Retinoblastoma
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Although treatment outcomes for retinoblastoma have improved, patients with a germline gene mutation carry a high risk for second cancers.

Background: Retinoblastoma is the most common intraocular malignancy of infants and children. With early diagnosis and treatment, survival is greater than 90%; however, patients with a germline retinoblastoma mutation have a substantial risk of having a second high-grade malignancy.

Methods: The recent developments in the diagnosis and treatment of retinoblastoma are reviewed.

Results: Identification of the retinoblastoma germline mutation is now possible with the discovery of the retinoblastoma gene. Patients with the germline mutation have a 51% cumulative risk over 50 years of developing a second malignancy. Several pilot studies using primary chemotherapy for retinoblastoma have shown promising results.

Conclusions: Risk assessment and genetic counseling have become more precise with the development of laboratory methods to identify the retinoblastoma gene. The development of primary chemotherapy regimens to reduce the size of retinoblastoma tumors may decrease the need for radiation therapy and thereby reduce the risk of radiation-related malignancies in patients with the germline mutation.

Introduction

Retinoblastoma is the most common intraocular malignancy of infancy and childhood. Prior to this century, retinoblastoma was a uniformly fatal disease. The development of the ophthalmoscope, general anesthesia, and surgical enucleation has improved prognosis so that survival rates currently exceed 90% in most industrialized countries.

Retinoblastoma represents the phenotypic expression of an abnormal or absent tumor suppressor gene known as the retinoblastoma gene (RB1).

Historical Perspective

Prior to knowledge of the RB1, children with retinoblastoma were classified as having either sporadic or inherited retinoblastoma. Clinically and histologically, inherited and sporadic tumors are indistinguishable from one another. Markers for the inherited variety include bilateral involvement and multifocal primary tumors in one eye. The absence of multiple tumors, however, does not exclude the possibility of inherited retinoblastoma. Historically, the retinoblastoma trait seemed to be transmitted in an autosomal dominant pattern. On occasion, a family would demonstrate a skipped generation indicating genetic carriers.

In the early 1970s, Knudson used knowledge about the time of clinical presentation of retinoblastoma and the number of cell divisions in the human retina to develop a “two-hit” mutational model. The neurosensory retina is nearly fully developed at birth and has only limited mitotic potential. This mitotic activity is considered a window of susceptibility during which mutational events can occur. According to Knudson’s model, the initial “hit” is a germline mutation and, as such, is found in all somatic cells of the offspring. The second “hit” or mutational event occurs in a single cell sometime during development. If this mutational event occurs in a retinal cell, a retinoblastoma will develop. The probability that one mutational event will occur during the time of retinal development is greater than two postnatal independent events and would explain why so-called inherited tumors present at a younger age. Knudson’s hypothesis was eventually proven correct with the discovery of the RB1, a recessive tumor suppressor gene in which both alleles must be inactivated or missing for tumor initiation.

Epidemiology

There is no predisposition for retinoblastoma by race or gender. Right and left eyes are affected equally. The incidence of retinoblastoma worldwide ranges from 1 in 14,000 live births to 1 in 34,000 (Table 1). In the United States, the incidence has remained stable from 1974 to 1985. Of three national population-based studies in the United States, the latest and largest study reported 220 cases from the Surveillance, Epidemiology, and End Results (SEER) program of the National Cancer Institute. The average annual incidence of retinoblastoma was 5.8 per million children under the age of 10 years and 10.9 per million under 5 years of age. There is a trend for worsening survival with increasing age at diagnosis through 2 years of age but no statistically significant difference in survival between children with unilateral and bilateral disease.

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Table 1. Incidence of Retinoblastoma

Epidemiology
Florida has two cancer registries that track retinoblastoma: the Florida Cancer Data System (FCDS) and the Statewide Patient Information Reporting System (SPIRS). SPIRS is a pediatric cancer registry maintained by the Florida Association of Pediatric Tumor Programs (FAPTP). A study conducted by FAPTP found that the incidence of retinoblastoma in Florida from 1981 to 1986 was four cases per million population for children under the age of 14 years. This study combined FCDS data with SPIRS data to ensure complete ascertainment of cases. Currently, more than 160 cases of retinoblastoma are in the FAPTP registry. Follow-up studies that examine outcome based on clinical features and primary therapy are in progress.

The Retinoblastoma Gene and Gene Product

The retinoblastoma gene, located on the long arm of chromosome 13 (13q14), is the first human cancer suppressor gene to be completely characterized. The RB1 locus contains 27 exons ranging in size from 31 to 1,889 basepairs. The 26 introns vary in size from 80 to 71,712 basepairs. The retinoblastoma gene product is a 928 amino acid phosphoprotein whose normal function is to suppress cell growth. The activity of the protein is regulated by phosphorylation. When the retinoblastoma protein is phosphorylated, it is inactive. With phosphorylation, it is able to repress DNA transcription and prevent cell division. Two normal copies of the retinoblastoma gene are present in most human cells. Their function is to limit growth of the cell. Only one normal copy of the protein is needed to accomplish this function. The process of phosphorylation is controlled by a cell-cycle-dependent kinase.

Most RB1 germline mutations are minute deletional defects, duplications, or point mutations that are detectable by molecular (DNA) analysis. Larger abnormalities are demonstrable by chromosome (cytogenetic) analysis or by a combination of both methods.

Clinical Features

Most infants and children with retinoblastoma are referred for evaluation because a parent or primary care physician detects crossed eyes (strabismus), an abnormal pupillary reflex (leukocoria), or decreased vision. Advanced tumors can present with spontaneous hyphema, secondary glaucoma, or chronic inflammation. The accuracy of clinical diagnosis of retinoblastoma has been steadily improving and is made with a high degree of confidence with indirect ophthalmoscopy when the ocular media are clear. Early lesions appear as flat, transparent, or slightly white placoid tumors in the neurosensory retina. As tumors enlarge, they have a white color with chalky, fleck-like deposits of calcium (Fig 1). Growth is either endophytic (into the vitreous) or exophytic (under the neurosensory retina). If vitreous hemorrhage obscures the fundus view, ultrasonography and computed tomography are indispensable in the workup. Calcium within the tumor is highly characteristic of retinoblastoma and usually is easily demonstrable by both methods (Fig 2). Computed tomography is also helpful in excluding orbital extension and in demonstrating pineal tumors (see trilateral retinoblastoma).

![Fig 1](https://via.placeholder.com/150)

Fig. 1. - Fundus of the left eye revealing a small retinoblastoma just outside the posterior pole. The slightly elevated semi-transparent to white tumor has a focus of opalescent white within it that probably represents early calcification.
Pathology

Most retinoblastomas are composed of undifferentiated cells with hyperchromatic nuclei and very scant cytoplasm. The mitotic rate is high and tumors often outgrow their blood supply, resulting in patches of necrosis 100 to 200 microns from nutrient vessels. The most important prognostic finding is the status of the optic nerve (Fig 3). The depth and extent of tumor invasion of the nerve strongly correlate with survival. Tumor present at the surgical margin of the optic nerve or tumor infiltration of the subarachnoid space has a poor prognosis. Focal signs of retinal differentiation (e.g., tumor rosettes and fleurettes) are common but have little prognostic importance.

Histogenesis

Controversy has surrounded the proposed histogenesis of retinoblastoma since Virchow first described the tumor as a retinal glioma in 1864. Almost 35 years later, Flexner and Wintersteiner reported the resemblance of the tumor rosettes to photoreceptors of the adult retina. In the 1920s, Verhoeff believed that the tumor arose from embryonic retinal cells and proposed the name "retinoblastoma." The subject of histogenesis lay moot for decades until the late 1960s, when Ts’o and associates studied the ultrastructural features of more differentiated tumors and found clear evidence of photoreceptor differentiation. These morphologic studies seemed to put the controversy to rest until Kyritsis et al demonstrated that cultured retinoblastoma cells could be induced toward either glial or neuronal differentiation based on the type of culture media. Immunocytochemical techniques have shown that most undifferentiated cells have features of rods and blue cones, while more differentiated cells resemble red and green cones. Differentiated areas also contain abundant Muller-like cells (a unique retina glial cell).

Retinocytoma

For several decades, clinicians have recognized a benign variant of retinoblastoma characterized by lack of growth and an appearance similar to treated retinoblastoma (but with no history of treatment). These benign tumors were initially called retinoma and spontaneously regressed retinoblastoma. In 1983, the first pathologic description of this benign variant was published and the term "retinocytoma" was proposed. The tumor was composed of neuronal cells showing photoreceptor differentiation, including large number of fleurettes and some glial cells (Fig 4). Retinocytomas have been reported in persons with germline mutations and, when present, have the same genetic implication as a typical retinoblastoma.

Spontaneously Regressed Retinoblastoma

Spontaneously regressed retinoblastoma has a characteristic histologic appearance with necrotic tumor cells encased in a calcified matrix. The mechanism of spontaneous regression (which probably occurs in less than 1% of cases) is not well understood. Unilaterally regressed tumors have been reported in persons with viable tumors in the opposite eye, making any immunogenic or humoral mechanism unlikely.
Second Primary Malignancies

Persons with bilateral retinoblastoma are at high risk of developing second primary malignancies throughout life. The cumulative incidence of second cancer 50 years after diagnosis is 51%. The mean latency between retinoblastoma and second malignancy is approximately 13 years. External-beam radiation increases the risk of second malignancy and shows a radiation dose–response relationship for all sarcomas. Most second malignancies are high-grade tumors having poor prognoses. Osteogenic sarcoma, the most common second tumor, often arises in the field of radiation. Other reported malignancies include neuroblastoma, chondrosarcoma, rhabdomyosarcoma, glioma, leukemia, sebaceous carcinoma, squamous cell carcinoma, and cutaneous melanoma.

Pinealoblastoma

Patients with heritable retinoblastoma are also at increased risk of pinealoblastoma. Unlike other second malignancies, pinealoblastoma usually occurs within the first four years of life. These tumors are highly invasive and usually lethal. Histologically, pinealoblastomas in patients with retinoblastoma often show evidence of retinal differentiation and cross-react with retinal tissue antigens. For these reasons, it is hypothesized that the pineal tumor is in fact a primary manifestation of RB1. The syndrome of bilateral retinoblastoma associated with pinealoblastoma is another manifestation of RB1 and has been termed "trilateral retinoblastoma." It is likely that many cases of trilateral retinoblastoma were misdiagnosed as metastatic retinoblastoma before the recognition of this entity.

Genetic Counseling

The risk to the offspring of an individual with retinoblastoma depends on whether the index patient has a germline mutation. Risk assessment is accomplished by obtaining a family history and determining if the index patient has unilateral or bilateral (or multifocal) tumor involvement. Parents and siblings of persons with retinoblastoma should be examined for occult retinocytoma or spontaneously regressed retinoblastoma. The presence of retinocytoma or a regressed retinoblastoma has the same genetic implications as retinoblastoma. Penetrance of RB1 mutations is high, meaning that approximately 90% of individuals with a germline RB1 mutation will develop retinoblastoma.

Laboratory techniques to identify RB1 are not routinely available; however, predictive testing for retinoblastoma has great potential for improving the effectiveness of genetic counseling by positively identifying germline mutations in persons with unilateral involvement and in asymptomatic carriers. The role of laboratory testing for RB1 and the method of harvesting tissue and transporting it are beyond the scope of this article. Several references on these subjects are available.

Treatment

Standard treatments for retinoblastoma have yielded excellent results when measured in terms of survival and preservation of vision. With conventional therapies, survival exceeds 90%. Standard therapy for unilateral retinoblastoma has traditionally been enucleation. For bilateral retinoblastoma, enucleation of the more advanced eye and external-beam radiotherapy for the less affected eye have been standard therapies. Over the last few decades, this general approach has witnessed an expanding role of eye-salvaging therapy, particularly external-beam radiation for medium-sized tumors and radioplaque therapy for smaller tumors. Some small tumors can be destroyed with cryotherapy or laser, depending on their location and thickness.

Despite the excellent cure rates, there are several drawbacks to the current arsenal of therapies. Enucleation sacrifices all vision and causes some degree of cosmetic deformity. External-beam radiotherapy is highly effective in destroying most tumors that fill less than half the eye, but failure rates increase with more advanced tumors. Most importantly, nearly 51% of patients with heritable retinoblastoma will develop a second malignancy within five decades of radiotherapy. These undesirable risks and outcomes have prompted a search for alternative therapies to salvage eyes and avoid the risk of radiotherapy.

Primary Chemotherapy for Intraocular Retinoblastoma

Chemotherapy has been historically regarded as ineffective for intraocular retinoblastoma, and its use has been restricted to treatment of extraocular disease. Pilot studies using drug regimens that may cross the blood-ocular barrier combined with supplemental laser and cryotherapy have reported favorable results.

Greenwald and Strauss treated six patients (11 eyes, 33 tumors) with 6 to 7 cycles of intravenous carboplatin and etoposide. Supplemental cryotherapy and laser were used for small, peripheral tumors (12 of 33 tumors) after chemotherapy was initiated. After 12 to 40 months of follow-up, eight eyes have been preserved, including five with large tumors (>10 mm) and all four eyes with vitreous seeding. One larger tumor showed local recurrence after chemotherapy and was treated secondarily with external-beam radiation and later enucleation. Four eyes with larger tumors required additional treatment for remote intraocular recurrence, two received external-beam radiation therapy, and two were enucleated.

Shields et al treated tumors in 20 patients (31 eyes, 54 tumors) with a two-month chemoreduction regimen of vincristine, etoposide, and carboplatin. A complete response was observed in 46%, and a partial response or no progression was noted in the remaining 54%. External-beam radiotherapy was required for incomplete calcification of vitreous seeds in nine of 14 eyes. Enucleation was avoided in all cases, with follow-up ranging from 2 to 13 months (mean = 6 months).

Gallie and associates treated 40 eyes in 31 patients using an expanding drug protocol from 1991 to 1996, starting with vincristine and teniposide with cyclosporine (8 eyes) and later adding carboplatin (32 eyes). The role of cyclosporine was to reduce tumor multidrug resistance. Supplemental laser and cryotherapy applications were used to consolidate tumor control. Five eyes eventually failed conservative therapy; one received external-beam radiation, two were enucleated, and two had radiation therapy and were later enucleated. Overall results were good with actuarial relapse-free rate of 89% for patients not previously treated and 67% for relapses.

The optimal role of carboplatin and etoposide in the management of intraocular retinoblastoma is being defined. A multicenter study is being organized to test the hypothesis that primary chemotherapy with consolidation therapy can improve the ocular salvage rate and visual function without compromising survival and can reduce the risk of radiation-related second malignancies.

Conclusions

Laboratory identification of the RB1 can now identify the germline mutation in patients with unilateral tumors and in carriers. Primary chemotherapy for retinoblastoma may help salvage some eyes with medium and large tumors and reduce the need for radiotherapy in others. The long-term safety of these chemotherapies in this particular population of patients is being studied. Reducing the need for radiotherapy in persons with retinoblastoma may also decrease the incidence of second malignancies.
References


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