Retinoblastoma: Clinical presentation, evaluation, and diagnosis

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INTRODUCTION

Retinoblastoma is the most common primary intraocular malignancy of childhood and accounts for 10 to 15 percent of cancers that occur within the first year of life [1]. Retinoblastoma typically presents as leukocoria (picture 1) in a child under the age of three years. Untreated retinoblastoma is a deadly disease; however, with advances in treatment, overall survival in the contemporary era is >95 percent. Prompt referral to an ocular oncologist and appropriate management by a multidisciplinary team are necessary to optimize overall and ocular survival and visual outcomes.

The clinical presentation, evaluation, and diagnosis of retinoblastoma are reviewed here. The treatment and prognosis of retinoblastoma and the approach to children with leukocoria are discussed separately. (See "Retinoblastoma: Treatment and outcome" and "Approach to the child with leukocoria".)

TERMINOLOGY

Retinoblastoma occurs in heritable and nonheritable forms (figure 1).

Heritable retinoblastoma — Heritable (also called hereditary, familial, or germline) retinoblastoma is associated with germline mutations (ie, mutations that occur in reproductive cells [sperm and eggs]) in the retinoblastoma (RB1) tumor suppressor gene. Heritable

retinoblastoma accounts for approximately 40 percent of all retinoblastoma cases. The term "heritable retinoblastoma" includes patients with bilateral or multifocal disease, those with a positive family history, and those with known germline mutations. It often does not indicate that the child inherited the mutation, but rather that child harbors a germline mutation that is heritable in future offspring. Of note, approximately 15 percent of unilateral retinoblastoma cases are also due to germline mutations and are therefore heritable. This is why specific testing for the mutation in the germline is paramount. Most cases of heritable retinoblastoma result from de novo mutations and the family history is positive in only a small proportion of cases. Hence, a negative family history does not exclude heritable retinoblastoma. Patients with heritable retinoblastoma must attain a second somatic mutation of the *RB1* gene in the retina in order to initiate tumorigenesis. (See 'Genetic predisposition' below and 'Family history' below.)

Nonheritable retinoblastoma — Nonheritable (also called nonhereditary, nonfamilial, sporadic, or somatic) retinoblastoma results from somatic mutations only (ie, both mutations/loss of function in the *RB1* gene occur in the retina cells). Patients with nonheritable retinoblastoma have unilateral, unifocal disease and tend to be diagnosed at a later age compared with heritable cases. Though the term "sporadic" is commonly used to describe nonheritable retinoblastoma, this is a misnomer since many sporadic cases (ie, cases without a prior family history) are actually due to de novo germline mutations and therefore are heritable.

EPIDEMIOLOGY

Incidence — Retinoblastoma occurs in approximately 1 in 15,000 to 1 in 16,600 live births in the United States and Northern Europe [2-4]. Retinoblastoma accounts for 13 percent of cancer in the first year of life [1]. Between 2005 and 2009, the annual incidence of retinoblastoma in the United States among children <15 years old was 4.1 per 1,000,000 [5].

The median age at diagnosis is 18 to 20 months: an average of 12 months for children with bilateral disease and 24 months for children with unilateral disease [6,7]. Approximately 95 percent of children with retinoblastoma present before the age of five years (figure 2) [2]. Nonetheless, cases of newly diagnosed retinoblastoma have been reported in children as old as 18 years [8-11] and, rarely, even in adults [12-14]. The incidence is similar in males and females, and there is no racial predilection [2].

Genetic predisposition — Retinoblastoma occurs in heritable (due to germline mutations) and nonheritable forms (due to somatic mutations) (figure 1). Germline mutations in the retinoblastoma (RB1) gene are present in approximately 40 percent of cases, predominantly in bilateral disease. Children with nonheritable retinoblastoma incur new somatic mutations in

one retinal cell from which the tumor arises. Approximately 10 percent of patients with retinoblastoma have a positive family history for the disease, suggesting that the majority of cases arise from somatic mutations or de novo germline mutations [15].

Bilateral retinoblastoma (which comprises approximately one-third of retinoblastoma cases) by definition results from germline mutations in the *RB1* gene [2,16]. Bilateral tumors occur more commonly among younger children, consistent with the presence of a germline rather than somatic mutation (figure 1). However, there is a broad spectrum of age at presentation for both bilateral and unilateral disease and age should not preclude genetic evaluation of patients with unilateral disease (figure 2) [2,17,18]. Unilateral retinoblastoma is seen in approximately two-thirds of all patients with this disease. However, germline mutations are found in approximately 15 percent of patients with unilateral disease. The presence of unilateral disease in no way rules out a germline mutation [18,19]. Clear multifocal, unilateral disease is indicative of a germline mutation. (See 'Genetic testing' below.)

The *RB1* mutation that causes heritable retinoblastoma causes a cancer predisposition syndrome. It is associated with an increased risk of developing second malignancies, including osteogenic sarcoma, soft tissue sarcomas (particularly leiomyosarcoma), and malignant melanoma [20-25]. (See "Pathogenetic factors in soft tissue and bone sarcomas", section on 'Retinoblastoma' and "Retinoblastoma: Treatment and outcome", section on 'Second malignancies' and "Retinoblastoma: Treatment and outcome", section on 'Long-term follow-up'.)

PATHOGENESIS

Retinoblastoma is caused by mutational inactivation of both alleles of the retinoblastoma (RB1) tumor suppressor gene in nearly all cases [26]. This gene maps to chromosome 13q14 and encodes a nuclear protein (Rb) that acts as a tumor suppressor [15,27-29]. A functional Rb protein restricts the cell's ability to progress from the G1 phase to the S phase of the cell cycle [30]. When active, Rb binds to E2F, a transcription factor. Loss of active, functional Rb causes cell cycle dysregulation. A "two-hit" model has been proposed to explain the different clinical features of heritable and nonheritable cases of retinoblastoma (figure 1) [31-34]. The cell of origin in retinoblastoma has been debated, but cone precursor cells appear to play a pivotal role in retinoblastoma tumorigenesis [35].

- In the **heritable** form, a germline mutation at the *RB1* locus (most common) or deletion of chromosome 13q (containing the *RB1* gene locus) is present in all cells of the body and a second "hit," occurring later in development, affects the remaining *RB1* allele within retinal progenitor cells [36-38]. Patients with heritable retinoblastoma are at risk of multifocal

and/or bilateral tumors. The second "hit" may be a second mutation in the *RB1* gene or silencing through epigenetic changes [39,40]. Heritable retinoblastoma demonstrates incomplete penetrance, with approximately 90 percent of genotypic carriers expressing the malignancy. Certain families with heritable retinoblastoma have been identified with much lower penetrance, possibly related to genetic modifiers or only partial inactivation of the *RB1* gene (eg, inactivation of *SYK*, a proto-oncogene necessary for the growth of retinoblastoma cells) [39-42]. Germline mosaicism for an *RB1* mutation may also result in disease, which can present either with unilateral or bilateral disease [43]. (See "Microdeletion syndromes (chromosomes 12 to 22)", section on '13q14 deletion syndrome (Retinoblastoma syndrome)'.)

- In most cases of **nonheritable** retinoblastoma, both allelic mutations arise spontaneously in a single somatic cell of the retina, resulting in the usual clinical scenario of a unifocal, unilateral tumor (figure 1) [33,44]. However, in a review of 1068 cases of unilateral nonheritable retinoblastoma, no *RB1* mutations were reported in 2.7 percent [45]. Approximately one-half of the tumors in which no mutation was detected were associated with a high level of *MYCN* amplification. Normally, *MYCN* promotes cell cycle progression; when amplified, *MYCN* promotes unregulated cell proliferation. These tumors also showed a distinct histology (undifferentiated cells with large, prominent, multiple nucleoli; necrosis; apoptosis; little calcification) and early age of diagnosis (median age 4.5 months versus 24 months in children with *RB1* mutations). These observations suggest that *MYCN* amplification may initiate retinoblastoma in a small subset of patients with unilateral disease (approximately 1 to 2 percent) without *RB1* mutations. Chromothripsis (a global event causing multiple simultaneous chromosome rearrangements at once) at the *RB1* locus also may initiate retinoblastoma in a small subset of patients [46].

NATURAL HISTORY

Untreated, retinoblastoma is a deadly disease. The tumors grow to fill the eye and destroy the globe [31]. Metastatic spread is typically diagnosed within the first 12 months of clinical presentation of retinoblastoma. If the tumor is confined to the eye, the survival rate for retinoblastoma with modern-day treatment is >95 percent [47]. However, the prognosis for eye salvage is far lower and depends on the stage of disease at diagnosis. Spontaneous regression may occur in a small number of cases but is a rare occurrence [48-50]. A small tumor with surrounding chorioretinal atrophy, called a retinoma or retinocytoma, can be a very rare benign manifestation of *RB1* mutation [51]. (See "Retinoblastoma: Treatment and outcome", section on 'Outcome'.)

The most common routes of metastatic spread are direct infiltration via the optic nerve to the central nervous system (CNS) or spread via the choroid into the sclera and into the orbit [52]. Additional routes of spread include dispersion of the tumor cells through the cerebrospinal fluid to the CNS; hematogenous dissemination to the lung, bone, liver, or brain; and lymphatic dissemination if the tumor spreads anteriorly into the conjunctivae, eyelids, or extraocular tissue. With intense multimodal therapy, the mortality rate for extra-orbital metastatic disease has improved and survival is >50 percent [53,54]. However, even with modern treatment strategies, survival rates for CNS disease from metastatic retinoblastoma remain dismal (<10 percent) [55].

In the United States, the most common cause of death for patients with heritable retinoblastoma is a secondary malignancy and not the initial primary retinoblastoma [56]. (See "Retinoblastoma: Treatment and outcome", section on 'Second malignancies'.)

CLINICAL PRESENTATION

Clinical features — Retinoblastoma typically presents as leukocoria (picture 1) in a child under the age of three years. Other common presenting symptoms include strabismus (picture 2), nystagmus, and a red inflamed eye [6,57]. In one retrospective review of 1654 patients with retinoblastoma, the most common presenting signs were leukocoria (54 percent) and strabismus (19 percent); the mean age at diagnosis was 20 months [6].

Because leukocoria is the most common finding of retinoblastoma and is also indicative of other diseases that may threaten vision, urgent referral to an ophthalmologist is warranted if leukocoria is seen. A child with strabismus should also be referred promptly. (See "Approach to the child with leukocoria", section on 'Referral' and "Evaluation and management of strabismus in children", section on 'Causes'.)

Less common presentations for retinoblastoma include decreased vision (4 percent), ocular inflammation (5 percent), and known family history of the disease (5 percent) [6]. Rare presentations include iris heterochromia, caused in some cases by neovascularization of the iris, called rubeosis iridis; vitreous hemorrhage (causing a dark rather than white light reflex) [58]; hyphema in the absence of trauma; glaucoma; anisocoria; orbital cellulitis from tumor necrosis; eye pain; and fever [6,31,59-62]. Approximately 75 percent of patients present with advanced intraocular disease (ie, group D or E) (table 1) [31,63]. Extraocular disease is more common at presentation in resource-limited countries [64].

Signs and symptoms in children with metastatic disease may include anorexia or weight loss, vomiting, headache, neurologic impairment, orbital mass, or soft tissue mass [65].

Ophthalmologic findings — In general, the classic presentation of early retinoblastoma is a solitary or multifocal, well-circumscribed, translucent intraretinal mass, as shown in panel 1 in the figure (picture 3). As the disease advances, the tumor becomes more pink in color, with dilated feeding blood vessels (as shown in panel 2 in the figure (picture 3)) and may exhibit one of three main growth patterns:

- **Exophytic** – The vertical growth of the tumor is beneath the retina, toward and into the subretinal space, often leading to exudative retinal detachment, as shown in panel 3 in the figure (picture 3). Tumor cells may break free and lead to subretinal seeds.

- **Endophytic** – The vertical growth of the tumor is toward and into the vitreous cavity. The tumor is friable, and, often, the vitreous is seeded with tumor cells. Tumor cells can enter the anterior chamber and layer behind the cornea, causing a pseudo-hypopyon. Spontaneous necrosis of the tumor can lead to a severe intraocular inflammatory response, presenting as pseudo-endophthalmitis.

- **Diffuse infiltrating retinoblastoma** – The tumor remains relatively flat (very little vertical growth) and grows intraretinally, mimicking retinitis. The ischemia that can occur leads to iris neovascularization (and iris heterochromia) in 50 percent of cases [66]. Diffuse infiltrating retinoblastoma is the least common growth pattern (occurring in approximately 2 percent of cases) and tends to present unilaterally in older children.

The growth pattern of retinoblastoma can vary as the tumor enlarges. An exophytic tumor can erode through the overlying retina and into the vitreous cavity, giving the clinical appearance of a combined exophytic-endophytic lesion, as shown in panel 4 of the figure (picture 3). The pattern of tumor growth does not appear to be associated with clinical outcome [67].

Intracranial tumors ("trilateral" retinoblastoma) — Intracranial tumors (often referred to as "trilateral" retinoblastoma) that are histologically similar occur in approximately 5 percent of patients with heritable retinoblastoma [68-71]. These tumors most commonly arise in the pineal gland (image 1), but tumors may also occur in the suprasellar or parasellar regions. These tumors are not metastatic nor from local spread, but, rather, they are separate primary tumors.

In >50 percent of cases, the intracranial tumor is detected on neuroimaging performed at the time of retinoblastoma diagnosis; the remaining tumors occur subsequent to initial diagnosis, typically before the age of five years. For this reason, children with retinoblastoma require

surveillance neuroimaging during the first few years after diagnosis, as discussed separately. (See "Retinoblastoma: Treatment and outcome", section on 'Imaging'.)

In one study, the mean age at diagnosis was 31 months and the average interval between diagnosis of retinoblastoma and the intracranial tumor was 21 months [68].

Family history — The family history is an important part of the assessment of a child with retinoblastoma. As previously discussed, patients with a positive family history of retinoblastoma are presumed to have heritable retinoblastoma due to an *RB1* germline mutation. These patients have a 50 percent risk of passing the mutation on to their offspring. Patients with an *RB1* germline mutation have a 90 percent chance of the mutation manifesting with retinoblastoma. As discussed below, genetic testing is suggested for all children with retinoblastoma, especially those with unilateral disease, since it can help assess the risk of retinoblastoma in other family members. (See 'Genetic testing' below.)

Family history is negative in 90 percent of patients with retinoblastoma. This is because many cases arise from de novo germline *RB1* gene mutations, and, therefore, previously affected family members will be lacking. The offspring and siblings of these patients are at risk of developing retinoblastoma and should undergo genetic testing and/or surveillance, as discussed below. (See 'Screening children at risk' below and 'Genetic testing' below.)

The family history may also be negative if one parent is a silent carrier or has somatic mosaicism for the *RB1* gene mutation [43].

Approximately 60 percent of cases of retinoblastoma arise from somatic mutations and are not heritable. (See 'Genetic predisposition' above.)

SCREENING CHILDREN AT RISK

Infants and children who are at increased risk of retinoblastoma on the basis of a positive family history should undergo routine screening soon after birth to facilitate early detection and treatment of disease. Consensus recommendations from the American Association of Ophthalmic Oncologists and Pathologists and endorsed by the American Association for Pediatric Ophthalmology and Strabismus and the American Academy of Pediatrics provide detailed guidance based upon the child's estimated risk, which is categorized as high, intermediate, or low [72]. It should be noted that any child with a confirmed *RB1* gene mutation is considered high risk.

Screening examinations are conducted as follows [31,72-74]:

- **Age zero to three years** – At-risk infants with a known *RB1* mutation should be evaluated by an ophthalmologist with experience in retinoblastoma within the first eight weeks after birth. Subsequent screening examinations are initially performed every one month until age one, two months until age two, and then spaced to every three months until age three if there are no concerning findings. Surveillance examinations are usually performed under general anesthesia to permit complete detailed examination of the ocular fundus. The risks associated with anesthesia are balanced by the benefit of improved ocular survival.

- **Age three to seven years** – Screening examinations are performed every four to six months. At this age, eye examinations may be performed in the office without general anesthesia at the discretion of the ophthalmologist, based upon the cooperation of the patient.

- **Impact of genetic testing** – As discussed below, siblings or offspring of an individual with a known germline *RB1* gene mutation should undergo genetic testing (see 'Genetic testing' below). Once results of genetic testing are available, ongoing clinical screening may or may not be necessary:

  - If genetic testing reveals that the child does **not** have a germline *RB1* mutation, screening under anesthesia can be discontinued. There is a small risk of a false-negative test; therefore, in-office screening should be performed at extended intervals [72].

  - If genetic testing reveals that the child **does** carry an *RB1* mutation, frequent screening should continue throughout early childhood (as above) with regular examinations every one to two years after age seven years.

The interval of screening depends in part on the expected risk for retinoblastoma based on family history, which can be refined by genetic testing (see 'Genetic testing' below). The schedule described above is appropriate for patients at intermediate to high risk (eg, if the affected family member is a first-degree relative with bilateral retinoblastoma). It is reasonable to perform screening evaluations less frequently in children deemed to be at lower risk based on family history (eg, if the affected family member is a second-degree relative with unilateral retinoblastoma) [72]. Detailed guidelines are based on the known familial or genetic risk of a patient; these have been endorsed by multiple pediatric and ophthalmic societies [72]. (See 'Genetic predisposition' above and 'Family history' above.)

Screening has been shown to improve outcomes. In one retrospective review of 1654 patients with retinoblastoma, those who had a positive family history and underwent surveillance for

retinoblastoma from birth were diagnosed at a younger age and earlier stage of disease than those who had a positive family history and did not undergo prospective surveillance [6]. In addition, prospectively screened patients had better ocular survival (71 versus 15 percent for unilateral tumors and 67 versus 43 percent for bilateral tumors).

EVALUATION

The evaluation in children with suspected retinoblastoma should be carried out by or in consultation with an ocular oncologist. Genetic testing and an evaluation for disease extent should be performed in all children. Formal staging studies (ie, bone marrow examination, lumbar puncture, and/or radionuclide bone scan) are **not** routinely performed, due to their low yield.

Disease extent — The evaluation typically includes the following:

- **Complete physical examination**.
- **Ophthalmologic examination under anesthesia (EUA)** – Performing the EUA permits complete visualization of the retina and identification of multifocal tumors and/or subretinal or vitreous seeding. The characteristic finding is a chalky, off-white retinal mass with a soft, friable consistency [31,62]. Intrinsic tumor calcification, tumor microvasculature, and seeding may also be seen. (See 'Ophthalmologic findings' above.)
- **Ocular ultrasonography** (B-scan, which is two-dimensional) – This may be performed prior to or during the EUA. Retinoblastoma is suggested on ultrasound if there is calcification within the mass (image 2), and the globe is generally of normal size, although advanced eyes may be buphthalmic [7,75-77].
- **Optical coherence tomography (OCT)** – OCT is usually performed during the EUA using a handheld device. OCT produces a high-resolution, two-dimensional image in a way that is analogous to pulse-echo ultrasound imaging but uses infrared light rather than sound to create the image. OCT can be a helpful tool for screening and diagnosis of retinoblastoma. The high-resolution images provided by OCT can detect small tumors that are not visible on funduscopy [78,79]. OCT is also commonly used for surveillance during and after treatment because it can detect recurrences masked by retinal scars.
- **Magnetic resonance imaging (MRI)** of the brain and orbits – The characteristic findings on MRI are an enhancing tumor mass with bright signal intensity on T1-weighted images, low intensity on T2-weighted images (ie, it appears dark compared with the vitreous), and

restricted diffusion-weighted imaging (image 3) [80]. Rarely, necrotic tumors in eyes harboring retinoblastoma may not demonstrate these classic MRI findings. MRI will not demonstrate calcifications; however, it is an important component of the evaluation in that it assesses tumor size, potential optic nerve involvement, and presence of an associated intracranial tumor (ie, trilateral retinoblastoma). (See 'Intracranial tumors ("trilateral" retinoblastoma)' above.)

Computed tomography (CT) is generally **avoided** in patients with suspected retinoblastoma because of the risk of radiation-induced second cancers in patients with possible heritable disease [81-84]. However, CT may occasionally be used for diagnostically challenging cases. Intraocular calcifications, suggestive of a diagnosis of retinoblastoma, are easily seen on CT (image 4). (See "Retinoblastoma: Treatment and outcome", section on 'Second malignancies'.)

There is no role for direct tumor biopsy for tissue diagnosis, given the risk of extraocular spread of disease. However, there is an evolving role for evaluating cell-free DNA in both blood and aqueous humor (referred to as a "liquid biopsy"). Preliminary reports suggest that this approach can provide valuable information that may inform diagnosis and prognosis [85-90]. The approach of using liquid biopsy for retinoblastoma has been adopted at several centers worldwide [87,90-92].

Metastatic evaluation — In the United States, metastatic disease is rarely present at the time of diagnosis, and formal staging studies (ie, bone marrow examination, lumbar puncture, and/or radionuclide bone scan) are **not** routinely performed, due to their low yield [93,94].

If there is clear evidence of tumor outside of the eye (ie, optic nerve invasion, choroidal involvement that is extensive), a full metastatic evaluation may be pursued, including [95,96]:

- Bone marrow aspiration and biopsy
- Lumbar puncture
- Radionuclide bone scan

Metastatic evaluation may also be warranted in group E retinoblastoma (table 1), in which choroidal and optic nerve invasion are more common [97]. Other risk factors for choroidal and optic nerve involvement include exophytic growth pattern, elevated intraocular pressure (especially if >34 mmHg), tumor thickness ≥15 mm, and iris neovascularization; however, the presence of these factors alone generally does not warrant performing a metastatic evaluation [98-100].

Genetic testing — Molecular genetic testing of peripheral blood leukocytes is suggested for all affected patients to evaluate for the presence of a germline *RB1* gene mutation (table 2):

- Patients with bilateral disease or positive family history (ie, heritable retinoblastoma) – In heritable forms retinoblastoma, molecular testing of peripheral white blood cells can identify the germline mutation in 90 to 95 percent of cases [74]. Patients in whom germline mutations are identified should be referred to a clinical geneticist for testing of parents and siblings, based upon the genetic mutation identified in the patient [72,101]. As discussed above, siblings of an affected patient should undergo clinical screening with regular eye examinations until results of genetic testing are available. (See 'Screening children at risk' above.)

- Patients with unilateral disease without a positive family history – In cases of unilateral disease without a positive family history (which is more likely due to somatic mutations), molecular testing should be performed initially on tumor cells, if available from enucleation, to identify the specific *RB1* mutation. This is seldom possible since most patients are treated with a globe-sparing approach. Advances in a liquid biopsy approach utilizing either peripheral blood or aqueous humor can detect somatic *RB1* mutations in circulating tumor DNA [90,102]. Identification of the mutation in the tumor tissue or tumor DNA from a liquid biopsy improves the sensitivity of germline testing. However, if tumor tissue or tumor DNA from a liquid biopsy is not available, routine genetic testing of the peripheral blood should still be done. Without tumor-directed testing, there is a small chance of false negative results.

The type of molecular test used varies between different centers and different laboratories. Sequencing is the technique used most commonly. As the cost of next-generation sequencing has declined, many centers have shifted to using this as the preferred approach. However, practice varies. A list of available laboratories that perform genetic testing for retinoblastoma can be found through the Genetic Testing Registry.

Genetic testing and counseling are important aspects in the management of patients with retinoblastoma in order to estimate the risk of disease in family members and future offspring [103]. It also can help parents understand the genetic consequences of each form of retinoblastoma, particularly as it relates to secondary cancers in children with heritable retinoblastoma. In addition, genetic testing can reduce the need for clinical screening of the patient's siblings [104]. (See 'Screening children at risk' above.)

If molecular genetic testing is not available or is uninformative, the family history and tumor presentation (eg, unilateral versus bilateral; unifocal versus multifocal) can be used to estimate

the risk of retinoblastoma in family members, which ranges from <1 to 45 percent.

DIAGNOSIS

The diagnosis of retinoblastoma can usually be made based on the dilated indirect ophthalmoscopic examination and imaging studies, as described above. The characteristic finding is a chalky, off-white retinal mass with a soft, friable consistency. (See 'Disease extent' above and 'Ophthalmologic findings' above.)

Pathology is **not** necessary to confirm the diagnosis. Biopsy is contraindicated because of the risk of tumor seeding.

When pathologic specimens are available (eg, in children who undergo enucleation for treatment of very high-risk tumors), the classic pathologic features of retinoblastoma include a small, round, blue cell tumor with Flexner-Wintersteiner rosette formation with clear central lumen (picture 4), Homer-Wright rosettes, and fleurettes.

CLASSIFICATION

Retinoblastoma is classified according to the extent of disease and the likelihood of globe salvage. Commonly used classification systems include the International Intraocular Retinoblastoma Classification (table 1) and the American Joint Committee on Cancer 8th edition TNM staging system (table 3) [105-107]. Other classification systems include the Philadelphia and St. Jude classifications [108,109]. The Reese-Ellsworth and Essen classifications were used in the era of primary radiotherapy; however, these systems are outdated and have limited clinical use in contemporary practice.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of retinoblastoma primarily includes other conditions that produce leukocoria (table 4). The approach to children with leukocoria is reviewed in greater detail separately. (See "Approach to the child with leukocoria", section on 'Causes of leukocoria'.)

Common alternative diagnoses include [110,111]:

- Coats disease, which is an exudative retinal vascular disorder characterized by retinal telangiectasias and subretinal exudation leading to serous retinal detachment (image 5). (See "Approach to the child with leukocoria", section on 'Coats disease'.)

- Persistent fetal vasculature (PFV), which typically presents shortly after birth and results from an idiopathic failure of the embryonic primary vitreous and hyaloid vascular system to involute during gestation (picture 5). (See "Approach to the child with leukocoria", section on 'Persistent fetal vasculature'.)

- Vitreous hemorrhage, which can occur in the setting of vitamin K-deficient bleeding of the newborn, advanced retinopathy of prematurity, PFV, trauma, or leukemia (picture 6). (See "Approach to the child with leukocoria", section on 'Vitreous hemorrhage'.)

- Ocular toxocariasis, which is an infection caused by roundworms (picture 7). (See "Toxocariasis: Visceral and ocular larva migrans".)

In a retrospective series of 2775 patients referred for management of retinoblastoma over a 40-year period, 22 percent were diagnosed with other conditions [111]. The most common conditions varied depending on the age of the child:

- <1 year – PFV (49 percent), Coats disease (20 percent), and vitreous hemorrhage (7 percent)
- 1 to 2 years – PFV (58 percent), Coats disease (11 percent), and vitreous hemorrhage (5 percent)
- 2 to 5 years – Coats disease (61 percent), toxocariasis (8 percent), and PFV (7 percent)
- >5 years – Coats disease (57 percent), toxocariasis (8 percent), and familial exudative vitreoretinopathy (6 percent)

Clinical features (eg, age, family history, retinal mass, retinal calcification) help to distinguish these conditions from retinoblastoma. However, consultation with an ocular oncologist specializing in retinoblastoma is suggested to establish the diagnosis before formulating a treatment plan.

SUMMARY AND RECOMMENDATIONS

- **Epidemiology** – Retinoblastoma is the most common primary intraocular malignancy of childhood. While rare overall, it accounts for 10 to 15 percent of cancers within the first year of life. The majority of cases are diagnosed in children younger than two years of age. Approximately one-third of cases are bilateral. Children who have a family history of retinoblastoma or a personal or family history of 13q deletion have an increased risk of developing retinoblastoma. (See 'Epidemiology' above.)

- **Heritable versus nonheritable retinoblastoma**

- **Heritable retinoblastoma** – Approximately 40 percent of retinoblastoma cases are heritable, meaning that they are caused by germline mutations in the retinoblastoma (*RB1*) gene (figure 1). Heritable retinoblastoma tends to present at an early age; most cases are bilateral and/or multifocal, and approximately one-quarter have a positive family history. (See 'Heritable retinoblastoma' above and 'Genetic predisposition' above.)

- **Nonheritable retinoblastoma** – Approximately 60 percent of retinoblastoma cases are nonheritable, meaning that they are caused by somatic *RB1* mutations present only in the tumor (figure 1). Children presenting with nonheritable retinoblastoma typically have unilateral and unifocal disease, have negative family history, and usually (but not always) present at a later age (See 'Nonheritable retinoblastoma' above.). Directed molecular testing should be done to determine the presence of a germline *RB1* mutation.

- **Natural history** – If untreated, retinoblastoma grows to fill the eye and destroys the internal architecture of the globe. Metastatic spread can begin within months, and death usually occurs within a year following metastasis. Spontaneous regression may occur in a small number of cases but is a rare occurrence. (See 'Natural history' above.)

- **Clinical presentation** – Retinoblastoma typically presents as leukocoria (picture 1) in a child under the age of three years. Other common presenting symptoms include strabismus (picture 2), nystagmus, and red eye. (See 'Clinical presentation' above.)

- **Screening at-risk children** – Children with a family history of retinoblastoma should undergo clinical screening and/or genetic testing for retinoblastoma. (See 'Screening children at risk' above and 'Genetic testing' above.)

- **Evaluation**

  - **Disease extent** – The evaluation in children with suspected retinoblastoma is carried out by or in consultation with an ocular oncologist and typically includes (see 'Evaluation' above):

    - Complete physical examination
    - Ophthalmologic examination under anesthesia (EUA)
    - Ocular ultrasonography
    - Optical coherence tomography (OCT)
    - Magnetic resonance imaging (MRI) of the brain and orbits

- **Metastatic evaluation** – Metastatic disease is rarely present at the time of diagnosis, and formal staging studies are **not** routinely performed. However, if there is clear evidence of tumor outside of the eye, a full metastatic evaluation should be pursued, including (see 'Metastatic evaluation' above):
  - Bone marrow aspiration and biopsy
  - Lumbar puncture
  - Radionuclide bone scan
- **Genetic testing** – Molecular genetic testing of peripheral blood leukocytes is suggested for all affected patients to evaluate for the presence of a germline *RB1* gene mutation (table 2). Patients in whom germline mutations are identified should be referred to a clinical geneticist for testing of parents and siblings based upon the genetic mutation identified in the patient. (See 'Genetic testing' above.)

- **Diagnosis** – The diagnosis of retinoblastoma is based chiefly upon the clinical findings on dilated indirect ophthalmoscopic examination and imaging studies. The characteristic finding is a chalky, off-white retinal mass with a soft, friable consistency (picture 3). Pathology is not necessary to confirm the diagnosis, and biopsy is contraindicated because of the risk of extraocular tumor seeding. However, there is an evolving role for "liquid biopsy" (evaluating cell-free DNA in both blood and aqueous humor) for molecular diagnosis. (See 'Diagnosis' above.)

- **Classification** – Retinoblastoma is classified according to the extent of disease and the likelihood of globe salvage (table 1 and table 3). (See 'Classification' above.)

- **Differential diagnosis** – The differential diagnosis of retinoblastoma primarily includes other conditions that produce leukocoria (eg, persistent fetal vasculature [PFV], Coats disease, vitreous hemorrhage, and ocular toxocariasis) (table 4). (See 'Differential diagnosis' above and "Approach to the child with leukocoria", section on 'Causes of leukocoria'.)

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