Retinoblastoma: a curable, rare and deadly blinding disease

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 diagnosis, detection 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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EDITORIAL

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

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**I am a child, not a case**

**Abby White**

Chief Executive: World Eye Cancer Hope UK

[www.wechope.org](http://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.

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

| Individual responsibilities | Parent ➔ | Health worker/nurse ➔ | Ophthalmologist ➔ | Specialist eye centre |
|----------------------------|----------|------------------------|-------------------|-----------------------|
| 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 | Believe the parents if they say they have seen something white inside the pupil and seek specialist advice. Treat it as a medical emergency | Learn to recognise retinoblastoma and to identify eyes that need enucleation | Same as for ophthalmologists, plus: Learn how to give focal or laser treatment to smaller tumours (usually in the second eye) |
| 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 | Learn how to test the red reflex (p. 23). Test all children during routine visits and immunisations | Counsel parents about the good cosmetic outcomes of enucleation with implantation. Show pictures of children with good outcomes | Create multidisciplinary teams who work closely together to coordinate the treatment of each child |

**The Ministry of Health’s responsibilities towards the above**

| Run public awareness campaigns so that parents know that treatment is possible and know when to see a doctor | Ensure that the red reflex test (p. 23) is included in the curriculum for nurses and health workers | Ensure there is at least one ophthalmologist per 100,000 population | 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. |

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**Further reading**

- Rb-NET website [http://cehc.lshtm.ac.uk/dr-links/rbnet/](http://cehc.lshtm.ac.uk/dr-links/rbnet/)
- Resource manual [http://cehc.lshtm.ac.uk/resource-manual-for-rb-management-sept-1-002/](http://cehc.lshtm.ac.uk/resource-manual-for-rb-management-sept-1-002/)
- Arclight [www.arclightscope.com](http://www.arclightscope.com)
Retinoblastoma in South Asia

Retinoblastoma is most common eye cancer in young children. With an increasing population in South Asia, the number of cases of retinoblastoma are on the rise. Dr Santosh G Honavar and Dr Purnima Rajkarnikar Sthapit leading experts in retinoblastoma in South Asia shed light on the prevalence of the disease in the region and discuss ways in which community eye health workers can help in prevention.

1. What is the incidence of retinoblastoma in South Asia, and is there any regional variation?

The incidence of retinoblastoma varies from 1 in 16,000 to 18,000 live births, and is reported to be fairly constant. It is estimated that about 8000 new cases of retinoblastoma occur every year in the world, of which about 2000-3000 are in South Asia.

2. What are the factors influencing the high incidence of the disease in the region?

There is no data to show that there is abnormally high relative incidence of retinoblastoma in South Asia. Socioeconomic status and consanguinity do not play a role. The only logical reason for the higher number of cases occurring in the region is a relatively higher crude birth rate (CBR) as compared to the rest of the world (including population size). For example, CBR in South Asia is 20.5 as compared to 12.5 in the United States and <10 in most of Europe.

3. Are males more prone to retinoblastoma than females in the region?

No, retinoblastoma generally does not show gender bias. However, it has been noted that male babies are brought to medical attention more commonly than the affected female children.

4. At what age does it develop?

Heritable retinoblastoma can be present at birth or soon thereafter, and generally before 12 months after birth. Sporadic retinoblastoma can have late onset, reported mostly between 1-3 years and up to 6 years.

5. Why is it important to detect early and how early must it be detected?

As with all cancers, early diagnosis of retinoblastoma can help save life, salvage the eye and optimise vision. Ideally, it should be detected as early as possible, at least when the child develops a white reflex or squint in case of sporadic retinoblastoma or risk-stratified screening in heritable retinoblastoma. Early diagnosis means that the tumor is smaller in size and still intraocular. Therefore the chances of saving life and the eye are high. In late presentations, the tumor frequently spreads extraocularly and to the optic nerve, in which cases even with optimum treatment, mortality is high.

6. What modes of screening are available in the region?

Unfortunately, there is no formal mode of screening available in the South Asia region. Formal mode of screening would be system-driven and time-bound routine primary screening by the paediatrician and health care workers. If any abnormality is found during primary screening, it would prompt secondary screening by an ophthalmologist. It is recommended to screen at birth and every time a child is immunised. Fixation, alignment and red reflex can be routinely and inexpensively checked by a paediatrician or a trained health care worker. If any of these are abnormal, then an ophthalmology referral would be warranted.

In addition, bilateral cases that present to a specialised retinoblastoma center, or a general ophthalmologist, should prompt screening of siblings and relatives in general, as these cases are germline and there is risk of familial disease.
7. What are the current systems in place to screen and treat retinoblastoma?
Health care in South Asia is predominantly government supported. A majority of government-supported ophthalmology facilities are not specialised to be able to dedicate talent, time and resources to manage retinoblastoma. Centres of excellence do exist in the government health systems but are few and very busy.

Non-Governmental facilities where treatment is driven by a trained ocular oncologist leading a team of paediatric oncologist, radiation oncologist, paediatric anaesthesiologist, ophthalmic oncopathologist, geneticist and an ocularist are very few in the region. The National Retinoblastoma Foundation at the Centre for Sight in Hyderabad, India is one such comprehensive retinoblastoma management facility.

8. What are the survival rates of patients with Retinoblastoma in South Asia?
There is a large variation from country to country and region to region. With early diagnosis and specialist treatment, there is scope for about 98% life salvage, 90% eye salvage and about 80% vision salvage.

9. What steps must health ministries and programme planners take to raise awareness and prevent it in the region?
There are several measures that the health ministries and programme planners may initiate:
- Public education about white reflex as a harbinger of retinoblastoma
- Sensitisation of paediatricians and health care workers about retinoblastoma
- Routine screening of fixation, alignment and red reflex at scheduled interactions with the health system
- Establishment of hub-and-spokes model for retinoblastoma management with “spokes” equipped to screen, diagnose and follow-up, and perform focal treatment and enucleation, and “hubs” to take care of the entire management by a team lead by a trained ocular oncologist.

10. Does the SA region have enough specialists to tackle the numbers?
Unfortunately no. There are very few trained ocular oncologists in the region and we certainly need more. A standard calculation is that one ocular oncology centre is able to take care of 100 new patients a year. On average there are two to three new cases per million total population, so one centre for 50 million population is a minimum need.

11. Any successful programmes that were done in the past or are being done in the region to raise awareness about Retinoblastoma? Any government or NGO’s working on this?
There are several NGOs in India including CanKids and Iksha foundation that work extensively on retinoblastoma. National Retinoblastoma Foundation at Centre for Sight, India runs programmes to sensitise paediatricians and ophthalmologists.

Nepal Cancer Relief Society in association with Tilganga Institute of Ophthalmology conduct training and awareness sessions for primary health workers for early referrals of children presenting with leucocoria to rule out Retinoblastoma.

12. How can community eye health workers of different cadres help in diagnosis, prevention and treatment?
Eye health workers can all be trained to screen for fixation, alignment and red reflex. They can also use a smartphone based application to take pictures of children and identify those with subtle white reflex.
A national retinoblastoma network: experiences in Kenya and the UK

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.

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.
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).

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.

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.
Understanding retinoblastoma: epidemiology and genetics

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.

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.
Germline retinoblastoma: estimating risk and counselling the family

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.

Germline 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.

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 early.

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.
**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                                      |

**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

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)
- 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 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.

Table 1 Could this be retinoblastoma?

| Listen to the child’s carer | What the parents say, or what you can see | Could this be retinoblastoma? |
|-----------------------------|------------------------------------------|-----------------------------|
| The parent/carer says they saw something white in the eye | Yes |
| 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 |
| 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 |
| 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

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.

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).

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.

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 |
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 ≥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,
Munier and colleagues developed a technique for injecting chemotherapy directly into the vitreous cavity. 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.

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 extracocular. 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)**                                   | Retinoblastoma ≤ 3 mm (in basal dimension or thickness) |
| 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 | |
| **Group B (low risk)**                                        | Retinoblastoma > 3 mm (in basal dimension or thickness) or |
| 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 | • Macular location (≤3 mm from foveola)  
• Juxtapapillary location (≤1.5 mm from disc)  
• Additional subretinal fluid (≤3 mm from margin) |
| **Group C (moderate risk)**                                   | Retinoblastoma with: |
| 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 | • 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)**                                       | Retinoblastoma with: |
| 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 | • 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)**                                  | Extensive retinoblastoma occupying >50% globe or with |
| 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 | • 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

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.

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.

Multidisciplinary approach

In order to reach – or maintain – high survival rates of over 95%, 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)

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.
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

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**Table 1** Treatment of intraocular retinoblastoma

| International Intraocular Retinoblastoma Classification (IIRC) | Treatment |
|---------------------------------------------------------------|-----------|
| **Definition**                                                | **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 | Unilateral: Enucleate Bilateral: Attempt ‘Second Eye’ Salvage: Systemic chemotherapy +/- focal treatment. IF EYE SALVAGE FAILS: enucleation. |
| If Enucleated look for: High Risk Histopathological Features: Retrolaminar optic nerve involvement Choroidal Invasion >3 mm | 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: 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 |

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

| Drug             | Dose: Mg/m² | Rate of infusion | Diluent |
|------------------|-------------|------------------|---------|
| Vincristine      | 1.5 mg/m² 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        | 300 mg/m² BSA D1 | 4-hour infusion | 0.4 mg/ml in 0.9% NaCl Note: Rapid infusion will lead to hypotensive crisis |
| Carboplatin      | 600 mg/m² BSA D1 | 1-hour infusion | 0.5 mg/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 |
tumours with basal diameter and height less than 16 mm and 8 mm respectively. Iodine (I\textsuperscript{125}) and Ruthenium (Ru\textsuperscript{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.\textsuperscript{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 jigged 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 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.

**Figure 2** A multidisciplinary team discussion in Malawi
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.

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 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

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

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. 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. 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.

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 extracranial 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                               | Regimen of each cycle |
|--------------|------------------------------------|-----------------------|
| Vincristine  | Children <3 years: 0.05 mg/kg       | Day 1: Vincristine + Etoposide + Carboplatin |
|              | For children >3 years: 1.5 mg/m² body surface area (BSA) | Day 2: Etoposide |
| Etoposide    | 10 to 12 mg/kg                     |                       |
| Carboplatin  | 28 mg/kg                           |                       |
| Regimen of each cycle | Drugs delivered |                       |

Enucleation is just one step in treating extraocular retinoblastoma. INDIA

Swathi Kaliki
Head of The Operation Eyesight Universal Institute for Eye Cancer: LV Prasad Eye Institute, Hyderabad, India.

Vijay Anand Reddy Palkonda
Consultant Radiation Oncologist: L V Prasad Eye Institute & Senior Consultant, Professor and Head: Department of Radiation Oncology, Director: Apollo Cancer Hospital, Hyderabad, India.
A 4-year-old girl (A) presented with retinoblastoma with extraocular extension. 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. 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

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 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 same, a recent survey of 58 surgeons in 32 countries on enucleation techniques and implants in retinoblastoma revealed wide variations in practice. 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:

a. Eyes that have failed conservative treatment strategies
b. 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 tenotomy 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 ➤
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.

Curved tenotomy scissors are then inserted by the lateral approach and the optic nerve is identified near the orbital apex.

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.

Pack the socket immediately with gauze and keep in place for 5 minutes to stop bleeding and avoid the formation of a haematoma.

Inspect the enucleated globe for any evidence of extrascleral extension of the tumour. Measure the length of optic nerve using calipers.

Send the globe for detailed histopathology analysis.

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.

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

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 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.
River blindness: reducing the prevalence of clinical disease

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.

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

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-vitreal 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-vitreal chemotherapy
- c. external beam radiotherapy
- d. laser photocoagulation
- e. exenteration.

ANSWERS

1. a, c and e. This disease has spread beyond the globe then external beam radiotherapy or laser photocoagulation are not appropriate.

2. b, c and d. This 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. 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 cancer in later life.

4. a, c and e. If the disease has spread beyond the globe then intravitreal chemotherapy or laser photocoagulation are not appropriate.
**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 jnbaker9@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@lsthm.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

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**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. Staphyloma

**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. a, b, c, d, e  
2. b, c, d, e  
3. a, b, c, d, e

---

**Next issue**

The next issue of the Community Eye Health Journal is on the theme Finding, training and retaining ophthalmic personnel
If you see something white inside a child’s eye, seek help

• 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

• 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

After healing, a prosthesis is fitted in the left eye

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

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.

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.
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. 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. 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.

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

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. 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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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.

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
- extrascleral 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.

If there is obvious extraocular extension such as an extrascleral nodule or orbital involvement in an enucleation 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.

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 ≥3mm in any dimension) or multiple foci of focal choroidal involvement totalling ≥3mm 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.

**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.

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 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)

Sastre, X. et al. Proceedings of the Consensus Meetings From the International Retinoblastoma Staging Working Group on the Pathology Guidelines for the Examination of Enucleated Eyes and Evaluation of Prognostic Risk Factors in Retinoblastoma. *Archives of Pathology & Laboratory Medicine* 133, 1199–1202 (2009) (free access)
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 ≤ 5mm from the base of any tumour | cN1 Evidence of preauricular, submandibular, and cervical lymph node involvement |
| cT1a Tumours ≤ 3mm and further than 1.5 mm from the disc and fovea | |
| cT1b Tumours > 3 mm or closer than 1.5 mm to the disc and fovea | |
| cT2 Intraocular tumour(s) with retinal detachment, vitreous seeding or sub-retinal seeding | |
| cT2a Sub-retinal fluid > 5 mm from the base of any tumour | |
| cT2b Tumours with vitreous seeding and/or sub-retinal seeding | |
| cT3 Advanced intraocular tumour(s) | |
| cT3a Phthisis or pre-phthisis bulbi | |
| cT3b Tumour invasion of the pars plana, ciliary body, lens, zonules, iris or anterior chamber | |
| cT3c Raised intraocular pressure with neovascularization and/or buphthalmos | |
| cT3d Hyphema and/or massive vitreous hemorrhage | |
| cT3e Aseptic orbital cellulitis | |
| cT4 Extraocular tumour(s) involving the orbit, including the optic nerve | |
| 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 | |

| Definition of distant metastasis (M) |
|-------------------------------------|
| cM0 No signs or symptoms of intracranial or distant metastasis | |
| cM1 Distant metastasis without microscopic confirmation | |
| cM1a Tumour(s) involving any distant site (e.g. bone marrow, liver) on clinical or radiological test | |
| cM1b Tumour involving the central nervous system on radiological imaging (not including trilateral retinoblastoma) | |
| pM1 Distant metastasis with microscopic confirmation | |
| pM1a Histopathological confirmation of tumour at any distant site (e.g. bone marrow, liver, or other) | |
| pM1b Histopathological confirmation of tumour in the cerebrospinal fluid or CNS parenchyma | |

| Definition of heritable trait (H) |
|----------------------------------|
| HX Unknown or insufficient evidence of a constitutional RB1 gene mutation | |
| H0 Normal RB1 alleles in blood tested with demonstrated high sensitivity assays | |
| 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 | |
Are we testing visual acuity adequately?

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 (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...
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 detectible 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.