

## Retinoblastoma: The Past, Present and the Future of the Disease

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### Abstract :

Retinoblastoma is the disease of the pediatric population. It occurs in children < 5 yrs of age. The disease may be unilateral or bilateral. It may be either heritable or sporadic. It has to be diagnosed early, because of its tendency to metastasize. Multidisciplinary approach is required to diagnose and treat the disease. Ophthalmological, radiological and pathological sciences work in tandem. In developing countries, the patients present in late stages. Chemotherapy, radiotherapy and surgery are required to treat the disease. The disease can be associated with lesions of the pineal gland and supra-sellar region so imaging of the brain is essential. This review mainly highlights the current scenario of the disease in terms of diagnosis and management and gives a brief account of the perceptions of it in past and future prospects

**Key words:** Multidisciplinary, Retinoblastoma, Scenario

### Introduction:

Vision is one of the most important component of the human sensory system. The eyes are responsible for the same. Retinoblastoma is the most common cancer of the eye in children, and it is almost always found in young children.<sup>(1)</sup> The disease has a prevalence of one in 18,000 children younger than 5 years old in the United States.<sup>(1)</sup> In developing nations, extra-ocular disease contributes to half of all retinoblastoma cases presenting to a tertiary care referral center.<sup>(2)</sup> Poverty and lack of awareness contribute to this. There has been a significant advancement as far as the diagnosis and treatment of the disease is concerned. The disease often presents itself in the form leukocoria. Nowadays imaging plays a significant role as far as disease diagnosis is concerned. If the eye examination is abnormal, further testing may include imaging studies, such as computerized tomography, magnetic resonance imaging, and ultrasound.<sup>(3)</sup> Ultimately biopsy is done to confirm the diagnosis. The various treatment modalities for retinoblastoma include<sup>(4)</sup> enucleation of the eye, external beam radiotherapy (EBR), brachytherapy, thermotherapy, laser photocoagulation, cryotherapy, systemic chemotherapy. Identifying RB1 gene mutation in a child may help in taking care of the future off-springs. Early diagnosis of the disease is

important as it can improve the chances of long term survival and possibility of saving useful vision.

### Discussion:

Retinoblastoma is a malignant tumor that originates from the immature cells of the retina. The lesion usually occurs due to the mutation in the RB1 gene. The disease can be heritable or non heritable. Non heritable form mainly occurs due to sporadic post-zygotic somatic mutation or chromosomal anomaly of chromosome number 13. The heritable form usually occurs because of the autosomal dominant transmission to the offspring. The heritable disease is more aggressive and tumors can be multifocal and bilateral [figure 1].<sup>(5)</sup> Early diagnosis of the disease is important because it has a tendency to metastasize to brain, lung, bone and liver. The disease can be unilateral or bilateral.

Rare associations with retinoblastoma: It is because of these that regular brain surveillance is necessary in patients with retinoblastoma.

1. Trilateral retinoblastoma: mainly comprises of bilateral retinoblastoma and pineal gland tumor, pineal lesion usually manifests 2 yrs after the eye lesions.
2. Quadrilateral retinoblastoma: It is a trilateral retinoblastoma with a lesion in the supra-sellar region.

### History of the disease

The disease was first recognized by the Dutch physician Petrus Pawius in 1597. The first enucleation for

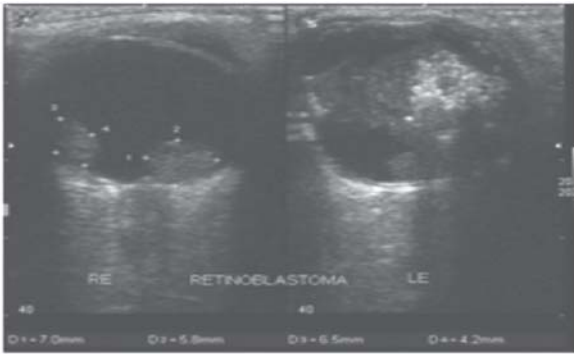
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**Figure 1 : 4 yrs old child presenting with two hypoechoic lesions in the right eye and a single huge hypoechoic lesion with internal foci of calcification in the left eye. This shows that retinoblastomas can be multifocal and bilateral**



retinoblastoma was done by James Wadrop in 1809. He was successful to an extent. By 1897, 17% of children survived (enucleation and exenteration were the only treatments available). However in 1905 it was said that “there is no case on record of a child from whom a gliomatous (retinoblastoma) eye has been removed, growing up and having children with glioma (retinoblastoma).” The first case that was successfully treated with radiation was in 1903. Over the years the disease has gone into the domain of the ophthalmologists.<sup>(6)</sup>

Until the late 1980s, radiation, photocoagulation and enucleation were the main available methods for treatment of retinoblastoma, and these did increase the survival rates among the sufferers to a considerable extent.

As survival improved in patients treated with radiation, however, it was realized that in the long term, these patients often developed second nonocular malignancies in the irradiated field.<sup>(7)</sup> In addition, as genetic testing became possible, it was noted that second (and third, and fourth) tumors were more common in patients with the RB1 gene mutation.<sup>(8)</sup>

By the 1990s, the most common cause of death in retinoblastoma patients was not the retinoblastoma itself but secondary cancers related to the patients' genetics or to their radiation treatment.

Now the clinicians started looking for the alternatives as the radiation on one hand improved the primary disease

but on the other hand induced the other malignancies in the irradiated field, the use of systemic chemotherapy was widely adopted. Systemic chemotherapy for retinoblastoma was first described by Kupfer in the 1950's.<sup>(9)</sup> Interest in chemotherapy grew starting in the 1990s. It has been found out that three cycles of carboplatin-based chemotherapy over 3 months can reduce the size of tumors by almost 50%.<sup>(10)</sup> Today the primary role of the chemotherapy is to reduce the size of the tumor and make it more amenable to surgical excision, and often it is complemented with external radiation as well. The disease in the past was diagnosed primarily on the basis of the clinical examination, but then with the advent of the ultrasound, computed tomography and the latest magnetic resonance imaging the disease relies heavily for diagnosis on imaging nowadays.

### Clinical presentation

The young children often present with leukocoria which is the commonest presentation. Strabismus is the other common presentation. The less common symptoms include glaucoma, proptosis, large mass in orbit, orbital cellulitis, phthisis bulbi, buphthalmos and cloudy cornea. Sometimes rubeosis iridis may be the presenting feature.

### Diagnosis

1. Clinical examination: The first suspicion of the disease in young child occurs when there is leukocoria identified. Ophthalmoscopy, slit lamp examination and routine visual acuity tests are usually done. IOP measurement is done under anesthesia as pediatric population is not very compliant.
2. Radiological examination: USG appears to be the cheapest and one of the best modalities. Both eyes can be screened quickly, without radiation. Absence of calcification in the lesion reduces the chances of the lesion being a retinoblastoma significantly. CT scan is done to look for intracranial extension and bone metastasis. MRI examination is excellent modality for determining the involvement of the optic nerve, brain and spinal cord. Since the retinoblastomas are associated with pineal gland and supra-sellar tumors, certain clinicians prefer to follow up such patients with regular MRI scans.

3. Histopathological diagnosis: usually a biopsy is obtained by the ophthalmologist and the slides are reviewed by the pathologist.

### Pathology

The tumor shows small round cells with hyperchromatic nuclei. The well differentiated components of the tumor are organized into the flexner-wintersteiner rosettes, homer-wright rosettes<sup>(11)</sup> and fluerettes.<sup>(12)</sup> The tumor also shows necrotic areas within.

The tumor may grow endophytically into the vitreous cavity, exophytically beneath the retina causing retinal detachment and maybe diffusely infiltrative.

Sometimes complete regression of the tumor is seen with resultant phthisis bulbi. The maybe fibrous mass with calcification left behind after treatment.<sup>(5)</sup>

### Role of imaging

Common locations of retinoblastoma: posterolateral wall of the globe is the most common site where the lesion tends to originate from.

### Imaging

The diagnosis of retinoblastoma is usually made on indirect ophthalmoscopy. Imaging is required (1) to evaluate the presence of extra-ocular extension and pineal and supra-sellar lesions, (2) when there is opaque media and (3) confirmation of diagnosis when ophthalmoscopy findings are equivocal

Mass with Calcification is the feature that is sought for in the imaging studies. So detecting a mass with calcification in child less than 5 yrs is the basis for diagnosing retinoblastoma. USG does not play any useful role in extra-ocular lesions

MRI on any given day is better than CT scanning, but ease of availability and low cost make CT more routinely utilized modality. MRI also is better as far as differentiating the different causes of the leukocoria is concerned.<sup>(13)</sup>

Exposing the pediatric population to radiation doses that are used in CT scanning may have disastrous effects in the future, again one more reason why MR is the imaging modality of choice.<sup>(14)</sup>

Clinical and imaging findings are together used for staging of the disease

### USG-

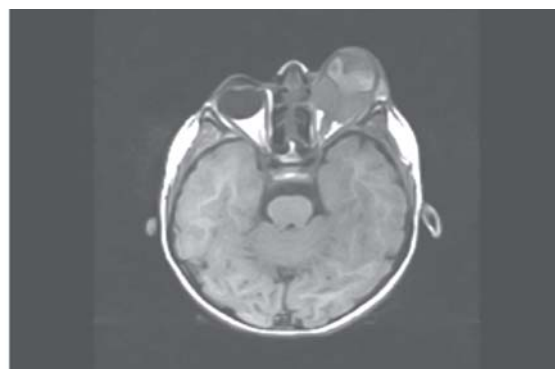
1. It appears as heterogeneous echotexture lesion within the globe.
2. There may be cystic areas that may be seen due to necrosis.
3. Echogenic foci of vitreous hemorrhage may be seen.
4. Echogenic foci with acoustic shadowing s/o calcifications may be seen.
5. Echogenic foci may be suggestive of the vitreous seeds sometimes.
6. Retinal detachment can be seen.
7. Vascularity on Doppler flow imaging can be detected which is suggestive of disease activity.

### CT : (primary modality for assessment of leukocoria)

1. Lobulated hyperdense lesion can be seen in the vitreous cavity in the endophytic variety.
2. Exophytic variety may show subretinal growth.
3. Calcification is the hallmark of the lesion which is easily seen on CT.
4. Vitreous becomes dense.
5. Extra-ocular extension in the form of the optic nerve thickening with enhancement, lesion in retro-orbital fat space and intracranial lesions can be seen.
6. Lesion shows heterogeneous enhancement on post contrast study.

MR : (mainly for determining the intracranial extension and involvement of optic nerve)

**Figure 2 : 3yrs old female child with mass in the left eye extending into the retro-orbital space and encasing the optic nerve with its involvement.**



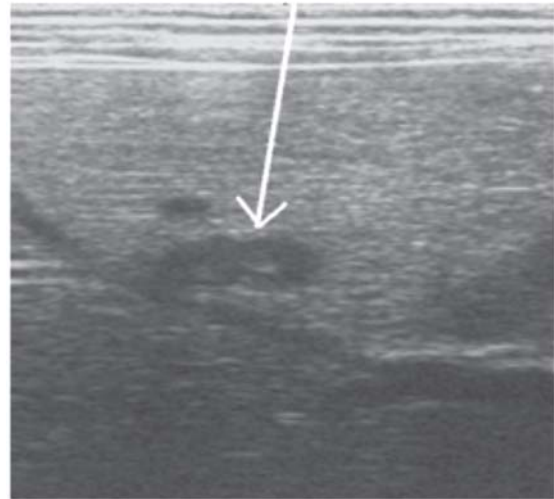
[Figure 2]

1. Lesion appears hyperintense relative to vitreous on T1W images and appears hypointense to vitreous on T2W images.
2. There is marked enhancement that is seen on postcontrast images.
3. There is enlargement and enhancement of the optic nerve that is seen s/o involvement.
4. Subretinal exudate is seen as hyperintense area on T1W and T2W images.
5. Spinal canal is assessed to look for any subarachnoid dissemination.
6. Sellar and pineal regions may show enhancing areas in trilateral and quadrilateral retinoblastomas.

**Metastasis:**

Since the tumor can metastasize to various organs, the following ways can be adopted to rule out metastasis. Lung, liver [figure 3]<sup>(6)</sup> and nodal metastasis- CT scanning Brain, Optic nerve, Leptomeninges -MRI, Bone- Bone scan and CT scan [figure 4] CSF dissemination-CSF analysis for malignant cells

**Figure 3 : USG of liver in a patient who is a known case of retinoblastoma shows hypo-echoic lesions within, which turned out to be liver metastasis.**



**Classification of intraocular retinoblastoma**

The International Classification for Intraocular Retinoblastoma takes into account the factors that affect globe salvage and survival in the present treatment scenario.

<b>Group A ( very favourable)</b>	Retinoblastoma ≤ 3mm in basal dimension.
<b>Group B ( favourable )</b>	Retinoblastoma > 3mm or with 1 or more of the following 1. Macular location. 2. Juxtapapillary location. 3. Subretinal fluid
<b>Group C ( doubtful)</b>	Retinoblastoma with 1 of the following 1. Subretinal seeds ≤ 3mm 2. Vitreous seeds ≤ 3mm 3. Both subretinal and vitreous seeds ≤ 3 mm
<b>Group D ( unfavourable)</b>	Retinoblastoma with 1 of the following 1. Subretinal seeds > 3mm 2. Vitreous seeds >3mm 3. Both subretinal and vitreous seeds >3 mm
<b>Group E ( very unfavourable)</b>	Extensive disease involving > 50% of the globe or 1 of the following 1. Neovascular glaucoma. 2. Opaque media from vitreous hemorrhage in vitreous, anterior chamber or subretinal space 3. Invasion of postlaminar optic nerve, choroid (>2mm), sclera, orbit or anterior chamber.

**Figure 4: 3 yrs old child with retinoblastoma in both eyes with bone metastasis involving the anterior walls of both middle cranial fossae and the lateral walls of both orbits with associated soft tissue component**



### Screening for retinoblastoma

Since retinoblastoma is a heritable disease the parents and siblings of the affected child must be screened to rule out latent subclinical disease.

### Treatment

As far as the treatment of the retinoblastoma is concerned prolonging the life is the main objective. Not to undermine the importance of the vision. But saving meaningful eyesight is less important than saving life. This is basis for the therapy that is planned. Of late with advent of newer drugs, chemotherapy has become the treatment of choice. After treatment the retinoblastoma tumor shrinks and may result in phthisis bulbi.

### Surgical management:

1. Enucleation- It is done in patients belonging to group D or E. patients who fail to respond to chemotherapy are also sometimes treated with enucleation.
2. Exenteration- The surgery is very extensive, and is hardly done nowadays. It is reserved only for the recurrences in the orbit.
3. Local surgical procedures - mainly reserved for small lesions in the eyeball. They may be used as a primary approach or following chemotherapy. E.g., Laser photocoagulation, Thermotherapy, Cryotherapy, Chemothermotherapy.

### Medical management: mainly vincristine, etoposide and carboplatin are used. <sup>(15)</sup>

1. Chemoreduction- here few cycles of chemotherapy are given in order to downstage the tumor so that local surgical procedures can be done instead of the enucleation.
2. Periocular chemotherapy- systemically administered drugs do not penetrate well into the vitreous cavity and subretinal space, therefore accounting for the recurrence. Nowadays carboplatin is found to be the most effective as far as this novel approach is concerned. But the drugs have significant side effects locally. <sup>(16)</sup>
3. Intra-arterial Chemotherapy - it has been found to be effective, especially melphalan. <sup>(17)</sup>
4. Chemoprophylaxis- invasion of anterior chamber, iris, ciliary body, choroid (massive), sclera and optic nerve beyond lamina cribrosa, extrascleral disease and disease in cut end of the optic nerve are features that once identified require additional cycles of chemotherapy.

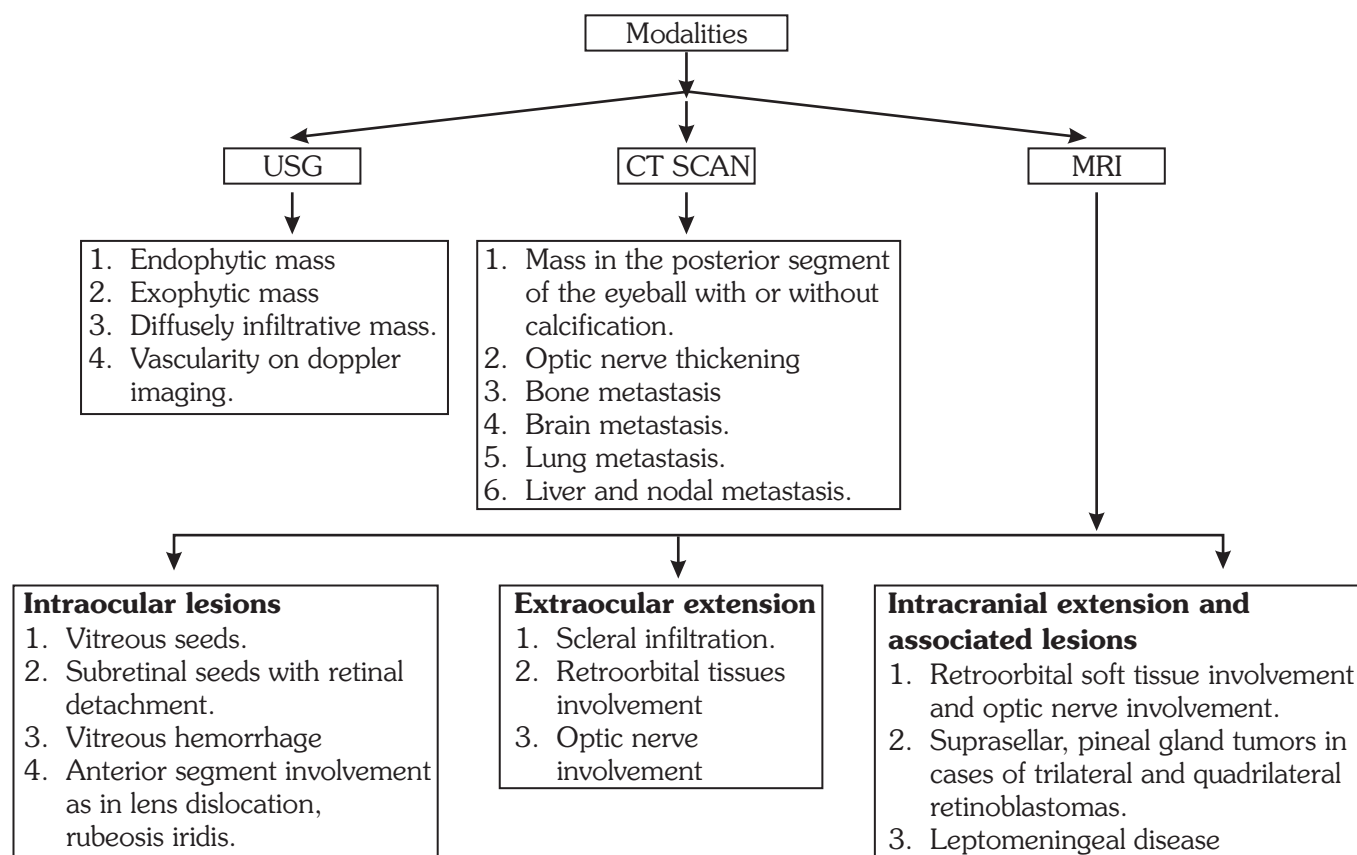
### Radiation therapy: Retinoblastoma responds well to radiation.

1. Brachytherapy- it is reserved for small and localized lesions.
2. EBRT- it is mainly reserved for extensive and multiple lesions and when other methods have failed. It runs the risk of inducing carcinogenesis in the adjacent tissues. Usually 40-45 cGY are used. Radiation therapy can cause cataract formation, may lead to osteo-radionecrosis and may affect the dentition in the young children.

### Preventive measures and post diagnosis and treatment surveillance

Blood and tumor samples are tested to determine if a patient with retinoblastoma has a mutation in the RB1 gene. Once the patient's genetic mutation has been found, other family members can be screened directly for the mutation. Children with a germline RB1 mutation develop new tumors for a few years after diagnosis and treatment; therefore they need to be examined frequently. Usually examinations are carried out every 2 to 4 months for at least 28 months. <sup>(18)</sup> The gap between serial examinations may be lengthened once the child becomes older.

### Imaging manifestations of the disease



Few children who present with unilateral disease will eventually develop disease in the opposite eye. Periodic examinations of the unaffected eye are performed until the germline status of the RB1 gene is known.

Post diagnostic surveillance is of utmost importance in the patients with small disease who have undergone less radical procedures perhaps to save the vision. These patients must be followed up regularly to look for the recurrent disease. USG is useful in this regard to determine the recurrence within the orbit and MR is useful to determine recurrence within the optic nerve and brain. USG is also useful in patients after they have undergone enucleation to determine recurrence.

Patients of Retinoblastoma are often associated with increased risk of osteosarcoma,<sup>(19)</sup> soft tissue sarcomas, melanoma, carcinomas, leukemias, lymphomas and various brain tumors later in life.<sup>(20)</sup> Therefore these pathologies must be kept in mind as well during the surveillance.

### Future prospects

1. Fetal MRI and 3D USG are being explored for in utero diagnosis of the disease. Their usefulness is being researched in western countries.<sup>(21)</sup>
2. Stem cell preservation with high dose chemotherapy has added one more dimension to the treatment of the disease. But still research is going on to determine the exact application.<sup>(22)</sup>
3. Community education efforts have been done which have promoted people to seek early medical help for the disease. Creating awareness and education in common masses especially in rural areas of the developing countries are easiest and most effective ways to prevent the advanced disease from occurring. This requires commitment from the people, health care professionals and the government.
4. Pharmacologic enhancement of radiotherapy, use of tumor tissue targeting techniques, differentiating agents, immunotherapy and employing certain

suppressor genes to prevent metastasis, these are some other spheres in the management of the retinoblastoma that are being investigated in western countries.<sup>(23)</sup>

### Conclusion:

Orbital retinoblastoma is a disease in the pediatric population that ultimately has fatal outcome. Multifaceted approach has to be employed especially in country like India. Various socio-economic barriers have to be overcome before some significant reduction in the morbidity and mortality can be made. In the past the diagnostic modalities were limited and the treatment options too were limited, enucleation was considered to be the best treatment. There has been a paradigm shift towards a conservative approach with advent of newer chemotherapeutic agents. The disease in the present day can be diagnosed earlier with availability of wide array of imaging techniques further improving the scope for survival and salvage of the eye. And with the ongoing research gene therapies, in utero diagnosis, stem cell techniques the chances are that we may be able to overpower the disease. Though there has been an improvement in the survival of the patients, yet we have a long way to go, and concerted efforts will be required.

### References:

1. Devesa SS. The incidence of retinoblastoma. *Am J Ophthalmol* 1975;80(2):263-265.
2. Bakhshi S, Bakhshi R. Genetics and management of retinoblastoma. *J Indian Assoc Paediatr Surg.* 2007;12:109-11.
3. de Jong MC, de Graaf P, Noij DP, Göricke S, Maeder P, Galluzzi P, et al. "Diagnostic performance of magnetic resonance imaging and computed tomography for advanced retinoblastoma: a systematic review and meta-analysis". *Ophthalmology* May 2014; 121(5): 1109-18.
4. Chintagumpala M, Chevez-Barríos P, Paysse EA, Plon SE, Hurwitz R. Retinoblastoma: review of current management". *Oncologist* 2007; 12(10) 1237-1246.
5. Soni HC, Patel SB, Goswami KG, Gohil Y. Pictorial essay: USG of retinoblastoma. *Indian J Radiol Imaging* 2006; 16: 657-68.
6. David H Abramson Retinoblastoma in the 20th Century: Past Success and Future Challenges The Weisenfeld Lecture. *Investigative Ophthalmology & Visual Science* August 2005; Vol.46, 2684-91.
7. Sagerman RH, Cassady JR, Tretter P, et al. Radiation induced neoplasia following externalbeam therapy for children with retinoblastoma. *Am J Roentgenol Radium Ther Nucl Med.*1969;105:529-535.
8. Abramson DH, Melson MR, Dunkel IJ, et al. Third (fourth and fifth) nonocular tumors insurvivors of retinoblastoma. *Ophthalmology.* 2001;108:1868-1876.
9. Kupfer C. Retinoblastoma treated with intravenous nitrogen mustard. *Am J Ophthalmol.* 1953;36:1721-1723.
10. Kim JW, Abramson DH, Dunkel IJ. Current management strategies for intraocularretinoblastoma. *Drugs.* 2007;67:2173-2185.
11. Michelle B. Crosby, G. Baker Hubbard, Brenda L. Gallie, and Hans E. Grossniklaus (2009) Anterior Diffuse Retinoblastoma: Mutational Analysis and Immunofluorescence Staining. *Archives of Pathology & Laboratory Medicine: August 2009, Vol. 133, No. 8, pp. 1215-1218.*
12. Kumar V, Abbas AK, Fausto N. Robbins and Cotran Pathologic Basis of Disease. Seventh Edition. Philadelphia: Elsevier Saunders, 2005, p. 1442.
13. Potter PD, Shields CL, Shields JA, Flanders AE. The role of magnetic resonance imaging in children with intraocular tumors and simulating lesions. *Ophthalmology.* 1996;103:1774-83.
14. Murphree AL, Samuel MA, Harbour JW, Mansfeld NC. Retinoblastoma. In: Ryan SJ, Schachat AP, editors. *In Retina.* 4th ed. Philadelphia: Mosby; 2006. pp. 558-607.
15. Rachna Meel, Venkatraman Radhakrishnan, and Sameer Bakhshi. Current therapy and recent advances in the management of retinoblastoma. *Indian J Med Paediatr Oncol.* 2012 Apr-Jun; 33(2): 80-88.
16. Schmack I, Hubbard GB, Kang SJ, Aaberg TM, Jr, Grossniklaus HE. Ischemic necrosis and atrophy of the optic nerve after periocular carboplatin injection for intraocular retinoblastoma. *Am J Ophthalmol.* 2006;142:310-5. [PubMed]
17. Yamane T, Kaneko A, Mohri M. The technique of ophthalmic arterial infusion therapy for patients with intraocular retinoblastoma. *Int J Clin Oncol.* 2004;9:69-73. [PubMed]
18. Abramson DH, Mendelsohn ME, Servodidio CA, et al. Familial retinoblastoma: where and when?. *Acta Ophthalmol Scand* 1998; 76 (3): 334-8.[PUBMED Abstract]
19. Maes P, Brichard B, Vermeylen C, Cornu G, Ninane J. Primary and secondary osteosarcoma of the face: a rare childhood malignancy. *Med Paediatr Oncol* 1998; 30; 170-174.
20. Ukijide Tateishi, Tadashi Hasegawa, Kuniyoshi Miyakawa, Minako Sumi, Noriyuki Moriyama. CT and MRI features of Recurrent Tumors and Second primary Neoplasms in Pediatric Patients with Retinoblastoma. *AJR* 2003; 181: 879-884 .
21. Maat-Kevit J.A., Oepkes D., Hartwing N.G. A large retinoblastoma detected in a fetus at 21 weeks of gestation. *Prenat. Diagn.* 1993;13:377-384. [PubMed]
22. kremens b., wieland r., rienhart h. high dose chemotherapy with autologous stem cell in children with retinoblastoma. bone marrow transplant. 2003;31:281-284. [PubMed]
23. White L. Chemotherapy in retinoblastoma: current status and future directions. *Am. J. Paediatr. Hematol. Oncol.* 1991;13:189-201. [PubMed].