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Examination of the most cutting-edge therapies available for the treatment of retinoblastoma

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Abstract:
The International Classification of Retinoblastoma (ICRB) staging, the presence or absence of genetic mutations, family psychological factors and cultural attitudes, and accessible institutional resources all have a role in the management of retinoblastoma, making it a difficult disease to treat. Institutional support must be considered in this therapy. PubMed was combed for reports on retinoblastoma and related treatments, such as chemo, chemo reduction, laser, cryotherapy, intravenous chemo, intra-arterial chemo, intravitreal chemo, plaque radiation, ophthalmic artery chemosurgery, intracameral chemo, transpupillary thermotherapy, radiation, external beam radiation, and brachytactic. For the purpose of this research, we will examine the wide variety of modern therapeutic approaches available in the year 2022. Consolidation therapies (cryotherapy and transpupillary thermotherapy [TTT]), radiation-based therapies (external beam radiotherapy [EBRT] and plaque radiotherapy], and enucleation are all examples of this. We also present a therapy strategy developed via collaboration between three major retinoblastoma treatment facilities in the Pakistan. Therefore, we advocate for

more dialogue and cooperation across the world's top retinoblastoma centers in order to establish consensus management strategies and maintain progress in the detection and treatment of this juvenile disease.
Keywords: treatment, oncology, retinoblastoma, algorithm, tumor

Introduction:
It is possible for retinal blastoma, the most prevalent type of ocular cancer in children, to be deadly if the patient does not undergo therapy for the condition. In high-income countries (HICs), where the disease-free survival rate is close to one hundred percent, retinal blastoma is considered to be a kind of cancer that can be treated and cured. [1] On the other hand, the prognosis is often discouraging in low- and middle-income countries (LMICs), which account for more than 80 percent of all cases globally [2,3]. It is anticipated that the bulk of retinoblastoma cases would originate from the continent of Asia (53 percent), which will be followed by the continents of Africa (29 percent), Latin America (8 percent), Europe (6 percent and North America (3 percent). [4] Given the pattern, it is expected that fewer than thirty percent of retinoblastoma patients would survive their disease. This statistic applies to people all across the globe. [5-7] This disparity is supported by statistics that have been compiled from developing countries and published in academic journals. According to these studies, survival rates in low-income countries range from 23 to 70 percent, whereas survival rates in upper-middle income countries range from 54 to 93 percent. [8] Historically, enucleation has been seen as the best option for treating advanced retinoblastoma, particularly in low- and middle-income countries. [9-19]. On the other hand, over the course of the last three decades, notable institutions have decreased the amount of globes they remove through enucleation in favor of procedures that retain the globe. [9-12]
Therapy for retinoblastoma may be rather different at various institutions situated in different parts of the world due to the fact that treatment of the disease is still in a continuous state of innovation. However, the majority of specialists in retinoblastoma have the same core goals, which are to first preserve the eyeball, then protect the patient's life by preventing the progression of the sickness, and finally enhance the patient's vision as much as possible. These are the three primary goals. The development of modern medications has placed an emphasis on providing the best visual acuity result possible and making significant advancements in the maintenance of the globe. When the disease is identified in its early, more manageable intraocular stage, the treatments that are now in use have shown their ability to maintain high survival rates. The development of these therapeutic methods has led to record-breaking rates of recovery and worldwide salvage at clinics where patients have access to a comprehensive armamentarium of treatment options to select from.
In this article, we present a full analysis of the numerous therapeutic modalities that are currently accessible for the treatment of retinoblastoma. We also address the approved indications for their usage and the most common toxicities that are related to their use. A search was conducted in PubMed, with a focus on research published between the years 1990 and 2020. This treatment algorithm is compiled from all of the most current research that has been conducted. The purpose of this algorithm is to provide referring doctors a straightforward and condensed framework for making decisions, which will, in the long run, lead to a decrease in the amount of time required for referrals. This strategy is intended to be used by the interdisciplinary team that is now working on retinoblastoma as a means of directing and organizing the many resources that are currently at their disposal.
A Method for the Pretreatment Protocol: According to the International Classification of Retinoblastoma, the stage of the tumour is a major factor in determining the best course of therapy (ICRB) [Table 1], extraocular clinical variables, germline testing findings, patient and family socioeconomic status, and accessible institutional resources all play a role in determining the best course of treatment. [13] It is essential to do a comprehensive first evaluation of the disease in order to get accurate information upon which to base a choice about the appropriate level of therapeutic intervention and to avoid unintended adverse consequences. Even before the patient is evaluated, it is of the highest importance to get a complete medical history from them. If there is a history of pineoblastoma in the family, it is possible that the child may need to undergo systemic chemotherapy to reduce the risk of developing the disease. This is the case even if the condition only affects one side of the body. Even if the illness only manifests itself on one side of the body, this is still the case. Throughout the whole of this procedure, a primary focus needs to be placed on determining whether or not pineoblastoma or optic nerve invasion has taken place. It is common practice for the pediatric oncologist to do a complete

blood count, get a urine sample, and carry out a thorough physical exam. It is standard procedure to follow up the first consultation with a more in-depth examination that is carried out while the patient is under general anesthesia. During this stage, the ICRB staging may be confirmed, and the first treatment can be given if necessary.

The response of the patient to the first treatment may be one factor that goes into determining the long-term effects. Therefore, this may be the most important choice that the ophthalmic oncologist takes in order to deliver an effective therapy with the desired level of strength while avoiding excessive harm. This choice was made with the end objective in mind, and its purpose is to help us get there. Table 2 provides a condensed form of the consensus that was achieved among three separate retinoblastoma institutions about a treatment strategy that is based on ICRB stage and laterality. In the next paragraphs, the various therapeutic modalities will each have their overarching goals, strategies, and techniques dissected into their component elements.

Chemotherapy Administered Through Intravenous Route (IVC): The use of systemic intravitreal chemotherapy, which was first used in the treatment of retinoblastoma in the early 1990s, is still a crucial component of this treatment today. IVC is frequently made up of two, three, or even four different chemotherapeutic drugs, each of which is administered once a month by means of a central or peripheral catheter for a total of six to nine cycles in a row. This treatment is typically used for patients who have advanced stages of cancer. [14] The chemotherapy technique that is used the great majority of the time is one in which vincristine, etoposide, and carboplatin are administered in conjunction with one another (VEC). However, despite the fact that vincristine is more likely to cause neurotoxicity than cyclophosphamide is, pediatric oncologists in Monterrey, Mexico, sometimes use cyclophosphamide instead of vincristine when there is a worry about neurotoxicity.

This illness has a number of symptoms, including myelosuppression and hemorrhagic cystitis.[15]

Table 1: Retinoblastoma Classification

1	2	3	4	5	6
Small	Bigger	Extensive	Diffuse seeds	Beside the optic nerve macula or	Contiguous seeds
Retinoblastoma with a diameter or thickness below 3 mm at its base	Diameter or thickness of the tumour at its base that is more than 3 mm OR tumour location that is greater than 3 mm indicate the presence of a retinoblastoma.	Invasions of the postlaminar optic nerve, choroid (>2 mm), sclera, orbit, and anterior chamber by a retinoblastoma, or by bleeding from a neovascular glaucoma into the subretinal space, vitreous, or anterior chamber, respectively; OR a retinoblastoma covering more than 50% of the globe.	Subretinal and vitreous tumour seeds farther than 3 mm from the primary tumour in a case of retinoblastoma	from the centre of the fovea outward, the tumour must be 1.5 millimetres from the optic disc and 3 millimetres from the subretinal fluid.	Cancer of the retina; subretinal seed tumours more than 3 mm from the main tumour seeding in the vitreous nascent stage 3 mm from tumour seeds in the subretinal and vitreous 3 mm from the tumour

Intravenous chemotherapy (IVC) is sometimes called to as "chemoreduction" because it causes a reduction in the size of the tumour after treatment. [14] The use of localized consolidation with thermotherapy, also known as cryotherapy or transpupillary thermotherapy, may be an effective method for improving the treatment of tumours in a number of situations. It has been observed that administering cryotherapy immediately before chemotherapy improves medication access to the intraocular spaces if both the cryotherapy and the chemotherapy are given within 48 hours of each other

after the thermal disturbance. This is only the case if the cryotherapy and the chemotherapy are both given within the same time frame. [16]

Patients having a history of retinoblastoma in their family or a diagnosis of bilateral illness [Figure 1] meet the current criteria for IVC. [14] There is also some suggestion that IVC may reduce the risk of secondary malignancies, metastasis, and pineoblastoma over the long term. These are all cancers that spread throughout the body. [17-19] Patients who weigh less than 6 kilogrammes and are waiting for intra-arterial chemotherapy, also known as "bridge treatment," are some of the other reasons for intravenous chemotherapy. This kind of treatment is also known as "bridge treatment" (IVC). [20] IVC may still be utilized in certain hospitals for the treatment of unilateral retinoblastoma; however, a research including 91 patients revealed that IAC is more effective than IVC for salvaging the patient's globe. This superiority includes superior control for subretinal and vitreous seeding, as well as solid tumour management. [21] As a consequence of this, the authors advocate for the use of IAC as opposed to IVC for the treatment of unilateral retinoblastoma.

Systemic chemotherapy, which is the standard form of the treatment, may cause a variety of unpleasant side effects, some of which include fever, alopecia, and cytopenia. [11] On the other hand, the intravenous chemotherapy treatment for retinoblastoma often only results in a few mild occurrences of systemic damage. While granulocyte colony-stimulating factor is usually unnecessary when standard dosages of VEC are given, its usage is highly recommended when cyclophosphamide is also used. Cyclophosphamide is not one of those drugs where a transfusion of blood components is required, as is often the case with other chemotherapy drugs. Patients are given the typical preventative measures for Pneumocystis jiroveci pneumonia. The nausea, vomiting, and constipation that may be adverse effects of chemotherapy can all be treated medically. IVC has not been linked to any cases of ocular discomfort or injury in any reported cases. It is very unusual for chemotherapy medications to cause kidney damage over the long term when the recommended dose is followed. Men may be at a higher risk of infertility after receiving a cumulative dosage of melphalan equal to or more than 140 mg/m2. And this is particularly true when the stakes are the greatest. When melphalan is present, there is an increased risk of infertility happening, despite the fact that infertility caused by recommended dosages of IVC is rather unusual. It is also unusual for someone to develop secondary acute myelogenous leukaemia after undergoing intravitreal chemotherapy for retinoblastoma. Higher exposure to chemotherapy, concurrent external beam radiation treatment (EBRT), and other risk factors have all been linked to the development of this kind of leukaemia. [19,22] Twenty-year real-world results for a large cohort of 964 eyes with retinoblastoma showed that groups A (96%), B (91%), C (91%), D (71%), and E (32%), all had persistent tumour control with avoidance of enucleation and/or EBRT. This was the case for the vast majority of people in every group except for Group D (71%). Indeed, this held true across all four study groups. [23]

After the enucleation is complete, it is of the utmost importance to carry out a thorough investigation of the histological properties of the globe. The ocular oncologist obtains vital information from the histopathology reports, which may be utilized to guide the treatment that will be delivered. When high-risk features are present, the administration of adjuvant intravitreal chemotherapy is absolutely necessary for the prevention of metastases. Invasion of the post-laminar optic nerve, considerable choroidal invasion (with a diameter of more than 3 millimetres), and extending outside the eye are some of the characteristics of this condition. [24-26] On the other hand, if the ocular pathologist determines that none of the aforementioned characteristics are present, then enucleation on its own may be curative, and subsequent chemotherapy may not be required. This would be the case if it were determined that none of the characteristics were present.

Chemotherapy Administered by Catheter Placed Straight in An Artery (IAC): In the year 1990, Akihiro Kaneko made important contributions to the area of targeted chemotherapy for the treatment of intraocular retinoblastoma.[4] Since that time, this therapeutic technique has established itself as a crucial component of the modern treatment of retinoblastoma, particularly for tumours that affect just one eye. This is especially true in cases when cancer has spread to many eyes. [27-30] Complex and costly, IAC is best carried out in an angiography suite by a highly trained neurosurgeon or interventional neurologist. This is because IAC is a procedure that requires angiography. During this technique, chemotherapeutic drugs are delivered into the ocular artery in a very selective manner using a microcatheter that is guided by fluoroscopy. IAC is probably not a solution that can be applied in developing countries because of its high cost and the need for specialized training. [31] In contrast to

the results obtained from IVC, those obtained from IAC led to a dose of chemotherapy that was directly applied to the eye that was 10 times greater. [31,32] Chemotherapy often consists of the patient being given one, two, or three drugs at a time over the course of three separate sessions, with each treatment lasting around one month. [14,31,33] The conventional therapy for ICRB stages B and C consists of administering melphalan at a dose of 5 milligrammes per day. In many cases, this is all that is necessary. [34] It may be necessary to raise the dosage or include topotecan or carboplatin into the treatment plan for more advanced disease with substantial vitreous or sub retinal seeding found in ICRB stages D and E, or for tumours that are resistant to therapy. [31] Due to its high rates of ocular damage, carboplatin is no longer used as a first-line therapy for cancer. However, it is still utilised as an alternative to melphalan when the total dosage is higher than 0.4 mg/kg, as will be discussed further on in this section when discussing tandem treatment of the other eye. As you read on, you'll learn more about this. [14] With the success of IAC for globe salvage in advanced cases and tumours that have gained resistance to it, the number of patients opting for this treatment method has increased over the last decade. [35-38] IAC treatment is often used as either a primary therapeutic option or as a worldwide salvage option. IAC therapy may be utilised as either the main or secondary treatment for individuals with unilateral, non-germline, group B, C, D, or E retinoblastoma. [Fig. 2]. It may also be used as a supplemental treatment for severe refractory sickness, either unilaterally or bilaterally, in those who are on the cusp of necessitating enucleation. [14,39,40] In cases when subretinal or vitreous seeds are located in close proximity to the retina, IAC is an useful treatment option. [41,31]

It is also used for low exposure IAC (less than two cycles) and tandem therapy for advanced bilateral cases, as well as rescue IAC for recurrences after first IAC treatment. The risk of increased vascular toxicity in the eye with improved vision, the effect on pineoblastoma prevention being unknown, and the therapy having limited impact on metastases that have already developed all contribute to the ongoing debate surrounding the use of tandem therapy and the potential increase in the number of children who die from the condition. [14] Patients with confirmed or suspected germline mutations are given adjuvant IVC treatment as first-line therapy at the three hospitals contributing to this study. This is done to reduce the risk of secondary cancers and problems such metastasis and pineoblastoma. Contrarily, those with unilateral somatic mutations cannot get first IAC therapy. [17,18,42] Since the genetic mutation is unknown at the time of presentation, the age of the patient is used as a surrogate, with infants less than six months being at greatest risk for a germline mutation. Furthermore, extreme care is advised, especially in the case of eyes belonging to groups D or E, which are suspected of displaying high-risk characteristics. In order to stop the disease from spreading, children with high-risk retinoblastoma need to undergo enucleation in addition to receiving an additional 6–9 rounds of high-dose intravenous chemotherapy (IVC). [25,43,44] IAC is typically reserved for usage in newborns who are at least three or four months old since the diameter of their vessels is too small to allow for its use in younger infants. [19] Bridge therapy with IVC is often administered to younger children until the patient's weight reaches 6 kg. [14]

Systemic toxicity has been seen in patients who have undergone IAC, despite the fact that chemotherapeutic medicines were administered in a localised fashion. It was discovered that one patient in every twelve had a condition known as transitory neutropenia. [20] Anticoagulation therapy is a therapeutic option for both the management and reversal of blue toe syndrome, as well as occlusion of the femoral artery. This treatment may be used for either condition. [30,45] Even more catastrophic complications, such as a tear in the carotid artery, a stroke, or even death, have seldom ever reported but have the possibility of occurring. [46] Strict attention must be paid to patient selection when using IAC as a stand-alone treatment option instead of systemic chemotherapy. This is due to the fact that metastases may develop from a variety of sources, such as an unexpectedly large choroidal invasion, invasion of the optic nerve, or extraocular extension.

Periorbital edoema, cutaneous hyperemia, madarosis, blepharoptosis, hair loss, and extraocular dysmotility are all potential adverse effects that might manifest in the area surrounding the eyes. The majority of people who have periocular symptoms report that they have recovered within a few days. [31,47,48] Ophthalmic artery spasm or occlusion, branch or central retinal artery occlusion, vitreous haemorrhage, and choroidal occlusive vasculopathy are all examples of serious ocular vascular issues. Treatment with primary intravitreal chemotherapy has been shown to cause rhegmatogenous retinal detachment in 8-16% of patients, which may be attributable to the fast regression of endophytic tumours. This detachment may occur as a result of rapid tumour regression of endophytic tumours

(IAC). [49] There is no correlation between vascular events and reduced globe salvage; however, these events can have an effect on visual acuity. [4,42] When comparing the risk of vascular events between using IAC as the primary therapy and using it after other treatments, there is no discernible difference between the two scenarios. [35]

Chemotherapy Administered Locally, Often in The Eye: In spite of significant progress made throughout the IVC and IAC eras in terms of survivability, tumour treatment, and globe salvage, a significant number of group D and E eyes often required enucleation as a result of vitreous seed recurrence. This was the situation despite the fact that the IVC and IAC periods were responsible for these advancements. [14,34] Kaneko and Suzuki were the first people to perform intravitreal chemotherapy, often known as IvitC, in 2003. Researchers found that using IvitC in combination with intraaqueous chemotherapy (IAC) was able to salvage several eyes that would have been lost otherwise. One of the current indications for the use of IvitC [Fig. 3] is the existence of vitreous seeds that do not react to conventional therapies. These vitreous seeds are also referred to as refractory or recurring vitreous seeds. IvitC is nearly never used as primary treatment because of how ineffective it is against the primary tumour; rather, it is used as global salvage therapy. It is crucial to note this fact since it is important to point out that IvitC. This is a crucial aspect that needs to be emphasised. Intravitreal chlorofluorocarbon injection should not be performed if any of the following conditions are met: the planned site of needle entry contains tumour or vitreous seeds; the tumour has invaded the pars plana; the anterior chamber has been seeded by the tumour. The use of ultrasonic biomicroscopy (UBM), which is accomplished through careful clinical evaluation, makes it possible for IvitC to be given in a risk-free manner.

Most often used medicines in IvitC are melphalan and topotecan, either alone or in combination. These drugs may be used alone or in combination. To control vitreous seeds while minimising the risk of unwanted effects, it has been shown that injection of 20-30 g every 2-4 weeks is sufficient. [50,51] If more than 0.1 millilitres of intravitreal injection solution is going to be injected into the eye, an anterior chamber paracentesis is done immediately before the injection. This is especially crucial to remember if many drugs must be administered simultaneously. After the injection has been given, the needle is removed while triple-freeze-thaw cryotherapy is administered to the injection site. After a period of thirty seconds of mild shaking, the eye is moved about in order to obtain uniform dispersion across the whole of the vitreous cavity, and copious amounts of irrigation are carried out after this step. Using sterile saline with the intention of cleansing the surface of the eye Following the treatment, the parents will get instructions instructing them to avoid from using eye drops, rubbing, or any other type of eye manipulation for a period of seven days. This includes any and all forms of eye manipulation. These precautions, also known as "anti-reflux mechanisms," prevent cancer cells from spreading to the orbital region (the extraocular space). Extraocular extension was observed in 0.4% of patients before anti-reflux safety measures were put in place. The current injection techniques have been shown in trials to significantly reduce risk, which now lies between 0% to 0.08%. A total of 0.4% of patients had extraocular extension. We were able to accomplish our goal by taking measures to prevent acid reflux. [52-60] There is a possibility that the likelihood of such occurrences will change depending on the method of injection that was used as well as the eye color of the patient. [60]

Chemotherapy That is Given in An Extremely Precise Intravitreal Manner: Precision intravitreal chemotherapy, or p-IvitC, has been used effectively to treat localised vitreous seeding since its discovery in 2018. More research on this therapy is being conducted at the present time. [61] With the p-IvitC method, the chemotherapeutic drug(s) are injected near a single vitreous seed or a targeted group of vitreous seeds using indirect ophthalmoscopy to treat dispersed vitreous seeds. The p-IvitC method treats diffuse vitreous seeds by injecting the agent(s) peripherally, rather than centrally, into the vitreous cavity. This is an alternative to the standard procedure for dealing with dispersed vitreous seeds. [62] When using the p-IvitC method, it is imperative that the eye not be moved after injection so as not to cause the drug to spread unintentionally. This is done in order to protect the patient from potential complications (s). In its stead, the eye is kept in a fixed posture, and the head is reoriented in such a way that the vitreous seed (or seeds) are placed in an inferior position. Because of this, gravity is able to play a role in reducing the amount of time that the vitreous seed is exposed to the macula as well as any other undesirable areas. [62] It seems that the performance of the drug is enhanced by using this strategy, which results in a reduction in the typical number of injections necessary from 4-5 to 2.6. Following a follow-up period of ten months, it was discovered that 13% of patients had developed

retinal pigment epithelial mottling. This ailment made its appearance in a region that was a considerable distance from the foveola. [62]

Chemotherapy That is Given Through the Intracauterine Route: IcamC stands for intracameral chemotherapy, which was developed by Munier et al. in 2017 with the purpose of increasing the quantity of medicine that is easily accessible in the anterior chamber. [62] Because traditional modes of chemotherapy delivery failed to achieve tumoricidal levels in the anterior chamber, aqueous seeding remained to be a reason for prompt anterior chamber plaque or enucleation irradiation. Since tumoricidal dosages of chemotherapy delivered by more traditional means were not reaching the anterior chamber, this was the situation. This was the result of traditional methods of chemotherapy delivery not being able to deliver sufficient dosages to the anterior chamber to kill tumour cells. [63] The first method outlined the process of suppressing the production of aqueous humour by the oral administration of acetazolamide at a dose of 5 milligrammes per kilogramme of body weight prior to the injection of the medicine. This dosage was determined by taking the patient's weight in kilogrammes. [63] Following that, a long needle with a gauge of 34 was used to extract aqueous fluid from the anterior and posterior chambers of the eye using a transcorneal technique. After that, a syringe exchange was performed so that an equal amount of melphalan could be administered in place of the aqueous solution (15-20). This was accomplished without pulling the needle out of the skin. [63] The amount that was obtained was fragmented in such a way that only one third of the dosage is delivered to the anterior chamber, while the remaining two thirds are delivered to the posterior chamber via a route that passes through the iris. Immediately after the administration of the injection, cryotherapy was applied to the entry site, and the needle was subsequently extracted from the skin. IcamC has also been given to patients in conjunction with plaque irradiation, and after three years of follow-up with one patient, the tumour was completely under control thanks to this treatment combination. [63,64] Iris heterochromia and the gradual formation of cataracts in the eye that was treated are two of the recognized adverse effects; nevertheless, corneal endothelial cell density does not change after a follow-up period of five years. [65] Topotecan might be utilized instead of melphalan, which would result in less adverse effects from the treatment while keeping the same degree of efficacy. Under these conditions, a transcorneal approach that also involves infusion into the aqueous of the anterior chamber is adequate, and the treatment may be performed on a monthly basis or more often if necessary. [63] The authors adopt a technique that is theoretically comparable to the delivery of topotecan via the intracameral route.

Therapies With a Particular Emphasis: Both intravenous and intraarterial chemotherapy are often used with targeted medicines in the treatment of tumour consolidation.[64] The two most common types of targeted treatment that are utilized right now are called transpupillary thermotherapy and cryotherapy (TTT). Lesions within the macula may cause a decrease in visual field size or acuity after treatment, regardless of the specific therapy chosen. This may be the case even if the treatment is focused. Scarring of the chorioretinal tissue is another potential side effect of any targeted therapy, although to a lesser extent. It is important to take into account alternative treatment procedures that are founded on chemotherapy when dealing with cancers that involve the fovea, especially if both eyes are afflicted by the condition.

Cryotherapy: Cryotherapy is an option that continues to be widely used because of its efficacy and popularity in the treatment and management of retinoblastoma. Indications for this procedure include, but are not limited to, the treatment of teeny-tiny tumours as well as foci of subretinal or preretinal seedsOn the same day as intravitreal chemotherapy, cryotherapy is given to the peripheral ora serrata in order to boost the drug concentration that enters the intraocular space (IVC). "Chemo-cryo" refers to the treatment method that combines chemotherapy with cryotherapy. [14] For peripheral lesions, the cryotherapy probe is put on the conjunctiva, and for more posterior lesions, the sclera is accessed by a conjunctival incision and the probe is placed directly on the sclera. The supine posture of the patient is required for both operations. We recommend a three-cycle freezing and thawing technique, during which the patient is asked to see the tumour enclosed in a solid ice ball, frozen solid, and then allowed to defrost before the next freezing cycle begins. The best way to treat cancer is to use a procedure that involves three cycles of freezing and thawing. Cryotherapy is now used as a standalone treatment option an extremely infrequent amount of the time. Instead, it is used in combination with other types of chemotherapy, most often chemotherapy administered intravenously but sometimes occasionally

chemotherapy administered intraarterially. Some patients who underwent intensive cryotherapy reported experiencing exudative and rhegmatogenous retinal detachment after the treatment. [14,66]

Thermotherapy of the transpupillary space (TTT): Transpupillary thermotherapy with a diode laser has almost replaced laser photocoagulation as the gold standard treatment for retinoblastoma. Similarly to how cryotherapy and chemotherapy may be used together as the main treatment for tumours smaller than 3 mm in diameter and 2 mm in thickness [Fig. 4], TTT and chemotherapy can be used together as the primary treatment for tumours of similar size. [67] Indirect ophthalmoscopy is used to conduct TTT, and a diode laser with a wavelength of 810 nm that is typically operated in a continuous mode is used. In order to treat the entire tumour, it is typically necessary to use a number of different locations. It is important to allow for sufficient application time in order to get a grey-white absorption in the shortest amount of time feasible. In order to get the desired results of a smooth scar or a completely calcified tumour, it is often essential to go through a number of TTT sessions, the number of which may vary anywhere from 2 to 6, with a gap of 4 weeks in between each session. When there is not an adequate response, when there is a recurrence of the tumour, or when the fundus is not strongly pigmented, indocyanine green, which is more often referred to as ICG, may be administered to augment the effects of TTT. It is typical practice to inject 0.3 mg/kg to 0.5 mg/kg of ICG into a patient around one minute before TTT. It's done this way so that it's as efficient as possible. [14] Focal cataract, iris atrophy, and anterior/posterior synechiae are all conditions that have been linked to TTT. When the medicine is used as prescribed, there is a low risk of more significant side effects, such as those that might put a patient's eyesight at risk. These dangers include vitreous haemorrhage, retinal neovascularization, vitreoretinal tension, and retinal detachment. Retinal vein obstruction is another concern. [68-70]

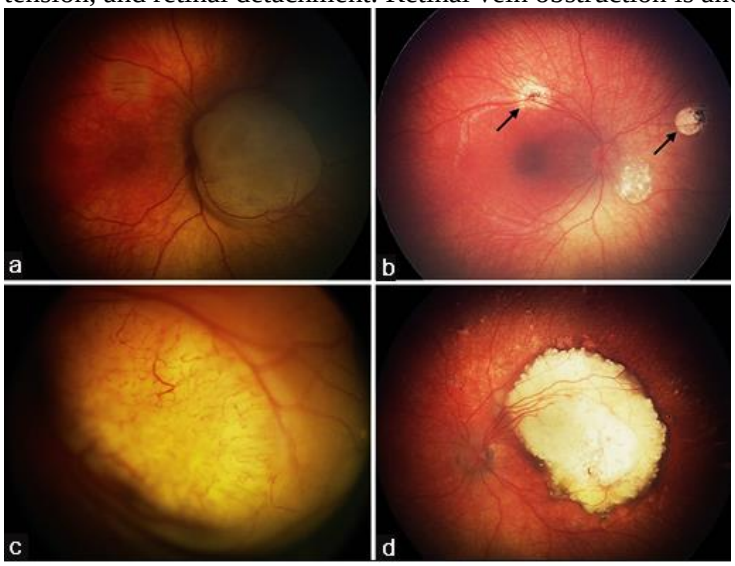


Figure 1: Modern treatment of retinoblastoma. The role of intravenous chemotherapy (IVC) in bilateral disease. A 4-month-old patient was diagnosed with a (a) Group B retinoblastoma in the right eye, and was treated with 6 cycles of standard-dose IVC, (b) achieving a complete regression of the tumor. Consolidation therapy with TTT was required during the course of the treatment, leaving flat scars (black arrows) and completely regressed tumors. The (c) left eye was diagnosed with Group D retinoblastoma, regressing to a (d) smaller calcified scar in the macular region after treatment

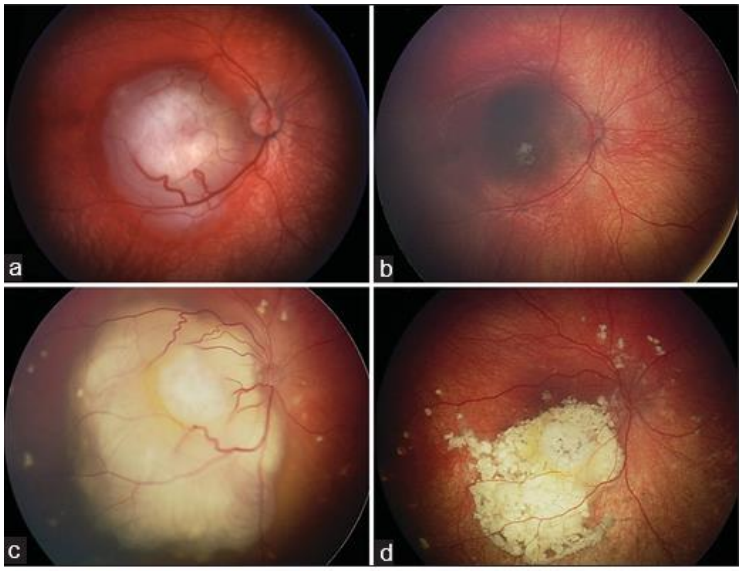


Figure 2: Modern treatment of retinoblastoma. The role of intra-arterial chemotherapy (IAC) in unilateral disease. (a) Unilateral group B retinoblastoma with macular involvement. Following 4 cycles of IAC, (b) the majority of the macula had been spared without the need for additional consolidation therapies. (c) Unilateral group D retinoblastoma with macular involvement and serous retinal detachment. After 4 cycles of IAC, the retina completely reattached leaving a (d) smaller calcified macular scar and scattered calcified subretinal seeds

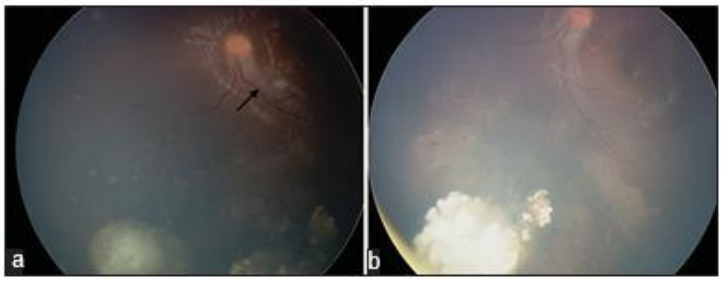


Figure 3: Modern treatment of retinoblastoma. The role of intraocular chemotherapy. Diffuse vitreous seeding from retinoblastoma managed with intravitreal chemotherapy (IvitC). (a) Active vitreous seeds surrounding the tumor and overlying the macula (black arrow), with (b) resolution after two cycles of IvitC with melphalan and one cycle of IvitC with topotecan

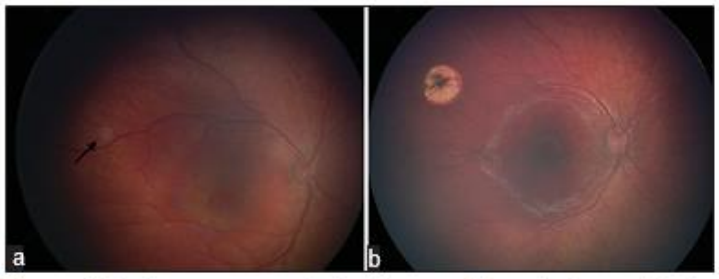


Figure 4: Modern treatment of retinoblastoma. The role of consolidation therapies. Group A retinoblastoma managed with transpupillary thermotherapy (TTT). (a) Subtle tumor (black arrow) temporal to the macula, with (b) regression 1 month after treatment

Figure 5: Modern treatment of retinoblastoma. The role of enucleation and prosthetic rehabilitation. (a) Unilateral Group E retinoblastoma that required (b) enucleation, with a dermo-lipid graft placed for economic reasons. (c) On follow-up 6 weeks later, a custom-made prosthesis was adjusted

Radiotherapy Executed Through the Use Of An External Beam: Prior to the development of intravenous chemotherapy, external beam radiation, also known as EBRT, was frequently utilized as a global salvage treatment. The practice of treating retinoblastoma with external beam radiation therapy (EBRT) is now largely considered to be of historical significance in the majority of industrialized nations. This is primarily due to the numerous negative effects that are associated with the treatment, as well as the improved patient outcomes that followed the development of effective chemotherapy. However, EBRT still has a place in some situations, such as when an extraocular tumour is present, when there is a recurrence in the orbit, or when there is a positive optic nerve margin after enucleation. These are all examples of situations in which the cancer has spread outside of the eye. [71] It has been reported that 71% of patients who were treated for orbital retinoblastoma with a combination of external beam radiation treatment (EBRT) and intravitreal chemotherapy (IVC) were effective in establishing tumour control. [72] Negative consequences of radiation treatment include a deficiency in tears, dry eye syndrome, radiation retinopathy, cataract, filamentary keratopathy, optic neuropathy, and retardation of orbital development. Orbital development retardation can lead to facial deformity. Tear deficit is another negative side effect. [73,74] One of the most potentially life-threatening side effects of external beam radiation treatment is the formation of a second primary tumour in the treated region (EBRT). Especially in patients who have been diagnosed with a form of retinoblastoma that occurs in the germline. It has been shown that this risk may reach as high as 53% by the age of 50, which indicates that persons with germline mutations have a larger probability of dying from second tumours than they do from retinoblastoma itself. This is because the likelihood of developing second tumours increases with age. [75-77] The most common secondary malignancy is osteosarcoma, followed by melanoma, epithelial tumours (of the bladder, breast, colon, kidney, lung, nasal cavity, prostate, retroperitoneum, thyroid, tongue, and uterus), and finally soft tissue sarcomas (uterus, bladder, , tongue, breast, colorectal, nasal cavity, kidney, prostate, lung, retroperitoneum, thyroid). Because of the possibility for these undesirable consequences, we suggest avoiding treatment with EBRT whenever feasible in favor of one of the numerous other viable therapeutic choices.

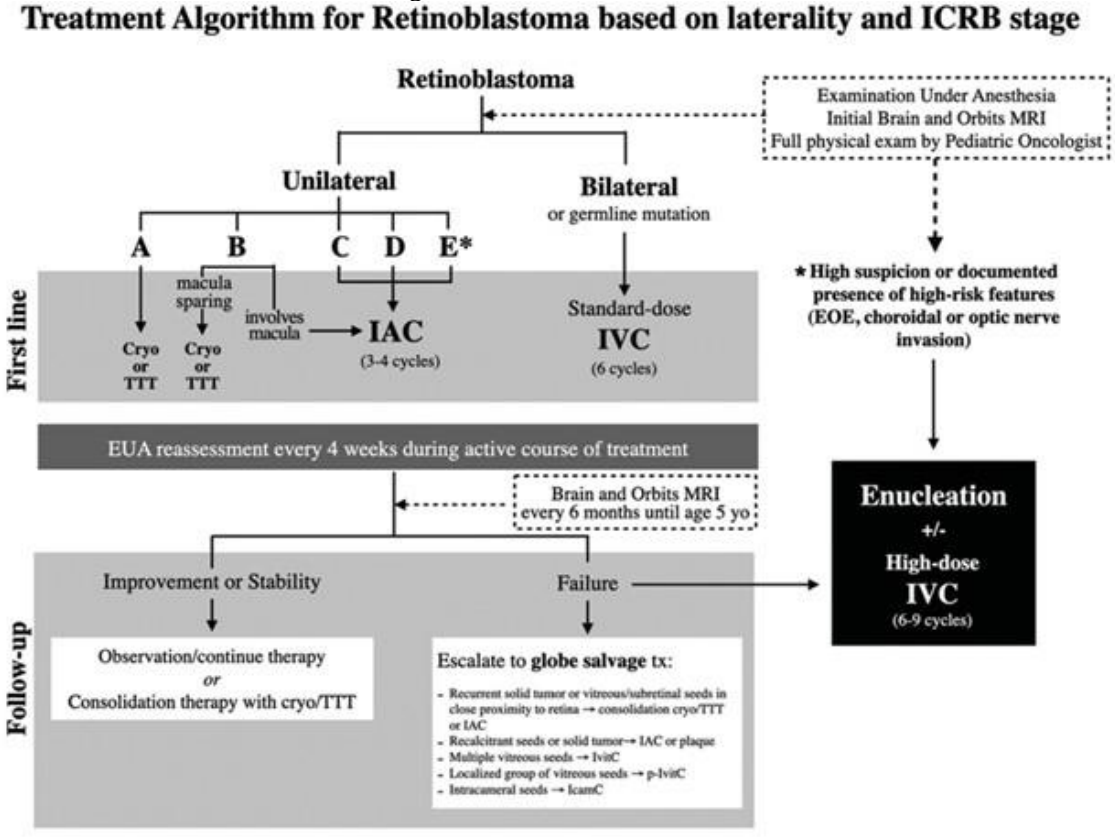
Radiation Therapy for Plaque: When it was discovered in 1929 that plaque radiation (also known as brachytherapy) was effective against recurrent tumours after EBRT, it was first used as a salvage treatment. [78,79] When intravitreal chemotherapy or intraarterial chemotherapy has already been tried and the tumour has returned, brachytherapy is often employed as a second line of defense. This is because brachytherapy is a more precise form of radiation therapy than either of the aforementioned chemotherapy methods. Medium-sized tumours are those that have a thickness that ranges from three to nine millimeters and a greatest basal diameter that is less than sixteen millimeters. [80] Plaque radiation is an additional treatment option for the management of diffuse anterior segment retinoblastoma in cases where there are no choroidal or retinal malignancies present. This therapy may be carried out with or without the use of IVC. In order to obtain optimal tumour coverage, it is customary procedure to add two millimetres of safety margin to the maximum basal diameter. If a tumour is less than 2 mm from the eye's optic nerve, it will need a plaque with a notched area. When there are at least three clock hours of malignancy in the nerve's immediate vicinity, a deep notch is used. In the Pakistan, iodine-125 is the most used isotope, and its tailored dosage has the capacity to deliver 35-40 Gy to the tumor's epicenter. Secondary plaque irradiation is given between one and two months following initial plaque irradiation (IVC), with the goal of minimizing the potential for adverse effects to the greatest extent feasible.

Plaque radiotherapy is more convenient than external beam radiation treatment (EBRT) since the whole dose may be administered in as little as two to four days using plaque radiotherapy. However, there is one little problem, which is that in order to install and remove the plaque, two separate processes are

required. [81,82] Plaque radiation, in comparison to EBRT, eliminates a greater number of potentially life-threatening adverse effects. These adverse effects include facial hypoplasia, ipsilateral orbit hypoplasia, and, most importantly, the risk of developing a second form of cancer. [83] Plaque irradiation, when used as a subsequent treatment after intraabdominal chemotherapy, was found to have a success rate of 79%. This was the case even when there was localized vitreous seeding present in the patient's tumour. [84, 85]

Enucleation: Even if there have been important breakthroughs in the treatment of retinoblastoma, the removal of the patient's eyeball by enucleation is still a viable therapeutic choice in the modern day [Fig. 5]. Extraocular extension, suspected invasion of the optic nerve or choroid, and recalcitrant tumours that have failed previous globe salvage therapies (such as IAC, IvitC, plaque radiotherapy, etc.) are some of the situations in which this procedure is reserved (e.g., IAC, IvitC, plaque radiotherapy, etc.). [11,86-88] Chemosis, blepharoptosis, conjunctival cysts, superior sulcus defect, pyogenic granuloma, lagophthalmos, exposure, enophthalmos, symblepharon, implant and infection are only a few of the known complications. [89] Wound healing time is crucial for patients who have had their orbits opened for implants. Antibiotics may be administered topically or taken orally to treat an infection, but in severe circumstances, removal of the implant may be necessary. The condition known as gigantic papillary conjunctivitis, which is brought on by prolonged contact with a prosthesis, requires the use of antibiotic-steroid ointments in addition to an excessive number of lubricants as a form of therapy. The removal of a patient's eye may have functional, physiological, and psychological consequences for them. [90] As a direct consequence of this, the process of prosthetic rehabilitation is of the utmost significance. In the majority of cases, it is recommended that a conformer be used during the first six weeks after an enucleation in order to facilitate cosmetic rehabilitation. This is done for the purpose of reducing scarring. [90] Molds are taken after the sixth week in order to produce a personalized ocular prosthesis. This is done since there is a lower risk of dehiscence, hemorrhage, or infection after this amount of time has passed. The early implantation of a prosthesis, as demonstrated by the research conducted at a number of different facilities, was found to improve the individual's quality of life overall. [90,91]

Table 2: Retinoblastoma Treatment Algorithm



Cryo, cryotherapy; EOE, extra ocular extension; EUA, examination under anesthesia; IAC, intraarterial chemotherapy; ; IcamC, intracameral chemotherapy; IVC, intravenous chemotherapy; IvitC, intravitreal chemotherapy; MRI, magnetic resonance imaging; p-IvitC, precision intravitreal chemotherapy; TTT, transpupillary thermotherapy; tx, treatment; yo, years-old.

The Protocol for the Subsequent Follow-Up: After the initial treatment has been given, patients are typically scheduled for follow-up appointments once every four weeks. These appointments are used to evaluate the patient's response to therapy, establish whether or not there have been any adverse effects, and select alternative treatments as required. Algorithm [Table 2] summarizes situations in which patients may be followed, globe salvage therapy may be maintained, altered, or intensified, or enucleation may be used instead of globe salvage. There are a few different ways to approach salvaging a globe: keep an eye on it, make some changes, or ramp up the intensity. The family should be notified about the implications of the RB1 mutation genetic findings for long-term follow-up as soon as possible throughout the course of therapy. In vitro fertilization with preimplantation diagnosis may also be explored as part of the process of family planning. It is OK for this to take place at any point over the course of therapy. Patients and their families, in addition to receiving medical care, are given the opportunity to participate in counselling sessions. Warning signs are handled at this time, and the grieving process is made more tolerable overall. These ancillary tests will be needed on a regular basis by the pediatric oncologist, especially if either a normal dosage or a high dose of IVC is being delivered. This is because additional tests are designed to detect any potential complications that may arise from the treatment. Before the age of 5, a high-resolution simple and contrasted MRI of the brain and orbits should be done religiously every six months. A pediatric oncologist may recommend further testing, such as blood samples, a lumbar puncture, or a full-body osseous gamma gramme.

Long-Term Monitoring of the Patient Who Does Not Have Cancer: Ideally, a person who has overcome retinoblastoma should be followed for the rest of their lives. This is especially true for people with germline abnormalities, since secondary malignancies may arise years after primary cancer therapy has ended. Assuming the tumour has been successfully treated, kids will need regular eye tests until the age of 7, following which the checkups will be spaced out throughout the rest of their lives. This continues until the patient reaches the age of 7, at which point the exams are no longer monitored. It is reassuring to know that the majority of patients will show signs of recurrence within three years of treatment, after which there will be very little recurrence because the treatment will have stopped working. [92] However, extremely late onset recurrences are still possible, even 11 years after the initial therapy was administered to treat the condition. This is entirely feasible. [93] As a consequence of this, pediatric oncologist appointments should be scheduled anywhere between once every year and once every two years. Visits to the ophthalmologist should centre on keeping tabs on any long-term side effects from the cancer treatment protecting the healthy eye (if one exists), and performing any preventative measures typically administered to someone of the patient's age (such as correcting refractive errors) (e.g. correction of refractive errors).

Conclusion: It is possible that an effective treatment for retinoblastoma may be challenging to develop. Because each person's situation is unique, treatment procedures need to be methodically altered to meet a wide range of sickness presentations, various pieces of equipment, and regional cultural norms or traditions. This is necessary because each individual case is different. It is very necessary to have strong coordination between the ocular oncologist who will be treating the patient and the multidisciplinary team in order to achieve effective treatment. Everyone who is engaged in this situation should put the health and well-being of the patient first and foremost in their thoughts and actions at all times.

This page offers a comprehensive review and discussion of the most current guidelines for the treatment of retinoblastoma all around the globe. In spite of the fact that the treatment of retinoblastoma could be different from one retinoblastoma center to another depending on the amount of experience and the resources that are available, an algorithm that visually summarizes the most current research is offered. The authors call for more collaboration in order to build a single treatment paradigm that is based upon the agreement of the most renowned and cutting-edge retinoblastoma facilities in the world. If we were to succeed in doing this, it would be a major advance in our battle against this illness.

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