All About Retinoblastoma

What is retinoblastoma?

Retinoblastoma is a cancer in the retina of the eye. The retina is the light-sensitive lining in the back part of the eye. It can affect one or both of the eyes. It causes a tumor to form within the eye, which can then grow and damage the internal structures of the eye.

What causes retinoblastoma and am I at risk?

Retinoblastoma is rare childhood cancer, affecting about 300 children in the United States every year. Although retinoblastoma can be diagnosed at any age, most children are diagnosed before the age of 2, and a majority of cases are diagnosed in children younger than 5 years of age. Retinoblastoma appears to equally affect boys and girls, as well as African Americans and Caucasians. Children who have a parent or sibling with this disease or children with a known mutation of chromosome 13q are at increased risk for developing retinoblastoma.

Retinoblastoma occurs when there is a mutation to the retinoblastoma gene (RB or RB1). This is a tumor suppressor gene that acts as a brake on cell division. This gene is present in all cells in the body. There are two copies of the RB1 gene in each cell. This gene is located on chromosome 13q. In order for retinoblastoma to occur, both copies of the gene need to have the mutation.

There are two types of retinoblastoma:

- **Congenital (heritable)**
  - A child with congenital retinoblastoma has an abnormality in the RB1 gene. Congenital retinoblastoma happens in two ways. This mutation can be inherited from a parent, even if they never had retinoblastoma—they are a “carrier” of the mutated gene or there is a germline mutation of these genes during fetal development. A germline mutation is any change to cells that are under development after conception.
  - Children with congenital retinoblastoma are more at risk to develop retinoblastoma in both eyes and may also have multiple tumor sites within the eye.
  - They may also be at a higher risk for other cancers including pineoblastoma, a tumor of the pineal gland at the base of the brain.
  - Occurs more frequently in younger children.

- **Sporadic (non-heritable)**
  - Also occurs as a result of the RB1 gene, but only in one cell in the eye.
  - Typically, these children only develop a tumor in one eye.
  - May occur in older children more often.

How can retinoblastoma be prevented?

Other than known genetic risk, there are no other known risk factors for retinoblastoma. There are no avoidable things you can do to prevent this cancer from happening.

What screening tests are used?

Outside of genetic screening/counseling in families with known chromosome 13q mutations, there are no routine screening tests for retinoblastoma.
What are the signs and symptoms of retinoblastoma?

The first sign of retinoblastoma may be when a parent or healthcare provider notices that the child’s eye looks abnormal.

The most common sign of retinoblastoma is called white pupillary reflex or leukocoria. This happens when there is no red reflex in the eye. The red reflex is caused by light being reflected from the retina. The retina has numerous blood vessels and a reddish appearance, thus light reflected from the pupil appears red. The red reflex is the same phenomenon responsible for "red-eye" seen when taking photos with a flash. In children with retinoblastoma, this reflex causes the light reflected from the pupil to appear white rather than red.

Other symptoms of retinoblastoma include:

- “Lazy eye” (strabismus)—when the eyes don’t appear to look or focus in the same direction. Usually, this is due to eye muscle weakness.
- Vision changes/problems.
- Pain in/around the eye.
- Redness in the whites of the eye.
- Eye bulging.
- Bleeding in the front of the eye.
- The pupil of the eye doesn’t get smaller when exposed to light.
- The iris (the colored part of the eye) may be different in each eye (example: one blue and one brown eye).

How is retinoblastoma diagnosed?

Retinoblastoma is made by a visual diagnosis by a healthcare provider. A fundoscopic eye exam (examination of the back of the eye, or retina) using an ophthalmoscope is also done to look into the eye. In order to get a better look at the pupil and the inside of the eye it will need to be dilated. This may be to be done under anesthesia, depending on the age of the child.

After this visual exam, if retinoblastoma is suspected, further imaging studies, such as MRI may be recommended. Genetic testing to determine if the RB(1) gene is present will also be performed to confirm the diagnosis. This genetic test can also determine if the child has the inheritable form or the sporadic form of the disease. If they are found to have the inheritable form, parents and siblings should be tested and be referred to a genetic counselor.

Blood testing and imaging of the brain will help to see if the disease has spread to other parts of the body. Abnormal blood counts may mean the retinoblastoma has spread. A brain MRI checks for another brain tumor which is associated with retinoblastoma (called a pineoblastoma). When this is present at diagnosis it is sometimes called trilateral disease.

How is retinoblastoma staged?

Staging is often used in cancer to help create a treatment plan. In retinoblastoma, staging is based on the location of the tumor as well as its size and if it has spread. Retinoblastoma is divided into 2 main groups: intraocular and extraocular.

- Intraocular: the cancer is within the eye.
- Extraocular: the cancer has spread outside the eye.

The International Classification system is used by most providers and divides intraocular retinoblastoma into 5 groups.

The International Grouping System:

- Group A: Small tumors that are less than or equal to 3 mm in size and only in the retina. These tumors are not near other important eye structures like the optic disc or the center of vision (foveola).
- Group B: Tumors that are larger than 3 mm and only in the retina.
- Group C: Tumors with small amounts of tumor under the retina (subretinal seeding) or into the jelly-like material in the eye (vitreous seeding).
- Group D: Larger, usually poorly defined tumors with widespread subretinal or vitreous seeding and retinal detachment.
• Group E: Large tumor that has spread to the front of the eye. It can bleed and can cause glaucoma.

It is also important to know whether the retinoblastoma is unilateral (affecting one eye) or bilateral (affecting two eyes). The tumor could look differently and be staged differently in each eye. If both eyes are affected, the treatment plan will be based on the eye with the more extensive disease. For example, if one eye is staged as group B and one is group E, treatment will be based on the group E staged eye.

How is retinoblastoma treated?

Treatment will be based on a number of factors including the stage, location, and size of the tumor as well as if the tumor as spread outside of the eye.

Surgery

Surgery for the treatment of retinoblastoma is usually only needed if the tumor is large when diagnosed and has already resulted in the loss of vision in the eye. In this case, enucleation, or total removal of the eye plus the optic nerve, would be used. It is possible that the removal of the eye will be necessary if other treatments used first to treat the tumor are not successful. This procedure is done under anesthesia and usually, the child can be fitted for an artificial eye after recovery.

Chemotherapy

Chemotherapy is the use of medications to kill cancer cells. These medications reach throughout the body-this is called systemic chemotherapy. Chemotherapy can be given in a number of ways including into a vein (IV), by mouth, or into a muscle. Chemotherapy treatments for retinoblastoma are usually given over several months. Sometimes, chemotherapy is given to shrink tumors that haven’t spread before other treatments are given. This is called chemoreduction. If the tumor has spread and the eye has been removed, chemotherapy may be used afterward; this is called adjuvant chemotherapy. If the tumor has spread to the brain, intrathecal chemotherapy, when medications are given directly into the cerebral spinal fluid, can be used.

Medications used in the treatment of retinoblastoma include carboplatin, cisplatin, vincristine, etoposide, cyclophosphamide, topotecan, and doxorubicin. These medications are used in combination called a regimen. Your child’s treatment plan will depend on the size and location of their specific tumor. There are short and long-term side effects of chemotherapy. Short-term side effects can include:

• Loss of hair (alopecia).
• Mouth sores (mucositis).
• Decreased appetite.
• Nausea/Vomiting.
• Fatigue.
• Increased infection risk.

Long-term and late effects of treatment occur months to even years after treatment. These can include:

• Kidney/bladder damage.
• Neuropathy/nerve damage.
• A risk of developing a secondary leukemia (AML).
• Damage to the heart.
• Fertility issues.

It is essential to talk with your care team about potential side effects prior to treatment as well as treatment for these side-effects and potential fertility preservation.

Intra-arterial Chemotherapy

Intra-arterial chemotherapy is a newer method of treating retinoblastoma that is still being studied in clinical trials. In this method, chemotherapy is given directly into the ophthalmic artery under general anesthesia. The most commonly used medication in this treatment is melphalan. Carboplatin and topotecan can also be given. This treatment does result in lower doses of chemotherapy being used and directed at one area of the body. Thus, it may result in fewer side effects. The short-
term side effects associated with this treatment include swelling around the eye, retinal detachment, bleeding, weakened eye muscles, and the loss of eyelashes. Because this treatment method is still being developed and studied, we don’t know much yet about long-term side effects.

**Intravitreal Chemotherapy**
This is another, newer method of giving chemotherapy directly into the vitreous humor, the jelly-like substance inside of the eye. This method may be used in combination with systemic and intra-arterial chemotherapy in children who have widespread tumor throughout the eye(s) that may not have responded to other treatments. Like intra-arterial chemotherapy, side effects of this treatment are focused around the eye.

**Cryotherapy**
Cryotherapy involves the killing of cancer cells by freezing them. Under general anesthesia, a small metal probe that has been cooled is inserted in the eye. This procedure usually needs to be done 2-3 times over the course of several months. It is only used in smaller tumors that are located near the front of the eye.

**Laser Therapy**
Laser therapy involves the use of focused light beams that can heat and destroy tumors. In laser photocoagulation, the laser is directed at the blood vessels that supply the tumors. The heat destroys them. This type of treatment can only be used in small tumors in the back of the eye. This treatment is performed under general anesthesia. Like cryotherapy, it is performed 2-3 times over the course of several months. Potential side effects are damage to the retina including retinal detachment.

In Transpupillary thermal therapy (TTT), a laser is also used, but the temperature used in this laser is lower than in photocoagulation. This can lower the risk of retinal side effects. It may also be used in combination with chemotherapy.

**Radiation**
In the past, radiation was used frequently for retinoblastoma but is not used as often today given the long-term effects of giving radiation to the eye and brain in young children. Proton therapy is being studied in the treatment of retinoblastoma, given its potential for more targeted therapy and fewer side effects. Brachytherapy may also be used in the treatment of retinoblastoma. This involves the placement of a radioactive implant into the eye near the tumor-delivering radiation to the tumor site.

**Clinical Trials**
There are clinical research trials for most types of cancer, and every stage of the disease. Clinical trials are designed to determine the value of specific treatments. Trials are often designed to treat a certain stage of cancer, either as the first form of treatment offered or as an option for treatment after other treatments have failed to work. They can be used to evaluate medications or treatments to prevent cancer, detect it earlier, or help manage side effects. Clinical trials are extremely important in furthering our knowledge of diseases. It is through clinical trials that we know what we do today, and many exciting new therapies are currently being tested. Talk to your provider about participating in clinical trials in your area. You can also explore currently open clinical trials using the OncoLink Clinical Trials Matching Service.

**Follow-Up Care and Survivorship**
For children with the inheritable form of retinoblastoma, follow-up is life-long due to the increased risk of a second cancer. These cancers are most often of the bone or soft tissues (sarcomas). It is essential that children with the inheritable form not smoke, as this has been shown to increase the risk of another cancer developing. It is also important to watch for disease in the opposite eye in children who are only affected in one eye. Disease in the other eye occurs most commonly in the inherited form of the disease. Children with inheritable retinoblastoma should have regular eye exams. Your healthcare provider will guide you on how often your child will need these examinations. Generally, if retinoblastoma is going to affect the other eye, it does so within three years of the diagnosis. Screening MRI’s are usually done every six months after the diagnosis of retinoblastoma, until the age of five.

After treatment for childhood cancer, you will be followed closely to monitor for the cancer coming back, to manage ongoing side effects, and to transition to survivorship. At first, you will have frequent appointments with providers and have ongoing tests to monitor your health and possible recurrence of your cancer. As time goes on, these visits and testing will become less
frequent. The oncology team will discuss the plan for follow up.

What can you do to live a healthy life after treatment? There is no supplement or specific food you can eat to assure good health, but there are things you can do to live healthier, prevent other diseases, detect cancers early and work with the social and emotional issues, including insurance, employment, relationships, sexual functioning, and fertility, that a prior cancer diagnosis sometimes brings with it. Your oncology team is there to support you and can help you find support resources.

It is important to have a plan for who will provide follow up care (an oncologist, survivorship doctor or primary care doctor). Talk with the team about developing a survivorship care plan or develop one using the Smart ALACC tool. Your child may benefit from being seen in a survivorship clinic. At a survivorship clinic, a provider can review your child’s history and provide recommendations. You can contact cancer centers in your area to see if they have a survivor's clinic or search for a clinic on OncoLink’s survivorship clinic list.

**Resources For More Information**

Retinoblastoma – the American Cancer Society

Retinoblastoma – St. Jude Children’s Research Hospital

The Eye Cancer Network: Provides disease specific educational information, support and networking for eye cancer patients and their caregivers.

OncoLink is designed for educational purposes only and is not engaged in rendering medical advice or professional services. The information provided through OncoLink should not be used for diagnosing or treating a health problem or a disease. It is not a substitute for professional care. If you have or suspect you may have a health problem or have questions or concerns about the medication that you have been prescribed, you should consult your health care provider.