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Retinoblastoma: Symptoms, Pathology, Genetics, and Treatments

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Retinoblastoma: Symptoms, Pathology, Genetics, and Treatments
Brittany Watznauer, B.S.
Abstract: Accounting for 3% of childhood malignancies, retinoblastoma incidence varies worldwide with a higher chance of survival in developed countries typically due to earlier detection. The most common symptom of retinoblastoma is leukocoria, abnormal whitening of the retina due to the tumor formation. Childhood survival rates for retinoblastoma have increased over the past couple decades due to modifications and advances in treatments and therapies. Treatment for retinoblastoma depend on tumor size, location, malignancy, and genetics. Tumors caused by amplified MYCN proto-oncogene (also known as N-Myc proto-oncogene protein hereafter known as MYCN) tend to be more aggressive with diagnosis at a younger age. Bilateral retinoblastoma is typically inherited, presenting earlier than unilateral retinoblastoma but later than amplified MYCN. When not caused by only a MYCN amplification, RB1 genes predispose a patient to retinoblastoma due to disruption in the pRb pathway. Since MYCN amplification is commonly a more aggressive retinoblastoma, removal of the eye (enucleation) is a preferred treatment to prevent additional metastasis. Bilateral treatments combine various approaches such as local treatment, chemotherapy, radiotherapy, or enucleation. Unilateral cases frequently receive the same aggressive approach as bilateral retinoblastoma patients to kill the tumor before it can metastasize in the blood or along the optical nerve to the brain and cerebrospinal fluid. Certain treatments, such as external-beam radiation, can lead to a second primary malignancy in retinoblastoma survivors. A highly skilled team of ophthalmologists, pediatricians, and oncologists aim to salvage vision (if possible) while preventing retinoblastoma metastasis by customizing the treatment towards each patient.

Keywords: Retinoblastoma, symptoms, leukocoria, RB1 mutation, genetics, treatments

Introduction:

Retinoblastoma (Rb) is a rare eye cancer (approximately 1/15,000-1/20,000 new cases annually) prevalent in children (Barbosa et al, 2008). Retinoblastoma commonly peaks in children under the age of one and gradually falls as children age with children older than five accounting for less than five percent of new diagnosis cases annually in developed countries (MacCarthy et al, 2013). Children in developing countries tend to be diagnosed at a later age. Because of this, there is a considerable survival gap between high-income and low-income countries (Chantada, 2011). The level of economic development is positively correlated to the survival rate of retinoblastoma (Canturk et al, 2011). In developed countries, ninety-nine percent of children are expected to achieve a long-term cure from retinoblastoma but are at risk for developing a secondary malignancy which is the greatest obstacle to longevity in retinoblastoma survivors (Jenkinson, 2015). Bilateral retinoblastoma presents by the age of one in about one-third of cases and two-thirds of cases are unilaterally affected children with a mean age of eighteen to twenty-four months (Jenkinson, 2015).
The eye begins developing at approximately 3 weeks gestation. The retina is considered to be terminally differentiated when the patient is three years old (Rodriguez-Galindo, Pappo, 2003). During the time of retinal development, the high amount of differentiation needed to form the mature retina leaves the eye susceptible to neoplasm development. Retinoblasts form the retina, a specialized-light tissue at the back of the eye. The retina detects color and light to generate a representation of the surrounding environment that is sent via the optic nerve to the primary visual cortex. Retinoblastoma develops when the immature retinal cells, rapidly growing cells of the inner cell layer at the back of the eye, become mutated and form a tumor. The tumor can develop unilaterally or bilaterally depending on inheritance patterns and mutations.

Retinoblastoma is most commonly detected because of leukocoria, the abnormal whitening of the pupil, that is observed in the flash of a camera when taking pictures. The whiteness of the pupil is by the tumor blocking the retinal cells at the back of the eye. The tumor changes the appearance of the retina from red to a pale caused or white color. In some cases, leukocoria is not observed inhibiting the early detection of retinoblastoma unless detected by an optometrist. If retinoblastoma is left untreated, the tumor cells will metastasis first to the other structures of the interior eye and then along the optic nerve to the brain, spinal cord, and body. Post-treatment, Retinoblastoma frequently produces other forms of cancer. Due to its highly penetrant nature, retinoblastoma can be fatal if not detected early or treated effectively.

Retinoblastoma is the primary intraocular malignant cancer in childhood (Mahoeny et al, 1990) accounting for 3% of childhood neoplasms (Barbosa et al, 2008). Retinoblastoma is most common in younger children, under the age of five. Retinoblastoma is associated with a RB1 mutation, a mutation to the retinoblastoma protein that is a tumor suppressor protein, on chromosome band 13q14. Depending on the development of the RB1 gene mutation, retinoblastoma can be familial-hereditary (5-10%), de novo-hereditary (20-30%) or sporadic (60-70%) (Gallie, 1997). Familial-heredity is the transmission of the RB1 mutation in an autosomal dominant pattern and typically present with bilateral presentation. Hereditary retinoblastoma also tends to develop earlier in adolescence than sporadic retinoblastoma. Sporadic retinoblastoma develops later because the retina cells become
mutated randomly. As a result, sporadic retinoblastoma is not usually unilateral. A bilateral presentation would require two random mutations in sporadic retinoblastoma cases. Hereditary retinoblastoma has the potential to develop as early as the third week of gestation. Due to the early development, retinoblastoma can progress and metastasis prior to birth. In some cases, retinoblastoma develops in the fetus and rapidly progresses prior to birth. In these situations, an aggressive approach is often taken to prevent the further progression of retinoblastoma. The most aggressive retinoblastoma cases use enucleation to prevent further spread. Sometimes, enucleation is used in conjunction with other treatments such as local treatments, chemotherapy, or radiation.

**Clinical Symptoms**

Retinoblastoma has little to no symptoms early in development. The symptoms overlap with other common ocular conditions commonly found in children as they mature. Retinoblastoma may be suspected if the eyes appear to be looking in opposite directions (although this could also indicate muscular problems). The most common symptom is leukocoria or abnormal whitening of the pupil (figure 1). This is commonly seen when a light is projected through the pupil onto the retina. Normally, this would generate a red pupil. However due to the retinoblastoma, the pupil will appear white or pale pink. In addition, patients may experience lazy eye, rapid involuntary movement, redness, or blurry vision. Lazy eye (known to physicians as strabismus) is a condition in which the eyes do not move together and is commonly the result of a mild weakness of the muscles controlling the eye. Because of the great overlap in symptoms among various eye diseases, doctors are usually slower to diagnose retinoblastoma and initially explore more common underlying conditions.

![Image of a child's eye showing leukocoria](attachment:image.png)

![Image of retinoblastoma optomap](attachment:image2.png)

a.) Visualization of Unilateral Retinoblastoma leukocoria as seen by a parent when taking a photo of their child

b.) retinoblastoma optomap image: visualization of what the optometrist sees with the lighter big circle being the tumor

Anatomical Pathology

The photoreceptor elements of the inner layer of the retina serve as the location for retinoblastoma formation. Retinoblastoma results in necrosis and calcification due to it being soft and friable with a tendency to outgrow the blood supply (Rodriguez-Galindo, Pappo, 2003). At the macroscopic level, small, white nodules form within the vitreous and retina due to the friability of retinoblastoma (Rodriguez-Galindo, Pappo, 2003). Microscopically, the degree of differentiation dictates the appearance of retinoblastoma (Rodriguez-Galindo, Pappo, 2003). Undifferentiated retinoblastoma is composed of small, round, densely packed cells. Several routes influence the dissemination of retinoblastoma. Choroidal invasion serves as a potential route for metastases by allowing access to a rich vascular network (Rodriguez-Galindo, Pappo, 2003). Choroidal invasion allows the tumor to gain access to systemic circulation. This allows metastases in the liver, bones, and bone marrow. Retinoblastoma can directly extend through the sclera into the orbital in more advanced cases. It can invade the iris and ciliary body. Retinoblastoma can also metastasize to the regional lymph nodes: preauricular and laterocervical lymph nodes in the CNS. Additionally, retinoblastoma can progress along the optic nerve and invade the subarachnoid space and intracranial cavity (Rodriguez-Galindo, Pappo, 2003).

The age of the patient corresponds to the laterality; patients with unilateral retinoblastoma have a higher chance of survival compared to bilateral retinoblastoma patients. Patients with bilateral presentation of retinoblastoma tend to be diagnosed in their first fourteen to sixteen months (Draper et al., 1992). Unilateral presentation is commonly diagnosed around thirty months (Draper et al., 1992). This correlation is linked to the form of inheritance. Familial- heredity is an inherited germline mutation which allows the neoplasm to develop early in development. Similarly, in developmental time is de-novo heredity, which generates the first-generation of the RB1 mutation either caused by a germ cell mutation or during embryogenesis. Bilateral presentation is responsible for about 40% of cases (Chaussade et al, 2018) but is highly penetrant, meaning that a high percentage of people with the allele mutation will exhibit clinical symptoms by developing the disease (Dommering et al, 2012). Furthermore, hereditary retinoblastoma increases the risk of a second primary malignancy, increasing mortality (Eng et al, 1993). On the other hand, unilateral retinoblastoma is typically sporadic, accounting for 60% of cases (Chaussade et al, 2018).
Molecular Pathology

Retinoblastoma is a typical mutation in one gene in that it is rare, highly penetrant, and not maintained in the population. A RB1 mutation on the long arm of chromosome thirteen predisposes the patients to retinoblastoma. This germline mutation is present in about fifteen percent of unilateral retinoblastoma and all bilateral retinoblastoma cases (Jenkinson, 2015). The mutation is inherited or de novo. Correlations of retinoblastoma with other genetic factors such as MYNC amplifications, MDM2/MDM4 levels, cyclin expression, and cyclin dependent kinase levels have also been identified.

RB1 Mutation

Children with bilateral retinoblastoma are predisposed due to a constitutional RB1 mutation and develop additional damage to the second RB1 allele that initiates retinoblastoma (Rushlow et al, 2013). The damage to the second allele involves the loss of the normal allele due to duplication of the mutant allele that causes loss of heterozygosity in approximately seventy percent of the patients (Rushlow et al, 2013). Hereditary retinoblastoma has one allele that is somatically mutated (a genetically altered allele acquired by a cell (other than the sperm and egg) that is inherited by the progeny of the cell during cell division) and the other allele is a constitutional mutation (a mutation that occurs in the germline cells that is inherited by every cell). Patients that are carriers of the constitutional mutation have variable expressivity and penetrance (de Oliveira Reis et al, 2012).

Hereditary retinoblastoma differs from sporadic retinoblastoma in that it has a RB1 germline mutation (Chassade et al, 2018). The RB1 germline mutation is associated with a somatic mutation. The retinoblastoma tumor develops from a somatic mutation is in a single cell of the retina. As retinoblastoma is an autosomal dominant mutation, the germline carrier of the RB1 mutation has a high risk of developing retinoblastoma (about 90% chance of developing a highly penetrant form) (Chaussade et al, 2018). The germline carrier of the RB1 mutation is also at a higher possibility of developing subsequent malignant neoplasms. On the other hand, patients with sporadic RB1 mutation do not have an increased risk of subsequent malignant neoplasms.

For hereditary retinoblastoma, biallelic mutations in the RB1 gene located on chromosome band 13q14 produces retinoblastoma in the retina (Dommering et al., 2012). This biallelic mutation inactivates the RB1 tumor suppressor gene which is 105kDa and 27 exons
The RB1 gene encodes a tumor suppressor gene that is an ubiquitously expressed nuclear protein. Because the tumor suppressor controls cell cycle regulation and various different cellular process, inactivation of the RB1 gene fails to inhibit the growth of the tumor (Figure 2). Bilateral presentation of retinoblastoma is commonly associated with a recurrent nonsense and frameshift mutations with high penetrance regardless of the premature stop codon location (Dommering et al., 2012). Non-hereditary retinoblastoma has two somatic retinal RB1 mutations but no germline mutation in the RB1 gene. As a consequent, they tend to have a unilateral presentation of retinoblastoma. Unilateral retinoblastoma is a non-familial disease in which both RB1 alleles are damaged in the developing retina (Rushlow et al, 2013).

Figure 2: Retinoblastoma is multicausal. The pRb acts as a brake to prevent uncontrolled proliferation of cells. Increases in MYC, an oncogene, inhibit tumor suppressor proteins, p53, leading to evasion of apoptosis. Mitogenic stimuli can lead to the overexpression of cyclin D and cyclin dependent kinase 4/6. Mitogenic stimuli can also cause gene mutations, gene deletions, or promoter methylations. The changes incurred by mitogenic stimuli increase E2F allowing for uncontrolled proliferation of the cell cycle which can increase tumor development due to failure of the cell to repair damaged DNA.

Cyclin D1 and p16

RB1 codes for pRb, which is a tumor suppressor oncogene that forms the Rb pathway through complex interactions with various inhibitors and kinases. Loss of p16 or over expression
of D-type cyclins can disrupt the function of pRB (figure 2). Therefore, another genetic cause of retinoblastoma is dysfunction of p16. Disregulation in the transition from G1 to S phase of the cell cycle is responsible for the initiation and progression of retinoblastoma. The initiation of retinoblastoma may be the result of disruptions in the cellular gene expression due to loss of function of p16 (Shiozawa et al, 1997). The p16 cyclin-dependent kinase/cyclin-pRb cascade is negatively regulated by p16 in the presence of pRb (wild-type retinoblastoma protein that is a tumor suppressor) (Lukas et al, 1995). CDK4 together with cyclin D1 promotes the phosphorylation of pRb that transitions the cell cycle to S phase (Goumenou et al, 2006). On the contrary, a functional pRb and the expression of p16 inhibits the entry of the cell cycle into S phase. Uncontrolled cell proliferation can be achieved with disruption in the various control mechanisms such as the overexpression of cyclin D1, the lack of expression of p16, or the lack of expression of pRb (Goumenou et al, 2006). Alteration in the control mechanisms lead to precancerous and malignant conditions in patients.

**MDM2 and MDM4**

Hereditary retinoblastoma has two mutated RB1 genes that have lost their function due to a somatic mutation to one allele and a constitutional mutation altering the other. Factors in addition to the mutations are believed to be responsible in the development of retinoblastoma such as MDM2 and MDM4. These polymorphisms are believed to influence retinoblastoma survival and development. In a study by de Oliveira Reis and colleagues, MDM2 rs2279744G was indicated to have a protective effect on the development of retinoblastoma due to its higher frequency in control cases (de Oliveira Reis et al, 2012). MDM2 and MDM4 oncogenes are genetic modifiers of retinoblastoma phenotype.

Located on chromosome 12q14.3-q15, MDM2 regulates RB1 function by inhibiting the ligation of pRB to the E2F-DNA complex which prevents growth suppression by pRB and using a 20S proteasomal vector to degrade pRB in a process that is ubiquitin independent and proteasomal dependent (Sdek et al, 2004). MDM2 is a negative regulator of tumor suppressor p53 (figure2). The p53 pathway influences a patient’s susceptibility to retinoblastoma due to its pivotal role in the apoptotic pathway that induces the loss or maintenance of mutated retinoblasts (Epistolato et al, 2011). Transcriptionally activated by p53, MDM2 promotes the proteolytic degradation of p53 functioning as a negative regulator in the feedback auto-regulatory loop of the p53 pathways (Epistolato et al, 2011). MDM2 is not amplified nor is p53 usually mutated in
retinoblastoma patients (Epistolato et al, 2011). Instead, p53 is repressed by the highly induced MDM2 which increases the susceptibility of the retinoblastoma lineage to constitutional polymorphisms of MDM2 and/or p53 (Epistolato et al, 2011).

MDM4 mutations and polymorphisms alter TP53 and RB1 regulations; therefore, they are associated with cancer risks. MDM4 is located on chromosome 1q32 (de Oliveira Reis et al, 2012). In MDM2 dependent processes, it regulates p53 stability. MDM4 competitively inhibits the ligation of MDM2 to C-terminal domain allowing MDM4 to regulate pRB rather than MDM2, which typically mediates pRB ubiquitination (de Oliveira Reis et al, 2012). De Oliveira Reis and colleagues found that patients who had the MDM2 rs2279744G allele and constitutional RB1 mutation on average experienced an onset of retinoblastoma symptoms at five months rather than ten months in patients with only a RB1 mutation (de Oliveira Reis et al, 2012). In addition, the MDM2 rs2279744 allele had a significant association with retinoblastoma survival whereas, the MDM4 rs116197192G allele was significantly higher in retinoblastoma patients indicating a possible association with an increased risk of cancer development (de Oliveira Reis et al, 2012).

No RB1 Mutation

Some patients with unilateral retinoblastoma lacking the RB1 mutation have an amplified MYCN oncogene (Rushlow et al, 2013). An increase in oncogenes within a cell can alter the mechanisms in the cell. These alterations help the cell evade apoptosis leading to the generation of a tumor cell. Rushlow and colleagues found that patients with an amplified MYCN oncogene, lacked RB1 mutations, lost heterozygosity, and had no evidence of promoter hypermethylation. These tumors develop in the retina and possess embryonic retinal markers but they differ in histology, molecularity, and clinical distinctions compared to tumors with a biallelic mutation (RB1+/−) (Rushlow et al, 2013). The MYCN amplified retinoblastoma tumors that lacked a RB1 mutation were more genetically stable (Rushlow et al, 2013). However, the MYCN amplified tumors were clinically more invasive, larger, and presented in patients at a lower median age than RB1 mutated retinoblastoma cases (4.5 months as opposed to 24 months) (Rushlow et al, 2013). The more aggressive nature of MYCN amplified cases requires a more aggressive treatment and therapy approach that will exploit MYCN dependency, combine multiple treatments, or remove the eye to prevent further progression of retinoblastoma.
Treatment options

Retinoblastoma is diagnosed using clinical appearances rather than biopsy unlike a majority of childhood malignancies. Biopsies increase the risk of promoting tumor dissemination causing retinal detachment, creamy white retinal mass, seeding within the vitreous gel or subretinal seeding (Jenkinson, 2015) To reduce radiation exposure in the patients, MRIs are the preferred staging equipment. For more advanced intraocular retinoblastoma cases, lumbar punctures, trephine biopsy, or bone marrow aspirations can be utilized (Jenkinson, 2015). With the improvements in treatment, the staging for intraocular retinoblastoma has evolved beyond being classified according to the likelihood of being successfully treated with external beam radiotherapy. However, staging of extra ocular retinoblastoma has been less developed.

Treatment options vary for intraocular retinoblastoma and extra ocular retinoblastoma. Early stages of intraocular retinoblastoma may be treated with one method but as the cancer gets more advanced, treatments are usually combined to increase the efficacy and chance of survival. For extraocular retinoblastoma, treatments are used in conjunction with one another in order to aggressively treat the cancer and prevent further spread. Extraocular retinoblastoma is less common in developed countries compared to developing countries with a lower income. Extraocular retinoblastoma may extend past the margin of resection along the optic nerve or it may spread to the soft tissue around the eye. Prior to the discovery of the high risk associated with secondary malignancies induced by radiation, external-beam radiotherapy was the standard of care to treat retinoblastoma. After this discovery was made, treatment switched from external-beam radiotherapy to chemotherapy. In the early twenty-first century, chemotherapy and focal laser treatment became an acceptable combination for the treatment of retinoblastoma. Treatment of retinoblastoma is multifocal. Options include radiation therapy such as brachytherapy or external-beam radiotherapy, enucleation, local treatment (such as laser therapy, cryotherapy, or brachytherapy), intravitreal chemotherapy, systemic chemotherapy, infusion of chemotherapy into ophthalmic artery (intra-arterial chemotherapy), and subconjunctival chemotherapy (subtenon chemotherapy).

The route of treatment is based on the stage of retinoblastoma and preference of the team of doctors. Treatments are commonly combined to generate a successful outcome. If one treatment method fails, a more aggressive second option is typically utilized. Each treatment option has its own risk, but the side effects also vary based on the patient. Side effects depend on
dosage, duration of treatment, type of treatment, size of area being treated, and frequency of
treatment. Patients using radiation therapy have an additional risk of side effects later in life due
to the cumulative effect of radiation.

**Radiation therapy**

Radiotherapy administers radiation laterally or anteriorly. Radiation therapy can be lens
sparing or delivered to the whole globe. External beam radiotherapy is used to salvage vision
when a primary treatment method was unsuccessful in treating intraocular retinoblastoma or after
enucleation of the other eye. Proton beam radiotherapy is a newer approach to treating
retinoblastoma that is hoped to reduce damage to healthy tissue at the anterior portion of the eye
or decrease the likelihood of secondary malignancies that are common with external beam
radiation. Plaque brachytherapy is used to treat localized, small tumors by placing a radioactive
plaque (typically Ru-106 or I-125) on the sclera at the base of the tumor to deliver radiation into
the apex of the tumor over the course of several days (Jenkinson, 2015).

**External-beam radiotherapy**

External-beam radiotherapy (EBRT) was the most commonly used retinoblastoma
treatment until the later twentieth century. EBRT was commonly used to achieve long-term
remission because retinoblastoma is a radiosensitive malignancy. The radiation used by EBRT
ranges from thirty-five to forty-six Gy. The radiation is administered into the tumor and some of
the surrounding tissue by a machine. Because of the accumulation effect of radiation, EBRT is
now commonly used when more conservative approaches fail or in metastatic cases as part of the
retinoblastoma management. When used in infants, EBRT can cause orbital deformities caused
by the failure of the bones to grow. In addition, EBRT can lead to subsequent infections in
patients especially those with hereditary retinoblastoma.

EBRT is commonly used in patients after enucleation when a portion of the tumor is
present beyond the optic nerve. EBRT is also used in patients unresponsive to other treatment
options that have a large amount of vitreous seeding, or tumors that derive from the vitreous
humour. Due to the negative side effects, standard EBRT has been modified into three different
treatments. One treatment is intensity-modulated radiation therapy, or IMRT. IMRT utilizes an
MRI or CT to generate a precise 3D image of the retinoblastoma tumor so that the radiation
beam can be given at different dosages to various parts of the desired treatment area. Proton
therapy is another option that is limited because of the special equipment. Rather than using x-
ray to treat the tumor, a proton beam is used because they do not damage tissue before the targeted tumor. The lack of damage to other structures of the eye is due to the protons not releasing energy until they reach a certain distance. The third modified treatment is stereotactic radiosurgery (SRS). SRS administers a high, single dosage of radiation. Multiple small, thin radiation beams are administered into the tumor at various angles to provide the highest dosage possible while decreasing the damage of radiation to healthy tissue surrounding the tumor. SRS is commonly used to treat trilateral retinoblastoma, or the development of pineoblastoma along with bilateral retinoblastoma.

**Brachytherapy**

Brachytherapy is also known as episcleral plaque radiation therapy or internal radiation therapy. Brachytherapy is used as a primary treatment for retinoblastoma or used when the patient relapses. It is a local ophthalmic therapy commonly used to avoid or significantly delay the administration of external beam radiotherapy, especially when chemotherapy is used as the primary treatment (Merchant et al, 2004). Over the course of several days, a small amount of radiation is administered to the tumor from the outside of the eye. Placed directly on the eye, the radioactive material is placed in a disc or plaque gradually killing the retinoblastoma cancer cells. While under anesthesia, the patient has the radioactive disc or plaque placed over the tumor and sewn into the sclera. The type and dosage of radiation determines the duration of treatment. While the radiation is implanted into the eye, the patient is typically hospitalized for monitoring. To protect the eye, the patient also wears a shield. Brachytherapy is used on tumors as a localized option when cryotherapy and laser treatment are not options.

**Enucleation**

Enucleation, or the removal of the eye affected by retinoblastoma, is a common treatment method that is a definitive cure for retinoblastoma before the tumor spreads. Enucleation is typically reserved for retinoblastoma cases where large tumors fill the vitreous resulting in little to no probability of salvaging vision. Enucleation is also used when the tumor extends into the anterior chamber or in the presence of neovascular glaucoma. Most children will be cured with prompt enucleation of a high-risk eye that is showing signs of potential tumor spread including bleeding inside the eye, orbital cellulitis, neovascular glaucoma, poor view inside the eye, suspicious optic nerve, a tumor anterior to the retina, or suspected extraocular disease after
imaging (Dimeras et al, 2012). To delay enucleation with any of those symptoms or conditions, would jeopardize the life of the patient because it would allow the disease to spread. The secondary goal should be to save the vision of patients with bilateral retinoblastoma who would become blind with enucleation of both eyes. Methods to save vision include chemotherapy in conjunction with focal laser treatment and cryotherapy, or external-beam radiotherapy as a last resort (Dimeras et al, 2012). However, it should be noted that families reject enucleation as a treatment because it may seem extreme given other treatment options available. In addition, social stigmas and poor understanding of quality of life for their child following unilateral enucleation also deters parents from seeking enucleation as a curative measure. If bilateral enucleation is necessary, the child can still live a full and highly productive life with the appropriate support (Dimeras et al, 2012).

Children with unilateral retinoblastoma receive similar treatment as patients with bilateral retinoblastoma. For severely affected eyes, enucleation is also used with unilateral retinoblastoma because the other eye is normal. Timely enucleation is pivotal in decreasing the risk associated with retinoblastoma and other treatment options such as metazoic spread, repeat examination under anesthesia, morbidity, and severe side effects of chemotherapy with focal laser treatment. Due to the potential of the tumor to spread, enucleation of eyes with intraocular retinoblastoma must be conducted carefully.

Enucleation is followed by chemotherapy that is adapted to be less aggressive than when chemotherapy is used as a primary treatment option. This is to target any cancer cells that may have spread during the enucleation process. Following enucleation, orbital implants are used to promote subsequent bone growth of the orbital as well as to improve cosmetic appearance. Various techniques are used for implantation. One implant technique is myoconjunctival. For this technique, rectus muscles are attached to the conjunctival fornices and a simple plastic implant inserted posterior to the orbital (Dimeras et al, 2012). This technique allows the patient to move the prosthesis for a more natural appearance.

**Local treatment**

Local treatment is used in retinoblastoma cases where vision can be salvage. Local treatment is administered directly into the tumor by an ophthalmologist. Cryotherapy and laser therapy are used as local therapies. They both have limitations. They are commonly used in
conjunctio

Cryotherapy

Cryotherapy is utilized as a primary treatment method for smaller tumors (less than 4-disc diameters) located in the anterior portion of the eye. However, it is not commonly used in patients with multiple retinoblastoma tumors. In smaller tumors, cryotherapy can also be used in conjunction with chemotherapy if the cancer is believed to be rapidly developing. Cryotherapy has been successful in treating patients when EBRT has failed (Abramson et al, 1982). Cryotherapy involves the application of a cryoprobe to the sclera in the proximal vicinity of the retinal tumor. The cryoprobe is cooled to a very low temperature to freeze and kill the retinoblastoma cells. Depending on the situation, cryotherapy approaches can be repetitive, intensive, and heavy. Cryotherapy can be successful for patients with tumors up to 3.5 mm in diameter and approximately 2.0 mm thick but repeated treatments are necessary (Shields et al, 1989). Cryotherapy is limited by the elevation, size, and location of the tumor (Abramson et al, 1982).

Laser therapy

Laser therapy can be used independently to target small tumors or with chemotherapy in larger tumors. Traditional laser therapy (photocoagulation) with an argon laser targeted the tumor vasculature around the tumor to eliminate the blood supply to the tumor, thus, killing the tumor. Newer laser therapy uses diode laser as a thermotherapy that administers infrared wavelengths directly to the surface of the tumor.

Chemotherapy

Chemotherapy can be administered with systemic or ophthalmic artery infusion to achieve chemoreduction of retinoblastoma. The administration can be conducted with or without intravitreal chemotherapy. The goal of chemotherapy is to shrink or eliminate the cancerous cells completely. Chemotherapy has become a more prominent treatment option with the development of new drugs and delivery mechanisms. Chemotherapy is used for treatment of metastatic retinoblastoma, for incidents of high-risk histopathological features as an adjuvant chemotherapy, for refractory or recurrent intraocular retinoblastoma to salvage vision and prevent enucleation, and as a chemoreduction strategy for intraocular retinoblastoma.

Systemic chemotherapy
Systemic chemotherapy options depend on the stage of retinoblastoma, with no set regimen for any particular pathology. The objective of systemic chemotherapy is chemoreduction (to decrease the tumor volume), to facilitate the usage of local treatments, and to prevent the long-term effects of radiation therapy. An advantage to systemic chemotherapy is its ability to treat or slow the growth of small, previously undetected tumors. As a result, it is less likely to have a local tumor recurrence in the subsequent few years. If there is a local tumor recurrence, local therapies can be used as an effective treatment. Patients with genetic retinoblastoma have an increased risk of developing new tumors due to the biallelic mutations that promote DNA damage.

Patients undergoing an ocular salvage treatment receive a chemoreductive treatment in combination with an aggressive local treatment. Ocular savage treatment is ideal for discrete tumors that have not invaded the vitreous. Another option for patients with extraocular and metastatic retinoblastoma involves an intensive chemotherapy approach. There is no standard treatment for patients with extraocular or metastatic disease. The approach can be a cisplatin-based regimen or a combination of the high-dose chemotherapy and autologous hematopoietic stem cell rescue. For patients with a high-risk pathology, various regimens are also used. Most regimens for high-risk retinoblastoma includes a combination of three drugs: carboplatin, vincristine, and etoposide. These three drug combinations may or may not alternate with an anthracycline or cyclophosphamide.

**Intra-arterial chemotherapy**

Intra-arterial chemotherapy is an infusion of chemotherapy into the ophthalmic artery. In an attempt to salvage vision, chemotherapy is directly delivered into the eye via the ophthalmic artery using cannulation. Unlike systemic chemotherapy, Intra-arterial chemotherapy has a common regimen because it is the most effective agent. Melphalan is the standard approach and is often used in conjunction with carboplatin or topotecan. The combination of drugs is ideal with advanced intraocular disease or when melphalan is not independently effective. Intravenous chemotherapy used with intravitreal chemotherapy is even more effective in treating vitreous seeding (Francis et al, 2017). Intravitreal chemotherapy is the direct administration of topotecan or melphalan into the vitreous seeds.

Common complications associated with intra-arterial chemotherapy are ptosis, retinal detachment, dysmotility, vitreous hemorrhage, optic atrophy, vascular and ischemic effects, and
phthisis (Yousef et al, 2016). Vascular complications are rare with intra-arterial chemotherapy but occlusion of the retinal artery and stenosis of the ophthalmic artery have been reported. (Shields et al, 1989) An additional risk of the intra-arterial chemotherapy treatment is the exposure of the patient to ionizing radiation during fluoroscopy which has a cumulative effect after multiple procedures.

**Subconjunctival Chemotherapy**

Subconjunctival chemotherapy is also known as subtenant chemotherapy due to the administration of Carboplatin into the subtenon space. This chemotherapy approach is typically used with high virtual tumor burdens in an attempt to salvage vision. Subconjunctival chemotherapy is combined with local ophthalmic therapies and systemic chemotherapies with vitreous disease (Marr et al, 2012). However, subconjunctival chemotherapy has progressively become less common due to the advance in intravitreal chemotherapy.

**Discussion**

Treatment options for retinoblastoma is highly dependent on anatomical pathology and histology. Newer modifications to treatments allow for a more customized approaches for retinoblastoma patients based on their histology and pathology. These newer therapies are also replacing older approaches that may have more serious risk factors and side effects. External-beam radiotherapy was once used as the primary treatment for retinoblastoma but with the discovery that is increased retinoblastoma patients' risks of developing a second primary malignancy after treatment it is now used when more conservative approaches have failed to kill the tumor cells.

Patients with high penetrance mutation have an increased risk of a second primary malignancy. Therefore, patients with a low penetrance mutation have a decreased risk of a secondary primary malignancy. The second malignancy was distributed throughout the RB1 gene without cluster in a particular region (Dommering et al, 2011). Subsequent malignant neoplasms common among germline carriers of RB1 mutation include osteosarcomas, melanomas, soft tissue sarcomas, and brain tumors (Dommering et al, 2011). These neoplasms are comparable to cancers caused by external-beam radiotherapy.

Retinoblastoma is a well-researched pediatric neoplasm. Treatments, therapies, and diagnosis of retinoblastoma is pivotal to survival rates. Additional genetic testing would provide
a deeper insight into the correlation of retinoblastoma and various genetic factors such as RB1 mutations, amplified MYCN, loss of p16, or overexpression of D-type cyclins. A more genetically targeted therapy could be used on patients depending on the genetic factor indicated by this additional testing. In addition, educating the public and new parents about retinoblastoma can help to bring awareness to the disease and further decrease the mortality of retinoblastoma.

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