Update of Retinoblastoma Management

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8.1 Introduction

Retinoblastoma is the most common pediatric ocular malignancy, with a majority of cases being diagnosed before age of 5 years [1–3]. In recent studies, the incidence is approximately 12 children in one million children under 4 years old and 0.49 cases per million in children between the ages of 4–9 years old [4]. This cancer is exceptionally notable for its rapid growth rate, with tumors doubling approximately every 15 days [5, 6]. While there are approximately 7000–9000 new cases documented worldwide each year, the mortality rates vary greatly between developed and developing countries [3, 7]. Nearly 100% of patients diagnosed with retinoblastoma in developed countries will survive; however, in developing countries, the death rates are as high as 39–70% [2, 3, 7]. If retinoblastoma is recognized and treatment is initiated at an early age, the prognosis is generally very good. On the other hand, severe morbidity and mortality are common when definitive treatment is delayed [2, 6, 8].

Retinoblastoma arises within immature retinal tissue when loss of function mutations affect both copies of the RB1 tumor suppressor gene in a neuroectodermal photoreceptor progenitor cell of the cone cell lineage. In 40% of retinoblastoma patients, one of the two contributory mutations originates in a germline

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cell, and the second mutation is somatic. Since most germline mutations occur in utero, only 10% of retinoblastoma is familial. In other words, not all patients with germline RB1 mutations have familial retinoblastoma, though all patients with familial retinoblastoma have a germline mutation. Notably, if a child has a germline RB1 mutation, there is a 95% chance that they will develop retinoblastoma as a result of an acquired somatic mutation in a second allele of the RB1 gene. All patients with germline RB1 mutations have an increased risk of developing secondary cancers in their lifetime. Of these cancers, the most common secondary cancers include melanoma, osteosarcoma, and soft tissue sarcomas [8, 9]. This chapter focuses on the genetic components, clinical features, diagnostic tools, treatment, long-term outcomes, and future directions concerning patients with retinoblastoma.

8.2 Genetics of Retinoblastoma

Retinoblastoma is a cancer that has been studied rigorously by its genetic components. It was the cancer that proposed the idea of the infamous "two hit hypothesis" formulated by Alfred Knudson in 1971 [10]. This hypothesis suggested that there must be two inactivating mutations that cause unregulated cell proliferation in retinal cells leading to retinoblastoma. The hypothesis was later confirmed in 1987 when RB1, a tumor suppressor gene key in the development of retinoblastoma, was cloned [11, 12]. The RB1 gene is located on chromosome 13q14 which encodes for a protein called pRB. pRB is a protein responsible for regulation of the cell cycle from the G1 to S phase, the phase responsible for DNA replication and cell growth [12–14]. This protein regulates cell activity via binding and inhibiting the function of E2F and DP transcription factors that are required for cell division. With mutations in pRB, there is limited inhibition of these transcription factors (E2F and DP) leading to unregulated cell proliferation and eventually tumor formation [15].

The pathophysiology of retinoblastoma requires inactivation of both alleles of the RB1 gene. This exemplifies the model of a "two hit hypothesis" for tumorigenesis in this childhood cancer. Several different mechanisms of inactivation of RB1 have been recorded ranging from single point mutations to large base deletions or substitutions, DNA rearrangements, mutations in RNA splicing, chromothripsis, or methylation of the RB1 promoter with a majority of these mechanisms resulting in a diminished effect, if any effect at all, of RB1 and subsequently the pRB protein [16–18].

Two forms of retinoblastoma exist: nonhereditary or hereditary. Nonhereditary disease accounts for approximately 60% of all retinoblastoma cases and results from two separate somatic mutations that occur within retinal cells during retinal development of a child. Patients with nonhereditary retinoblastoma typically present at older ages, with a median age of 22 months, no family history of

retinoblastoma, and unilateral eye involvement. Because these patients do not harbor the RB1 mutation in any other cells other than retinal progenitor cells, they are not at increased risk of developing second malignancies or to pass down mutated RB1 genes to their offspring [8].

Hereditary pattern of disease is responsible for the other 40% of all retinoblastoma cases. Heritable retinoblastoma can be further classified into familial or sporadic retinoblastoma. In familial disease, there is inheritance of a mutated RB1 gene from either of the patient's biological parents. The familial, heritable form of retinoblastoma makes up approximately 10% of all retinoblastoma cases. Sporadic, heritable retinoblastoma occurs in about 30% of all retinoblastoma patients. With this, parents will have normal RB1 genes, but patients will harbor the RB1 mutation in all of their cells. This is believed to be caused by a new mutation in a parent's gamete prior to conception [7, 19, 20]. Up to 90% of patients with bilateral retinoblastoma are thought to have the hereditary form of the disease [1]. Patients with hereditary retinoblastoma usually present at an earlier age, with a median age of diagnosis at 11 months old [8]. Due to the fact that every cell in these patients' bodies will have the RB1 mutation, they are also at risk for other cancers later in life [9]. Regardless of sporadic or familial heritable retinoblastoma, patients have a 50% chance of passing down the RB1 mutation down to their offspring in an autosomal dominant fashion.

At diagnosis of retinoblastoma, it is very important to screen for and differentiate between hereditary and nonhereditary disease given the consequences that can arise with hereditary disease. Because of this, typically tumor tissue and blood lymphocyte samples will be tested for mutations in RB1. These mutations may be alterations in the RB1 exons itself, the introns surrounding the RB1 gene or in the promoter region for the RB1 gene. This has a sensitivity of approximately 75% for finding inactivating RB1 mutations [8, 21]. When a negative test results, quantitative PCR may be used to look for entire or partial gene deletions as well as gene duplications with a sensitivity of about 95% [22]. Generally, if there are no RB1 mutations in lymphocyte DNA, the patient's retinoblastoma is determined to be nonheritable without the chance of passing down mutations to offspring. In cases of patients with heritable retinoblastoma, the RB1 mutation is passed down in an autosomal dominant fashion; however, there in some cases, carriers of the RB1 mutation will show reduced expression or incomplete penetrance resulting in either unilateral eye involvement or later onset of disease [23–26].

With new technology arising, prenatal genetic testing has been made possible to test retinoblastoma susceptibility in utero. This is generally done in patients with a positive family history of retinoblastoma via DNA analysis of fetal cells from either chorion sampling or amniocentesis. For parents with known RB1 mutations, preimplantation techniques have also been designed where specific DNA mutations are screened for in the sperm and ova and then implanted via in vitro fertilization. While this makes the likelihood small that the child will have retinoblastoma in a parent

with a germline mutation, these techniques can be very expensive and take expertise that is not available at all institutions [27–29].

In conclusion, genetic testing is very important in the clinical course of retinoblastoma as it can indicate the risk of developing future neoplasms as well as determine treatment courses.

8.3 Clinical Features and Staging of Disease

The most common presentation of retinoblastoma is leukocoria followed by strabismus. Rarely it can present as a red inflamed eye, microphthalmos, or orbital cellulitis [2]. In a review by Fang et al., the median age of presentation of retinoblastoma in patients at a tertiary hospital in China was 17.2 months with the most common symptoms being leukocoria in 57% of patients and strabismus in 16.1% of patients [30].

Tumors themselves are typically round and opaque with translucent thickening of the sensory retina. As the tumor grows, they develop vascular supply and often lose adhesion to the retina. This will disseminate into surrounding ocular tissues leading to seeding which can occur in the subretinal or vitreous space. As disease advances, patients may also develop extraocular disease, proptosis, or metastatic disease [18, 31].

Retinoblastoma conveys three main growth patterns including exophytic, endophytic, and diffuse infiltrating. With exophytic growth, there is a growth of the tumor from the retina into the subretinal space resulting in retinal detachment [32]. Endophytic growth consists of tumor growth into the vitreous cavity. Lastly, diffuse infiltrating, which only occurs in about 2% of all retinoblastoma cases consists of a flat pattern of tumor growth usually in the posterior retina. With these, calcifications are rarely visible and are often misdiagnosed as uveitis [33, 34].

The tumor is staged using the International Classification of Retinoblastoma. Each eye is staged separately.

- **Group A**: tumors smaller than 3 mm away from the optic nerve of macula (Fig. 8.1a).
- **Group B**: Tumors larger than 3 mm, macular or juxtapapillary retinal tumors, tumors with subretinal fluid (Fig. 8.1b).
- **Group C**: Tumors with focal subretinal or vitreous seeding within 3 mm of edge of the tumor (Fig. 8.1c).
- **Group D:** Tumors with diffuse subretinal or vitreous seeding >3 mm from edge of the tumor (Fig. 8.1d).
- **Group E:** Large tumor touching the lens, tumor involving the ciliary body or aqueous, neovascular glaucoma, phthisis or cellulitis (Fig. 8.1e, f) [35–37].

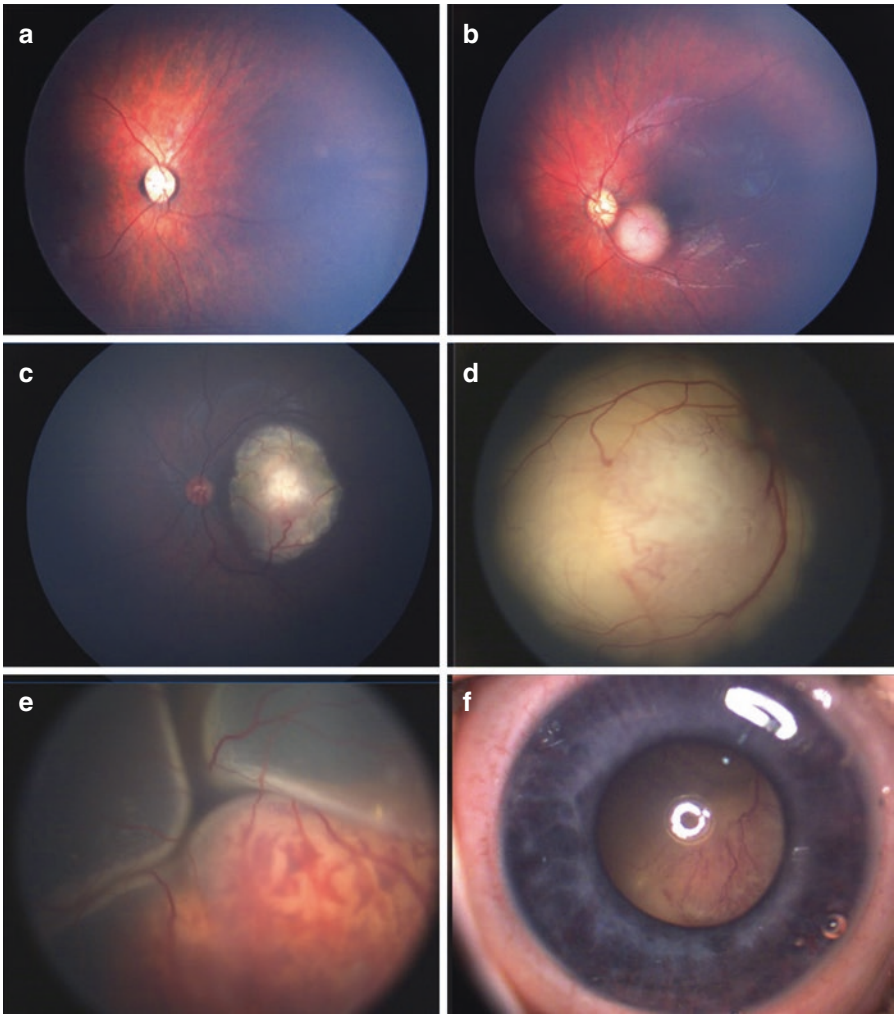

Fig. 8.1 Staging of retinoblastoma. International Classification of retinoblastoma characterizes eyes as small Group A tumor (**a**) and Group B tumor (**b**). Tumors with localized seeds are classified as Group C (**c**) and tumors with diffuse seeds are classified as Group D (**d**). Large tumors with total retinal detachment (**e**) and neovascularization of the iris (**f**) are classified as Group E

8.4 Pathology

Retinoblastoma is a small blue cell tumor. The cells characteristically are arranged in a ring around the central lumen and this arrangement of cells is called Flexner Wintersteiner rosette. Homer Wright rosettes are cells arranged around a fibrillary center. Cells that undergo photoreceptor differentiation are called Fleurettes.

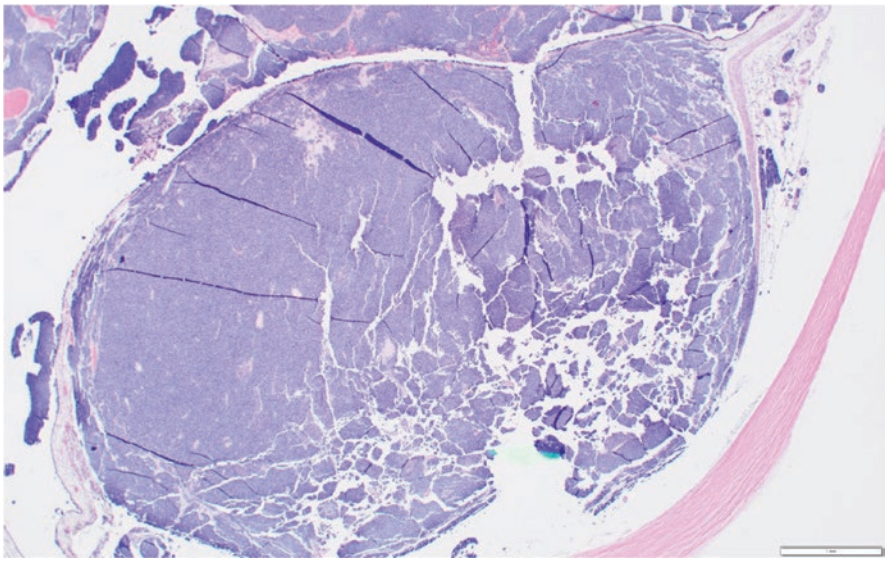

Fig. 8.2 Pathology of retinoblastoma. Pathology of retinoblastoma shows clumps of small blue cells and calcification appears purple

Retinoblastoma tumor can invade the optic nerve, choroid, anterior chamber, iris, ciliary bodies, or sclera [37–39]. These high-risk features are very important to diagnose early on as they carry a risk of systemic metastasis in 24% of patients [40] (Fig. 8.2).

8.5 Diagnosis

Retinoblastoma is diagnosed clinically with the aid of ancillary testing. Lesions that appear similar or mimic retinoblastoma are known as "pseudo-retinoblastomas." [41] According to a study by Huang et al., retinoblastoma is misdiagnosed in about 6–30% of cases resulting in an unnecessary enucleation [42]. Patients who are suspected of having retinoblastoma may undergo several other diagnostic imaging techniques such as ultrasonography, fluorescein angiography, computed tomography, MRI, ultrasound biomicroscopy, and optical coherence tomography.

In order to take pictures for further evaluation, RetCam™ was designed as a wide-angle fundus camera to capture and save fundoscopic images [43]. Fluorescein angiography works with RetCam™ to show the vascular pattern of retinoblastoma. With this, fluorescein dye is injected peripherally and then recorded on the instrument showing the arterial and venous phases of the vessels associated with the tumor [43, 44].

Ultrasonography is a noninvasive and very useful modality to diagnose retinoblastoma. In 90% of retinoblastoma tumors, there is calcification, and the ultrasound detection of calcium is key to the diagnosis (Fig. 8.3a). Ultrasound is also useful for tumor monitoring and detection of recurrence [45, 46].

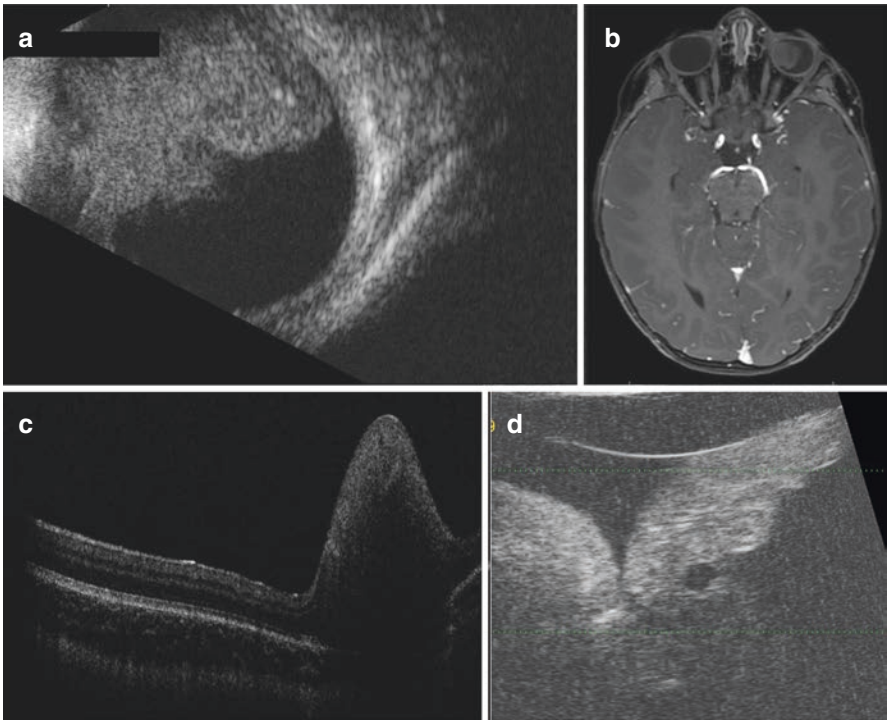

Fig. 8.3 Imaging of retinoblastoma. Ultrasonography shows an elevated retinal tumor with hyperreflective echo suggestive of calcification (**a**). Magnetic resonance imaging of retinoblastoma shows a hyperintense mass on T1 imaging (**b**). Optical coherence tomography shows an elevated intraretinal tumor (**c**). Ultrasound biomicroscopy is useful to rule out ciliary body infiltration in retinoblastoma (**d**)

MRI is a very common modality used to diagnose and routinely image patients with new or treated retinoblastoma. Tumors will show as hyperintense in comparison to the vitreous humor on T1 weighted imaging (Fig. 8.3b) and hypointense on T2 weighted images. On T2 imaging and after contrast, tumors will still appear hypointense and surrounding retinal fluid will not enhance [53]. MRI has the advantage of also estimating optic nerve involvement or choroidal infiltration [54]. Patients with retinoblastoma, especially hereditary form, are screened with cerebral MRI every 6 months until the age of 3 years to detect tumors in the pineal or Sella turcica region (pineoblastoma) which can arise with retinoblastoma [55, 56].

Optical Coherence tomography (OCT) is a diagnostic technique that utilizes light echoes to produce high-resolution, cross-sectional images of the eye. This is exceptionally valuable in diagnosing retinoblastoma as it can detail the structure and depth of the tumor (Fig. 8.3c) [48, 49]. OCT is routinely used to monitor treatment outcomes and look for small tumors or seeding [50]. Lastly, OCT is superior in identifying changes in foveal anatomy posttreatment which can often impact visual function [51, 52].

Ultrasound biomicroscopy is a high-resolution ultrasound that is useful to image the anterior ocular structures (Fig. 8.3d). For retinoblastoma patients, it is useful to detect ciliary body invasion. It is also useful prior to intravitreal chemotherapy to ensure the location of the injection is free of tumor [11, 47].

8.6 Treatment

Treatment for retinoblastoma has made remarkable improvements in the past 25 years. The goals of treating retinoblastoma are to salvage the life of the child, to prevent metastatic disease, and to preserve vision the best possible [37]. Prior to advances in therapy, enucleation and external beam radiotherapy were the treatment of choice to eradicate retinoblastoma. These treatments come with costs though both physically and psychologically. This section will focus on different categories of treatment including local, systemic, intra-arterial/intravitreal, radiation, and surgical therapies of retinoblastoma.

8.6.1 Local

Local therapy of retinoblastoma are treatment options that are typically done under ophthalmoscopic guidance to treat tumors as seen through indirect ophthalmoscopy. The two main local therapies done by ophthalmologists are cryotherapy and laser therapy.

Cryotherapy is a treatment that acts to freeze the tumor itself facilitating tumor death and better chemotherapy penetration. This is usually done to treat tumors that are less than 3 mm in thickness anterior to the equator. In one session, tumors are treated under indirect ophthalmoscope three times using the "freeze and thaw" technique. Tumors may be treated in several sessions with cryotherapy and the objective is to create a flat scar with no more viable tumor tissue [57–59]. Chemo-cryo therapy can also be used which describes a treatment process in which cryotherapy is done on the same day as systemic or intra-arterial chemotherapy to increase drug concentration at the tumor site [59].

Laser transpupillary thermotherapy (TTT) is another commonly used therapy and can be used as the primary treatment of retinoblastoma tumors when the tumor is less than 3 mm or it can be used in combination with other therapies for larger or more complex tumors [60, 61]. With this therapy, a small laser is focalized on the tumor site and the temperature output from the laser is raised over the course of the treatment. The temperature increase is designed to kill the tumor cells that the laser focalizes on. This treatment may last anywhere from 10 to 20 min and may take several different sessions to achieve tumor eradication [59]. It is important to note that the clinical response may appear earlier in patients with more pigmented retinal epithelium and therefore settings of the laser should be adjusted depending on the patients' pigmentations [62]. Chemothermotherapy is another advantageous treatment option that combines the use of chemotherapy and TTT. With this treatment, chemotherapy, usually carboplatin or recently a combination of etoposide and

carboplatin is given 1–2 h before TTT. The point of this is to allow better penetration of the chemotherapy into the tumor cells. The course of chemothermotherapy treatment is anywhere from 1 to 6 cycles each separated by 28 days [63].

8.7 Systemic Chemotherapy

Systemic intravenous chemotherapy (IVC) is often used as primary or adjunct therapy in the treatment of retinoblastoma. The indications to use systemic chemotherapy include extraocular retinoblastoma, prophylaxis for extraocular or metastatic spread, in cases of hereditary/bilateral disease, to decrease the risk of trilateral retinoblastoma, and in combination with local therapy to shrink the tumor [59]. To be effective, the chemotherapeutic agent must be able to cross the blood-brain barrier and/or the blood-retinal barrier. Drug choices for systemic chemotherapy in retinoblastoma take expertise as many factors such as age, tumor type, resistances, and complications must be taken into consideration. IVC usually involves a 2–4 drug regimen for anywhere from 6 to 9 months [59]. The drug classes that are most effective against retinoblastoma include alkylating agents, topoisomerase inhibitors, and anthracyclines. This includes vincristine, etoposide, and carboplatin. Systemic chemotherapy is often combined with local transpupillary thermotherapy and cryotherapy for tumor regression (Fig. 8.4). The

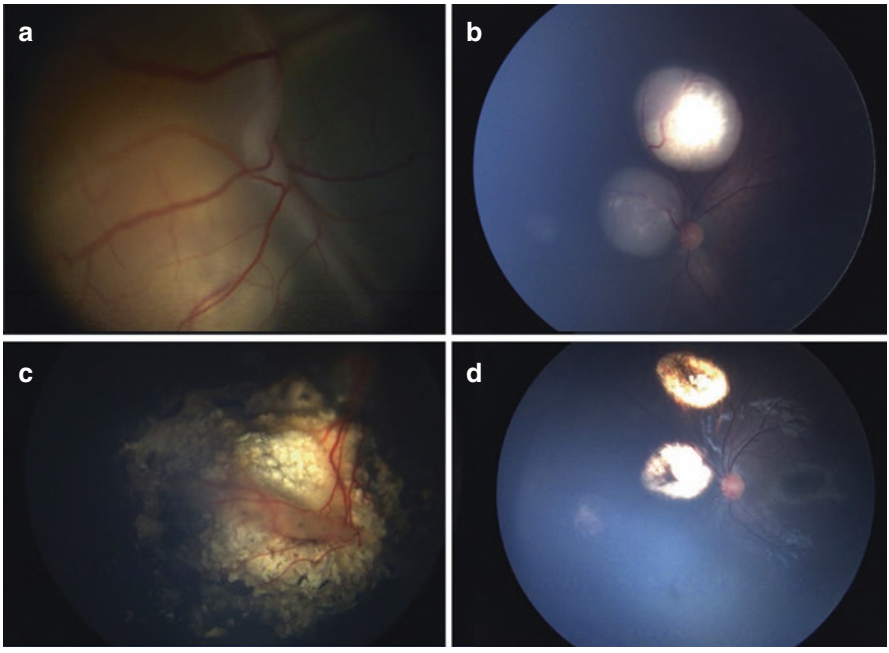

Fig. 8.4 Systemic chemotherapy for retinoblastoma. Bilateral retinoblastoma presented with Group E (**a**) in the right eye and Group B (**b**) in the left eye. Following 6 cycles of systemic chemotherapy and local therapy, both eyes showed a nice response (**c**, **d**)

outcome of retinoblastoma defined as the absence of enucleation and external beam radiation in a large study was Group A (96%), Group B (91%), Group C (91%), Group D (71%), and Group E (32%) [37].

8.8 Intra-Arterial Chemotherapy

Intra-arterial chemotherapy (IAC) has revolutionized the treatment of retinoblastoma and is the primary treatment for unilateral retinoblastoma and for recurrence of retinoblastoma after systemic chemotherapy [70]. The remarkable success of IAC in achieving high rates of clinical remission without significant local or systemic toxicity is owed to the very high concentration of drug produced in tumor tissue when drug is infused directly into the circulation of the eye. Since the chemotherapeutic is not diluted into the systemic circulation, there is a very high first-pass drug concentration. The small blood volume of the eye, and removal of dilution effects associated with systemic administration, allows for a 300-fold increase in chemotherapeutic concentration despite a 90% total dose reduction. IAC is performed by a neuroendovascular surgeon under general anesthesia [71]. In current clinical practice, IAC is usually administered directly into the ophthalmic artery (in 95–97% of cases). In some patients with atypical anatomical variations (3–5%), IAC may be administered into an external carotid artery branch that anastomoses with the ophthalmic artery, most commonly the middle meningeal artery. To administer chemotherapy into the infusion vessel (ophthalmic artery or middle meningeal artery), a microcatheter (≤3 French) is placed into the infusion vessel over a microguidewire (0.008″ to 0.014″). In most cases, the surgeon initially advances a larger guiding catheter (i.e., 4 French outer diameter with 0.038″ lumen) from the femoral artery to the ipsilateral common carotid artery under fluoroscopic guidance [70, 72, 73]. Angiography is performed to delineate the ophthalmic artery circulation and select the infusion vessel. The guiding catheter is then stationed in the internal carotid artery or external carotid artery to support the coaxial microcatheter. After the microcatheter is introduced into the guiding catheter, it is placed into the infusion vessel using fluoroscopic guidance further aided by a mask image of the target infusion vessel superimposed on the live fluoroscopic image.

Once the microcatheter is placed in the infusion vessel, the anatomy and flow dynamics of the ophthalmic circulation are assessed by microcatheter angiography. Particular attention is given to the identification of retrograde or competitive countercurrent flow that may compromise the chemotherapy dose reaching the target tumor tissue. A variety of methods have been described to optimize ocular hemodynamics, including balloon occlusion of the external carotid artery to suppress countercurrent competitive flow [74–76].

Melphalan is an alkylating agent with a short half-life that is commonly used in IAC because retinoblastoma cell lines are very sensitive to it in small doses [77]. In an in vivo rabbit model by Daniels et al., melphalan was proven to have excellent vitreous and retinal drug penetration when administered via IAC [78]. When melphalan is administered systemically for the treatment of retinoblastoma,

prohibitively severe adverse effects are common. While melphalan is the first-line medication for IAC, combination multi-agent chemotherapy may also be used for IAC if there is a poor response to melphalan IAC or a previous exposure to systemic chemotherapy. Melphalan is typically combined with topotecan and carboplatin for combination multi-agent IAC therapy [70]. Recent studies also show that administration of verapamil before administering melphalan increases the sensitivity of tumors to melphalan, rendering treatment more successful [79]. The limitations of IAC include the need for repeated treatments (also true for other retinoblastoma treatments) and potential lack of access to advanced neuroendovascular surgical care [80, 81]. Notably, IAC carries a small risk of stroke, retinal ischemia, retinal hemorrhage, femoral artery occlusion, and ophthalmic artery occlusion. Procedure-related ophthalmic artery occlusion may preclude additional IAC treatments. In theory, exposure to ionizing radiation during IAC may increase the risk of secondary malignancy in children with germline RB1 mutations. Overall, IAC is advantageous in treating retinoblastoma as it incurs less systemic side effects, higher rates of clinical remission, and ultimately lower risk of resistance to chemotherapy [70]. In an analysis of 70 eyes treated with IAC, the treatment was primary in 36 eyes and secondary in 34 eyes [81]. After treatment with IAC and a mean follow-up of 19 months, globe salvage was achieved in 72% of primary-treated cases and in 62% of secondary-treated cases. By the international classification of retinoblastoma, the globe salvage rate was group B (100%), group C (100%), group D (94%), and group E (36%). In the study, the combined incidence of ophthalmic, retinal, and choroidal vascular ischemia was 1%. There was no patient with stroke, seizure, neurologic impairment, limb ischemia, secondary leukemia, metastasis, or death.

8.9 Intravitreal Chemotherapy

Intravitreal chemotherapy (IVitC) is a treatment option for retinoblastoma which involves administering chemotherapy directly through the vitreous in order to achieve maximum drug concentration [82, 83]. It is used for recurrent and persistent vitreous seeds There is a risk of tumor dissemination and hence after needle withdrawal, cryotherapy is performed. Typically, melphalan or topotecan are administered intravitreally every 1–4 weeks. Munier et al. reported the first few patients with intravitreal chemotherapy with this modified technique and had a global retention rate of 87% [84]. The most common side effect of intravitreal chemotherapy is the development of RPE changes in the quadrant of injection.

8.10 Radiation

Radiation is a modality that has been used to treat retinoblastoma throughout the years. In 1931, retinoblastoma was termed a radiosensitive tumor [64]. External Beam Radiotherapy (EBRT) has been used in the past to treat retinoblastoma, but due to its lack of specificity, retinal toxicity, induction of cosmetic deformities, and

ability to induce other neoplasms in individuals with hereditary disease, it is sparingly used. Sarcomas have been identified as the most common secondary malignancy to occur following EBRT [65]. There are also several reports of decreased visual acuity ranging from 5/200 to 20/50 with the use of EBRT. The most common encountered intraocular problems associated with EBRT include cataract formation, retinopathy, and optic neuropathy [66, 67]. Because of the sensitivity of radiation therapy, plaque radiation therapy was introduced as a viable option to treat retinoblastoma.

Plaque radiation therapy also known as brachytherapy is designed to give direct radiation to tumor tissue. Iodine-125 or Ruthenium-106 are the most commonly used radioactive materials for this treatment [68]. The plaques are commonly custom-made for retinoblastoma tumors consisting of several radioactive seeds that are concave to reflect the curvature of the surface of the eye. The ideal tumor candidate for this therapy is typically less than 16 mm in diameter and less than 9 mm in thickness (Fig. 8.5c, d). It is also preferred that there be no vitreous or subretinal seeding [69]. The globe salvage rate following plaque brachytherapy has been reported to be 95% [85]. The most common complications with plaque brachytherapy include radiation retinopathy and cataract.

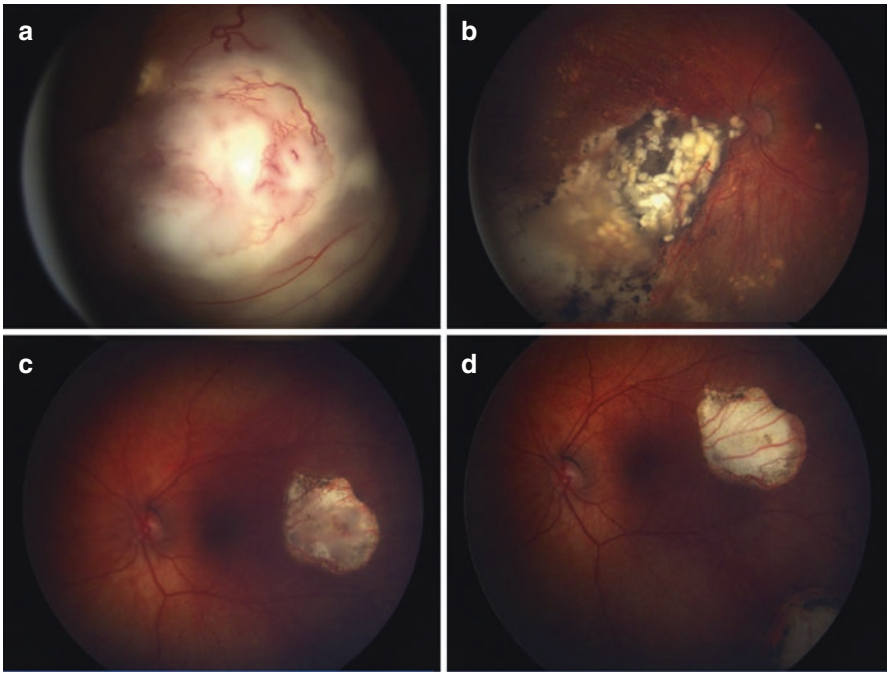

Fig. 8.5 Treatment of retinoblastoma. Large Group D retinoblastoma (**a**) treated with intra-arterial chemotherapy showing a good tumor regression (**b**). Recurrent retinoblastoma (**c**) treated with plaque brachytherapy showing a flat tumor (**d**)

8.11 Enucleation

Enucleation is the treatment of choice for advanced unilateral Group E retinoblastoma with high-risk features. Enucleation is also the treatment of choice when other therapies have failed [84, 85]. During enucleation the extraocular muscles are attached to an implant to provide symmetric ocular motility. For best cosmetic outcomes, the implant should replace 70–80% of the volume originally maintained by the enucleated eye. A prosthetic eye will then be placed on top of this implant [7, 86].

8.12 Extraocular Retinoblastoma

Orbital retinoblastoma encompasses the spectrum of primary clinical manifestation (primary), orbital recurrence following enucleation (secondary), inadvertent perforation or intraocular surgery in an eye with unsuspected retinoblastoma (accidental), intraoperative discovery of extraocular or optic nerve extension (overt), and full-thickness scleral, extrascleral, and optic nerve transection involvement on histopathology (microscopic) [87]. Extraocular retinoblastoma is generally more common in developing countries in part by decreased medical services but also the lack of comprehensive management for retinoblastoma in advanced disease [88]. Orbital invasion has a 10–27 times higher risk of systemic metastasis [89]. The treatment of orbital retinoblastoma involves a combination of high-dose chemotherapy, exenteration, and radiation therapy.

8.13 Metastatic Retinoblastoma

While uncommon in developed countries, metastatic retinoblastoma is a complication of untreated and/or advanced retinoblastoma. This occurs in less than 5% of retinoblastoma cases [90]. Unfortunately, a large majority of metastatic cases take place in developing countries due to inadequate access to medical care [2]. Metastatic disease is the leading cause of death in children with retinoblastoma. The most common sites of metastasis are CNS, bone, and bone marrow [91]. Tumor spread may occur directly via the extension of the optic nerve, or by the invasion of the choroid or orbit into nearby lymph nodes followed by hematogenous spread. Metastatic retinoblastoma is diagnosed typically with MRI and cerebrospinal fluid analysis. If there is extension into bone, bone marrow biopsies and immune-cytology are recommended [91, 92]. Treatment of metastatic retinoblastoma is usually palliative and involves chemotherapy and radiotherapy [93]. According to a study by Hu et al. the median survival time post-diagnosis of metastatic retinoblastoma is 6 months [91].

8.14 Long-Term Visual Outcomes

Recall that the goals of treatment of retinoblastoma are to eradicate tumors for survival, preserve the eye both externally and internally, and to maximize visual outcomes. Best treatment outcomes tend to stem from earlier disease presentation. In a study by Suzuki et al., the long-term visual outcomes after IAC therapy detected no severe eye damage or systemic events and for those eyes without macular involvement, visual acuity remained over 20/60 [94]. In another study, 50% of group D tumors that were salvaged via IAC, had less than 20/200 vision, 60% had strabismus, and 22% had nystagmus. This study also noted that TTT was the biggest risk factor for worsened visual outcomes [95]. While not all eyes affected by retinoblastoma can be salvaged (especially group D and E tumors), the presence of factors that may already cause diminished visual acuity should be fully understood while deciding treatment plans. If a patient already has lost visual acuity due to macular involvement, retinal detachment, or extensive seeding, salvage therapy may not be necessary as the visual outcomes will not improve. This is to be taken into consideration when determining treatment plans and counseling caretakers [96].

Patients with retinoblastoma will be monitored closely with frequent eye exams until the age of 7 [37]. Notably, most recurrences of retinoblastoma reappear within 3 years after treatment with a small likelihood of recurrence thereafter [97]. For patients with hereditary disease, close surveillance and monitoring are necessary to identify and treat secondary malignancies if they are to appear later in life [9].

Key Points

1. Retinoblastoma is the most common intraocular malignancy of childhood and is transmitted as an autosomal dominant condition.
2. Early detection is key for long-term survival and for the preservation of vision.
3. The treatment options include local therapy, systemic chemotherapy, intra-arterial chemotherapy, intravitreal chemotherapy, plaque brachytherapy, external radiation, and enucleation.
4. Patients with retinoblastoma are at a risk of second cancer and hence external radiation use must be minimized and these patients should be monitored for second malignancy.

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