

Community Eye Health Journal



Early diagnosis and treatment can save the life of a child with retinoblastoma. **INDIA**
SWATHI KALIKI

Retinoblastoma: a curable, rare and deadly blinding disease



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Every year, thousands of babies and children in low- and middle-income countries lose their sight and their lives to a treatable childhood eye cancer called retinoblastoma; usually because it was not recognised and treated in time.

Although retinoblastoma is relatively uncommon, it can have devastating consequences for the children affected by it. If treated too late, it can lead to the loss of the eye, invasion of the brain and death.

Retinoblastoma does not affect everyone equally. In high-income countries, fewer than 5% of children die as a result of the condition, thanks to early diagnosis and specialist treatment. In Africa, however, it is typical to see 70% of children with retinoblastoma die, mainly because they presented too late. When mothers do present at a tertiary centre with a child who has advanced retinoblastoma, they often report that they have had several interactions with different health

professionals over many months or even years, but did not get the referral or care they needed. Every health professional reading this issue of the *Community Eye Health Journal* has a chance to redress this balance. We need to find and treat children with retinoblastoma early, before it causes disfigurement or death.

Doing so successfully requires adopting a multidisciplinary, multi-level and internationally collaborative approach that looks at the health system as a whole (see page 4). Raising awareness of retinoblastoma in the community, improving the detection and diagnosis of the condition, setting up good referral systems and offering good

Continues overleaf ►





About this issue

Retinoblastoma is a rare condition with devastating consequences. If left untreated, it can lead to loss of the eye, invasion of the brain and death. In this issue, we offer information and guidance about the detection, diagnosis and treatment of retinoblastoma, including advice about screening

for family members when genetic testing is not available, and a step-by-step guide to enucleation. We hope that every health professional reading this journal will raise awareness of this condition so that – globally – we have a better chance to save the life, eyes and sight of children with retinoblastoma.

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counselling and high quality treatment (including good prosthetics) are all needed to increase the uptake of services and save lives.

Ministry of health

Ministries of health have the power to make dramatic improvements to the early detection and treatment of retinoblastoma. They can:

- Create public health campaigns to raise awareness that 'seeing something white' inside a child's eye is a medical emergency
- Include basic ocular history taking and eye examination techniques in the curriculum of community nurses
- Offer subsidised access to specialist treatment for children with this life-threatening condition.

Parents must be made aware that they should seek help urgently if they see something white inside their child's eyes. Emphasise that parents should not let their child be turned away and must not take 'no' for an answer if they feel there is something wrong.

A worthwhile investment

Investing resources in the early detection and referral of children with retinoblastoma has wider benefits in the fields of childhood blindness in low- and middle-income countries, as the same criteria (something white in the eye) will also help with the early detection of childhood cataract. Late presentation of childhood cataract is the leading cause of treatable blindness in children, and is entirely preventable if cataracts are detected and treated in time.

In the community

Nurses and health workers seeing children in the community can check children's eyes during routine immunisation appointments, for example. **Something abnormal, white or shiny, or a squint, may be the first sign of retinoblastoma and requires urgent specialist referral.** Listen to

Community Eye Health Journal
VOLUME 31 • NUMBER 101 • 2018



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Online edition and newsletter
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Retinoblastoma

When should we suspect?



White reflex



Deviated eye



Red eye



Enlarged eye



Deviated eye with
white reflex

**If you see any of the above features,
see your doctor immediately!**



Shrunken eye

**Recognise the
disease early and
save a child's life**

the parents and/or carers. If they have seen something white or abnormal in their child's eye, believe what they say, take it seriously and seek specialist advice.

In Tanzania, community nurses have been trained to examine the red reflex (p. 23) using an Arclight ophthalmoscope. The Arclight is an affordable, solar-powered and easy-to-use ophthalmoscope. It has shown preliminary promise; the community nurses found it easy to learn and began picking up cases of

cataract and retinoblastoma by using it. Nurses can learn how to examine the red reflex at the same time as examining the child's other systems.

Tertiary centres

At tertiary centres, histopathologists have a crucial role: once the eye is removed the child may be able to leave hospital completely cured or may need chemotherapy

Continues overleaf ➤

**Public health
awareness
campaigns can
support the early
detection of
retinoblastoma**
INDIA

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Published by the International Centre for Eye Health, London School of Hygiene & Tropical Medicine.

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ISSN 0953-6833.

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The *Community Eye Health Journal* is supported by:



or radiotherapy; this decision must be based on accurate histopathological staging (page 18).

International collaboration

To promote this multi-level, multi-disciplinary and internationally collaborative approach, the Commonwealth Eye Health Consortium has provided start-up funding for an Rb-NET known as Rb-NET, which has already generated specific country plans, a set of core outcome indicators, best practice protocols and a practical resource manual (<http://cehc.lshtm.ac.uk/dr-links/rbnet/>).

Basic clinical research questions still need to be answered. For instance, researchers in Uganda have shown an improvement in survival by giving chemotherapy before surgery on the basis that so many children have extra-ocular spread at time of presentation. On the other hand, a small study from Tanzania showed that 60% of children for whom there was good histology after enucleation had complete excision of the tumour with low risk and never needed chemotherapy. So which should come first in these settings – chemotherapy or surgery? By combining multi-centre and multi-country clinical research, as Rb-NET has started to do, we can begin to answer these questions and prevent needless tragedies.

This issue of the *Journal* demonstrates that there is real momentum and determination to improve outcomes for children with Rb in all countries across the world. It contains concise, practical information that should help all of us to make a difference.

I am a child, not a case



Abby White

Chief Executive: World Eye Cancer Hope UK
www.wechope.org

Patients with retinoblastoma are first and foremost children who happen to have cancer in their eye(s). Defining a child as a 'case' dehumanises them and draws attention away from thoughts about their complete wellbeing and that of their family.

A child with retinoblastoma is not a medical specimen. They are a complete individual with thoughts, feelings, hopes, dreams, likes and dislikes. They have the ability to generate every kind of emotion in those who care for them. They are desperately loved, and most parents would give their own eye if it could spare their child's suffering.

In evaluating different treatments, we must weigh the value of each treatment in relation to the child's complete wellbeing. We must look beyond the physical body to embrace and care for the child's emotional health, during therapy and long after into adulthood.

Perhaps if we collectively take care to consider 'children', 'families' and 'survivors' rather than 'cases', we will together establish a level ground on which we can both treat the cancer, and heal the spirit in equal measure to set the child up for a healthy, happy future.

Rb-NET website

<http://cehc.lshtm.ac.uk/dr-links/rbnet/>

Resource manual

<http://cehc.lshtm.ac.uk/resource-manual-for-rb-management-v-sept-1-002/>

Arclight

www.arclightscope.com

Table 1 Roles and responsibilities in the detection, referral and treatment of retinoblastoma

Individual responsibilities			
Parent →	Health worker/nurse →	Ophthalmologist →	Specialist eye centre
<p>Seek help urgently if you see something white inside the centre of the eye (the pupil) OR if you take a photograph and only one eye has a red dot in the centre</p> <p>Do not let anyone turn you away and do not take no for an answer until a doctor at a hospital has examined the child's eyes using a bright light</p>	<p>Believe the parents if they say they have seen something white inside the pupil and seek specialist advice. Treat it as a medical emergency</p> <p>Learn how to test the red reflex (p. 23). Test all children during routine visits and immunisations</p>	<p>Learn to recognise retinoblastoma and to identify eyes that need enucleation</p> <p>Counsel parents about the good cosmetic outcomes of enucleation with implantation. Show pictures of children with good outcomes</p> <p>Learn how to enucleate, taking more than 15 mm of optic nerve. Always examine the fundus of the fellow eye when you perform an enucleation: there could be a small tumour which is treatable by laser</p> <p>Refer all children with signs of retinoblastoma in two eyes to a national or specialist centre for urgent treatment</p>	<p>Same as for ophthalmologists, plus:</p> <p>Learn how to give focal or laser treatment to smaller tumours (usually in the second eye)</p> <p>Create multidisciplinary teams who work closely together to coordinate the treatment of each child</p> <p>Include in this team: ophthalmologists, oncologists, histopathologists, nurses, child life specialists or play therapists and/or counsellors</p> <p>Offer general and genetic counselling to parents/carers</p> <p>Refer parents to other sources of support for their child's learning and development</p>
The Ministry of Health's responsibilities towards the above			
<p>Run public awareness campaigns so that parents know that treatment is possible and know when to see a doctor</p>	<p>Ensure that the red reflex test (p. 23) is included in the curriculum for nurses and health workers</p>	<p>Ensure there is at least one ophthalmologist per 100,000 population</p>	<p>Support the development of national retinoblastoma centres and referral networks. Offer subsidised access to specialist treatment for all children with retinoblastoma. Provide screening services for siblings and accommodation or travel subsidies for the parents or carers of these young children.</p>

A national retinoblastoma network: experiences in Kenya and the UK



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Retinoblastoma is a rare disease. Saving the lives of the children affected requires early detection, good referral systems and expert care by a multidisciplinary team. Setting up a national and joined-up service is an essential first step.



Children who are part of the Child Life programme for retinoblastoma play outside the national retinoblastoma centre in Kenyatta. **KENYA**

Because retinoblastoma is rare, it is sensible to gather those people with the expertise to manage children with retinoblastoma (and the resources and equipment to do so) in one or more designated national centres. In large countries, with high birth rates, several centres must be designated. All retinoblastoma centres in a country need to work together as part of a national service with standard management protocols. The national service must be audited on a regular basis and the data shared at national meetings where all centres that see and treat children with retinoblastoma are represented.

Experiences in Kenya

A study in the year 2000 reviewed the presentation and management of retinoblastoma at Kenyatta National Hospital (the largest referral hospital in Kenya). It showed that there were significant gaps in the management of patients presenting with retinoblastoma. This led to poor outcomes for patients, many of whom were dying. In an attempt to bridge some of these gaps, a retinoblastoma working group was formed involving ophthalmologists, paediatric oncologists, radiation oncologists and pathologists. Due to limited funding and competing job demands, this working group had limited success.

In 2007, the group was contacted by Daisy's Eye Cancer fund (now known as World Eye Cancer Hope) who, together with a retinoblastoma expert from the Hospital for Sick Kids, Toronto, reignited the determination to improve the management of patients with retinoblastoma in Kenya. With their financial support and expertise, the first Kenya National Retinoblastoma meeting was held in 2008 and participants from all over Kenya attended, including ophthalmologists, paediatric oncologists, radio-oncologists, pathologists,

ophthalmic clinical officers, nurses, parents of children with retinoblastoma, retinoblastoma survivors and a child-life specialist (see panel overleaf).

A situation analysis revealed that the challenges were similar in all regions of the country and included:

- Lack of awareness about the disease both among the public as well as medical workers
- Poor referral networks
- Lack of psychosocial and financial support for affected families
- Lack of standardised management protocols
- Delayed and often scanty histopathology reports
- Lack of chemotherapy drugs
- Lack of communication between referral centres
- Poor follow-up of patients.

To address these issues, the group set four broad objectives (with attendant activities).

1. Standardise the management of retinoblastoma

- Design a standardised treatment protocol
- Standardise histopathology reporting using standard request and reporting forms
- Prepare a chemotherapy regimen according to international standards
- Establish sources and funding for the chemotherapeutic agents.

2. Improve awareness about retinoblastoma

- Education of primary health care workers especially those in maternal child health
- Use of the media, retail chains, transport and communication industry to spread awareness among the public
- Nationwide posters about Rb.

Continues overleaf ➤



3. Develop partnerships for resource mobilisation

- Target faith-based organisations, non-governmental organisations, corporates, community development fund and local government authorities for funding
- Organise fund raising events like marathons/ walks.

4. Provide psychosocial support to patients and their families

- Establish an association / support group of affected families
- Create information resources including a website and pamphlets
- Construct accommodation facilities for families of children undergoing long term treatment, especially those from remote areas.

Four committees were set up, one for each objective, and given tasks to be accomplished each year. A steering committee was formed to coordinate annual meetings and oversee the activities of each committee.

The Kenya National Retinoblastoma Strategy (KNRbS) was launched and included everyone who attended the first meeting. An annual KNRbS meeting was held for the next six years, during which achievements of the previous year would be reviewed and new tasks set out.

In those six years, the KNRbS was able to achieve the following:

- Ratification, publication and distribution of Kenya Retinoblastoma Best Practice Guidelines
- Improved access to chemotherapy
- Improved globe salvage therapy
- Inclusion of eye inspection for white reflex and squint as part of routine maternal child health care
- Establishment of a fund to enable each family affected by retinoblastoma to enrol in the National Health Insurance Fund which covers almost all aspects of retinoblastoma treatment, as well as other diseases.

Experiences in the UK

The development of national services in the UK occurred because of concerns that uncommon children's conditions with a risk of mortality were being treated in units that were under-equipped to treat them.

It is advisable to have two centres in the UK in case one centre is unable to treat the condition, say due to lack of staff or closure due to infection for example.

A true multi-disciplinary team evolves over time. Core medical staff members should include ophthalmologists, paediatric oncologists and histopathologists. Ideally there should be two of each so that leave is covered and colleagues can give advice when difficult situations arise either informally or at multi-disciplinary meetings.

Additional support staff are needed. In the UK, support staff include Clinical Nurse Specialists in oncology and ophthalmology, orthoptists to monitor vision in children, psychologists and a representative from the retinoblastoma patient support group in the UK (Childhood Eye Cancer Trust: CHECT). Figure 1.

Every support staff member has an important role to fulfil. The representative from CHECT is important as the parents feel that there is someone to speak to who is not a member of the hospital. Parents are likely to become distressed and this will affect the child and other members of the family. Counselling either by a psychologist or a member of staff (who has an understanding of the trauma that the family is undergoing) is of great benefit.

We hold multidisciplinary meetings with all staff members at least once a month to discuss patients who have had enucleations and treatment.



ASHWIN REDDY

Figure 1 Core members of the Royal London Retinoblastoma Team, Barts Health NHS Trust, London, UK

Child Life: improving treatment and saving costs by caring for the whole child

Retinoblastoma treatment is a stressful and potentially traumatic experience for children, who have to cope with the challenges of hospitalisation, illness, and disability. Child life specialists (known as play therapists or play specialists in some countries) work closely with children and families in these situations, offering emotional support practical tools and advice to help them cope better.

Child life specialists help to explain medical jargon to parents and children, and prepare them for procedures, usually through play.

In Figure 2, a child is practising the use

of a mask in preparation for surgery. She overcame her initial apprehension by first putting the mask on a simple cloth doll (a pattern that can be easily sewn by people in the local community for very little money).

The father also demonstrates one of the four key comfort positions (back to chest), which gives solid comfort to the child during this procedure. See <http://bit.ly/comfortpositions>.

These techniques reduce stress and can save costs: if a child is calm, and the parent knows what to do, a procedure can be completed by just one medical professional, rather than two or more.

Figure 2 A child practises the use of a mask, Kenya



WWW.WECHOPE.ORG

Understanding retinoblastoma: epidemiology and genetics



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Retinoblastoma is usually initiated by a random mutation of a gene in a retinal cell. It is important to try and recognise if the child has germline retinoblastoma, as this may affect both eyes of the child. Siblings and future children of the child with retinoblastoma are at greater risk of developing this cancer.

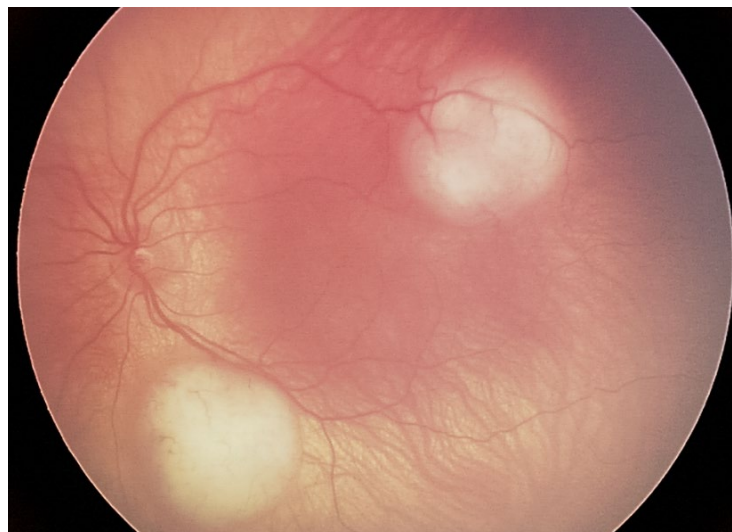


Figure 1 Multifocal retinoblastoma, suggesting germline disease

Retinoblastoma is the most common eye cancer of childhood. However, it is a relatively rare disease, occurring in approximately one out of every 16,000–18,000 live births in the global population.¹ Its incidence is similar across populations, and does not vary according to gender, ethnicity or socio-economic status. Worldwide, approximately 8,000 children develop retinoblastoma each year, with the vast majority presenting with the disease before the age of 5 years.

Retinoblastoma originates in a photoreceptor cell of the retina and is associated with a mutation in the *RB1* gene (which is normally responsible for tumour suppression). Each person inherits two copies (or alleles) of the *RB1* gene – one from each parent. For retinoblastoma to occur, both copies in a single retinal cell must undergo a mutation.

Retinoblastoma is categorised by whether the mutation is germline (hereditary) or non-germline (occurring sporadically).

Germline retinoblastoma

In many cases of germline retinoblastoma, a mutated *RB1* allele is inherited from a parent and is present in all the cells of a child's body. A second mutation in a retinal cell results in a tumour.

Children with germline retinoblastoma often present at a young age (median of 15 months).

Tumours can occur in multiple locations in one eye (multifocal disease, Figure 1) and in both eyes (bilateral).

A child that presents with bilateral disease is 100% likely to have a germline mutation. Germline retinoblastoma may occur in an asymmetrical manner, with a different grade of tumour in each eye at presentation. Children may even present with unilateral retinoblastoma initially, becoming bilateral later.

It is very important that germline retinoblastoma is recognised. If you see a child with retinoblastoma in

one eye, do not assume that it is non-germline: it is estimated that 10–20% of children who present with unilateral disease have germline retinoblastoma. Ask about family history of retinoblastoma, or about removal of an eye in childhood of a family member, and **always examine the second eye to look for early signs of tumour**. Refer the family for genetic counselling and testing, if available (see p. 8).

Retinoma

A retinoma is a benign precursor of retinoblastoma. Retinomas should be looked for in the parents of an affected child. The presence of a retinoma in a parent or sibling confirms that the disease is inherited (and therefore germline) in that family.

Mosaicism

Occasionally, a random mutation in the *RB1* gene may occur very soon after conception. Depending on the stage of development at which this occurs, some of the child's body cells will have the mutated *RB1* gene, and others will not; this is known as mosaicism. If the mutated *RB1* gene is present in the germ cells, the child can pass the mutation on to future generations.

Non-germline retinoblastoma

Non-germline retinoblastoma affects just one eye. It is the more common type of retinoblastoma. As the name implies, non-germline retinoblastoma is not inherited from parents and cannot be passed on to future generations. It develops due to two random mutations in the *RB1* gene in one cell of the retina. It is also known as 'sporadic' or 'somatic' retinoblastoma.

Recently, it has been found that retinoblastoma may occur even in the presence of non-mutated *RB1* genes, due to activity associated with the *MYCN* oncogene.² This is rare, occurring in fewer than 3% of children with unilateral retinoblastoma. It tends to present at an earlier age, often before 6 months.

Reference

- 1 Kivelä T. The epidemiological challenge of the most frequent eye cancer: retinoblastoma, an issue of birth and death. *Br J Ophthalmol* 2009;93:1129–1131.
- 2 Rushlow DE, Mol BM, Kennett JV, et al. Characterisation of retinoblastomas without *RB1* mutations: Genomic, gene expression, and clinical studies. *Lancet Oncol* 2013;14:327–334. Available at: www.ncbi.nlm.nih.gov/pubmed/23498719

Germline retinoblastoma: estimating risk and counselling the family



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Even when a diagnosis of germline retinoblastoma cannot be confirmed by genetic testing, the risk to family can still be estimated and used to plan follow-up eye examinations.



If a child has germline retinoblastoma, siblings are also at risk. INDIA

Genetic laboratories can detect many mutations in the retinoblastoma gene and genetic testing is used to assess whether individuals – and their relatives – have a significant chance of developing retinoblastoma.

However, genetic testing is not available in many treatment centres in low- and middle-income countries. In this situation, clinicians should evaluate the likelihood that a child has germline retinoblastoma, based on the clinical presentation and family history:

- Germline retinoblastoma occurs at a younger age (median of 15 months)
- Tumours are usually bilateral and multifocal, but may be unilateral
- Others in the family are affected, either with retinoblastoma, or, rarely, with a second tumour
- There is a history of childhood enucleation in a parent or other close relative
- Parents or siblings may have a retinoma on examination (Figure 1, p. 7).

If a child has **germline** retinoblastoma (see p. 7), his or her siblings (and potential offspring) are at risk of developing the condition. They must undergo a full retinal examination at regular intervals so that any tumours can be detected and treated as early as possible.

If a child presents with unilateral retinoblastoma, always examine the second eye very carefully until the child is 5 years of age so any signs of bilateral retinoblastoma can be identified and treated.

Estimating the risk of germline disease

To support decision making in the absence of genetic testing, an algorithm (Figure 1) can be used to estimate the risk to family members if a child has retinoblastoma. The algorithm was developed by reviewing the outcomes of children in our unit who had undergone genetic testing.

Table 1 shows the estimated risk that a sibling, child or more distant relative of someone with retinoblastoma will also develop a tumour in the retina. Important factors are whether more than one person in the family has retinoblastoma and, if there is no-one else affected on the family, whether the affected person has multifocal/ bilateral or unilateral retinoblastoma. The categories are grouped by the level of risk, with more than 1% being considered 'high risk' and 1% or less 'low risk'.

Use Table 1 to decide whether the relationship to the affected person and the clinical scenario merits the use of a 'high-risk' (orange) or 'low-risk' (green) screening protocol. Table 2 gives the suggested screening protocols, which set out when, and how often, family members must undergo detailed retinal examinations to look for early signs of a tumour.

It is important to speak to parents or carers and explain the risk to their child and the fact that siblings and the child's future children may also develop retinoblastoma. Emphasise that the regular eye examinations suggested in Table 2 will help to diagnose any disease early so that it can be treated successfully. Listen to parents' concerns. Ensure they know when and where to bring family members for examinations and allow enough time to answer any questions they may have.

Second tumours

People with germline retinoblastoma are also at risk of developing other tumours later in life. These second tumours are most commonly osteosarcomas, soft tissue sarcomas or melanomas. The risk is increased if the child was treated with external beam radiotherapy. These second tumours most commonly occur between 10 and 50 years of age and can occur anywhere in the body. There is no effective screening for second tumours, so it is important for the patient and their medical team to be aware that they may occur. Sun protection is important, as is regular checking of the skin for melanomas.

Note: If a child presents with unilateral retinoblastoma, always examine the second eye very carefully so any signs of bilateral retinoblastoma can be identified and treated early

Figure 1 Flow chart. Assess the risk to family members using Table 1 then follow the suggested screening protocol given in Table 2

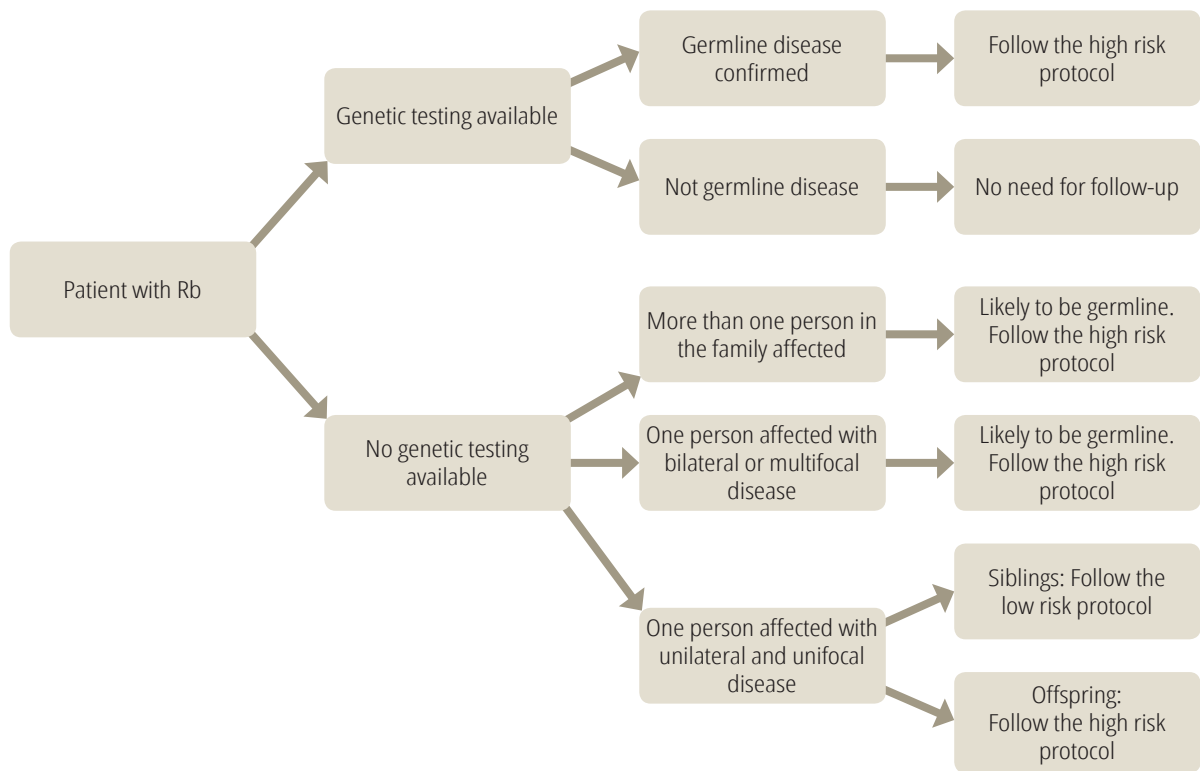


Table 1 Estimated risks of developing retinoblastoma in siblings and offspring of a child presenting with retinoblastoma

	More than one affected person in family	The child has bilateral or multifocal retinoblastoma	The child has unilateral unifocal retinoblastoma
Siblings of Rb child	50%	5%	1%
Offspring of child who had Rb	50%	50%	5–10%
More distant relatives of child with Rb	Need to assess the family tree, may be at risk	Not at increased risk	Not at risk

High risk Low risk

Table 2 High risk and low risk screening protocols for offspring or siblings of children with retinoblastoma

Age of sibling or offspring	High risk	Low risk
2 weeks	Screen by 2 weeks	
4 weeks		Screen by 4 weeks
Up to 6 months	4 weekly	6 weekly
6–12 months	Every 4–6 weeks	9 months and 12 months
1–2 years	Every 2 months until 18 months Then at 21 months and 24 months	16 and 22 months
2–3 years	Every 4 months	Every 6 months
After 3 years	Stop, unless there is a family history of late onset	Stop

Detecting retinoblastoma



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It is important to learn the early signs of retinoblastoma. Early detection, diagnosis and treatment depends on it.

The most common early signs (see Table 1) of retinoblastoma are:

- Something white in the eye, often first noticed by parents. Confirm by conducting a red reflex test (see p. 23)
- Squint: one eye turns in or out (not as common).

Signs of more advanced retinoblastoma include:

- Forward displacement of the eye (proptosis)
- A visible tumour (fungating mass) involving just the globe, or extending to the orbit and/or the face.

Less common signs of retinoblastoma include:

- Poor vision, whether noticed by the parents or a health worker
- Nystagmus (constant eye movements)
- Hyphaema (bleeding into the anterior chamber)
- Pseudohypopyon (cells in the anterior chamber appearing as a layered white material)
- Periocular inflammation
- Phthisis bulbi (shrinkage of the globe)
- Raised pressure in the eye (glaucoma)
- Enlargement of the globe
- Change in iris colour (heterochromia).

Retinoblastoma affecting both eyes

Signs of **germline retinoblastoma** are usually present in both eyes within the first few months of life (or even at birth in some instances). They include:

- Carers saying the eyes are not normal
- A white reflex in the pupil (or something white in the eye, noticed by the parents in one or both eyes)
- Occasionally nystagmus (searching eye movements as a result of the tumour involving the central part of the retina (macula) in both eyes).

Retinoblastoma affecting one eye

Children with **non-germline retinoblastoma** usually present later, often at the age of 2–3 years. The most



Leucocoria. An abnormal or white reflex is the most common sign of retinoblastoma.

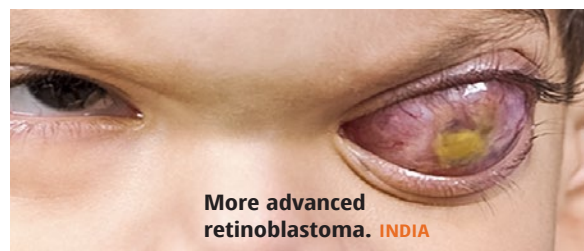
common presenting features in patients with non-germline retinoblastoma are **leucocoria** (an abnormal white reflection from the retina) and **squint** (less common).

Note: If a child presents with unilateral retinoblastoma in the first year of life, it may be germline (p. 7). The child has a greater risk of developing more tumours in the same or the other eye. Careful screening of the fellow eye, throughout childhood, is essential for all children suspected of having germline disease.

What are you likely to see where?

In high-income countries, children with retinoblastoma may present with reduced vision, an acute red eye or orbital inflammation.

In low resource settings advanced cases with proptosis (forward displacement of the eye) or fungating orbital masses are seen more commonly due to late presentation.



More advanced retinoblastoma. INDIA

Table 1 Could this be retinoblastoma?

	What the parents say, or what you can see	Could this be retinoblastoma?
Listen to the child's carer	The parent/carer says they saw something white in the eye	Yes
Look at the child's eyes	The eyes look normal but the parent/carer says they saw something white in the eye	Yes
	The eyes are not looking in the same direction; they are not straight	Squint is quite common in children It is rarely due to retinoblastoma
	One of the pupils is not black; it may be white or yellow-orange	This could be cataract or retinoblastoma
	One of the eyes is bigger than the other or bulges forward	This may be proptosis due to advanced retinoblastoma
Examine the pupil and red reflex	Look at the pupils. They should be black. Do a red reflex test (p. 23)	Suspect retinoblastoma if anything in the pupil looks abnormal

Digital flash photography

Digital flash photography, often from a mobile phone, can show the white reflex in the pupil in some cases and lead to earlier detection; however, squint, refractive errors, and photographs taken from an angle can also produce the appearance of a white reflex, with only a minority of cases having retinoblastoma.

So, although most causes of an absent red pupil reflex on a photograph are not retinoblastoma it is still a useful public education tool. In Honduras, it was associated with a reduction in the proportion of children with retinoblastoma presenting with advanced disease.

Classification and staging of retinoblastoma



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Classifying and staging retinoblastoma is an essential first step when planning how to manage a child with the condition; it also gives important information about prognosis.



Doctors look for signs that retinoblastoma has spread via the optic nerve. **INDIA**

Classification schemes in cancer are mainly used to compare the results of different treatments and to enable a prognosis to be given.

Classification of extraocular disease

If retinoblastoma is left untreated, it will extend beyond the eye. Unfortunately, this is the type most commonly seen in low- and middle-income countries. The tumour can penetrate the globe wall and be visible in and around the eye. It can also reach the central nervous system via the optic nerve, or it can spread to other parts of the body via the blood stream (metastases).

In 2006, Chantada and colleagues developed the International Retinoblastoma Staging System (IRSS; Table 1).¹ It sub-classifies the disease from stage 0–IV. Stage 0 is intraocular disease, usually having a good

outcome with treatment, and stage IV is retinoblastoma with metastases, which has a poor prognosis.

Classification of intraocular disease

For intraocular retinoblastoma, the first classification system was introduced by Reese and Ellsworth (R-E) in the 1960s to predict the chances of saving the eye following external beam radiotherapy. When intravenous chemotherapy for intraocular retinoblastoma was introduced in the 1990s, the R-E classification system was no longer appropriate and a new classification scheme, the International Intraocular Retinoblastoma Classification (IIRC) scheme, was developed.²

The IIRC scheme groups tumours from A-E, depending on their size, location, and additional features,

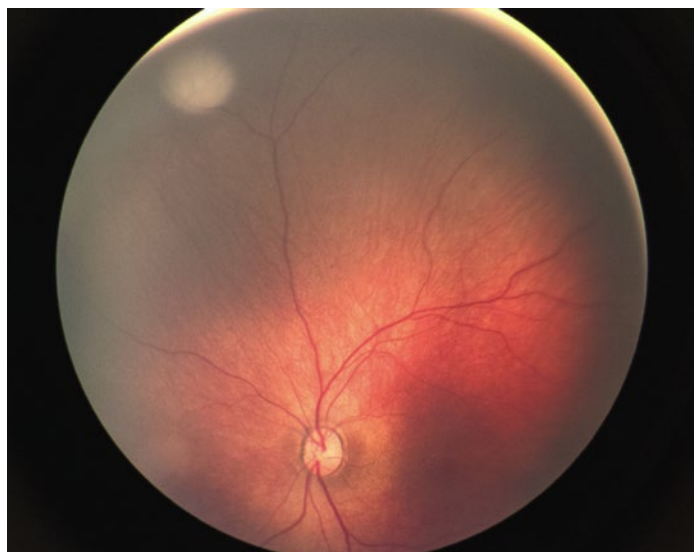
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Table 1 International Retinoblastoma Staging System (IRSS)

Stage	Clinical Description
0	Patient treated conservatively
I	Eye enucleated, completely resected histologically
II	Eye enucleated, microscopic residual tumour
III	Regional extension
a.	Overt orbital disease
b.	Preauricular or cervical lymph node extension
IV	Metastatic disease
a.	Heamatogenous metastasis (without central nervous system involvement) 1 Single lesion 2 Multiple lesions
b.	Central nervous system extension (with or without any other site of regional or metastatic disease) 1 Prechiasmatic lesion 2 Central nervous system mass 3 Leptomeningeal and cerebrospinal fluid disease

Figure 1 Intraocular retinoblastoma: stages A-E

A Small post-equatorial tumour confined to the retina



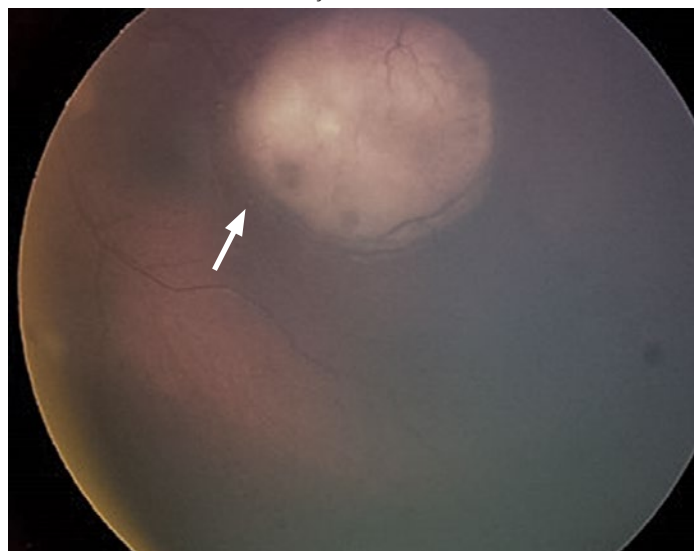
IDO DIDI FABIAN

B Foveal tumour confined to the retina



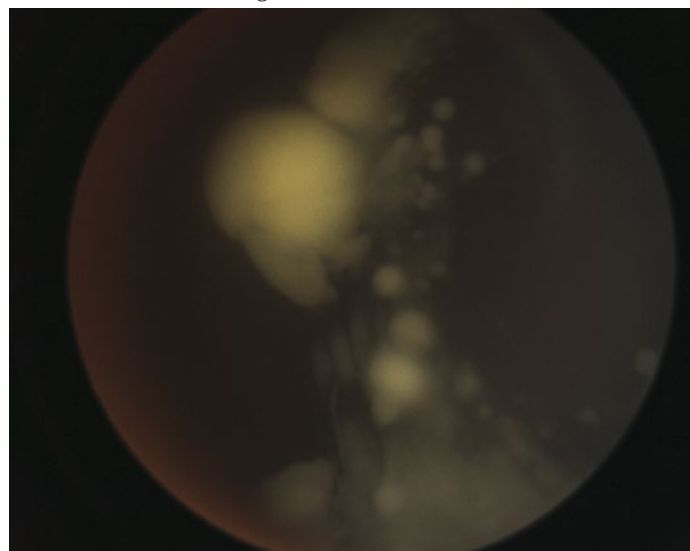
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C Retinal tumour surrounded by a cuff of subretinal seeds (arrow)



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D Diffuse vitreous seeding



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including the presence of retinoblastoma 'seeds' (small colonies of cancerous cells in the vitreous) and/or retinal detachment.

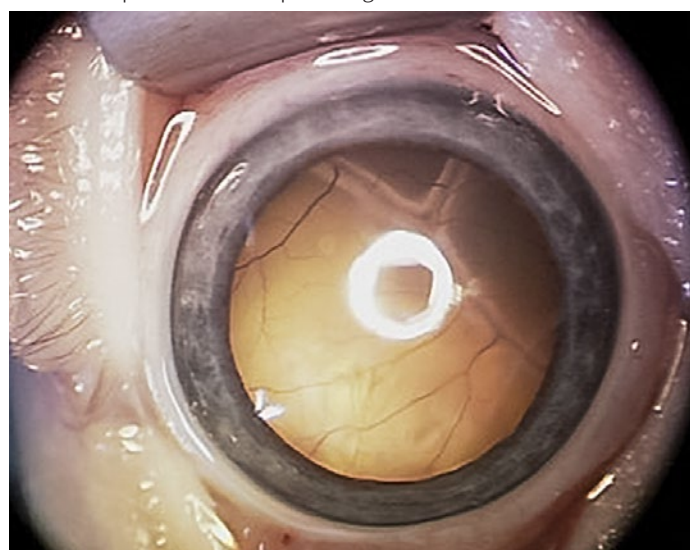
Shields and colleagues developed a modified scheme, the Intraocular Classification of Retinoblastoma (ICRB), which differed from the IIRC mainly in the definitions of the advanced groups, D and E. In 2006, the ICRB scheme was found to successfully predict the outcome of intravenous chemotherapy.³

- For eyes in groups A–C: the globe could be salvaged in $\geq 90\%$ of eyes.
- For eyes in group D: the globe could be salvaged in 47% of eyes.
- Group E eyes underwent primary enucleation and were excluded from analysis.

Both the IIRC and ICRB classification systems (see Table 2, overleaf) are now used as the main classification schemes for intraocular retinoblastoma and serve clinicians and researchers across the world.⁴ The images in Figure 1 correspond to each category.

Intravenous chemotherapy was found to be effective in treating tumours confined to the retina; however, vitreous seeds seemed to be resistant to the treatment. In 2012,

E Large tumour touching the crystalline lens, resulting in elevated intraocular pressure and expanded globe



IDO DIDI FABIAN

The cTNMH scheme is available in the online edition of this article. www.cehjournal.org

Munier and colleagues developed a technique for injecting chemotherapy directly into the vitreous cavity.⁵ They used a classification system that grouped retinoblastoma seeds, based on their morphology and size, as dust, spheres and clouds. Since the introduction of the intravitreal technique, the classification of vitreous seeds is now commonly used to predict the number of injections needed to control the various seed types.⁶

Another classification system that is used for all cancer types, including retinoblastoma, was created by the American Joint Committee on Cancer (AJCC). The TNM scheme classifies cancer according to involvement of the primary site: tumour (T), lymph nodes (N) and presence of systemic metastasis (M). The recently published 8th edition includes a hereditary (H) component for Rb, making it the cTNMH scheme

(c for clinical). The cTNMH categories are based on whether the tumour burden is determined to be intraretinal, intraocular, advanced intraocular or extraocular.⁷ The TNM scheme also has a pathological (pTNM) sub-classification which is widely used by ophthalmic pathologists. Read this article online to see the full scheme: www.cehjournal.org.

Summary

Classification and staging systems for retinoblastoma have evolved as new treatments became available. Several schemes are currently available. For disease confined to the globe, the IIRC, ICRB and cTNMH systems are available, along with additional classifications describing vitreous seeds. For extraocular disease, the IRSS and cTNMH schemes can be used.

Table 2 Classification systems for Intraocular Retinoblastoma

	International Intraocular Retinoblastoma Classification (IIRC)	Intraocular Classification of Retinoblastoma (ICRB)
Group A (very low risk)	All tumours are 3 mm or smaller, confined to the retina and at least 3 mm from the foveola and 1.5 mm from the optic nerve. No vitreous or subretinal seeding is allowed	Retinoblastoma ≤ 3 mm (in basal dimension or thickness)
Group B (low risk)	Eyes with no vitreous or subretinal seeding and discrete retinal tumour of any size or location. Retinal tumours may be of any size or location not in group A. Small cuff of subretinal fluid extending ≤5 mm from the base of the tumour is allowed	Retinoblastoma > 3 mm (in basal dimension or thickness) or <ul style="list-style-type: none"> • Macular location (≤3 mm to foveola) • Juxtapapillary location (≤1.5 mm to disc) • Additional subretinal fluid (≤3 mm from margin)
Group C (moderate risk)	Eyes with focal vitreous or subretinal seeding and discrete retinal tumours of any size and location. Any seeding must be local, fine, and limited so as to be theoretically treatable with a radioactive plaque. Up to one quadrant of subretinal fluid may be present	Retinoblastoma with: <ul style="list-style-type: none"> • Subretinal seeds ≤ 3 mm from tumour • Vitreous seeds ≤ 3 mm from tumour • Both subretinal and vitreous seeds ≤ 3 mm from tumour
Group D (high risk)	Eyes with diffuse vitreous or subretinal seeding and/or massive, non-discrete endophytic or exophytic disease Eyes with more extensive seeding than Group C Massive and/or diffuse intraocular disseminated disease including exophytic disease and >1 quadrant of retinal detachment. May consist of 'greasy' vitreous seeding or avascular masses. Subretinal seeding may be plaque-like	Retinoblastoma with: <ul style="list-style-type: none"> • Subretinal seeds > 3 mm from tumour • Vitreous seeds > 3 mm from tumour • Both subretinal and vitreous seeds > 3 mm from retinoblastoma
Group E (very high risk)	Eyes that have been destroyed anatomically or functionally with one or more of the following: Irreversible neovascular glaucoma, massive intraocular haemorrhage, aseptic orbital cellulitis, tumour anterior to anterior vitreous face, tumour touching the lens, diffuse infiltrating retinoblastoma and phthisis or pre-phthisis	<ul style="list-style-type: none"> • Extensive retinoblastoma occupying >50% globe or with • Neovascular glaucoma • Opaque media from haemorrhage in anterior chamber, vitreous or subretinal space • Invasion of postlaminar optic nerve, • choroid (>2 mm), sclera, orbit, anterior chamber

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Managing and treating intraocular retinoblastoma



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In order to improve the survival rates of children with retinoblastoma, a collaborative and multidisciplinary approach is essential, as is a listening ear for parents who may struggle with the difficult decisions facing them



It is important to consider the whole child, not just the eyes. INDIA



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Enucleation remains the mainstay of treatment for advanced intraocular retinoblastoma. This is particularly important in unilateral retinoblastoma in groups C, D and E (Table 1) in low-resource countries, where follow-up may be poor. Acrylic implants and shells/prostheses may cost less than US \$10 each and, if available, will ensure that the social and emotional welfare of the child and parents are catered for.

The importance of listening to parents

Doctors who deal with retinoblastoma and enucleation regularly can forget how terrifying it all is for the newly diagnosed family. Taking time to truly listen to parents and address their concerns are an essential part of counselling about treatment and rehabilitation options. Surgery can save a life, but so too can a quiet, listening presence and responsive, empathetic guidance that meets the family in their place of pain and helps them to find a way out of it. The parents of a child whose life has been saved by unilateral enucleation may also be helpful in counselling other families who may think about refusing enucleation due to fear about the outcome.

*With thanks to
Abby White of
World Eye Cancer Hope
for her contribution on
counselling parents.
www.wechope.org*

Good prostheses ensure that the social and emotional welfare of the child and the parents are catered for.



SWATHI KALIKI

Multidisciplinary approach

In order to reach – or maintain – high survival rates of over 95%,¹ it is essential that there is a collaborative multidisciplinary approach with a trained pathologist and a paediatric oncologist. Otherwise, high-risk features such as massive choroidal invasion and/or retrolaminar optic nerve invasion will not be detected and the child could still die from metastases (secondary spread of the tumour), despite enucleation.

Systemic chemotherapy

This may be given systemically as first line treatment for children with intraocular retinoblastoma in groups B, C and D (Tables 1 and 2), particularly those affected in both eyes. Regular follow-up is *essential*. If systemic chemotherapy is given, with additional focal therapy (see below), enucleation can be avoided in over 95% of eyes with groups B or C retinoblastoma.

Focal therapy

Focal therapy includes transpupillary thermotherapy (TTT), laser photocoagulation, cryotherapy, and plaque radiotherapy. Of these, laser and cryotherapy are likely to be available in low-income countries. All of these can be used either alone (in infants with retinoblastoma identified as being in Group A and possibly Group B), or after initial systemic chemotherapy in Groups B, C & D retinoblastomas. Focal therapy works best for small tumours (less than 5 mm), or recurrences with no associated vitreous and/or subretinal seeds.

Laser photocoagulation

Laser treatment is likely to be more readily available than TTT as the laser used for diabetic retinopathy in adults can be modified and used as an indirect laser for treating retinoblastoma. Treatment involves application of argon 532/810 nm laser (above 65 °C)

Continues overleaf ➤

either directly on the tumour, or in a ring-like fashion around it to coagulate the feeding blood vessels, leading to ischaemic tumour damage. In the next 2-3 sessions, the tumour is repeatedly covered with laser burns. Complications include vitreous seeding, vascular occlusions, pre-retinal fibrosis and associated retinal traction and vitreous haemorrhage.

Cryotherapy: Anterior/peripheral small tumours

This involves the application of sub-freezing temperatures (down to -90 °C) directly to the tumour mass, resulting in damage to the vascular endothelium

with secondary thrombosis and infarction of the tumour. Tumours are typically treated by triple freeze-thaw technique through the conjunctiva in two sessions with a 3-weekly interval (Figure 1). Complications include lid oedema, conjunctival chemosis (swelling), serous retinal detachment, vitreous condensation (which can result in vitreous haemorrhage) and tractional retinal detachment.

Plaque therapy: Larger tumours or areas of relapse

Radioactive plaque brachytherapy can be used for

Continues overleaf ►

Table 1 Treatment of intraocular retinoblastoma

International Intraocular Retinoblastoma Classification (IIRC)	
Definition	Treatment
A Small tumours <3 mm outside macula	Focal treatment. If no focal treatment available either: Send to a site with focal treatment or if no focal treatment is available in country please seek expert guidance
B Bigger tumours >3 mm or Tumours in the macula or Tumours with sub-retinal fluid	Focal treatment with or without (+/-) systemic chemotherapy up to 6 cycles
C Localised (within 3 mm from the tumour) vitreous or sub-retinal seeds	Unilateral: Enucleate Bilateral: Attempt 'Second Eye' Salvage: Systemic chemotherapy 6 cycles +/- focal treatment
D Diffuse (> 3 mm away from the tumour) vitreous or sub-retinal seeds If Enucleated look for: High Risk Histopathological Features: Retrolaminar optic nerve involvement Choroidal Invasion >3 mm	Unilateral: Enucleate Bilateral: Attempt 'Second Eye' Salvage: Systemic chemotherapy +/- focal treatment. IF EYE SALVAGE FAILS: enucleation. Post Enucleation: If low risk histopathological features present – no further treatment If high risk histopathological features present: 6 cycles of chemotherapy
E Any of the following: <ul style="list-style-type: none"> tumour touching the lens neovascular glaucoma tumour in the anterior chamber opaque media due to vitreous haemorrhage aseptic orbital cellulitis phthisis bulbi. 	Enucleation. If low risk – no further treatment. If high risk histopathological features present (as for Group D): 6 cycles of chemotherapy

Table 2 Standard dose systemic chemotherapy given every 3 weeks for Intraocular Rb

Drug	Dose: Mg/m ²	Rate of infusion	Diluent
Vincristine	1.5mg/m ² body surface area (BSA D1) (to a max. of 2mg/ dose)	Slowly over 10 minutes	Not less than 10mls of 0.9% NaCl Note: Risk of extravasation
Etoposide	300mg/m ² BSA D1	4-hour infusion	0.4mg/ml in 0.9% NaCl Note: Rapid infusion will lead to hypotensive crisis
Carboplatin	600mg/m ² BSA D1	1-hour infusion	0.5mg/ml in D5% or DNS
Requirements before each cycle			
ANC >1; Platelets >100; Check that Hb, Renal profile, LFT's and Magnesium levels are adequate			
Age	Dose modifications		
< 6 mth	Give 50% of the dose for each drug		
6–12 mths	Give 75% of the dose for each drug		
12+ mths	No modification		

Figure 1a A child with a Group D retinoblastoma in one eye has been treated with systemic chemotherapy and the main tumour has calcified (A). However, a new tumour (B) has formed peripherally/anteriorly which was detected at a regular follow-up visit. Regular follow-up is essential as new tumours can be difficult to detect in the early stages.

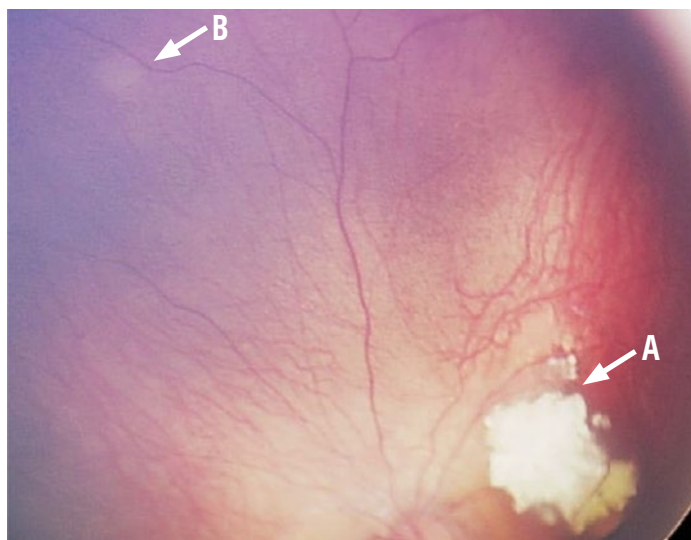
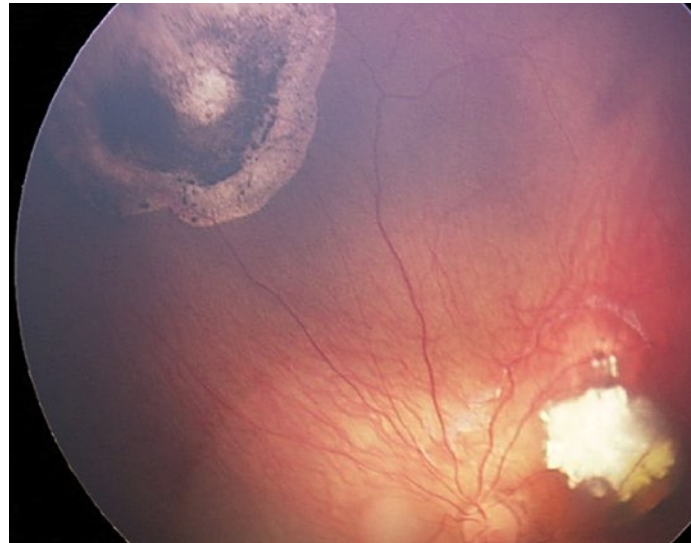


Figure 1b The new peripheral tumour has been treated with two sessions of triple freeze-thaw cryotherapy, spaced 3 weeks apart, resulting in a flat scar. If the tumour had not been detected during a regular follow-up visit, the child would have returned with an untreatable tumour in the eye which would have required enucleation and the child would have been at risk of metastasis and death.



tumours with basal diameter and height less than 16 mm and 8 mm respectively. Iodine (I^{125}) and Ruthenium (Ru^{106}) radio-isotopes are most commonly used. Gold plaques carrying radio-active seeds are sutured to the base of the tumour, to provide 40 Gray (Gy) to the tumour apex over a period of 2–4 days, and the plaque is then removed. Major complications include cataract, radiation retinopathy or papillopathy, optic neuropathy, scleral necrosis and keratopathy.

External beam radiation therapy

External beam radiation therapy (EBRT) for the treatment of retinoblastoma has decreased drastically due to the increased risk of second non-ocular malignancies, particularly in infants under the age of 12 months who have germline retinoblastoma. However, it does have an important role in children with extraocular retinoblastoma in the orbit (see page 19).

Intravitreal chemotherapy

The vitreous contains no blood vessels, therefore drug concentration from systemic chemotherapy is less effective. Melphalan and topotecan (either singly or in combination) are the chemotherapeutic agents that have been given by direct intravitreal injection.²

Intravitreal injection should not be given:

- if there is tumour at the site of the injection
- if tumour extends to the ciliary body
- if there is a bullous retinal detachment or vitreous haemorrhage which obscures the view of the vitreous and retina.

An ultrasound biomicroscope (UBM) or direct vision may be used before treatment to assess the injection site for tumour.

A small diameter needle must be used (30G or smaller). The site of injection should be 3 mm from the limbus into the pars plana. We suggest using a

triple freeze-thaw cryotherapy at the injection site as the needle is withdrawn. The eyeball is then gently jiggled with forceps to distribute the drug evenly throughout the vitreous.

The recommended dose of intravitreal melphalan is 20–30 microgrammes for a maximum of 6 injections over 2–3 months, depending on the distribution and extent of vitreous seeds and response to prior injection. Eye salvage rates have significantly improved as a result of this treatment.

Intra-ophthalmic artery chemotherapy

Although not widely available in low-resource countries, direct treatment of the eye via intra-ophthalmic artery chemotherapy has overtaken the use of EBRT for retinoblastoma once systemic chemotherapy and focal therapies have been exhausted. This treatment should be used with caution as first-line treatment for unilateral advanced retinoblastoma (Groups D and E) as they may metastasise. This is particularly relevant if follow-up is poor.

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Figure 2 A multidisciplinary team discussion in Malawi





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Standard reporting of high-risk histopathology features in retinoblastoma

Once an eye with retinoblastoma is excised, accurate histopathological staging is essential in order to determine whether the child can leave the hospital completely cured, or may need chemotherapy or radiotherapy.



Figure 1 If there is obvious extraocular extension such as an extrascleral nodule or orbital involvement in an exenteration specimen, the specimen should be sampled in such a way as to confirm this microscopically.

Further reading

<https://www.rcpath.org/profession/publications/cancer-datasets.html> includes the current dataset for retinoblastoma and other tumours (free access).

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Surgical treatment for retinoblastoma is limited to enucleation (removal of the eye) or exenteration (removal of the eye and contents of the orbit). Histopathological examination of such specimens yields important information which must be taken into account when considering prognosis and making decisions about future management and treatment.

Standard histopathological reporting

When histopathologists are dealing with cancer specimens, their reports should include standard and appropriate information items, commonly known as a dataset. In the UK, histopathologists use datasets produced by the Royal College of Pathologists. Data items are reviewed every two years and aligned with the international tumour, node, metastasis, (TNM) classification. The TNM classification for retinoblastoma has recently been updated from TNM7 to TNM8. The newest dataset for retinoblastoma from the Royal College of Pathologists (RCPath), released in early 2018, reflects the changes in the TNM classification. Visit <http://bit.ly/RBdataset>

Histological high-risk features: rationale

The RCPath dataset for retinoblastoma records whether tumour is present in specific structures. Presence of tumour in any of these structures is considered a histological high-risk feature (HHRF). Retinoblastoma specimens with HHRFs indicate that the patient is at higher risk for metastasis (tumour spread) than a patient whose specimen does not have such features.

Detection of HHRFs by the histopathologist influences management decisions. The histopathologist examining the specimen should therefore specifically seek such features. The structures where tumour presence is regarded as an HHRF are:

- anterior chamber
- iris

- trabecular meshwork
- Schlemm's canal
- ciliary body
- choroid (above a certain threshold)
- sclera
- extraocular structures
- retrolaminar optic nerve (including the cut end).

Gross examination of specimens

The RCPath dataset for retinoblastoma includes recommendations for macroscopic examination and sampling of globe and exenteration specimens. Even if resources are limited, it is useful to sample the cut end of the optic nerve separately (if length allows) as well as a 'PO block' of the globe (see panel). If the globe is being opened fresh to sample tumour for cytogenetics, the optic nerve should be sampled first. This will avoid artefactual contamination.

The sampled optic nerve should be embedded transversely, so that a full cross-section can be evaluated. It can either be embedded on the true resection margin (surgeon's cut end) or the pathologist's cut end, as long as the orientation is known to the reporting pathologist.

For further information on what to look for microscopically (with figures), read this article on www.cehjournal.org.

PO block

This is a slice which includes the cornea, pupil and optic disc. It is typically obtained by making two parallel slices from anterior to posterior, one either side of the limbus. The orientation of the parallel slides may be sagittal, transverse or oblique, depending on the location of the tumour and any other pathology to be sampled.

Management of retinoblastoma with extraocular tumour extension



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Survival rates in children with extraocular tumour extension can be improved with a combination of chemotherapy, surgery, and radiotherapy.



Enucleation is just one step in treating extraocular retinoblastoma. INDIA

In high-income countries, the survival rate of children with retinoblastoma has improved over the years: from 5% to >95%. This improvement is a result of early diagnosis and intervention by specialist retinoblastoma teams. However, in low- and middle-income countries, the survival rate continues to remain low, with 39% mortality rates in Asia and 70% in Africa.¹ The high death rate in low- and middle-income countries is mainly related to the delay between onset of symptoms and start of treatment. This is due to a combination of factors: poor access to health care services, poor socio-economic conditions and poor education; resulting in advanced disease at presentation. Added to this is poor compliance with treatment; in particular, refusal for potentially life-saving enucleation due to cultural beliefs.

While leucocoria (a white reflex) is a common presenting sign of retinoblastoma in most high-income countries, an enlarged eye or proptosis with extraocular tumour extension remains the most common presenting sign in low- and middle-income countries.² It was previously estimated that only 9% of patients with orbital extension of retinoblastoma (stage III disease: see page 11) live for more than two years after diagnosis of retinoblastoma. However, recent literature suggests

that, with a combination of chemotherapy, surgery and radiotherapy, the five-year survival rate of patients with stage III disease (orbital extension of retinoblastoma) is >50%, while the prognosis for stage IV disease with systemic metastasis or central nervous system involvement still remains dismal.³

Recommended treatment for retinoblastoma with extraocular tumour extension

Assessment of disease spread

Perform a general examination and examine both eyes thoroughly, preferably under anaesthesia. Since bone marrow and cerebrospinal fluid are two potential sites for tumour spread, bone marrow aspiration and cerebrospinal fluid analysis are recommended before starting treatment. If there is enlargement of regional lymph nodes, a fine needle aspiration biopsy can be undertaken to determine if the tumour has spread to the nodes. A magnetic resonance imaging or computed tomography of the orbit should be done to ascertain the extent of the disease.

Treatment

In this article, we describe the treatment protocol we have used in our clinic since the year 2000. Treatment includes several cycles of high-dose systemic chemotherapy, followed by surgery (enucleation or exenteration), and then external beam radiotherapy to the orbit. Whenever there is an overt extraocular tumour extension, including gross optic nerve extension or extrascleral tumour extension, high-dose systemic chemotherapy should be given every 3 weeks as the primary treatment. Primary enucleation or orbital exenteration should be avoided until after the tumour shrinks so that surgery is more successful without leaving behind tumour residue. Various combinations of chemotherapy have been reported in the literature. We currently use the combination of vincristine, etoposide, and carboplatin, and have found it to be effective (Table 1, Figure 1).

Table 1 High-dose systemic chemotherapy for retinoblastoma with extraocular extension

Drug	Dose	
	Children <3 years	For children >3 years
Vincristine	0.05 mg/kg	1.5 mg/m ² body surface area (BSA)
Etoposide	10 to 12 mg/kg	200 mg/m ² BSA
Carboplatin	28 mg/kg	560 mg/m ² BSA
Regimen of each cycle	Drugs delivered	
Day 1	Vincristine + Etoposide + Carboplatin	
Day 2	Etoposide	

Figure 1 Line diagram depicting the recommended protocol for retinoblastoma with extraocular extension

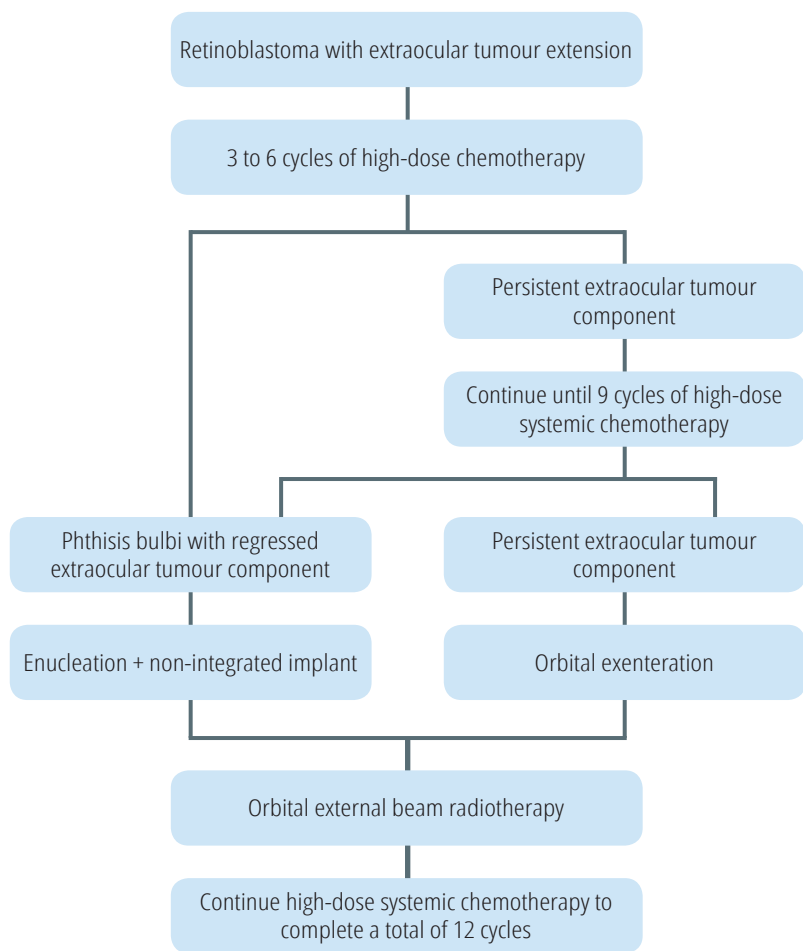
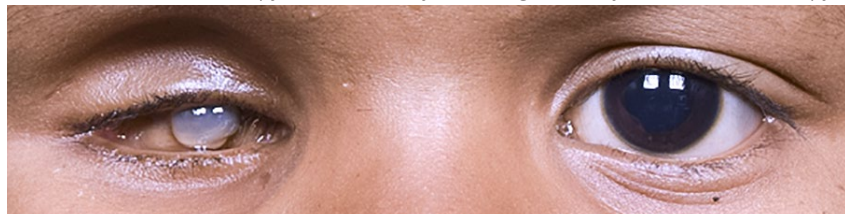


Figure 2 Treatment of a retinoblastoma patient with extraocular extension

2a A 4-year-old girl (A) presented with retinoblastoma with extraocular extension.



2b The globe became phthisical after 6 cycles of high-dose systemic chemotherapy. She subsequently underwent enucleation with polymethyl methacrylate implant, orbital external beam radiotherapy, and 6 more cycles of high-dose systemic chemotherapy.



2c Post-treatment, the child is doing well with a good cosmetic result and a customised ocular prosthesis.



High-dose systemic chemotherapy is given until the extraocular component of the tumour regresses. An average of 6 cycles of high-dose systemic chemotherapy results in complete regression of the extraocular tumour component in 95% cases, thus avoiding the need for orbital exenteration (Figure 2). Repeat magnetic resonance imaging or computed tomography of the orbit can be used to determine regression or persistence of extraocular tumour.

In eyes with regressed extraocular tumour, secondary enucleation with placement of an implant is performed. In eyes with residual extraocular tumour despite a maximum of 9 cycles of high-dose systemic chemotherapy, secondary orbital exenteration is recommended.

Six weeks after surgery, external beam radiation (45 to 50 Gy) is delivered to the orbit. The radiation field should include the regional lymph nodes if the patient had regional lymph node involvement at presentation.

Post-radiation, high-dose systemic chemotherapy is continued to complete a total of 12 doses of chemotherapy. In cases with stage IV disease at presentation with central nervous system involvement, additional intrathecal chemotherapy is recommended.

Using this treatment protocol, in our recent analysis of 20 patients with stage III disease who were compliant with treatment, 17 patients survived and were doing well at a median follow-up duration of 77 months.³ Three patients died despite adherence to treatment protocol. All patients who were noncompliant to treatment eventually died due to the disease. All patients with stage IV disease died despite aggressive multimodal treatment.

In summary, early diagnosis and appropriate treatment of retinoblastoma is crucial to improve the chances of life, globe, and vision salvage. In patients with delayed presentation including extraocular extension of retinoblastoma but without systemic or central nervous system metastases, multimodal treatment in specialist centres improves the chances of survival. The compliance to treatment plays a very important role in determining the likelihood of survival.

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How to do an enucleation for retinoblastoma



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Despite many advances in treatment, removal of the eye is sometimes unavoidable and can bring resistance from parents. Safe enucleation with implant followed by a well fitted prosthesis will encourage other parents to agree to this life-saving procedure.



The eye is prepared for surgery. INDIA

The three main goals of treatment of retinoblastoma are to save the child's life, to keep the eye, and to preserve vision. With recent advances in the management of retinoblastoma, especially with the introduction of chemotherapy, the need for enucleation has significantly reduced. However, enucleation is still the treatment of choice in cases with advanced intraocular retinoblastoma or in cases where saving the globe has failed.

Though the basic principles of surgery remain the same¹, a recent survey of 58 surgeons in 32 countries on enucleation techniques and implants in retinoblastoma revealed wide variations in practice.² In this article, we will discuss the surgical steps of enucleation and implant placement using the myoconjunctival technique for retinoblastoma.

Indications for enucleation

Primary enucleation is the preferred treatment in eyes with advanced unilateral intraocular retinoblastoma, corresponding to Group E in the International Intraocular Retinoblastoma Classification (Table 1, p. 11).

Secondary enucleation is performed in:

- Eyes that have failed conservative treatment strategies
- Phthisical eyes after-high-dose chemotherapy (see article on treatment of extraocular Rb).

Pre-operative evaluation

Prior to performing an enucleation for retinoblastoma, it is important to try and exclude metastatic disease. Bone marrow evaluation and cerebrospinal fluid analysis is recommended in cases with advanced retinoblastoma. If possible, orbital imaging by computerised tomography (CT) or magnetic resonance imaging (MRI) should be performed prior to enucleation to rule out extrascleral tumour extension or gross optic nerve involvement, which is seen as optic nerve thickening on the scan.

In cases with gross optic nerve thickening or those with extrascleral extension, systemic chemotherapy is recommended as the primary treatment, and after regression of the extraocular tumour, enucleation is performed as secondary treatment.

Since the operation is performed under general anaesthesia, suitable investigations must also be performed. Blood haemoglobin levels of a minimum of 10 grams per decilitre, white blood cell count of <15,000 per cubic millimetre, and a platelet count of >100,000 per cubic millimetre of blood are preferred.

Myoconjunctival technique of enucleation and implant

There should be minimal manipulation of the globe during the operation. Avoid perforating the globe and obtain an adequate length of optic nerve (>15 mm).

Here we describe the surgical technique practiced in our centre, which ensures minimal globe manipulation and produces an adequate length of optic nerve. Go to www.dropbox.com/s/7gbnovs9lyeokoz/N302626%20enucleation.mp4?dl=0 to see a video for the surgical steps of the procedure.

- 1 Perform indirect ophthalmoscopy before starting the operation to confirm the eye procedure will be done on the correct eye.
- 2 Gently place a wire speculum.
- 3 If the globe is enlarged or the orbit is small or tight, perform a lateral canthotomy to increase the working space.
- 4 Use conjunctival scissors to perform a perilimbal conjunctival peritomy around the whole eye. Take care to preserve the conjunctiva – handle it gently to minimise post-operative conjunctival scarring.
- 5 Perform a tenotomy in all four quadrants using curved tenotomy scissors. The dissection should be carried out to the equator of the globe in order to ease prolapse of the globe in the later stages of surgery.

- 6 Gently place a muscle hook under each of the four rectus muscles. Place muscle traction sutures 2 to 3 mm from the muscle insertion. Be gentle during needle entry into the muscle to avoid globe perforation.
- 7 The order of tagging and cutting the rectus muscles is based on the distance to the limbus: first medial, then inferior, then lateral, and finally the superior rectus. Insert absorbable muscle-tagging sutures

- through the muscle, 4 to 5 mm from the traction sutures. Cut the muscles in between the traction suture and tag suture with conjunctival scissors.
- 8 The superior oblique and inferior oblique muscles are now identified and cut. It is preferable to use cautery to cut these muscles in order to minimise bleeding during surgery.

Continues overleaf ➤

Figure 1 (A–U)

Surgical steps of enucleation and implant for retinoblastoma

A Instruments and sutures needed for enucleation and implant



B The eye to be enucleated is confirmed by indirect ophthalmoscopy



C 360 degrees perlimbal conjunctival peritomy being performed



D Anterior Tenon's dissected in all four quadrants



E Rectus muscle identified with muscle hook



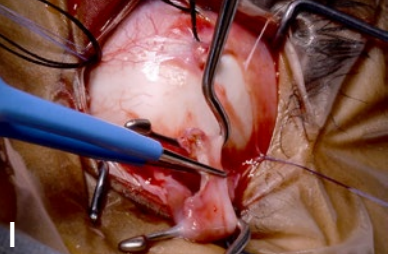
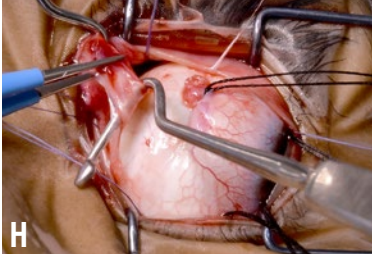
F Traction suture placed at muscle insertion and tag suture placed 4–5 mm away from traction suture



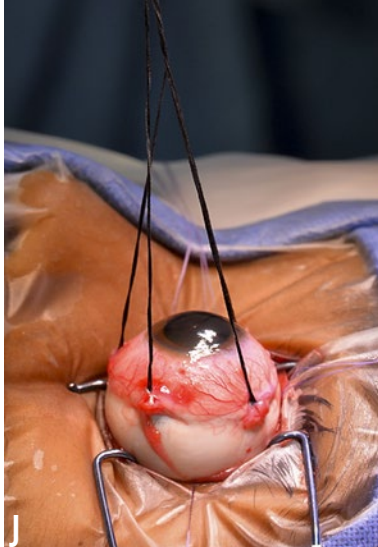
G Rectus muscle dis-inserted. This procedure is repeated till all 4 recti muscles are dis-inserted



H Superior and **I** inferior oblique muscles identified and dis-inserted directly



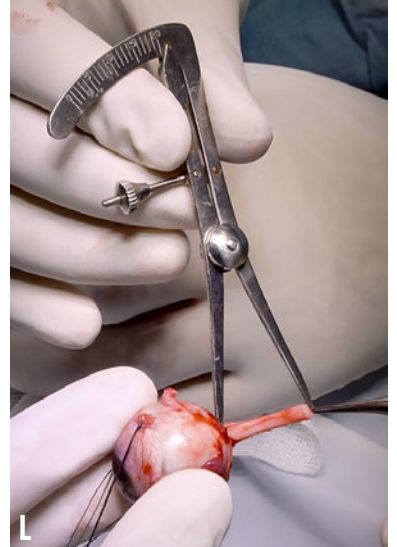
J The globe prolapsed out of the socket with the aid of traction sutures



K Adequate length of optic nerve is cut



L The globe is inspected and the length of optic nerve is measured

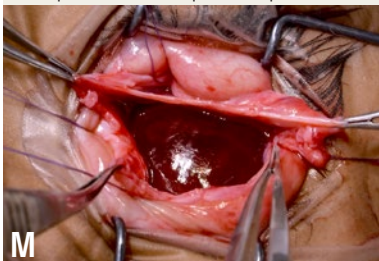


- 9 After all six of the extraocular muscles have been severed, use the four traction sutures to exert gentle traction on the globe and facilitate globe prolapse. This is an important step to obtain an adequate length of optic nerve subsequently. If there is resistance to globe prolapse, there may be several reasons. If the eye speculum is too tight, replace it with the correct eye speculum. If the surgical space is too narrow (due to a small orbit), perform a small lateral canthotomy or a relaxing horizontal conjunctival incision laterally. It may also be due to incomplete severing of extraocular muscles, so check these again.
- 10 Curved tenotomy scissors are then inserted by the lateral approach and the optic nerve is identified near the orbital apex.
- 11 The optic nerve is then cut just above the orbital apex to avoid damage to the important structures there. This ensures adequate length of the optic nerve (>15 mm). Give hypotensive anesthesia and/or a reverse Trendelenburg position (the head is 15–30 degrees higher than the feet) to ensure minimal bleeding during this step.
- 12 Pack the socket immediately with gauze and keep in place for 5 minutes to stop bleeding and avoid the formation of a haematoma.
- 13 Inspect the enucleated globe for any evidence of extrascleral extension of the tumour. Measure the length of optic nerve using calipers.
- 14 Send the globe for detailed histopathology analysis.
- 15 After stopping the bleeding, identify the posterior Tenon's capsule. Place an adequate-sized implant in the intraconal space. The implant is secured in place by suturing the posterior Tenon's capsule with absorbable sutures. The author prefers to use non-integrated implant for retinoblastoma cases.
- 16 The tag sutures attached to the cut end of the recti muscles are then brought out externally through the conjunctival fornices.
- 17 The anterior Tenon's capsule and the conjunctiva are then closed with absorbable sutures in two layers.
- 18 The tag sutures are then knotted to each other, thus completing the myoconjunctival technique of enucleation.
- 19 An iris-painted or a plain conformer with a draining pore is then placed in the socket. The conformer can be secured in place with central suture tarsorrhaphy.
- 20 A pressure patch is applied for 24 hours.

Postoperative care

- The pressure patch is removed after 24 hours
- Patient is given oral antibiotics for 1 week
- Topical antibiotics are prescribed for 2 weeks and topical steroids are tapered over 6 weeks
- The suture tarsorrhaphy is removed after 1 week
- Based on the histopathology report, further treatment may be required. Presence of high-risk features on histopathology (refer to page 17 for further details) are an indication for adjuvant systemic chemotherapy
- Dispense customised ocular prosthesis 6 weeks after enucleation.

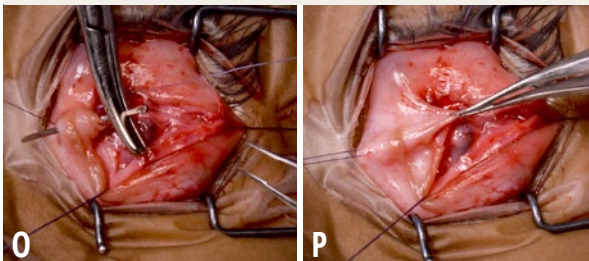
M Posterior Tenon's capsule and intraconal space are identified. Adequate sized implant is placed



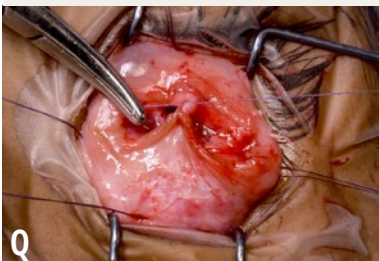
N Posterior Tenon's capsule is sutured



O, P Both ends of the tag sutures of the recti muscles are exteriorised at the respective fornices



Q Anterior Tenon's capsule is sutured



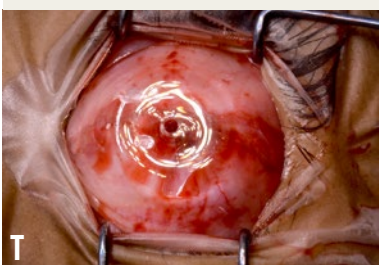
R Conjunctiva is sutured



S Myoconjunctival tag sutures are knotted



T Adequate size conformer is placed



U Suture tarsorrhaphy is performed



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Testing the red reflex

A red reflex test can detect cataract and retinoblastoma. Both conditions require urgent referral.

Why is it important to test the red reflex?

The red reflex test can reveal problems in the cornea, the lens, the vitreous, and the retina; it is particularly useful in young children who may develop eye diseases but who are too young to complain of not seeing.

What are the causes of an abnormal red reflex?

- Cataract
- Retinoblastoma
- Other uncommon diseases of the vitreous or retina

When to test the red reflex for retinoblastoma

It is important to test the red reflex after birth, at the age of six weeks, during routine consultations, or when parents are concerned about the child's vision or the appearance of her or his eyes.

How to test the red reflex

- The red reflex is much easier to see in a darkened room, so switch off the lights and draw the curtains, or ask the parents and child to go with you into a room which is dark.
- Use a direct ophthalmoscope (or an ArcLight) with the lens power set at '0'. Make sure the batteries are charged.
- Sit about half a metre (50 cm) away. Hold the ophthalmoscope close to your eyes.
- Encourage the child to look at the light source and direct the light at the child's eyes. You should see an equal and bright red reflex from each pupil.
- Pay attention to the colour and brightness of the red reflex. It should be identical in both eyes (Figure 1). Any absence of the red reflex, or a difference between the eyes, or an abnormal colour in the pupil (Figures 2–4) may indicate retinoblastoma or another serious eye condition.

To determine whether the red reflex is normal, comparison with the red reflex of a parent may be helpful. If you are not sure whether the reflex is normal, dilate the pupil for a complete examination. **If you are unable to dilate the pupil, refer the child to a specialist.**

What to do if the red reflex is abnormal

If possible, ask another colleague to check too. If the red reflex is abnormal, explain to the parents or carers that their baby/child may have an eye disease that will need to be treated. **Do not mention cancer or removal of the eye.**

Refer the child to a specialist for a complete eye examination. If possible, speak to the eye specialist by phone or text to explain the situation and confirm clinic times and dates.

Refer the baby/child to an eye specialist with an accompanying letter or note.

Make sure the parents know where to go and when. Emphasise that they must go in the next few days at the latest.



The red reflex is easier to see in a darkened room. TANZANIA

Figure 1 The normal red reflex

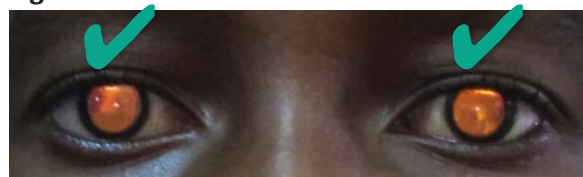


Figure 2 Right eye: the normal red reflex. Left eye: the absence of a red reflex is abnormal and could indicate a serious condition. Refer the child to a specialist.



Figure 3 Right eye: the normal red reflex. Left eye: the wrong colour in a red reflex (here white) could indicate a serious condition. The child in this image has a cataract in the left eye. Refer the child to a specialist.

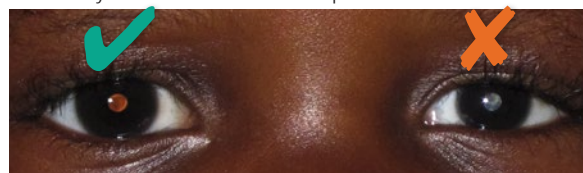


Figure 4 Right eye: the normal red reflex. Left eye: the wrong colour in a red reflex (here yellow-white) could indicate a serious condition. The child in this image may have retinoblastoma in the left eye. Refer the child to a specialist urgently.

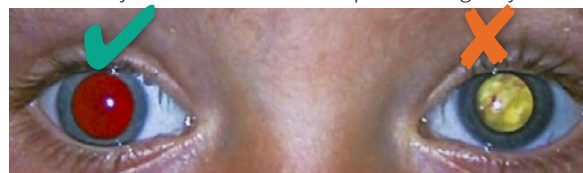
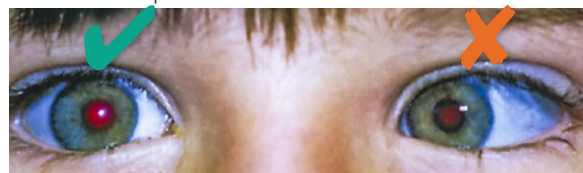


Figure 5 Right eye: the normal red reflex. Left eye: the red reflex is less bright and the corneal reflection (white spot on the cornea) is not centred. This is a squint, which may be the result of a serious underlying condition. Refer the child to a specialist.



Adapted from the poster: 'See RED' produced by JR Ainsworth, UK National Retinoblastoma Service, Birmingham, UK and the Childhood Eye Cancer Trust. www.chect.org.uk. First published in the *Community Eye Health Journal* French edition, Issue 8, 2011.

Making gains sustainable: partnering with WASH to stop the transmission of trachoma



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Partnering with the WASH sector is essential if face washing and environmental improvement components of SAFE are to succeed.

There has been impressive progress in recent years to eliminate trachoma. Large numbers of trichiasis operations and antibiotic treatments have contributed to a reduction in the number of people at risk of trachoma, from 325 million in 2011 to 182 million in 2016. In turn, many of the countries that were once among the most endemic, such as Uganda and Tanzania, are now on a path to achieve elimination.

The World Health Organization-endorsed SAFE strategy for trachoma elimination and treatment involves:

- Surgery to correct trichiasis
- Antibiotics for *C. trachomatis* infection
- Facial cleanliness to reduce transmission
- Environmental improvements to reduce risk of transmission and infection.

As countries progress towards elimination, new expanded partnerships and strategies to implement facial cleanliness (F) and environmental improvements to prevent the transmission of trachoma (E), usually known as 'F&E', are becoming increasingly important to sustain the progress being made.

Through two major partnership initiatives, The Queen Elizabeth Diamond Jubilee Trust's Trachoma Initiative and the UK's Department for International Development (DFID) SAFE Program, new efforts are being made to partner with the water, sanitation and hygiene (WASH) sectors. The International Coalition for Trachoma Control (ICTC) 'All you need for F&E' toolkit is providing programme managers with leading practices about partnering with the WASH sector to conduct joint planning and coordination of F&E activities. Additionally, through the Neglected Tropical Disease NGO Network (NNN) WASH Working Group, a

cross-sectoral partnership of key NTD and WASH stakeholders, priorities are being identified so that gaps in the implementation of F&E work can be filled.

In Uganda, messages that promote facial cleanliness are being directly integrated into community programmes led by WASH stakeholders. Incorporating facial cleanliness promotion into existing structures, such as the Mother Care Group (which already educates mothers about hand washing and sanitation) avoids duplication of efforts. Moreover, working alongside WASH organisations and community groups that have an



Children learn about hygiene and its link to trachoma and diarrhoea. TANZANIA

established trusted presence in the community increases the uptake of healthy behaviours, since community members are already engaged with the work being done.

Similarly, in Tanzania, partners are working with district health officers to involve community and religious leaders in community-led total sanitation and hygiene (CLTS-H) projects. By equipping leaders with information about trachoma prevention, communities can mobilise and take ownership over their own health behaviour. CLTS-H is recognised as being a crucial element in the uptake of sustained healthy behaviours, and it can be implemented with limited resources.

In Uganda, partners are also working with health authorities to revise national and school sanitation guidelines to include F&E education for the prevention of trachoma. This increases the reach of hygiene messages and ensures sustainability even after trachoma programmes reach completion. This also strengthens national health programmes and systems, which are an important building block for the achievement of Universal Health Coverage.

Despite significant progress, the trachoma community on its own cannot implement the F&E components of SAFE on a large enough scale. New partnerships are needed at all levels to ensure F&E interventions will reach all communities and be sustained. Scaling up WASH activities will contribute to the elimination of other NTDs and government health priorities such as diarrhoea, a major cause of childhood mortality. Partnering with the WASH sectors and scaling up activities will not only put the trachoma community on the path to achieve global elimination, but also help the world achieve the 2030 Sustainable Development Goals, with no one left behind.

Learning about hygiene. TANZANIA



River blindness: reducing the prevalence of clinical disease



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- 3 World Health Organization 2018. River blindness: shifting from prevention to surveillance and elimination.

It may be time to widen the focus of onchocerciasis programmes to include the prevention and treatment of clinical disease of the eyes and skin.

The once well-known – and disturbing – image of a person with river blindness (onchocerciasis) is now thankfully much less common, thanks to successful ivermectin distribution programmes that have reduced the prevalence of *Onchocerca volvulus* infection over the past 30 years.¹

However, as we celebrate this remarkable success, we must not forget those people who are still affected by clinical onchocerciasis (onchocercal eye and skin disease). There is a general perception that onchocerciasis is now much less of a public health problem than in past decades, and that new cases of onchocercal disease are few. This assumption needs to be backed up by solid research, especially in countries that are highly endemic and/or where the distribution of ivermectin has not been regularly achieved due to violent conflict. These countries include South Sudan and the Democratic Republic of Congo.

Surveys of onchocercal eye disease, which were common some 30 years ago, are rarely conducted these days.² A major factor for this is the current focus on elimination of transmission rather than prevention of disease.³

Unlike the global lymphatic filariasis programme, the global onchocerciasis programme has not had a strong individual patient care component in recent years. This is understandable, in part, because ivermectin is also used to reduce the clinical symptoms and signs of onchocercal disease. In addition, the expertise (ophthalmology and dermatology) needed for clinical assessment has not been readily available to national onchocerciasis programmes. Approaches to the care of those with onchocerciasis are listed in Table 1.

However, perhaps the most important unknown is the lack of reliable figures as to how many people are suffering from onchocercal eye and skin disease. This information is needed to provide treatment and care for those affected by both existing and new disease.



A boy guides a man who has river blindness. WEST AFRICA

Knowing the true reduction in eye and skin disease will allow us to accurately document the success that has been achieved and identify remaining any gaps that need attention. It should also encourage further support for those who have irreversibly lost vision or suffer from the severe forms of onchocercal skin disease.

As neglected tropical diseases gain ever more prominence in the context of Universal Health Care, we need to celebrate the successes in reducing the devastating effects of all diseases including onchocerciasis. Clinical onchocerciasis results in significant disability for the affected individual, which also impacts families and communities. We must actively look for remaining cases – both old and new – as is done with other disability- and stigma-inducing diseases such as lymphatic filariasis and leprosy. We should remember that the Global Program for Onchocerciasis Control was begun because there were patients that needed treatment and support. The ongoing challenge now is finding out how many people are still suffering from clinical onchocerciasis and its consequences – and what is being done to help them.

Table 1 Approaches to providing care for people with onchocerciasis

	Approach	Target community	Comments
A	Community drug distribution (PCT)	Whole endemic community	Will eventually reduce/eliminate incidence of new disease
B	Individual patient treatment/management	Those presenting with specific onchocercal symptoms	Includes ivermectin as well as specialised care for eyes and skin
C	Rehabilitation and care	Those permanently blind and their families	Includes links to associations for the blind, self-care groups, etc.

Test your knowledge and understanding

This page is designed to help you to test your own understanding of the concepts covered in this issue, and to reflect on what you have learnt.



A baby is prepared for chemotherapy. INDIA

SWATHI KALIKI

We hope that you will also discuss the questions with your colleagues and other members of the eye care team, perhaps in a journal club. To complete the activities online – and get instant feedback – please visit www.cehjournal.org

Tick ALL that are TRUE

Question 1

The following are clinical features of retinoblastoma in a child aged 18 months:

- ☐ a. white-yellow pupil reflex
- ☐ b. strabismus
- ☐ c. painful red eye
- ☐ d. decreased visual acuity
- ☐ e. proptosis

Question 2

The following are true for germline (hereditary) retinoblastoma:

- ☐ a. there is always a history of another family member having retinoblastoma
- ☐ b. tumours are often in both eyes
- ☐ c. there is a risk of other types of cancer in later life
- ☐ d. tumours are often multi-focal
- ☐ e. children present at an older age than non-hereditary cases.

Question 3

The following are methods of treating intra-ocular (stage 0 or 1) retinoblastoma:

- ☐ a. external beam radiotherapy
- ☐ b. intra-vitreous chemotherapy
- ☐ c. enucleation
- ☐ d. laser photocoagulation
- ☐ e. systemic chemotherapy.

Question 4

The following are methods of treating extra-ocular (stage 2, 3, 4) retinoblastoma:

- ☐ a. systemic chemotherapy
- ☐ b. intra-vitreous chemotherapy
- ☐ c. external beam radiotherapy
- ☐ d. laser photocoagulation
- ☐ e. exenteration.

ANSWERS

1. a, b, c and e are TRUE. A child of 18 months will not present with decreased visual acuity. A child with Rb may present with a turned in or turned out eye (strabismus), a white, yellow reflex in the pupil (leukocoria), a red painful eye due to secondary glaucoma from intra-ocular tumour or a protrusion of the eye due to spread of the tumour into the orbit.
2. b, c and d are TRUE. Germline (hereditary) disease may present as a first case with no previous family history. In germline retinoblastoma the children are usually younger at presentation (median age of 15 months as compared to 24 months for non-germline cases). Bilateral, multifocal disease is common in germline (hereditary) disease. As all cells in the body already have one Rb gene mutation, second cancers in other sites may occur later in life.
3. b, c, d and e are TRUE. External beam radiotherapy is no longer used to treat Rb confined to the globe, as it was found to be associated with an increased risk of cancers in patients with germline retinoblastoma.
4. a, c, and e are TRUE. If the disease has spread beyond the globe then intravitreal chemotherapy or laser photocoagulation are not appropriate.

Picture quiz



A 2-year-old male is brought by his parents. The history is that a white reflex was noted in the eye several months ago. The eye has now become red and painful (A). The patient is then lost to follow-up and comes back 6 months later with proptosis and frontal bossing (B).

Tick ALL that are TRUE

Question 1 What is your diagnosis?

- ☐ a. Endophthalmitis
- ☐ b. Coats disease
- ☐ c. Congenital glaucoma
- ☐ d. Retinoblastoma
- ☐ e. Staphylococcal

Question 2 How will you confirm the extent of disease?

- ☐ a. Clinical examination
- ☐ b. Computed tomography or magnetic resonance imaging of the orbit
- ☐ c. Cytology of bone marrow aspirate
- ☐ d. Cytology of cerebrospinal fluid
- ☐ e. All the above

Question 3 What is the treatment of choice for the left eye?

- ☐ a. Primary enucleation followed by 6 cycles of systemic chemotherapy
- ☐ b. Primary exenteration followed by 6 cycles of systemic chemotherapy
- ☐ c. Primary enucleation followed by orbital external beam radiotherapy
- ☐ d. Primary exenteration followed by orbital external beam radiotherapy
- ☐ e. Combination treatment of systemic chemotherapy, enucleation, and orbital external beam radiotherapy

ANSWERS

1. (d) Retinoblastoma
2. (e) All the above. Clinical examination confirms the laterality of disease. Imaging of the orbit confirms the presence of extraocular extension, and confirms the presence or absence of optic nerve extension without associated intraocular extension. The two most common sites of metastases from retinoblastoma are cerebrospinal fluid and bone marrow. Cytology from these two sites is indicated in all cases of retinoblastoma with extraocular extension. 3. (e) Combination treatment of systemic chemotherapy, enucleation, and orbital external beam radiotherapy. Primary enucleation or exenteration should not be done in cases with extraocular or optic nerve extension, since this can worsen the prognosis due to tumour spill over. The ideal treatment modality is a multimodal approach of chemoreduction followed by surgery, radiotherapy, and adjuvant chemotherapy.

ANNOUNCEMENTS & RESOURCES

2018 ROP Africa Symposium

The International Pediatric Ophthalmology and Strabismus Council and The Department of Pediatric Ophthalmology at The Red Cross War Memorial Children's Hospital, Cape Town are proud to announce the 2018 ROP Africa Symposium.

Date: 3–4 September 2018

Venue: Surgical Skills Training Centre, Red Cross War Memorial Children's Hospital, Cape Town, South Africa

Mark your calendars for this international 2-day clinical conference and hands-on workshop for ophthalmologists and neonatologists caring for infants with retinopathy of prematurity. For more details, contact:

Jenny Baker at jbaker9@uic.edu



Courses

MSc Public Health for Eye Care, London School of Hygiene & Tropical Medicine

Fully funded scholarships are available for Commonwealth country nationals. The course aims to provide eye health professionals with the public health knowledge and skills required to reduce blindness and visual disability.

For more information visit

www.lshtm.ac.uk/study/masters/mscphec.html

or email romulo.fabunan@lshtm.ac.uk

Free online courses

ICEH Open Education for eye care programme offers a series of online courses in key topics in public health eye care. All the courses are free to access.

Courses:

Global Blindness, Eliminating Trachoma, Ophthalmic Epidemiology Basic Principles (1) and Application to Eye Disease (2).

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World Retinoblastoma Awareness week

To increase awareness about Retinoblastoma every year seven days from the second Sunday in May is celebrated as 'World Retinoblastoma Awareness Week', this year it will be celebrated from **May 13th to May 19th 2018**

Next issue



The next issue of the *Community Eye Health Journal* is on the theme **Finding, training and retaining ophthalmic personnel**

Key community eye health messages

If you see something white inside a child's eye, seek help



DIMARAS H, KIMANI K, ET AL. LANCET SEMINAR, 2012

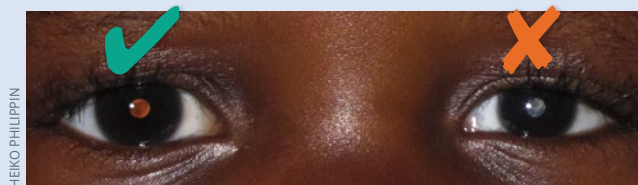
- This is easier to see in the early morning or late evening, or by a dim light
- Vision may not be affected
- Be determined. Do not let anyone turn you away until a specialist eye doctor has looked inside the child's eyes
- Health workers: believe the parents/carers and refer to a specialist – it is an emergency

Test the red reflex if you are able to



HEIKO PHILIPPIN

Left eye: the absence of a red reflex is abnormal and could indicate a serious condition. The reflex in the right eye is normal



HEIKO PHILIPPIN

Left eye: The wrong colour reflex (here white). The child has a cataract in the left eye and needs urgent treatment to avoid permanent vision loss

- The reflex should be the same in both eyes
- Check the red reflex in a relative's eye for comparison if you are unsure
- An abnormal, or absent, red reflex in one or both eyes is serious and may indicate cataract or retinoblastoma
- An absent red reflex is also abnormal
- An abnormal red reflex is an emergency. Refer the child to a specialist urgently
- If you have any doubts, refer to a specialist who can examine the back of the eye

Enucleation saves lives. With well fitted prostheses, children can have an attractive outcome



SWATHI KALIKI

After healing, a prosthesis is fitted in the left eye



SWATHI KALIKI

There is very little difference between the two eyes, allowing this girl to have a normal life



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Epidemiological and genetic considerations in retinoblastoma

Retinoblastoma is usually initiated by a random mutation of a gene in a retinal cell. It is important to try and recognise if the child has germline retinoblastoma, as this may affect both eyes of the child. Siblings and future children of the child with retinoblastoma are at greater risk of developing this cancer.

Incidence

Retinoblastoma (Rb) is the most common intraocular malignancy of childhood, but a relatively rare disease, occurring in approximately 1: 16,000-18,000 live births.¹ Its incidence is uniform across populations, with no gender or ethnic predilection and no environmental or socio-economic factors. Worldwide, approximately 8,000 children develop Rb each year. Of these, over 80% are from low- to middle-income countries from Asia and Africa. Rb develops in early childhood, with the vast majority of cases presenting before the age of 5 years.

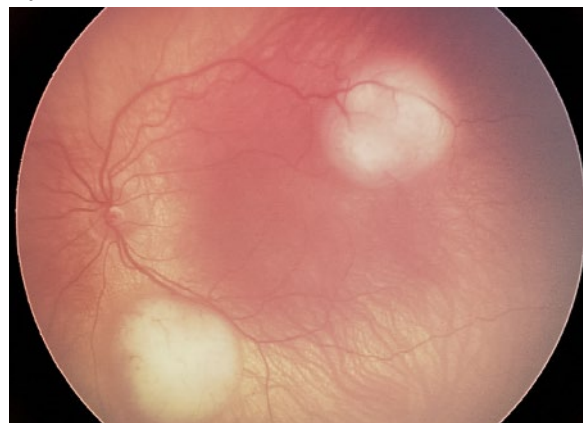
Aetiology

Rb can be inherited or develop *de novo* (sporadic) in a child with no family history of Rb. The cancer can involve one or both eyes and may present in an asymmetrical manner, with different grade eyes at presentation or even a unilateral presentation, with disease developing in the other eye later. The disorder originates in a photoreceptor cell of the retina early in childhood. In most instances, there is a mutation in the *RB1* gene. *RB1* loss initially produces a retinoma (Figure 1), the benign precursor of Rb, and causes genomic instability that subsequently leads to the cancerous tumour known as retinoblastoma. Interestingly, retinomas should be looked for and can be found in the parents of affected children, confirming that the disease is inherited in that family.

Figure 1 A right eye nasal retinocytoma incidentally found by an optometrist in an asymptomatic 8-year old boy with 20/20 vision. The patient was thereafter monitored in a specialised retinoblastoma service, with unchanged tumour on consecutive examinations.



Figure 2 Multifocal retinoblastoma in the left eye of a 1-year old child.



Characteristics of hereditary and sporadic disease

Patients diagnosed with Rb are categorised by whether the mutation is germline or non-germline (i.e. somatic). In germline disease, a single *RB1* allele is mutated in every cell of a child's body. An additional 'hit' in the second allele in the developing retina will result in clinical Rb. These children usually present with bilateral and multifocal disease (Figure 2) at a young age, median of 15 months, but can present with unilateral disease, albeit less frequently. A patient that presents with bilateral disease is 100% germline. However, it is estimated that 10–20 % of unilateral cases are also germline, emphasising the importance of genetic testing in addition to clinical examination.

Somatic (non-germline) cases usually present at a later age (median: 24 months) with unilateral and unifocal disease. In order for the disease to develop in somatic cases, two consecutive 'hits' need to occur in a retinal cell, resulting in mutation of both *RB1* alleles and development of clinical Rb.

Mosaicism

All heritable cases are germline, but not all germline cases have a familial history. This is because a mutation can occur at or after conception in an individual with no family history of Rb. Depending on the stage of development at which the mutation occurs, some of the foetus' cells will have a mutated *RB1* allele, and others will not, resulting in a mosaicism. Children with mosaicism are at increased risk of developing Rb. The disease in this scenario has no family history. The siblings of the affected child are not at risk, but offspring may be at risk and should therefore be screened soon after birth.

Developing Rb genetics and counselling

It was long believed that mutated *RB1* genes are a prerequisite to develop Rb. Recently, however, researchers have found that Rb may arise even in the presence of non-mutated *RB1* genes when the *MYCN* oncogene is amplified.² These cases are relatively rare, occurring in <3% of unilateral Rb cases, and present earlier, at a median age of 4.5 months.

The field of Rb molecular genetics has evolved significantly since the *RB1* gene was cloned in the mid-1980's.² Today, genetic laboratories are able to detect specific mutations and correlate them to the probability of developing Rb in an individual and her or his relatives. It has also set the basis for the development of screening programmes, which are discussed by Rosser et al in the current issue.

Knowledge of the genetic status has direct impact on the recommended screening frequency and also

on the recommended screening protocol for siblings and offspring. Individuals harboring a germline mutation are also at risk of developing secondary

non-Rb malignancies later in life, a risk that is further intensified if treated with external-beam radiotherapy, a treatment modality that used to be commonly used for Rb.³

Genetic testing, however, is not available in all centres across the world, being particularly sparse in low-resource countries. Much effort is put into improving Rb management and public health related to Rb in these

countries. Genetic testing and screening will depend on genetic services being developed in these settings. Until then, clinicians should use epidemiological and clinical signs, including the age of presentation, laterality, tumour focality, presence of retinoma in a parent and family history of Rb, to counsel patients and their families.

“Genetic testing is not available in all centres across the world, being particularly sparse in low-resource countries.”



From the field

How we manage patients with retinoblastoma

Vikas Khetan

Senior Consultant: Sankara Nethralaya, Chennai, India.

When a child with retinoblastoma reports to our centre, a message is immediately passed on to a physician who treats retinoblastoma.

The child is then expedited to reach the physician, where a proper history is taken. After initial evaluation, drops are applied for pupillary dilatation. After the dilatation, the fundi are examined and a quick assessment of tumor volume and initial staging and grouping of the tumour in the eyes is made.

The child then undergoes ultrasound of both eyes, irrespective of it being unilateral presentation. An MRI of the

orbits and brain is then advised. The MRI usually happens the same day and reporting takes place within a few hours. Once this information is available, the child is scheduled for an examination under general anaesthesia. Following this, the treatment plan is discussed with the parents.

In case of an orbital presentation, or an MRI showing optic nerve involvement, additional testing in the form of cerebrospinal fluid (CSF) analysis and a bone marrow aspirate is conducted and evaluated. Staging of the tumour is then performed as per the tests.

If enucleation is planned, we always ask for an opinion from another retinoblastoma expert.

“If enucleation is planned, we always ask for an opinion from another retinoblastoma expert.”

The option of performing genetic testing is also discussed with the parents; however, this is not routinely done as a standard of care as the testing is often expensive and not many parents can afford it. Our aim therefore shifts to the management of the child.

We have an ocular oncologist in the team who visits our hospital to examine these children in case they require chemotherapy. We are also equipped to perform brachytherapy when needed.

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- 1 Kivelä T. The epidemiological challenge of the most frequent eye cancer: retinoblastoma, an issue of birth and death. *Br J Ophthalmol* 2009;93:1129–1131.
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- 3 Kleinerman RA, Tucker MA, Tarone RE, et al. Risk of new cancers after radiotherapy in long-term survivors of retinoblastoma: an extended follow-up. *J Clin Oncol* 2005;23:2272–9.

Standard reporting of high-risk histopathology features in retinoblastoma



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Once an eye with retinoblastoma is excised, accurate histopathological staging is essential in order to determine whether the child can leave the hospital completely cured, or may need chemotherapy or radiotherapy.

Histopathology examination in retinoblastoma

Surgical treatment for retinoblastoma is limited to enucleation (removal of the eye) or exenteration (removal of the eye and contents of the orbit). Histopathological examination of such specimens yields information which may affect decisions about further treatment. This information should be part of the clinical information when considering future management and prognosis.

Standard histopathological reporting of specimens

When histopathologists are dealing with cancer specimens, their reports should include standard and appropriate information items, commonly known as a dataset. In the UK, histopathologists use datasets produced by the Royal College of Pathologists. Data items are reviewed every two years and aligned with the international tumour, node, metastasis, (TNM) classification. The TNM classification for retinoblastoma has recently been updated from TNM7 to TNM8. The newest dataset for retinoblastoma from the Royal College of Pathologists (RCPATH), released in early 2018, reflects the changes in the TNM classification (see p. 34).

Histological high-risk features: rationale

The RCPATH dataset for retinoblastoma records whether tumour is present in specific structures. Presence of tumour in any of these structures is considered a histological high-risk feature (HHRF). Retinoblastoma specimens with HHRFs indicate that the patient is at higher risk for metastasis (tumour spread) than a patient whose specimen does not have such features.

Detection of HHRFs by the histopathologist influences management decisions. The histopathologist examining the specimen should therefore specifically seek such features. The structures where tumour presence is regarded as an HHRF are:

- anterior chamber
- iris
- trabecular meshwork
- Schlemm's canal
- ciliary body
- choroid (above a certain threshold)
- sclera
- extraocular structures
- retrolaminar optic nerve (including the cut end).

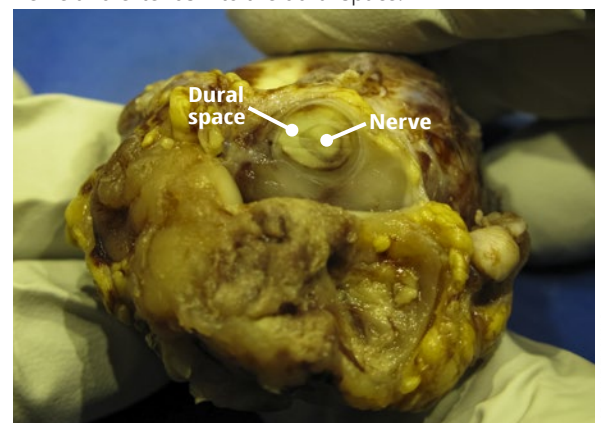
Gross examination of enucleation and exenteration specimens

The RCPATH dataset for retinoblastoma includes recommendations for macroscopic examination and sampling of globe and exenteration specimens. Even if resources are limited, it is useful to sample the cut end

of the optic nerve separately (if length allows) as well as a 'PO block' (see panel) of the globe. If the globe is being opened fresh to sample tumour for cytogenetics, the optic nerve should be sampled first. This will avoid artefactual contamination.

The sampled optic nerve should be embedded transversely, so that a full cross-section can be evaluated. It can either be embedded on the true resection margin (surgeon's cut end) or the pathologist's cut end, as long as the orientation is known to the reporting pathologist.

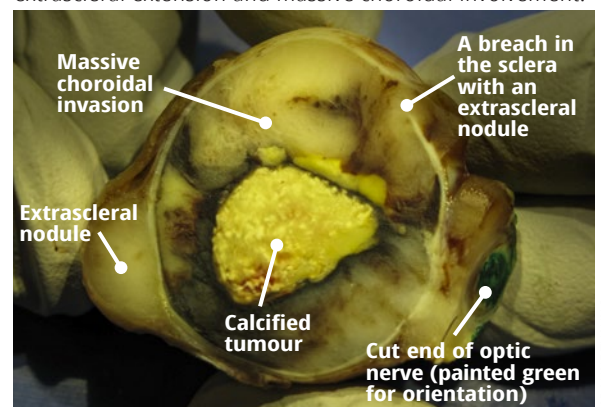
Figure 1 An exenteration specimen after the pathologist has cut the end of the optic nerve. Tumour partly fills the nerve and extends into the dural space.



CAROLINE THAUNG

If there is obvious extraocular extension such as an extrascleral nodule or orbital involvement in an exenteration specimen, the specimen should be sampled in such a way as to confirm this microscopically.

Figure 2 A globe with advanced retinoblastoma. There is extrascleral extension and massive choroidal involvement.



CAROLINE THAUNG

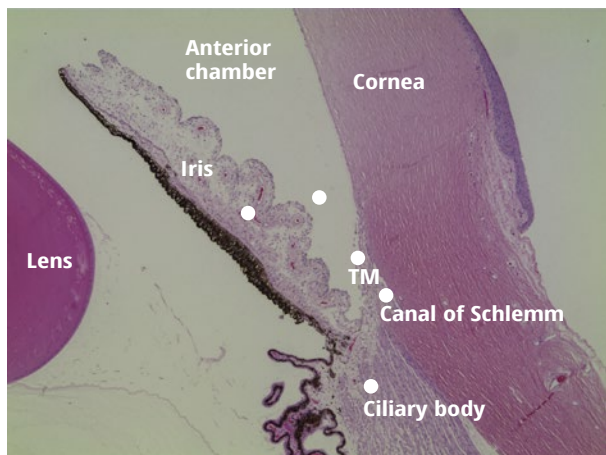
PO block

This is a slice which includes the cornea, pupil and optic disc. It is typically obtained by making two parallel slices from anterior to posterior, one either side of the limbus. The orientation of the parallel slides may be sagittal, transverse or oblique, depending on the location of the tumour and any other pathology to be sampled.

Eye structures can become distorted in advanced retinoblastoma, making microscopic examination difficult. If the globe is disorganised, PAS stain can help with orientation by highlighting Descemet's membrane, the lens capsule and Bruch's membrane.

Anterior segment and ciliary body

Figure 3 A normal anterior segment. Structures that may be involved in HHRF retinoblastoma are indicated with a white dot.



The anterior chamber is the space bounded by the cornea anteriorly, iris leaflets posteriorly and angle/trabecular meshwork peripherally. Schlemm's canal is not always easy to identify histologically, but lies adjacent to the trabecular meshwork. The ciliary body consists of the pars plicata (ciliary muscle covered internally by a double layer of ciliary epithelium) and the more posterior pars plicata.

Figure 4 An anterior segment with HHRF retinoblastoma involving the anterior chamber, iris and trabecular meshwork.

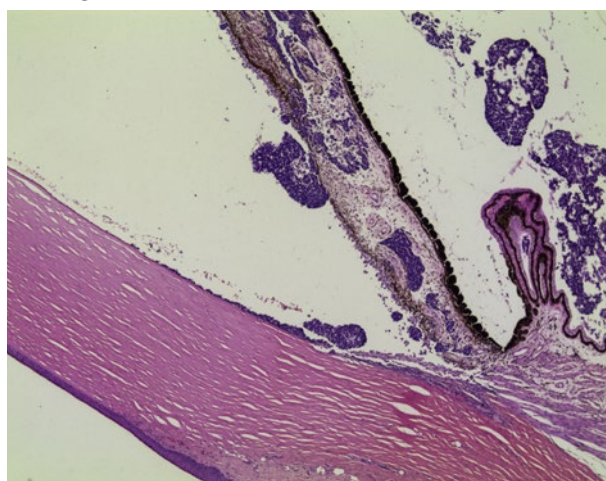
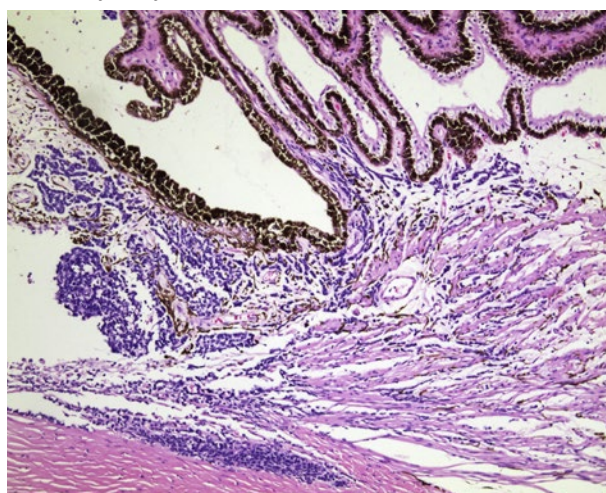


Figure 5 In this HHRF case, the iris, trabecular meshwork and ciliary body are invaded.

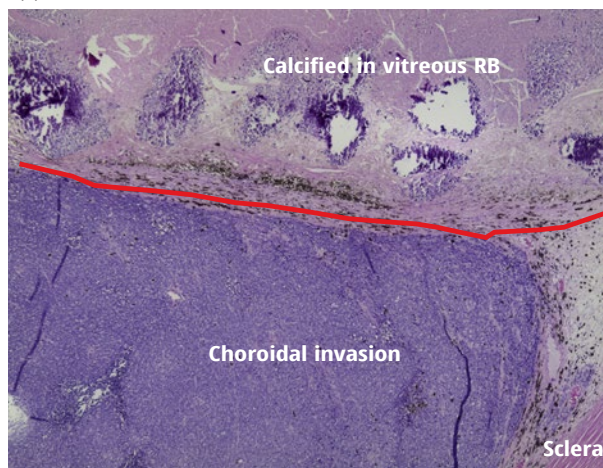


Choroid

The choroid lies between Bruch's membrane and the sclera. It consists of a capillary network (choriocapillaris) closer to Bruch's membrane, and a vascular stroma towards the sclera. If retinoblastoma invades the choroid, tumour deposits will be seen beneath Bruch's membrane. Bruch's membrane can be difficult to see. It is highlighted with PAS stain, and the retinal pigment epithelium (RPE) may also be a useful landmark.

It is useful to comment on focal choroidal involvement (deposits measuring <3mm either singly or in aggregate), but this is not an HHRF. HHRF relating to the choroid is defined as: massive choroidal invasion (a deposit ≥ 3 mm in any dimension) or multiple foci of focal choroidal involvement totalling ≥ 3 mm or any full-thickness choroidal involvement (ie touching the sclera).

Figure 6 This is the case from Figure 2, demonstrating massive choroidal invasion. The intraocular structures are largely obliterated. Residual RPE (red line) indicates the approximate border of the choroid.



Optic nerve

A transverse cross-section of the optic nerve which is free from tumour is confirmation that the (surgeon's) cut end is free from tumour. However, retrolaminar optic nerve involvement should also be assessed as it is an HHRF.

Figure 7 This is a normal optic nerve with the lamina cribrosa highlighted (between the red lines). Retinoblastoma invading posterior to the lamina cribrosa is an HHRF.

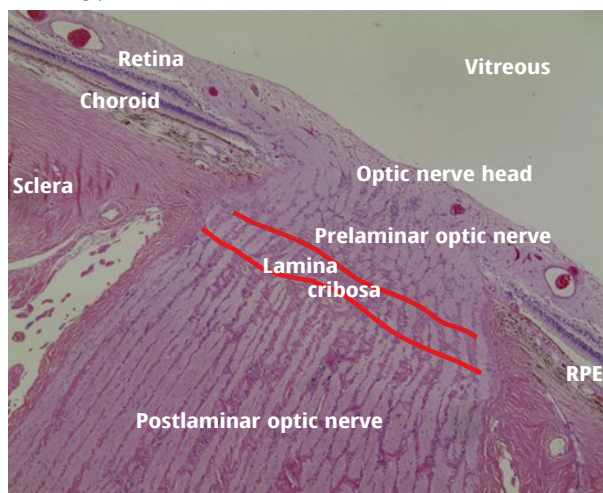


Figure 8 This is optic nerve with retinoblastoma invading past the lamina cribrosa (red line): postlaminar invasion.

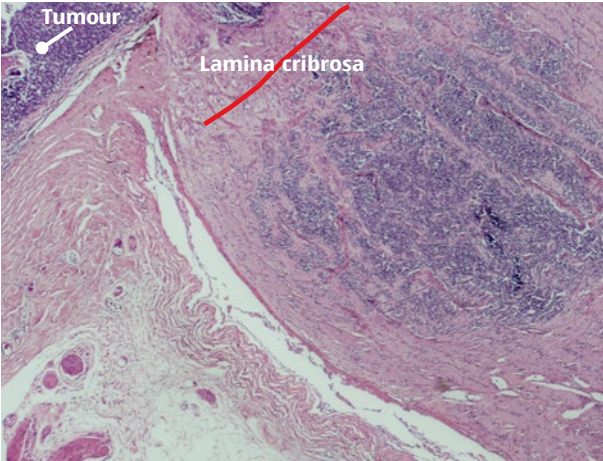
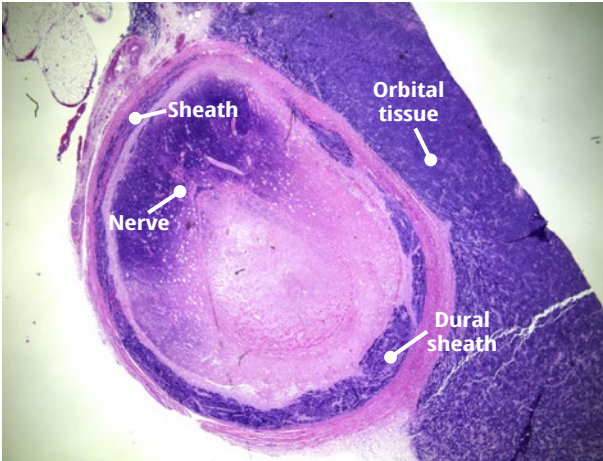


Figure 9 This is the optic nerve from the case illustrated in Figure 1. Retinoblastoma invades the nerve and surrounds it within the dural sheath. Tumour invades the sheath and there is also tumour in the adjacent orbital tissue.



Sclera and extraocular
If extrascleral fibroconnective tissue is fibrotic, it is not always straightforward to discern the difference between partial thickness scleral involvement and extrascleral involvement. However, both are considered HHRFs.

Checklist for assessing HHRF on microscopy This is a suggested ordering of examination in order to assess whether HHRF are present, with the easiest to detect listed first.

Structure	Tips on detection
Optic nerve cut end	easiest to assess in transverse section
Extraocular structures	identify the sclera
Retrolaminar optic nerve	identify the lamina cribrosa
Sclera	
Choroid (≥3mm single or aggregate, or touching sclera)	bounded by RPE/Bruchs' and sclera
Anterior chamber → iris → angle (trabecular meshwork and Schlemm's canal)	
Ciliary body	

Further reading
<https://www.rcpath.org/profession/publications/cancer-datasets.html> includes the current dataset for retinoblastoma and other tumours (free access).
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Brennan, R. C. et al. Comparison of high-risk histopathological features in eyes with primary or secondary enucleation for retinoblastoma. *Br J Ophthalmol* 99, 1366–1371 (2015) (free access)
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TNM8: The updated TNM classification for retinoblastoma

The TNM classification for retinoblastoma, which is developed by the American Joint Committee on Cancer (AJCC), has recently been updated from TNM7 to TNM8. The newest dataset for retinoblastoma from the UK's Royal College of Pathologists (RCPATH), released in early 2018, reflects the changes in the TNM classification.

Definition of primary tumour (cT)			Definition of regional lymph nodes (cN)		
cTX		Unknown evidence of intraocular tumour	cNX		Regional lymph nodes cannot be assessed
cT0		No evidence of intraocular tumour	cN0		No regional lymph nodes involvement
cT1		Intraocular tumour(s) with sub-retinal fluid \leq 5mm from the base of any tumour	cN1		Evidence of preauricular, submandibular, and cervical lymph node involvement
	cT1a	Tumours \leq 3mm and further than 1.5 mm from the disc and fovea	Definition of distant metastasis (M)		
	cT1b	Tumours $>$ 3 mm or closer than 1.5 mm to the disc and fovea	cM0		No signs or symptoms of intracranial or distant metastasis
cT2		Intraocular tumour(s) with retinal detachment, vitreous seeding or sub-retinal seeding	cM1		Distant metastasis without microscopic confirmation
	cT2a	Sub-retinal fluid $>$ 5 mm from the base of any tumour		cM1a	Tumour(s) involving any distant site (e.g. bone marrow, liver) on clinical or radiological tests
	cT2b	Tumours with vitreous seeding and/or sub-retinal seeding		cM1b	Tumour involving the central nervous system on radiological imaging (not including trilateral retinoblastoma)
cT3		Advanced intraocular tumour(s)	pM1		Distant metastasis with microscopic confirmation
	cT3a	Phthisis or pre-phthisis bulbi		pM1a	Histopathological confirmation of tumour at any distant site (e.g. bone marrow, liver, or other)
	cT3b	Tumour invasion of the pars plana, ciliary body, lens, zonules, iris or anterior chamber		pM1b	Histopathological confirmation of tumour in the cerebrospinal fluid or CNS parenchyma
	cT3c	Raised intraocular pressure with neovascularization and/or buphthalmos	Definition of heritable trait (H)		
	cT3d	Hyphema and/or massive vitreous hemorrhage	HX		Unknown or insufficient evidence of a constitutional RB1 gene mutation
	cT3e	Aseptic orbital cellulitis	H0		Normal RB1 alleles in blood tested with demonstrated high sensitivity assays
cT4		Extraocular tumour(s) involving the orbit, including the optic nerve	H1		Bilateral retinoblastoma, retinoblastoma with an intracranial CNS midline embryonic tumour (i.e. trilateral retinoblastoma), patient with family history of retinoblastoma, or molecular definition of constitutional RB1 gene mutation
	cT4a	Radiological evidence of retrobulbar optic nerve involvement or thickening of the optic nerve or involvement of the orbital tissues			
	cT4b	Extraocular tumour clinically evident with proptosis and orbital mass			

Are we testing visual acuity adequately?



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Visual field testing has benefited from advances in computerised technology and is considered highly accurate and reliable, whereas visual acuity testing still relies on the examiner to apply their best judgement. Is it time to reconsider?



Visual acuity being tested using a tumbling E chart. SIERRA LEONE

PETER CATON/SIGHTSAVERS

Visual acuity (VA) is perhaps the single most important piece of information obtained during an eye examination. Great importance is attached to it, as well as to any change noted. VA was chosen to be a primary outcome measure in numerous clinical trials on macular degeneration, cataract surgery, refractive surgery and others.

Therefore, VA testing should ideally benefit from the latest development in computerised technology and diagnostic algorithms. Is that really the case? While some may argue that the Early Treatment Diabetic Retinopathy Study (ETDRS) chart has revolutionised and standardised VA testing, one could wonder whether the ETDRS VA test methodology has more in common with a computerised visual field test or Goldmann perimetry.

In fact, much can be learned from visual field testing. Whereas VA and VF tests examine different aspects of the visual function, the progress made in the field of VF testing over the last 20 years might lead us to revisit the methodology used to test VA.

A typical automated 24-2 visual field test assesses the vision threshold in 52 locations, attaching a numerical value to each location. In contrast, a VA test checks the vision threshold in only a single location. Moreover, at each of the 52 locations used in a visual field test, the outcome is on a continuous scale, divided into 40 discrete steps (from 1 dB to 40 dB). Typically, VA is expressed as one of just 10 discrete steps (0.1–1.0), and the standard ETDRS chart has 11 steps (11 lines span the 0.1–1.0 range). In VF testing, in order to achieve a more accurate estimation of the endpoint, the threshold is typically crossed multiple times, in opposing directions (from seeing to non-seeing, again

to seeing, and back to non-seeing), whereas in VA testing the threshold is crossed only once.

In VF testing, each patient reply determines the brightness of the next stimulus projected, forming a dynamic, interactive test, whereas in VA testing the same questions are asked in the same order. In VF testing, the computer determines the final threshold value for each location, based on a complex algorithm, whereas in VA testing it is the examiner who relies on their best judgment. A VF test is not considered complete without reliability scores, whereas reliability and repeatability are not part of a VA test.

In visual field testing, during the course of a full-threshold 24-2 VF test, 8 VF locations are routinely checked twice, to measure repeatability. If so, why not routinely repeat VA measurements, say, 3–4 times? If a 24-2 SITA visual field test takes under 7 minutes,

determining the final threshold value reliably some 52 locations, shouldn't a comparable VA test take under 1 minute? Hence, should a well-designed and executed computerised VA test take any longer than a manual Snellen or ETDRS VA test takes?

In addition, not all patients need to have their test start point at the 20/200 letter size. An improved algorithm may take into account previous documented VA measurements, the population the subject belongs to (i.e. a school screening test versus a retina clinic) and/or pre-test probability modelling.

After noticing these methodological differences between visual field and VA tests, we can ask why we so casually accept a testing procedure that does not stand up to other diagnostic procedures' standards. While it may be argued that variability in

“Much can be learned from visual field testing.”



the subjective human response limit any potential benefits of incorporating more refined approaches, I believe that the progress made during the 20 years of automated VF testing serves as evidence contradicting this opinion. In fact, precisely because of the variability inherent in these subjective psychophysical tests, averaging multiple responses, as well as utilising thresholding algorithms, may allow more refined endpoints.

Others may argue that more refined VA results are of little clinical benefit, since VA is primarily used as a means to refract patients, and the smallest meaningful change in a prescription (1/4 spherical diopter) is roughly the equivalent of one Snellen chart line.

Following are several scenarios where our limited ability to test for VA accurately may sometimes get in the way of our goals. For example:

- 1 The enormous deterioration in vision that occurs when a patient's VA reduces from 20/200 to 20/400 is barely detectable using current methods.
- 2 More accurate VA data (with scores along a continuous scale (such as 20/32 vs. 20/37), along with reliability and confidence intervals, could increase the power of clinical trials, enabling a decrease in sample size, or alternatively, could shorten the

duration of the study. With current methods, this is not possible.

- 3 We are unable to conveniently quantify low VA (such as 20/800 vs. 20/900) and the less-than-ideal measurements of 'finger-counting' and 'hand-motion'.

In summary, it might turn out to be worthwhile to question the methods we currently use to test visual acuity in both clinical and the research settings.

Your contribution is welcome

Using more expensive equipment to test VA in the same way as VF testing would be helpful in a scientific setting (as LogMar was intended to do), but something low cost and fit for purpose is required for everyday use. We would like to see that happen, and you can help! Using the ideas and principles discussed in this article, think about how VA testing can be made more accurate and more reliable using charts and equipment that are easily available in countries with limited resources.

Write to admin@cehjournal.org with a 400-word description of your idea/approach – the best suggestions will be published in a future issue of the *Community Eye Health Journal*. Photographs are very welcome. Explain to patients that their photograph will be published online and obtain their written permission (we need to see a copy of this). The editor's decision is final.