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Original Article

Episcleral Iodine-125 radioactive plaque brachytherapy as a salvage treatment for retinoblastoma in the era of intra-arterial chemotherapy

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ABSTRACT

Background. Retinoblastoma shows high rates of recurrence after initial chemotherapy (systemic or intra-arterial). Our aim was to evaluate the effectiveness of iodine-125 radioactive plaque brachytherapy as a salvage treatment with globe-preserving attributes after initial chemotherapy in patients with intraocular retinoblastoma.

Methods. The effect of brachytherapy was investigated retrospectively in 17 eyes of 17 patients who were followed up due to retinoblastoma between May 2012 and June 2018 and who received iodine-125 radioactive plaque brachytherapy as a salvage treatment after systemic or intra-arterial chemotherapy. The regression, ocular toxicity, and enucleation rates were evaluated at the end of the follow-up period.

Results. The tumor locations were post equator, macular, anterior to the equator, and peripapillary in 5, 3, 7, and 2 patients, respectively. Regression was initially and rapidly observed in 17 of the 17 eyes that underwent brachytherapy. Enucleation was performed in 5 (29.42%) of these patients due to recurrence with diffuse tumor involvement, and 4 of the tumors were located anterior to the equator. In 12 (70.58%) patients, the eyes were protected from enucleation following local brachytherapy.

Conclusions. Radioactive plaque brachytherapy can be applied as an effective salvage therapy with successful results in retinoblastoma patients who have received initial systemic or intra-arterial chemotherapy. Post equator-located solitary tumors have the highest success rate.

Key words: retinoblastoma, cancer, eye, brachytherapy, iodine-125.

Retinoblastoma, which can occur unilaterally or bilaterally, is the most common intraocular malignancy of childhood, constituting 11% of all cancers in the first year following birth and 3–4 % of all pediatric cancers.[1-3] The annual global incidence of retinoblastoma is 1 in 15,000–20,000 live births, and about 8000 new cases occur each year.[2] A study in the United States determined a 10-year survival rate of 90.3% in patients with bilateral retinoblastoma and 96.1% in those with unilateral retinoblastoma.[4] In a study conducted in Turkey, the 10-year survival rate of patients with unilateral retinoblastoma were found to be 90.74%, with 87.35% in bilateral cases.[5] Another study from a tertiary referral center in Turkey reported a 96.1% survival rate in a 20-year period.[6] In less developed countries, the 5-year survival rate is lower as 60.2%.[7]

The treatment methods include chemotherapy (intravenous, intra-arterial, intravitreal, periocular), focal therapies (thermotherapy, photocoagulation, cryotherapy, brachytherapy), external beam radiotherapy, and enucleation. With recent increases in treatment options, eye protection has become an important goal.[8,9] Selecting the appropriate treatment is determined by considering the size of the tumor,

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whether it is unilateral or bilateral, macular involvement, the tumor's relationship with other tissues such as the optic disc, choroid, and sclera, the patient's age and general health status, and the family's wishes.[10,11] In recent years, recurrences after previous systemic or intra-arterial chemotherapy are generally managed by intra-arterial chemotherapy as a salvage treatment.[12,13] However, vascular complications from intra-arterial chemotherapy can cause total visual loss and can therefore be devastating, particularly in patients where this is the only seeing eye.[14]

Our aim was to evaluate the effectiveness of iodine-125 plaque brachytherapy as a salvage treatment in patients with recurrences after systemic or intra-arterial chemotherapy and to emphasize its role, particularly in patients' whose parents are concerned about the vascular complications of intra-arterial chemotherapy.

Material and Methods

Following the approval of the local ethics committee (Cerrahpaşa School of Medicine Ethic Committee reference no.: E-83045809-604.01.02-35245), the effect of brachytherapy was investigated retrospectively in 17 eyes of 17 patients who were followed-up due to intraocular retinoblastoma at a tertiary clinic between May 2012 and June 2018. The patients' files were reviewed, and the patients who had received iodine-125 radioactive plaque brachytherapy as a salvage treatment for tumor recurrence after the completion of primary systemic or intra-arterial chemotherapy were enrolled in the study. The data were collected from the patients' files and included the patient's gender, age at the time of brachytherapy, laterality of the tumor, and tumor classification according to the International Classification of Retinoblastoma. Any treatments prior to brachytherapy were noted. The tumor response (regression or recurrence), need for enucleation, radiation-related complications, metastasis, and fatal events were evaluated at the end of the follow-up period. Recurrences were defined as the progression of the main tumor and the occurrence of a new tumor (aside from the main tumor) that could not be managed by cryotherapy or laser. Regression was defined as a decrease in the tumor basal diameter and thickness and the inactivation of the tumor. The regression and enucleation rates evaluated at the end of the follow-up period were the main outcomes.

An individualized brachytherapy plan was generated for each patient. Tumors adjacent to the optic disc (peripapillary; Figures 1 and 2) were managed with notched plaques. The maximum tumor diameter and distance from the inner sclera were used for treatment planning. The prescription dose was 45–50 Gy to the prescription point, which was defined as the tumor distance from the inner sclera plus 1 mm to account for scleral thickness. The mean dose was 70.04 cGy per hour, and the mean duration of the brachytherapy was 68.8 hours. The plaque diameter was chosen based on the largest diameter of the tumor and included a lateral margin of 2 mm around the target. All episcleral plaques were inserted under general anesthesia following careful tumor localization by indirect ophthalmoscopy and temporary disinsertion of the extraocular muscles, if required. The plaques were temporarily affixed to the globe with nonabsorbable sutures and subsequently removed under general anesthesia after delivery of the prescribed radiation dose based on the calculated treatment time. The iodine-125 sources (Eckert & Ziegler BEBIG, Berlin, Germany) were loaded in Collaborative Ocular Melanoma Study type plaques (Eckert & Ziegler BEBIG, Berlin, Germany).

Before and after the application of the radioactive plaque, the patients were regularly examined under general anesthesia in operating room conditions at intervals of 3–4 weeks, and the images were recorded using a Retcam® (Clarity Medical Systems, Inc., Pleasanton, CA). The radioactive plaque treatments were all performed by the same surgeon (AS), who also conducted the regular examinations.

The statistical analysis was performed using SPSS version 21.0. The descriptive statistics were expressed as mean ± standard deviation for the continuous data, and the categorical variables were presented as percentages. The globe salvage rates were assessed using the Kaplan–Meier survival analysis method.

Results

The 17 patients who received plaque brachytherapy included 11 (64.7%) boys and 6 (35.3%) girls with a mean age of 32 ± 10.3 months (range, 24–56 months) at the time of the radioactive plaque application. The mean interval between the first diagnosis and the radioactive plaque application was 21 ± 10.83 months (range: 10–48 months). The mean post-brachytherapy follow-up time was 23 ± 17.11 months (range, 6–50 months). The tumor locations were post equator, macular, anterior to the equator, and peripapillary in 5, 3, 7, and 2 patients, respectively. The tumors were classified as group B in 5 (30%) eyes, C in 1 (5%) eye, and D in 11 (65%) eyes (Table I). Thirteen (76%) of the 17 patients had bilateral retinoblastoma, and all these patients had previously received systemic chemotherapy. Four of the 13 patients with bilateral retinoblastoma had had the other eye enucleated. Nine patients had received intra-arterial chemotherapy as a salvage treatment before the plaque treatment. Two patients underwent plaque brachytherapy for the same eye for different tumors. Initial regression was observed in 17 of the 17 eyes that underwent brachytherapy (Figures 1-4). Enucleation was performed in 5 (29,42 %) of these patients due to diffuse tumor recurrence. In total, globe salvage was ensured in 12 (70.58%) eyes among the 17 patients after brachytherapy (Figures 1-4). The local control rate was 70.58 % at 2 years (Figure 5). In all the patients who required enucleation, the surgery was performed within the first 6 months of therapy. Two (11.76%) patients developed cataract, and 2 (11.76%) had radiation maculopathy after treatment. One patient who

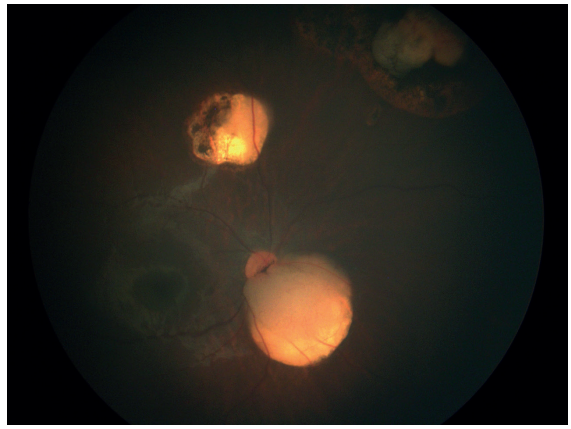

Fig. 1. Patient 1 peripapillary tumor recurrences after systemic chemotherapy.

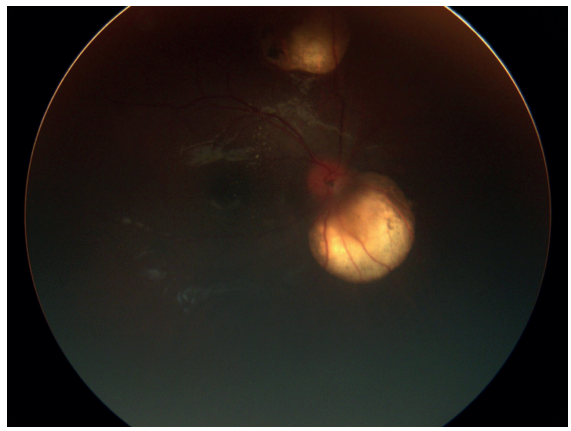

Fig. 2. The tumor was successfully treated by notched iodine-125 plaque brachytherapy.

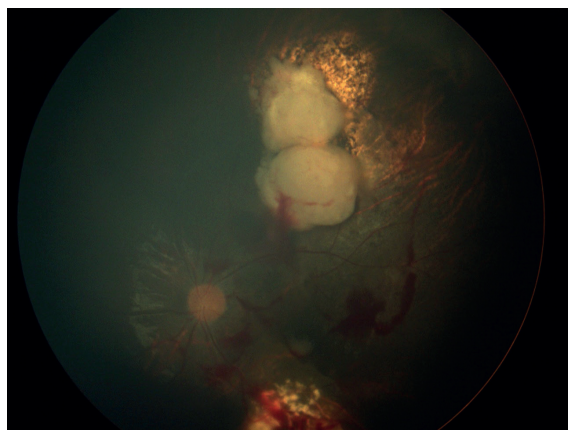

Fig. 3. Patient 12, tumor recurrences beneath to the previous scar. The fellow eye was enucleated.

Table I. Tumors demographic features, previous treatments and brachytherapy results case by case.

Patients' demographics							Treatment			Follow-up (mo)		
Patient no	Age @treatment (mo)	Gender	OD / OS / OU	Stage of treated eye	Stage of fellow eye ICRB	Tumor location	Systemic chemotherapy	IAC	IVC, no	Brachytherap time from dx	Post op	Enucleation
1	24	M	OU	OD/D	B	peripapillary	yes	no	no	19	42	-
2	22	F	OU	OD/B	B	macular	yes	no	no	16	24	-
3	38	M	OU	OD/D	enucleated	post equatorial	yes	no	no	28	44	-
4	32	F	OS	OS/B	Normal	peripapillary	yes	yes	no	26	16	-
5	56	F	OU	OD/D	B	pre equatorial	yes	yes	yes ,2	48	4	+
6	58	M	OD	OD/C	Normal	pre equatorial	yes	no	yes ,2	46	18	-
7	36	M	OU	OS/D	B	post equatorial	yes	yes	yes,2	14	6	+
8	32	M	OD	OD/D	Normal	pre equatorial	yes	yes	yes,3	18	16	-
9	24	F	OU	OD/B	B	macular	yes	yes	no	14	24	-
10	30	M	OU	OD/D	B	pre equatorial	yes	yes	yes,3	10	4	+
11	36	M	OU	OD/B	D	post equatorial	yes	no	no	24	46	-
12	24	M	OU	OS/D	enucleated	post equatorial	yes	yes	yes,1	14	34	-
13	30	F	OU	OD/D	B	pre equatorial	yes	no	yes,3	16	4	+
14	28	M	OU	OS/B	enucleated	macular	yes	yes	no	18	46	-
15	26	M	OU	OD/D	enucleated	pre equatorial	yes	no	no	16	50	-
16	26	F	OD	OD/D	Normal	pre equatorial	yes	yes	yes,4	14	4	+
17	34	M	OU	OS/D	B	post equatorial	yes	yes	yes,2	16	12	-

OD: Right eye, OS: Left eye, OU: Both eyes mo: months
ICRB: intraocular classification of retinoblastoma; IAC: intra-arterial chemotherapy, IVC: intravitreal chemotherapy, RAP: radioactive plaque brachytherapy Post op: Post operation after plaque brachytherapy, Enuc: enucleation

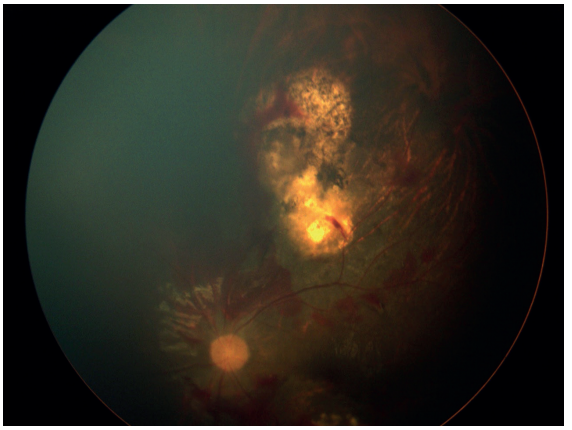

Fig. 4. The tumor totally regressed after iodine-125 plaque brachytherapy.

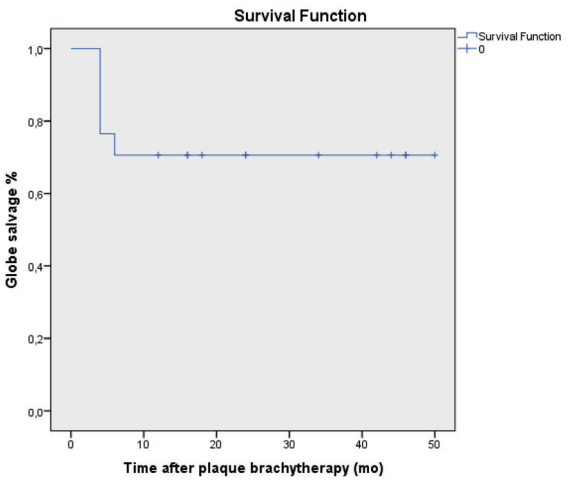

Fig. 5. Kaplan-Meier analysis of globe salvage.

had high risk factors pathologically was lost during follow-up after enucleation. They had subsequently developed metastasis and died 6 months after enucleation.

Discussion

The primary goal in the treatment of retinoblastoma is to ensure survival and, if possible, to protect the eye. The success of globe-protecting treatment has increased with the introduction of localized therapies such as intra-arterial chemotherapy and intravitreal chemotherapy following reduction with systemic chemotherapy.[10,11]

In their 1993 study, Hernandez et al. mentioned plaque brachytherapy as an effective primary treatment modality as well as in cases where other modalities had failed.[15] In recent years, several reports have shown that brachytherapy is still on the agenda of ocular oncologists in the era of intra-arterial chemotherapy. In the study conducted by Echegaray et al. in 2019, only 2 of their 11 patients who received brachytherapy had recurrence.[16] In that study, both recurrent eyes were identified as Group D tumors. No recurrences were observed in the Group A, B, or C patients. In our study, no recurrence was observed in either the Group B or C tumors, whereas recurrence was seen in the Group D patients. Eye preservation was achieved with brachytherapy in 12 (70.58%) eyes of the 17 patients in our study, all of whom had already received intra-arterial chemotherapy or systemic chemotherapy. In their study, Francis et al. reported their brachytherapy results as a salvage/adjuvant following intra-arterial chemotherapy for intraocular retinoblastoma and concluded that brachytherapy was effective after intra-arterial chemotherapy.[17]

We had a high success rate with the group B and C tumors in our study. Recurrences after plaque brachytherapy were seen in the group D tumors located anterior to the equator and were eventually enucleated. Solitary tumors with no previous intravitreal chemotherapy (IVC) or tumors that had received limited IVC had a higher success rate. We observed that the failed group consisted of tumors that responded very well to the initial therapy but had a diffuse endophytic recurrence early within the first year following brachytherapy. The other risk factor was previous IVC. We concluded that the eyes that had produced vitreous or subretinal seedings were more prone to failure after brachytherapy.

We preferred brachytherapy over intra-arterial chemotherapy in the patients whose fellow eyes were already enucleated and had solitary recurrences. Stathopoulos et al. reported a

17% risk of acute choroidal ischemia after intra-arterial chemotherapy, and one third of these patients in their study developed total visual loss.[14] Shields et al. also detected retinal vascular abnormalities at a rate of 13% and choroidal vascular abnormalities at a rate of 11% by fluorescein angiography after intra-arterial chemotherapy.[18] Our main concern was potential severe vascular (e.g., total ophthalmic artery occlusion) complications as a result of intra-arterial chemotherapy in the only seeing eye. In our opinion, radiation complications can be more easily managed than severe vascular complications following intra-arterial chemotherapy in patients who have only one functional eye. Although it is very well known that external beam radiotherapy increases secondary cancer risk in retinoblastoma patients, there have been no reports of secondary cancer after radioactive plaque brachytherapy.[19,20] In our study, we did not observe any secondary cancer following brachytherapy.

Among our patients, two (11.76%) developed cataract, and two (11.76%) had radiation maculopathy. Abouzeid et al. reported only one case of radiation retinopathy in their patients who received an average dose of 50 Gy to the tumor apex using Ru-106.[21] Echegaray et al. confirmed a rate of 18% for non-proliferative retinopathy and 9% for cataract after a mean apical dose of 44 Gy.[16] Our apical radiation dose (45–50 Gy) was similar to that used in those studies, with similar results. Clinicians should therefore follow up if the development of radiation retinopathy side effects is suspected in these patients.

The weakness of our study was its retrospective design. However, in the management of retinoblastoma, the treatment modality is decided individually and based on many different parameters, such as patient age, the condition of the fellow eye, and previous treatment responses. Because of this, even if a treatment protocol has been established, the tumor response can affect the treatment choice dynamically.

A strength of our study was that each patient's follow-up was undertaken by the same experienced ocular oncologist and recorded in detail to allow the collection of homogenous data that could be analyzed without any bias. This further provided a standard evaluation of each patient. An additional strength was the relatively long mean follow-up (almost 2 years) after radioactive plaque treatment.

In conclusion, radioactive plaque brachytherapy can be applied as an effective treatment option with successful results in retinoblastoma patients who have received systemic or intra-arterial chemotherapy prior to brachytherapy. Our results were similar to those of previous reports. Plaque brachytherapy can be used not only in Group A and B tumors, but also in advanced tumors as a globe-saving procedure. Tumors located in the post-equatorial region in our study responded with a high success rate. Eyes with anteriorly located recurrences and eyes that had previously had multiple IVC to control seedings had a lower chance of treatment success with brachytherapy. Solitary tumors located posteriorly were the best candidates for brachytherapy, and brachytherapy can thus be recommended to patients' parents who are concerned about the vascular complications of intra-arterial chemotherapy.

Ethical approval

Following the approval of the local ethics committee (Cerrahpaşa School of Medicine Ethic Committee reference no.: E-83045809-604.01.02-35245).

Author contribution

The authors contribution to the paper as follows: study conception and design: AMS, AŞ, ÖU; data collection: BBO, AŞ; analysis and interpretation of results: AMS, TTC, DU; draft manuscript preparation: AMS, AŞ, TTC, ÖU. All authors reviewed the results and approved the final version of the manuscript.

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Conflict of interest

The authors declare that there is no conflict of interest.

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