Retinoblastoma occurs in approximately 1 in 14,000-34,000 live births.¹,² No predisposition to race, sex or laterality of the eye is noted. The majority of cases of retinoblastoma are sporadic (no family history and no affected family members on ophthalmic examination).

Retinoblastoma occurs as a result of loss of the tumor suppressor gene located on band 14, on the long arm of chromosome 13 (13q14). ⁴,⁵ In genetically transmitted disease, the abnormality results in the development of usually bilateral, multifocal tumors in relatively younger patients. This deletion also predisposes these children to other non-ocular tumors such as osteosarcoma in later stages of life. In contrast, sporadic tumors occur in older children and tends to be unifocal and unilateral. However, 10-20% of unilateral disease can also be genetically transmitted.

The average age at diagnosis of retinoblastoma in American children is 18 months, and evidence indicates that Asian children present later than their western counterparts.¹,⁶⁻⁸ Bilateral cases are diagnosed earlier than unilateral cases.¹,⁹

**Clinical Features**

The most common presentation of retinoblastoma is leukocoria (61-70 %) (Fig 1) and strabismus (22-48%) ¹,¹⁰,¹¹. On fundus examination retinoblastoma appears as a slightly white, flat, translucent lesion in the sensory retina (Fig 2).

Moderately advanced lesions may present as unilateral or bilateral leukocoria (Fig 3).
Based on the growth pattern, the tumor can be classified into endophytic, exophytic, mixed (both endophytic and exophytic) and diffusely infiltrative tumors. Spontaneous regression of retinoblastoma occurs in about 1 percent of patients. It is often seen in eyes with phthisis bulbi and following an episode of severe inflammation.

Local spread to the orbit, distant metastasis to brain, spinal cord, skull bones, distant bones, viscera and lymph nodes may occur in advanced retinoblastoma.

On ocular ultrasonography retinoblastoma appears as an irregular mass lesion with high surface reflectivity and high internal reflectivity resulting in orbital shadowing all due to the presence of calcium. Computerized tomography and magnetic resonance imaging allow detection of extraocular disease, intracranial metastasis and pinealoblastoma. Retinoblastoma appears as an intraocular mass with calcium on CT scan; it appears as a hyperintense to vitreous lesion in T1 weighted image and hypointense to vitreous in T2 weighted images on MRI. (Fig 4)

Histopathology

Retinoblastoma appears as a basophilic mass with lightly eosinophilic areas due to necrosis of tumor and/or multiple dense basophilic foci (due to calcification) within areas of necrosis may be seen. The tumor may be well differentiated or poorly differentiated. Poorly differentiated retinoblastoma consists of small to medium-sized round cells with hyperchromatic nuclei and scanty cytoplasm. High mitotic figures are often observed. A well-differentiated tumor may show: (i) rosettes, or (ii) fleurettes. Seventy percent of retinoblastomas are known to contain rosettes.

Rosettes are of two types:
- Flexner-Wintersteiner rosette
- Homer-Wright rosette

In a Flexner-Wintersteiner rosette, columnar cells are arranged around a clear central lumen. The nuclei of the cells are arranged near the base of the tumor. The lumen contains hyaluronidase resistant glycosaminoglycans, which are found between photoreceptor and retinal pigment epithelium.

In a Homer-Wright rosette, the cells are arranged radially around a central tangle of neural fibers.

Fleurettes represent further differentiation and present as flower bouquet-like aggregates of tumor cells with bulbous eosinophilic processes projecting through the fenestrated membrane. They are seen in 6-10 percent of the retinoblastoma cases.

Differentiation of the tumor does not have prognostic value.

Management

Management options in retinoblastoma include enucleation, in an eye without visual potential, if more than half the globe is involved by the tumor, or in the presence of glaucoma and anterior chamber involvement. Eyes with visual potential (unilateral/bilateral cases) are managed conservatively with modalities that include cryotherapy, laser photocoagulation, transpupillary thermotherapy (TTT), thermochemotherapy, chemoreduction, plaque brachytherapy and external beam radiotherapy.

International classification of retinoblastoma

As early classifications were deemed insufficient in this era of chemoreduction of retinoblastoma, a new revised classification has been devised to offer prognosis of the affected eye.
**Group Tumor characteristics**

<table>
<thead>
<tr>
<th>Group</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Small tumor (≤ 3mm)</td>
</tr>
<tr>
<td>B</td>
<td>Larger tumor (≥ 3mm)</td>
</tr>
<tr>
<td>C</td>
<td>Focal seeding</td>
</tr>
<tr>
<td></td>
<td>- Subretinal and or vitreous seeds ≤ 3 mm from tumor</td>
</tr>
<tr>
<td>D</td>
<td>Diffuse seeding</td>
</tr>
<tr>
<td></td>
<td>- Subretinal and or vitreous seeds ≥ 3 mm from tumor</td>
</tr>
<tr>
<td>E</td>
<td>Tumor &gt;50 % globe</td>
</tr>
<tr>
<td></td>
<td>- Neovascular glaucoma</td>
</tr>
<tr>
<td></td>
<td>- Opaque media due to intraocular hemorrhage</td>
</tr>
<tr>
<td></td>
<td>- Postlaminar optic nerve invasion, choroid (&gt;2 mm), sclera, orbit anterior chamber involvement</td>
</tr>
</tbody>
</table>

**Treatment of retinoblastoma** ⁴, ¹⁵

**Management of retinoblastoma confined to the eye:** Eyes with visual potential (unilateral/bilateral cases) are managed conservatively. Primary or recurrent tumours anterior to equator, ≤ 4 mm in diameter and less than 3 mm thickness, confined to the retina are treated with triple freeze thaw cryotherapy. Tumors 3-4 mm in diameter, 2 mm thick confined to the retina are treated with 2 rows of deep laser burns around the tumor. Slightly larger tumors confined to the retina can be treated with transpupillary thermotherapy, which is increasing the tumor temperature by 6-8°C above body temperature.

Larger tumors or those with vitreous or subretinal seeds are treated with external beam radiation delivering 3500-4000 cGy, 200 cGy fractions delivered over a 4-5 week period. Plaque brachytherapy with episcleral plaque applicators (Iodine - 125 or Ruthenium - 106) can be used to treat tumours ≤ 15 mm in diameter and 6-8 mm in height, at least 2 mm from optic disc and fovea with or without localized vitreous seeding. Plaque therapy has the advantage of limited radiation to normal tissue, thereby limiting complications. Radiation in any form is associated with complications such as retinopathy, cataract and in bilateral germinal tumors, the increased risk of second malignant neoplasms in later years ¹⁶. The risk of second malignant neoplasms is highest when the child subjected to radiation less than 1 year of age. Hence it is preferable to avoid radiation and CT scan in retinoblastoma infants less than one year of age.

Contemporary management of large tumors, tumors close to optic nerve (Fig 5) / fovea or those extending beyond the retina involves using chemoreduction. Triple drug chemoreduction using vincristine, etoposide and carboplatin are used in multiple cycles to “chemoreduce” the tumor and the residue is destroyed using focal treatments such as laser photocoagulation, cryotherapy etc., The tumor is replaced with chorioretinal atrophy and calcific residue with chemoreduction and local treatment. (Fig 6, 7) Current focus is on local chemotherapy and one of the avenues being explored is cannulation of the ophthalmic artery and melphalan infusion through the same.
Subconjunctival carboplatin chemotherapy is also used as an adjunct to systemic chemotherapy.

This shift from radiation to chemoreduction is primarily aimed at reducing the increased risk of second malignant neoplasms associated with the use of radiation.

Enucleation is indicated in retinoblastomas involving more than half the globe, presence of glaucoma and anterior chamber involvement. A long optic nerve stump (≥10 mm in length) should be obtained during enucleation. If post enucleation histopathological examination shows tumor invasion beyond lamina cribrosa, anterior segment involvement (Fig. 8) or extensive choroidal invasion, adjunctive chemotherapy is necessary to decrease risk of subsequent metastatic disease.

Involvement of the cut-end of optic nerve with tumor has to be treated aggressively with adjunctive chemotherapy and radiation.

Management of extraocular retinoblastoma:
(Fig 9 – showing orbital recurrence of retinoblastoma)

Extraocular retinoblastoma is managed with a multimodal approach of chemoreduction to reduce the tumor, excision of the tumor followed by additional chemotherapy and radiation to the affected part. Intracranial involvement is treated with intrathecal chemotherapy in addition to CNS radiation and systemic chemotherapy.

Prognosis

The overall 5-year survival is around 90 percent in retinoblastoma. Patients with germinal mutations are more likely to die due to second nonocular tumors, which develop at a later age. Involvement of the cut end of the optic nerve indicates poor prognosis and possible intracranial metastatic disease if adequate (at least 10 mm) length of the optic nerve stump was obtained during enucleation. Tumor invasion into the ocular coats, extensive choroidal invasion and anterior chamber seeding are associated with an increased risk of subsequent metastatic disease. Extraocular, central nervous system involvement and hematogenous spread carry a poor prognosis.

References


