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Retinoblastoma: Current Treatments and Future Considerations

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Retinoblastoma (RB) is the most common primary pediatric eye cancer. The management of RB is constantly evolving, and treatments vary among different centres worldwide. Early detection and treatment are essential to prevent cancer spread and optimize patient survival. Higher survival rates owing to multimodal chemotherapy and advances in local drug administration have allowed for increasing focus on the secondary goal of globe salvage. This issue of *Ophthalmology Rounds* explores current treatment modalities for RB, including targeted chemotherapy, focal therapies and surgery, and novel advancements in individualized care and gene therapy.

Retinoblastoma (RB) has a global prevalence of approximately 1 in 17,000 children, making it the most common primary eye cancer of childhood.[1] It occurs following biallelic mutation of the *RB1* gene in a retinal cell. Loss of the tumour-suppressive functions of the retinoblastoma protein leads to uncontrolled cell division and subsequent genomic changes during tumour progression.

The primary goal of therapy is to prioritize the child's survival by detecting and treating tumours early and preventing their spread. Secondary goals include eye salvage and optimizing vision. Primary management depends on the disease staging, laterality, and vision potential, and involves collaborative decisions between the family and multidisciplinary team. Higher survival rates owing to multimodal chemotherapy and advances in local drug administration have allowed for increasing focus on the secondary goal of globe salvage (**Figure 1**).

Targeted Chemotherapy for RB

Intravenous Chemotherapy

External beam radiation therapy (EBRT) emerged as the first eye salvage therapy for advanced intraocular RB in the early 1950s.[2] In the 1980s, studies found that EBRT increases the lifelong risk of second malignant neoplasms in individuals with heritable RB.[3–6] In the 1990s, a shift toward multi-agent intravenous chemotherapy (IVC) to shrink tumour size – most commonly carboplatin, etoposide, and vincristine – followed by consolidation with focal laser and cryotherapy, revolutionized RB management.[7,8] This led to high globe salvage rates for International Intraocular Retinoblastoma Classification (IIRC)[9] Groups A–C/stage cT1/2 eyes (i.e., tumours restricted to the retina or with only focal seeding or retinal detachment).[10–12] Although ocular survival remained <50% in more advanced Group D and E/stage cT2/3 eyes,[10,13–16] IVC contributed to a significant decrease in EBRT use and incidence of radiation-induced second cancers. Group E/cT3 eyes, which demonstrate high-risk signs such as neovascular glaucoma and aseptic orbital cellulitis, are still best treated with enucleation.[17–19]

Adverse events include myelosuppression, which can result in systemic infections requiring antibiotics, transfusion of platelets, or red blood cells, and nonspecific gastrointestinal toxicity causing dehydration and failure to thrive.[20] Although the acute toxicities of IVC, including nausea and vomiting, can be managed in developed countries, it can be fatal in up to 5% of patients in resource-limited settings.[21] Other long-term risks include ototoxicity from high-dose carboplatin,[22–24] acute myelogenous leukemia from etoposide,[25] and potential negative impacts on future fertility.[26]

IVC is administered over 4-6 cycles (every 3 weeks) depending on the extent of disease and protocol. We favour IVC for first-line therapy of bilateral RB, when both eyes require reduction in tumour size prior to administration of focal therapies or when tumours are too close to the fovea or optic nerve. It is also considered as a "bridge therapy" for unilateral disease in children <3 months of age,[27] until there is sufficient vascular maturation for intra-arterial chemotherapy (IAC), when IAC poses other technical challenges, and as adjuvant therapy for high-risk histopathology following enucleation.

IAC

In 2008, IAC was proposed to achieve higher drug concentrations reaching the tumour, with less systemic exposure and toxicity.[28,29] IAC involves selective catheterization of the ophthalmic artery under fluoroscopic guidance and targeted drug delivery into the affected eye.[29,30] Studies demonstrate that IAC improves globe salvage in advanced unilateral RB (Group D and E eyes) compared with IVC, with fewer systemic complications and no difference in overall survival. Among many studies, a 5-year follow-up of Group D/E eyes that underwent IAC demonstrated a globe salvage rate of 70%.[31] In a multicentre randomized control trial, the 2-year progression-free globe salvage was significantly higher in children treated

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Figure 1. Treatment modalities for retinoblastoma.

	Surgical Treatment	Focal Ablation	Cytotoxic Treatment	Radiation Therapy
Intraocular	Tylectomy	Laser	Intracameral	
		Cryotherapy	Intravitreal	
Ocular	Enucleation		Periocular	Plaque Brachytherapy
			Episcleral Cup	
Orbital			Intra-arterial Chemo	External Beam
				Proton Beam
Systemic			Systemic Chemo	

with IAC (53%) compared to IVC (27%).[32] The improved globe salvage of advanced intraocular RB with IAC led to its application for less advanced eyes. Abramson et al. found that all treatable eyes with less advanced disease were salvaged using IAC without the need for EBRT.[33] In a recent meta-analysis of 20 studies (1467 eyes) assessing outcomes and complications following IAC, 318 of 906 advanced eyes (35.6%; 13 studies) were salvaged, 174 of 543 (32.0%; 16 studies) were enucleated, and 8 of 513 (1.6%; 6 studies) developed metastatic disease.[34]

Though uncommon, IAC is associated with potential ocular and systemic toxicities. Ocular toxicities include transient periorbital edema, redness, ptosis, and forehead hyperemia. Ischemic and occlusive chorioretinopathy, central retinal artery occlusion, vitreous hemorrhage, and retinal detachment have also been reported.[35] Though uncommon, these complications may be vision threatening. Systemic side effects are mild compared to IVC but may include bronchospasm, nausea and vomiting, neutropenia, and groin hematoma.[36] Neurologic complications are rare.

There is no consensus to date on the optimal IAC protocol or drug combination. We use a triple-agent chemotherapy regimen (melphalan, topotecan, carboplatin) every 3-4 weeks, with the number of doses dependent on tumour response (median 3) evaluated under anesthesia immediately before each dose. Chemoreduction is consolidated with focal therapies if required. Our current indications for IAC include as primary therapy for unilateral disease (Groups B-D/stage cT1-2), and bilateral asymmetric disease where the fellow eye either requires enucleation for advanced disease or has small tumours amenable to focal therapies alone. IAC is also effective as second-line therapy for residual or recurrent disease, either following prior IAC or other therapies.

Intravitreal Chemotherapy (IVitC)

The presence of vitreous seeds at diagnosis poses a challenge in terms of prognosis for tumour control and eye salvage, owing to the avascularity of the vitreous and poor chemotherapy delivery.[34] This dramatically changed with the introduction of direct chemotherapy injection into the vitreous cavity in 2012.[37,38] The initial hesitation to perform these procedures was driven by the principle of preserving eye wall integrity during treatment of intraocular RB, for fear of extraocular dissemination.[38,39] However, a retrospective cohort study involving >3500 injections at 10 retinoblastoma centres worldwide reported no extraocular events when using the safety-enhanced technique described by Munier et al.[38,40] This technique includes identifying an injection site free of tumour, seeding and retinal detachment by ultrasound biomicroscopy (UBM), performing an anterior chamber paracentesis to lower the intraocular pressure and prevent reflux during injection, and sterilization of the needle tract via triple freeze and thaw cryotherapy.[37] Injections are repeated every 3-4 weeks depending on seed response, with a consolidation dose provided following seed regression. Melphalan is the most common agent, with topotecan combined if monotherapy fails to control seeding. Our current indications for IVitC are primary or secondary therapy for vitreous seeding, in combination with other modalities targeting the associated retinal tumours. Potential toxicities include infection, vitreous hemorrhage, cataract, retinal detachment, and salt-and-pepper retinopathy from melphalan toxicity.[41]

Intracameral Chemotherapy (ICC)

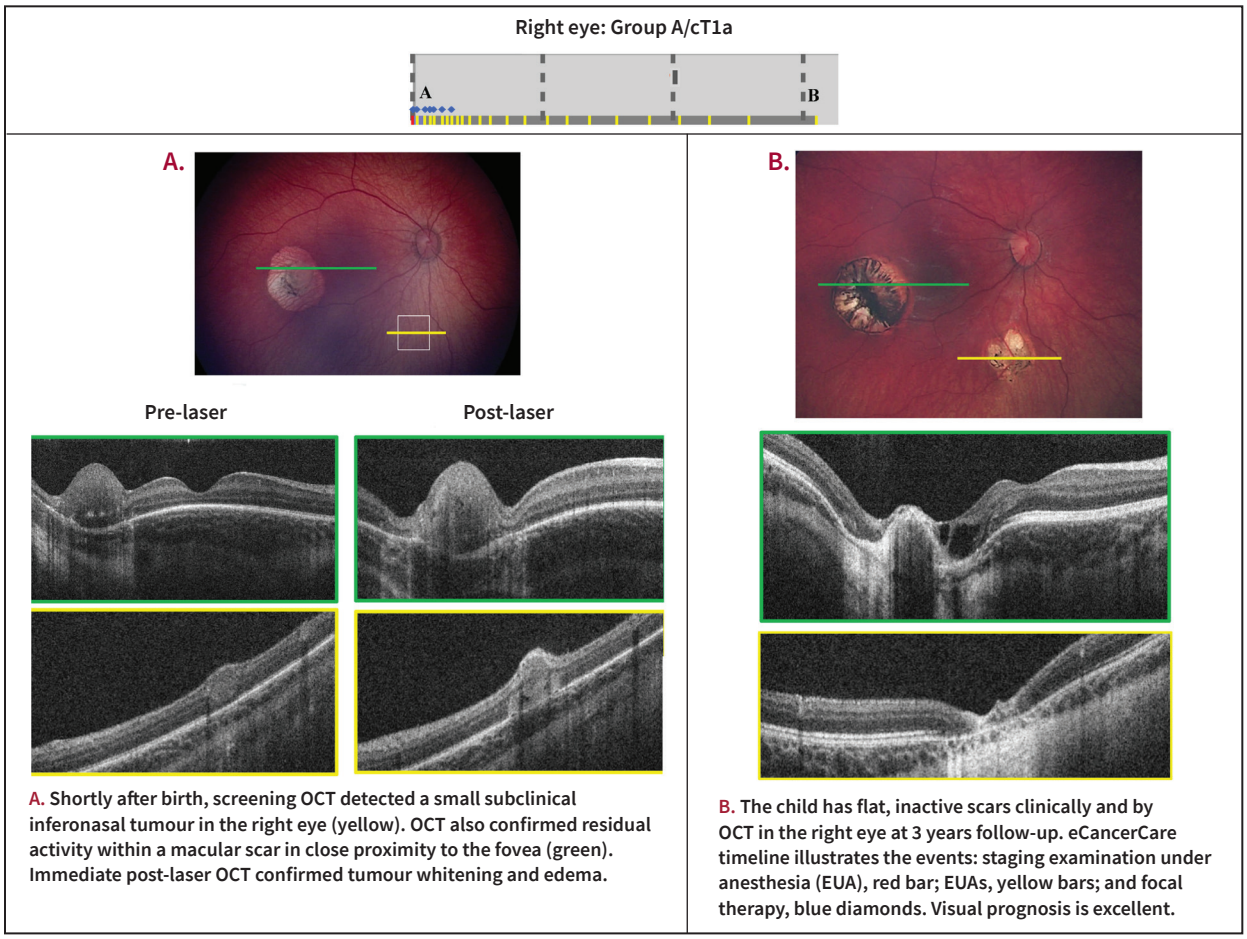
IAC and IVitC are poorly effective in controlling anterior chamber seeding because they are unable to achieve tumouricidal concentrations in the aqueous humour.[42] In most cases, presence of anterior chamber seeding portends a poor prognosis and is an indication for enucleation. This was challenged by the recent introduction of ICC by Munier et al.[43–47] The safety-enhanced ICC technique involves intracameral injections under pharmacologic suppression of aqueous secretion to prevent drug dilution.[47] A 34-gauge long needle is used to remove aqueous humour from both anterior and posterior chambers.[47] While maintaining needle position, the syringe is exchanged and the aspirated volume is replaced with melphalan or topotecan.[47,48] One-third of the volume is administered into the anterior chamber and two-thirds into the posterior chamber via a transiridal approach at a site free of tumour by UBM.[47] Triple freeze and thaw cryotherapy is applied at the injection site. The largest retrospective study of ICC for anterior chamber seeding reported globe preservation in 85% and 100% survival without metastasis.[44] Adverse events include iris heterochromia and atrophy, cataract, and posterior synechiae.[44] At present, we consider ICC for select cases of diffuse anterior RB with good visual potential and no concern for extraocular disease.[47,49] The promising safety and efficacy render ICC a valuable targeted treatment modality that continues to be explored.

Periocular Chemotherapy

To increase intraocular cytotoxic drug concentration while minimizing systemic toxicity, local periocular chemotherapy has been explored. Periocular carboplatin achieves higher concentration within the vitreous than intravenous administration.[50] However, local injection is associated with atrophy of the optic nerve and severe orbital fibrosis with limited ocular motility.[51] A Phase I study of periocular topotecan demonstrated mild local toxicity and no incidence of systemic toxicity.[52] Periocular topotecan in fibrin sealant successfully reduced the volume of small and recurrent RB with no ocular adverse events.[53] Yousef et al. found that periocular topotecan was effective and led to fewer motility complications compared to carboplatin.[54]

Novel drug delivery mechanisms suitable for periocular use are being studied. Two parallel single-site Phase I dose-escalation studies at The Hospital for Sick Children and Phoenix Children's Hospital, Phoenix, Arizona, evaluated the safety and efficacy of sustained-release topotecan delivered locally using a novel episcleral plaque ("chemoplaque").[55,56] The silicone plaque is glued to the sclera for 42 days and facil-

Figure 2. **This child was confirmed by amniocentesis to carry the familial pathogenic *RB1* mutation prenatally. Following early-term delivery at 36 weeks' gestation, the child was examined at frequent intervals (yellow bars, eCancerCare timeline) and small tumours were treated in both eyes.**



A. Shortly after birth, screening OCT detected a small subclinical inferonasal tumour in the right eye (yellow). OCT also confirmed residual activity within a macular scar in close proximity to the fovea (green). Immediate post-laser OCT confirmed tumour whitening and edema.

B. The child has flat, inactive scars clinically and by OCT in the right eye at 3 years follow-up. eCancerCare timeline illustrates the events: staging examination under anesthesia (EUA), red bar; EUAs, yellow bars; and focal therapy, blue diamonds. Visual prognosis is excellent.

itates diffusion of topotecan throughout the eye, without systemic absorption. Forty-one eyes/participants were treated at 5 dose levels (DLs). Three participants were enrolled as primary therapy; 38 were enrolled after standard therapies failed. Sustained complete response was seen in 27/39 evaluable eyes (69%); DL1 43%, DL2 83%, DL3 89%, DL4 67%, DL5 40%. Ocular toxicity at DL1-3 was manageable inflammation but at DL4/5 was severe "dose-limiting toxicity." No participant had study-related systemic toxicity. Mean follow-up is 2 (range 0.2–3) years. This exciting new treatment has the potential to expand the multimodal treatment paradigm for intraocular RB.

Focal Therapies

Focal therapies, including laser and triple freeze and thaw cryotherapy, play a pivotal role in consolidating the response following chemotherapy (IVC, IAC, or periocular), by precisely destroying any remaining tumour cells.[57] Laser and/or cryotherapy are also indicated as first-line therapy for small (<3 mm) Group A/cT1 tumours that spare the fovea and optic nerve,[58] and as second-line therapy for retinal tumour recurrences. Focal therapies are performed under general anesthesia and repeated every 3-4 weeks, with the number of sessions dependent on tumour response. Given the more precise associated scar, we prefer laser for posterior tumours, especially in proximity to the fovea or optic nerve, and cryotherapy for more peripheral tumours.

The most common lasers used for RB treatment are 532 nm frequency-doubled neodymium Nd:YAG and 810 nm semiconductor diode, delivered transpupillary by indirect ophthalmoscopy.[59] While both photocoagulation and thermotherapy approaches have been described, we prefer photocoagulation. Laser is delivered confluently over the tumour surface and encircling laser disrupts the tumour blood supply. Therefore, laser is typically initiated following the completion of chemotherapy. Given its deeper penetration, 810 nm laser is delivered with or without 532 nm laser for large, calcified tumours. Potential complications include cataract, iris atrophy, retinal detachment, seeding, vitreous traction, and extraocular disease extension with aggressive laser. We start treatments at low power and titrate power and duration to achieve adequate tumour/retinal whitening.

Hand-held optical coherence tomography (OCT) enables precision laser therapy by identifying small subclinical tumours[60,61] and tumour recurrences,[62] differentiating tumour edge recurrences from gliosis,[63] assessing foveal architecture, and confirming tumour relationship to the fovea[62,64] and optic nerve.[63] OCT directs diagnosis, treatment, or follow-up decisions in 94% of sessions.[65] OCT is particularly useful in screening for invisible tumours in at-risk neonates who inherit the *RB1* mutation of an affected parent.[62,66,67] Early detection of these tumours when they are small is important, as they develop within the macula early in life and are visually significant.[68,69] Furthermore, smaller tumours may be amenable to primary laser therapy, which is preferable to chemotherapy, as both IVC and IAC pose challenges for neonates. At our centre, we perform screening OCT of the posterior pole to localize small invisible tumours that are not seen clinically (**Figure 2**).[65] Callipers are used to map the tumour location on the associated fundus image, and anatomic landmarks (such as vessel bifurca-

tions) are used to guide 532 nm laser photocoagulation.[70] The accuracy of localization of an initial test laser shot is confirmed by OCT, and the laser is completed. Post-laser OCT confirms adequate treatment. While the standard screening of at-risk neonates involves dilated retinal exam within the first week of life and postnatal genetic testing of cord blood, our centre offers prenatal diagnosis of heritable RB by amniocentesis. Neonates confirmed to carry the familial *RB1* mutation are offered early-term delivery (36 weeks' gestation) at a high-risk obstetrics centre, to allow for dilated retinal examination and screening OCT within the first 48 hours of life. This approach reduces the probability of eyes having tumours at birth to 21% compared with 50% at full term and is associated with better visual outcomes.[69] Posterior pole screening OCT is repeated until 9 months of age, when new tumours tend to arise peripherally.

OCT is also useful in guiding the treatment of perifoveal tumours. Classic laser treatment of perifoveal RB threatens vision due to proximity to the fovea or papillomacular fibres, or the migration of laser scars. Our centre uses an OCT-guided sequential fovea-sparing laser technique.[71] Once the fovea is located by OCT, laser is initially applied to a crescent-shaped area involving the outer tumour (fovea-sparing) and adjacent retina. The initial laser is thought to destroy the blood supply to the tumour, and the resultant scar creates a force that pulls the tumour away from the fovea, where it can be subsequently lasered.[71] OCT is also used to identify areas of residual or recurrent disease.

Indocyanine green (ICG)-potentiated thermotherapy is a valuable addition to the treatment options for RB.[72,73] The administration of ICG dye intravenously prior to laser enhances the absorption of 810 nm diode with potentially reduced laser parameters. In addition to the direct effect of laser, the photodynamic effect of ICG is thought to generate reactive oxygen, which destroys tumour cells.[72] We consider ICG-potentiated laser for the treatment of tumours resistant to conventional laser therapy.

Surgery

Intraocular procedures in eyes with active RB were traditionally avoided due to the risk of iatrogenic extraocular extension and metastasis. This was challenged by IVitC with enhanced safety precautions, with no reported extraocular tumour spread.[40,71] In 2013, Ji et al. reported on the success of pars plana vitrectomy (PPV) for a child with recurrent refractory vitreous seeding.[74] The role of tumour endoresection in the multimodal management of RB refractory to standard therapies was further explored in China, due to high rates of parental refusal of enucleation and treatment abandonment. In 2017, Zhao et al. reported on the use of planned PPV and endoresection as an alternative to enucleation in 21 monocular children with refractory RB.[75] With this intervention, 86% of eyes were salvaged with no cases of metastasis or death, and 78% achieved functional visual acuity. The organ-conserving surgical endoresection of RB with specific safety precautions was later coined "tylectomy".[76] In a study of 960 children with intraocular RB across 29 Chinese centres, eye salvage with tylectomy demonstrated superior 5-year disease-specific survival compared to eye salvage without tylectomy (96% vs. 90%), and comparable to primary enucleation (96% vs. 95%).[76]

While enucleation remains the safest treatment modality for RB, especially for Group E/cT3 and advanced Group D/cT2 eyes, safety-enhanced tylectomy may contribute to salvage of eyes refractory to standard therapy in select cases. Contraindications include obscuration of the optic disc or evidence of optic nerve or extraocular involvement. Safety precautions include careful selection of tumour-free sclerotomy sites, continuous infusion of melphalan in a balanced salt solution, and triple-freeze thaw cryotherapy to the sclerotomy sites. Barricade laser around tumours prior to and during surgery and silicone oil stabilize the retina. Soft tumours are endoresected with the vitrector and a fragmatome is used to disrupt calcified tumours. Both an undiluted vitreous specimen and the vitrectomy cassette fluid are sent for cytologic analysis. Informed family consent and a collaborative approach between the RB specialist and vitreoretinal surgeon are imperative. Our early tylectomy experience after failed standard of care included 8 eyes (all Group D/cT2b) of 8 children since 2018. At a median follow-up of 15 months, globe salvage was 88% with no case of extraocular extension or metastasis.

Aqueous Humor (AH) Liquid Biopsy

Unlike many other cancers, RB is diagnosed clinically without biopsy or genetic tumour markers to prognosticate the response to therapy. Most tumours arise secondary to biallelic mutation of the *RB1* gene. Additional genetic changes, termed somatic copy number alterations (SCNAs), contribute to tumour progression.[77-80]

Following the introduction of IVitC and safe access to AH by paracentesis, Berry et al. demonstrated that AH contains tumour-specific cell-free deoxyribonucleic acid (cfDNA; DNA fragments released by cells), which has biomarker potential and can serve as a "liquid biopsy" for RB.[81] Somatic copy number alteration profiles can be identified in AH and predict tumour response to therapy.[82] Specifically, the presence of chromosome 6p gain is a potential prognostic biomarker of aggressive disease,[82,83] while AH profiles without SCNAs retrospectively correlated with better therapeutic response and eye salvage.[82] Longitudinal AH sampling over the treatment period reflects a real-time measure of therapeutic response.[82,84] Increases in AH tumour fraction (the proportion of cfDNA that is tumour-derived) correspond with residual activity.

Recently, the first prospective study evaluating AH at diagnosis and longitudinally throughout therapy confirmed that 6p gain and/or focal MYCN gain were associated with aggressive disease behaviour.[85] In addition, decreases in tumour fraction during treatment correlated with regression of intraocular disease. In summary, AH liquid biopsy demonstrates exciting prognostic potential. Although clinical findings currently guide our management of RB, AH liquid biopsy is a promising adjunct to predict response to globe salvage therapies. Furthermore, the identification of important biomarkers may allow for future study of targeted therapies, allowing for individualized, precision care.

Gene Therapy and Oncolytic Virus Treatments

Gene therapy is another modality being studied to locally treat intraocular RB and avoid the toxicity of systemic chemotherapy. In a Phase I dose escalation study, Chévez-Barrios et al. evaluated the feasibility and safety of adenovirus-mediated gene therapy as a treatment for vit-

reous seeds in children with refractory RB facing imminent enucleation.[86] Intravitreal administration of an adenoviral vector carrying herpes simplex thymidine kinase (AdV/TK) suicide gene followed by systemic ganciclovir achieved clinical resolution of vitreous seeds in 7/8 eyes with an acceptable safety profile. However, all eyes were later enucleated because of progression of their primary tumours, which were not treated with gene therapy.[86] This approach was not developed following the introduction of IVitC.

Other studies have reported on the efficacy of specific oncolytic adenoviruses, such as H101 and VCN-01, in inhibiting RB *in vivo* and *in vitro*. H101 is a replication-selective adenovirus designed to replicate within cancer cells with a defective p53 pathway, causing subsequent cytopathic effects. Song et al. demonstrated that H101 effectively targets RB cells *in vitro*, reduces tumour burden, and prolongs survival times in mice.[87] VCN-01 is an oncolytic adenovirus designed to replicate in tumour cells with high levels of free E2F-1, a consequence of *RB1* pathway dysfunction. VCN-01 was found to be safe and effective in preclinical models, with promising results in early Phase I data.[88] A Phase I study is currently active and recruiting children with refractory or relapsed RB.[89] Overall, oncolytic adenoviruses show promise as adjuvant therapies for treating RB, though further research is needed.

Conclusions

The management of RB is constantly evolving, with the primary goal being to save the child's life. Despite many available treatments for eye salvage, enucleation remains an important and safe treatment for advanced eyes. Advances in targeted chemotherapy have been invaluable in treating previously intractable forms of RB characterized by vitreous and anterior chamber seeding. Focal laser and cryotherapy continue to play a pivotal role in consolidating treatment after chemotherapy. OCT-guided laser therapy enables secondary prevention of RB through prenatal diagnosis and early treatment of high-risk neonates. Tylectomy is now cautiously considered in select cases refractory to standard therapies. AH liquid biopsy demonstrates the potential for disease prognostication and development of targeted therapies. Advancements in targeted therapies for retinoblastoma promise to improve survival, globe salvage and quality of life for affected children worldwide.

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