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# Focal therapies for retinoblastoma

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## ABSTRACT
Currently, the primary treatment for retinoblastoma is intravenous and/or intraarterial chemotherapy. However, adjuvant focal therapies are also an essential component in the treatment of this cancer. The article discusses the methods of focal treatment of retinoblastoma: cryotherapy, transpupillary laser thermotherapy, transpupillary laser thermotherapy with intravenous indocyanine, brachytherapy, enucleation, and intraarterial and bicameral injections of melphalan. Particular attention is given to the latest methods of treatment including topical chemotherapy (intravitreal injections) and intraarterial chemotherapy. These modern topical treatments help salvage the eye in an increasing number of patients with advanced retinoblastoma.
**KEY WORDS:** retinoblastoma, thermotherapy, cryotherapy, melphalan, brachytherapy.

## INTRODUCTION

Retinoblastoma is the most common intraocular malignancy affecting children. If left untreated, retinoblastoma spreads to other parts of the body, leading to a fatal outcome. The incidence of retinoblastoma in Europe is rising and it is currently estimated at 1 per 13,844 live births [1]. At present, the survival of children affected by the condition in developed countries has climbed to almost 100% [2].

The primary goal of retinoblastoma treatment is to save the patient's life. Other goals include salvaging the eye and preserving as much vision as possible. The choice of treatment is determined by the severity of retinoblastoma. The therapeutic modality depends principally on tumor location and size, presence of subretinal seeding and vitreous seeding, and anterior ocular involvement. The therapeutic approach is modified when metastases are found, or infiltration of the optic nerve or orbital tissues is detected. In addition, the choice of treatment depends on factors including the patient's age, presence of germline RB1 gene mutation, condition of the other eye, visual potential of both eyes, availability of various therapeutic modalities, and even cultural considerations. The last of the listed factors, which may appear to be of minor importance, actually has a very strong impact on medical management and even on the development of new therapeutic methods. In the countries of the Far East, such as China and Japan, enucleation is extremely difficult to accept by the child's parents and, more broadly, by the society as a whole. In fact, both physicians and parents are willing to accept a high risk to the child's life which is associated with conservative treatment of very advanced retinoblastoma, to avoid enucleation that would lead to the child's social rejection. These cultural factors, coupled with Japan's high level of economic development, have contributed to the development of two extremely important retinoblastoma treatments – intraarterial chemotherapy and intravitreal chemotherapy – in this country. In some Western countries, such as Germany and Canada, parents are far more accepting of the decision to remove an eyeball if there is no chance to preserve vision and attempts to salvage the eye would impose an enormous burden on the patient. Fortunately, advanced methods of treatment are associated with high cure rates and safety, so it is less and less common for physicians and the child's parents to be confronted with the dramatic choice between conservative treatment and eye removal.

Currently, the leading methods for treating retinoblastoma include systemic chemotherapy (administered intravenously) and selective focal intraarterial chemotherapy. They are complemented by adjuvant focal therapies, such as transpupillary thermotherapy, laser photocoagulation, cryotherapy, brachytherapy, and intravitreal chemotherapy. The methods are effective in destroying the tumor without causing serious, life-threatening systemic side effects. In addition to safety, other benefits of focal modalities in the treatment of retinoblastoma include simple application, short duration, low cost, and lack of involvement of many specialists in various fields. The new-

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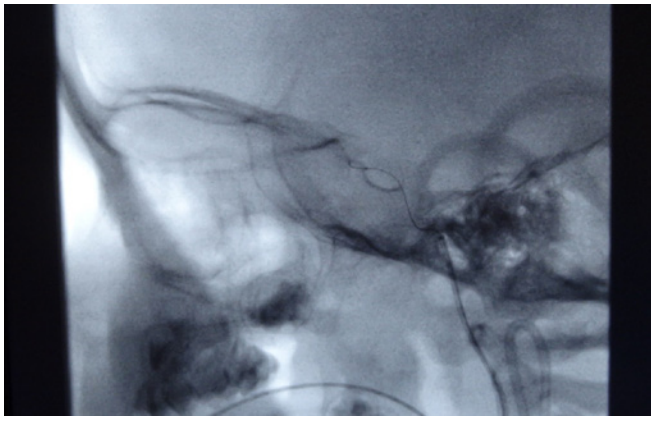

**Figure 1.** Intraarterial chemotherapy. The arrow marks the catheter inserted into the ophthalmic artery

est type of focal treatment, which is increasingly being used as first-line therapy, is selective intraarterial chemotherapy. Other focal therapies for retinoblastoma are used to treat tumors after systemic chemotherapy, but may also be selected as primary treatment for small tumors and as adjuvant treatment when a recurrence is diagnosed.

## SELECTIVE INTRAARTERIAL CHEMOTHERAPY

Selective intraarterial chemotherapy (IAC – intraarterial chemotherapy or OAC – ophthalmic artery chemosurgery) is one of the key treatments for intraocular retinoblastoma. High efficacy of intraarterial chemotherapy is attributed to the fact that the concentration of chemotherapeutics that can be achieved with this treatment modality in ocular tissues is several times higher compared to systemic chemotherapy [3]. Another important factor contributing to the high efficacy of IAC procedures is that they can be performed with the use of melphalan. Melphalan is a drug with potent cytotoxic effects against retinoblastoma cells demonstrated *in vitro* [4]. However, it may not be used for systemic therapy because of its toxic effects affecting primarily bone marrow cells. It is only through the selective delivery of the drug directly to the ophthalmic artery that therapeutic concentrations of melphalan can be achieved in the eye, with minimal exposure to the whole body. IAC is classified as a method of focal chemotherapy in view of the targeted delivery of chemotherapeutic agents directly to the tumor area. However, unlike other focal modalities, this method of treatment requires close cooperation between specialists in different disciplines and carries the risk of systemic complications. Chemotherapeutic doses used in IAC may affect the whole body, and in some cases (concurrent treatment of both eyes in infants) they must be reduced because of the potential for systemic complications.

The three most common drugs used in IAC include melphalan, topotecan, and carboplatin. However, only melphalan is used as monotherapy. Most typically, three IAC procedures are performed with less than a month between them, with two or three drugs administered during a single IAC procedure.

Compared to systemic chemotherapy, IAC is characterized by higher efficacy, shorter treatment period, and markedly lower systemic toxicity. A disadvantage of the IAC procedure is elevated toxicity to ocular tissues (chorioretinopathy and toxic neuropathy).

**Description of procedure:** The catheter is usually inserted through the femoral artery, and then threaded through the heart, and the common carotid and internal carotid arteries, to the area of the entry to the ophthalmic artery (Figure 1). Once there, the tip of the microcatheter is stabilized, and drugs are administered. The procedure is performed by interventional radiologists or neurosurgeons.

**Indications:** IAC is a highly effective procedure in the treatment of retinal or subretinal tumors. Patients with vitreous seeding or involvement of the anterior segment of the eye respond less well to this method of delivering chemotherapy. IAC can be used as a primary treatment for tumors classified by the International Classification of Retinoblastoma (ICRB) as groups B, C, D, or E. It may also be considered as a secondary treatment after failure of other therapeutic modalities or even after previously failed primary IAC.

**Complications:** *Common:* bronchospasm during the procedure (easily reversible with epinephrine), choroidal atrophy, skin congestion around the upper eyelid, droopy eyelid, spasm of the ophthalmic artery or one of its branches, transient paralysis of the oculomotor muscles [5]. *Rare:* stroke, loss of vision associated with vascular complications in the optic nerve, retinal detachment, upper eyelid skin ulceration, myelosuppression, femoral artery spasm, femoral artery bleeding.

## INTRAVITREAL MELPHALAN INJECTIONS

Intravitreal chemotherapy was proposed as a treatment for retinoblastoma as early as in the second half of the 20th century, but was abandoned because of extraocular tumor seeding observed after treatments. The technique was reintroduced in 2012, but with strict safety measures. The precautions include reducing intraocular pressure prior to injection by means of anterior chamber paracentesis or ocular massage to prevent vitreous reflux, and cryotherapy applied during needle removal at the injection site to destroy any active tumor cells that may have escaped from the vitreous chamber. The introduction of intravitreal injections of melphalan (IVIM) represented a milestone in the treatment of retinoblastoma, significantly improving therapeutic outcomes. Active seeding of cancer cells in the vitreous used to be a widespread cause of treatment failure in retinoblastoma. Other forms of therapy are not effective in treating cancerous cells seeded in the vitreous. Intravenous and intraarterial chemotherapy fails to provide adequate concentrations of chemotherapeutic agents in the vitreous [6, 7]. The effects of teleradiotherapy-based treatment of tumors seeding the vitreous were likewise unsatisfactory because of the altered hypoxia-adapted metabolism of retinoblastoma cells in the vitreous [8]. The pioneers in the delivery of chemotherapy directly into the vitreous were Kaneko, Suzuki, and Inomata.

They found high efficacy of melphalan against retinoblastoma cells *in vitro* and initiated intravitreal melphalan injections [9, 10]. Based on the extrapolation of data on the effective dose of melphalan from experiments in rabbits to a human eye model, the dose of melphalan in a single injection was determined to be between 20 and 30 micrograms, depending on the size of the eye. This dosage regimen has been recognized since then [11]. Another therapeutic agent that can be used for intravitreal injections is topotecan. Even though it is less effective against retinoblastoma cells *in vitro* than melphalan, it exhibits reduced toxic effects on the retinal pigment epithelium [12].

**Description of procedure:** Melphalan is injected with a 30-33 G needle through the pars plana (similarly to the administration of anti-VEGF agents). When choosing an injection site, special care should be taken to ensure that it is tumor-free. The activity of melphalan gradually declines after reconstitution, so the injection should be performed as soon as possible after preparation. Most commonly, three to six cycles of injections are given.

**Indications:** active vitreous seeding of retinoblastoma; usually this applies to tumors classified as ICRB groups C, D or E. Intravitreal injections are usually administered after the initiation of systemic or intraarterial chemotherapy in order to minimize the risk of retinoblastoma seeding beyond the eye during injections.

**Complications:** retinal and choroidal atrophy around the injection site, generalized retinal toxicity, sterile inflammatory reaction of the anterior segment of the eye and in the vitreous. *Rare:* retinal atrophy in the posterior pole region (unintentional drug injection into Cloquet's canal), mechanical lens damage, extraocular tumor seeding.

## BICAMERAL INJECTIONS OF MELPHALAN

Bicameral injections (intracameral chemotherapy) are a relatively novel, and not yet widely used, method for the treatment of retinoblastoma seeds in the aqueous humor of the anterior and posterior chambers of the eye. The method was described in detail by Munier in 2017 [13]. Using the technique, it is possible to achieve a sufficiently high concentration of the chemotherapeutic agent (melphalan) in the aqueous humor to obtain a cytotoxic effect of the drug on retinoblastoma cells.

**Description of procedure:** A 34 G needle is inserted through the corneal periphery into the anterior chamber. Complete aspiration of aqueous humor from the anterior and posterior chambers is performed. Without removing the needle, the syringe is exchanged for one containing melphalan at a concentration of 15 μg/ml. In the next step, the drug is administered, with 1/3 of the dose distributed to the anterior chamber, and the remaining 2/3 to the posterior chamber. The volume of drug is the same as the volume of aspirated aqueous humor minus the volume of drug that is later injected into the vitreous. To administer the drug into the posterior chamber, the needle should be passed through the base of the iris in an area which is free of tumor infiltration. Following the injection, as the needle is withdrawn, corneal cryotherapy is applied to the entry site.

Bicameral drug injection should be accompanied by intravitreal injections to prevent bidirectional flow of tumor cells between the posterior chamber and the vitreous. Typically, six rounds of intracameral injections are performed.

**Indications:** retinoblastoma seeds in the anterior and posterior chambers of the eye (classified as the ICRB group E).

**Complications:** cataract, iris stromal atrophy.

## PERIOCULAR CHEMOTHERAPY

Periocular chemotherapy is practically no longer used in view of the availability of advanced chemotherapeutic techniques producing high concentrations of chemotherapeutics in tumors located on the retina (intraarterial chemotherapy) or in the vitreous (intravitreal injections of melphalan). In this form of therapy, the chemotherapeutic agent was administered by periocular injection under the Tenon's capsule. The most commonly used agent was carboplatin [14]. However, in view of high prevalence of topical adverse effects and low efficacy, the method has now been abandoned.

## TRANSPUPILLARY THERMOTHERAPY

Transpupillary thermotherapy (TTT) has been used to treat intraocular tumors for several decades. The energy source is a diode laser emitting electromagnetic radiation with a wavelength of 810 nm (in the infrared range). The target tissue for the energy associated with laser radiation is the retinal pigment epithelium and choroidal melanocytes, where thermal energy is accumulated, inducing a destructive effect on the adjacent cancerous tissues. Thermal energy is delivered in a controlled manner by using low laser power, long exposure time, and large focus size in order to induce tissue hyperthermia rather than coagulation. Tumor tissue is heated to approximately 45-60°C, which induces tumor cell necrosis and closure of blood vessels [14-16]. Laser energy can be delivered to the target tissue using indirect ophthalmoscope, surgical microscope, or transscleral probe. Thermotherapy can be used in conjunction with chemotherapy (so-called thermochemotherapy).

**Description of procedure:** The laser beam is focused directly on the tumor. The procedure is performed until the tumor tissue appears slightly more pale. Since the safety of the procedure requires slow hyperthermia rather than coagulation, the treatment of one small tumor may take up to several minutes.

**Indications:** The method is suitable for the treatment of tumors located on the retina, with diameters of up to 1.5 DD (disc diameter), located both in the posterior pole region and at the extreme periphery of the retina [15, 16]. Transpupillary thermotherapy can be used as a primary treatment for small tumors or consolidation treatment after systemic chemotherapy or IAC. Transpupillary thermotherapy is often used to treat early detected retinoblastoma recurrences after primary treatment.

**Complications:** sectoral iris atrophy, sectoral lens opacity, vitreous seeding of retinoblastoma. *Rare:* corneal haze, vitreous hemorrhage, serous retinal detachment.

## INDOCYANINE GREEN-ENHANCED TRANSPUPILLARY THERMOTHERAPY

Intravenous administration of indocyanine green as a photosensitizer, with an energy absorption peak for an electromagnetic wave of 805 nm, which is similar to the wavelength of a diode laser (810 nm), enhances the effect of laser thermotherapy, and facilitates the treatment of tumors that are larger in size or located on calcifications and in areas of choroidal atrophy – without contact with the retinal pigment epithelium [17].

Indocyanine green-enhanced transpupillary thermotherapy (ICG-TTT) has been used in the treatment of retinoblastoma for over a decade [18, 19, 20]. Before that, it was used in ophthalmology to treat choroidal melanoma and choroidal metastases of breast cancer [21, 22].

**Description of procedure:** It is essentially the same as in TTT. However, immediately prior to the procedure, indocyanine green at a dose of 0.6 mg/kg is administered intravenously.

**Indications:** The method can be used with success in the treatment of retinoblastoma tumors larger than 1.5 DD or located on calcifications. The upper size limit for tumors to be treated with TTT has not been strictly determined as yet. The authors of the present paper have used ICG-TTT to treat tumors with a diameter of 4 DD, achieving a therapeutic success.

**Complications:** similar as in TTT.

## LASER PHOTOCOAGULATION

The role of laser photocoagulation in the focal treatment of retinoblastoma is declining because of the risk of cancer cell seeding into the vitreous following the rupture of the retinal internal limiting membrane. In the past, attempts were made to use laser photocoagulation for creating a double row of coagulation foci around the tumor to suppress its blood supply and shrink its size [14]. With newer models of 532 nm lasers, it is possible to set the minimum power and continuous mode of instrument operation, and direct the focus directly at the tumor surface. Laser photocoagulation is similar to TTT, but an increase in laser power may cause rupture of the retinal internal limiting membrane and induce seeding of cancer cells into the vitreous [14].

## CRYOTHERAPY

Cryotherapy is a commonly used topical treatment for retinoblastoma. It uses extreme cold to freeze an active tumor. Cryotherapy is inexpensive and fast, and its therapeutic efficacy has been repeatedly validated [23-25]. Cryotherapy units use either nitrous oxide or carbon dioxide. The temperature at the applicator tip is approximately –70°C. Cryotherapy produces a direct cytotoxic effect through the formation of ice crystals in the cytoplasm and the disruption of the cell membrane [25].

**Description of procedure:** After locating the tumor using indirect ophthalmoscope, a probe is applied under visual control through the conjunctiva to the sclera where the tumor is located. Three cycles of tumor freezing and thawing are used. The tumor must be completely within the freezing zone.

**Indications:** Cryotherapy is best suited for relatively small tumors (2.5 mm in width × 1 mm in height), located in the region between the equator and peripheral retina. It is also possible to apply cryotherapy in the treatment of tumors located posterior to the equator, after making a conjunctival incision, which facilitates deeper insertion of the cryoapplicator tip (a technique called open cryo). Similarly to TTT, cryotherapy can be used as a primary treatment for small tumors or consolidation treatment after systemic chemotherapy or IAC. Cryotherapy is commonly used to treat retinoblastoma recurrence after primary treatment.

**Complications:** ocular tenderness after the procedure, transient edema of the conjunctiva and eyelids, hemorrhages into the vitreous. *Rare:* serous retinal detachment, retinal tear.

## BRACHYTHERAPY

Brachytherapy is a treatment technique based on direct irradiation of pathological lesions. It involves placing a radiation source directly within or near the site of tumor (or another type of pathological lesion). Brachytherapy is a tumor irradiation technique associated with minimal risk of damaging nearby normal tissues. In ophthalmology, it is most commonly used in the therapy of intraocular tumors such as choroidal melanoma in adults and retinoblastoma in children [26].

Unlike teleradiotherapy (external beam radiation therapy – EBRT), brachytherapy is a technique capable of delivering ionizing radiation precisely to the tumor tissue. Consequently, it does not cause orbital bone deformities in young children and carries a considerably lower risk of second cancers in the treated orbit. This is especially important in patients with the germline RB1 gene mutations who are at risk of developing other cancers over the years. Furthermore, brachytherapy is more effective than EBRT in treating retinoblastoma in selected cases [4].

Currently, ruthenium ($^{106}$Ru) is the most commonly used isotope in Europe, while iodine (125I) is preferred in the USA [28, 29]. $^{106}$Ru emits β particles with a penetration of 10% of the surface dose down to 5-6 mm through water or tissue. $^{106}$Ru plaques are suitable for the treatment of tumors up to 6 mm in thickness because of the strong inhibition of radiation within the tissue [30, 31].

Compared with $^{125}$I plaques, treatment based on 106Ru plaques reduces the dose of radiation delivered to sensitive ocular structures including the lens, macula, and optic disc. Serious complications, such as cataract or optic nerve atrophy, are less common after $^{106}$Ru brachytherapy compared to

$^{125}$I [21, 32]. Another advantage of using ruthenium plaques compared to iodine ones is that the former have a reduced thickness (1 mm vs. 3 mm), which is particularly important in the treatment of infants [33].

**Description of procedure:** Following precise tumor localization using indirect ophthalmoscope and scleral depression, a radioactive plaque is affixed to the sclera using sutures. Where needed, the extraocular muscle is temporarily severed from its attachment (once the plaque is taken out, the muscle is reattached). The plaque is removed after a strictly defined period which depends on plaque activity (the plaque is inactivated; the half-life of $^{125}$I is shorter than $^{106}$Ru) and tumor thickness.

**Indications:** The method is suitable for the treatment of tumors up to 5-6 mm in height (ruthenium plaques) or larger (iodine plaques). Radioactive plaques can also be used to treat vitreous tumor seeds located close to the eyeball wall [25]. In view of associated complications, brachytherapy is generally used as a secondary treatment after other forms of therapy have failed.

**Complications:** neovascularization, vitreous hemorrhage, cataract, radiation retinopathy, and optic nerve atrophy.

## ENUCLEATION

Enucleation is the oldest focal treatment for retinoblastoma. Since modern therapies, both systemic and focal, are now available, enucleation is performed less and less frequently.

**Description of procedure:** The procedure should be performed gently, without applying excessive pressure to the eyeball, so as to reduce the risk of cancer seeding. Enucleation due to retinoblastoma should preferably be done using Foster enucleation snare to sever the optic nerve (Figure 2). The instrument leaves a relatively long stump of the optic nerve, which maximizes the safety of treatment, when optic nerve infiltration is suspected. Whenever possible, children should always receive an orbital implant after eye removal surgery. This provides a markedly better cosmetic outcome by stimulating orbital growth and enables mobility of the epiprosthesis [14, 12]. The implant, made of hydroxyapatite, undergoes some degree of orbital integration, as it becomes overgrown by fibrous tissue and blood vessels from the rectus muscles affixed to it.

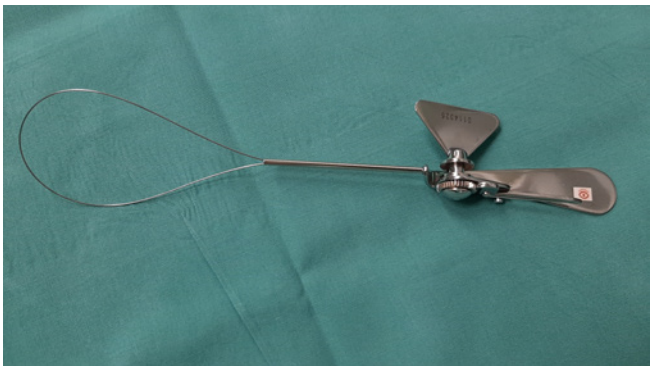

**Figure 2.** Intraarterial chemotherapy. The arrow marks the catheter inserted into the ophthalmic artery

**Indications:** the main indications for enucleation include secondary glaucoma associated with retinoblastoma, confirmed extraocular infiltration of retinoblastoma, and recurrence of retinoblastoma after failure of all previous therapeutic modalities.

**Complications:** Transient tenderness in the orbital region and tissue edema are common. The most dangerous complication is a rupture or puncture of the eyeball during the procedure, which can lead to cancer seeding into the orbit.

## CONCLUSIONS

Currently used therapies for retinoblastoma are associated with very high cure rates. The treatments described above are capable of saving the life, salvaging the eye, and often maintaining useful visual acuity in retinoblastoma-affected children. Treatment takes many months, and various therapies used often need to be repeated. In highly developed countries, the survival rate among treated patients is 95-98% [12]. However, it must be stressed that the observed high level of efficacy is due to the involvement and cooperation of physicians of various specialties including an ophthalmologist, oncologist, radiotherapist, radiologist, interventional radiologist and pathologist.

## DISCLOSURE

The authors declare no conflict of interest.

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