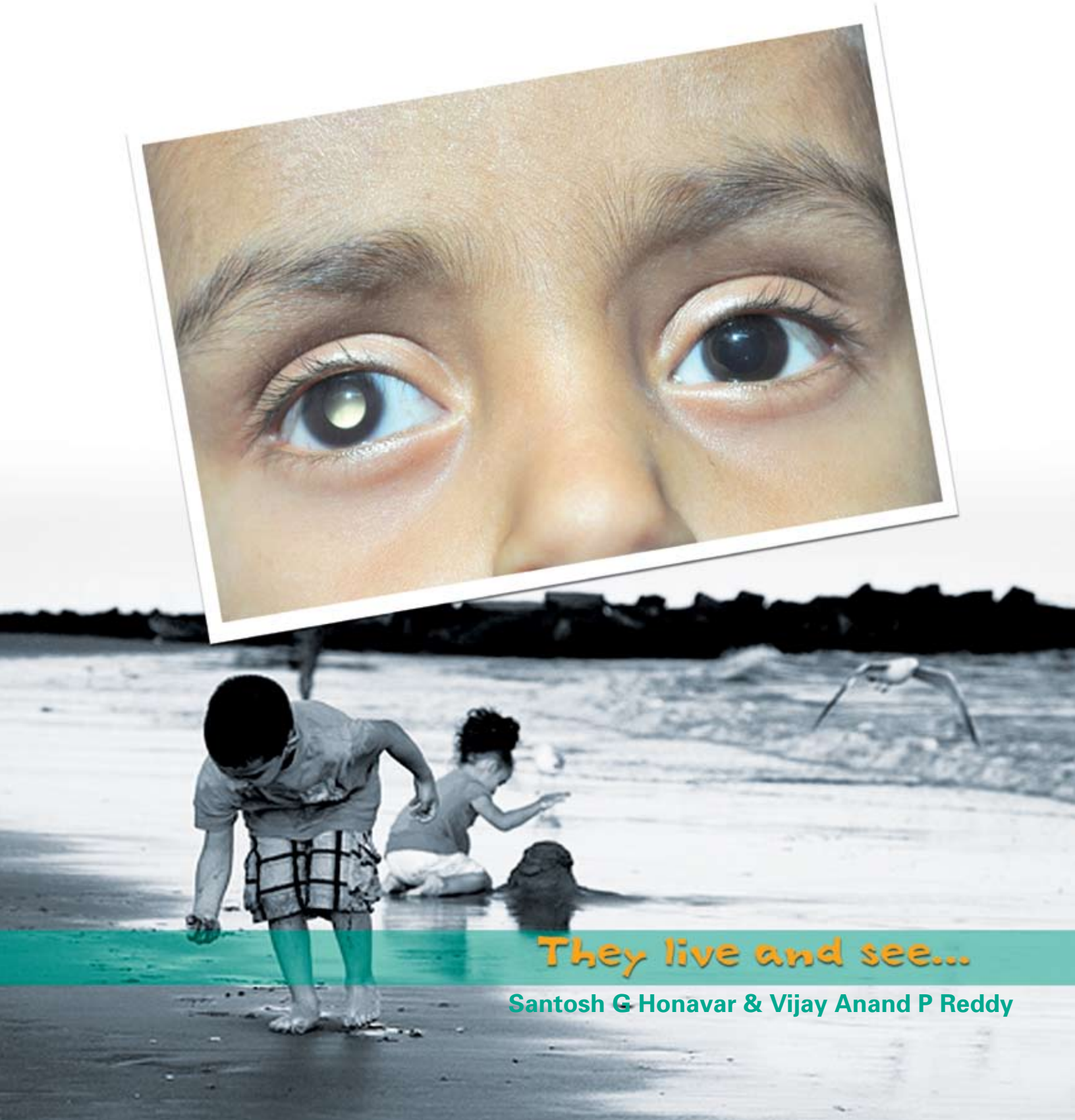
# Retinoblastoma



They live and see...

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## Author

Born in Pune, Dr Honavar studied in Bangalore and had his basic medical education at the Bangalore Medical College. He was the Best Graduate of the Bangalore University in 1988. He received post-graduate training in Ophthalmology, followed by a senior residency in Ophthalmic Plastic Surgery, Pediatric Ophthalmology and Glaucoma at the Dr Rajendra Prasad Center for Ophthalmic Sciences, All India Institute of Medical Sciences, New Delhi. During his residency training at the All India Institute of Medical Sciences, he was adjudged the Best Resident.

Dr Honavar further trained in Ocular Oncology and was mentored by Prof Jerry Shields and Prof Carol Shields at the Wills Eye Hospital, Thomas Jefferson University, Philadelphia, PA, USA. He thereafter established and now heads the comprehensive Ocular Oncology Service at the LV Prasad Eye Institute, Hyderabad, the first such facility in the country. His current research interests comprise of tumors of the ocular surface, orbit, retinoblastoma, and pediatric lacrimal disorders.

Dr Honavar has extensively published in peer-reviewed journals (over 125 manuscripts) and has written several book chapters. The worth of Dr Honavar's scientific work can be gauged by his cumulative citation index of 617, H Index of 16 and G Index of 22. He is the reviewer for American Journal of Ophthalmology, Asian Journal of Ophthalmology, British Journal of Ophthalmology, Clinical and Experimental Ophthalmology, Eye, Indian Journal of Ophthalmology, Journal of Ophthalmic Plastic and Reconstructive Surgery, Ophthalmology and Retina.

Some of the major awards and honors to his credit include Gold Medals and the Best Graduate Award by the Bangalore University for excellence in MBBS, 1988; State Award for Academic Excellence by the Government of Karnataka, 1988; Pfizer Post-graduate National Award & Medallion, 1990; Col Rangachari Gold Medal by the AIOS, 1992; Most-Promising Young Ophthalmologist-in-Research Citation, an International Award by the 'Physicians in Research', USA, 1994, 1996, 1997, and 1998; Best-Resident Award by the Dr Rajendra Prasad Center for Ophthalmic Sciences, All India Institute of Medical Sciences, New Delhi, 1995; ARVO-Santen International Fellowship by the ARVO, 1996; Zeigler International Fellowship by the Orbis International, New York, USA, 1999; Young Scientist Award by the Indian Society of Oncology, 2000; Dr Vengala Rao Award for the best scientific paper by the Andhra Pradesh State Ophthalmological Society, 2001; Achievement Award by the Andhra Pradesh State Ophthalmological Society, 2001; Best of Show Award for the video film by the American Academy of Ophthalmology, 2002; Achievement Award by the American Academy of Ophthalmology, 2002; Best of Show Award for the video film by the American Academy of Ophthalmology, 2006; Dr Surya Prasad Rao Oration by the Andhra Pradesh State Ophthalmological Association, 2006; and Dr Siva Reddy International Award by the AIOS, 2007.

Dr Honavar has been active in the organization of scientific meetings. The International Congress of ocular Oncology that he conducted in 2004 brought together delegates from 66 countries. Sunayana 2007, the annual meeting of the AIOS broke the records in terms of number of delegates and set very high standards. Cutting Edge 2007 proved to be landmark event.

Dr Honavar's overall research contributions that have had very significant impact on the diagnosis and management of retinoblastoma and its outcome. The comprehensive multispecialty Children's Eye Cancer Center that he has established at the LV Prasad Eye Institute in collaboration with the SightSavers international has done pioneering work and is now recognized as one of the best in the World. Dr Honavar is currently the Chairman of the Indian Retinoblastoma Group that plans to work in standardization of diagnosis and management of retinoblastoma across the country.

Despite the recent developments and improved prognosis, delayed diagnosis and treatment has been a major detriment in the management of retinoblastoma. This monograph is an attempt to propagate basic information on the current diagnosis and treatment of retinoblastoma to the peer group. This educational effort is supported by the SightSavers International and the LV Prasad Eye Institute.

## Author

Dr Vijay Anand P. Reddy graduated in 1982 from Osmania Medical College, Hyderabad, one of the prestigious Medical Colleges of India. He was the Best Out-going student and the Most Popular Student Leader of Osmania Medical College.

He then did his post-graduation from MNJ Institute of Oncology, Hyderabad & Tata Memorial Hospital, Mumbai.

Dr. Reddy has thereafter trained and taken the best from the pioneers of current oncological practices, in the Best Oncology Centres in the world- Tata Memorial Hospital, Mumbai; Adyar Cancer Institute, Chennai; Memorial Sloan Kettering Institute, New York, USA; The New York Hospital, Medical Centre of Queens, New York, USA; The New York Medical College, Valhalla, USA; The Booth Memorial, Long Beach Memorial Centre, LA, USA; The Children's Hospital of Philadelphia, Philadelphia, USA; The Middle Sex Hospital, London, UK; The Royal Marsden Hospital, London, UK; The Christ Hospital, Manchester, UK; Peter McCullum Cancer Institute, Melbourne, Australia to name a few.

His areas of interest are Head & Neck Cancers, Brain tumours, Ophthalmic Tumours & Gynaec Cancers.

Dr. Vijay Anand P. Reddy has several publications, national and international, to his credit. He is a very engaging and in the know Speaker and has delivered more than 500 Invited Lectures, extensively across India and Asia. He has also written chapters for several oncology books, to name a few - Proptosis as a Manifestation of Acute Myeloid Leukemia – Paediatric Clinics of North India 2008; Surgical Atlas of Orbital Diseases 2009; Breast Cancer Management (In Press). With a keen interest in academics, he is also the faculty for the Indian College of Radiation Oncology (ICRO) Course.

During his journey as a specialist, he has several awards and honours to his credit – "INTERNATIONAL CANCER RESEARCH TECHNOLOGY TRANSFER AWARD", Awarded in 1992, 1996 by UICC, Geneva, Switzerland; "NARGIS DUTT MEMORIAL FOUNDATION AWARD" 1995, Awarded by Nargis Dutt Memorial Foundation, Flushing, New York, USA; "BEST SCIENTIFIC PAPER AWARD" 1996, at XVIII National Conference of Assoc. Oncologists of India" at Aurangabad, India; "YOUNG SCIENTIST AWARD" 1996, Awarded by Indo-American Cancer Congress, New York, USA 1996; "YOUNG INVESTIGATOR'S AWARD" 2001, Awarded at New Delhi by Eli Lilly & Company, USA; "BEST POSTER" AWARD 2008, Awarded by American Academy of Ophthalmology at Atlanta, GA, USA.

Other than an astute clinician, he is also has leadership skills well-expressed as the Secretary of OMC- Student Chapter, President of AROI – AP Chapter, Secretary General of Indian College of Radiation Oncology (ICRO).

Dr Reddy is eager to imbibe new breakthroughs in oncology and contribute to his patients and peers. He is an active member of American Society of Clinical Oncology (ASCO), American Society for Radiation Oncology (ASTRO), European Society of Medical Oncology (ESMO), "International Union Against Cancer", UICC, Geneva, Association of Radiation Oncologists of India (AROI), Indian College of Radiation Oncology (ICRO), Indian Society of Oncology (ISO), Indian Brachytherapy Society (IBS).

Due to his passion for intellectual exchange, Dr. Reddy has been very active, often instrumental in organizing several academic meetings like the AROICON National meet - 1992; Intra Coronary Brachytherapy Conference - 1997, 1999; ISO – 2001; International Ocular Oncology Conference –2004; CANCER CI – 2003, 2006, 2008; 31st National Conference of Association of Radiation Oncologists of India (AROICON) - 2009; and many more. He has also organized several Workshops on Tumour Volume Delineation for IMRT.

From the time when Ocular oncology in India was at its nascent stage, Dr Reddy has been a pioneer in breaking new ground in care specific for the Indian patient and being associated as Consultant Oncologist to L.V. Prasad Eye Institute, the prestigious Eye Institute in India, he feels fortunate to have gained vast experience in treating ophthalmic tumours especially Retinoblastoma.

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# 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 ophthalmoloscope 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 technique 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 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.

## 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 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]

Mutational analysis of the RB1 gene in Indian patients with retinoblastoma

Ata-ur-Rasheed M, Vemuganti G, Honavar SG, Ahmed N, Hasnain S, Kannabiran C.

Ophthalmic Genet. 2002;23:121-8

Twenty-one probands, twelve with bilateral and nine with unilateral retinoblastoma, were screened 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. Six out of seven mutations involved the formation of premature termination codons by means of single base substitutions (2), frameshifts due to splice-site mutations (2), or deletion and duplication (2). One missense mutation was identified. Of the remaining fourteen patients, seven with bilateral disease had no mutations in peripheral blood (7 cases) or tumors (3/7 cases). Analysis of the peripheral blood of seven patients with unilateral disease also showed no mutations. Mutations were detected in about one-third of the cases, suggesting that hemizygous deletions at the RB1 locus or mutations outside the coding regions of RB1 may be responsible for the disease in the remaining patients.

Mutational screening of the RB1 gene in Indian patients with retinoblastoma reveals eight novel and several recurrent mutations

Kiran VS, Kannabiran C, Chakravarthi K, Vemuganti GK, Honavar SG

Hum Mutat. 2003; 22:339

Retinoblastoma is the most common primary intraocular malignancy in children, caused by inactivation of the RB1 gene on chromosome 13. We carried out a mutational screen 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 disease. Forty-seven patients were screened for mutations in all exons and promoter of the RB1 gene by single strand conformation polymorphism followed by sequencing. Tumors were available from 27 patients (12 bilateral and 15 unilateral retinoblastoma) while only peripheral blood was available from 20 patients, all with bilateral disease. Mutations were found in 22 patients, 9 from the analysis of tumors and 13 from peripheral blood. Eight novel mutations were identified, including 4 single base changes, 2 small deletions and 1 duplication. These are 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). Almost all mutations produced nonsense codons or frameshifts. Recurrent mutations, especially at CpG sites were seen predominantly. Detectable mutations in exons were found in 46% of patients tested. Large deletions, epigenetic changes as well as mutations in non-coding regions may be the cause of disease in the remainder of patients. Knowledge of the full range of mutations can aid in the design of screening tests for individuals at risk.

## Histopathology of Retinoblastoma

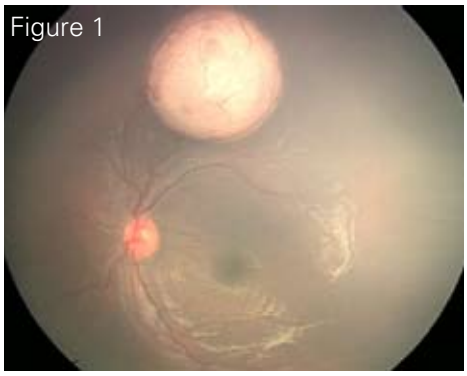
On low magnification, basophilic areas of tumor are seen along with eosinophilic areas of necrosis and more basophilic areas of calcification within the tumor. Poorly differentiated tumors consist of small to medium sized round cells with large hyperchromatic nuclei and scanty cytoplasm with mitotic 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 (precipitated DNA released after tumor necrosis) can be found in the walls of the lumen of blood vessels. [2]

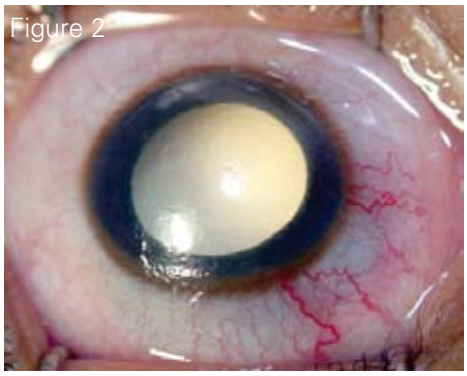
## Clinical Manifestations of Retinoblastoma

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 signs and symptoms 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.

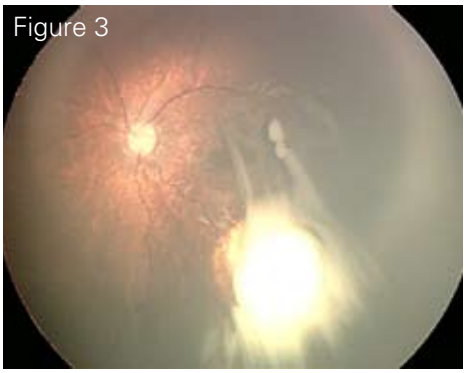
Moderately advanced lesions usually present with leucocoria due to the reflection of light by the white mass in the fundus (Figure 2). As the tumor grows further, three patterns are usually seen: [10]

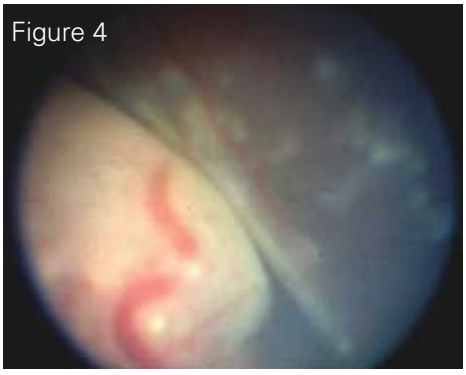
- Endophytic, in which the tumor grows into the vitreous cavity (Figure 3). A yellow white mass progressively fills the entire vitreous cavity and vitreous seeds occur. The retinal vessels are not seen on the tumor surface.
- Exophytic, in which the tumor grows towards the subretinal space (Figure 4).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

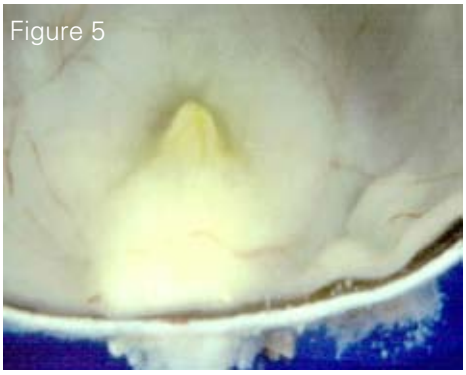
Figure 1. Early manifestation of retinoblastoma with a localized tumor at the posterior pole

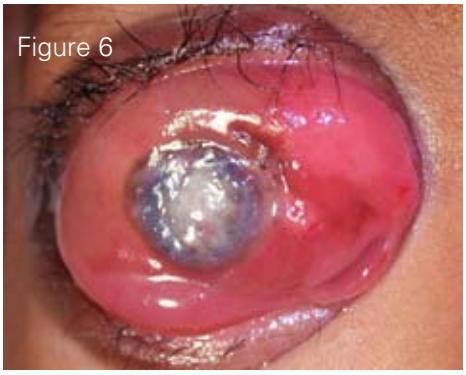
Figure 2. Lecocoria is the most common clinical presentation of retinoblastoma

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.

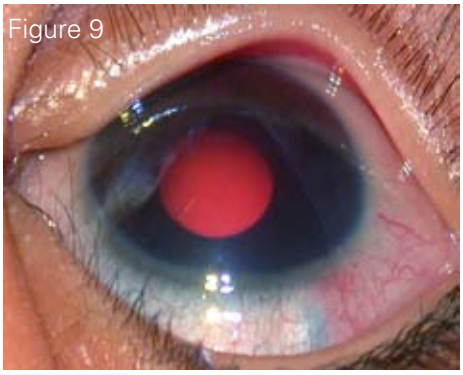






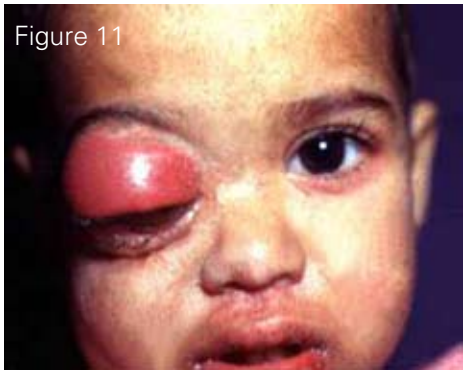



Figure 3. Endophytic tumor with vitreous seeds

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.

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

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]

## 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]

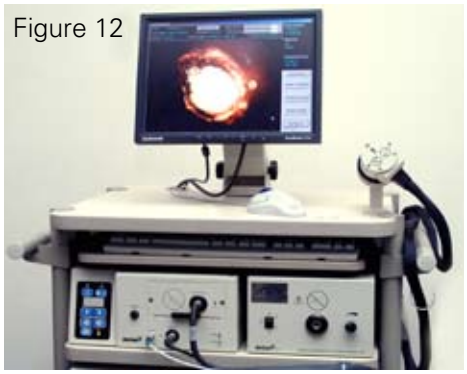
A child with suspected retinoblastoma necessarily needs complete ophthalmic evaluation including a dilated fundus examination under anaesthesia.[10] The intraocular pressure is measured and the anterior segment is examined for neovascularization, pseudohypopyon, hyphema, and signs of inflammation.[10] 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]

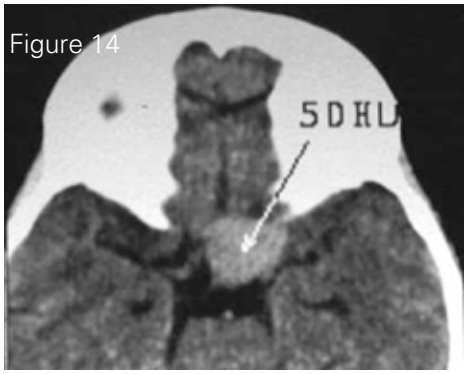
## Classification of Retinoblastoma

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







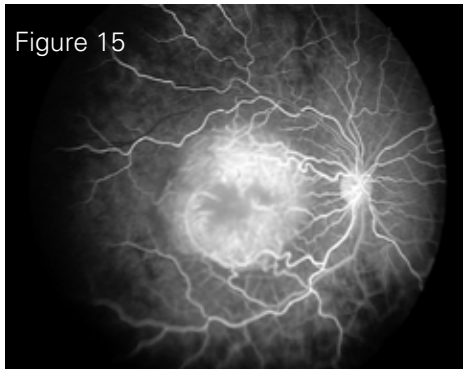




Figure 12. RetCam, a wide-angle digital fundus camera and image archival system helps in documentation and assessment of tumor regression on follow-up

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

**Table 2. International Classification of Intraocular Retinoblastoma**

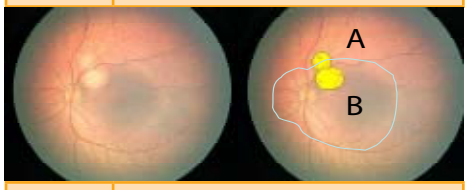
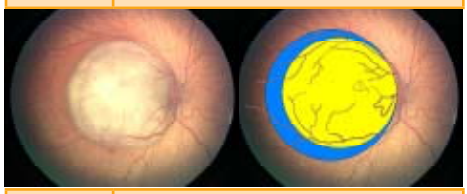
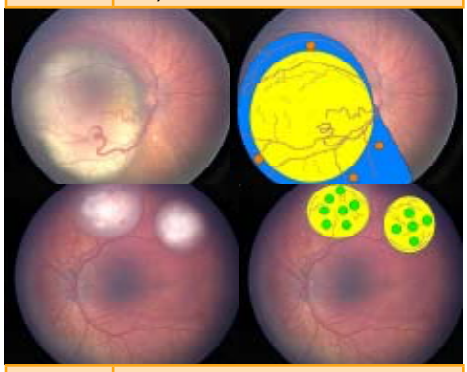
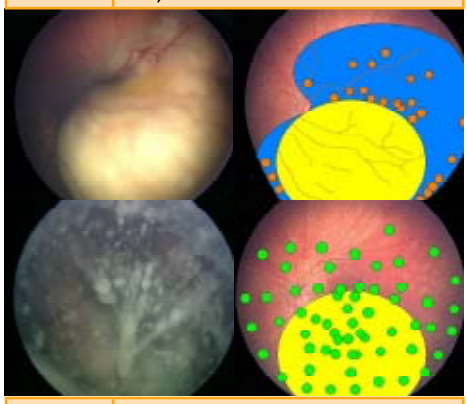
| | |
|---|---|
| Group A | Small tumors (< 3 mm) outside macula |
| |   |
| Group B | Bigger tumors (> 3 mm) or any tumor in macula or any tumor with subretinal fluid |
| |  |
| Group C | Localized seeds (subretinal or vitreous) |
| |  |
| Group D | Diffuse seeds (subretinal or vitreous) |
| |  |
| Group E | Tumor touching the lens, Neovascular glaucoma, Tumor anterior to anterior vitreous face involving ciliary body or anterior segment, Diffuse infiltrating retinoblastoma, Opaque media from hemorrhage, Tumor necrosis with aseptic orbital cellulitis, and Phthisis bulbi |
| |  |

**Table 3. 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 |
| | A Overt orbital disease |
| | B Preauricular or cervical lymph node extension |
| Stage IV | Metastatic disease |
| | A Hematogenous metastasis |
| | 1 Single lesion |
| | 2 Multiple lesions |
| | B CNS Extension |
| | 1 Prechiasmatic lesion |
| | 2 CNS mass |
| | 3 Leptomeningeal disease |

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 (Table 2). [23, 24]

The new International Staging system is the first such for retinoblastoma and incorporates five distinct stages (Table 3). [25] Staging is based on collective information gathered by the clinical evaluation, imaging, systemic survey and histopathology.

## 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, genetist and an ophthalmic oncopathologist. The management strategy depends on

| Table 4. 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 (< 3mm 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 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 chemotherapy for 12 cycles |
| F. Hematogenous or Central Nervous System Metastasis, International Staging, Stage 4 | |
| 1. | Palliative therapy in discussion with the family |

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 4).

## Management of Intraocular Retinoblastoma

A majority of children with retinoblastoma manifest at the 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 for life, eye and possible vision salvage.

There are several methods to manage intraocular retinoblastoma - focal (cryotherapy, laser photocoagulation, transpupillary thermotherapy, transscleral 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.

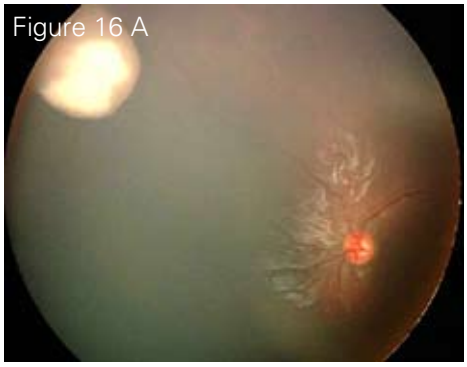
### Cryotherapy

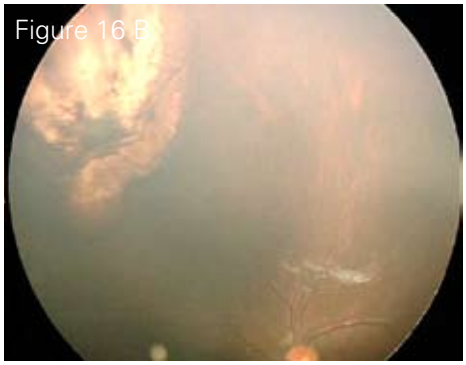
Cryotherapy is performed for small equatorial and peripheral retinal tu-

mors 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]

## Laser Photocoagulation

Laser photcoagulation 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 coagulate 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. 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. [10]



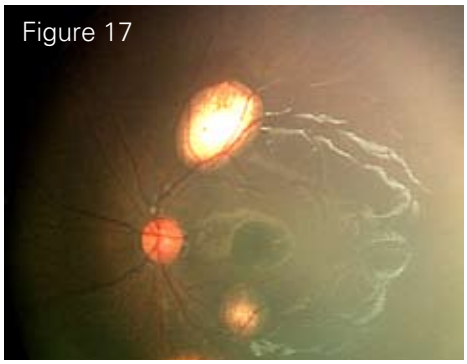




Figure 16. A peripheral retinal tumor that underwent Cryotherapy (16 A). The tumor has completely regressed but the scar is much larger than the tumor itself (16 B)

Figure 17. Two 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.

## Thermotherapy

In thermotherapy, focused heat generated by infrared radiation is applied to tissues at subphotocoagulation levels to induce tumor necrosis.[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 a 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 are focal iris atrophy, focal paraxial lens opacity, retinal traction and serous retinal detachment. 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 with chemoreduction protocol is termed chemothermotherapy.

## 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 less than 16 mm in basal diameter and less than 8 mm thickness.

| Table 5. Current Indications of Plaque Brachytherapy in RB | |
|---|---|
| 1. | Residual or recurrent tumor following chemoreduction and/or focal treatment |
| 2. | Contraindication to Chemotherapy |
| 3. | Primary treatment of an isolated Group B tumor |

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.

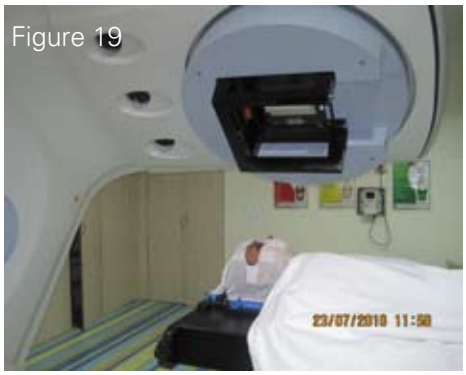
Plaque brachytherapy requires precise tumor localization and measurement of its basal dimensions. The tumor thickness is measured by ultrasonography. The data is used for dosimetry on a three-dimensional computerized tumor modeling system. The plaque design is chosen depending on the basal tumor dimensions, its location, and configuration. 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 by either Cobalt-60 (γ-rays) or Linear Accelerator (X-rays). It is preferable to use Linear Accelerator (Figure 19) with multibeam technique with open eyes (Figure 20) (multibeam IMRT).

Newer methods of delivering External Beam Radiotherapy are being used to increase dose conformity to the target, minimize dose to the surrounding structure and to reduce toxicity (Figure 21&22). These include Intensity Modulated Radiotherapy (IMRT), Image Guided Radiotherapy (IGRT), Stereotactic Radiotherapy (SRT) and Proton Beam therapy.



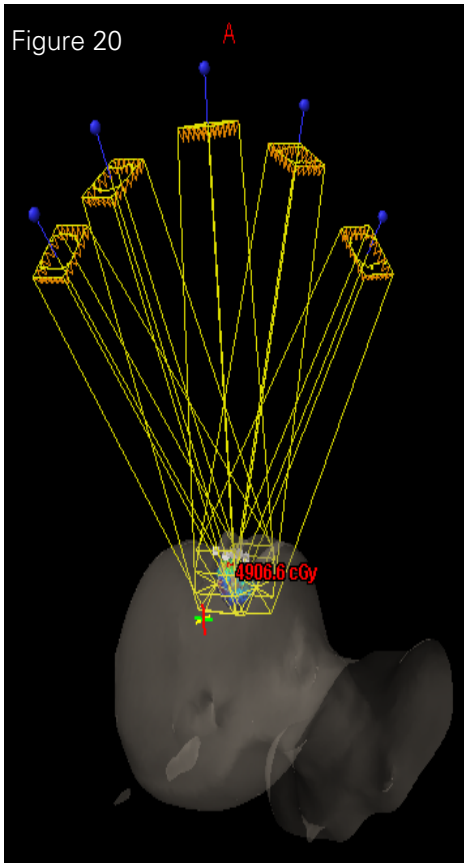
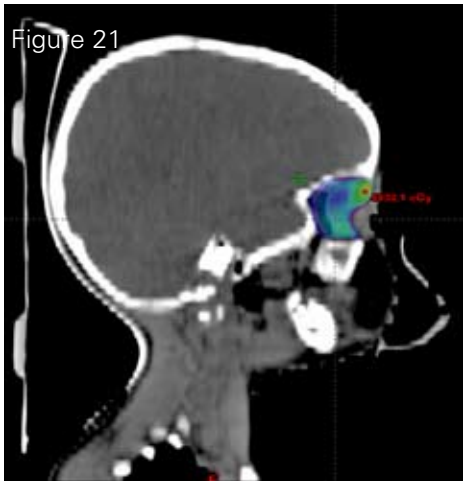
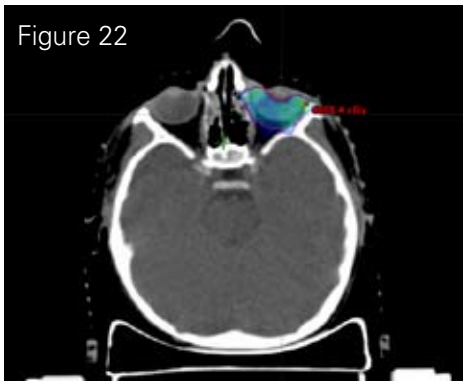




Figure 18. Ruthenium 106 plaque
Figue 19: Treatment Position - Linear Accelerator
Figure 20: Multi Beam IMRT




| Table 6. The indications of external radiotherapy | |
|---|---|
| 1. | Residual disease after Chemotherapy and local therapy |
| 2. | Diffuse vitreous seeds |
| 3. | Recurrence after chemotherapy |
| 4. | Post enucleation – High risk features<br>a. Sclera involvement<br>b. Extraocular extension<br>c. Optic nerve involvement |

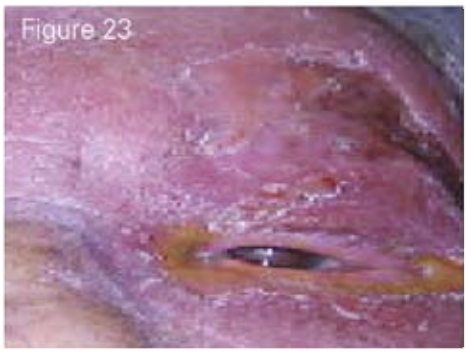
The total dose of Radiation to be delivered ranges from 3500 cGy to 4600 cGy depending on alternate day or daily fractionation and dose per fraction.

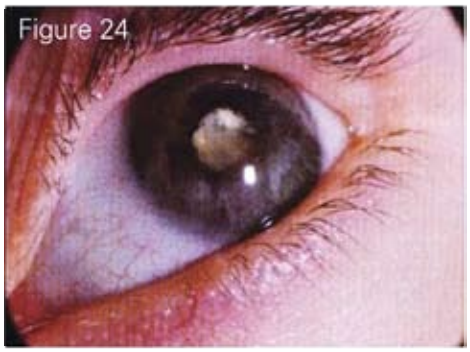
The major problems with external beam radiotherapy are the stunting of the orbital growth, dry eye, cataract, radiation retinopathy and optic neuropathy (Table 7, 8, 9, 10; Reference: 62, 63, 64, 65, 66).

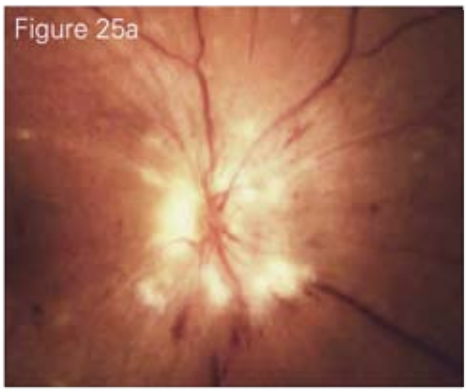
| Table 7. External Beam Radiation Sequelae (Ref. 62, 63, 64) | |
|---|---|
| 1. | Radiation blepharoconjunctivitis (Figure 23) |
| 2. | Dry Eye |
| 3. | Iritis, Neovascular Glaucoma |
| 4. | Cataract (Figure 24) |
| 5. | Radiation Retinopathy and Neuropathy (Figure 25A & 25B) |
| 6. | Orbital and mid-facial growth retardation (Figure 26) |
| 7. | Secondary malignancies (Figure 27) |
| 8. | Neurocognitive deficits |

| Table 8. Radiation effects on the eye and orbital tissues (Ref. 66) | | |
|---|---|---|
| **Tissue** | **Effect** | **Dose (cGy)** |
| Conjunctiva | Conjunctivitis<br>Telangiectasis | 5500-7500<br>3000 |
| Cornea | Keratitis, edema, mild ulcer, scarring, perforation | 3000-5000<br>>6000 |
| Lens | Cataract | 200 (threshold)<br>1600 |
| Retina | Retinopathy | >4650 |
| Optic nerve | Optic neuropathy | >5500 |
| Lacrimal system | Atrophy<br>Stenosis | 5000-6000<br>6500-7500 |
| Eyelid | Lash loss<br>Erythema<br>Telangiectasis | 4000-6000<br>3000-4000<br>>5000 |
| Orbit | Implant extrusion | Not specified |
| **Note:** These are effects seen with conventionally fractionated (<250 cGy/day) megavoltage photon therapy. | | |

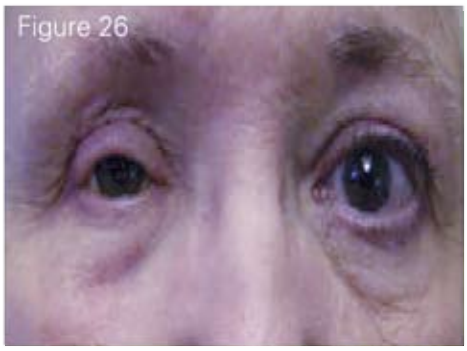
Figure 21 - 22: IMRT - Dose Conformity - Lens Sparing







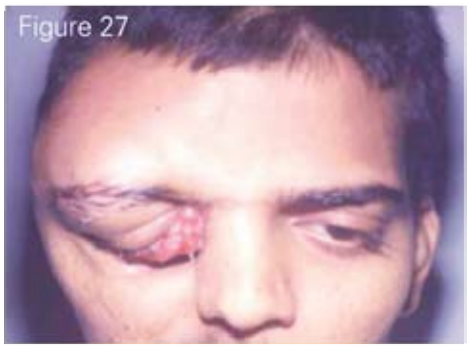




**Table 9. Incidence of Radiation Cataract with EBRT in RB (Ref. 65)**

| Series (Year) | Number of Eyes | Method | Dose (Gy)/fraction no. or dose | Eye Salvage (%) | Incidence of Cataract |
|---|---|---|---|---|---|
| Blach (1996) | 113 | Lateral collimated 6 MV photon field | 42-46/21-23 fraction | 84 | 22 |
| Phillips (2003) | 47 | Single and two field technique | 30-50/2 Gy | 72 | 23 |
| Choi (2010) | 32 | Lateral or ant & lateral 6 MV photon field | 35-55/1.6-2.0 Gy | 74 | 28 |
| Schipper (1983) | 54 | Oblique 6 MV photon enhanced dynamic wedge | 45/15 fraction | 81 | 33 |
| Hermandez (1996) | 34 | Ant & lateral 4 MV photon field | 34.5-49.5/1.5-2.0 Gy | 73 | 41 |

**Table 10. Incidence of Radiation Cataract with Plaque Brachytherapy in RB (Ref. 65)**

| Series(Year) | Number of Eyes | Method | Dose (Gy) to tumor apex | Eye Salvage(%) | Incidence of Cataract (%) |
|---|---|---|---|---|---|
| Abouzeid (2008) | 41 | $^{106}$Ru | 50 | 76 | 10 |
| Schueler (2006) | 175 | $^{106}$Ru | 50-70 | 87 | 17 |
| Shields (2001) | 208 | $^{125}$I, $^{106}$Ru, $^{60}$Co, $^{192}$I | 40 | 79 | 31 |
| Merchant (2004) | 25 | $^{125}$I | 44 | 60 | - |
| Shieldss (2006) | 84 | $^{125}$I | 40 | 95 | 43 |

Figure 23. Radiation blepharoconjunctivitis

Figure 24. Cataract

Figure 25. a&b: Radiation Retinopathy and Neuropathy

Figure 26. Orbital and mid-facial growth retardation

Figure 27. Osteosarcoma of the frontal bone in a 20-year-old patient with bilateral retinoblastoma who had undergone external beam radiotherapy at 1-year age

External beam radiotherapy can induce second malignant neoplasm especially in patients with the hereditary form of retinoblastoma (Figure 27). 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]

## 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 11) Minimum-manipulation surgical technique should be necessarily practiced.[11] It is important 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 important to obtain a long optic nerve stump, ideally more than 15 mm, but never less than 10 mm (Figure 28). [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 stumps may be kept long and traction exerted with an artery clamp. 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 traction on the eyeball.

**Table 11. 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. | Avoid biointegrated implant if postoperative radiotherapy is necessary |

The scissors is moved posteriorly to touch the orbital apex while "strumming" the optic nerve. The scissors is lifted by 3 or 4 millimeters off the orbital apex (to preserve 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 generally 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 inspected for optic nerve (Figure 28) or extraocular extension (Figure 29) of tumor.

Eyes manifesting tumor necrosis with aseptic orbital cellulitis pose specific problem. These patients should be imaged to rule out extraocular extension. Enucleation is best performed when the inflammation is resolved. [11] A brief course of preoperative oral and topical steroids help control inflammation. Patients with retinoblastoma presenting as phthisis bulbi 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 an 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 implants 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 30).

## 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 however not curative and must be associated with intensive local 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, for 6 cycles. [7-10] (Table 12)

Standard dose chemoreduction is provided in ICIOR groups A-C. [10] In high dose chemoreduction, the dose of etoposide and carboplatin is increased. This is indicated in ICIOR groups D tumors. [10]

With chemoreduction and sequential local therapy, it is now possible to salvage many 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

**Table 12. 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/m$^2$ (0.05 mg/kg for children < 36 months of age and maximum dose < 2mg), Etoposide 150 mg/m$^2$ (5 mg/kg for children < 36 months of age), Carboplatin 560 mg/m$^2$ (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 |





Figure 28. Enucleated eyeball showing 18 mm optic nerve stump. Note the proximal portion of the optic nerve is thickened indicating tumor infiltration

Figure 29. Enucleated eyeball showing extrascleral tumor extension.

Figure 30. Retinoblastoma in the right eye following enucleation with orbital implant by the myoconjunctival technique (30 A). Excellent cosmesis follwing fitting of a custom ocular prosthesis (30 B).

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 31 shows a juxtapapillary tumor regressed with chemoreduction alone. Transpupillary thermotherapy was not performed because of the crucial location. Figure 32, 33 and 34 show that the resulting scar with chemoreduction was much smaller than the original tumor with 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 13).

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.

Table 13. 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

### Periocular Chemotherapy

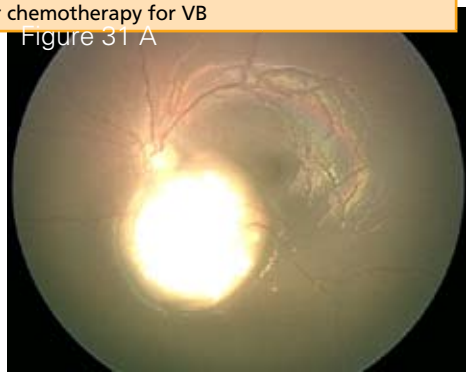
Carboplatin delivered deep posterior subtenon has been demonstrated to be efficacious in the management of Reese Ellsworth Group VB retinoblastoma with vitreous seeds because it can penetrate the sclera and achieve effective concentrations in the vitreous cavity. This modality is currently under trial. Our early results have shown that periocular chemotherapy achieves 70% eye salvage in patients with retinoblastoma with diffuse vitreous seeds (Figure 35).[37]

### Follow-up Schedule

The usual protocol is to schedule the first examination 3–6 weeks after the initial therapy. In cases where chemoreduction therapy has been administered, the examination should be done every 3 weeks 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.

## 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.



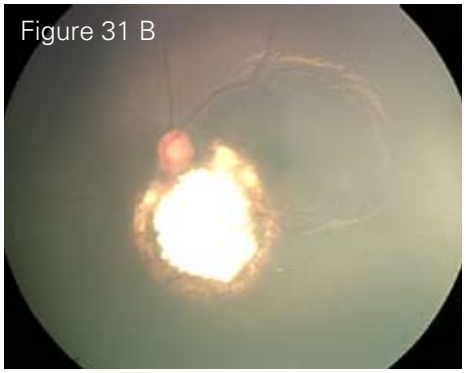
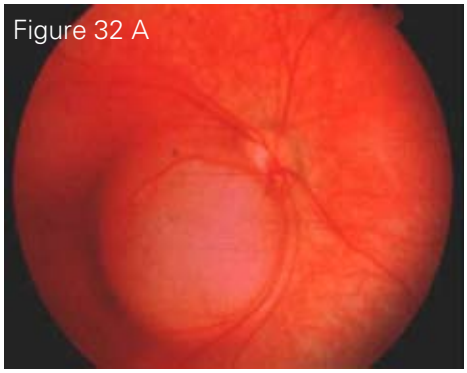
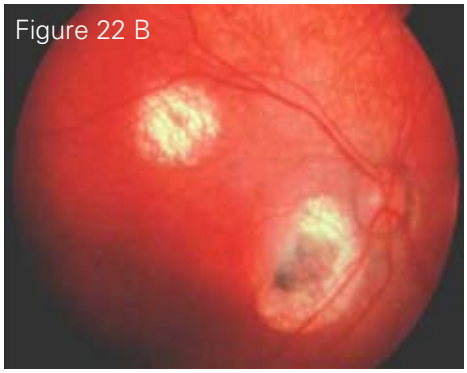
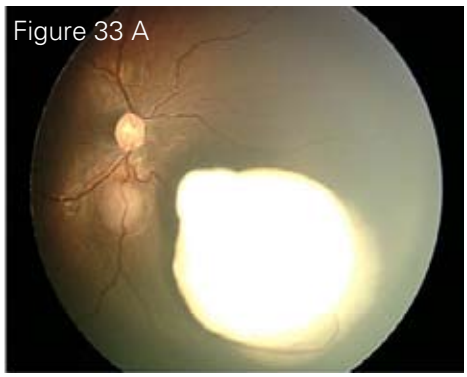
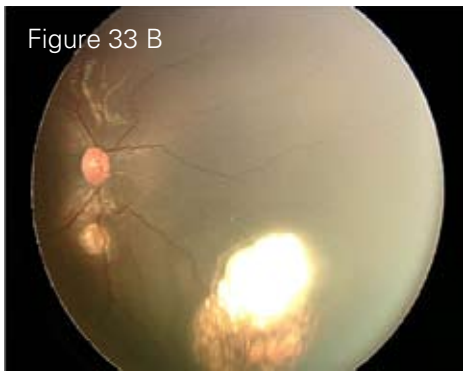



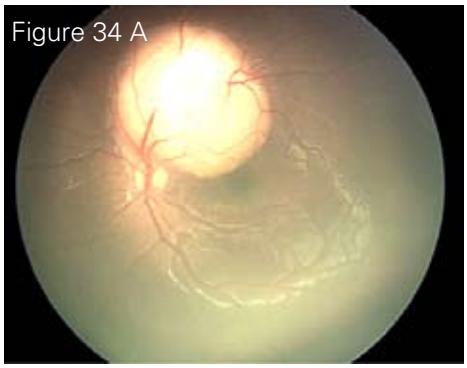

Figure 31. Juxtapapillary retinoblastoma in a 6-month-old child (31 A), completely regressed with 6 cycles of chemoreduction alone (31 B).





## 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 14). [39, 41-49]

Factors predictive of recurrence of retinal tumors, vitreous seeds, and subretinal seeds following chemoreduction for retinoblastoma

Shields CL, Honavar SG, Shields JA, Demirci H, Meadows AT, Naduvilath TJ

Arch Ophthalmol. 2002;120:460-4

OBJECTIVE: To identify the clinical features of eyes with retinoblastomas that predict the recurrence of retinal tumors, vitreous seeds, and subretinal seeds following treatment with chemoreduction. DESIGN: Prospective nonrandomized single-center clinical trial. SETTING: Ocular oncology service at Wills Eye Hospital of Thomas Jefferson University (Philadelphia, Pa) in conjunction with the division of oncology at Children's Hospital of Philadelphia. PARTICIPANTS: There were 158 eyes with 364 tumors in 103 consecutive patients with retinoblastoma managed with chemoreduction between June 1994 and August 1999. INTERVENTION: All patients received treatment for retinoblastoma with 6 cycles of chemoreduction using vincristine, etoposide, and carboplatin combined with focal treatment (cryotherapy, thermotherapy, or plaque radiotherapy) for each retinal tumor. MAIN OUTCOME MEASURES: The 3 main outcome measures included recurrence of retinal tumors, recurrence of vitreous seeds, and recurrence of subretinal seeds. The clinical features at the initial examination were analyzed for their association with the main outcome measures using a series of Cox proportional hazards regressions. RESULTS: All retinal tumors, vitreous seeds, and subretinal

Figure 32. Multifocal retinoblastoma (32 A) following chemoreduction and transpupillary thermotherapy (32 B). Note flat scars that are much smaller than the original tumor.

Figure 33. Multifocal retinoblastoma (33 A) regressed following chemoreduction and transpupillary thermotherapy (33 B).

Figure 34. A juxtapapillary retinal tumor in a 9-month-old child (34 A) completely regressed with 6 cycles of chemoreduction and transpupillary thermotherapy (34 B). Note the completely exposed fovea following treatment, thus maximizing visual potential.

seeds showed an initial favorable response of regression during this treatment regimen. Using Kaplan-Meier estimates, at least 1 retinal tumor recurrence per eye was found in 37% of eyes at 1 year, 51% at 3 years, and no further increase at 5 years. By multivariate analysis, the only factor predictive of retinal tumor recurrence was the presence of tumor-associated subretinal seeds at the initial examination. Of the 54 eyes that had vitreous seeds at the initial examination, vitreous seed recurrence was found in 26% of eyes at 1 year, 46% at 3 years, and 50% at 5 years. By univariate analysis, the only factor predictive of vitreous seed recurrence was the presence of tumor-associated subretinal seeds at the initial examination. Of the 71 eyes that had subretinal seeds at the initial examination, subretinal seed recurrence was detected in 53% of eyes at 1 year, 62% at 3 years, and no further increase at 5 years. By multivariate analysis, factors predictive of subretinal seed recurrence included a tumor base greater than 15 mm and a patient age of 12 months or younger at diagnosis. There were no patients who developed retinoblastoma metastasis, pinealoblastoma, or second malignant neoplasms. CONCLUSIONS: Chemoreduction combined with focal therapy is effective for selected eyes with retinoblastomas. Eyes with subretinal seeds at initial examination are at particular risk for recurrence of retinal tumor and vitreous seeds. Younger patients with large tumors are at risk for recurrence of subretinal seeds. Retinal tumor and subretinal seed recurrence seems to manifest within 3 years of follow-up. Close follow-up of all patients treated with chemoreduction is warranted.

Chemoreduction plus focal therapy for retinoblastoma: factors predictive of need for treatment with external beam radiotherapy or enucleation

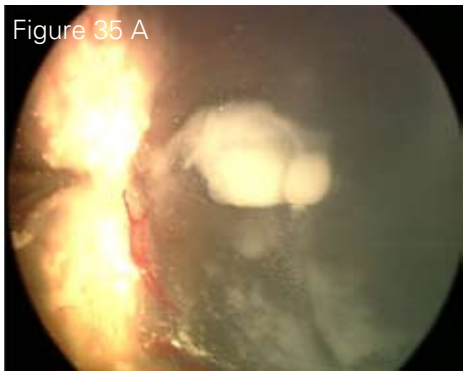
Shields CL, Honavar SG, Meadows AT, Shields JA, Demirci H, Singh A, Friedman DL, Naduvilath TJ

Am J Ophthalmol. 2002;133:657-64

PURPOSE: To report the results of chemoreduction and focal therapy for retinoblastoma with determination of factors predictive of the need for treatment with external beam radiotherapy or enucleation. DESIGN: Interventional case series. METHODS: One-hundred three patients with retinoblastoma (158 eyes with 364 tumors) at the Ocular Oncology Service at Wills Eye Hospital of Thomas Jefferson University in conjunction with the Division of Oncology at Children's Hospital of Philadelphia from June 1994 to August 1999 were enrolled for this prospective clinical trial. The patients received treatment for retinoblastoma with six planned cycles (one cycle per month) of chemoreduction using vincristine, etoposide, and carboplatin combined with focal treatments (cryotherapy, thermotherapy, or plaque radiotherapy). The two main outcome measures after chemoreduction and focal therapy were the need for external beam radiotherapy and the need for enucleation. The clinical features at the time of patient presentation were analyzed for impact on the main outcome measures using a series of Cox proportional hazards regressions. RESULTS: Using Reese-Ellsworth (RE) staging for retinoblastoma, there were nine (6%) eyes with group I disease, 26 (16%) eyes with group II disease, 16 (10%) eyes with group III disease, 32 (20%) eyes with group IV disease, and 75 (48%) eyes with group V retinoblastoma. All eyes showed initial favorable response with tumor regression. The median follow-up was 28 months (range, 2-63 months). Failure of chemoreduction and need for treatment with external beam radiotherapy occurred in 25% of eyes at 1 year, 27% at 3 years, and no further increase at 5 years. More specifically, external beam radiotherapy was necessary at 5 years in 10% of RE groups I-IV eyes and 47% of RE group V eyes. Multivariate factors predictive of treatment with external beam radiotherapy included non-Caucasian race, male sex, and RE group V disease. Failure of chemoreduction and the need for treatment with enucleation occurred in 13% eyes at 1 year, 29% at 3 years, and 34% at 5 years. More specifically, enucleation was necessary in 15% of RE groups I-IV eyes at 5 years and in 53% of RE group V at 5 years. Multivariate factors predictive of treatment with enucleation included patient age older than 12 months, single tumor in eye, and tumor proximity to foveola within 2 mm. Overall, of the 158 eyes, 50% required external beam radiotherapy or enucleation and 50% were successfully managed without these treatments. No patient developed retinoblastoma metastasis, pinealoblastoma, or second malignant neoplasms over the 5-year follow up. CONCLUSIONS: Chemoreduction offers satisfactory retinoblastoma control for RE groups I-IV eyes, with treatment failure necessitating additional external beam radiotherapy in only 10% of eyes and enucleation in 15% of eyes at 5-year follow-up. Patients with RE group V eyes require external beam radiotherapy in 47% and enucleation in 53% at 5 years.

Table 14. Histopathologic high-risk factors predictive of metastasis

| | |
|---|---|
| 1. | Anterior chamber seeding |
| 2. | Iris infiltration |
| 3. | Ciliary body infiltration |
| 4. | Massive choroidal infiltration |
| 5. | Invasion of the optic nerve lamina cribrosa |
| 6. | Retrolaminar optic nerve invasion |
| 7. | Invasion of optic nerve transection |
| 8. | Scleral infiltration |
| 9. | Extrascleral extension |



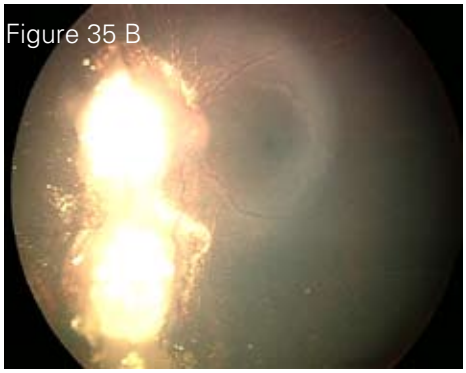




Figure 35. Retinoblastoma with massive vitreous seeds (Figure 35 A). Following 6 cycles of high-dose chemoreduction and periocular carboplatin injection, the tumour and the vitreous seeds show complete regression (Figure 35 B).

Periocular carboplatin as an adjunctive therapy in the treatment of advanced retinoblastoma

Honavar SG, Shome D, Naik M, Reddy VAP

Proceedings of the XII International Congress of Ocular Oncology, Vancouver, Canada, 2005

Purpose: To evaluate the role of periocular carboplatin injections as an adjunctive therapy in retinoblastoma patients, with vitreous seeds.Methods: We studied our first 10 patients with group V B (Reese-Ellsworth classification) retinoblastoma who received deep posterior sub-tenon injections of carboplatin as an adjunctive therapy in addition to systemic chemotherapy. We compared the results with a cohort of 10 patients with similar severity of disease who received similar therapy except that they did not receive periocular carboplatin injections as a part of therapy protocol. The main outcome measures studied were tumor regression and final visual outcome. Results: In the study group, 7 patients (70%) showed complete regression of tumor while 3 patients (30%) had progression of tumor and needed enucleation. In the control group, 3 patients (30%) responded to therapy and 7 patients (70%) required enucleation. Although the above result was not statistically significant (p=0.1789), it was highly significant clinically (40% absolute benefit increase). Side effects included transient periocular inflammation in all. Conclusion: Periocular carboplatin has a potential beneficial role as an adjunctive therapy in the treatment of advanced intraocular retinoblastoma.

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 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.

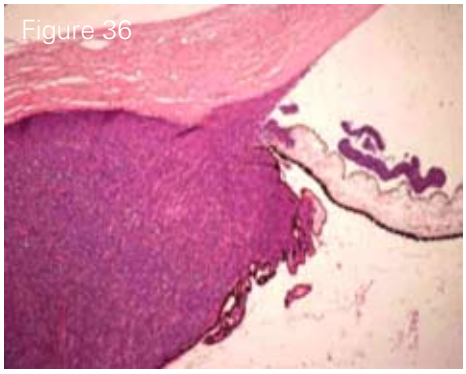
## Adjuvant Therapy

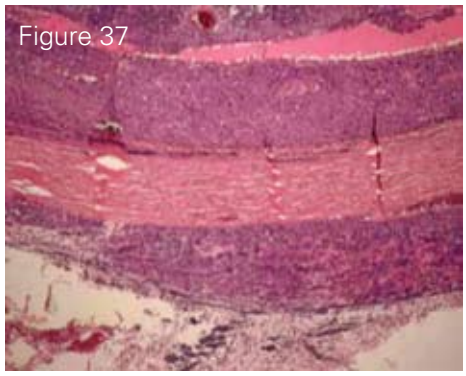
Studies on the efficacy of adjuvant therapy to minimize the risk of metastasis initiated in the 1970s were marked by variable results and provided no firm recommendation. [18] A recent study with a long-term follow-up provides useful information. [13, 50] It included a subset of patients with unilateral 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.

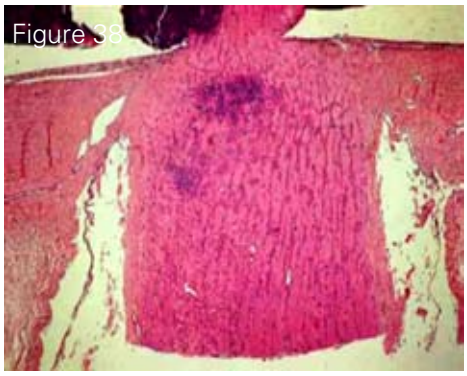
Our current practice is to administer 6 cycles of a combination of carboplatin, etoposide and vincristine (identical to the protocol used for chemoreduction of intraocular retinoblastoma) in patients with histopathologic high-risk characteristics. All patients with extension of retinoblastoma up to the 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.

# 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 multicenter 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]



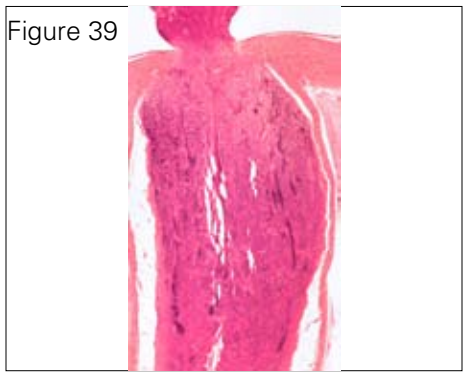




Figure 36. Histopathology of retinoblastoma showing anterior chamber seeding, iris infiltration, trabecular meshwork infiltration and ciliary body invasion.

Figure 37. Histopathology of retinoblastoma showing massive choroidal infiltration, scleral infiltration and extrascleral extension.

Figure 38. Histopathology of retinoblastoma showing infiltration of the optic nerve beyond the lamina cribrosa.

Figure 39. Histopathology of retinoblastoma showing optic nerve infiltration to the level of transection

Postenucleation adjuvant therapy in high-risk retinoblastoma

Honavar SG, Singh AD, Shields CL, Meadows AT, Demirci H, Cater J, Shields JA

Arch Ophthalmol. 2002;120:923-31

PURPOSE: The main purpose of this study was to determine the efficacy of postenucleation adjuvant therapy in preventing metastasis in cases of high-risk retinoblastoma. METHODS: This was a retrospective, nonrandomized comparative study. Of 1020 consecutive patients with retinoblastoma had were managed at a referral center between January 1974 and December 1999, 80 (8%) of those analyzed had unilateral sporadic cases that were treated by primary enucleation and that had high-risk characteristics for metastasis on histopathology reports (anterior chamber seeding, iris infiltration, ciliary body infiltration, massive choroidal infiltration, invasion of optic nerve lamina cribrosa, retrolaminar optic nerve invasion, invasion of optic nerve transection, scleral infiltration, and extrascleral extension). The main outcome measure was the development of metastasis at a minimum follow-up period of 12 months. RESULTS: There were 44 male and 36 female patients, with age ranging from 1 day to 16 years (median, 33 months). A single histopathologic high-risk characteristic was present in 50 patients (62.5%). Thirty patients (37.5%) manifested 2 or more high-risk characteristics. Forty-six patients (58%) had received postenucleation adjuvant therapy (chemotherapy with or without orbital external beam radiotherapy). Adjuvant therapy was not administered in 34 patients (42%). Metastasis occurred in 10 patients (13%) at a median of 9 months (range, 6-57 months) following enucleation. Eight (80%) of those who developed metastasis had not received adjuvant therapy. A significant difference (P =.02) was found in the incidence of metastasis between the group that had received adjuvant therapy (4%; 2/46) and the group that had not (24%; 8/34). The beneficial effect of adjuvant therapy was statistically significant in subgroups of patients with massive choroidal infiltration (P =.04) or retrolaminar optic nerve invasion (P =.04). There were no adjuvant therapy-related serious systemic complications. CONCLUSION: Postenucleation adjuvant therapy is safe and effective in significantly reducing the occurrence of metastasis in patients with retinoblastoma manifesting histopathologic high-risk characteristics.

## Clinical Manifestations

There are several clinical presentations of orbital retinoblastoma.

a. Primary Orbital Retinoblastoma

Primary orbital retinoblastoma refers to clinically or radiologically detected orbital extension of an intraocular retinoblastoma at the initial clinical presentation, with or without proptosis or a fungating mass (Figure 40). Silent proptosis without significant orbital and periocular 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 named secondary orbital retinoblastoma (Figure 41). Unexplained displacement, bulge or extrusion of a previously well-fitting conformer or a prosthesis is an ominous finding suggestive of orbital recurrence.

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 42).

d. Overt Orbital Retinoblastoma

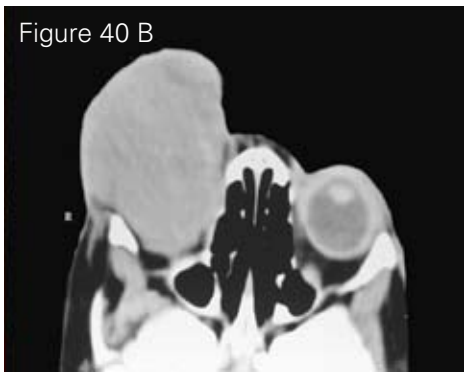
Previously unrecognized extrascleral or optic nerve extension discovered during enucleation qualifies as overt orbital retinoblastoma. Pale pink to cherry red episcleral nodule, generally in juxtapapillary location or at the site of vortex veins, may be visualized during enucleation. An enlarged and 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.

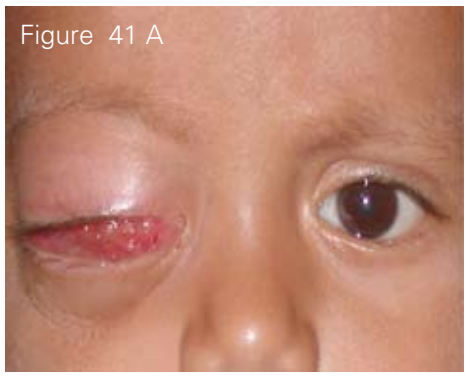
e. Microscopic Orbital Retinoblastoma

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 transection 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.

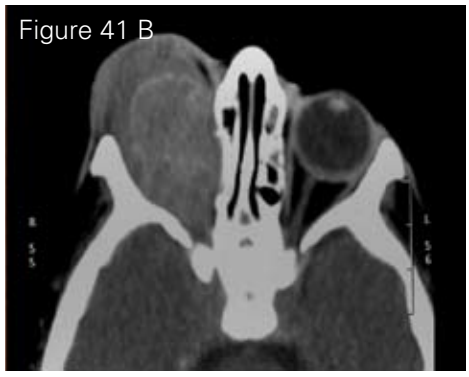
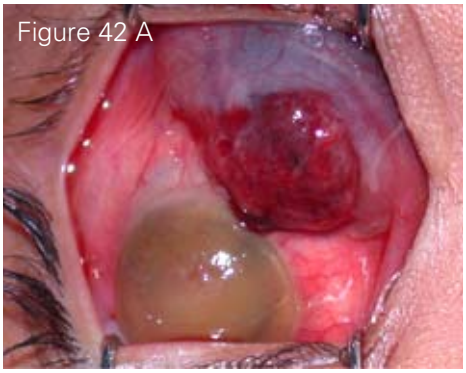




Figure 40. Primary orbital retinoblastoma manifesting with proptosis (40 A). Computed tomography scan shows massive orbital tumor (40 B).

Figure 41. Secondary orbital retinoblastoma following enucleation, manifesting with extrusion of the prosthetic eye (41 A). CT can shows an orbital tumor (41 B).



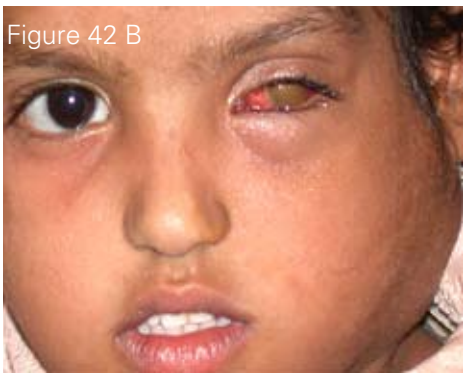




Figure 42. A child with retinoblastoma misdiagnosed as traumatic hyphema in the left eye and treated with hyphema drainage without a baseline ultrasonograpy evaluation presents after 1 year with extraocular extension (42 A) and regional lymph node metastasis (42 B).

## 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 prevent 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), orbital radiotherapy, and additional 12 cycle standard dose chemotherapy.[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 residual 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 43). [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 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. There are specific guidelines for planned intraocular surgery in patients with treated retinoblastoma. [15]

If an extraocular extension is macroscopically visualized during enucleation, special precaution is taken to excise it

Management of orbital retinoblastoma

Honavar SG, Reddy VAP, Murthy R, Naik M, Vemuganti GK

Proceedings of the XI International Congress of Ocular Oncology, Hyderabad, India, 2004

PURPOSE: Retinoblastoma with orbital extension carries poor life prognosis. We aimed to evaluate the results of a multimodality treatment protocol in such cases. METHODS: Prospective clinical trial of an initial 3 cycle high dose chemotherapy followed sequentially by enucleation, orbital radiotherapy and extended 12 cycle chemotherapy in 6 consecutive patients having retinoblastoma with orbital extension. RESULTS: All the patients were free if local recurrence or systemic metastasis at a mean follow-up of 12 months and achieved an acceptable cosmesis. Transient bone marrow suppression was a common complication (75%). CONCLUSION: Early results of a multimodal treatment protocol for retinoblastoma with orbital extension are encouraging.

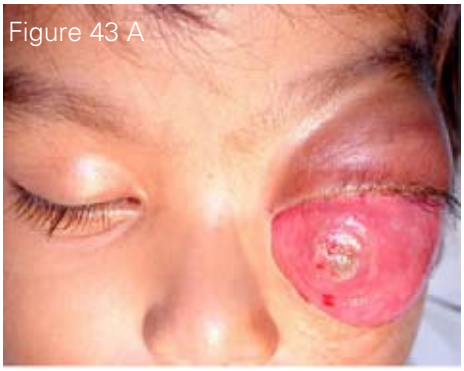


Figure 43 A

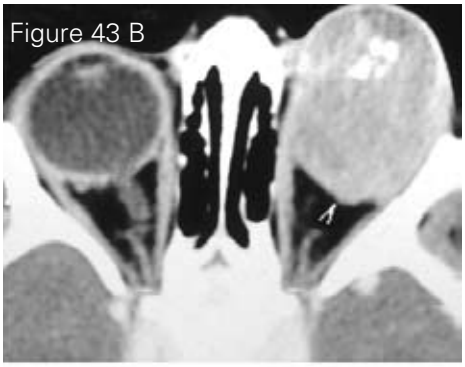


Figure 43 B


Figure 43 C

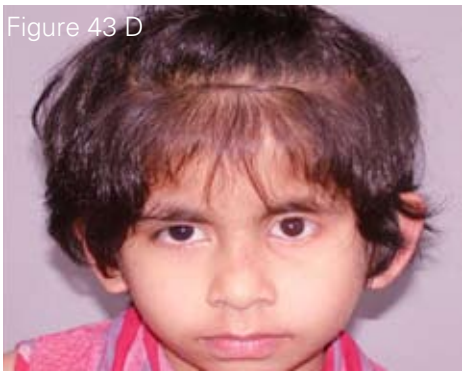


Figure 43 D

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 is recommended. [16]

## 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 aspirations 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 in retinoblastoma 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 10% of patients in advanced countries. However, it is a major contributor to retinoblastoma related mortality in developing nations. Until recently, the prognosis with metastatic retinoblastoma was

Intraocular surgery after treatment of retinoblastoma

Honavar SG, Shields CL, Shields JA, Demirci H, Naduvilath TJ

Arch Ophthalmol. 2001;119:1613-21

OBJECTIVES: To analyze the results of intraocular surgery in patients treated for retinoblastoma and to assess the ocular and systemic outcomes. DESIGN: Retrospective noncomparative case series. PATIENTS: Forty-five consecutive patients who underwent an introcular surgery after treatment for retinoblastoma. MAIN OUTCOME MEASURES: (1) Recurrence of retinoblastoma, (2) need for enucleation, and (3) systemic metastasis. Overall outcome was defined as favorable in the absence of any of these measures and unfavorable in the presence of 1 or more. RESULTS: Thirty-four patients (76%) underwent a single procedure of cataract surgery, a scleral buckling procedure, or pars plana vitrectomy and 11 (24%) underwent a combination of 2 or more surgical procedures. In all, 16 patients (36%) achieved final visual acuity better than 20/200. Unfavorable outcomes included recurrence of retinoblastoma in 14 patients (31%), enucleation in 16 (36%), and systemic metastasis in 3 (7%). Five patients (20%) who underwent cataract surgery, 5 (63%) who underwent a scleral buckling procedure, and 9 (75%) who underwent pars plana vitrectomy manifested an unfavorable outcome. The median interval between completion of treatment for retinoblastoma and intraocular surgery was 26 months in patients with a favorable outcome vs 6 months in those with an unfavorable outcome. CONCLUSIONS: Intraocular surgery after treatment for retinoblastoma may be justified in certain exceptional clinical situations. Cataract surgery is safe and effective in most cases. However, the need for a scleral buckling procedure and pars plana vitrectomy may be associated with a higher risk for recurrence of retinoblastoma, enucleation, and systemic metastasis, and a cautious approach is warranted.

Figure 43. A child with primary orbital retinoblastoma (43 A), showing massive orbital tumor on computed tomography scan (43 B). Following 12 cycles of high-dose chemotherapy, extended enucleation and orbital external beam radiotherapy (43 C). The child is alive and well and wears a custom ocular prosthesis 3 years following completion of treatment (43 D).

Vitrectomy in eyes with unsuspected retinoblastoma

Shields CL, Honavar S, Shields JA, Demirci H, Meadows AT

Ophthalmology 2000;107:2250-5

OBJECTIVE: To analyze patient management and prognosis after vitrectomy in eyes with unsuspected retinoblastoma. DESIGN: Retrospective, noncomparative case series. PARTICIPANTS: Eleven consecutive patients who had undergone vitrectomy on an eye with unsuspected retinoblastoma. MAIN OUTCOME MEASURES: The two main outcome measures were ultimate patient management and the development of retinoblastoma metastasis. RESULTS: Of more than 900 consecutive patients with retinoblastoma managed on the Ocular Oncology Service at Wills Eye Hospital in Philadelphia, 11 (1%) had prior vitrectomy in an eye with viable tumor before referral to us for suspected retinoblastoma. The main preoperative diagnoses included vitreous hemorrhage in seven patients (64%), toxocariasis in two patients (18%), toxoplasmosis in one patient (9%), and endophthalmitis in one patient (9%). In no case was retinoblastoma suspected before vitrectomy. The mean patient age at vitrectomy was 6 years. Retinoblastoma was later suspected during vitrectomy in two patients (18%), on cytologic examination of the vitrectomy specimen in eight patients (73%), and after referral in one patient (9%). The mean interval between vitrectomy and referral to us was 23 days. On examination, the globe was classified as Reese-Ellsworth group Vb in all 11 patients (100%). Anterior chamber tumor cells were clinically visible in four eyes (36%), hyphema in two eyes (18%), and iris neovascularization in two eyes (18%). Retinoblastoma cells were visualized in the vitreous in seven eyes (64%) and not visualized in four eyes (36%) that had vitreous blood. Enucleation was necessary in all 11 patients (100%). Adjuvant treatment was delivered in 10 patients (91%), using orbital radiotherapy in nine patients (82%) and chemotherapy in nine patients (82%). Histopathologic evidence of retinoblastoma invasion was documented in the episclera (two eyes; 18%), anterior chamber (seven eyes; 64%), iris (five eyes; 45%), ciliary body (five eyes; 45%), choroid (three eyes; 27%), and optic nerve (four eyes; 36%; prelaminar, two eyes; postlaminar, two eyes). The vitrectomy ports, Tenon's fascia, cut end of the optic nerve, and orbit were free of tumor. Of the 10 patients who received prophylactic chemotherapy, radiotherapy, or both in addition to enucleation for prevention of retinoblastoma metastasis, none (0%) experienced metastasis or orbital recurrence during the mean follow-up of 7 years (range, 0.2-24 years) from the time of retinoblastoma diagnosis. However, one patient was referred to us after the development of metastatic retinoblastoma, and despite aggressive chemotherapy and radiotherapy after enucleation, died 24 months later. CONCLUSIONS: Retinoblastoma may present with atypical features such as vitreous hemorrhage or signs of vitreous inflammation, particularly in older children. Vitrectomy should be avoided in these cases until the possibility of underlying retinoblastoma is excluded. If vitrectomy is performed in an eye with unsuspected retinoblastoma, enucleation combined with adjuvant chemotherapy, radiotherapy, or both without delay is advised to prevent systemic tumor dissemination.

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 extra ocular 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 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.

## 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. 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.

## References

1. Bishop JO, Madsen EC: Retinoblastoma. Review of current status. Surv Ophthalmol 19: 342-366, 1975.

2. Shields JA, Shields CL. Intraocular tumors – A text and Atlas. Philadelphia, PA, USA, WB Saunders Company, 1992.

3. Albert DM: Historic review of retinoblastoma. Ophthalmology 94; 654-662, 1987.

4. Jackson E: Report of the committee to investigate and revise the classification of certain retinal conditions. Trans Am Ophthalmol Soc 24:38-39, 1926

5. Ata-ur-Rasheed M, Vemuganti G, Honavar S, Ahmed N, Hasnain S, Kannabiran C. Mutational analysis of the RB1 gene in Indian patients with retinoblastoma. Ophthalmic Genet. 2002;23:121-8.

6. Kiran VS, Kannabiran C, Chakravarthi K, Vemuganti GK, Honavar SG. Mutational screening of the RB1 gene in Indian patients with retinoblastoma reveals eight novel and several recurrent mutations. Hum Mutat. 2003;22:339.

7. Shields CL, Honavar SG, Shields JA, Demirci H, Meadows AT, Naduvilath TJ. Factors predictive of recurrence of retinal tumors, vitreous seeds, and subretinal seeds following chemoreduction for retinoblastoma. Arch Ophthalmol. 2002;120:460-4.

8. Shields CL, Honavar SG, Meadows AT, Shields JA, Demirci H, Singh A, Friedman DL, Naduvilath TJ. Chemoreduction plus focal therapy for retinoblastoma: factors predictive of need for treatment with external beam radiotherapy or enucleation. Am J Ophthalmol. 2002;133:657-64.

9. Shields CL, Honavar SG, Meadows AT, Shields JA, Demirci H, Naduvilath TJ. Chemoreduction for unilateral retinoblastoma. Arch Ophthalmol. 2002;120:1653-8.

10. Murthy R, Honavar SG, Naik MN, Reddy VA. Retinoblastoma. In: Dutta LC, ed. Modern Ophthalmology . New Delhi, India, Jaypee Brothers; 2004:849-859.

11. Honavar SG, Singh AD. Management of advanced retinoblastoma. Ophthalmol Clin North Am. 2005;18:65-73.

12. Vemuganti G, Honavar SG, John R. Clinicopathological profile of retinoblastoma in Asian Indians. Invest Ophthalmol Vis Sci 2000; 41(S):790.

13. Honavar SG, Singh AD, Shields CL, Meadows A, Shields JA. Does adjuvant chemotherapy prevent metastasis in high-risk retinoblastoma? Investigative Ophthalmology and Visual Science, 2000, 41(S):790

14. Honavar SG, Rajeev B. Needle Tract Tumor Cell Seeding Following Fine Needle Aspiration Biopsy for Retinoblastoma. Investigative Ophthalmology and Visual Science 1998; 39: S 658.

15. Honavar SG, Shields CL, Shields JA, Demirci H, Naduvilath TJ. Intraocular surgery after treatment of retinoblastoma. Arch Ophthalmol. 2001;119:1613-21.

16. Shields CL, Honavar S, Shields JA, Demirci H, Meadows AT. Vitrectomy in eyes with unsuspected retinoblastoma. Ophthalmology. 2000;107:2250-5.

17. Honavar SG, Reddy VAP, Murthy R, Naik M, Vemuganti GK. Management of orbital retinoblastoma. XI International Congress of Ocular Oncology. Hyderabad, India, 2004. pp. 51.

18. Stallard HB: The conservative treatment of retinoblastoma. Trans Am Opththalmol Soc UK 1962; 82:473-534.

19. Murphree AL, Benedict WF: Retinoblastoma: Clues to human oncogenesis. Science 1984: 223:1028-1033.

20. Knudson AG: Mutation and cancer: Statistical study of retinoblastoma. Proc Natl Acad Sci, USA 1971:68: 820-823.

21. Abramson DH, Frank CM, Susman M, Whalen MP, Dunkel IJ, Boyd NW 3rd. Presenting signs of retinoblastoma. J Pediatr. 1998; 132:505-8.

22. Ellsworth RM. The practical management of retinoblastoma. Trans Am Ophthalmol Soc 1969: 67: 462-534.

23. Linn Murphree A. Intraocular retinoblastoma: the case for a new group classification. Ophthalmol Clin North Am. 2005;18:41-53.

24. Shields CL, Shields JA. Basic understanding of current classi-

fication and management of retinoblastoma. Curr Opin Ophthalmol.2006;17:228-34.

25. Chantada G, Doz F, Antoneli CB, et al A proposal for an international retinoblastoma staging system Pediatr Blood Cancer 2006:47;801-805

26. Shields CL, Santos MC, Diniz W et al. Thermotherapy for retinoblastoma. Arch Ophthalmol 1999; 117: 885-893.

27. Shields CL, Shields JA, Cater J et al. Plaque radiotherapy for retinoblastoma, long term tumor control and treatment complications in 208 tumors. Ophthalmology 2001;108: 2116-2121.

28. Ellsworth RM. Retinoblastoma. Modern problems in ophthalmology. 1977; 96:1826-1830.

29. Hungerford JL, Toma NMG, Plowman PN, Kingston JE. External beam radiotherapy for retinoblastoma: I, whole eye technique. Br J Ophthalmol. 1995; 79: 112-117.

30. Abramson DH, Frank CM. Second nonocular tumors in survivors of bilateral retinoblastoma; a possible age effect on radiation-related risk. Ophthalmology. 1998; 105: 573-580.

31. Shields JA, Shields CL, Sivalingam V. Decreasing frequency of enucleation in patients with retinoblastoma. Am J Ophthalmol 1989; 108:185-8.

32. Ferris FL, 3rd, Chew EY. A new era for the treatment of retinoblastoma. Arch Ophthalmol 1996; 114:1412.

33. Kingston JE, Hungerford JL, Madreperla SA, Plowman PN. Results of combined chemotherapy and radiotherapy for advanced intraocular retinoblastoma. Archives of Ophthalmology 1996; 114:1339-43.

34. Gallie BL, Budning A, DeBoer G, Thiessen JJ, Koren G, Verjee Z, et al. Chemotherapy with focal therapy can cure intraocular retinoblastoma without radiotherapy. Arch Ophthalmol 1996; 114:1321-8.

35. Murphree AL, Villablanca JG, Deegan WF, 3rd, Sato JK, Malogolowkin M, Fisher A, et al. Chemotherapy plus local treatment in the management of intraocular retinoblastoma. Arch Ophthalmol 1996; 114:1348-56.

36. Shields CL, De Potter P, Himelstein BP, Shields JA, Meadows AT, Maris JM. Chemoreduction in the initial management of intraocular retinoblastoma. Arch Ophthalmol 1996; 114:1330-8.

37. Honavar SG, Shome D, Reddy VAP. Periocular carboplatin in the management of advanced intraocular retinoblastoma. Proceedings of the XII Intrernational Congress of Ocular Oncology, Vancouver, Canada, 2005.

38. Abramson DH, Niksarli K, Ellsworth RM, Servodidio CA. Changing trends in the management of retinoblastoma: 1951-1965 vs 1966-1980. J Pediatr Ophthalmol Strabismus 1994; 31:32-7.

39. Singh AD, Shields CL, Shields JA. Prognostic factors in retinoblastoma. J Pediatr Ophthalmol Strab 2000; 37:134-41.

40. Ajaiyeoba IA, Akang EE, Campbell OB, Olurin IO, Aghadiuno PU. Retinoblastomas in Ibadan: treatment and prognosis. West African Journal of Medicine 1993; 12:223-7.

41. Kingston JE, Hungerford JL, Plowman PN. Chemotherapy in metastatic retinoblastoma. Ophthalmic Paediatr Genet 1987; 8:69-72.

42. White L. Chemotherapy for retinoblastoma: where do we go from here? Ophthalmic Pediatr and Genet 1991; 12:115-30.

43. Kopelman JE, McLean IW, Rosenberg SH. Multivariate analysis of risk factors for metastasis in retinoblastoma treated by enucleation. Ophthalmology 1987; 94:371-7.

44. Magramm I, Abramson DH, Ellsworth RM. Optic nerve involvement in retinoblastoma. Ophthalmology 1989; 96:217-22.

45. Messmer EP, Heinrich T, Hopping W, de Sutter E, Havers W, Sauerwein W. Risk factors for metastases

in patients with retinoblastoma. Ophthalmology 1991; 98:136-41.

46. Shields CL, Shields JA, Baez KA, et a. Choroidal invasion of retinoblastoma: Metastatic potential and clinical risk factors. Br J Ophthalmol 1993; 77:544-8.

47. Shields CL, Shields JA, Baez K, Cater JR, De Potter P. Optic nerve invasion of retinoblastoma. Metastatic potential and clinical risk factors. Cancer 1994; 73:692-8.

48. Chantada GL, de Silva MTG, Fandino A, et a. Retinoblastoma with low risk for extraocular relapse. Ophthalmic Genet 1999; 20:133-40.

49. Khelfaoui F, Validire P, Auperin A, Quintana E, Michon J, Pacquement H, et al. Histopathologic risk factors in retinoblastoma: a retrospective study of 172 patients treated in a single institution. Cancer 1996; 77:1206-13.

50. Honavar SG, Singh AD, Shields CL, Demirci H, Smith AF, Shields JA. Post-enucleation prophylactic chemotherapy in high- risk retinoblastoma. Arch Ophthalmol 2002; 120:923-31.

51. Ellsworth RM. Orbital retinoblastoma. Trans Am Ophthalmol Soc 1974;72:79-88.

52. Leal-Leal C, Flores-Rojo M, Medina-Sanson A, et al. A multicentre report from the Mexican Retinoblastoma Group. Br J Ophthalmol 2004;88:1074-1077.

53. Kao LY, Su WW, Lin YW. Retinoblastoma in Taiwan: survival and clinical characteristics 1978-2000. Jpn J Ophthalmol 2002;46:577-580.

54. Badhu B, Sah SP, Thakur SK, et al. Clinical presentation of retinoblastoma in Eastern Nepal. Clin Experiment Ophthalmol 2005;33:386-389.

55. Pratt CB, Crom DB, Howarth C. The use of chemotherapy in extraocular retinoblastoma. Med and Pediatr Oncol 1985;13:330-333.

56. Kiratli H, Bilgic S, Ozerdem U. Management of massive orbital involvement of intraocular retinoblastoma. Ophthalmology 1998;105:322-326.

57. Goble RR, McKenzie J, Kingston JE, et al. Orbital recurrence of retinoblastoma successfully treated by combined therapy. Br J Ophthalmol 1990;74:97-98.

58. Doz F, Khelfaoui F, Mosseri V, et al. The role of chemotherapy in orbital involvement of retinoblastoma. The experience of a single institution with 33 patients. Cancer 1994;74:722-732.

59. Antoneli CB, Steinhorst F, de Cassia Braga Ribeiro K, et al. Extraocular retinoblastoma: a 13-year experience. Cancer 2003;98:1292-1298.

60. Dunkel IJ, Aledo A, Kernan NA, Kushner B, Bayer L, Gollamudi SV, et al. Successful treatment of metastatic retinoblastoma. Cancer 2000; 89:2117-21.

61. Rodriguez-Galindo C, Wilson MW, Haik BG, Lipson MJ, Cain A, Merchant TE, et al. Treatment of metastatic retinoblastoma. Ophthalmology 2003; 110:1237-40.

62. Gordon KB, Char DH, Sagerman RH. Late effects of radiation on the eye and ocular adnexa. Int J Radiat Oncol Biol Phys. 1995;31:1123-39.

63. Alberti W. Acute and late side effects of radiotherapy for ocular disease: an overview. Front Radiat Ther Oncol. 1997;30:281-6.

64. Finger PT. Radiation therapy for orbital tumors: concepts, current use, and ophthalmic radiation side effects. Surv Ophthalmol. 2009 Sep-Oct;54(5):545-68.

65. Choi SY, Kim MS, Yoo S, Cho C, Ji Y, Kim K, Seo Y, Park KD, Lee J, Lee TW. Long term follow-up results of external beam radiotherapy as primary treatment for retinoblastoma. J Korean Med Sci. 2010 Apr;25:546-51.

66. Bardenstein, D.; Char, D. H. Ocular toxicity. In: Madhu, J. J., Flam, M. S., Legha, S. S., Phillips, T. L., eds. Chemoradiation: An integrated approach to cancer treatment. Lea & Febiger; 1993:591-600.

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# Apollo Cancer Hospital Hyderabad

Apollo Cancer Hospitals, Hyderabad is a centre of excellence in cancer care. Modelled on the lines of cancer establishments of international repute, the hospital is committed to provide comprehensive cancer care from prevention to treatment and rehabilitation. Apollo Cancer Hospitals is located in Apollo Health City Campus- a 550-bed tertiary care centre at Jubilee Hills, Hyderabad. Spread over a campus area of 35 acres, the hospital has a built-up area of 190,000 square feet. It has over 50 medical and surgical disciplines each supported by sophisticated technology and experienced medical professionals. Apollo Hospitals, Hyderabad handles close to 100,000 patients a year. International patients from Tanzania, the USA, the UAE, Kenya, Oman and neighbouring Asian countries are treated by the hospital every year. The first ever PET CT scanner in India was installed at Apollo Hospitals, Hyderabad in January of 2005. Thus at Apollo Cancer Hospitals, one has the advantage of not only receiving the services of a stand-alone Cancer unit, but also the expertise and support from a large Super-Speciality group, which results in a holistic approach towards patient care and cure. Each facility offers dedicated services for Comprehensive Cancer Care and is a leader in Surgical, Medical and Radiation Oncology.

Apollo Cancer Hospitals believes that early detection is the key to successful treatment. 'Apollo Cancer Check' - containing a range of investigations which are gender-specific and covering the common cancers is offered.

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