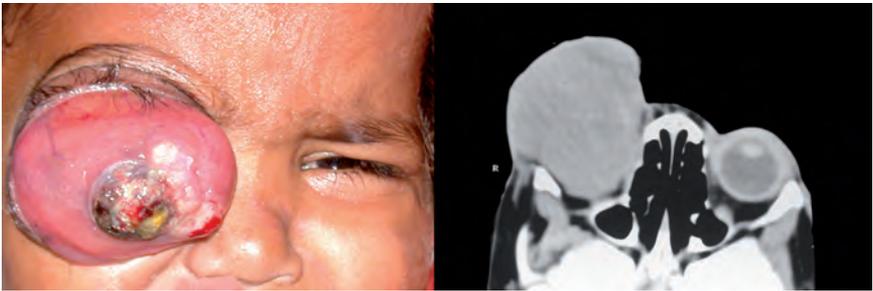


Figure 32. Primary orbital retinoblastoma manifesting with proptosis (left). Computed tomography scan shows massive orbital tumor (right).



Figure 33. Secondary orbital retinoblastoma following enucleation, manifesting with extrusion of the prosthetic eye (left). CT can shows an orbital tumor (right).

c. Accidental Orbital Retinoblastoma

Inadvertent perforation, fine-needle aspiration biopsy or intraocular surgery in an eye with unsuspected intraocular retinoblastoma should be considered as accidental orbital retinoblastoma and managed as such (Figure 34).



Figure 34. A child with retinoblastoma misdiagnosed as traumatic hyphema in the left eye and treated with hyphema drainage without a baseline ultrasonography evaluation presents after 1 year with extraocular extension (left) and regional lymph node metastasis (right).

d. Overt Orbital Retinoblastoma

Previously unrecognized extrascleral or optic nerve extension discovered during enucleation qualifies as overt orbital retinoblastoma. Pale pink to cherry red episcleral nodule, generally in juxtapapillary location or at the site of vortex veins, may be visualized during enucleation. An enlarged and inelastic optic nerve with or without nodular optic nerve sheath are clinical indicators of optic nerve extension of retinoblastoma that should be recognized during enucleation.

e. Microscopic Orbital Retinoblastoma

In several instances, orbital extension of retinoblastoma may not be clinically evident and may only be microscopic. Detection of full-thickness scleral infiltration, extrascleral extension and invasion of the optic nerve on histopathologic evaluation of an eye enucleated for intraocular retinoblastoma are unequivocal features of orbital retinoblastoma. Tumor cells in choroidal and scleral emissaria and optic nerve sheath indicate possible orbital extension mandating further serial sections and detailed histopathologic analysis.

Diagnostic Evaluation

A thorough clinical evaluation paying attention to the subtle signs of orbital retinoblastoma is necessary. Magnetic resonance imaging preferably, or computed tomography scan of the orbit and brain in axial and coronal orientation with 2-mm slice thickness helps confirm the presence of orbital retinoblastoma and determine its extent. Systemic evaluation, including a detailed physical examination, palpation of the regional lymph nodes and fine needle aspiration biopsy if involved, imaging of the orbit and brain, chest X-ray, ultrasonography of the abdomen, bone marrow biopsy and cerebrospinal fluid cytology are necessary to stage the disease. Technetium-99 bone scan and positron-emission tomography coupled with computed tomography may be useful modalities of the early detection of subclinical systemic metastases. Orbital biopsy is rarely required, and should be considered specifically when a child presents with an orbital mass following enucleation or evisceration where the primary histopathology is unavailable.

Management of Orbital Retinoblastoma

Primary orbital retinoblastoma has been managed in the past with orbital exenteration, chemotherapy or external beam radiotherapy in isolation or in sequential combination with variable results.⁵⁵⁻⁶⁰ It is well known that local treatments have a limited effect on the course of this advanced disease. Orbital exenteration alone is unlikely to achieve complete surgical clearance and preclude secondary relapses; external beam radiotherapy does not generally prevent systemic metastasis; and chemotherapy alone may not eradicate residual orbital disease.⁵⁵⁻⁶⁰ Therefore, a combination therapy is considered to be more effective. We have developed a treatment protocol comprising of initial three drug (Vincristine, Etoposide, Carboplatin) high dose chemotherapy (3-6 cycles) followed by surgery (enucleation, extended enucleation or orbital exenteration as appropriate) after radiological confirmation of complete resolution of the extraocular component of the tumor, orbital radiotherapy, and extended high-dose chemotherapy for 12 cycles.¹⁷ In 6 carefully selected cases without intracranial extension and systemic metastasis, there was dramatic resolution of orbital involvement. All the involved eyes became phthisical after 3 cycles of high dose chemotherapy. No clinically apparent orbital tumor was found during enucleation. All patients completed the treatment protocol of orbital external beam radiotherapy, and additional 12 cycle standard

chemotherapy. All the patients were free of local recurrence or systemic metastasis at a mean follow-up of 36 months (range 12-102 months) and achieved acceptable cosmetic outcome (Figure 35).¹⁷

Our treatment protocol outlined for primary orbital retinoblastoma is currently under evaluation for secondary orbital retinoblastoma and early results have been very encouraging. Surgical intervention in such cases may be limited to excision of the residual orbital mass or an orbital exenteration depending on the extent of the residual tumor after the initial 3-6 cycles of high-dose chemotherapy.

All eyes that have undergone an intraocular surgery for unsuspected retinoblastoma should be promptly enucleated.¹⁶ Conjunctiva



Figure 35. A child with primary orbital retinoblastoma (top left), showing massive orbital tumor on computed tomography scan (top right). Following 12 cycles of high-dose chemotherapy, extended enucleation and orbital external beam radiotherapy (bottom left). The child is alive and well and wears a custom ocular prosthesis 3 years following completion of treatment (bottom right).

overlying the ports with about 4 mm clear margins should be included en-bloc with enucleation. Random orbital biopsy may be also obtained, but there is no data to support its utility. If immediate enucleation is not logistically possible, then the vitrectomy ports or the surgical incision should be subjected to triple-freeze-thaw cryotherapy and enucleation should be performed at the earliest possible convenience. Histopathologic evaluation of such eyes may include specific analysis of the sites of sclerotomy ports or the cataract wound for tumor cells.

If an extraocular extension is macroscopically visualized during enucleation, special precaution is taken to excise it completely along with the eyeball, preferably along with the layer of Tenon's capsule intact in the involved area.¹¹

All patients with accidental, overt or microscopic orbital retinoblastoma undergo baseline systemic evaluation to rule out metastasis. Orbital external beam radiotherapy (fractionated 45-50 Gy) and 12 cycles of high dose chemotherapy are recommended.¹⁶

4. Metastatic Retinoblastoma

Metastatic disease at the time of retinoblastoma diagnosis is very rare. Therefore, staging procedures such as bone scans, lumbar puncture, and bone marrow aspiration at the initial presentation are generally not recommended. The common sites for local spread and metastasis include orbital and regional lymph node extension, central nervous system metastasis, and systemic metastasis to bone and bone marrow. Metastasis usually occurs within one year of diagnosis of the retinoblastoma. If there is no metastatic disease within 5 years of retinoblastoma diagnosis, the child is usually considered cured.

Metastatic retinoblastoma is reported to develop in fewer than 5% of patients in developed countries. However, it is a major contributor to retinoblastoma related mortality in developing nations. Until recently, the prognosis with metastatic retinoblastoma was poor. Conventional dose chemotherapy using vincristine, doxorubicin, cyclophosphamide, cisplatin, and etoposide combined with radiation therapy has yielded only a few survivors. Dismal results with conventional therapy has prompted the use of high dose chemotherapy with hematopoietic stem cell rescue. Twenty-five patients with extraocular disease or invasion of

the cut end of optic nerve received high-dose chemotherapy including carboplatin, etoposide, and cyclophosphamide followed by autologous hematopoietic stem cell rescue. The three year disease-free survival was 67%.^{60,61} All except one patient with central nervous system disease, however, died. The main side effects were hematological, mucositis, diarrhoea, ototoxicity, and cardiac toxicity. Overall the response rate suggested that the treatment regimen was promising in patients with bone or bone marrow involvement, but not in patients with central nervous system disease.

Children's Oncology Group is conducting a trial for the treatment of metastasis retinoblastoma. In this trial, the patients will be stratified into 3 groups: orbital/nodal disease, central nervous system disease, and systemic disease. Each patient will undergo induction therapy with cisplatin, cyclophosphamide, vincristine, and etoposide. Those with systemic metastasis or central nervous system disease will then receive high dose therapy with etoposide, carboplatin and thiotepa.

Conclusion

There has been a dramatic change in the overall management of retinoblastoma in the last decade. Specific genetic protocols have been able to make prenatal diagnosis of retinoblastoma. Early diagnosis and advancements in focal therapy have resulted in improved eye and vision salvage. Chemoreduction has become the standard of care for the management of moderately advanced intraocular retinoblastoma. Periocular chemotherapy is now an additional useful tool in salvaging eyes with vitreous seeds. Efficacy and complications of intraarterial chemotherapy and safety of direct intravitreal chemotherapy are being explored. Enucleation continues to be the preferred primary treatment approach in unilateral advanced retinoblastoma. Post-enucelation protocol, including identification of histopathologic high-risk characteristics and provision of adjuvant therapy has resulted in substantial reduction in the incidence of systemic metastasis. The vexing orbital retinoblastoma now seems to have a cure finally with the aggressive multimodal approach. Future holds promise for further advancement in focal therapy and targeted drug delivery.

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