Cancer Association of South Africa (CANSA)

Fact Sheet on Childhood Retinoblastoma

Introduction
The human senses are man's most important contact to the environment. The human brain combines the fireworks of neurons of seeing, hearing, smelling, tasting, and touching into a meaningful whole. But individuals usually do not think about their senses until an organ stops working.

Humans have five senses: the eyes to see, the tongue to taste, the nose to smell, the ears to hear, and the skin to touch. By far the most important organs of sense are our eyes. The human eyes perceive up to eighty per cent (80%) of all impressions by means of sight. And if other senses such as taste or smell stop working, it is the eyes that best protect man from danger.

Retinoblastoma is a paediatric cancer that requires a careful integration of multidisciplinary care. Treatment of retinoblastoma aims to save the patient's life and preserve useful vision and, therefore, needs to be individualised. The management of intraocular retinoblastoma has evolved to a more risk-adapted approach that aims to minimize systemic exposure to drugs, optimise ocular drug delivery, and preserve useful vision. For patients presenting with extraocular retinoblastoma, treatment with intensive chemotherapy is required, including consolidation with high-dose chemotherapy and autologous hematopoietic stem cell rescue. While most patients with orbital disease and a large proportion of patients with systemic extra–central nervous system (CNS) metastases can be cured, the prognosis for patients with intracranial disease is dismal.
Retinoblastoma (Rb)
Retinoblastoma (Rb) is a cancerous tumour that grows in the retina of the eye, a layer of nerve tissue in the back of the eye that senses light and sends images to the brain.

A cancer of early childhood, retinoblastoma can affect developing foetuses in the womb, as well as newborns, babies, toddlers, and children up to 5 years old.

Many parents first see signs of Rb after noticing that their child's pupil (the dark circular area in the middle of the iris, the coloured part of the eye) appears whitish in bright light. Some parents notice this effect in photographs. This happens because the pupil is translucent (transparent) so, retinal tumours that lie behind the pupil may become noticeable.

While the majority of children who develop Rb are born with it, most are not diagnosed at birth. The average age at diagnosis is between 12 to 18 months. When diagnosed, most kids are treated successfully and able to preserve their sight while maintaining good vision.

Causes of Retinoblastoma (Rb)
Retinoblastoma occurs when nerve cells in the retina develop genetic mutations. These mutations cause the cells to continue growing and multiplying when healthy cells would die. This accumulating mass of cells forms a tumour. Rb cells can invade further into the eye and nearby structures. Rb can also spread (metastasise) to other areas of the body, including the brain and spine.

In the majority of cases, it is not clear what causes the genetic mutations that lead to Rb. However, it is possible for children to inherit a genetic mutation from their parents.

Gene mutations that increase the risk of Rb and other cancers can be passed from parents to children. Hereditary Rb is passed from parents to children in an autosomal dominant pattern, which means only one parent needs a single copy of the mutated gene to pass the increased risk of Rb on to the child. If one parent carries a mutated gene, each child has a 50 percent chance of inheriting that gene.

Although a genetic mutation increases a child's risk of Rb, it does not mean that cancer is inevitable.

Children with the inherited form of Rb tend to develop the disease at an earlier age. Hereditary Rb also tends to occur in both eyes, as opposed to just one eye.
Rb occurs due to mutations in a tumour suppressor gene (called RB1) located on chromosome #13. Two mutations (or gene changes) are necessary to ‘knock-out’ this gene, and cause uncontrolled cell growth. In inherited Rb (40 percent of the cases), the first mutation is inherited from a parent, while the second occurs during the development of the retina. In sporadic Rb (60 percent of the cases), both mutations occur during development of the retina. Sporadic means ‘occurs by chance’. Alterations in the RB1 gene have also been found in other tumours, including osteosarcoma and breast cancer.

Most children with inherited Rb generally have tumours involving both eyes. (In fact, all cases involving both eyes should be considered hereditary). The RB1 gene is an autosomal dominant gene, which
means that both males and females are equally affected, and there is a 50/50 chance, with each pregnancy, for a parent to transmit the gene to a child. When a child inherits the gene, there is a 75 to 90 percent chance for the second mutation to occur, resulting in Rb. This means that some children who inherit the mutation may never get the second mutation, and may, therefore, never develop Rb. They can, however, still transmit the gene to their offspring – this means that their children could develop the disease.

Consider the following statistics:
- 60 percent to 75 percent of Rb cases involve one eye (unilateral). Of these, about 15 percent are inherited, and the remaining 60 percent are sporadic.
- 25 percent of Rb cases are bilateral (both eyes) and hereditary.
- 15 percent of Rb cases are unilateral (one eye) and hereditary.

Any individual with a positive family history of Rb may want to seek genetic counselling to identify the specific risks of passing the gene or disease to their children (St Christopher Hospital).

**Incidence of Retinoblastoma (Rb)**
Neither the *South African Paediatric Tumour Registry* nor the *National Cancer Registry* provide any information on the incidence of Retinoblastoma.

Retinoblastoma is a relatively uncommon tumour of childhood that arises in the retina and accounts for about 3% of the cancers occurring in children younger than 15 years.

Retinoblastoma is a cancer of the very young child; two-thirds of all cases of retinoblastoma are diagnosed before age 2 years. Thus, while the estimated annual incidence in the United States is approximately 4 cases per 1 million children younger than 15 years, the age-adjusted annual incidence in children aged 0 to 4 years is 10 to 14 cases per 1 million (approximately 1 in 14,000–18,000 live births).

**Differential Diagnoses of Retinoblastoma (Rb)**
Retinoblastoma, the most common intraocular malignancy of childhood, exists in sporadic and heritable forms. Children with Rb frequently (but not always) present with leukocoria. Leukocoria literally means ‘white pupil’. It occurs when the pupil (the round hole in the coloured part of the eye) is white rather than the usual black. Differential diagnoses of leukocoria include:

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Pathophysiology</th>
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<tbody>
<tr>
<td>Cataract</td>
<td>Opacification (to become opaque) of the lens</td>
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<tr>
<td>Coat’s disease - a very rare congenital, nonhereditary eye disorder, causing full or partial blindness, characterized by abnormal development of blood vessels behind the retina. It can have a similar presentation to that of retinoblastoma</td>
<td>Accumulation of sub-retinal fluid and lipid</td>
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<td>Primary persistent hyperplastic vitreous</td>
<td>Remnants of embryologic mesenchymal tissue in vitreous cavity</td>
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<td>Retinal detachment</td>
<td>Fluid under the retina</td>
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<tr>
<td>Retinoblastoma</td>
<td>Ocular tumour</td>
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“The aim of the present study was to investigate the expression of microRNA (miR)-338-5p in retinoblastoma (RB), thereby evaluating whether it could have potential as a biomarker to screen patients with RB from healthy controls. The results revealed that miR-338-5p was significantly upregulated in patients with RB compared with in healthy controls. There was no significant difference in the expression of miR-338-5p between patients with RB of different age, sex, tumor stage or binocular disease. Receiver operator characteristic analysis indicated that serum miR-338-5p combined with neuron-specific enolase (NSE) had a larger area under the curve compared with serum miR-338-5p alone when diagnosing RB. In addition, suppression of miR-338-5p induced slower proliferation of ACBRI-181 and Y79 cells at 2, 3, 4 and 5 days compared with the negative control group. Flow cytometric analysis indicated that transfection with miR-338-5p inhibitor leads to significant cell cycle arrest in ACBRI-181 and Y79 cells compared with in the negative control group. Furthermore, transfection with miR-338-5p inhibitor significantly decreased ACBRI-181 and Y79 cell migration and invasion, suggesting that miR-338-5p may serve an oncogenic role in the progression of RB. In conclusion, the low expression of miR-338-5p in the serum of patients with RB suggests that it may be involved in the formation of RB. Serum miR-338-5p has the potential to be a tumor marker of RB, and, in combination with NSE, miR-338-5p may improve the early diagnosis rate of RB.”

Grading of Retinoblastoma (Rb)
A number of systems have been devised to stage Rb, with various end-points, and multiple systems are often used concurrently.

The International Retinoblastoma Classification predicts overall survival:

- **Stage 0**: patients treated conservatively
- **Stage I**: eye enucleated, completely resected histologically
- **Stage II**: eye enucleated, microscopic residual tumour
- **Stage III**: regional extension
  - A: overt orbital disease
  - B: pre-auricular or cervical lymph node extension
- **Stage IV**: metastatic disease
  - A: haematogeneous metastasis without CNS involvement
    - single lesion
    - multiple lesions
  - B: CNS metastatic involvement
    - Pre-chiasmatic lesion
- CNS mass
- leptomeningeal disease

**Screening of Retinoblastoma (Rb)**

In children with a positive family history of retinoblastoma, early-in-life screening by fundus exam is performed under general anaesthesia at regular intervals according to a schedule based on the absolute estimated risk, as determined by the identification of the *RB1* mutation in the family and the presence of the *RB1* mutation in the child. Infants born to affected parents have a dilated eye examination under anaesthesia as soon as possible in the first month of life, and a genetic evaluation is performed. Infants with a positive genetic test are examined under anaesthesia on a monthly basis. In infants who do not develop disease, monthly exams continue throughout the first year; the frequency of those studies may be decreased progressively during the second and subsequent years. Screening exams can improve prognosis in terms of globe sparing and use of less intensive, ocular-salvage treatments in children with a positive family history of retinoblastoma.

Common practice for the parents and siblings of patients with retinoblastoma is to have screening ophthalmic examinations to exclude an unknown familial disease. Siblings continue to be screened until age 3 to 5 years or until it is confirmed that they do not have an *RB1* gene mutation.

**Treatment of Retinoblastoma (Rb)**

For children with Rb in their eyes only, we use a mild form of chemotherapy to avoid or delay radiation therapy whenever possible. After the chemotherapy causes the Rb tumours to shrink, laser treatment is used, followed by cryotherapy (freezing treatment), and plaque brachytherapy (a form of focused radiation therapy) to cure the remainder.

Treatment of Rb is usually customised for each patient, and depends upon the age of the child, the involvement of one or both eyes, and whether or not the cancer has spread to other parts of the body.

The main treatment options are as follows:

**Enucleation** - enucleation (removal of the eye) is the most common treatment for Rb. During an enucleation, the eye is surgically removed. This is necessary because it is the only way to remove the cancer completely. It is not possible to remove the cancer from within the eye without removing the entire eye.

The removal of the eye is done under general anaesthesia. In the operation, the entire eye is removed along with a long piece of optic (eye) nerve as one specimen, and is sent to a pathologist for examination under a microscope.

The eyebrow, lids, and muscles of the eye are all left in place. Blinking, tearing, and movement of the brow are not affected from this surgery. The operation takes less than an hour and is not painful. Children go home the same day and are usually examined in the office on the following day when post-operative instructions and care are explained.
Prosthetic Replacement - a ball of plastic, rubber, or coral is placed where the eye had been so there is no cavity or hole. After the socket heals, it will look like the tissue on the inside of the lip.

The child is fitted for a prosthesis or false eye approximately three weeks after the operation. The prosthesis is made of plastic to look exactly like the other eye. The prosthetic eye does not move as well as a natural eye and tends to move better up and down than it does side to side. And, of course, the prosthetic eye does not see. There is currently no way to transplant or replace an entire eye.

When both eyes are involved, sometimes the more involved or “worse” eye is enucleated, while the other eye may be treated with one of the vision-preserving treatments, such as external beam radiation, plaque therapy, cryotherapy, laser treatment, or chemoreduction.

**External Beam Radiation Treatment** - external beam radiation has been used since the early 1900’s as a way to save the eye and the child’s vision. Rb is sensitive to radiation, and frequently the treatment is successful. The radiation treatment is performed on an outpatient basis five times per week over a three to four week stretch.

Custom-made plaster-of-paris moulds are made to prevent the head from moving during treatment and sometimes sedatives are prescribed prior to treatment.

Tumours usually get smaller (regress) and look scarred after external beam radiation treatment but they rarely disappear completely. In fact, they may even become more obvious to the parent as they shrink, because the pinkish-grey tumour mass is replaced by white calcium.

Immediately after treatment, the skin may be sunburned or a small patch of hair may be lost in the back of the head from the beam exit position. Long-term effects can include cataracts, radiation retinopathy (bleeding and exudates of the retina), impaired vision, and there may be temporal bone suppression, characterized by bones on the side of the head which do not grow normally.

Radiation can also increase a child’s risk of developing other tumours outside the eye for those children who carry the abnormal Rb gene in every cell of their bodies.

**Radioactive Plaques** - radioactive plaques are disks of radioactive material that were developed in the 1930’s to radiate Rb. Today, the isotope iodine-125 is used and the plaques are custom-built for each child.

According to New York State radiation safety rules, the child must be hospitalized for this procedure, and he or she undergoes two separate operations (one to insert the plaque and another to remove it) over three to seven days. Following the use of radioactive plaque, long-term effects including cataracts, radiation retinopathy, and impaired vision may occur.

**Laser Therapy** - laser therapy, which includes photocoagulation and laser hyperthermia (A type of treatment in which body tissue is exposed to high temperatures to damage and kill cancer cells), is a non-invasive treatment for Rb. Lasers very effectively destroy smaller Rb tumours. This type of treatment is usually done by focusing light through the pupil onto and surrounding the cancers in the eye.
A new delivery system of the laser, called a diopexy probe, enables treatment of the cancer by aiming the light through the wall of the eye and not through the pupil. Our physicians at Memorial Sloan Kettering were the first worldwide to use the diopexy probe.

Laser treatment is done under local or general anaesthesia, usually does not have any post-operative pain associated with it, and does not require any post-operative medications. Laser may be used alone in addition to external-beam radiation, plaques, or cryotherapy.

“Retinoblastoma is a rare form of cancer of the retina most prevalent in young children. We successfully show that laser induced cell disruption, mediated by gold plasmonic nanoparticle is a potential and efficient therapy to kill the cancerous cells. The proof of concept is demonstrated in vitro on cultured Y79 retinoblastoma cancer cells with a nanosecond laser at 527 nm, for both attached cells at the bottom of a petri dish and for floating, clustered cells in a viscous vitreous phantom comprised of hyaluronan (HA). We report a cellular death of 82% after irradiation in classic culture medium and a cellular death of 98% in vitreous phantom, for similar number of nanoparticles in each sample. It is found that the NPs efficiently penetrate the floating Y79 clusters cells in the vitreous phantom, leading to a cellular death of over 85% even within the centre of the aggregates. The proposed treatment technique is based on a similar nanosecond laser used to eliminate floaters in the vitreous, but with much lower (100 to 1000 times) fluences of 20 J.cm⁻².”

Cryotherapy - cryotherapy freezes smaller Rb tumours and is performed under local or general anaesthesia. A pen-like probe is placed on the sclera adjacent to the tumour and the tumour is frozen. Cryotherapy usually has to be repeated many times to successfully destroy all of the cancer cells.

Cryotherapy causes the lids and eye to swell for one to five days; sometimes the swelling is so much that the children are unable to open their lids for a few days. This can be frightening for the child and parents, but is usually harmless. Eye drops or ointment can be given to reduce the swelling.

Chemoreduction - chemoreduction is the treatment of Rb with chemotherapy. Chemotherapy given intravenously to your child passes through the blood stream, and, if successful, causes the tumours to shrink within a few weeks. Chemotherapy, with one or more drugs, can be given once, twice, or more often.

Depending on the drugs used, the child may or may not be hospitalized during this process. After chemotherapy, the child is re-examined and any remaining tumours are treated with cryotherapy, laser, or radioactive plaque. Systemic chemotherapy alone rarely, if ever, cures intraocular Rb. Children may require as many as twenty treatments every three weeks.

“Targeting the mammalian target of rapamycin (mTOR) is a promising strategy for cancer therapy. Temsirolimus, a FDA-approved anticancer drug with efficacy in certain solid tumors and hematologic malignancies, is a potent mTOR inhibitor. In this work, we are the first to provide preclinical evidence that temsirolimus is an attractive candidate for retinoblastoma treatment as a dual inhibitor of retinoblastoma and angiogenesis. We show that temsirolimus selectively inhibits growth, survival and migration of retinoblastoma cells while sparing normal retinal and fibroblast cells, with IC₅₀ value that is within the clinically achievable range. Temsirolimus potently inhibits retinal angiogenesis via targeting biological functions of retinal endothelial cells. Our mechanism analysis demonstrates that..."
temsirolimus inhibits retinoblastoma and angiogenesis via suppressing mTOR signalling and secretion of proangiogenic cytokines. In line with in vitro data, we further demonstrate the inhibitory effects of temsirolimus on retinoblastoma and angiogenesis in in vivo xenograft mouse model. Our findings provide a preclinical rationale to explore temsirolimus as a strategy to treat retinoblastoma and highlight the therapeutic value of targeting mTOR in retinoblastoma.”

**Intra-arterial Chemotherapy** - intra-arterial chemotherapy is a new treatment for advanced Rb in which the chemotherapy drug is injected directly into the ophthalmic artery (the blood vessel that leads to the eye). The patient is given general anaesthesia by an anaesthesiologist. A thin tube is inserted through a blood vessel (the femoral artery) in the groin (the top part of the leg) and threaded up to the ophthalmic artery, where the chemotherapy is then injected into the eye. This method of chemotherapy delivery is designed to minimize the drug’s exposure to the rest of the body and to reduce side effects. The most common drugs used for this treatment are melphalan and topotecan. The average number of treatment sessions is about three for each eye, each session being delivered at four-week intervals. After a successful treatment, the tumours will shrink. If needed, residual tumours may be treated with laser, cryotherapy, or plaque.

Metastatic Rb - although it is rare, Rb can spread (metastasise) to the brain, the central nervous system, and the bones. In these cases, chemotherapy is prescribed by a paediatric oncologist and is administered through the peripheral blood vessels or into the brain for months to years after initial diagnosis of metastatic disease.

The results have been very promising. A new intrathecal medication (delivered into the fluid that surrounds the brain and spinal cord) is available for patients whose Rb has spread to the surface of the brain.

**McMahon, J.F., Jabbour, P. & Shields, C.L. 2019.**

“Intra-arterial chemotherapy (IAC) continues to provide a globe-sparing alternative as primary treatment for retinoblastoma with few adverse events. While there is growing evidence to highlight the utility of IAC in children with retinoblastoma, adult cases treated with primary IAC have not previously been characterized. We describe a rare case of Group D retinoblastoma in a 23-year-old adult treated successfully with IAC and intravitreal chemotherapy. This is a retrospective case report of a single patient. Subsequent to IAC and intravitreal chemotherapeutic treatments, at last follow-up 14 months following initial presentation and 8 months since last treatment, the retinoblastomademonstrated complete regression into a partially calcified scar, with complete resolution of intravitreal and subretinal seeds and no evidence of tumor recurrence. Visual acuity improved to 20/30 in the left eye. There were no adverse events from therapy. Despite its rarity, it is important to consider retinoblastoma in the differential diagnosis of a white mass, even in an adult. Furthermore, this case highlights the utility of IAC for retinoblastoma, despite older patient age.”

**Survivorship & Follow-Up Care** - most children with Rb - more than 95 percent - survive the cancer and have normal lives. Children with unilateral Rb have one eye whose sight is not affected even though they may have had one eye removed. It is important for children with vision in one eye to wear protective eyewear during sports and other activities.
Rb is a life-threatening disease, but it is rarely a fatal one if treated appropriately. With the correct treatment and appropriate follow-up both for eyes and for cancers in other parts of the body, a child with Rb has a very good chance of living a long life.

The majority of children with bilateral Rb retain at least one eye with good vision, and many are able to retain the use of both eyes. However, all children with bilateral disease and the 15 percent of unilateral patients who have the familial form of Rb will be at much higher risk for other cancers not involving the eyes throughout their lives.

Five years after a Rb diagnosis, children with the inherited form of the disease are more likely to die from second tumours than from Rb. The most common second tumours are osteogenic sarcoma (a cancerous tumour which affects the bones), soft tissue sarcomas, and cutaneous melanomas (tumours of the skin, muscle, and connective tissue).

Although the reported incidences of these tumours vary widely, the risk appears to be about 1 percent a year. This risk is also increased by the use of external-beam radiation, although the amount of increase depends on the age at which the child was treated.

Follow-up appointments with an ophthalmologist and a paediatric oncologist are very important when a child is diagnosed with Rb. Frequency of examinations depends upon the age of the child, the ophthalmologist’s suspicion of new tumours, whether one or both eyes are involved, and the type of treatment that the child has received. Parents are encouraged to talk to the treating oncologist and to call with questions between visits.

Contemporary management of retinoblastoma in the context of a low-resource country
Ademola-Popoola, D.S., Opocher, E. & Reddy, M.A. 2019. Retinoblastoma (RB) is the most common ocular cancer, and it typically presents before the age of 5 years in over 90% of cases. In high resource countries, RB patients tend to survive and retain their sight. This is not the case in low-resource countries because of late presentation and delayed intervention arising mostly from sociocultural and socioeconomic challenges. RB has no gender or racial predilection; the incidence is estimated as 1:16,000-1:18,000 livebirths or 11/1 million children under 5 years. Most of the world’s RB cases are found in Asia and Africa while most RB treatment centres are in America and Europe. RB is easy to detect by caregivers as a glowing white ‘cat eye reflex’ at night or when captured on camera. Health workers at primary care level can detect RB in early life if red reflex test and/or squint (Hirschberg) tests are deployed as part of wellness checks done especially during routine immunisation and well-baby clinics in the first 24 months of life. In most cases of RB, biopsies for histological confirmation are not required for diagnosis and treatment decisions to be made. Clinical information, ophthalmic evaluation and imaging modalities are typically used. There have been significant changes in the management of RB using various treatment modalities such as enucleation with orbital implant, use of chemotherapy delivered through intravenous, intravitreal, pericocular and intra-arterial routes and targeted treatment with laser, cryotherapy and brachytherapy. Algorithm for management and development of the national RB program within the context of a low-resource country is presented from review of data extracted from Mendeley library, PubMed library, Google Scholar and One Network; full-text articles were mostly retrieved through the American Academy of Ophthalmology.
About Clinical Trials
Clinical trials are research studies that involve people. They are conducted under controlled conditions. Only about 10% of all drugs started in human clinical trials become an approved drug.

Clinical trials include:
- Trials to test effectiveness of new treatments
- Trials to test new ways of using current treatments
- Tests new interventions that may lower the risk of developing certain types of cancers
- Tests to find new ways of screening for cancer

The South African National Clinical Trials Register provides the public with updated information on clinical trials on human participants being conducted in South Africa. The Register provides information on the purpose of the clinical trial; who can participate, where the trial is located, and contact details.

For additional information, please visit: www.sanctr.gov.za/

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