

Retinoblastoma (RB) — Symptoms and Treatment

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Retinoblastoma is a highly malignant tumor of the eye that manifests in the first 3 years of life. It is considered as the most common intraocular cancer of childhood. Up to 4% of all pediatric malignancies are reported to be retinoblastomas. In the following article, you will gain an overview of the symptoms and treatment of retinoblastoma to achieve a perfect score on your next medical exam.



Definition of Retinoblastoma

It is a common congenital malignant tumor that arises from the neurosensory retina on one or both eyes.

Epidemiology of Retinoblastoma

It is considered the most common intraocular cancer of childhood with an incidence of 1 in 20,000 people. Up to 300 new cases of retinoblastoma are diagnosed each year in the United States. Fortunately, up to 95% of children with retinoblastoma who are diagnosed in the United States survive their malignancy.

The survival rate in the developing world for children with retinoblastoma is 50%. This can be explained by the earlier detection of the disease in the United States. These

tumors are highly malignant; therefore, early detection makes it possible to diagnose the patient while the disease is still contained within the eye without apparent distant metastases. In the developing world, retinoblastoma is often diagnosed after the tumor has invaded the orbit and reached the brain.

- In 25–30 % the disease is bilateral.
- It is more common in whites than in negroes.
- No sexual predilection has been reported.

Genetic Basis of Retinoblastoma

Retinoblastomas occur in children. It has been estimated that retinoblastoma has an annual incidence of 1 per 20,000 live births in the United States. An association between environmental factors and geographic demographics with the risk of retinoblastoma was not found, hence, the speculation that the disease is genetic-based has emerged.

Retinoblastoma can be inherited as a familiar tumor. Familial retinoblastoma accounts for 6% of the cases of retinoblastoma, and the remainder is reported to be sporadic cases with a negative family history of retinoblastoma.

Retinoblastoma can be classified as:

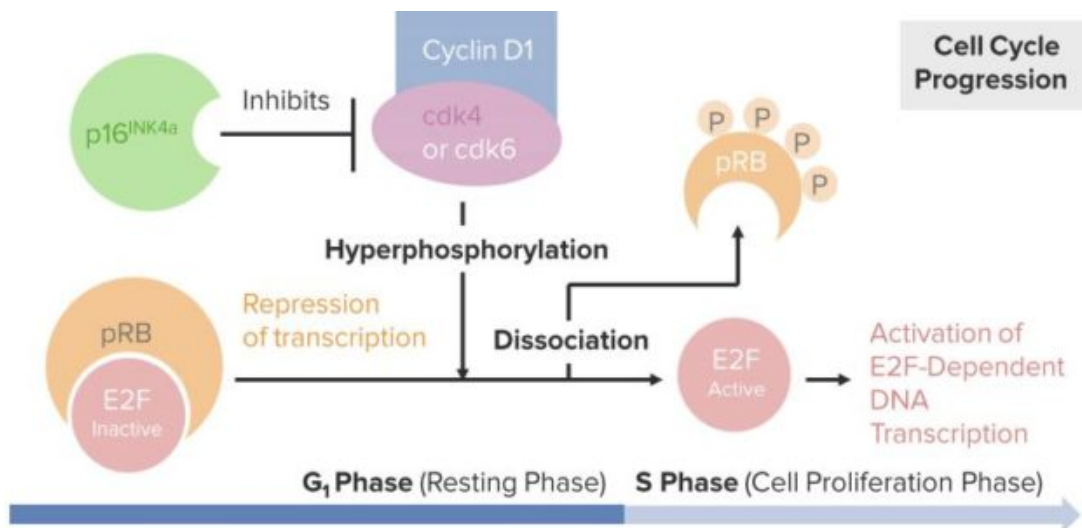
- Familial or nonfamilial
- Heritable or nonheritable
- Bilateral or unilateral

The most commonly used classifications are the first and third one. Meaning, you will find in most clinical notes the diagnosis to be written as familial bilateral retinoblastoma or sporadic unilateral retinoblastoma for instance. It should be noted that familial bilateral retinoblastoma is caused by a germline mutation that is heritable. On the other hand, unilateral sporadic retinoblastoma is most likely to be nonheritable.

The retinoblastoma gene is **located on the long arm of chromosome 13 on the locus 13q14**. An intact gene protects against retinoblastoma. For retinoblastoma to develop, both copies of this gene must be lost, deleted, mutated or inactivated. Therefore, this gene is believed to be a [tumor suppressor gene](#).

It is important to understand how this gene is affected in familial and sporadic cases of retinoblastoma from a clinical point of view. If the child has a familial “heritable” form of the disease, all cells in his or her body will have a loss of function of the retinoblastoma gene. Accordingly, the patient will be at an increased risk of developing other malignancies in other organs distant from the retina.

On the other hand, a patient with unilateral sporadic retinoblastoma will most likely have a nonheritable form of the disease. The loss of the gene will occur because of a two-hit phenomenon that is confined to the retina. The mutation will be somatic and will not affect other cells of the body. Therefore, the risk of malignancy in other parts of the body will not be increased.



"Retinoblastoma. Molecular Pathology" Image created by Lecturio

Life-Threatening Complications of Retinoblastoma

Patients with retinoblastoma **might develop metastasis, neuroblastic intracranial malignancy, or second primary tumors**. These complications might be life-threatening to the child.

Distant metastases are more likely to occur when the retinoblastoma invades the lamina cribrosa in the optic nerve, the sclera, the orbit, or the anterior chamber. Moreover, patients with retinoblastoma who do not receive adjuvant chemotherapy are at an increased risk of developing [metastases](#).

An association between hereditary retinoblastoma and neuroblastic intracranial malignancy has been established and reported in the literature. Moreover, the risk of developing a second primary tumor in the next 30 years after the diagnosis of hereditary retinoblastoma was reported to be as high as 35 %.

The most common second primary tumors include:

- Osteogenic sarcoma of the femur
- Spindle cell sarcoma
- Chondrosarcoma
- Rhabdomyosarcoma
- Glioma
- Leukemia
- Squamous cell carcinoma and malignant [melanoma](#)

Clinical Presentation of Retinoblastoma

Retinoblastoma presents in one of the four clinical stages of retinoblastoma:

1. Quiescent stage

Small retinoblastoma tumors can be an incidental finding on ophthalmoscopy. They appear as subtle, transparent lesions in the sensory retina. Larger tumors might be associated with leukocoria (white pupil).

Other presenting features include a squint, nystagmus and defective vision.

The growth patterns of retinoblastoma can be classified into intraretinal, endophytic, and exophytic. Tumors that are limited to the substance of the retina are classified as intraretinal retinoblastoma. If the tumor grows from the retina towards the vitreous cavity, the **term endophytic is used**. If the tumor grows from the retina externally, the term exophytic is used.

2. Glaucomatous stage

Arises from untreated tumors that present with redness, pain and excessive tearing.

3. Extraocular stage

Due to progressive tumor enlargement, the tumor burst the globe open through the sclera at the limbus. This results in fungating masses and proptosis.

4. Stage of metastasis

The metastasis may be lymphatic to preauricular lymph nodes, direct extension via the optic nerve to the brain and hematogenous spread to the brain and other organs.

Reese-Ellsworth Classification for Conservative Treatment of Retinoblastoma

The treatment of retinoblastoma needs to be as conservative as possible to salvage the affected eye. Accordingly, this classification system takes into account the outcome of the affected eye and not the systemic prognosis of the patient.

Group	Description	Affected-eye Salvage
I	<ul style="list-style-type: none">• A solitary tumor less than 4 disc-diameters in size, or• Multiple tumors none over 4 disc-diameters in size and all at or behind the equator	Very likely
II	<ul style="list-style-type: none">• A solitary tumor, 4 to 10 disc-diameters in size, or• Multiple tumors, 4 to 10 disc-diameters in size and behind the equator	Likely
III	<ul style="list-style-type: none">• Any tumor anterior to the equator• A solitary tumor that is larger than 10 disc-diameters in size and behind the equator	Doubtful
IV	<ul style="list-style-type: none">• Multiple tumors, some of which are larger than 10 disc-diameters in size• Any tumor extending anteriorly to the ora serrata	Unlikely
V	<ul style="list-style-type: none">• Massive tumors involving over half of the retina• Vitreous body seeding	Very unlikely

Diagnostic Workup for Retinoblastoma

The diagnosis of retinoblastoma is confirmed by **taking a detailed history, performing an adequate physical examination, and using a set of ocular examinations** that include external ocular examination, slit-lamp examination, and binocular indirect ophthalmoscopy with scleral indentation. The tumors can be visualized with indirect ophthalmoscopy and this is usually enough to confirm the diagnosis.

[Fluorescein angiography](#) is used to assess the vascularity of the tumor. Ultrasonography and computed tomography scans of the orbit are helpful in understanding the extent of the tumor. Magnetic resonance imaging is helpful in evaluating the status of the optic nerve, orbit, and brain.

Treatment of Retinoblastoma

The two most important goals of treatment of retinoblastoma are to:

- Save the patient's life
- Save the eye globe

Accordingly, one should **not focus very much on the visual acuity after treatment.** Preference should be given to saving the patient from the life-threatening complications we mentioned. The second most important goal is to save the eye globe for cosmetic, psychological, and social reasons that are obvious.

The treatment plan should be initiated by an expert ophthalmologist oncologist. If you are not experienced enough, consult an expert or refer your patient to an expert. The treatment of choice is chemo-reduction plus focal adjuvant treatment. If the Reese-Ellsworth classification puts the patient in group IV or V, enucleation might be the only option. If the tumor is large, however, the chances of eye-globe salvage are good, one should attempt chemo-reduction with or without external beam radiotherapy.

If chemo-reduction is being considered for a patient with intraocular retinoblastoma, the following regimen should be used for a total of 6 monthly cycles:

Day 1: vincristine, etoposide, and carboplatin

Day 2: etoposide alone

After chemo-reduction is performed, focal therapies are needed to remove the tumor. Focal therapies include:

- Laser photocoagulation
- Thermotherapy
- Cryotherapy
- Plaque radiotherapy

Laser photocoagulation is the focal therapy of choice for small retinoblastomas behind the equator of the eye. Laser photocoagulation, however, is rarely used after the application of chemo-reduction. Thermotherapy, on the other hand, can be used after chemo-reduction.

If the patient has advanced disease, no hope for useful vision in the affected eye, or invasion of the optic nerve, choroid, or orbit, enucleation is the treatment modality of choice.

References

Diagnosis and Management of Retinoblastoma by Carol Shields and Jerry Shields.
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