Original Article

Brachytherapy of intra ocular tumors using 'BARC I-125 Ocu-Prosta seeds': An Indian experience

Vikas Khetan[1], Lingam Gopal[1,2], Mahesh P Shanmugam[3], Aditi Gupta[1], Tarun Sharma[1], Pramod Bhende[1], Siva Muthukumar[4], R Subramaniam[5], Thayalan Kuppuswamy[6], SK Saxena[7], Ashutosh Dash[7]

Aim: To report our experience of brachytherapy using 'BARC I-125 Ocu-Prosta seeds' for the management of intraocular tumors with regard to tumor control, globe preservation visual outcome, and patient survival at Sankara Nethralaya, Chennai, India between September 2003 and May 2011. **Materials and Methods:** We reviewed records of 35 eyes of 35 patients who underwent ophthalmic brachytherapy between September 2003 and May 2011. Twenty-one cases had choroidal melanoma, nine had childhood retinoblastoma, two had adult-onset retinoblastoma, and there were one case each of vasoproliferative tumor, retinal angioma, and ciliary body melanoma. Brachytherapy was administered using a 15- or 20-mm gold plaque with or without a notch. Brachytherapy was the primary treatment modality in all tumors other than retinoblastoma, wherein brachytherapy was done post chemoreduction for residual tumor. **Results:** For choroidal melanomas, the mean radiation dose was 68.69 ± 15.07 (range, 47.72-94.2) Gy. The eye salvage rate was 13/20 (65%) and tumor control rate was 16/20 (80%) at an average follow-up of 24.43 ± 24.75 (range, 1.5-87.98) months. For retinoblastoma, the mean dose was 45.85 ± 3.90 (range, 39.51-50.92) Gy. The eye salvage rate and tumor control rate was 5/6 (83.3%) at an average follow-up of 38.36 ± 31.33 (range, 4.14-97.78) months. All eyes with retinoblastoma needed additional focal therapy for tumor control and eye salvage. **Conclusion:** The results of this retrospective study confirms that the use of 'BARC I-125 Ocu-Prosta seeds' in episcleral plaques to treat intraocular tumors offers a viable option for the management of intraocular cancers.

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Episcleral plaque brachytherapy containing sealed radioisotope sources has gained substantial popularity as one of the main treatment modalities for intraocular tumors given its potential for preservation of vision and the eye. Being conformal; it concentrates the radiation within the targeted zone and reduces the amount of energy delivered to normal structures, with limited or no radiation exposure to the other eye.[1-2]

Uveal melanoma is the most common primary intraocular malignancy in the Caucasian population and is infrequently seen in non-white races. India enjoys a low incidence of malignant melanoma of the uveal tract. The most common location for this type of cancer to develop is the choroid.

Retinoblastoma is a relatively uncommon tumor of retina, occurring in babies and children younger than 15 years of age. In both cases where the tumor is intraocular, patients with these diseases may not recognize its presence until the tumor grows to a size that impairs vision by obstruction, retinal detachment, hemorrhage, or other complications. Before the development of modern eye conserving treatment modalities, enucleating was historically the mainstay of treatment for these cancers.[3]

Many patients with uveal melanoma have a reasonable chance of surviving and retaining the eye with good vision. Retinoblastoma is most often a curable cancer with >90% of the children surviving the disease with a large number of them retaining the eye if detected early. Therefore, it is important to identify these lesions and begin treatment early.

Titanium encapsulated ^{125}I seeds containing 74-185 MBq (2-5 mCi) activity is currently the most commonly used isotope for plaque radiotherapy. In this communication, we describe our initial experience in episcleral plaque brachytherapy using 'BARC I-125 Ocu-Prosta seeds' for the treatment of intraocular tumors at our center. The way these seeds are made has been published earlier.[4]

Materials and Methods

This is a retrospective study of all patients that underwent brachytherapy for intraocular tumors at one tertiary care center.

Dosimetry (dose calculation)

Precise dosimetry is crucial in terms of the risk for normal tissue toxicity as well as tumor dose prescription. Dose calculation was done using the plaque simulator software version (Bebig GmbH, Berlin, Germany). In order to perform the dose calculation, our initial effort was focused towards the modeling of the eye by making use of computerized tomography or magnetic resonance imaging data of axial cut from the center

[1]Departments of Ocular Oncology and Vitreoretinal Services, Sankara Nethralaya, Chennai, Tamil Nadu, India, [2]Ophthalmology, National University Hospital, Singapore, [3]Ocular Oncology and Vitreoretinal Services, Sankara Eye Hospitals, Bangalore, Karnataka, [4]Chief Medical Physicist, [5]Consultant Radiation Oncologist, Dr. Rai Memorial Cancer Institute, [6]Consultant Medical Physicist, Dr. Kamakshi Memorial Hospital, Chennai, Tamil Nadu, [7]Radiopharmaceuticals Division, Bhabha Atomic Research Center, Mumbai, Maharashtra, India

Correspondence to: Dr. Vikas Khetan, Department of Ocular Oncology and Vitreoretina, Sankara Nethralaya, 18, College Road, Chennai - 600 006, Tamil Nadu, India. E-mail: drvk@snmail.org

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of the eye. Subsequently, modeling of the tumor was performed using the ultrasound. The longitudinal, circumferential, and apical diameters data were fed into the software. The fundus image is next uploaded on the software to obtain a graphic representation that provide information about the exact tumor location and also the exact distance from optic disc to fovea. Based on the information availed, the prescription point is defined as the tumor apex if the apical height exceeds 5 mm, and 5 mm depth from the interior sclera if the apex is less than 5 mm high. The number of seeds for a particular tumor and their placement on the plaque was decided upon by the dosimetry program based on the available radioactivity of each seed. The diameter of the tumor treated decided the diameter of the plaque used which was at least 2 mm larger than the tumor diameter. The planning was done along with a radiophysicist and a radiation oncologist. The average dose rate in our study was with a prescription dose of 40-90 Gy (depending on the tumor) delivered in 5-10 consecutive days.

^{125}I sources

'BARC I-125 Ocu-Prosta seeds' consisting of ^{125}I source of dimension 4.75 mm (l) × 0.8 mm (ϕ) encapsulated in titanium capsules [Fig. 1] after quality assurance tests[5] were supplied by Radiopharmaceuticals Division of Bhabha Atomic Research Center, Mumbai (BARC).[6,7] Precise individual seed activity is a prerequisite for accurate dose calculations. In order to preclude dosimetric errors in the treatment planning study, seeds from only one batch were used in each case.

Selection of plaques

We used gold plaques of various sizes depending on the size and location of the tumor.

Preparation of plaque

Plaque preparation was carried out on the previous day of surgery. The number of seeds and their pattern and location on the plaque was dictated by the tumor location and configuration. After the completion of basic dosimetry, a customized configuration containing appropriate number of radioactive seeds (typically eight to 15) were glued on to the plaque using cyanoacrylate glue to achieve a desired localized radiation delivery to the tumor. The typical activity used is were 74-111 MBq (2-3 mCi) per seed so as to achieve treatment dose rates of 0.5-1.25 Gy/h, with a prescription dose of 40-90 Gy (depending on the tumor) delivered in 5-10 consecutive days. Seed positioning was straightforward as seeds were manufactured to conform dose requirement.

Surgical procedure

The surgery was performed under peribulbar/retrobulbar anesthesia for adult patients and under general anesthesia for children. The technique of surgery is well-described and is done routinely at major ocular oncology centers and hence not discussed in detail in this article.

Results

Between September 2003 and May 2011 the procedure of I-125 brachytherapy using BARC Ocu-prosta seeds was performed for 35 eyes of 35 patients at Sankara Nethralaya, Chennai, India. The type of tumor along with baseline tumor size is depicted in Table 1.

Overall, five patients (14.29%) were lost to follow-up.

Nine eyes underwent enucleation, thus, yielding an overall globe salvage rate of 26/35 (74.29%). Out of nine; five eyes (three having choroidal melanoma and one having retinoblastoma) were enucleated for persistent tumor growth, one eye with adult-onset retinoblastoma for late recurrence of tumor, and three eyes with choroidal melanoma for complications of radiation retinopathy. The mean duration of enucleation from brachytherapy was 4.72 ± 2.38 (range, 1.48-6.74) months for five eyes with persistent tumor growth, 50.6 months for one eye with late recurrence of tumor, and 28.10 ± 9.23 (range, 18.67 to 37.12) months for three eyes with radiation retinopathy.

Choroidal melanomas

Twenty-one eyes of 21 patients underwent brachytherapy for choroidal melanoma. The group comprised 10 females and 11 males. The mean age was 41.57 ± 12.48 (range, 24-63) years, the mean follow-up duration was 24.43 ± 24.75 (range, 1.5-87.98) months, and the mean dose to the apex was 68.69 ± 15.07 (range, 47.72-94.2) Gy. Mean tumor radial diameter was 10.17 ± 2.64 (range, 6.9-15.15) mm; mean tumor

Table 1: Baseline data of the study eyes

	Mean±SD or *n* (%)			VPT *n*=1	Retinal angioma *n*=1	CB melanoma *n*=1
	Choroidal melanoma *n*=21	Retinoblastoma *n*=9	Adult-onset retinoblastoma *n*=2			
Age (years)	41.57±12.48	1.56±1.10	49.00±22.63	42	26	41
Gender						
Male	11 (52.38)	5 (55.56)	1 (50)	0	1	0
Female	10 (47.62)	4 (44.44)	1 (50)	1	0	1
Follow-up (months)	24.43±24.75	38.36±31.33	29.16±32.31	39.29	33.8	24.3
Radiation dose (Gy)	68.69±15.07	45.85±3.90	38.10±3.06	40.88	46.19	63.81
Tumor dimensions (mm)						
Radial	10.17±2.64	7.23±2.33	8.94±0.17	11.5	6.7	10.5
Height	6.44±1.68	3.74±1.41	5.73±1.87	3.4	3.6	7
Circumferential	10.15±2.64	9.12±3.04	7.69±3.66	8.1	6.7	7.3

SD: Standard deviation, VPT: Vasoproliferative tumor, CB: Ciliary body height was 6.44 ± 1.68 (range, 2.8-9.2) mm; and mean tumor circumferential diameter was 10.15 ± 2.64 (range, 5.6-16.03) mm. One patient was lost to follow-up. Thus, further analysis was done for 20 patients. Thirteen of the 20 eyes could be salvaged with brachytherapy (65%). Seven eyes underwent enucleation, four for persistent tumor growth as noted on B-scan; and three for severe radiation retinopathy. Overall, the tumor control rate was 16/20 (80%), since three eyes were lost due to radiation-induced complications, the tumor itself showing reduction in size. Exenteration was performed in one orbit 10 days after enucleation when the enucleated specimen on histopathological examination showed evidence of extraocular spread in the form of presence of tumor cells in episclera overlying the tumor. Figs. 2-4 showing a case of choroidal melanoma pretreatment, posttreatment, and last follow-up showing signs of radiation retinopathy.

For retinoblastoma, brachytherapy was used as a part of multimodal treatment, in eyes where single active tumor was remaining after chemoreduction. Brachytherapy was performed for nine eyes of nine patients. This group comprised four females and five males. The mean age was 18.78 ± 13.14 (range, 1-48) months. The mean follow-up duration was 38.36 ± 31.33 (range, 4.14-97.78) months. The mean radiation dose was 45.85 ± 3.90 (range, 39.51-50.92) Gy. Mean tumor radial diameter was 7.23 ± 2.33 (range, 4.3-12.13) mm; mean tumor height was 3.74 ± 1.41 (range, 2.3-6.1) mm; and mean tumor circumferential diameter was 9.12 ± 3.04 (range, 5.0-12.33) mm. Three patients were lost to follow-up. Thus, further analysis was done for six patients. The eye salvage rate was 5/6 (83.3%). One eye underwent enucleation for persistent tumor growth after 6 months. All five eyes required additional focal therapy for complete tumor regression and one eye underwent scleral buckling surgery for rhegmatogenous retinal detachment. Figs. 5 and 6 showing a case of retinoblastoma pre- and posttreatment.

Adult-onset retinoblastoma

Brachytherapy was performed for two eyes of two patients (one female and one male). Female patient was 33 years; whereas, the male patient was 65-years-old. One patient was lost to follow-up after 6 months and hence not included in analysis. The mean dose was 38.10 ± 3.06 (range, 35.90-40.23) Gy. Mean tumor radial diameter was 8.94 ± 0.17 (range, 8.82-9.06) mm; mean tumor height was 5.73 ± 1.87 (range, 4.4-7.05) mm; and mean tumor circumferential diameter was 7.69 ± 3.66 (range, 5.1-10.27) mm.

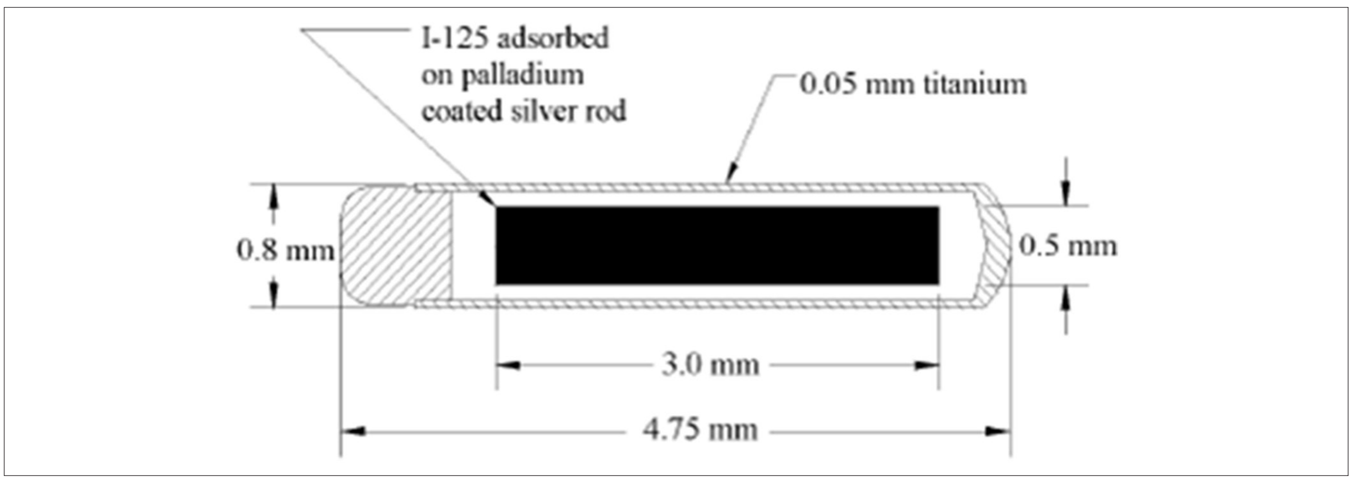

Figure 1: Titanium encapsulated I-125 seed

Figure 2: A case of choroidal melanoma pre treatment

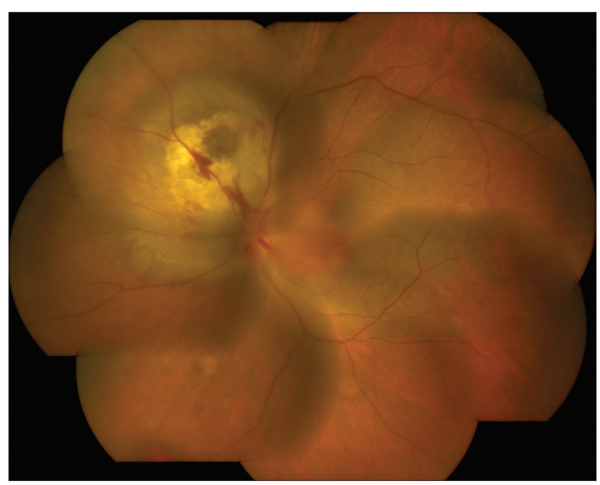

Figure 3: A case of choroidal melanoma 2 months posttreatment

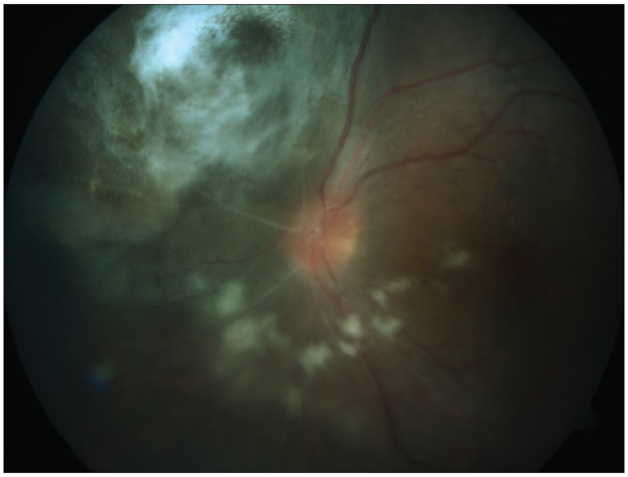

Figure 4: Regressed choroidal melanoma with radiation retinopathy changes

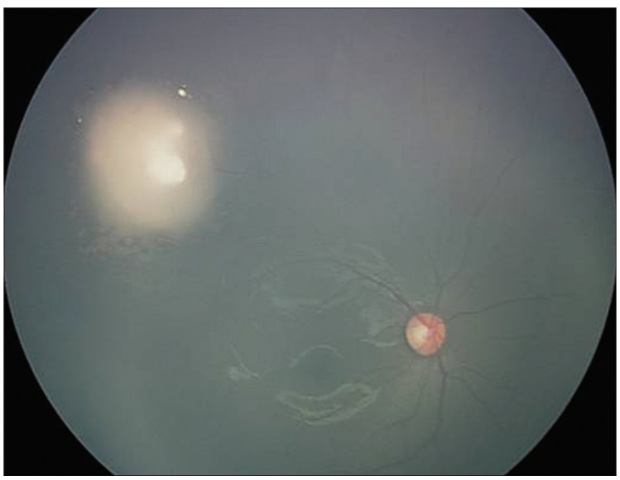

Figure 5: A case of retinoblastoma pretreatment

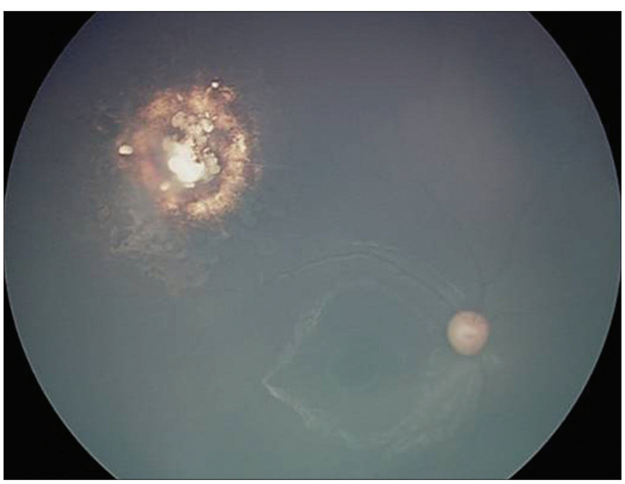

Figure 6: Regressed retinoblastoma posttreatment

The second patient was stable with maintained vision till a follow-up of 52.01 months, but then developed reactivation of the tumor and the eye was subsequently enucleated.

Other intraocular tumors

A 42 year-old-female with vasoproliferative tumor was treated with brachytherapy (40.8 Gy). The radial diameter of tumor was 11.5 mm; height was 3.4 mm; and circumferential diameter was 8.1 mm. Although the tumor regressed partly, she needed further surgery in the form of vitrectomy for increasing vitreous membranes. After a follow-up of 39.29 months, the retina was detached and the vision could not be salvaged.

A 26-year-old male with retinal angioma had brachytherapy to a large tumor since all other attempts at inducing regression failed (repeated laser photocoagulation and cryotherapy, intravitreal bevacizumab). The radial diameter of tumor was 6.7 mm; height was 3.6 mm; and circumferential diameter was 6.7 mm. A radiation dose of 46.19 Gy was used. Over a 33.80 months follow-up, he needed vitreoretinal surgery for traction retinal detachment and vitreous hemorrhage although the angioma had regressed to a great extent. The patient was stable at the last follow-up.

The patient with ciliary body melanoma was a 41-year-old female who received a radiation dose of 63.81 Gy. The radial diameter of tumor was 10.5 mm; height was 7.0 mm; and circumferential diameter was 7.3 mm. Over a follow-up of 40 months, the tumor was controlled and the patient was stable with maintained vision at the last follow-up.

Discussion

Treatment of intraocular tumors using episcleral plaque brachytherapy is a well-established technique. In this study, we are reporting our experience in the management of intraocular tumors with ^{125}I brachytherapy in India, where the technique is relatively new.

Episcleral plaque brachytherapy is a highly specialized procedure and should only be undertaken in centers with requisite expertise. Most patients with very small uveal melanomas (<2.5 mm height and <10 mm in largest basal dimension) can be observed for tumor growth before treatment. There is now a tendency to treat every melanoma patient with a clinical diagnosis of medium-sized choroidal melanoma (between 2.5 and 10 mm in height and <16 mm basal diameter) as candidates for episcleral plaques if the patient is otherwise healthy and without metastatic disease. Patients with gross extrascleral extension, ring melanoma, and tumor involvement of more than half of the ciliary body are not suitable for plaque therapy.[8]

Our selection of number of ^{125}I seeds and their distribution on the plaque is based on the comparative radiation dose to the sclera, tumor, fovea, optic nerve, and opposite eye wall. This to a large extent is based on the dosimetry planning. It is important to note that less radiation to the macular retina will result in preservation of central vision.

A variety of radioactive isotopes such as iodine-125, palladium-103, cesium-131, and ruthenium-106 are used in episcleral plaque brachytherapy. Currently, the most widely used plaque is iodine-125. The low-energy gamma rays allow a unidirectional, shielded radiation field. Cobalt-60 plaques have been largely abandoned due to their high-energy gamma rays preventing all shielding and consequently giving off radiation in all directions. The uranium fission produced ^{106}Ru plaques emit high-energy beta rays but with poor depth of tissue penetration, limiting their use to irradiate small tumors under 6 mm in thickness. For this reason, Ru plaques are not very commonly used, although it is convenient for the user in terms of logistics due to ready availability and long half-life (~1 year). Conversely, by virtue of being primarily a β-emitter, ^{106}Ru has the inherent advantage of sparing surrounding tissues such as the lens, macula, and optic disc. Several authors have reported that local tumor control rates and need for enucleation appear to be inferior with ^{106}Ru compared to ^{125}I, especially when apical tumor height is considered.[9-12] Large scale production process to avail ^{103}Pd and ^{131}Cs for seed brachytherapy application has not been established in India.

The excellent screening characteristics, good tissue penetration, low oxygen enhancement ratio, customizability of the distribution of the radiation on the plaque, and high relative biological effectiveness make ^{125}I an ideal source for local radiotherapy treatment of intraocular tumors. Though the half-life of ^{125}I is short, but the seeds can be reused several times.

Overall, medium-sized ocular melanomas can be controlled using ^{125}I seed plaques delivering a dose of 75-85 Gy to retain vision. The technology developed at Radiopharmaceuticals Division, BARC has led to the large scale production of ^{125}I brachytherapy source of high reproducibility over long periods.

While any portion of the eye can be involved by cancer, the most common tissue involved is the highly vascular choroid. The visual outcome of an eye treated with episcleral plaques brachytherapy depends mainly on the tumor size and location as well as on the development of radiation retinopathy and papillopathy. Accurate measurement of the tumor dimensions and design, placement, and verification of the plaque each contribute to the success or failure of this treatment. In the present study, radiation retinopathy was noted in six eyes, five having choroidal melanoma and one having retinoblastoma.

One limitation of the study is small sample size. Hence, we are not able to compare our results to the published literature. Another limitation is the loss to follow-up of around 15% patients. However, since our institute is a referral center, patients come from far-flung areas and there are financial and regional constraints in their continuing regular follow-ups. Hence, some of them continue follow-ups with their local specialists.

Another limitation of the study is the learning curve for the treating physicians as for any new technique.

Conclusion

Episcleral plaque brachytherapy using 'BARC I-125 Ocu-Prosta seeds' offers patients potentially eye- and vision-sparing alternatives to enucleation. In terms of survival, iodine brachytherapy is a safe alternative to enucleation in managing medium and some large uveal melanomas. It is anticipated that 'BARC I-125 Ocu-Prosta seed' has opened a new therapeutic window for the treatment of ocular cancer patients in India. These observations deserve further investigation, which will improve our ability to preserve vision and possibly life, and lead to a better quality of life for our patients with ocular tumors.

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