Ocular brachytherapy in the treatment of retinoblastoma. Experience in the Hospital Infantil de México

Braquiterapia ocular en el tratamiento del retinoblastoma. Experiencia en el Hospital Infantil de México

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Abstract

Objective: To describe results and complications of salvage eye treatment with brachytherapy in patients with diagnosis of bilateral retinoblastoma (Rb) and only one eye. **Methods:** Case series where we included all retinoblastoma patients treated with ocular brachytherapy with Iodine-125 at the Hospital Infantil de Mexico after failure of eye salvage with intravenous chemotherapy, focal transpupillary laser or transconjunctival cryotherapy and external beam radiotherapy. **Results:** We analyzed 7 patients, 2 females and 5 males. Two had hereditary retinoblastoma and all had bilateral disease. Mean follow-up after treatment was 5.35 years (range 3.3–11 years). Tumor control was achieved in five of seven patients; two patients undergone enucleation due to failure to achieve tumor control. One of the patients died because of secondary neoplasm. **Conclusions:** Ocular brachytherapy treatment in a tertiary care center offers possibilities of ocular preservation in patients with bilateral Rb and maximum oncological treatment.

Key words: Retinoblastoma. Brachytherapy. Cancer. Acquired blindness. Salvage therapy.

Resumen

Objetivo: Describir los resultados del tratamiento con braquiterapia ocular en ojos únicos en pacientes con retinoblastoma (Rb) bilateral, así como las complicaciones de su uso como tratamiento primario o secundario. **Métodos:** Serie de casos donde se identificaron todos los pacientes con Rb en el Hospital Infantil de México tratados con braquiterapia ocular con yodo-125 como salvamento ocular después del fallo en el control de la neoplasia mediante quimioterapia intravenosa, tratamiento focal con láser o crioterapia y radioterapia externa. **Resultados:** Se incluyeron un total de siete pacientes, dos pacientes eran del sexo femenino, y cinco, de sexo masculino. Dos pacientes tenían Rb hereditario y seis eran bilaterales. Tres de los ojos tratados con braquiterapia eran derechos. El seguimiento promedio de estos pacientes fue de 5.35 años (rango 3.3 a 11 años). El éxito del tratamiento se alcanzó en cinco de los siete pacientes. Dos pacientes fueron enucleados a pesar del tratamiento con braquiterapia por falla en el control de la neoplasia. Uno de los pacientes falleció por neoplasia

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secundaria. Conclusiones: El tratamiento con braquiterapia ocular en un hospital de tercer nivel ofrece posibilidades de preservación ocular en pacientes con Rb bilateral y tratamiento oncológico máximo.

Palabras clave: Retinoblastoma. Braquiterapia. Cáncer. Ceguera adquirida. Terapia de salvamento.

Introduction

Ocular salvage in intraocular retinoblastoma (Rb) is a process that involves the use of several local and systemic treatments to prevent enucleation. Generally it is indicated to perform eye rescue in the less affected eye in those patients with bilateral Rb, or in those cases with tumors confined to the retina and that have not detached the retina more than 3 mm around the lesion and are not accompanied by diffuse vitreous seeding. There are several therapeutic options to control intraocular tumors. The most used focal treatments are cryotherapy¹, direct photocoagulation of the tumor^{2,3}, thermotherapy⁴, external radiotherapy^{5,6} and, more recently, intravitreal chemotherapy injections⁷ and supraselective intra-arterial chemotherapy^{8,9}. All these treatments have complications and sequelae and their use is limited to intraocular tumors. External radiotherapy is another therapeutic option and is indicated when focal treatment is not sufficient to stop the progression of the tumor. However, it is associated with an increased risk of developing new neoplasms other than Rb¹⁰, since the area of the treatment field and, to a lesser extent, the tissues of other parts of the body are exposed to the effects of radiation, which produces changes in the DNA of patients who may have an altered genome¹¹. Focal radiotherapy or brachytherapy is a method that has demonstrated efficacy in the control of intraocular tumors without increasing the risk of secondary neoplasms¹². Likewise, brachytherapy has been used successfully in the control of patients with previously treated Rb with intra-arterial chemotherapy¹³ representing a viable option in the treatment of Rb. In this work we report the experience in the treatment of Rb with brachytherapy in the Ophthalmology department of the Hospital Infantil de México in conjunction with the Cancer Institute of Guatemala.

Patients and methods

Patients with Rb diagnosed at the Hospital Infantil de México treated with ocular brachytherapy and with at least 1 year of follow-up were included. All patients were initially treated in our hospital and were grouped according to the International Classification of Rb¹⁴.

The treatments prior to brachytherapy were individualized. Each patient received a systemic chemotherapy-based treatment with a double or triple scheme at the consideration of the pediatric oncologist. The type of focal treatment and the amount administered was determined by the pediatric ophthalmologist depending on the location, size of the tumor and presence or not of vitreous seedings. The amount of laser applications, cryotherapy, cycles of chemotherapy and external radiotherapy that each patient received are described in Table 1.

Brachytherapy was indicated in those patients for a single eye whose treatment with photocoagulation (810 nm diode laser), transconjunctival cryotherapy, intravenous chemotherapy and even external radiotherapy did not achieve tumor control. It was done following the international standards for equatorial or peripheral tumors whose diameter is less than 15 mm at its base and no more than 10 mm in height^{15,16}. The treatment was performed in Guatemala City by one of the authors (MBP), with the assistance of one of the coauthors (NCLM).

All patients underwent a complete ophthalmological examination that included visual acuity, binocular ophthalmoscopy, ocular ultrasonography and retinal photographs with a RetCam III (Clarity Medical Systems, Pleasanton, Calif). Likewise, all the patients had a complete oncological follow-up that included clinical examinations and orbital and brain imaging with nuclear magnetic resonance to identify intraocular, orbital and intracranial relapses.

The seven patients of our series traveled to Guatemala for the placement of the brachytherapy plaque with their own resources and through donations from various foundations for childhood cancer. The follow-up in all cases was carried out at the Hospital Infantil de México.

All the patients were treated using circular Bebig-type 16-mm diameter plaques (Eckert & Ziegler, Berlin, Germany), with a gold coating and thirteen iodine-125 seeds, with a median activity of 1,858 millicuries per seed. Irradiation was left for 90 hours with a maximum total dose of 89.9 Grays, previously calculated according to tumor size. The iodine-125 seeds were adhered to the internal surface of the plaque according to the planning made by the radiotherapist and prior to the

Table 1. Clinical characteristics of patients with bilateral retinoblastoma treated with ocular brachytherapy

Patient	1	2	3	4	5	6	7
Sex	F	F	M	M	M	M	M
Family history	No	No	No	No	Yes	No	Yes
Age at diagnosis (months)	15	22	14	35	2	20	21
Age at the time of brachytherapy (months)	76	120	56	64	68	36	37
Laser applications	7	4	8	8	10	14	10
Cryotherapy	2	7	0	4	3	0	6
Chemotherapy cycles	8	7	15	6	8	16	10
External radiotherapy	1	2	No	1	1	1	1
Baseline visual acuity	20/30	20/40	20/32	20/60	20/400	20/80	20/100
Final visual acuity	20/40	20/80	20/32	Enucleation	20/400	20/200	Enucleation
Secondary neoplasms	No	No	No	No	No	No	Yes
Follow-up after brachytherapy (months)	134	76	54	53	42	53	39

surgical procedure. Upon compliance with the calculated dose, the iodine-125 implant was removed, with a procedure similar to implantation.

The surgical technique was the following: under general anesthesia after antisepsis of the periorcular region with placement of sterile fields and a blepharostat, the conjunctiva was dissected on the planned area for the placement of the episcleral plaque; indirect ophthalmoscopy with sterile technique and scleral indentation was performed to accurately identify the location of the tumor base; the identified planned area was marked with indelible ink. In case the tumor was below any extraocular muscle, it was disinserted for the adequate conformation of the plaque to the eyeball curvature and precise placement at the base of the tumor. Subsequently, the plaque was sutured to the sclera with Vicryl 6-0, making sure that there was a minimal movement to guarantee the emission of radiation in the planned area and to decrease energy dissipation in healthy retinal areas. Hemostasis was performed by compression with gauze and swabs; Tenon's capsule and conjunctiva were closed with interrupted Vicryl 6-0 sutures. The plaque was maintained during the period calculated for radiation emission (on average 72 h). Once the planned radiation period finished, the plaque was removed through a new surgical procedure, under general anesthesia and with a sterile technique. Finally, if an extraocular muscle had

been disinserted, it was sutured again in its original insertion.

The treatment was defined as a success if complete control and inactivity of the tumor were achieved for one year after initiating brachytherapy. Inactivity criteria were defined by the tumor regression patterns described by Singh¹⁷: type 0, no visible remnant; type I, completely calcified remnant ("cottage cheese" appearance); type II, completely non calcified remnant with grayish translucent tissue ("fish flesh" appearance); type III, a combination of types I and II, and type IV, atrophic chorioretinal flat scar.

The procedures used in all our patients were performed with the authorization of the Ethics Committee of both hospitals and with the informed consent of the parents of the patients.

Descriptive statistics were used to evaluate the results using Excel software.

Results

During the period from 1997 to December 2016, from a database of 406 patients with Rb, seven patients with bilateral disease who were treated with episcleral brachytherapy for rescue of the less affected eye were identified. The average age at the time of brachytherapy was 5.3 years (range: 3 to 10 years). The indication for treatment with ocular brachytherapy was decided

after failure to control the tumor despite focal and systemic treatment. Two patients were female. Twenty-five percent of the patients had familial Rb. All patients had a previous history of chemotherapy with a combination of carboplatin, etoposide and cyclophosphamide. The average time from diagnosis of Rb to plaque placement was 3.8 years (range 1.3 to 8 years). The average follow-up of this patients was 5.35 years (range 3.3 to 11 years). [Table 1](#) depicts the general characteristics of the patients studied.

Regarding the characteristics of the tumors, [Table 2](#) shows the measurements, locations, presence or absence of vitreous seedings, as well as the preoperative clinical photographs in the last follow-up of each of the seven patients included in this study.

Treatment success was achieved in five of seven patients (71.4%). In two patients the tumor was not controlled, so they had to undergo enucleation; one of them died due to a secondary neoplasia in the paranasal sinuses.

Five patients had complications and all of them received previous treatment with external radiotherapy. The most frequent complication was post-radiation cataract (28.6%), while post-brachytherapy hemorrhage, post-radiation maculopathy and severe dry eye occurred in one case each, with a frequency of 14.3%. The two patients who developed post-radiation cataract were treated with phacoemulsification and intraocular lens implantation, and showed a final visual acuity of 20/40 and 20/200, respectively. The patient with post-brachytherapy hemorrhage showed resolution with conservative treatment, with a final visual acuity of 20/32. Radiation maculopathy was successfully treated with three applications of intravitreal antiangiogenic therapy (bevacizumab). Currently, this patient has a visual acuity of 20/80. The patient who developed severe dry eye did not respond to replacement with artificial tears and lacrimal plugs, developing partial corneal opacity and superficial corneal vascularization. His final visual acuity was 20/400. [Table 3](#) describes the complications developed in our series.

Discussion

Brachytherapy is a treatment modality for intraocular cancer that has been used for the treatment of Rb for almost a century¹⁸. Its use has been extensive in the most important referral centers worldwide, and different reports have been published on its effectiveness¹⁹⁻²¹. Most of the world's referral centers use iodine-125; however, ruthenium has also demonstrated efficacy for controlling this neoplasm²².

Table 2. Morphological characteristics of the tumors of patients treated with ocular brachytherapy with iodine-125 for ocular salvage

Patients	1	2	3	4	5	6	7
Baseline (mm)	3 x 3	4.5 x 3	6 x 6	4.5 x 6	9 x 18	4.5 x 6	15 x 9
Height (mm)	3	3	3	3	4	3	4
Vitreous seedings	No	No	No	Yes	No	No	Yes
Location	Peripheral	Peripheral	Peripheral	Peripheral	Macular	Equatorial	Peripheral
Pre-treatment
Post-treatment

Table 3. Ocular complications in patients treated with ocular brachytherapy with iodine-125 for ocular salvage

Complication	N (%)
Cataract	2 (28.6)
Retinal hemorrhage	1 (14.3)
Radiation maculopathy	1 (14.3)
Severe dry eye	1 (14.3)

As a primary treatment, radiotherapy plaque offers up to 88% success in tumors no larger than 15 mm in their base and 9 mm in thickness, and with absent or minimal vitreous seedings²¹. If secondary treatment is used in recurrent tumors or after failure of other treatments, such as the patients in this series, radiotherapy plaques offer a 92% rate of tumor control after focal laser treatment or cryotherapy, 92% after chemoreduction, 75% after external radiotherapy and 66% after chemoreduction and external radiotherapy²⁰. In our series, we had an eye salvage of 71.4%, since two treated eyes did not respond to treatment and had to be enucleated. Likewise, the effectiveness of brachytherapy has been reported to persist despite previous focal treatments²³.

The American Society of Brachytherapy Guidelines for the treatment of Rb recommend the use of this method as a secondary treatment after the failure of focal and systemic treatment¹⁵. They also establish that the tumors ideal for this treatment are those located anterior to the equator. In our series, five of the seven patients met this criterion.

In a series of 208 cases, Shields, et al. reported the following complications in patients with secondary treatment: cataract (31%), proliferative retinopathy (20%), papillopathy (21%), non-proliferative maculopathy (12%), proliferative maculopathy (10%) and glaucoma (7%)²¹. In our series, cataract was the most frequent complication, since it was present in all patients with a history of external radiotherapy, followed by non-proliferative maculopathy, vitreous hemorrhage and severe dry eye. The occurrence of radiation maculopathy has been reported in patients even after 40 years of treatment²⁴, so it is possible that this complication appears in more patients in our series with a longer follow-up.

The tumors that responded optimally to treatment were those with peripheral location, small size (base and height less than 6 mm) and without vitreous seedings;

being the cases 1, 2 and 3 those with a better final visual acuity, with 20/40, 20/80 and 20/30, respectively.

In our series, we had two cases of treatment failure with the use of focal radiotherapy. During the follow-up period, two enucleations were performed on the eyes previously treated with this method. The first patient was enucleated 2 months after receiving brachytherapy since the tumor and vitreous seedings progressed despite treatment. The second patient was enucleated 1 year and 8 months after brachytherapy due to lack of control of tumor activity despite multiple focal and systemic treatments. This patient died of a second neoplasm 3 years and 10 months after brachytherapy.

Despite the benefits of this treatment, in Mexico there is very limited access to brachytherapy for different intraocular tumors in adults, and there are still no reports of the results due to the short time it has been used. In public pediatric hospitals in our country, there are not enough economic and infrastructure resources to implement brachytherapy as a routine treatment in patients with Rb. The incorporation of this treatment in national referral hospitals will provide additional alternatives to patients with aggressive Rb that cannot be controlled with supraselective intra-arterial chemotherapy¹³.

In conclusion, the application of ocular brachytherapy in a tertiary referral hospital offers the possibility of ocular preservation in certain patients with good visual acuity that failed maximum oncological treatment. Eye salvage in patients with Rb is a very long, complex and expensive process. In addition, it requires the intervention of a multidisciplinary medical team and different treatment options that allow avoiding the loss of the eyeball without putting the patient's life at risk.

Conflicts of interest

The authors declare no conflicts of interest.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

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