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Review of Clinical Presentations of Retinoblastoma

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1. Introduction

A retinoblastoma is a neuroblastoma. It is a rare eye tumor of childhood that arises in the retina and represents the most common intraocular malignancy of infancy and childhood -**1**. It may occur at any age-**2,** but most often it occurs in younger children, usually before the age of two years. Most affected children are diagnosed before the age of five years-**1**,**3**. Intraocular tumours may exhibit a variety of growth patterns and is commonly seen in advanced countries. Extraocular retinoblastoma is common in developing countries because of delay in diagnosis.-**4**,**5**.

In 60% of cases, the disease is unilateral (non hereditary) and the median age at diagnosis is two years. Retinoblastoma is bilateral (hereditary) in about 40% of cases with a median age at diagnosis of one year-**1**. Trilateral retinoblastoma is rare and refers to bilateral or unilateral retinoblastoma associated with an intracranial primitive neuroectodermal tumor in the pineal or suprasellar region-**6**. The median time interval from diagnosis of retinoblastoma to the development of a pineal region tumor was 24 months whereas the median time interval for the development of a suprasellar region tumor was 1 month-**6.** Untreated, retinoblastoma is fatal. In the developing countries, retinoblastoma presents with advanced disease with resultant 5 year survival of less than 50%-**7** whereas patients present with intraocular disease in the developed countries due to availability of resources for early detection and treatment. The survival rate in these nations has improved from approximately 30% in the 1930s to over 90% in the 1990s -**8**,**9.** In the middle income countries, the survival rate is about 70% -**10.** Retinoblastoma occurs equally in males and females and there is no predilection for any race or any particular eye-**11**.

2. What are the common symptoms of retinoblastoma

a. Leucocoria (white papillary reflex or cat's eye) is the most common accounting for about 60%- 80% of cases.-**1**,**4**,**5**. This is the most common type of presentation where there is high level of awareness such as in high income countries
b. Strabismus occurs in about 20% of cases-**1**,**4**
c. Orbital inflammation is seen in cases of tumour necrosis-**4**
d. Proptosis follows orbital invasion. Secondary microbial infections are often present. This is a common type of presentation in most developing nations-**12** due mainly to socioeconomic and cultural limitations resulting in delayed presentation -**10**

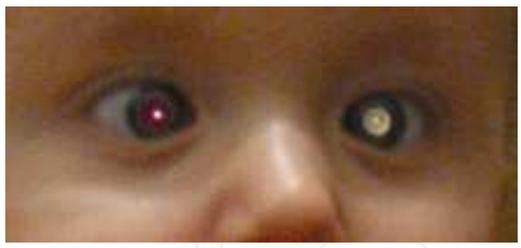

Fig. 1. Left leucocoria in a child with retinoblastoma. Courtesy. Wikipedia

Fig. 2. Crossed eye in a child with retinoblastoma. Courtesy. Wikipedia

Fig. 3. Courtesy. www.arquivosdamorte.com

Fig. 4. Courtesy. projectmedishare.wordpress

Advanced extra ocular retinoblastoma in African and South American children above

e. Metastatic spread involves the brain/central nervous system, bones (especially skull bones and long bones), liver, spleen, Lymph nodes etc. This is worse in undeveloped economies due to late presentation and paucity of means of diagnosis -(-**1**,**4**,**5**,**12**)

f. Decrease in visual acuity-**12**

Fig. 5. Courtesy. inctr.ctisinc.com.

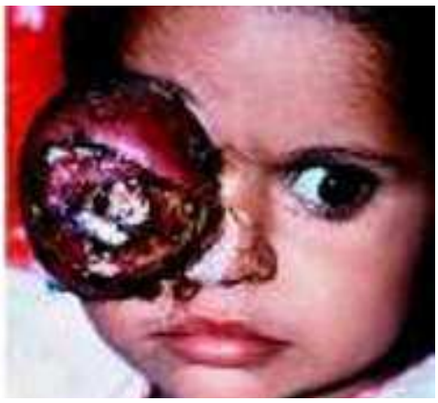

Fig. 6. Courtesy. www.jornallivre.com.br

3. What are the common signs of retinoblastoma

The clinical signs-**5**,**12** vary with the stage of the tumour at the time of presentation.

a. Early intraretinal tumour is a flat lesion which appears transparent or translucent. This type is commonly seen in high income countries where increase in awareness and early presentation are the norms
b. Endophytic tumour projects from retinal surface toward the vitreous as a friable mass, frequently associated with fine blood vessels on its surface-**4**. The tumour resembles cottage cheese if calcified. Vitreous seeding may be present

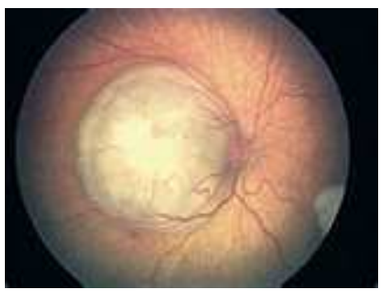

Fig. 7. Endophytic tumour. Courtesy. www.retinoblastomainfo.com

c. Exophytic tumour. This grows from the retina outward into the subretinal space with progressive retinal detachment. It may become a multilobulated mass with overlying retinal detachment. As the orbital structures are invaded, proptosis increases. Sometimes the grossly detached retina may be visible just behind the clear lens. Presence of vitreous hemorrhage may make the fundus hazy. Clinically, they may resemble coats disease

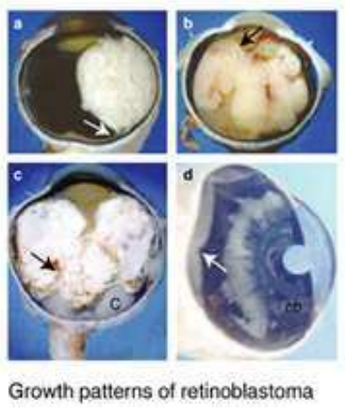

Fig. 8. Fundus pictures of Retinoblastoma. Courtesy. journals.cambridge.org

Fig. 9. Large exophytic retinoblastoma with calcification producing exudative retinal detachment. Courtesy. Wikimedia commons

d. Occasionally, a retinoblastoma can assume a diffuse infiltrating feature characterized by a relatively flat infiltration of the retina by tumour cells without an obvious mass. In such cases, diagnosis may be more difficult and this pattern can simulate uveitis or endophthalmitis

4. Less frequent signs of clinical presentations

a. Secondary glaucoma with or without buphthalmos-**4**,**13**. This is rare. Pain may be a feature
b. Anterior segment invasion-**4**, **13.** Multifocal iris invasion may be associated with hyphema and iris neovascularization; painful red eye with pseudohypopyon due to tumour seeding into the anterior chamber. This is mostly unilateral involvement with no family history.-**4**
c. Associated conditions. 13q deletion syndrome has retinoblastoma, dysmorphic features, mental retardation which may be associated in some patients-**1**

5. Differential diagnosis of retinoblastoma

Some patients diagnosed initially with possible retinoblastoma prove, on referral to ocular oncologists and radiologists, to have pseudoretinoblastoma-**4**,**5**,**13** and not retinoblastoma The more frequently encountered being

Persistent hyperplastic primary vitreous
Coats disease
Ocular toxocariasis
Others include:
Preseptal or orbital cellulitis in extraocular spread
Cataract
Retinopathy of prematurity
Uveitis
Myelinated nerve fibre, optic nerve glioma, medulloepithelioma
Organizing vitreous hemorrhage
High myopia
High anisometropia
Retinal detachment

6. Classifications of retinoblastoma (Rb)

Several classifications of retinoblastoma have been developed to assist in prediction of globe salvage with preservation of useful vision where possible. There are two classifications for intraocular retinoblastoma currently in use.

1. Reese-Ellsworth classification. Originally used to predict visual prognosis of affected eyes and globe salvage after external beam radiotherapy. It is still useful to compare newer treatment modalities with older ones-**5**

Reese-Ellsworth classification of Retinoblastoma

Group i. Favorable

a. Solitary tumour less than 4 disc diameter in size at or behind the equator
b. Multiple tumours, all less than 4 disc diameters in size all at or behind the equator.

Group ii. Favorable

a. Solitary tumour, 4 to 10 disc diameters in size at or behind the equator
b. Multiple tumours , 4 to 10 disc diameters in size behind the equator

Group iii. Doubtful

a. Any lesion anterior to the equator
b. Solitary tumours larger than 10 disc diameters behind the equator

Group iv. Unfavorable

a. Multiple tumours, some larger than 10 disc diameters
b. Any lesion extending to the anterior ora serrata

Group v. Very Unfavorable

a. Massive seeding involving over half of retina
b. Vitreous seeding

2. ABC classification of retinoblstoma-**5**

To predict the preservation of the eye using all modern therapeutic methods

Group A. Small tumours <3mm (about 0.1 inch) confined to the retina
Group B. Larger tumours confined to the retina
Group C. Localized seeding of the vitreous or under the retina <6.00mm (0.2inch) from the original tumour
Group D. Widespread vitreous or sub retinal seeding which may have total retinal detachment
Group E. No visual potential, eye cannot recover

Others

3. Philadelphia Practical Grouping System of Retinoblastoma Based on Clinical Features.-**14**

To quantify retinoblastoma and its associated features without need to refer to complex qualification criteria. Proceeding from the lowest to the highest grouping is meant to imply worse ocular prognosis. This is a simpler and newer classification to Reese-Ellsworth.

Group	Abbreviations	Features	success*
1.	T	Tumour only#	100%
2.	T+SRF	Tumour + subretinal fluid	91%
3.	T + FS	Tumour +focal seeds SRS ≤ 3mm from tumor VS ≤ 3mm from tumor	59%
4.	T +DS	Tumour +diffuse seeds SRS >3mm from tumor VS > 3mm from tumor	12%
5.	High Risk	Tumor plus(any one) a. Neovascular glaucoma b. Opaque media from hemorrhage c. Invasion of post laminar optic nerve, choroid (<2mm), sclera, orbit or anterior chamber.	NA

*success after treatment with systemic chemotherapy with or without local consolidation is defined as avoidance of enucleation or need for external beam radiotherapy.
# Regardless of tumour number, size or location
DS=Diffuse seeds, FS=Focal seeds, SRF=Sub retinal fluid, SRS=Sub retinal seeds, T= Tumour, VS=Vitreous seeds, NA= Not applicable because these patients had primary enucleation.

4. International retinoblastoma classification

It is useful in guiding the selection of the most appropriate treatment methods and predicting chemo reduction success.-**15**,**16**

Group	Features
A	Small tumour ≤3mm
	Large tumour >3mm
B	Macular ≤3mm to foveola
	Juxtapappilary: ≤3mm to disc
	Subretinal fluid: ≤3mm from the margin
	Focal seeds
C	Subretinal seeds ≤3mm
	Vitreous seeds ≤3mm
	Both subretinal or vitreous seeds ≤3mm
	Diffuse seeds.
D	Subretinal seeds > 3mm
	Vitreous seeds: > 3mm
	Both subretinal and vitreous seeds > 3mm
E	Extensive retinoblastoma occupying more than 50% or
	Neovascular glaucoma or opaque media from hemorrhage to anterior chamber, vitreous or subretinal space

5. Classification encompassing entire spectrum of retinoblastoma disease stages-**17**.

This is an internationally proposed work to adopt a uniform staging system in which patients are classified according to the extent of the disease and the presence of overt extra ocular extension.

Stage 0. Confined to the retina. Eye treated conservatively.

Stage 1. Confined to the retina. Eye enucleated, resected histologically.

Stage 2. Confined to the globe. Eye enucleated, microscopic residual tumour.

Stage 3. Regional extra ocular spread. a. Overt orbital disease. b. preauricular or cervical lymph node extension

Stage 4. Distant metastasis. 1. Hematogenous metastasis: a. Single lesion. b. Multiple lesions. 2. Central nervous system (CNS) extension: a. prechiasmatic lesion. b. CNS mass. c. Leptomeningeal disease.

6. Extra-ocular retinoblastoma have 4 major types-**4**,**5**.

   a. Optic nerve involvement
   b. Orbital invasion
   c. CNS involvement
   d. Distance metastasis.

These are rare in developed countries such as the United States of America but unfortunately are still common in the developing nations due to delayed presentation and lack of access to proper health facility-**4.**

7. Racial differences in the time of presentations of retinoblastoma patients

An African series recorded a substantial delay before first presentation compared to what obtained in Europe-**11,18**. Essentially, many that delayed in African setting would have sought alternative treatments from spiritualists, traditional healers or quacks. Financial difficulties in funding treatment also caused delays-**18**. The series found a mean lag time value of 10 months in the study while the study done in London and Argentina showed lag time of 8 weeks-**19** and 6 months-**20** respectively**.** It was concluded that prolonged lag time is associated with higher risk of extra-ocular spread-**19**, **20**. Also, in the same study, disease staging at presentation was found to be more advanced in the African series and in India-**21** compared to what obtains in Europe and America. In Argentina, over 60% of the cases recorded had intraocular disease-**20** when compared with African series-**7** where majority presented with large extraocular, sometimes fungating disease(Figures 3). In developing countries, retinoblastoma is unfortunately accompanied by a high mortality rate due to a significantly delayed diagnosis made at advanced stages of the disease-**18**,**21,22**

8. Are there differences in presentation in children and adults?

Anterior segment invasion by diffuse retinoblastoma is seen in older children with average age of 6 years as compared to 18 months in typical cases-**4**,**5**. This is unilateral and nonhereditary. Retinoblastoma in adults is very rare. Age at presentation was from 20 years and above among the 23 recorded cases in literature.-**3** Clinical presentations were essentially different compared to those in children**- 3**.

9. Laterality

Bilaterally affected children would carry one germinal mutation from conception and thereafter acquire the second mutation necessary for the expression of Rb. Unilaterally affected children would have to acquire two somatic mutations and this would explain why they would present at a later age than bilateral patients. The bilateral retinoblastoma patient present earlier in time than does unilateral retinoblastoma patients -**23**. Within early or advanced intraocular disease categories, the unilateral retinoblastoma patient will present later than does the bilateral. A series found that bilaterally affected children were diagnosed at an average age of 13months compared to the average of 24months for unilateral Rb patients-**23**. This average age for diagnosis of unilateral retinoblastoma is higher in developing nations-**18**,**21** because of late presentation.

Trilateral retinoblastoma patients manifest either as unilateral or bilateral diseases and are characterized by early onset and predisposition to developing secondary non-ocular, intracranial malignancies -**24**, **25**. Most cases of trilateral retinoblastoma, which occur in about 8% of heritable retinoblastoma-**25** are found in the midline pineal region, but they can also occur in the suprasellar and parasellar regions. These tumors usually occur several years after successful management of ocular retinoblastomas without evidence of direct extension or distant metastasis. -**26**. The nonocular tumors frequently present include intracranial primitive neuroectodermal tumors and sarcomas -**27**.

It is possible that many cases of pineoblastoma were previously misinterpreted as metastatic retinoblastoma to the brain. Unlike other second tumors, the pineoblastoma usually occurs

during the first 5 years of life-**25** whereas second tumors often take many decades to develop, the incidence increasing with time, with a median age of17years (10- 32years)-**28**. The mean interval from the time of diagnosis of retinoblastoma to discovery of the intracranial tumor was 21.5 months-**29**. Unfortunately, pineoblastoma is usually fatal. Hence, patients with bilateral or familial retinoblastoma are advised to have screening for pineoblastoma using computed tomography or magnetic resonance imaging of the brain twice yearly for the first 5 years of life. In some cases the intracranial tumor preceded the diagnosis of retinoblastoma.-**25**,**30**.

Unilateral intraocular retinoblastoma associated with intracranial tumor was more likely to occur in patients with suprasellar region tumors than pineal region tumors ($P < 0.015$). The median survival after the diagnosis of an intracranial tumor was 6 months regardless of the location of the intracranial tumor. For patients who received no treatment for the intracranial tumor the median survival was 1 month whereas it was 8 months for those who received treatment. Children who were asymptomatic at the time of diagnosis of the intracranial tumor had a better overall survival than those who were symptomatic ($P = 0.002$).-**6**. Tumors of the suprasellar region present earlier than tumors of the pineal region after the diagnosis of intraocular tumors. The intracranial tumour represents ectopic foci of retinoblastoma rather than metastatic spread-**31**

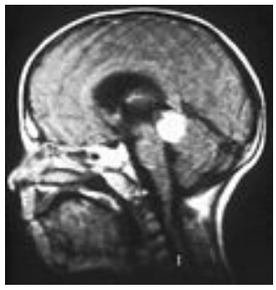

Fig. 10. Aspect of trilateral retinoblastoma on MRI. Courtesy. Wikimedia commons

10. A short mechanistic explanation for the clinical manifestations

Leucocoria is caused by massive replacement of vitreous by tumor and altered red pupillary reflex.

Strabismus is due to loss of central vision following retinal detachment, vitreous hemorrhage, glaucoma or optic nerve involvement singly or in combination.

Proptosis is as a result of tumour growth with displacement of normal tissues or seeding into the tissues and consequent enlargement of the tissues.

Orbital inflammation follows release of toxins from tissue necrosis.

Mucopurulent or fungating ocular mass results from mixed microbial infections due to neglect or mismanagement.

Convulsions and neurological deficits arise from spinal cord or brain metastasis.

Palor is due to anemia following bone marrow metastasis, oncogenic drug administration and radiotherapy

Easy brusability/ bleeding diasthesis are due to low platelet count following bone marrow involvement, oncogenic drug use or radiotherapy

Bone masses following metastasis may produce aches and discomfort

Headache results from raised intracranial pressure.

Blindness results from optic nerve involvement, retinal detachment, vitreous hemorrhage

11. Clinical diagnosis of retinoblastoma

Diagnosis is made from history, physical, histological and radiological examinations; blood chemistry, cerebrospinal fluid and marrow aspiration analysis.

1. Intraocular tumours
   a. Well dilated fundoscopy is mandatory to visualize tumours and classify the condition. It is done under general anesthesia
   b. Indirect ophthalmoscopy with scleral indentation after full dilatation of both eyes is a must. Tumours anterior to the equator are visualized **22**. This method determines:
      - The unilateral or bilateral nature of the lesions
      - The number of tumors
      - Their position in the retina (posterior pole and anterior retina)
      - The tumor size (diameter and thickness)
      - The subretinal fluid and tumor seeds
      - The vitreous seeding: localized or diffuse
      - The anatomical relations with the optic disc and macula.

All these parameters should be taken into account for grouping the retinoblastoma and for making therapeutic decisions - **22**.

   c. Ocular ultrasound detects size, location and extent of tumour**22**

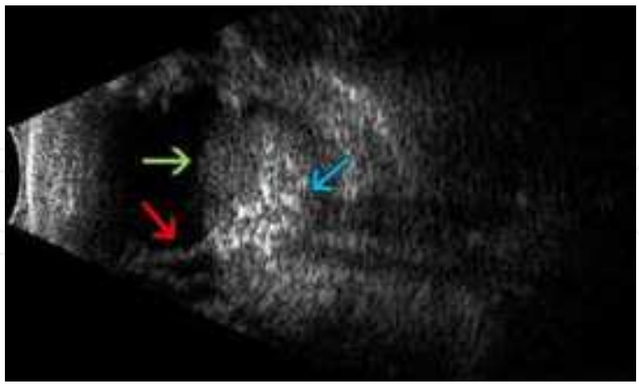

Fig. 11. Ocular ultrasound of large exophytic retinoblastoma. Courtesy. www.retinaatlas.com

   d. Cranial/ orbital computed tomography (CT) scan can detect intraocular calcifications and extent of the tumour-**22**.
   e. Magnetic resonance imaging (MRI) of the brain and orbits is the most sensitive means of evaluating for extraocular extension. It gives better delineation of the optic nerve and also the pineal area-**22,32**

f. Ultrasound biomicroscopy: provides adequate resolution of retinoblastoma anterior to the ora serrata in the ciliary region. Failure to detect anterior tumors early can compromise the chances of saving the eye and increase the risk of extraocular disease-**33**

2. Extraocular tumours
   a. Optic nerve involvement- MRI and histology

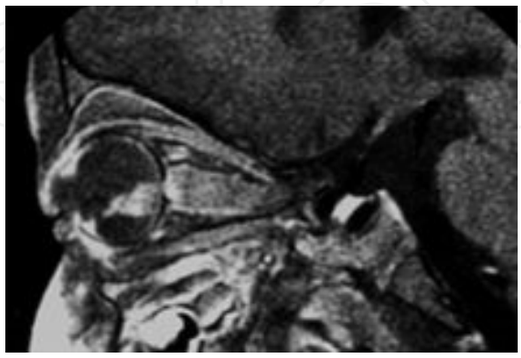

Fig. 12. MRI pattern of retinoblastoma with optic nerve involvement (sagittal enhanced T1-weighted sequence). Courtesy. Wikipedia

   b. Orbital invasion causing proptosis/lid swelling - orbital ultrasound and CT scan.
   c. Central nervous system (CNS) involvement causing brain and spinal cord lesions- MRI, CT scan and intracranial pressure.
   d. Metastatic disease-. Abdominal ultrasound detects pathology of the involved abdominal organs. During physical examination, Liver, spleen and bone masses and enlargements could be palpated.
      Skeletal survey
      Bone marrow assay
      Blood chemistry
      Cerebrospinal fluid analysis and cytology
   e. Non ocular tumours: MRI is the choice in detecting pinealoblastomas especially if a contrast material is added **22.**

12. Metastatic retinoblastoma

Significant differences were found in the occurrence of metastasis: in Low income countries (LICs), 32% (range, 12-45%); in lower Middle income countries (MICs), 12% (range, 3-31%) and in upper MICs, 9.5% (range, 3-24%; p = 0.04).-**34**

An average of 12 months elapsed between initial diagnosis of eye disease and the first signs and symptoms of metastasis-**35** Those at greatest risk for metastasis show features of retinoblastoma invasion beyond the lamina cribrosa in the optic nerve, in the choroid (>2 mm dimension), sclera, orbit, or anterior chamber-**35**. Optic nerve invasion was the commonest extraocular site of spread-**18**. Advanced extraocular retinoblastoma correlates with longer lag times from the onset of symptoms to the diagnosis-**20**. A study showed that at presentation, the mean patient age was 45 months (range, 13-86 months) and all patients with metastatic retinoblastoma had histopathologic or MRI evidence of unilateral

extraocular disease characterized by optic nerve involvement, extrascleral extension, or both.-**36**

When retinoblastoma extends outside the eye, it is difficult to cure, even with sophisticated and intense treatments-**35**,**37**. The prognosis for survival is very poor in developing nations where these treatment modalities are scarce.

Of the 71 orbital recurrence cases followed up over a period of 3–208 months (mean 34.8 months) in a study, 60 patients developed metastatic disease (85%), and 53 of the 71 patients died from metastatic retinoblastoma (75%).-**38**. In developing countries, the diagnosis of retinoblastoma is frequently made at later stages of the disease when extraocular dissemination has already occurred; therefore, ocular and patient survival rates are lower in these countries than in developed countries-**34.** Metastatic spread is uncommon in developed countries because of early detection and proper therapy-**8**.

Presenting symptoms of metastasis -38,39

Eye: eye lid swelling, visible mass in the orbit, ill fitting prosthesis, Ocular deviation, bleeding socket.

Constitutional signs: lethargy, somnolence, fever, irritability, headache, anorexia, vomiting.

Bone: Pains in the back or limbs

Presenting signs of metastasis-38 ,39

Focal neurologic deficit/seizure/nystagmus

Mass on the bone, body, eye or orbit (proptosis)

Pallor, Easy bruisability eyelid ecchymosis, eyelid swelling involving contra lateral eye.

Nose bleed

Hepatosplenomegaly

Fig. 13. Metastatic retinoblastoma in an African child. Courtesy. righthealth.com

Fig. 14. Retinoblastoma with extension into choroid. Courtesy. www.thirdeyehealth.com

13. Useful tests to determine the extent of metastatic disease[40]

MRI of brain and orbit

Computed tomography scan of the brain and spine cord

Lumber puncture for CSF analysis

Electoencephalogram

Bone marrow aspiration

Bone scans

Automated blood chemistry analysis

Histopathology of enucleated/ exenterated eye, orbital biopsy, optic nerve and extrascleral extension.

14. Are some patients at particular risk?

1. Children with the heritable form of retinoblastoma are at high risk for developing subsequent malignancies, most commonly sarcomas. This risk is greater for those children with the heritable form of the disease who were exposed to ionizing radiation at age <1 year-**41.** The most frequent non ocular tumors encountered are osteogenic sarcomas of the skull and long bones, soft tissue sarcomas, cutaneous melanomas, brain tumors, and lung and breast cancer. Patients who survive a second tumor are at risk for a third, fourth and even fifth non ocular tumor-**42**. Subsequent malignant neoplasms are a major cause of premature death in survivors of hereditary retinoblastoma-**43**

2. Patients presenting with high-risk pathology features, such as microscopic tumor invasion of the postlaminar optic nerve (i.e. beyond the lamina cribrosa), choroid, or sclera, are at higher risk of extraocular retinoblastoma relapse. However, the relapse rate is different among the different groups. Such cases are more frequent in developing countries, occurring in more than 50% of children in some middle income countries compared to developed countries-**10**
3. Patients presenting with glaucoma and or buphthalmia have a significantly higher risk for the occurrence of pathology risk factors (PRF) including those resulting in microscopically residual disease. Major choroidal invasion and postlaminar optic nerve, scleral extension and possibly anterior segment invasion were considered PRFs-**44**,**45**

15. Recurrence of retinoblastoma tumours

a. Intraocular tumors may regrow after aggressive local and systemic therapy. Following chemoreduction and focal consolidation, tumor recurrence was found in 18% of tumors at 7 years and the most important factor predictive of recurrence was increasing tumor thickness-**14**.
b. The diagnosis of orbital tumor recurrence was made between 1 and 24 months after enucleation in a study (mean 6 months), with 69 of the 71 patients (97%) being diagnosed within the first 12 months-**38.**
c. Relapse. When analyzing patterns of failure in the 19 eyes that relapsed following external beam radiotherapy, a total of 28 failure sites were identified and consisted of progression to vitreous seeds in 7(25% of failure sites), recurrences from previously existing tumours in 10cases (36% of failure sites) and development of new tumours in previously uninvolved retina in 11 instances (39% of failure sites)-**40.**

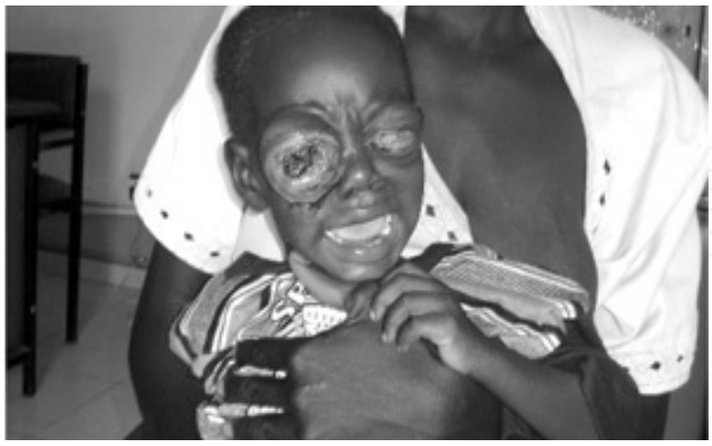

Fig. 15. Recurrent right retinoblastoma after enucleation in a 2 year old child with advanced bilateral retinoblastoma. Courtesy. Jacky Adura

16. Regression of retinoblastoma tumours

Retinoblastoma shows a variety of regression patterns.

a. Spontaneous regression of retinoblastoma is possible and may be asymptomatic resulting in the development of a benign retinocytoma or it can be associated with inflammation and ultimately phthisis bulbi-**5**
b. In evaluating retinoblastoma regression patterns following chemoreduction and adjuvant therapy, regression patterns included type 0 (no remnant), type 1 (calcified remnant), type 2 (noncalcified remnant), type 3 (partially calcified remnant), and type 4 (flat atrophic scar). The retinoblastoma assumes a smaller size with stable margins and frequently, some degree of calcification-**46.** Some tumors become completely calcified whereas others have minimal or no calcification. Following chemoreduction, most small retinoblastomas (3mm or less) result in a flat scar, intermediate tumors (3- 8mm) in a flat or partially calcified remnant and large tumors (8mm or more) in a more completely calcified remnant-**46**.

17. Retinoblastoma mortality – Prognosis

Mortality from retinoblastoma is increased in metastasis-**35**, trilateral cases -**25** and second malignant neoplasms-**47**, the last two are seen mostly in association with bilateral retinoblastoma-**48** and in sporadic unilateral cases that are hereditary-**49**

If left untreated, the mortality rate of retinoblastoma is about 99%. The major factor in mortality rates for patients with retinoblastoma is whether or not the tumor is confined to the eye. Extraocular spread increases mortality rates markedly. If there are tumor cells at the cut end of the optic nerve (with an enucleation), the mortality rate is much higher. Even if tumor is in the lamina cribrosa but the cut end of the optic nerve is free of tumor, mortality rates are elevated. However, when tumor is confined to the globe when enucleated, survival rates are greater than 92%-**48**

In evaluating long-term visual outcome following chemoreduction, the clinical factors that predicted visual acuity of 20/40 or better were a tumor margin at least 3 mm from the foveola and optic disc and an absence of subretinal fluid-**22**,**50**. Retaining visual function depends on the tumor size and location-**48**.

Over 95% of children with retinoblastoma in the United States and other medically developed nations survive their malignancy, whereas approximately 50% survive worldwide-**22**. This discrepancy is largely due to earlier detection in the United States and developed nations when the tumor is confined to the eye, whereas in underdeveloped regions, retinoblastoma is often detected after it has invaded the orbit or brain-**51**. The survival rate of patients with retinoblastoma is low in Nigerian, an underdeveloped nation, due to high mortality associated with late presentation and poor facility for detection and treatment-**52** unlike in developed countries. Again, in some African or Asian countries, the survival rate is virtually zero, because most patients do not complete therapy or are lost to follow-up-**53**. The mean interval from diagnosis of the ocular tumor to death was 46 months and from diagnosis of the intracranial tumor to death was 17 months-**29**

18. Late adverse effects of therapy for retinoblastoma[54,55]

1. Patients who received external beam irradiation are at risk for the development of secondary tumors within and outside the field of treatment. Radiation optic neuropathy and retinopathy can occur. Patients can experience ocular surface abnormalities, severe dry eye and cataracts. Radiation can also affect growing orbital bones, producing facial hypoplasia and contracted socket. Pituitary dysfunction may occur.
2. Chemotherapeutic agents are known to produce numerous potential side-effects. These include lowered immune status, increased incidence of secondary leukemia, infertility; auditory, cardiac, gonadal and renal dysfunction.
3. Cryotherapy can cause retinal thinning and retinal holes. This can be followed by retinal detachment, vitreous hemorrhages, tumor seeding and cataract.
4. Laser treatments can be associated with iris burns, vitreous hemorrhage, and tumor break with vitreous seeding.
5. Intra arterial chemotherapy: Risks associated with general anaesthesia, bleeding from arterial puncture, hematoma or arterial thrombus; drop in vision or total loss of vision in the affected eye, 3rd nerve palsy and sometimes risk of cerebrovascular accident
6. Psychological/Visual effects. The child may be blind from enucleation or from the disease itself. The child may present with low self esteem, limited social function and limited educational attainment.

   Another study showed that vitreoretinal complications occurred in 6.8% of patients undergoing therapy for retinoblastoma. These included retinal tears, rhegmatogenous and tractional retinal detachment, subretinal fibrosis, vitreous traction bands, preretinal fibrosis and pseudo-vitreous seeding. They were more often seen when systemic chemotherapy was combined with external beam radiation, cryotherapy and local chemotherapy-**56.**

19. Complication of retinoblastoma

Metastasis to the orbit, the optic nerve and then to the central nervous system. Other distant spread may involve the abdominal organs, bones and lymph nodes.

Loss of eye in enucleation

Blindness

Cosmetic deformity from enucleation, prosthesis and potential orbital hypoplasia secondary to external beam radiation therapy.

Second malignancy. This is mainly seen in patients with bilateral retinoblastoma who receive external beam radiation therapy-**55.**

Life threatening especially in advanced cases.

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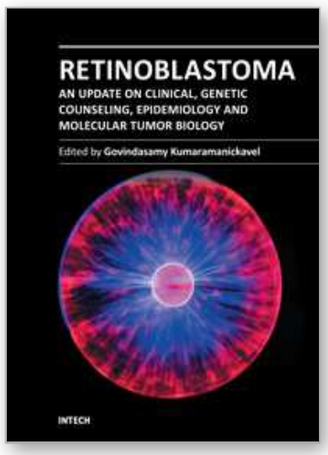

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Retinoblastoma is the first tumor suppressor gene discovered ever. The discovery opened a new avenue in the field of oncology leading to the identification of 35 tumor suppressor genes, till date in our genome. This book is an excellent compilation of both clinical and basic science information that meets the needs of a young clinician and a researcher at the same time. It also has abundant information on recent advances and cutting-edge knowledge in intracellular molecular cross-talking of retinoblastoma protein with various cellular viral-like proteins.

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