Head and neck: Retinoblastoma

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Identity

Alias
Retinal glioma; Fungus hematodes

Note
Retinoblastoma is a malignant primary intraocular tumor predominantly encountered in infancy and early childhood. Another striking definition of retinoblastoma is that it is a childhood cancer that can be completely cured with radiotherapy alone. This tumor develops from the retina and by the age of 5 years, 90% of cases are diagnosed.

Classification

Note
Retinoblastoma is evaluated on genetic basis, laterality and focality. Approximately 85% of retinoblastomas are sporadic and 15% of cases are familial. Unilateral tumors account for 60% of cases and bilateral involvement is seen in 40% of patients. Eighty-five percent of unilateral tumors have somatic mutations and 15% have germinal mutations. Conversely, 90% of bilateral tumors have germinal mutations and 10% have postzygotic somatic mutations. When both eyes are involved multifocality is the rule. There is an average of five tumors per eye in bilateral cases. Trilateral retinoblastoma is a rare and often lethal condition in which there is an undifferentiated neuroectodermal tumor in the pineal gland or in para/supra sellar region of the midbrain. Ninety percent of pinealoblastomas develop in patients with bilateral disease. Unilateral cases have a 0.5% risk of developing trilateral retinoblastoma.

<table>
<thead>
<tr>
<th>Group</th>
<th>Description</th>
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</table>
| I     | a. Solitary tumor, less than 4 disc diameters in size, at or behind the equator.  
       | b. Multiple tumors, none over 4 disc diameters in size, all at or behind the equator. |
| II    | a. Solitary tumor, 4 to 10 disc diameters in size, at or behind the equator.  
       | b. Multiple tumors, 4 to 10 disc diameters in size, behind the equator. |
| III   | a. Any lesion anterior to the equator.  
       | b. Solitary tumors larger than 10 disc diameters behind the equator. |
| IV    | a. Multiple tumors some larger than 10 disc diameters.  
       | b. Any lesion extending anteriorly to the ora serrata. |
| V     | a. Massive tumors involving half of the retina.  
       | b. Vitreous seeding. |

Table 1. Reese-Ellsworth classification for intraocular retinoblastoma.

<table>
<thead>
<tr>
<th>Group A</th>
<th>Description</th>
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<tbody>
<tr>
<td></td>
<td>All tumors ≤ 3mm, confined to the retina, at least 3 mm from the foveola, 1.5 mm from the disc. No</td>
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</table>
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<table>
<thead>
<tr>
<th>Group</th>
<th>Description</th>
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<tbody>
<tr>
<td>A</td>
<td>Vitreous or subretinal seeding. (Very low risk).</td>
</tr>
<tr>
<td>B</td>
<td>Discrete retinal tumor of any size and location without vitreous or subretinal seeding. Subretinal fluid extending ≤ 5mm from the tumor base is allowed. (Low risk).</td>
</tr>
<tr>
<td>C</td>
<td>Discrete retinal tumors of any size and location with focal vitreous or subretinal seeding treatable with brachytherapy. One quadrant of subretinal fluid is allowed. (Moderate risk).</td>
</tr>
<tr>
<td>D</td>
<td>Diffuse vitreous or subretinal seeding associated with massive, nondiscrete endophytic or exophytic tumor. &gt; 1 quadrant of retinal detachment. (High risk).</td>
</tr>
<tr>
<td>E</td>
<td>Eyes destroyed anatomically and functionally by: neovascular glaucoma, intraocular hemorrhage, tumor in the anterior vitreous, tumor touching the lens, aseptic orbital cellulitis, diffuse type retinoblastoma, phtisis bulbi. (Very high risk).</td>
</tr>
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Table 2. International Classification of Retinoblastoma (Murphree).

Clinics and pathology

Note
Leukocoria (white reflex from the pupillary aperture) (60%) and strabismus (20%) are the two major presenting signs of retinoblastoma (see Figure 1A). Rarely patients may present with buphthalmus, pseudo-hypopyon, hyphaema, vitreous hemorrhage, and pseudo-orbital cellulitis. A typical retinoblastoma is a round or oval shaped, variably vascularized pink mass. It may sometimes appear chalky white because of calcification. Endophytic retinoblastoma grows into the vitreous cavity and accounts for 60% of typical retinoblastomas (see Figure 1B). Exophytic tumors (39%) grow under the subretinal space and cause retinal detachment. Rarely the tumor may show diffuse growth pattern (1%) in which there is no detectable mass but a sheet-like dissemination of the malignant cells within the retina. This latter type of presentation usually occurs in older children. Currently, the Reese-Ellsworth (RE) and International Classification of Retinoblastoma (ICRB) systems are used in staging the disease, which is very important in treatment planning (see tables above).

Phenotype / cell stem origin

The cell of origin of retinoblastoma is a topic of hot debate. In simple terms, the cell of origin is the cell in which the tumor suppression activity of pRB is first required. This may not necessarily be the cell in which loss of RB1 gene occurs. Several models and hypotheses exist on the cell of origin. It was long believed that a retinal multipotent cell committed to cone differentiation was the cell of origin. Recent studies found strong expressions of minimicrosome maintenance protein 2 (MCM2) and ABCG2 (a casette-binding transmembrane protein that confers drug resistance) on retinoblastoma cells that favors a neural cancer stem cell origin. Also tumor cells were found to express CD44 (hyaluronate receptor), PROX1 and syntaxin 1A (retinal progenitor markers), CD90 (retinal ganglion cell marker) and CD133 (photoreceptor cell marker) all supporting the cancer stem cell theory. Against the stem cell theory, some studies showed expression of mature neural cell markers including MAP2, NSE, synaptophysin and opsin suggesting mature neural and amacrine cells as the source of retinoblastoma. Others observed that a fully differentiated retinal horizontal cell could reenter the cell cycle and could form tumor foci.

Etiology

Inactivation of both wild type alleles of the retinoblastoma susceptibility gene (RB1) is postulated to cause the development of retinoblastoma.

Epidemiology

Retinoblastoma accounts for 4% of all pediatric cancers and the cumulative incidence is 1/18000-30000 live births per year regardless of sex, race or geographic predilection. Each year, 5000 to 8000 new cases of retinoblastoma are diagnosed on the global scale. Retinoblastoma is responsible for 1% of all deaths below 15 years of age. The incidence of hereditary retinoblastoma is relatively constant in various parts of the world. However, there seems to be increased incidence of non-hereditary sporadic retinoblastoma in underdeveloped parts of the world. This was partly related to the widely common human papilloma virus infections in those areas. Advanced paternal age is also associated with more sporadic gene mutations.
Retinoblastoma is composed of small, round densely packed cells with large hyperchromic nuclei and basophilic cytoplasm. There may be vast areas of necrosis and calcification because of rapid tumor growth and insufficient blood supply. Various degrees of photoreceptor differentiation are evidenced by typical cellular arrangements. Flexner-Wintersteiner rosettes are aggregates of cuboidal or columnar cells around a central lumen, considered as an aborted attempt to form photoreceptors (see Figure 1C). A more advanced step towards photoreceptor formation is the fleurette type rosettes. These are formed by tumor cells with eosinophilic cellular extensions arranged in a semicircular fashion with bulb-like endings. It is believed that red and green cones participate in the formation of these rosettes whereas blue cones tend to form structures called bacillettes.

Histopathological demonstration of tumor cells 1 mm beyond the lamina cribrosa, scleral invasion, clumps of cells within more than 50% of choroidal thickness are established risk factors for extraocular dissemination of retinoblastoma. Increased intraocular pressure, iris neovascularisation and buphthalmus are risk factors for optic nerve invasion (see Figure 1D).

**Treatment**

Several options exist depending on the stage and laterality of the tumor.

1. **Chemotherapy:** Systemic chemotherapy has become the most commonly used method worldwide within the past 10 years for almost all intraocular retinoblastomas. The rationale is to shrink the tumor (chemoreduction) so that subsequent local consolidation treatments are used to further destroy the tumor and thus avoid enucleation or external beam radiotherapy.

   In general, eyes having a potential of a useful vision but containing large tumors untreatable with local methods, children under the age of one year, and advanced bilateral cases are eligible for chemoreduction. Current protocols include vincristine, carboplatin and etoposide or teniposide. A successful outcome can be obtained in 100% of
Figure 2
A. RE IIib or ICRB group C retinoblastoma before chemotherapy.
B. The same eye shown above following 9 cycles of VEC chemoreduction protocol.
C. Multiple small tumors easily treatable with TTT.
D. Atrophic scars following TTT.
E. Osteogenic sarcoma of the maxillary sinus 11 years after external beam radiotherapy.

group A, 93% in group B, 90% in group C, and 47% in group D eyes. Most tumors regress more than 50% within 3-4 weeks. The most important complication of chemoreduction therapy is recurrence of the tumor, which is more common in macular tumors. Also, new ocular tumors may develop while under systemic chemotherapy. Transient myelosuppression, cytopenia and neutropenia occur in 100% of patients. The
development of secondary non-ocular cancers following chemotherapy is an unresolved issue. Preliminary studies suggest an increased incidence of AML particularly in patients who had received teniposide, which acts on chromosome 11q35. (see Figure 2A and 2B).

2. Local chemotherapy: Local administration of chemotherapeutic agents is in use to deliver higher concentrations of the drug into the eye and avoid systemic toxicity and side effects. Large molecules can easily pass the sclera regardless of lipophilicity. Injection of carboplatin into the subtenon space is effective against localized mild amounts of vitreous seedings but this effect is transient and rarely curative. Additionally, carboplatin is rapidly cleared from the vitreous limiting its effects. To overcome this inconvenience, a sustained delivery system of carboplatin from fibrin sealants is developed. Recently, supralselective intra-arterial infusion of melphelan to the ophthalmic artery resulted in satisfactory tumor regression in eyes that would otherwise have to be enucleated.

3. Enucleation: This time-honored surgical treatment is indicated for most of group E or RE V eyes where there is no prospect of vision. Eyes with elevated intraocular pressure, rheobase iridis, tumor in the anterior chamber, buphthalmus and evidence for optic nerve involvement need to be enucleated. Failure of prior chemotherapy and radiotherapy are other indications for enucleation. In general, enucleation becomes necessary in 75% of unilateral cases because of the advanced stage at the time of diagnosis. Likewise, enucleation of at least one eye (the worst eye) becomes unavoidable in 60% of bilateral cases. Bilateral enucleation may be performed in 1% of cases.

4. Cryotherapy: Rapid freezing of the tumor to -90°C damages the vascular endothelia causing platelet plugs to form thrombosis and induces tumor ischemia. In addition, intracellular ice crystal formation causes rupture of the cellular membranes. All tumors with less than 5 mm basal diameter and few vitreous seedings close to the tumor can successfully be treated with cryotherapy.

5. Brachytherapy: Iodine-125 and Rhenium-106 radioactive plaques are widely used to treat solitary tumors having 6-15 mm basal diameters and less than 9 mm thickness. The trend is to prescribe 4000-4500 cGy radiation to the tumor apex. To overall success rate is 90% but there is a tumor recurrence rate of 12% at one year. Radiation induced retinopathy and optic neuropathy are the most common complications.

6. Transpupillary thermotherapy (TTT): 810 nm infrared diode laser is used for this treatment. Tumors smaller than 3 mm of basal diameter without vitreous seedings can be reliably treated with TTT either primarily or following chemoreduction. Because of technical difficulties, peripheral tumors are avoided. The power is usually set at 200-1000 mW and 1.2 to 3 mm spot sizes are used for 1 minute each, aiming directly the tumor. The result is a flat and atrophic scar. There is an overall 86% success rate with complications including focal iris atrophy, lens opacities, optic disc atrophy, retinal tractions, vascular occlusions, and retinal hemorrhages. (see Figure 2C and 2D).

7. External Beam Radiotherapy (EBRT): This modality continues to be very effective in selected patients despite fears for secondary cancers. Eyes with multifocal tumors not treatable by other local techniques, macular tumors where other methods may ultimately destroy the central vision, and advanced bilateral disease are good candidates for EBRT. Also, EBRT can be performed after failure of other methods as a salvage therapy, in patients with extraocular orbital tumor invasion or tumor at the surgical margin of the resected optic nerve. The target tumor receives 4200-4600 cGy radiation in 180-200 cGy fractionated doses daily. Local tumor control rates vary between 50% to 88% depending on the stage of the disease. If vitreous seedings are present the success rate of EBRT is only 17%. The most significant concern with the use of EBRT is the development of second non-ocular and periocular cancers particularly in survivors of hereditary retinoblastoma. There is a 400-600 fold increase in the risk of developing second cancers in hereditary retinoblastoma if treated with EBRT and this risk is further multiplied by 8 if the treatment is given below the age of 1 year. Second malignant tumors develop in 4.4% of patients during the first 10 years, in 18.3% within 20 years and in 26.1% after 30 years. The most common second cancers include osteogenic sarcoma, leimyosarcoma, pinealoblastoma, skin melanoma, Hodgkin's lymphoma, lung and breast carcinomas. (see Figure 2E).

8. Gene Therapy: The preliminary results of intravitreal injection of adenovirus carrying the coding sequence of thymidine kinase followed by ganciclovir injection appear promising. In human subjects, this treatment decreased vitreous seedings but main tumors remained intact.

9. Experimental Therapies:
- COX-2, which is expressed in retinoblastoma, is a prostaglandin synthetase promoting angiogenesis, suppressing apoptosis and increasing tumor invasiveness. The role of COX-2 inhibitors is investigated in retinoblastoma.
- Oxidative stress, which is high in retinoblastoma, upregulates aA-crystallins, member of heat shock proteins, helping tumor cells to escape apoptosis. Anti-aA-crystallins therapy is thought to have a potential to limit tumor growth in retinoblastoma.
- Retinoblastoma cells can produce VEGF and basic fibroblast growth factor both of which induce angiogenesis. The initial enthusiasm on anti-angiogenic drugs vanished because it was found that these drugs were active against immature vasculature found in the periphery of the tumor. Vessels that are more central had pericyte components and thus became mature no
more dependant on angiogenic stimuli. This seriously limits the effects of anti-angiogenic agents.
- Arsenic trioxide has been shown to have effect on retinoblastoma cells by generating reactive oxygen species which oxidize lipids in the mitochondria membranes. This results in cytchrome C release and activation of the caspase system leading to apoptosis.
- Retinoblastoma contains many hypoxic areas where cellular proliferation is slower compared to areas close to blood vessels. These slow proliferating cells usually do not respond to available chemotherapeutic drugs. 2-deoxy-D-glucose (2-DG), a glycolytic inhibitor, holds promise against these non-responding cell populations.

**Prognosis**

With increased awareness and early diagnosis coupled with the current diagnostic techniques and management options, 99% of children with intraocular retinoblastoma survive the disease and 90% of patients retain useful vision in at least one eye. The prognosis is still dismal if there is orbital extension of the tumor or distant hematogenous metastasis.

**Cytogenetics**

**Note**
Retinoblastoma develops because of inactivation of both alleles of the RB1 tumor suppressor gene after two successive mutations (M1 and M2). In patients with hereditary (germinal) retinoblastoma, the germline contains an inactivated RB1 allele that is also present in all cells of the individual. The tumor develops when the other allele is lost (M2) in a retinal cell. The result is bilateral and multifocal tumors. In non-hereditary cases, both M1 and M2 occur in a single retinal cell thus producing unilateral and unifocal disease.

**Genes involved and proteins**

**Note**
The RB1 is the first gene to be discovered to have tumor suppression function. In most cases, the first allele is lost because of a point mutation (M1). Most mutations are non-sense which produces a premature stop codon and a resultant non functional protein. Loss of heterozygosity (M2) is responsible for the loss of the second allele in 60% of tumors. It is now recognized that M1 and M2 are not sufficient to drive the cell into malignant transformation and that other genomic changes (M3-MX) are necessary. Recent studies identified gains and amplifications at 1q32 (MDM4 and KIF14 genes) and 6p22 (E2F3 and DEK genes) as M3 and M4 respectively. Less frequent but important genomic changes include 16q22 loss (CDH11 and RB1L2 genes) and 2p24 gains (MYCN and DDX1 genes).

**RB1**

**Location**
13q14

**Note**
The retinoblastoma gene RB1 is localized on chromosome 13q14. In only 3% of tumors, karyotypically visible large deletions can be demonstrated in this location.

RB1 spans 180 kb and is composed of 27 exons. This gene encodes a 4.8 kb mRNA and the protein is a 110 kD nuclear phosphoprotein (pRB) containing 928 aminoacids. This protein has anti-oncogenic function, induces differentiation and blocks the anti-apoptotic properties of MDM2. The tumor suppressor function is through E2F at the cell cycle checkpoint between G1 and S-phase entry. The protein has many pockets which bind several molecules the most important being E2F transcription factors.

When pRB is in normal hypophosphorylated state, E2F1 is bound and the cell cannot enter the S-phase. When pRB is phosphorylated or other competing molecules for the pockets including SV40 virus, papillomavirus or adenovirus oncproteins bind, E2F1 is released and the cascade for uncontrolled cellular proliferation proceeds.

**References**

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*This article should be referenced as such:*