**Retinoblastoma**

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1. A 3-year-old boy has been referred for evaluation of right leukocoria. An examination under anesthesia is consistent with group E disease. His left eye has a normal retina.

What would be the most appropriate treatment for this child?

A. Intra-arterial chemotherapy

B. External beam radiation therapy

C. Systemic chemotherapy and focal treatments

D. Enucleation

E. Thermotherapy and cryotherapy

**Explanation**

According to the International Classification of Retinoblastoma, a group E eye is defined by the presence of advanced intraocular disease, with the presence of one or more of the following poor prognosis features:

 i. Tumor touching the lens

 ii. Tumor anterior to the vitreous involving the ciliary body or the anterior segment

 iii. Diffuse infiltrating retinoblastoma

 iv. Neovascular glaucoma

 v. Opaque media from hemorrhage

 vi. Tumor necrosis with aseptic orbital cellulitis

 vii. Phthisis bulbi

In the presence of these factors, ocular salvage treatments are not indicated, and enucleation is the recommended treatment.

2. A 2-year-old boy with unilateral retinoblastoma has undergone enucleation of the right eye. Pathology of the enucleated eye shows a retinoblastoma occupying 90% of the vitreous cavity with massive choroidal involvement and disease past the lamina cribrosa but without extending to the cut end of the optic nerve. MRI of the brain, bone scan, bone marrow aspirates and biopsies, and cerebrospinal fluid are negative for disease.

What would be your treatment recommendation?

A. Cisplatin-based chemotherapy followed by consolidation with high-dose chemotherapy and autologous hematopoietic stem cell rescue

B. Observation

C. Adjuvant chemotherapy with six cycles of vincristine, carboplatin, and etoposide (VCE)

D. Orbital radiation therapy

E. Adjuvant chemotherapy with six cycles of VCE and orbital radiation therapy

**Explanation**

This patient has high-risk pathology and elevated risk of recurrence, and therefore adjuvant chemotherapy is indicated. However, radiation therapy is not indicated because of the absence of trans-scleral disease or involvement of the cut end of the optic nerve. Intensive chemotherapy and autologous hematopoietic stem cell rescue is indicated only in the setting of metastatic disease.

3. A 3-year-old girl presented with left eye leukocoria. Examination under anesthesia revealed advanced intraocular retinoblastoma (group E) of the left eye and no evidence of disease in the right eye. An enucleation of the left eye was performed.

Which of the following histological features in the enucleated eye would indicate the need for adjuvant chemotherapy?

A. Massive vitreous seeding

B. Complete retinal detachment

C. Focal choroidal involvement

D. Subretinal seeding

E. Optic nerve involvement past the lamina cribrosa

**Explanation**

High-risk pathology is defined by massive choroidal involvement (more than 3 mm in thickness), scleral invasion, or involvement of the optic nerve past the lamina cribrosa. Patients presenting with any of these features in the enucleated eye should receive adjuvant chemotherapy. For patients with trans-scleral involvement or extension of the disease to the cut end of the optic nerve, radiation therapy is also indicated. Focal involvement of the choroid is common but is not associated with an increased risk of dissemination. Vitreous and subretinal seeding are important for response to treatment and ocular survival but are not associated with increased risk of extraocular spread. A complete retinal detachment is not uncommon in advanced intraocular retinoblastoma but has no prognostic relevance.

4. You are asked to see a 4-week-old infant born to a mother with history of bilateral retinoblastoma. Genetic testing done at birth shows the presence of a germline *RB1* mutation. However, examination under anesthesia shows normal retinas with no evidence of retinoblastoma.

As you discuss all of these results with the parents, what would be your recommendation for the next step?

A. Funduscopic examination under anesthesia in 4 weeks

B. Repeat genetic testing

C. MRI of brain and orbits

D. Chemotherapy with single-agent carboplatin

E. Dilated eye examination in 6 months

**Explanation**

This infant has hereditary retinoblastoma; the presence of a germline mutation of the *RB1* gene carries a high risk of developing bilateral retinoblastoma. Tumors typically develop throughout the first 2 years of life but are not always present at birth. Therefore, regardless of disease status at birth, these infants need to be examined very frequently, typically every 3 to 4 weeks, with dilated funduscopic examinations under anesthesia. Delaying the funduscopic examination for 6 months is not appropriate. MRI of brain and orbits should be performed in all patients with new diagnosis of retinoblastoma but is not necessary at this point; trilateral retinoblastoma usually develops 2 to 3 years after the diagnosis of bilateral retinoblastoma. There is no proven role for chemotherapy to prevent the development of disease.

5. A 9-month-old infant has been diagnosed with bilateral retinoblastoma. Examination under anesthesia shows group B disease in the right eye and group D disease in the left eye. What would be the most appropriate initial management of this patient?

A. Enucleation of the group D eye and focal therapy of the group B eye

B. Bilateral radiation therapy

C. Systemic or intra-arterial chemotherapy and focal treatments with laser and cryotherapy

D. Bilateral enucleation

E. Bilateral laser and cryotherapy only

**Explanation**

This is a typical presentation of patients with bilateral retinoblastoma. Upfront enucleation is typically recommended only for group E eyes, and focal treatments only, with no chemotherapy, is only recommended for group A eyes. In all other scenarios, the standard of care is to use chemotherapy to reduce the intraocular tumor burden and then proceed with aggressive focal consolidation. Chemotherapy can be given systemically or by direct delivery into the ophthalmic artery. Although radiation therapy as sole mode of therapy is a reasonable option, the risk of second malignancies and orbital growth delay, particularly significant at this age, makes radiation a less desirable treatment in the upfront setting. Radiation is now more commonly used as salvage treatment in patients with disease progression after more conservative treatments. Laser therapy (thermotherapy or photocoagulation) and cryotherapy are extremely important in the management of intraocular retinoblastoma; however, group B and D eyes, as is seen in this patient, need chemoreduction first, followed by focal treatments. This patient has a good chance of ocular salvage, particularly the group B eye, and thus bilateral enucleation is not typically recommended.

6. A 4-year-old girl you have been treating for bilateral retinoblastoma presents to the clinic with a 1-week history of headaches, vomiting, and progressive lethargy. What intracranial malignancy do you suspect as you evaluate the patient?

A. Medulloblastoma

B. Atypical theratoid rhabdoid tumor

C. Optic pathway glioma

D. Pineoblastoma

E. Choroid plexus carcinoma

**Explanation**

Survivors of bilateral retinoblastoma have an elevated risk of pineoblastoma, which occurs in up to 10% of cases. It is also called trilateral retinoblastoma, and it usually occurs 2 to 3 years after the diagnosis of retinoblastoma; most tumors are in the pineal gland, but a small proportion of cases present with a supratentorial neuroectodermal tumor. The incidence of medulloblastoma, atypical teratoid rhabdoid tumor, optic pathway gliomas, and choroid plexus carcinomas is not significantly elevated in children with bilateral retinoblastoma.

7. You are counseling the parents of a 7-year-old girl who was treated for bilateral retinoblastoma at 18 months of age and who was successfully treated with chemotherapy and focal treatments, without needing radiation therapy. The parents are interested in knowing more about the risk of second cancers.

What malignancy is your patient at highest risk of developing?

A. Leiomyosarcoma

B. Breast cancer

C. Pineoblastoma

D. Melanoma

E. Osteosarcoma

**Explanation**

All the tumors listed may occur in survivors of bilateral retinoblastoma. Osteosarcomas account for approximately 30% of second cancers in survivors of bilateral retinoblastoma and are the most common second malignancies both inside and outside the irradiation fields. Approximately 50% of osteosarcomas occur within the irradiation fields, and 25% to 30% of tumors occur in the extremities. Leiomyosarcoma is one of the most common soft tissue sarcomas in this population, and it typically occurs in the uterus; therefore, female survivors of bilateral retinoblastoma, as with the case under discussion, should be counseled about this possibility. Pineoblastoma, also called trilateral retinoblastoma, occurs in a small proportion of patients with bilateral retinoblastoma, typically before 5 years of age. Melanoma is also a common malignancy among survivors of bilateral retinoblastoma, and those with family history appear to have a higher incidence.

1. A 3-year-old boy is referred to you for evaluation of right leukocoria. Funduscopic examination under anesthesia reveals a large amelanotic mass occupying more than two-thirds of the vitreous space in his right eye, with massive retinal detachment, consistent with group E retinoblastoma. The left eye is normal. An MRI confirms the funduscopic findings and shows no extraocular disease. What is the most appropriate next step in the management of this child’s disease?
	1. Enucleation
	2. Systemic chemotherapy
	3. Brachytherapy
	4. Needle biopsy
	5. Intravitreal chemotherapy

**Answer: a (Enucleation)**

This boy has unilateral group E retinoblastoma. The standard of care for advanced intraocular disease is enucleation, followed by risk-adapted chemotherapy based on pathology. In some cases, systemic or intra-arterial chemotherapy together with intensive focal treatments may be offered for unilateral group E retinoblastoma, but the risks and benefits of this conservative approach need to be discussed in detail with the family. Brachytherapy may be used for small tumors that are not amenable to laser or cryotherapy but not for large tumors occupying the cavity. Intravitreal chemotherapy is used for the treatment of vitreous seeds. Finally, a biopsy is not recommended in the management of retinoblastoma because of the risk of orbital contamination. Retinoblastoma is one of the few malignancies in which treatment decisions are made without histologic confirmation.