Retinoblastoma: Review of Current Management

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LEARNING OBJECTIVES

After completing this course, the reader will be able to:

1. Discuss the need for a multidisciplinary approach to the management of children with retinoblastoma.
2. Identify the patient factors that need to be considered when choosing the most appropriate initial and subsequent treatment for a child with retinoblastoma.
3. Describe the role of genetics in the follow-up of retinoblastoma patients.

ABSTRACT

The most common ocular cancer in children is retinoblastoma. It affects approximately 300 children in the U.S. every year. It can affect one or both eyes and the disease can be inherited. Altered discoloration of the pupil and strabismus are the usual symptoms that lead to medical attention. Subsequent appropriate diagnostic studies and care provided by a multidisciplinary team, including an ophthalmologist, a pediatric oncologist, a radiation oncologist, and a geneticist, among others, often result in optimal short-term and long-term care. The best initial and subsequent treatments are based on whether the child has unilateral or bilateral disease, the stage of the disease, and the age of the child. Enucleation, chemotherapy, and various forms of radiation therapy along with local ophthalmic therapies can be used in the treatment of retinoblastoma. Cure rates are high in children when the tumor is confined to the eye and has not spread systemically or into the orbit or brain. 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. Exciting discoveries using animal models are providing new insights into the development of this disease and opening new avenues for targeted therapies that may lead to high cure rates with minimal toxicities. The Oncologist 2007;12:1237–1246
Epidemiology
Retinoblastoma is the most common malignant ocular tumor in childhood and affects approximately 1 in 18,000 children <5 years of age in the U.S. [1]. The incidence is higher in developing countries, and in some countries in Central and South America retinoblastoma is one of the most common solid tumor malignancies in children [2]. The reason for this higher incidence is not clear. Lower socioeconomic status and the presence of human papilloma virus sequences in the retinoblastoma tissue have been implicated [3]. A higher risk for diseases like retinoblastoma in children born through in vitro fertilization was described previously, but a recent large study does not support this association [4]. Approximately 80% of children with retinoblastoma are diagnosed before 3 years of age. The diagnosis of retinoblastoma in children 6 years or older is extremely rare. Children with bilateral retinoblastoma constitute about 20%–30%. Patients with bilateral disease usually present at a younger age (14–16 months) than patients with unilateral disease (29–30 months) [5, 6]. In approximately 20% of children diagnosed with bilateral retinoblastoma, there is a family history of the disease [7]. Histologically, retinoblastoma develops from immature retinal cells and replaces the retina and other intraocular tissues. It displays a high mitotic and apoptotic rate, and because of this elevated turnover of tumor cells, there are many areas of necrosis and dystrophic calcification.

Genetics
The study of retinoblastoma has provided valuable insights into the genetic basis of cancer. A “two-hit” model, as proposed by Knudson, was developed based on the finding that children with bilateral retinoblastoma developed multifocal, bilateral tumors at an earlier age than children with unilateral, unifocal tumors [8, 9]. According to the two-hit model, two events are necessary for the retinal cell or cells to develop into tumors. The first mutational event can be inherited (germline or constitutional) and would then be present in all cells in the body. The second event or “hit” results in the loss of the remaining normal allele and occurs within a particular retinal cell or cells with dysregulation of the cell cycle and inappropriate entry into S phase [10].

In the sporadic, nonheritable form of retinoblastoma, both mutational events occur within a single retinal cell after fertilization (somatic events), resulting in unilateral retinoblastoma. Unilateral multifocal retinoblastoma can develop if the first mutation occurs during development such that more than one retinal cell contains this hit. Conversely, not all children with unilateral disease represent somatic events. Overall, 85% of children with unilateral disease represent somatic events, but 15% represent the hereditary form with constitutional mutations in the \(RB1\) gene [11]. The \(RB1\) gene was localized and then cloned based on rare children with retinoblastoma who carry a cytogenetically visible constitutional deletion at chromosome 13q14.2 [12]. Even in cases of bilateral retinoblastoma, the majority of children do not have a family history of the disease, and disease is a result of de novo mutations in the \(RB1\) gene that primarily occur during spermatogenesis [13, 14]. This suggests that mutations in the retinoblastoma gene locus (\(RB1\)) occur more commonly during spermatogenesis or that the paternal chromosome in the early embryo is at a higher risk for mutation. Studies of retinoblastoma tumors in both the hereditary and nonhereditary forms reveal that the second hit or mutation frequently results in loss of heterozygosity of polymorphic markers that flank the \(RB1\) gene in the tumor. Loss of heterozygosity can arise from allelic loss, mitotic recombination, or loss of whole chromosome 13.

Genetic counseling in families with retinoblastoma is an important aspect in their care and should be coordinated with a medical geneticist or genetic counselor who is part of the retinoblastoma team. The identification of genetically susceptible family members can lead to early diagnosis that cannot only be life saving but may avoid the need for enucleation of the affected eye. Genetic analysis also provides important information with regard to the risk for parents (and long-term survivors of retinoblastoma) to have additional children with retinoblastoma. For example, healthy parents of a child with bilateral retinoblastoma have a 7% risk with each pregnancy of having a child with retinoblastoma because of the possibility of germline mosaicism (i.e., more than one sperm or egg carrying an \(RB1\) mutation). Genetic testing for \(RB1\) mutations is clinically available in certified DNA diagnostic laboratories (http://www.genetests.org) and can detect constitutional mutations in approximately 90% of patients with bilateral disease [15]. Patients with bilateral disease can be assumed to have a constitutional mutation and DNA obtained from a blood sample is examined directly for mutations. Children with unilateral tumors may or may not have a germline constitutional mutation. Therefore, for these cases, a frozen tumor specimen and a blood sample are sent for analysis. There is a wide variety of different \(RB1\) mutations, including whole gene deletions, and small frameshift, nonsense, splice site, and missense mutations. Somatic changes can also include silencing of the \(RB1\) promoter by methylation. Therefore, genetic analysis often includes complete sequencing of the coding region, analysis for deletions and rearrangements, methylation analysis, and RNA analysis [16].

Mutation(s) identified in the tumor are then studied in a DNA sample obtained from blood. Presence of the muta-
tion in blood is presumptive evidence of a germline or constitutional mutation. Once the germline mutation is identified then all siblings or offspring of the patient should be tested for that specific mutation in order to determine the need for surveillance for retinoblastoma [17]. Identification of the same mutation in another young family member should prompt frequent evaluations by an ophthalmologist using appropriate examination techniques. The frequency of such evaluations may be every 1–2 months for the first year of life, followed by every 2–3 months for the next year, and then every 3 months until 3 years of age, and finally every 4–6 months until the age of 6. This schedule can be modified by the examiner based on his own clinical experience.

Knowledge of the specific mutation identified in the family has also been used to perform preimplantation genetic diagnosis in order to implant in vitro fertilized embryos that are unlikely to carry the mutation [18]. Even with extensive molecular analysis, the causative mutation is not always identified. In these cases, if there are multiple family members with retinoblastoma, then predictive genetic testing can be performed by linkage analysis using polymorphic markers that flank the RBL gene, a technique also referred to as indirect genetic testing.

**CLINICAL PRESENTATION AND DIAGNOSIS**

The most common presentation of retinoblastoma in the developed world is leukocoria (an abnormal white discoloration in one or both pupils). This is usually first noticed by a parent or relative [19]. Leukocoria is the result of an altered pupillary red reflex in the eye and usually occurs when there is a large tumor present; however, it can occur also with smaller tumors associated with retinal detachment. Because retinoblastoma has a white appearance, the normal red reflex is replaced by a white or creamy pink discoloration of the pupil and can be better visualized with dilation of the pupil and the aid of an ophthalmoscope. The second most common sign of retinoblastoma is strabismus [20]. Strabismus (misalignment of the eye) in this case results from a loss of central vision in one or both eyes causing the ocular misalignment. Heterochromia (different color of pupils), hyphema (blood in the anterior chamber), glaucoma (increased intraocular pressure), and orbital cellulitis/inflammatory presentation are less common presentations [21]. In patients with more advanced disease, the presenting signs and symptoms correlate with the degree of extraocular invasion, which can result in orbital swelling and proptosis.

Funduscopy typically reveals a large white to creamy colored main tumor, frequently with satellite lesions in the retina, subretinal space, and/or vitreous. The satellite tumors of the subretinal space and vitreous are referred to as “seeds.” A secondary serous retinal detachment is often associated with large retinal tumors and subretinal seeds. To confirm the presence of the tumor, a detailed examination under anesthesia through dilated pupils is performed.

Ultrasoundography of the eyes is often performed to identify and analyze the intraocular mass. Heterogeneity and calcifications provide strong evidence for the diagnosis of retinoblastoma. Ultrasoundography is not as sensitive as computed tomography (CT), which is the ideal imaging format to detect intraocular calcifications. CT, however, raises the concern of exposure to radiation in children <1 year of age with germline mutations [22]. However, it is still frequently used to confirm the diagnosis. 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 [23]. Pineoblastoma is a malignancy that is associated with retinoblastoma in rare cases and when present it is referred to as trilateral retinoblastoma.

MRI of the brain and spinal cord and cytologic examination of cerebral spinal fluid are also indicated when there is gross evidence of involvement of the optic nerve by imaging studies or microscopic involvement beyond the lamina cribrosa on histopathologic examination of the enucleated eye. A bone marrow examination and a bone scan are indicated only when the clinical examination is suggestive of metastases or a blood count abnormality is present.

The diagnosis of retinoblastoma is based on examination by an ophthalmologist and imaging studies. A biopsy is rarely indicated because the procedure carries a theoretical risk for extraocular dissemination that would convert an intraocular, curable tumor into extraocular, metastatic disease with an extremely poor prognosis. Therefore, in the absence of a tissue diagnosis, benign conditions that can mimic the more ominous retinoblastoma must be carefully excluded. These diseases usually can be differentiated from retinoblastoma by an ophthalmologist skilled in ocular oncology. These conditions include *Toxocara canis* endophthalmitis, persistent hyperplastic primary vitreous, and Coats’ disease [24–27]. These conditions usually produce total loss of vision in the affected eye and therefore, to establish the correct diagnosis, enucleation is an accepted procedure in cases where the diagnosis is still in question from clinical examination.

Retinoblastoma can invade the optic nerve into the chiasm or disseminate through the subarachnoid space. From the subarachnoid space the tumor cells can spread to the brain and spinal cord. Tumors can also invade the choroid and the vascular layer, and spread hematogenously to the bone and bone marrow [28–32]. Tumors can spread ante-
riorly and involve the aqueous venous channels, conjunctiva, and lymphatics or invade the sclera into the orbit with eventual spread to regional lymph nodes.

**TREATMENT**

Management of a child with retinoblastoma requires a multidisciplinary approach. Ophthalmologists, pediatric oncologists, pediatric radiation oncologists, pathologists, genetic counselors, social workers, nurses, and others play important roles in the cure of the disease, salvage of vision, and support of the child with vision loss and potential long-term sequelae. Many therapeutic options are available, and the indications for a specific modality or a combination of modalities vary with each patient. Furthermore, management varies for children with intraocular disease and extraocular spread of the tumor. Most patients with unilateral disease present with advanced intraocular disease and therefore usually undergo enucleation, which results in a cure rate >95%. Children with involvement of both eyes at diagnosis usually require multimodality therapy (chemotherapy, local therapies). Failure to control disease in children with bilateral disease may lead to external beam radiation (EBR) therapy. Enucleation is usually reserved for eyes with recurrent disease and no useful vision.

**Management of Intraocular Disease**

Staging of the disease has facilitated the assessment of treatments and measurement of outcomes in oncology. The Reese-Ellsworth (R-E) classification for intraocular retinoblastoma, developed in the 1960s, was used during the last 40 years in assessing outcomes of therapy, and this classification facilitated the comparison of results from various studies [33]. The R-E classification was devised to predict prognosis in eyes that were treated with EBR therapy. The classification scheme has five groups. Eyes with disease consistent with the lower groups have a lower risk for enucleation following EBR and group V eyes have the highest risk for enucleation. With the advent of other therapies, including chemotherapy, which has increasingly replaced EBR therapy in the treatment of intraocular disease, the usefulness of the R-E scheme is less apparent. Several alternative schemes have been proposed recently by Shields et al. [34] and by Murphree [35], among others [34–35]. The classification proposed by Murphree is the basis for several protocols for the treatment of intraocular retinoblastoma within the Children’s Oncology Group (COG). While the R-E classification and the classification proposed by Murphree and others address intraocular disease, another classification system has been proposed by Chantada et al. [36] to address extraocular disease and microscopic disease following enucleation.

**Enucleation**

Most children with unilateral retinoblastoma present with advanced disease, and most of them require enucleation. Other indications for enucleation are for children with bilateral disease where enucleation may be indicated for the eye with the most advanced disease that does not respond to chemotherapy (rarely, enucleation is indicated for both eyes), for the eye that has failed all known effective therapies, when active tumor is present in an eye with no vision, when glaucoma is present as a result of neovascularization of the iris or tumor invasion into the anterior chamber, and when direct visualization of an active tumor is obstructed by conditions including hemorrhage, corneal opacity, or cataract [37]. Enucleation is curative in >95% of patients with unilateral disease. Care should be taken to avoid perforation of the globe during surgery and to obtain a long segment of the optic nerve in order to minimize the chance of leaving tumor at the surgical margin [38]. Orbital implants made of silicone, plastic, hydroxyapatite, and MedPore are used at major treatment centers. By connecting the implants to the orbital muscles, excellent cosmetic appearance can be achieved. Complications such as wound dehiscence and conjunctival erosion, although rare, may be seen with all types of implants.

**EBR Therapy**

EBR therapy is an effective means of curing retinoblastoma. The most common indication for EBR is for the eye in a young child with bilateral retinoblastoma who has active or recurrent disease after completion of chemotherapy and local therapies. Children with small tumors within the macula that do not respond to chemotherapy or have recurrent disease following chemotherapy can benefit from EBR. With EBR therapy, the entire tumor-bearing area of the globe is included along with at least 1 cm of the optic nerve. The prescribed dose to the tumor ranges from 42 Gy to 46 Gy, with the radiosensitive lens receiving significantly less. Preservation of the eye with control of the disease using EBR therapy is in the range of 58%–88%. Radiation therapy has only a 50% local control rate in R-E groups IV and V disease, with a 95% rate of preservation of the eye in R-E groups I–III. In a report of 63 R-E group Vb eyes (tumors with vitreous seeds) that were irradiated at initial diagnosis, the ocular survival rate was 53.4% at 10 years [39]. However, the probability of developing a second cancer following initial EBR therapy for group Vb disease in patients with bilateral disease was 29.7% by 10 years after diagnosis.

Patients with hereditary disease who received EBR therapy are reported to have a cumulative incidence of second cancers of 35%, compared with 6% for those who did not
receive EBR [40]. Furthermore, patients who are < 1 year of age and who receive radiation therapy are several times more likely to develop second and subsequent malignancies than those who are > 12 months of age and receive radiation therapy [41]. In a cohort of patients with hereditary retinoblastoma, a strong relationship between radiation dose and the development of soft tissue sarcomas was reported [42].

In subsequent follow-up of this cohort, significantly higher risks for melanoma, cancers of the bone, nasal cavities, and brain, and soft tissue sarcomas (with an excess of leiomyosarcoma) were documented [43, 44]. Cataracts, optic nerve damage, total retinal vascular occlusion, vitreous hemorrhage, and facial and temporal bone hypoplasia are other complications associated with EBR therapy [45]. Proton beam radiation therapy offers promise in reducing the significant long-term side effects associated with conventional EBR therapy [46].

**Brachytherapy**

Brachytherapy involves the placement of a radioactive implant (plaque), usually on the sclera adjacent to the base of a tumor. Iodine-125 (125I), gold, and more recently ruthenium have been used [47]. The intention is to deliver a dose of 4,000 – 4,500 cGy transclerally to the apex of the tumor over a period of 2–4 days. This treatment is limited to tumors that are < 16 mm in base and 8 mm in thickness, and can be used as the primary treatment or, more frequently, in patients who had failed initial therapy including previous EBR therapy [48 – 51]. This modality can also be used when there is a peripheral tumor with focal vitreous seeding around it. Relative contraindications include larger tumors and those that involve the macula. Good tumor control has been reported with this modality [52]. Side effects are less common than with EBR and include optic neuropathy, radiation retinopathy, and cataract formation. Second malignancies do not appear to be associated with this type of local therapy. An orbital implant with 125I seeds was shown to be effective in treating patients who were at high risk for orbital recurrence after enucleation [53].

**Thermotherapy**

Thermotherapy involves the application of heat directly to the tumor, usually in the form of infrared radiation. A temperature between 45°C and 60°C is the goal of this therapeutic approach and is below the coagulative threshold and therefore spares the retinal vessels from coagulation [54, 55]. Thermotherapy alone can be used for small retinoblastomas that are ≤ 3 mm in diameter without vitreous or subretinal seeds. In a study of 91 tumors, 92% of the tumors that were < 1.5 mm in diameter were controlled with thermotherapy alone [56].

**Chemothermotherapy**

Larger tumors or tumors with subretinal seeds are usually treated with a combination of thermotherapy and chemotherapy. Tractional and vaso-occlusive complications that can be seen with thermotherapy alone appear to be less frequent when thermotherapy is used in combination with chemotherapy (chemothermotherapy). Chemotherapy and thermotherapy are delivered within hours of each other. In one study of 188 retinoblastomas, tumor control was achieved in 86% of cases [57]. The complications of chemothermotherapy included focal iris atrophy, paraxial lens opacity, sector optic disk atrophy, retinal traction, optic disk edema, retinal vascular occlusion, retinal detachment, and corneal edema. Chemothermotherapy may be especially useful for patients with small tumors adjacent to the fovea and optic nerve, where radiation therapy or laser photocoagulation may result in significant visual loss.

**Laser Photocoagulation**

Laser photocoagulation is recommended only for small posterior tumors [58 – 60]. The treatment is delivered with an argon or diode laser or a xenon arc. The purpose of this treatment is to coagulate all the blood supply to the tumor. Indirect ophthalmoscope laser photocoagulation has significantly improved the delivery of photocoagulation. Effective therapy usually requires 2–3 sessions at monthly intervals. Complications of this treatment include retinal detachment, retinal vascular occlusion, retinal traction, and preretinal fibrosis.

**Cryotherapy**

Cryotherapy induces tumor tissue to freeze rapidly, resulting in damage to the vascular endothelium with secondary thrombosis and infarction of the tumor tissue. Cryotherapy may be used as primary therapy for small peripheral tumors or for small recurrent tumors previously treated with other modalities. Tumors are typically treated three times per session, with one or two sessions at monthly intervals. Ninety percent of tumors < 3 mm in diameter are cured permanently, and complications are few and rarely serious [61, 62]. Transient conjunctival edema and transient localized serous retinal detachments can occur. Vitreous hemorrhage can be observed in large or previously irradiated tumors.

**Chemotherapy**

Chemotherapy has been used to treat intraocular retinoblastoma since the early 1990s. Chemotherapy is used to reduce the size of the tumor to allow local ophthalmological therapies, including cryotherapy and laser photocoagulation, or thermotherapy, to eradicate the remaining disease. This
combination of therapies has been promoted to avoid EBR therapy and/or enucleation and thereby decrease the potential for long-term side effects while salvaging some useful vision. The common indications for chemotherapy for intraocular retinoblastoma include tumors that are large and that cannot be treated with local therapies alone in children with bilateral tumors. Chemotherapy can also be used in patients with unilateral disease when the tumors are small but cannot be controlled with local therapies alone. Such patients constitute only 10%–15% of all patients with unilateral disease. Most patients with unilateral disease are diagnosed with advanced intraocular disease and undergo enucleation. Numerous studies have been published that show that chemotherapy is very effective in eliminating the need for EBR/enucleation in R-E group I–III eyes, while proving to be significantly less successful in eyes with group IV or V disease [34, 63–70]. Selected patients with group IV disease have also had a very good response to chemotherapy, and EBR and enucleation were avoided. The chemotherapy regimen commonly used consists of carboplatin, vincristine, and etoposide. Cyclosporine has been used in addition to these three agents in some institutions in order to try to overcome drug resistance [71]. Others have used carboplatin and vincristine without etoposide and older studies used cyclophosphamide and doxorubicin. The chemotherapy regimens from the different groups of investigators vary in the number and frequency of chemotherapy cycles. All these regimens are well tolerated, with the expected side effects of myelosuppression and its consequences, which include invasive bacterial infections. Ototoxicity and renal toxicities are rare. There is also the potential risk for second malignancies, especially when using etoposide (an epipodophyllotoxin) [72, 73]. The RE groups I–III and part of group IV correspond to group B disease of the new international classification scheme that is a modification of the one proposed by Murphree. Patients who have group B disease will be treated with carboplatin and vincristine in the proposed COG trial, and their event-free survival (EFS) at 2 years will be estimated, where an event is described as the need for nonprotocol chemotherapy or EBR/enucleation.

Chemotherapy alone is not very effective in avoiding EBR/enucleation in patients with R-E group V eyes, especially those with vitreous seeds. Friedman et al. [70] showed that only 53% of 30 group V (C, D, or E in the proposed classification) eyes could be controlled with chemotherapy alone. Data from Chan et al. [74] and Villalblanca et al. [75] suggested that approximately 40% of group C and 70% of group D eyes failed systemic chemotherapy alone. Based on these data, the trial proposed by the COG involves systemic chemotherapy with carboplatin, vincristine, and etoposide along with subtenon carboplatin for group C and D eyes [76, 77]. Eyes with diffuse vitreous seeding present a particularly difficult management problem and, as mentioned above, rarely respond to chemotherapy alone. Although EBR therapy is modestly successful in patients with vitreous seeds, new approaches are needed. A recent phase I study using adenoviral vectors to deliver the herpes simplex thymidine kinase gene followed by ganciclovir demonstrated durable clinical and histopathologic responses in heavily pretreated patients with vitreous seeds [78].

Management of Extraocular Disease

Patients with extraocular disease have a very poor prognosis with respect to survival. Recently, there have been encouraging data to suggest that patients with regional extraocular disease may benefit from a combination of conventional chemotherapy and EBR and those with distant metastatic disease may benefit from high-dose chemotherapy and EBR in conjunction with bone marrow stem cell transplantation. Regional extraocular disease includes patients with orbital, preauricular disease and patients with tumor found at the optic nerve surgical margin. Chantada et al. [79] reported a 5-year EFS rate of 84% in 15 patients with orbital or preauricular disease treated with chemotherapy that included vincristine, doxorubicin, and cyclophosphamide or vincristine, idarubicin, cyclophosphamide, carboplatin, and etoposide. These patients also received EBR of 4,500 cGy administered to the optic nerve chiasm for patients with orbital disease and to the involved nodes for those with preauricular lymphadenopathy. A subsequent study showed that 12 patients with positive optic nerve surgical margins were all event-free survivors following chemotherapy as above and orbital radiation therapy of 4,000–4,500 cGy. A similar successful study was reported from Brazil [80].

Patients with metastatic extraocular disease have a poor prognosis when treated with regimens of conventional doses of chemotherapy. There are several reports now suggesting that high-dose chemotherapy with stem cell rescue combined with EBR for areas of bulky disease at diagnosis is beneficial, with some long-term survivors among patients with metastatic disease not involving the central nervous system (CNS) [81–85]. It is rare for a patient with metastatic CNS involvement to survive using the therapies described above. The proposed trial by the COG for patients with metastatic disease involves conventional chemotherapy, stem cell harvest, high-dose chemotherapy with stem cell rescue, and EBR of involved sites.
HIGH-RISK HISTOPATHOLOGIC FEATURES IN ENUCLEATED EYES OF PATIENTS WITH UNILATERAL RETINOBLASTOMA

There is no consensus on the histopathologic prognostic factors present in enucleated eyes that could predict dissemination of the disease. Postlamina optic nerve spread of tumor, massive choroidal invasion, and extrascleral extension have been recognized as risk factors for dissemination of disease. Other factors like focal choroidal, anterior chamber, ciliary body, and iris involvement by tumor have not been clearly established as risk factors for spread of the disease. Extensively necrotic retinoblastoma was also recently described as a high-risk factor [86].

When there is evidence of active tumor at the surgical margin of the optic nerve at the time of enucleation, the associated mortality rate has been described to be as high as 50%–81% [32, 87–94]. When tumor cells are present in the optic nerve posterior to the lamina cribrosa, the mortality rate is in the range of 13%–69% [32, 38, 87–98]. It is generally accepted that tumor involvement anterior to the lamina cribrosa is not associated with greater mortality.

The significance of choroid involvement and its effect on the prognosis are less clear. There are reports that claim that choroidal invasion by tumor does not contribute to a poor outcome, while others claim that choroidal invasion can result in mortality in the range of 11%–81% [32, 87–102]. The combination of choroidal invasion along with any degree of optic nerve invasion has also been recognized as a risk factor with an adverse influence on outcome by some groups [48, 103].

Recent studies suggest that adjuvant chemotherapy effectively reduced the incidence of metastases in patients with retinoblastoma with massive choroidal invasion or postlaminar optic nerve invasion [104, 105]. These statistical figures have been drawn from several retrospective studies performed in the past and are difficult to interpret because of the significant variations in the definition of high-risk features and the different treatment regimens used for each series. Therefore, to study this issue prospectively the COG has opened a clinical trial to study the pathology of the enucleated eyes in all unilateral patients from participating institutions in North America and assign high-risk status based on well-defined histopathologic features. These patients are then eligible to receive adjuvant chemotherapy consisting of six cycles of carboplatin, vincristine, and etoposide. Patients who do not have high-risk features as defined by the protocol do not require further therapy and will be observed. This will represent the first study in North America to prospectively evaluate histopathologic features and outcome in patients with unilateral disease. Similar studies have been initiated in Europe.

PRECLINICAL MODELS

Current therapies contribute significantly to vision salvage in patients with intraocular disease and overall cure rates in patients with extraocular disease. However, these therapies are not without significant morbidities. A better understanding of the pathogenesis of retinoblastoma may lead to therapies with fewer long-term morbidities. To this end, emphasis is placed on the development of preclinical models [106]. Retinoblastoma is uniquely a human disease; no natural occurring animal model exists. Xenograft models of retinoblastoma using cell lines derived from patients’ tumors and injected into the vitreous have been developed in immunocompromised mice and have been found to be useful in studying therapeutic modalities [107–109]. These models resemble patients with vitreous seeds and closely mimic the progression of nonmetastatic as well as metastatic human disease; however, the response of primary tumors and the immune component of the therapy cannot be studied. Transgenic mouse models of retinoblastoma have also been developed [110, 111]. Because RB1 gene mutations do not result in retinoblastoma in mice, multiple members of the RB gene family have been genetically deleted or sequestered using the targeted expression of simian virus 40 T-antigen [112]. These animals are immunologically competent but exhibit multifocal disease that is genetically and phenotypically distinct from human disease. Although neither model is identical to human disease, both models have been useful in preclinical testing of novel approaches to treating retinoblastoma [113, 114]. A recent study with preclinical models suggests a potential target for chemotherapy in retinoblastoma [115, 116]. This potential target is the MDMX–p53 interaction, which is antagonized by nutlin-3 and efficiently kills retinoblastoma cells. Local delivery of nutlin-3 is considered a potential option to treat retinoblastoma.

SUMMARY

Imaging techniques and a variety of treatment modalities have resulted in vast improvements in the management of children with retinoblastoma. There is at present great cooperation among various investigators internationally to share experiences and identify common areas of clinical and biologic research in retinoblastoma. There is widespread acknowledgment that awareness of the symptoms of the disease and early detection accompanied by early intervention will significantly reduce visual and systemic morbidity and mortality. Molecular genetic studies with identification of germline mutations have made a tremendous impact on the management of the siblings and offspring of affected individuals and have obviated the need for prolonged clinical screening under anesthesia for many
unaffected children. They have also enabled the possibility of preimplantation genetic diagnosis, an option that is likely to be considered by many affected individuals. Epidemiologic and biologic studies to understand the factors that promote dissemination of the disease are increasingly gaining importance. Animal models to better understand the pathogenesis and treatment of retinoblastoma are being pursued vigorously. Initiation of cooperative group trials will further define the effectiveness of therapeutic options for this rare disease.

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