

CMEARTICLE

Retinoblastoma

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ABSTRACT Retinoblastoma is the most common intraocular malignancy in children and one of the very few life-threatening ophthalmic conditions. Genetically, the disease may be heritable or non-heritable. It can have unilateral or bilateral involvement and can present either sporadically or with a positive family history. Leukocoria and strabismus are the most common presentations. Diagnosis is made by indirect ophthalmoscopy aided by imaging techniques. Multidisciplinary management is aimed at saving lives, salvaging the globe and maintaining good vision. The use of neoadjuvant chemotherapy and focal treatments, such as cryotherapy, laser photocoagulation, transpupillary thermotherapy, brachytherapy and periocular chemotherapy, form the mainstay of globe preserving treatment in retinoblastoma. In developing countries, retinoblastoma is unfortunately accompanied by a high mortality rate due to delayed diagnosis made at advanced stages of the disease. Early diagnosis and timely management are vital for a good prognosis.

Keywords: chemoreduction, intraocular tumour, leukocoria, retinoblastoma
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INTRODUCTION

Retinoblastoma (Rb) is a rare malignant intraocular neoplasm that originates in the primordial retinal cells. It represents the most common intraocular malignancy of childhood, accounting for 3% of all paediatric cancers.⁽¹⁾ Rb is one of the very few life-threatening ophthalmic conditions, but it is potentially curable. Early diagnosis and timely treatment with novel therapeutic approaches for Rb has enabled clinicians to save not only a child's life but also the eyeball and vision.

The Rb gene (*RB1*) is located on the long arm of chromosome 13 (13q) and has an autosomal dominant pattern of inheritance. The disease is caused by inactivation of both alleles of the *RB1* gene; several mutations involving exons as well as introns have been identified in the *RB1* gene in children with retinoblastoma. Retinoblastoma can be familial or non-familial.⁽²⁾ It has been estimated that about 40% of tumours are germinal/heritable, with mutations occurring in germ cells. The remaining 60% of tumours are non-germinal/non-heritable, with mutations in non-germinal/somatic cells.⁽²⁾ Non-heritable Rb is unilateral, with the average age of diagnosis at 24 months. Children with heritable Rb have a much earlier age of diagnosis (ranging from newborn to 12 months), and about 85% have bilateral and multifocal eye involvement.⁽²⁾ In addition, heritable Rb is associated with a greater risk of other malignant neoplasms such as osteosarcoma and soft tissue sarcoma. Genetic counselling is thus an important aspect in the care of such patients. It aids in early diagnosis of genetically susceptible family members and also predicts the chances of survivors having children with Rb. However, owing to the high mortality rate of children with Rb in developing countries, most cases are usually sporadic.

CLINICAL PRESENTATIONS: TYPICAL AND ATYPICAL

Leukocoria (white reflex in the pupil) is the most common clinical

presentation of Rb.⁽³⁾ White reflex in a child is more often noticed by parents under dim illumination or during flash photography. As the tumour grows, it becomes a constant observation. Strabismus is the second most common presentation (20%), and is usually associated with macular involvement causing impairment of vision. Proptosis occurs secondary to extraocular spread and is not uncommon in developing countries. Other uncommon or atypical presentations of Rb include cataract, buphthalmos secondary to tumour-related glaucoma, iris nodules resembling chronic granulomatous uveitis, pseudohypopyon or endophthalmitis (masquerade syndrome), aseptic periorbital or orbital inflammation with preseptal/orbital cellulitis-like picture in necrotic tumours.⁽⁴⁾ Another rare presentation is phthisis bulbi as a sequel to necrosis of the tumour; patients with this condition need to undergo imaging to exclude extraocular extension and optic nerve involvement. In more advanced cases, the tumour may extend out of the eye and take the form of a fungating mass or present as a metastatic form with either enlarged regional lymph nodes or signs of intracranial extension (Figs. 1–4).

DIAGNOSIS

Clinical examination aided by appropriate imaging studies is the key to timely diagnosis and successful intervention. A thorough systemic examination is important as a pre-requisite for general anaesthesia, as well as to rule out 13q deletion syndrome, which is marked by the presence of low-set ears, telecanthus, hypertelorism, simian crease in the palms and a broad thumb.⁽⁵⁾

Ocular examination

Ocular examination (staging examination under general anaesthesia) includes anterior segment evaluation (cornea, anterior chamber and iris), which can be easily performed using a surgical or binocular handheld slit lamp microscope. This is followed by

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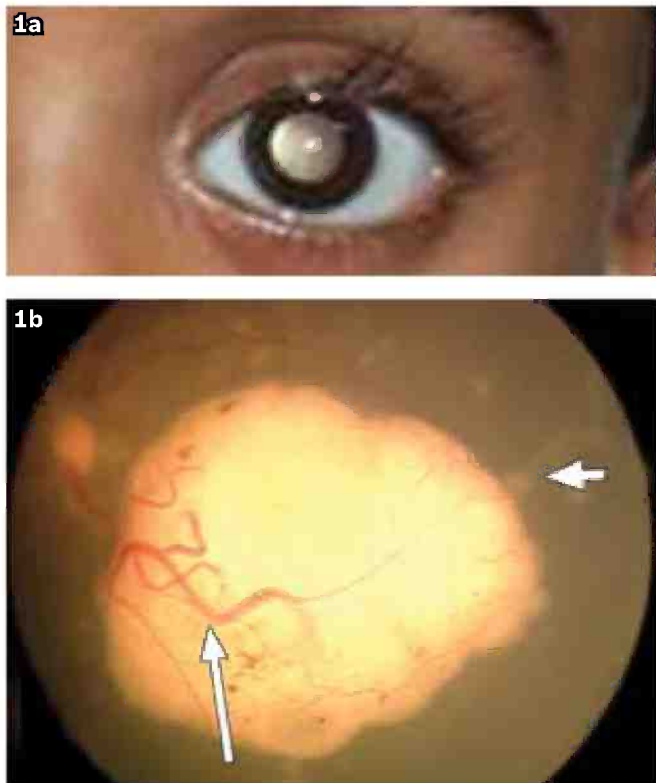


Fig. 1 Retinoblastoma starts in the sensory retina, and may grow into the subretinal space (exophytic) or the vitreous (endophytic) with time. White reflex in the pupil (leukocoria) results from the reflection of light through the pupil by the tumour. Tumours in the posterior pole that are about 3 mm in basal diameter can produce a leukocoria reflex, and leukocoria can be easily documented by flash photography. (a) A three-year-old child with leukocoria in the left eye. (b) Fundus photograph shows a large, creamy-white retinoblastoma tumour growing into the vitreous cavity (endophytic growth pattern), along with seeding into the vitreous and surrounding retina (arrowhead). Note the overlying feeder vessels (arrow).

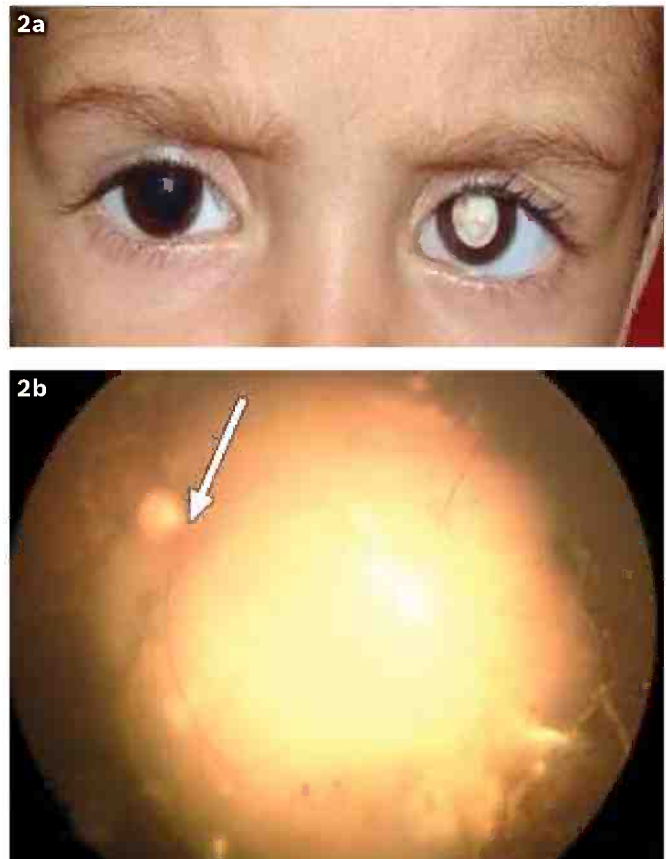


Fig. 2 Strabismus is caused by involvement or obscuration of the fovea by the tumour, resulting in vision impairment. (a) Left esotropia with leukocoria in a two-year-old child. (b) Fundus photograph shows a large retinoblastoma tumour involving the macula, with associated feeder vessels and intense vascularity. Note that the tumour is obscuring the margin of the disc partially (arrow). All children with a history of white reflex through the pupil and squinting of the eye require detailed indirect ophthalmoscopy under anaesthesia to rule out retinoblastoma.

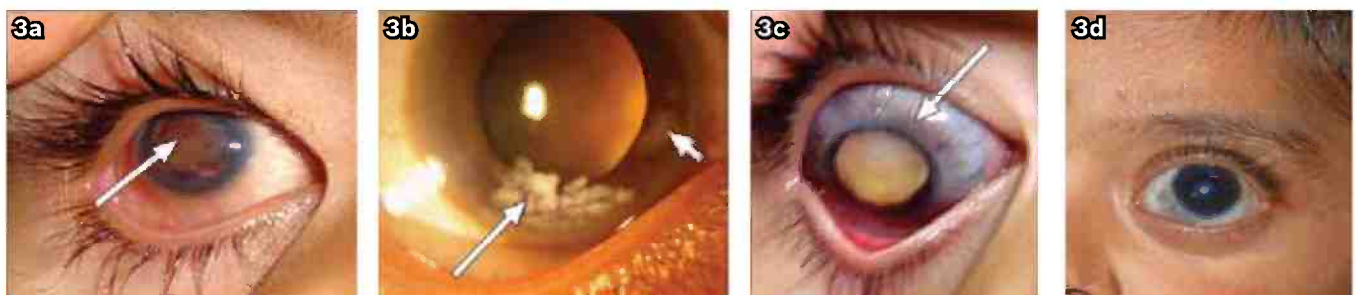


Fig. 3 Atypical clinical presentations of intraocular retinoblastoma. (a) A one-year-old child presented with leukocoria along with blood staining of the cornea (arrow). (b) Endophytic tumour may sometimes involve the anterior chamber, simulating intraocular inflammation (masquerade syndrome). Anterior chamber seeding in a four-year-old child forming a clump in the inferior aspect of the anterior chamber (arrow), along with iris nodules on the iris surface (arrowhead) [reprinted with permission from Atypical presentations of retinoblastoma. JPOS 2004; 41: 18-24] (c) A two-year-old child with a large staphyloma along with central leukocoria. Note the bulging of the thinned out sclera with uveal tissue through the limbus and ciliary body area (arrow). This finding is usually associated with raised intraocular pressure. (d) Another presentation associated with raised intraocular pressure and secondary glaucoma is buphthalmos, presenting with increased corneal diameter and in some cases, associated corneal clouding.

indirect ophthalmoscopy with indentation under full mydriasis to examine the entire retina. A typical Rb lesion in early stages appears as a creamy white tumour with angiomatous dilatation of the vessels. Endophytic Rb, which grows towards the vitreous, is usually associated with vitreous/subretinal seeds. Exophytic Rb, on the other hand, grows outwards and often produces secondary serous retinal detachment. The number of tumours, the tumour size (diameter, thickness), laterality and distance from the optic disc and macula, as well as the presence of subretinal fluid and

sub-retinal/vitreous seeds should be looked for.

Following detailed examination of the eye under general anaesthesia, the tumour is grouped according to the International Retinoblastoma Classification (Group A to E).⁶ This is important for therapeutic decision-making, and enables a practical approach to be taken in order to judge the results of chemotherapy. Wide-field retinal digital imaging system is extremely useful in photographically documenting the size and location of the Rb tumour.

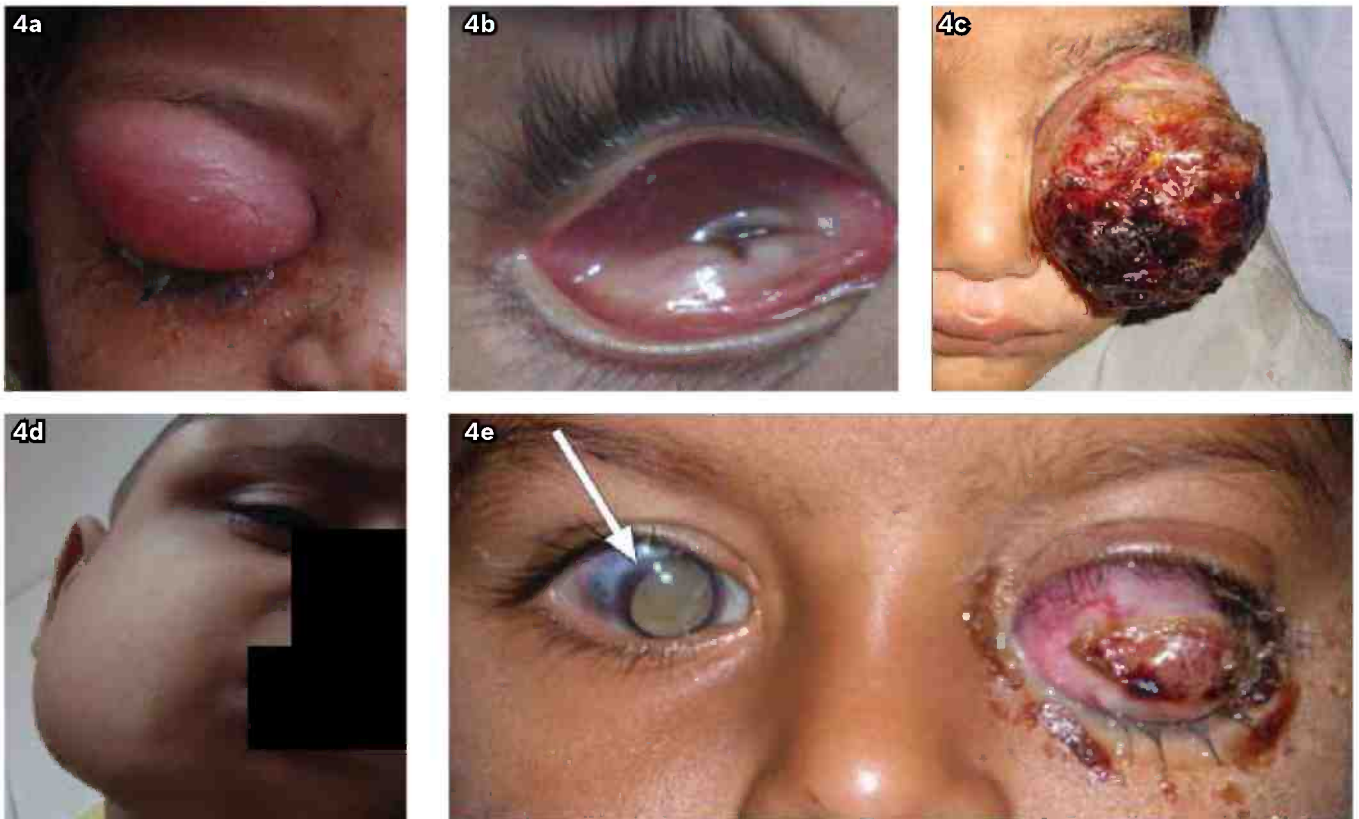


Fig. 4 Clinically advanced retinoblastoma. (a) A large retinoblastoma tumour may become necrotic and produce inflammatory signs similar to those seen in bacterial orbital cellulitis. Note the severe upper lid oedema in this child. (b) In some cases, owing to spontaneous necrosis and regression of the tumour, the eye becomes phthisical. Children presenting with primary phthisical eye require imaging of both eyes and detailed ophthalmoscopic examination of the other eye to rule out retinoblastoma. Photograph shows phthisical eye in a 5-year-old child. Note the disorganised globe where no ocular structures are identified, and the child had advanced intraocular retinoblastoma in the other eye. (c) In some advanced cases, the tumour may extend out from the eye into the soft tissues of the orbit, resulting in massive extraocular involvement or (d) metastatic retinoblastoma. (e) A child presenting with proptosis of one eye and a staphylomatous eye. Note the bluish discoloration of the uveal tissue through the thinned sclera in the supero temporal quadrant of the right eye (arrow).

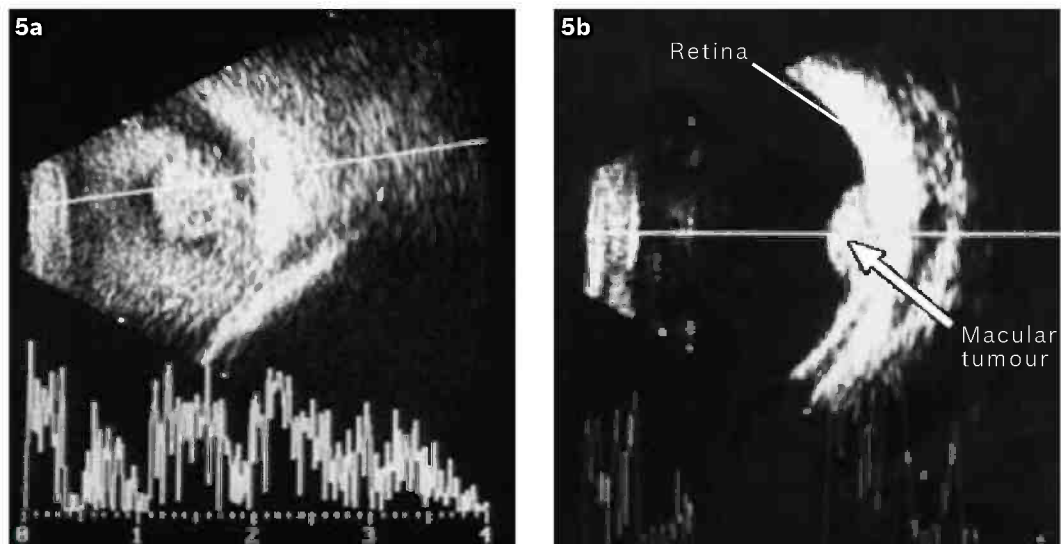


Fig. 5 US is an important diagnostic aid for diagnosis of retinoblastoma and to monitor the tumour size before and after treatment. The usual appearance on the B-scan sonography is that of an acoustically solid mass with high internal reflectivity (representing calcium). B-scan images show (a) a large endophytic tumour with foci of calcification and (b) a medium-sized retinoblastoma revealing a mass with dense echoes (arrow). The child had a macular lesion on indirect ophthalmoscopy.

Imaging studies

Imaging studies, including ultrasonography (US), computed tomography (CT) and magnetic resonance (MR) imaging, are frequently used to diagnose Rb as well as to rule out retrobulbar spread or the presence of intracranial metastasis or associated

pinealoblastoma. US (Fig. 5) is an inexpensive, easily available and non-invasive method to demonstrate Rb as an intraocular mass more hyperechoic than the vitreous, with characteristic calcifications as indicated by high reflectivity.⁽⁷⁾ On A-scan, a combination of low amplitude (corresponding to areas of necrosis

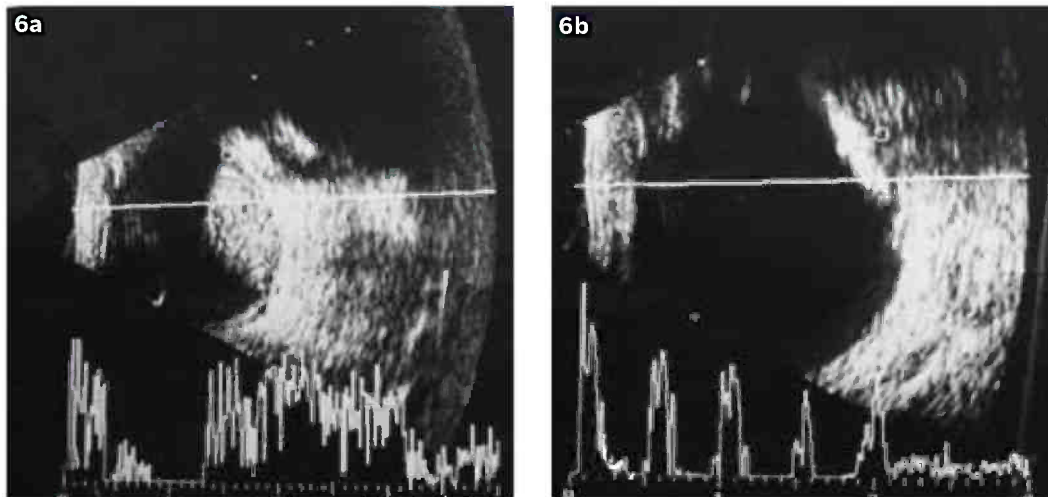


Fig. 6 Serial US A- and B-scans of a child (a) pre-chemotherapy and (b) post-chemotherapy (eight cycles) show a reduction in tumour size.

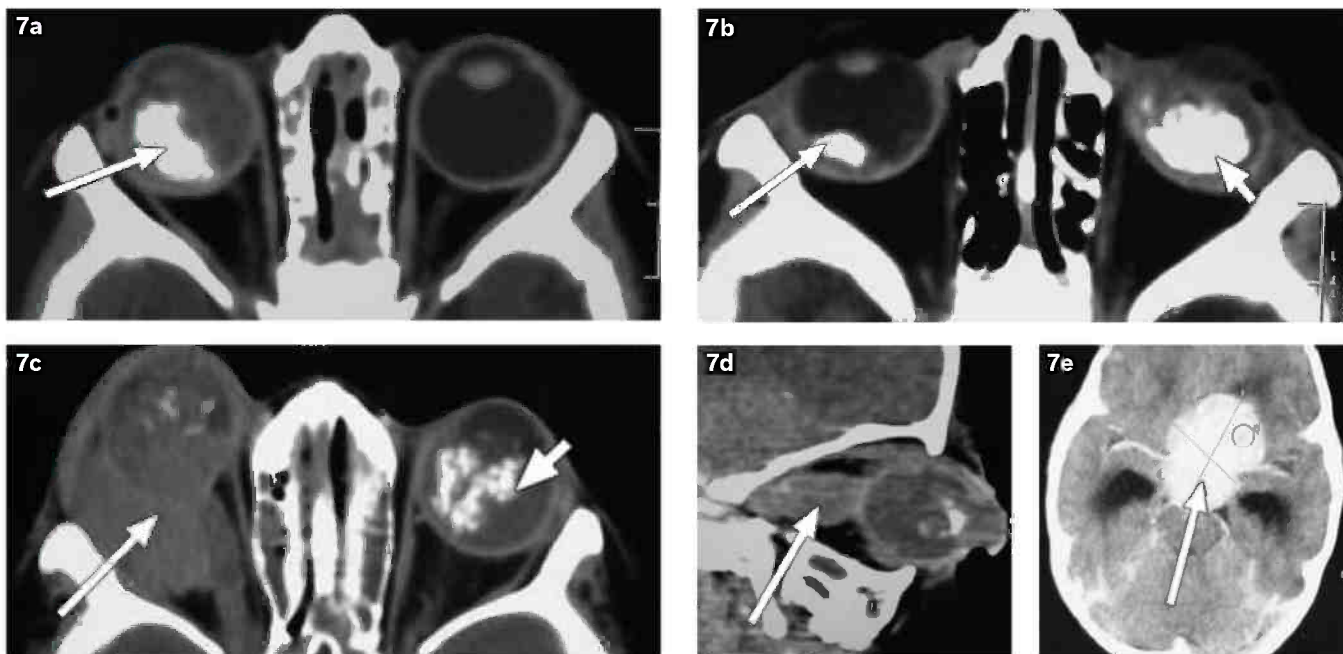


Fig. 7 CT is useful for demonstration of intraocular calcium, and size and extent of the tumour. (a) Axial CT image shows a large calcified retinoblastoma in the right eye (arrow). (b) Axial CT image of bilateral retinoblastoma shows a small calcified tumour in the right eye (arrow) and an extensive calcified tumour in the left phthisical eye (arrowhead). (c) Axial CT image of bilateral retinoblastoma shows advanced intraocular involvement of the left eye (arrowhead) and gross extraocular involvement of the right eye (arrow). (d) Sagittal CT image shows gross thickening of the optic nerve (arrow); and (e) axial sections of the brain shows a suprasellar lesion (arrow) in a child with advanced retinoblastoma.

and high amplitude (corresponding to calcifications) spikes is characteristic. US is also very helpful in monitoring tumour size, especially during chemoreduction (Fig. 6). However, it is less sensitive for very small subtle calcifications and not useful for identification of extraocular spread. When in doubt regarding detection of subtle intraocular calcifications, CT is the preferred imaging modality; however, unlike MR imaging, it involves exposing the child to low-dose radiation. The radiation exposure is important, especially in heritable Rb, as it has been associated with risk of a second malignant neoplasm (SMN).

CT (Fig. 7) typically shows an intraocular mass with a higher density than the vitreous body, calcified in 90% of cases and moderately enhanced after injection of iodine contrast agent. Demonstration of intraocular calcium is highly characteristic for Rb, especially in children below three years of age. Other

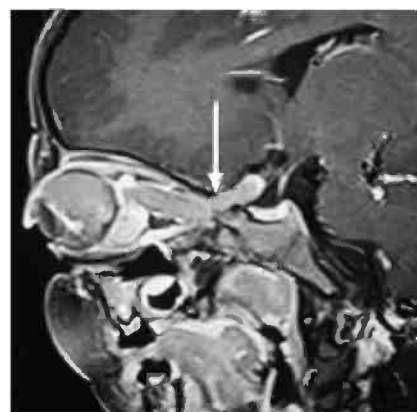


Fig. 8 MR imaging with contrast enhancement provides the best definition of the soft tissues and can detect even small degrees of optic nerve and orbital invasion. T1-W MR image with gadolinium enhancement shows a large intraocular tumour with optic nerve extension beyond the optic canal (arrow).

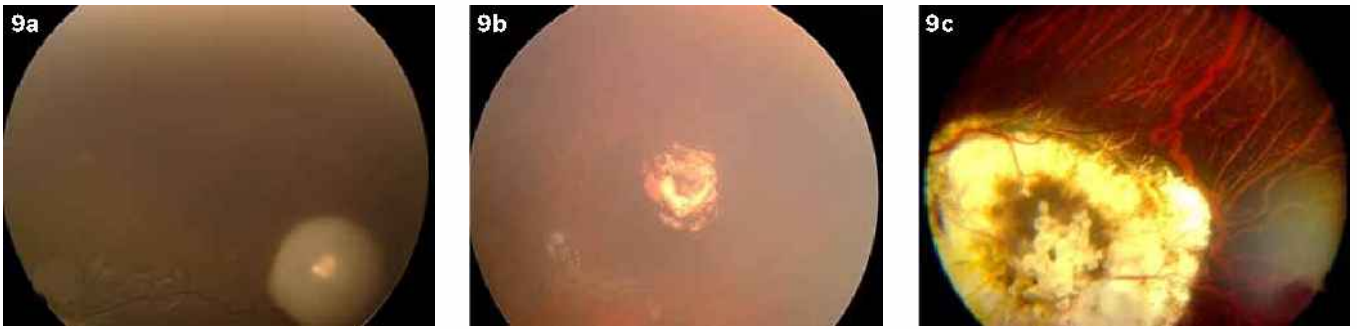


Fig. 9 Retinoblastoma after globe preserving treatments. Wide-angle fundus photographs show (a) an isolated peripheral chemotherapy-reduced tumour with fish-flesh areas and a calcific foci within (mixed pattern regression); (b) a flat scar achieved after laser treatment of a small isolated retinoblastoma lesion; and (c) a large chorioretinal scar with a central, partially regressed calcific tumour residue seen secondary to cryotherapy of a peripheral group B retinoblastoma.



Fig. 10 Photographs show the enucleation specimen (a) of a five-year-old child presenting with advanced retinoblastoma with staphylomatous eye. Note that the tumour has invaded the anterior chamber and extruded through the cornea (arrow). (b) Cut section of the same eye shows the tumour filling the whole globe and invading the anterior chamber completely.

pathological conditions that may be associated with intraocular calcium deposits are microphthalmos with or without colobomatous cyst, retinopathy of prematurity, cytomegalovirus retinitis, toxocariasis, astrocytoma of the retina, medullo-epithelioma and optic nerve drusen.⁽⁸⁾ Spiral CT is considered superior to conventional CT, since it can be done in children without general anaesthesia and is associated with less radiation exposure.⁽⁸⁾

MR imaging (Fig. 8) with gadolinium enhancement and fat suppression is the preferred modality for evaluation of extraocular/ optic nerve invasion, subarachnoid seeding and intracranial involvement, and for diagnosis of rare cases of trilateral Rb (bilateral Rb and pinealoblastoma).⁽⁸⁾ It is also efficient in distinguishing Rb from pseudotumour conditions such as Coats' disease and other differentials. The mass on MR imaging appears isointense or slightly hyperintense to the vitreous on T1-weighted sequences, with a relatively low signal intensity on T2-weighted sequences. As compared to traditional techniques, this newer high-resolution technique has superior contrast and spatial resolution.⁽⁹⁾

Specific investigations for metastasis

Specific investigations for metastasis are conducted only on



Fig. 11 Photograph shows a three-year-old child with a right-sided prosthesis showing satisfactory cosmetic appearance post enucleation.

clinical, imaging or pathological finding suggesting extraocular extension and pointing toward possible metastasis. These include analysis of cerebrospinal fluid, bone marrow biopsy and bone imaging.

DISEASES SIMULATING RB

The three main diseases that often mimic Rb are persistent hyperplastic primary vitreous, Coats' disease and *Toxocara canis* endophthalmitis.^(2,8) Other uncommon differentials that may also present with white reflex include congenital cataract, retinopathy of prematurity, Norrie disease and congenital retinal folds.

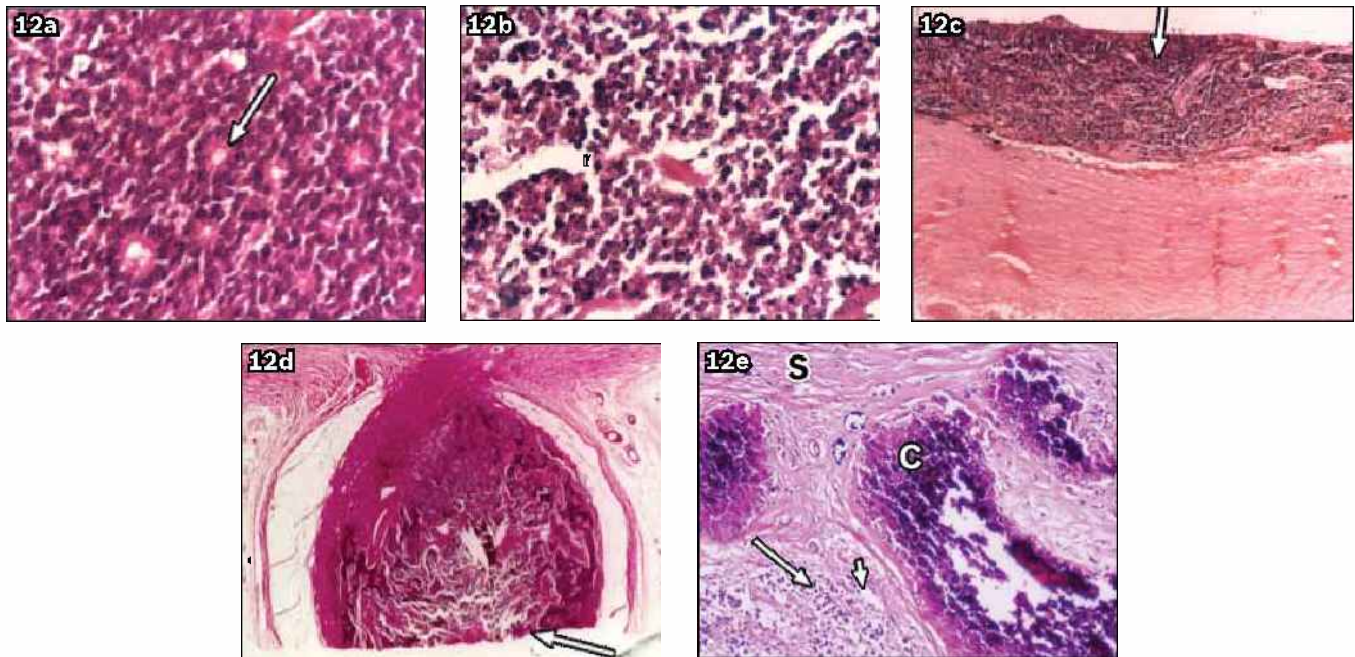


Fig. 12 Microscopically, retinoblastoma is a neuroblastic tumour with viable tumour cells and areas of necrosis and calcifications. Photomicrograph of (a) well-differentiated retinoblastoma tumour shows numerous Flexner-Wintersteiner rosettes (arrow) (Haematoxylin & eosin, $\times 200$); (b) poorly differentiated retinoblastoma tumour shows numerous mitotically active cells with scanty cytoplasm (Haematoxylin & eosin, $\times 200$); (c) low power view shows tumour cells in the choroid (arrow) (Haematoxylin and eosin, $\times 400$); (d) entire optic nerve, including the resected margin (arrow), shows tumour cells (Haematoxylin and eosin, $\times 400$); and (e) post-chemotherapy section of retinoblastoma tumour shows few viable cells (arrow) and plenty of foamy macrophages (arrowhead) (S: sclera; C: calcifications).

MANAGEMENT OF CHILDREN WITH RB

Comprehensive management of Rb requires a multidisciplinary approach. The combined efforts of the ophthalmologist, paediatric oncologist, radiation oncologist and ocular pathologist are aimed at saving the child's life, the affected eye and if possible, vision.⁽¹⁰⁾ The new international classification helps in disease staging, decision on treatment plan and prediction of prognosis with regard to salvaging the affected eye with chemoreduction. The treatment approaches of Rb can best be classified as those that aim to preserve the globe (conservative methods) and those where the globe is to be sacrificed (enucleation).

Conservative management

Conservative management includes chemoreduction, where intravenous drugs are administered to reduce the tumour size, thus allowing the use of focal methods for consolidation of the tumour. Presently, chemoreduction forms the mainstay of globe preserving therapy for early intraocular Rb.⁽¹¹⁾ This has the advantage of avoiding the use of external beam radiation therapy (EBRT), which causes side effects such as cataract, radiation retinopathy and neuropathy and increases the risk of an SMN, facial growth retardation and facial asymmetry. This approach is most successful for localised Rb tumours. The choice of agents, as well as the number and frequency of cycles, varies according to different protocols used; however, the standard regimen consists of six cycles of standard doses of vincristine, etoposide and carboplatin. A major drawback is its ineffectivity in the majority of cases with subretinal/vitreous seeds, which require further management in the form of EBRT or enucleation.

Various focal treatments are available, which can be used either alone or in combination as per requirement. Cryotherapy⁽¹²⁾ is performed for small equatorial and peripheral Rb (3 mm in basal diameter and 2 mm in thickness). In addition to its direct cytotoxic effects, cryotherapy permits a greater influx of chemotherapeutic agents into the vitreous cavity by disrupting the blood retinal barrier. Triple freeze thaw cryotherapy is applied and can be repeated at 4–6 weeks interval until complete tumour regression. Complications include scar progression, edge recurrence and rarely, retinal tear and detachment. Laser application in the form of transpupillary thermotherapy (TTT) has replaced the traditional photocoagulation method of treatment, where two rows of overlapping laser burns are used for delimiting the tumour and coagulating its blood supply. In TTT, hyperthermia of tumour cells by infrared laser causes cell death by apoptosis, thus sparing damage to the blood vessels and preventing associated field defects. TTT can be used alone for small tumours or synergistically with chemotherapy (chemothermotherapy);⁽¹³⁾ the increase in cell temperature increases the uptake of platinum-based chemotherapeutic agents.

Plaque brachytherapy⁽¹⁴⁾ involves the placement of a radioactive implant (Ruthenium-106 and Iodine-125) on the sclera, corresponding to the base of the tumour, to transsclerally irradiate the tumour. Primary plaque brachytherapy is currently indicated in cases of chemofailure, tumour recurrence and where chemotherapy is contraindicated. This method decreases the spread of radiation to the orbit and periorbital area, and prevents any bony problems associated with EBRT. Another major advantage is the reduced risk of SMNs. Periocular chemotherapy



Fig. 13 Complications associated with radiation management of retinoblastoma. Photographs show (a) a severely contracted socket; (b) facial asymmetry associated with radiotherapy treatment in a five-year-old child; and (c) periocular dermatitis associated with radiation.

in the form of carboplatin delivered in the sub-Tenon's space has been shown to be beneficial in Rb with vitreous and subretinal seeds. The major side effects reported are fibrosis, ocular motility disturbance, scleral melting, choroiditis, retinitis, maculopathy and optic neuropathy.

The Rb lesion undergoes changes in size and morphology with chemoreduction and focal treatments (Fig. 9). The regression patterns described for Rb are complete tumour disappearance with no observable scar (type 0), calcified mass showing a cottage-cheese appearance (type 1), less vascular translucent tissue with a fish-flesh appearance (type 2), mixed pattern regression involving both type 1 and 2 (type 3) and tumour regression with a flat atrophic chorioretinal scar (type 4).⁽¹⁰⁾

Enucleation

In recent years, there has been a tremendous decrease in the frequency of primary enucleation. However, it is still a modality of choice for advanced intraocular Rb with anterior chamber tumour invasion, iris neovascularisation, secondary glaucoma, tumours occupying more than 50% of vitreous volume and tumours associated with hyphaema or vitreous haemorrhage where the tumour characteristics cannot be visualised. While enucleating an eye with Rb, minimal manipulation 'no-touch' surgical technique is practised, with special precautions to ensure that the eye is not accidentally perforated during surgery.⁽¹⁵⁾ A long optic nerve stump,

preferably more than 10 mm, minimises the chance of leaving part of the tumour at the resected end. The enucleated eye is examined for macroscopic optic nerve and extraocular extension (Fig. 10), and should be sent for histopathological examination. The use of orbital implants (non-integrated and integrated) and prosthesis helps in achieving an acceptable cosmetic appearance following enucleation (Fig. 11).

HISTOPATHOLOGIC FEATURES

On gross section, Rb appears as a white tumour arising from the sensory retina with or without foci of calcification or necrosis. Microscopically, it is classified into well-differentiated tumours containing Flexner-Wintersteiner rosettes and poorly differentiated tumours with less or absent rosettes.⁽¹⁶⁾ Histopathological high-risk features for recurrence or metastasis include invasion of the optic nerve by the tumour, massive choroidal invasion, orbital extension, and involvement of the anterior chamber, ciliary body and iris (Fig. 12).

EXTERNAL BEAM RADIATION THERAPY

EBRT is reserved for cases that are non-responsive to chemotherapy and those that recurred after completion of treatment. Where histopathological evidence suggests extraocular spread, such as invasion of the resected margin of the optic nerve or scleral involvement, EBRT is also recommended. The main disadvantage

of this therapy is the associated facial cosmetic problems (Fig. 13) and the increased incidence of SMNs. Newer stereotactic methods and intensity modulated radiation therapy aim to deliver radiation in a more localised fashion so as to decrease the chances of SMNs.

GENETIC ANALYSIS

Genetic screening for *RB1* mutation by DNA analysis of the child's tumour and peripheral blood can help in the identification of patients with a germline mutation. This is important in the current management of children with Rb, since it aids planning for better follow-up care, prevents unnecessary examination under anaesthesia and enables early tumour detection in predisposed individuals.⁽¹⁷⁾

MANAGEMENT OF EXTRAOCULAR AND METASTATIC DISEASE

This group of patients has a very poor prognosis with respect to survival. Recent research has shown that a combination of conventional chemotherapy and EBRT is effective in treating regional extraocular spread (orbital, preauricular disease and presence of tumour at the cut end of the optic nerve), and high-dose chemotherapy along with EBRT and bone marrow stem cell transplantation, in treating distant metastatic disease.⁽¹⁸⁾

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