Incidence

Retinoblastoma is the most frequent neoplasm of the eye in childhood occurring in about 1 in 14,000 - 18,000 live births. Thus, an estimated 300 children develop retinoblastoma each year in the United States. The incidence of retinoblastoma may be not distributed equally around the world. It appears to be higher (6-10/10^6 children) in Africa, India and among children of Native American descent in the North American continent. The increased incidence in those groups is primarily seen in unilateral cases. Whether these geographical variations are due to ethnic or socioeconomic factors is not well known. However, the fact that even in industrialized countries an increased incidence of retinoblastoma is associated with poverty and low levels of maternal education, suggests a role for the environment.

Retinoblastoma presents in two distinct clinical forms: 1) Bilateral or multifocal, hereditary (40% of cases), characterized by the presence of germline mutations of the \(RB1\) gene. Multifocal retinoblastoma may be inherited from an affected survivor (25%) or be the result of a new germline mutation (75%). 2). All but about 10% of unilateral or unifocal retinoblastomas are non-hereditary (60% of cases). About 10% of germline cases are unilateral; in the absence of a positive family history, however, it is not possible without genetic screening to determine which unilateral cases are capable of being transmitted to the next generation.

Clinical Manifestations

Retinoblastoma is by definition a tumor of the young child, and the age at presentation correlates with laterality. Patients with bilateral retinoblastoma tend to present at a younger age (usually before one year of age) than patients with unilateral disease (often in the second or third year of life). Half of the cases of retinoblastoma diagnosed during the first year are bilateral, compared with < 10% of cases diagnosed after one year of age. It is uncommon for retinoblastoma to be diagnosed during the first month of life, except in familial cases where examination has been recommended early; however, regardless of the family history, more than 90% of neonatal cases have either bilateral disease at presentation or will develop asynchronous bilateral retinoblastoma.

However, the presenting features of retinoblastoma vary depending on where in the world an affected child is seen. In developing countries, extraocular dissemination occurs more frequently so, patients usually present with proptosis.

---

and an orbital mass sometimes with preauricular adenopathy (Figure 1). In that setting, it is not uncommon to find severely affected children with extensive extraocular disease presenting with malnutrition, irritability, usually caused by glaucoma or increased intracranial pressure or fever of unknown origin.

Figure 1: Proptosis and leucokoria in a child with retinoblastoma

In developed countries, the most common presenting sign is leukocoria, which is occasionally first noticed after a flash photograph (Figure 2). Even though leukocoria is a quite specific sign with small differential diagnosis, it is often overlooked by paediatricians. Strabismus is the second most common presenting sign, and usually correlates with macular involvement.

Figure 2: A child with retinoblastoma presenting as leucokoria
Strabismus is a non-specific sign, often present in normal children, so it is also often overlooked. Very advanced intraocular tumors may become painful as a result in secondary glaucoma. Poor vision may be reported by older children.\(^3\) Differential diagnosis must be made with other childhood disease that can present with leukocoria, such as persistent hyperplastic primary vitreous, retrolental fibrodysplasia, Coat's disease, congenital cataracts, toxicariasis and toxoplasmosis. Patients may also present a red painful eye and orbital swelling resembling orbital celulitis and this not necessarily correlates with extraocular extension.\(^4\)

In familial cases, the diagnosis is usually made through screening, although almost 50% of familial cases are diagnosed later in life, when patients present with the typical signs of retinoblastoma, underscoring the importance of genetic counseling. Since tumors can develop up to 28 months of age in patients with family history, a thorough ophthalmological examination under anesthesia should be performed shortly after birth and periodically thereafter. Although most patients with bilateral retinoblastoma carry a germline mutation of the \(RB1\) gene, only a small proportion (5-6%) carry a deletion involving the 13q14 locus, which is large enough to be detected by karyotype analysis. Patients with the 13q-syndrome are characterized by typical facial dysmorphic features, subtle skeletal abnormalities, and different degrees of mental retardation and motor impairment.\(^5\) Dysmorphic features more consistently found include thick anteverted ear lobes, high and broad forehead, prominent philtrum, and short nose. A proportion of patients also have overlapping fingers and toes, microcephaly and delayed skeletal maturation. The severity of the deficits correlate with the size of the deletion; normal psychomotor development may be seen in those patients in whom the deletion is restricted to the 13q14 band.

Figure 3: Patient with 13q14 syndrome


Tips for genetic counseling

Ó DH Abramson (with permission)
Differential Diagnosis

When retinoblastoma presents as a mass:

- Medulloepithelioma.
- Astrocytic Hamartoma
- Toxocara canis granuloma
- Infected emboli of subacute bacterial endocarditis or toxoplasmosis.
- Other types of severe uveitis

When RB present as a retinal detachment

- Coats’ disease
- Retrolental fibroplasia

Persistent hyperplastic vitreous

Figures for Differential Diagnosis

A1: Coats Disease: Note massive retinal detachment and telangiectatic vessels
A2: Coats Disease: Fluorescein angiogram showing telangiectatic vessels

B: Persistent Hyperplastic Primary Vitreous: Note elongated ciliary processes
B2: MRI showing left microphthalmia, disorganized anterior segment, and persistence of fetal vasculature, findings consistent with PHPV.

C: Medulloepithelioma showing as a amelanotic mass arising from the ciliary body
C2: MRI showing mass with cystic changes consisting with the diagnosis of medulloepithelioma
Retinoblastoma in developing countries.

Is retinoblastoma more frequent in developing countries?

There is some evidence that retinoblastoma is more frequent in certain populations such as Namibia and Alaska. The highest prevalence in South America was reported in tropical Brazil. However, reliable statistics for cancer incidence in many developing countries are usually lacking and these findings should be confirmed in larger, properly designed, population-based studies. The accurate estimation of the incidence of this tumor and its relationship to particular areas is a priority to develop strategies for disease control. To try to elucidate potential mechanisms explaining this observation, Orjuela et al found sequences of the Human Papilloma Virus (HPV) in enucleation specimens of patients with retinoblastoma in Mexico. Since HPV infection affects young women in child-bearing age and follows a similar geographic distribution to retinoblastoma, Orjuela et al suggested that there may be an association between these two phenomena. However, a direct effect of the HPV in the tumorigenesis of retinoblastoma is yet to be proven and further study is warranted to confirm this observation. More recent studies failed to find any association between HPV and retinoblastoma. Orjuela et al found that low intake of fruits and vegetables during pregnancy correlated with a higher risk of having a baby with sporadic retinoblastoma in Mexico. Recently, Mexican investigators showed that retinoblastoma is more frequent in the Chiapas region. Another recent study showed that retinoblastoma was the second more common malignancy in Malawi. Therefore, a study to assess the incidence of retinoblastoma in Latin America and other developing countries is needed to answer these questions.

Do media campaigns for early diagnosis work?

Dra Ligia Fu

Servicio de Hematooncologia Pediatrica

Hospital Escuela,

Tegucigalpa, Honduras.

A campaign for early diagnosis of retinoblastoma was implemented in Honduras (one of the poorest countries of Latin America with 60% of the population being younger than 60% and a low literacy rate along with socioeconomical problems including infectious diseases and malnutrition). Even though the care of children with cancer is not a priority of the public health offices in Honduras, the medical
team of the Unidad de Hematooncologia Pediatrica of the Hospital Escuela, the main tertiary care center in Honduras, developed a comprehensive program to assist the families with children with retinoblastoma, including an early diagnosis campaign. The current survival estimates of children with retinoblastoma are greater than 90% in developed countries but an evaluation done in Honduras in 2000 showed that only 15% of children referred to our center survived. Patients presented with advanced disease at diagnosis, so we hypothesized that earlier diagnosis could improve the situation.

Therefore, we designed a program to disseminate information to the Honduran population about the link between leukocoria and retinoblastoma. In 2003, we developed a flyer that included a picture of a child with leucokoria and recommendations for parents to seek medical attention if they suspected that their child could have leucokoria.

Is there a case for screening the general population?

Children with family history for retinoblastoma have been screened for many years by dilated examination under anesthesia, therefore, the disease's natural history is well known. Retinoblastoma presents at a narrow age interval, which constitutes a well-defined target population. In addition, retinoblastoma occurs at an age when routine visits to the pediatrician are more common than in any other age. However, the final aim of screening programs is to reduce the mortality of a neoplasm and screening programs, though effective are not the only way of reducing mortality. Other smaller-scale measures may have an impact in mortality as well. Mortality rates of retinoblastoma are high in developing countries mainly because of late diagnosis. If the disease could be diagnosed earlier, there would be a better chance of cure for these children. Instead of launching costly screening programs to the general population where only 1/14-17,000 cases would be detected, one initial step to be undertaken in these countries is to effectively screen all affected family members in order to at least detect all familial cases in early intraocular stage. Reducing abandonment of treatment of children that could be cured will also result in dramatic improvements since up to 30% of children in Central America abandon therapy. Measures to reduce both treatment abandonment and late detection of familial cases are probably the most cost/effective initial measures to be taken in many developing countries where a treatment program is not well established. Improvement of diagnostic procedures and treatments may also impact cure rates. Therefore, costly screening programs are difficult to justify in countries with more prevalent health problems such as poor hygiene, deficient sanitation, lack of universal vaccination, malaria or other high prevalence diseases that cause even higher mortality. Human development and a good accessibility to high quality medical care are the only sustainable measures that could reduce retinoblastoma mortality in developing countries.
Why retinoblastoma is diagnosed late in developing countries?

The successful management of retinoblastoma depends on the ability to detect the disease while it is still intraocular. Disease stage correlates with delay in diagnosis. In developing countries, late referrals are strongly associated with orbital and metastatic disease. It is for this reason that eye assessment should be performed in all newborns and at all subsequent health supervision visits by the primary care provider.


More information about retinoblastoma in developing countries is available in these Oncopedia cases:

Retinoblastoma Orbital Relapse in a patient from Sierra Leone

Orbital Relapse after intraocular retinoblastoma

Diagnostic evaluation

The diagnosis of intraocular retinoblastoma is usually made without pathologic confirmation. An examination under anesthesia with a maximally dilated pupil and scleral indentation is required to examine the entire retina. A careful examination of the iris and the anterior chamber is first performed, and the intraocular pressure is measured. Retinoblastoma usually appears as a mass projecting into the vitreous, although the presence of retinal detachment or vitreous hemorrhage may make its visualization difficult. Endophytic tumors are those that grow inward to the vitreous cavity. Because of its friability, endophytic retinoblastoma may seed the vitreous cavity. (Figure N2) Exophytic retinoblastoma grows into the subretinal space, thus causing progressive retinal detachment and subretinal seeding. (Figure N1) Often times exophytic tumors resemble Coats' disease. Less frequently, retinoblastoma can adopt an infiltrative pattern, without an obvious mass (Figure N3). This infiltrative pattern appears to be more frequent among older children.
A very detailed documentation of the number, location, and size of tumors, the presence of retinal detachment and subretinal fluid and the presence of vitreous and subretinal seeds, must be performed.

Figure N1: Exophytic Retinoblastoma. Note enlarged vessels, areas of calcification, luteal pigment denoting the macular origin of the tumor, and a small retinal detachment surrounding the tumor.

Figure N2: Endophytic Retinoblastoma with massive vitreous seeding.
**Imaging studies**

Additional imaging studies that aid in the diagnosis include bi-dimensional ultrasound, CT scan and MRI. These imaging studies are particularly important to evaluate extraocular extension and to differentiate retinoblastoma from other causes of leukocoria. CT scan is very helpful to detect calcification, and MRI is very helpful in the differential diagnosis with Coats’ disease and other inflammatory conditions, and with persistent hyperplastic primary vitreous (PHPV). Head and orbit MRI are needed to evaluate the possibility of extraocular extension. MRI is preferred to CT to avoid the exposure of patients with the germline mutation to radiation.

Figure 4: Massive orbital and optic nerve extension of retinoblastoma (CT scan)

Figure 5: Skull bone metastasis of retinoblastoma (CT scan)
Figure 6: Mandibular metastasis in retinoblastoma (CT Scan)
Figure 7: MRI illustrating bilateral retinoblastoma
Ancillary studies

Evaluation of metastatic disease also needs to be considered in a subgroup of patients. In industrialized nations, metastatic disease occurs in very few patients, usually in association with distinct intraocular histologic features, such as deep choroidal and scleral invasion, or with involvement of the iris-ciliary body and optic nerve beyond the lamina cribrosa. In these cases, additional staging procedures, including bone scintigraphy, bone marrow aspirates and biopsies, and lumbar puncture, must be performed. Bone marrow aspiration and biopsy are recommended only in high risk children, including those with extraocular dissemination, especially when massive extraocular extension exists. The use of multiple sites and immunocytology may increase the yield of this procedure. Retinoblastoma cells tend to gather forming rosettes or clumps, but occasionally it may infiltrate diffusely the bone marrow resembling leukemia. Circulating blasts have also described in patients with advanced disease.

Figure 8: Bone marrow aspiration showing metastasis of retinoblastoma (May Grunwald Giemsa X100)
The CSF should be examined also in high risk patients only. It is important to note that cells may adhere to the tube and avoid detection at a regular count. In all cases, an examination of the cytocentrifugate, with immunocytology if possible, should be done to improve the yield of this procedure.

Figure 9: Appearance of retinoblastoma cells in the CSF (May Grunwald Giemsa X 100)
**Diagnostic and extent of disease evaluation**

- Mandatory tests

  Ocular examination under anesthesia by an experienced ophthalmologist
  Eye B-scan ultrasound
  CT/MRI of the CNS and orbit with and without contrast

- Tests for advanced disease (Stage 2 or higher)

  Bone marrow aspiration and biopsy (at least 4 sites)
  Lumbar puncture with microscopic examination of the cytospin
  Bone scintigraphy
  Abdominal ultrasound

**Staging and grouping of retinoblastoma**

It is essential to recognize different scenarios for grouping and staging retinoblastoma. One is related to disease extension in the eye, important to
predict eye preservation and the remaining one to assess the extraocular extension, to help predict patient survival.

The Reese-Ellsworth grouping for intraocular retinoblastoma was developed in the 1960s to predict which eyes would have a greater chance of being preserved after external-beam radiotherapy. Since this modality is not recommended as an up-front treatment alternative nowadays, a new grouping system was developed with the goal of classifying intraocular disease based upon the result of modern treatment modalities such as chemoreduction. However, the Reese-Ellsworth system is still the gold standard against which newer systems should be tested. There is even more controversy for the use of a staging system for extraocular disease. There are at least 5 staging systems that aimed to evaluate patient survival. Because of that, it is impossible to compare treatment results among groups. In Latin America for example, the Argentinean group used the Grabowski-Abramson classification, the Brazilian group used the CCG staging system and the Mexican group utilized the St Jude classification. In order to develop a common staging system, and following the initiative of the Argentinean and Brazilian groups, a committee of retinoblastoma experts from large centers worldwide has developed a consensus staging system. It has been further discussed by investigators from centers in South and North America, Europe, and South Africa into a consensus document. This proposed staging system is aimed to stage patients according to their risk for death of retinoblastoma and is not related to ocular survival. For this staging system to be successful, it is critical to have precise definitions of invasion of ocular coats and processing of enucleated eyes to achieve reliable and comparable results.

**The Reese-Ellsworth grouping system**

Group I: very favorable for maintenance of sight

A. Solitary tumor, smaller than 4 disc diameters in size, at or behind the equator

B. Multiple tumors, none larger than 4 disc diameters in size, all at or behind the equator

Group II: favorable for maintenance of sight

A. Solitary tumor, 4-10 disc diameters in size, at or behind the equator

B. Multiple tumors, 4-10 disc diameters in size, behind the equator

Group III: possible for maintenance of sight

A. Any lesion anterior to the equator
B. Solitary tumor, larger than 10 disc diameters in size, behind the equator

Group IV: unfavorable for maintenance of sight
A. Multiple tumors, some larger than 10 disc diameters in size
B. Any lesion extending anteriorly to the ora serrata

Group V: very unfavorable for maintenance of sight
A. Massive tumors involving more than one half the retina
B. Vitreous seeding

International Classification for Intraocular Retinoblastoma

Group A
Small tumors away from foveola and disc
- Tumors < 3 mm in greatest dimension confined to the retina, and
- Located at least 3 mm from the foveola and 1.5 mm from the optic disc

Group B
All remaining tumors confined to the retina
- All other tumors confined to the retina not in Group A
- Subretinal fluid (without subretinal seeding) < 3 mm from the base of the tumor

Group C
Local subretinal fluid or seeding
- Local subretinal fluid alone > 3 to < 6 mm from the tumor
- Vitreous seeding or subretinal seeding < 3 mm from the tumor

Group D
Diffuse subretinal fluid or seeding
- Subretinal fluid alone > 6 mm from the tumor
- Vitreous seeding or subretinal seeding > 3 mm from tumor
Group E

Presence of any or more of these poor prognosis features

- More than 2/3 globe filled with tumor *
- Tumor in anterior segment
- Tumor in or on the ciliary body
- Iris neovascularization
- Neovascular glaucoma
- Opaque media from hemorrhage
- Tumor necrosis with aseptic orbital cellulitis
- Phthisis bulbi

Figure 10: Group A: Small tumor (≤ 3 mm) confined to the retina, distant from the foveola and optic nerve.

Figure 11 Group B: Tumor > 3 mm, confined to the retina
Figure 12: Group B: Small tumors ($\leq$ 3mm), confined to the retina, but in close proximity to optic nerve and foveola.

Figure 13: Group C: Tumor with localized subretinal fluid and local seeding
Figure 14: Group D: Tumor with diffuse seeding

Group E: Tumor in anterior segment
International Retinoblastoma Staging System

**Stage 0.** Patients (eyes)treated conservatively

**Stage 1:** Patients enucleated with completely resected tumors

**Stage 2.** Incompletely resected Resected tumor with microscopic residual disease

**Stage 3.** Regional extension

  a. Overt orbital disease

  b. Preauricular or cervical lymph node extension

**Stage 4.** Metastatic disease

  1. Hematogenous metastasis
     1. 1. Single lesion
     2. 2. Multiple lesions
2. CNS extension
   1. 1. Prechiasmatic lesion
   2. 2. CNS mass
   3. 3. Leptomeningeal and CSF disease

---


---

### Treatment

**Enucleation:**

Enucleation is the simplest and safest therapy for retinoblastoma. An orbital implant is usually fitted during the same procedure, and the extraocular muscles are attached to it. In the past, orbital implants were avoided because it was felt that they would interfere with the palpation of the socket and clinical detection of orbital recurrence. However, with the better understanding of the histologic risk factors, and the availability of better imaging techniques to detect orbital disease, implants should be placed at the time of the enucleation. Resection of a long optic nerve stump is mandatory. When enucleation is performed in the first two years of life a facial asymmetry develops because of inhibition of the orbital
growth. Enucleation of a child with a suspected retinoblastoma should be performed by an experienced pediatric ophthalmologist.

**When is enucleation indicated as the initial treatment of retinoblastoma?**

Secondary glaucoma

Invasion of anterior segment (anterior chamber, iris)

Rubeosis iridis

Impossibility of close follow up or limitations for using local therapies

Reese-Ellsworth Group Vb eyes in unilateral non hereditary patients

**When is enucleation not indicated as the initial treatment?**

Massive extraocular dissemination

Less advanced intraocular disease and ability of performing and adequate local therapy and follow up

**When is orbital exenteration indicated?**

Virtually never. Orbital exenteration should not be attempted as an initial procedure in cases with orbital extension of retinoblastoma, since this is a chemo and radio sensitive neoplasm. Preoperative chemo (2 to 4 cycles) or radiotherapy usually shrinks the tumor sufficiently enough to perform a secondary enucleation.

**When is secondary enucleation indicated?**

Lack of tumor control after local therapy

After neoadjuvant chemotherapy in extraocular disease

**Which surgical procedures should be avoided in retinoblastoma?**

Pars plana vitrectomy

Enucleation taking a short optic nerve stump

Anterior chamber paracentesis

Orbital exenteration in extraocular disease
Focal therapies

Focal treatments are used for small tumors (< 3-6 mm), usually in patients with bilateral disease, and in combination with chemotherapy.

*Photocoagulation* with argon laser is used for the treatment of tumors situated at or posterior to the equator and for the treatment of retinal neovascularization due to radiation therapy.\(^2\) The treatment is directed to delimit the tumor and coagulate all blood supply to the tumor, and 2 or 3 monthly sessions are usually required.

*Cryotherapy* is used for the treatment of small equatorial and peripheral lesions. One or two monthly sessions of triple freeze and thaw are performed, and tumor control rates are usually excellent.\(^3\)

*Transpupillary thermotherapy,* which applies focused heat at subphotocoagulation levels, usually with diode laser. In thermotherapy, the goal is to deliver a temperature of 42 - 60 °C for 5 to 20 minutes to the tumor, sparing retinal vessels from photocoagulation.\(^4\)

*Radiotherapy,* Retinoblastoma is a very radiosensitive tumor. Radiotherapy in combination with focal treatments can provide excellent tumor control! However, since radiation therapy increases the risk of second malignancies, contemporary management of intraocular retinoblastoma is designed to avoid or delay its use, and the role of radiation is mainly as salvage method for eyes that have failed chemotherapy and focal treatments, usually due to progression of vitreous and subretinal seeding. Radiation therapy continues to have a major role in the treatment of patients with extraocular disease.

Since most of the patients with intraocular retinoblastoma undergoing radiotherapy have multifocal disease, the entire retinal surface needs to be irradiated to a uniform dose. Several techniques can be used, usually through lateral or anterior fields.\(^5\) Recommended total doses are 4,000 to 4,500 cGy, in 180-200 fractions, although doses of 3,600 cGy are under investigation in conjunction with other techniques.

Radioactive plaque technique is useful when treating localized tumors, both because the procedure time is short, and because a high dose of irradiation is delivered to the areas of interest while minimizing radiation effects to the extraocular structures.\(^6\) Indications for plaque therapy include solitary tumors with a diameter ranging between 6 and 15 mm, tumor thickness of 10 mm or less, and location of the lesion more than 3 mm from the optic disc or fovea. The radioactive implant is placed on the sclera over the base of the tumor, and is kept for 2 to 4 days, the time needed to deliver approximately 4,000 cGy to the apex of the tumor. Different radioactive episcleral plaques can be used, although \(^{125}\)I is the most widely used. Control rates of 85-90% can be achieved.
Chemotherapy

In the past, chemotherapy was only used to treat metastatic disease, however, in recent years, most groups have used chemotherapy as primary treatment for intraocular disease not amenable for local therapy in order to decrease tumor size and make the tumors suitable for local therapy. This approach, called chemoreduction, may avoid either enucleation or EBRT in selected cases. Carboplatin is the agent most frequently used, since it has good penetration into the eye and high activity in retinoblastoma. Vincristine and etoposide are also used; however their penetration into the eye is lower. Recent animal studies suggest that the combination of carboplatin and topotecan is very active achieving a high penetration to the vitreous. Most intraocular tumors usually show dramatic shrinkage after systemic chemotherapy; however, consolidation with local treatment appears to be needed in most cases to prevent relapse.

Tumor location, patient age and size of tumor correlate with response to chemotherapy. Salvage rates for R-E groups I-III eyes approaches 100% using these techniques. For those patients with early intraocular disease, a two-drug regimen with vincristine and carboplatin seems to be equally effective than the three-drug regimen, where etoposide is also given. For patients with advanced intraocular tumors (R-E groups IV-V), ocular salvage rates are not better than 50%, and external beam radiation therapy is usually required. However, the use of radiation therapy is usually delayed for several months, which allows for a better orbital growth and a decrease in the risk of second malignancies. A major proportion of failures occur because of progression of tumor in the vitreous, or as subretinal implants, two areas of difficult access for antineoplastic agents. Carboplatin diffuses well into the vitreous. Intraocular concentrations are 7 to 10 times higher when carboplatin is administered subconjunctivally, and animal studies have shown a dose-dependent inhibition of intraocular tumor growth by subconjunctival carboplatin. These encouraging preclinical data, however, have not been effectively translated into an improvement in the outcome of advanced eyes; prospective studies are planned in the Children's Oncology Group to evaluate the role of this modality of carboplatin administration.

Thus the treatment of patients with advanced intraocular disease (R-E groups IV and V, International Groups C and D) remains a major challenge. Although randomized studies have not been performed, compared to radiation and focal treatments alone, chemoreduction does not seem to improve overall ocular salvage significantly for patients with very advanced intraocular disease. Central retinal tumors usually respond better to chemotherapy than do tumors in the peripheral retina, but large central tumors may be associated with subretinal seeds, which ultimately may cause treatment failure. With the addition of aggressive sequential focal therapies, globe retention is no better than 50% for R-E group V eyes (Group D) and most patients eventually require radiation.
major proportion of failures occur because of progression of tumor in the vitreous or as subretinal implants, two areas of difficult access for antineoplastic agents. In contrast to the highly protein-bound etoposide, which remains in the plasma and lacks intraocular penetration, carboplatin diffuses well into the vitreous. The intraocular penetration of carboplatin is enhanced by disruption of the blood-vitreous barrier by the tumor, and it is enhanced after cryotherapy. Topotecan also has a good passage to the vitreous and it is being investigated as an alternative agent for retinoblastoma.

Even though chemoreduction followed by local treatment became an established therapy for intraocular retinoblastoma, there are several unanswered questions. One of the most important ones is: *Is there any benefit for chemoreduction for Group Vb eyes compared with external-beam radiotherapy?*

Other concerns include the long-term results and safety of current strategies, since some drugs used are known to induce secondary leukemia, especially epipodophylotoxins. Therefore, the composition of chemotherapy regimens is still on discussion as well as the duration of treatment. Since tumor control is heavily dependant on local therapy, which in turn is influenced critically by the expertise of the treatment group, there is a methodological bias for determining the efficacy of any chemotherapy regimen. The status of the contralateral eye also is important for deciding the treatment modality and may also influence the eye preservation rate. Finally, this treatment is tedious and needs meticulous management and technical support only available in specialized centers.

Figure 16: Chemoreduction in Retinoblastoma

A: Before chemotherapy

B: After 2 courses of vincristine and carboplatin
Chemoreduction in developing countries

Chemoreduction regimens have been employed successfully in developing countries, however limitation for their use include: lack of availability of sophisticated therapies, uncertain follow up of high risk patients, advanced disease, lack of trained personnel and insufficient staffing of services. All these features should be considered before starting a chemoreduction program in a developing country since it should be never underestimated that enucleation is curative in most cases of intraocular retinoblastoma and repeated intentions of preserving eyes with advanced disease may result in extraocular dissemination which is seldom curable. However, a recent study including patients from Brazil and Argentina showed that chemoreduction did not increase the risk for extraocular relapse.

Current recommendation for treatment of intraocular retinoblastoma by the Children’s Oncology Group (COG)

<table>
<thead>
<tr>
<th>R-E Group</th>
<th>ABC Group</th>
<th>Treatment Focal Tx</th>
<th>Chemotherapy</th>
<th>Radiation</th>
</tr>
</thead>
<tbody>
<tr>
<td>I - II</td>
<td>A -</td>
<td>+</td>
<td>-</td>
<td>If PD</td>
</tr>
<tr>
<td>I - III</td>
<td>B +</td>
<td>VCR 0.05 mg/kg d 1</td>
<td>CBP 18.6 mg/kg d 1</td>
<td>If PD</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>X 2 - 6 courses</td>
<td></td>
</tr>
<tr>
<td>IV - V</td>
<td>C - D +</td>
<td>VCR 0.05 mg/kg d 1</td>
<td>CBP 14 mg/kg d 1</td>
<td>If PD</td>
</tr>
<tr>
<td></td>
<td>+ subtenon(carboplatin)</td>
<td></td>
<td></td>
<td>If massive vitreous seeding at diagnosis, consider early low dose (26Gy) EBRT</td>
</tr>
</tbody>
</table>
Current recommendations for the treatment of intraocular retinoblastoma at the Hospital JP Garrahan (Buenos Aires, Argentina)

<table>
<thead>
<tr>
<th>R-E Group</th>
<th>ABC Group</th>
<th>Treatment</th>
<th>Chemotherapy</th>
<th>Radiation</th>
</tr>
</thead>
<tbody>
<tr>
<td>I - II</td>
<td>A</td>
<td>Focal Tx</td>
<td>VCR 0.05 mg/kg d 1 If PD</td>
<td></td>
</tr>
<tr>
<td>I - III</td>
<td>B</td>
<td>+</td>
<td>CBP 18.7 mg/kg d 1 If PD</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>X 2 - 6 courses If PD</td>
<td></td>
</tr>
<tr>
<td>IV - V</td>
<td>C - D</td>
<td>+</td>
<td>VCR 0.05 mg/kg d 1 If PD</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>+/- subtenon carboplatin</td>
<td>CBP 18.7 mg/kg d 1 If massive vitreous seeding at diagnosis (45Gy) EBRT</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>x3</td>
<td>ETO 3.3 mg/kg d 1, 2 If massive vitreous seeding at completion of chemotherapy</td>
<td></td>
</tr>
<tr>
<td>V b</td>
<td>E</td>
<td>Enucleation</td>
<td>X 4-6 courses</td>
<td></td>
</tr>
</tbody>
</table>

Newer approaches:

The New York group recently published their experience utilizing intra-arterial chemotherapy through the cateterization of the ophthalmic artery. 41,40 Based upon the initial experience from Japan, Melphalan was the drug selected. 40 Even though the initial results are promising, this is an aggressive procedure, only available in selected centers.

Adjuvant chemotherapy in retinoblastoma
Some histopathological features are considered as risk factors for extraocular relapse after enucleation. Those include invasion to the choroid, sclera, optic nerve and the anterior segment. The role of adjuvant chemotherapy for patients with putative histopathological risk factors for relapse to reduce the relapse rate is a matter of controversy. A careful post-enucleation histopathological staging is essential to define groups with different risks of relapse. A major limitation for an appropriate tailoring of adjuvant therapy in developing countries is the lack of reliable pathological examination of enucleated eyes. Sometimes, pathological examination is never performed. There are wide variations in the definitions of the degree of invasion to the ocular coats among many centers. The International Retinoblastoma Staging Working Group is currently drafting a guideline for eye processing intended to be disseminated in developing countries and providing consensus definitions for the different degrees of invasion to the ocular coats. In developing countries, the pediatric oncologist faces the dilemma of prescribing adjuvant chemotherapy to all patients with putative risk factors, or to avoid it in controversial cases and treat aggressively those who relapse. Adjuvant chemotherapy does not eliminate completely the possibility of extraocular relapse and in groups with low relapse rate; its benefit is not proven.

Because of the low relapse rate of most patients in these populations; a randomized study comparing adjuvant treatment versus observation would require an enormous number of patients. Many authors consider extraocular relapse as a catastrophic event, and recommend adjuvant therapy for all patients with histopathological risk factors. However, in recent years some groups show that many of relapsed patients can be salvaged by intensive therapy. Therefore, avoiding adjuvant chemotherapy for patients with low relapse rate and treating aggressively those who relapse is a reasonable alternative.

There is almost universal agreement that there is no need of adjuvant chemotherapy for patients with intraretinal disease and in those with prelaminar optic nerve invasion. The role of chemotherapy in isolated choroidal invasion is controversial. It has been suggested that once the tumor reaches the choroid, it may gain access to the systemic circulation giving rise to hematogenous metastasis. Choroidal invasion may only be relevant when it is combined with post-laminar optic nerve invasion.

Despite there is no agreed definition for grading choroidal invasion, most centers discriminate between different degrees of invasion to the choroid (denominated major and minor, full and partial, massive and focal by different groups) and some recommend adjuvant chemotherapy for the cases with more advanced disease. However, comparison among published series is problematic because of the lack of a standardized definition for discriminating between the various degrees of choroidal invasion, and so the International Retinoblastoma Staging Working Group recently reached a consensus about this issue amalgamating the COG and the French Society of Pediatric Oncology definitions. In addition, a very careful examination of no less than 12 slides of each eye is essential for fully establishing the degree of choroidal invasion. The current treatment protocol from the Children’s Oncology Group (COG ARET 0332) prescribes adjuvant chemotherapy
with carboplatin, etoposide and vincristine for patients with either isolated massive choroidal invasion or any degree of choroidal invasion in an eye that also has any degree of optic nerve extension (including pre-laminar). Other groups (such as most Latin American centers) do not routinely use adjuvant therapy for isolated choroidal invasion or when it is combined with is associated to prelaminar optic nerve invasion.

Figure 17: Choroidal invasion

Invasion to the optic nerve beyond the lamina cribrosa is a major risk factor for relapse especially when the cut end is involved. 23, 26

Figure 18: Post laminar optic nerve extension.
When the cut end is free of tumor, the management is controversial. Patients with concomitant major choroidal with or without scleral invasion have a greater risk of relapse and adjuvant chemotherapy is usually indicated. Patients with invasion of the cut end of the optic nerve are uniformly considered as having high risk of relapse. Survival rate has been reported as low as 40%.

There has been considerable debate about whether patients with postlaminar optic nerve invasion need adjuvant therapy to prevent extraocular relapse. However, most centers recommend adjuvant therapy in an attempt to reduce the relapse rate. Recent series reported a survival rate in the range of 90% with tailored therapy. In that series, patients with lower risk (i.e. those with isolated retrolaminar invasion with less than 20% of invasion along the optic nerve) could be spared safely from chemotherapy. However, a very careful pathological examination is necessary for establishing this risk group and the results should be reproduced in other centers. The most adequate chemotherapy regimen for this population is not known. Since CNS relapse is the most frequent event, drugs with good CNS coverage should be used. The role of intrathecal chemotherapy in these situations remains to be established. According to our limited experience, patients with microscopic scleral involvement are at high risk for extraocular relapse and should receive adjuvant therapy.

The role of intrathecal chemotherapy in these situations remains to be established. According to our limited experience, patients with microscopic scleral involvement are at high risk for extraocular relapse and should receive adjuvant therapy.
Invasion to the resection margin of the optic nerve

These children usually present with advanced intraocular disease, often with glaucoma and, on occasions, buphthalmia, but no evidence of overt disease and the treating group recommends enucleation as primary treatment. On occasions, the invasion to the optic nerve is seen in the imaging studies done at diagnosis.

In these cases, a careful examination of the whole optic nerve, preferentially by MRI should be done to rule out intracranial dissemination. The CSF should be also evaluated to look for occult metastatic disease in the CSF. Cases where the optic nerve is enlarged in the imaging studies should be classified as Stage 3 for the IRSS and a recent report shows the beneficial effect of preoperative chemotherapy in this population. In order to accurately assign a proper stage, a comprehensive pathological examination of the enucleated eye is essential. A short optic nerve stump may result in tumor invasion through the resection margin that could be avoided if a longer stump had been obtained. Consequently, enucleation should be done by an experienced ophthalmologist to obtain a long optic nerve stump (of at least 10 mm) thereby avoiding leaving a tumor residue, however in patients with buphthalmia, this could be problematic. In developing countries, it is not uncommon to receive patients enucleated at other institutions presenting a short optic nerve stump with tumor beyond the resection margin. Even though it is controversial if the ophthalmologist should go back and try to identify the remaining portion of the orbital optic nerve to try to resect the distal part as far as possible, the patients should be treated in the same way as those with an appropriate stump. It is important to evaluate the presence of microscopic invasion of the subarachnoid space. This is an uncommon feature of retinoblastoma and these patients should receive the same treatment than those with tumor at the resection margin of the optic nerve. The CSF should be careful looked at to detect occult dissemination.

The optimal treatment of patients with invasion to the resection margin of the optic nerve is under investigation. It should include multimodal therapy including enucleation, radiotherapy and chemotherapy. However, the most effective and less toxic regimen has yet to be determined. The traditional approach for the post-enucleation treatment of these patients included adjuvant systemic and intrathecal chemotherapy along with radiotherapy. The survival rate for these patients ranged from 40 to 70%. Intrathecal chemotherapy usually included methotrexate, cytarabine and dexamethasone which may not be active in retinoblastoma and is potentially neurotoxic. Therefore, current regimens omit intrathecal chemotherapy and use more intensive intravenous therapy including agents at higher doses and with better penetration to the CNS such as carboplatin. Current chemotherapy regimens include moderately intensive
systemic carboplatin-based chemotherapy but the addition of alkylating agent may improve the prognosis as was shown in a recent series. \textsuperscript{31} These patients usually receive radiotherapy to the orbit, including the chiasm, but its role has not been prospectively evaluated and only a cooperative multicentric study could provide an answer to that question. Current series report a survival rate in the range of 70\% but the treatment is associated to late sequelae.

Adjuvant therapy in retinoblastoma

General agreement that patients with the following features do not need adjuvant therapy

1. Intraretinal invasion
2. Prelaminar optic nerve invasion
3. Minor choroidal invasion

General agreement that patients with the following features need adjuvant therapy

1. Invasion to the resection margin of the optic nerve
2. Scleral invasion

Controversial subgroups

1. Major choroidal invasion
2. Postlaminar optic nerve extension with resection margin free of tumor
3. Anterior segment invasion

Central Nervous System Disease

Intracranial dissemination occurs by direct extension through the optic nerve, and its prognosis is dismal. \textsuperscript{26, 27, 32, 33} (In the past, children with trilateral disease were thought to have progressed in this manner.) Treatment for these patients should include platinum-based intensive systemic chemotherapy and CNS directed therapy. Although intrathecal methotrexate (with or without cytarabine) has been traditionally used, there is no preclinical or clinical evidence to support its use. Other intrathecal agents with documented effect against retinoblastoma include topotecan and thiotepa. However, there is no evidence that their use can impact outcome. Although the use of irradiation in these patients is controversial,
responses have been observed with craniospinal irradiation, using 25-35 Gy to the CNS and the spinal axis, and a boost (10 Gy) to sites of measurable disease. Therapy intensification with high-dose chemotherapy and autologous stem cell rescue has been explored, but its role is not yet clear. Despite the intensity of the treatment and the documented responses of the intracranial disease, patients succumb to their disease, and survivors are anecdotal.

Trilateral Retinoblastoma

The prognosis for patients with trilateral retinoblastoma is dismal; patients die of disseminated neuraxis disease in less than 9 months. The rare survivors are usually those diagnosed with screening imaging, and treated with intensive chemotherapy with or without craniospinal radiation. Pineoblastoma occurring in non-retinoblastoma patients is also associated with a poor prognosis. However, with an appropriate aggressive multimodal approach, these patients can be cured. Pineoblastoma is a chemosensitive neoplasm, and it appears to have a steep dose-response curve for alkylating agents. Studies in older patients with primary pineoblastoma have recently shown that a treatment with complete resection and intensive alkylator- and cisplatin-based therapy, followed by craniospinal irradiation (36 Gy with boost to pineal gland to 59 Gy), and consolidation with high-dose chemotherapy and autologous stem cell rescue, may produce survival rates in more than two thirds of the patients. It is therefore possible that similar treatment guidelines could be used for trilateral retinoblastoma. One must, however, consider the serious long term toxicities of such doses of radiation in the very young child. Therefore, current strategies are directed towards avoiding irradiation using intensive chemotherapy followed by consolidation with autologous stem cell rescue, an approach similar to those being used in the treatment of brain tumors in infants.

Figure 19: Trilateral retinoblastoma (MRI)
Because of the poor prognosis of trilateral retinoblastoma, screening neuroimaging is a common practice. One fourth of the cases in the literature correspond to cases found during screening. Given the short interval between
the diagnosis of retinoblastoma and the occurrence of trilateral retinoblastoma, routine screening might detect the majority of cases within two years. While it is not clear whether early diagnosis can impact survival, it is usually recommended to perform neuroimaging every 6 months until 5 years of age.

(Extracranial) Metastatic Retinoblastoma

Hematogenous metastases occur to the bones, bone marrow and, less frequently, to the liver. Although long term survivors have been reported with conventional chemotherapy, these cures should be considered anecdotal; metastatic retinoblastoma is not curable with conventional chemotherapy. In recent years, however, small series have shown that metastatic retinoblastoma can be cured using high-dose chemotherapy and autologous stem cell rescue.\textsuperscript{24, 35, 36} The approach is similar to metastatic neuroblastoma; patients receive short and intensive induction regimens usually containing alkylating agents, anthracyclines, etoposide and platinum compounds, and are then consolidated with autologous hematopoietic stem cell transplant. Using this approach, the outcome appears to be excellent. As for any megatherapy consolidation, the agents selected may be important. In general, recurrences are intracranial, and for this reason, agents with proven efficacy in intracranial retinoblastoma should be used. In this regard, the combination of carboplatin and etoposide has been shown to be effective against CNS disease, and for this reason it should be part of the regimen.\textsuperscript{10} In the largest published series, seven patients received consolidation with the CARBOPEC combination (carboplatin 1250-1750 mg/m\textsuperscript{2}, etoposide 1750 mg/m\textsuperscript{2}, and cyclophosphamide 6.4 g/m\textsuperscript{2}), 5 of them were cured, and two patients failed due to CNS relapse. \cite{24} Other groups have used a thiotepa-based consolidation (thiotepa 900 mg/m\textsuperscript{2}, etoposide 750 - 1200 mg/m\textsuperscript{2}, and carboplatin 1500 mg/m\textsuperscript{2}).\textsuperscript{24} There is strong rationale for using thiotepa: retinoblastoma is responsive to alkylating agents such as thiotepa, a group of agents for which dose escalation is shown to overcome resistance. Furthermore, thiotepa has excellent CNS penetration. An interesting observation is that patients with distant (outside orbit and skull) bone metastases that show good response to induction chemotherapy may not require radiation therapy when treated with autologous stem cell rescue.

The international COG protocol for metastatic retinoblastoma (Ira J Dunkel)

The Children’s Oncology Group has just launched a study of multi-modality therapy for extra-ocular retinoblastoma (COG ARET 0321) and hopes that other cooperative groups or major centers around the world will participate. In this study, patients with Stage 2 & 3 extra-ocular retinoblastoma (orbital disease, regional nodal disease, and/or optic nerve margin positivity) will receive aggressive conventional chemotherapy and involved-field external beam radiation therapy. Those with Stage 4a and 4b metastatic disease (as well as those with trilateral retinoblastoma) will receive aggressive conventional induction
chemotherapy, have autologous stem cells harvested, receive high-dose carboplatin, thiotepa and etoposide with ASCR, and then (depending on response) will be considered for external beam radiation therapy.

Orbital retinoblastoma

Most patients with disease disseminated to the orbit and or the preauricular lymph nodes are curable with an aggressive approach using neoadjuvant chemotherapy, enucleation and adjuvant therapy with chemo and radiotherapy. Orbital exenteration is no longer recommended for these patients and chemotherapy should be the first approach. Tumors usually shrink and therefore enucleation is possible after two or three cycles. In cases with overt extraocular disease, distant metastatic disease should be readily ruled out since patients with metastasis should receive a more intensive approach.

Orbital relapse after enucleation is also curable with the same approach.

Figure 20: Orbital relapse after enucleation


More information about treatment of retinoblastoma is available in these Oncopedia cases:

Massive optic nerve involvement in retinoblastoma

Orbital relapse after intraocular retinoblastoma

Extraorbital retinoblastoma

Some full-text references are now available in the Cure4Kids Digital Library.