



Palladium-103 plaque brachytherapy for retinoblastoma: Long term follow up

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ABSTRACT

Purpose: Radiation has been used in the treatment of retinoblastoma. Herein, we present the novel use of palladium-103 plaque brachytherapy as primary treatment.

Observation: An 8-year-old asymptomatic girl presented was found to have a solitary peripheral retinoblastoma in her right eye. She was treated with primary palladium-103 plaque brachytherapy (47.4 Gray over 5 consecutive days). A secondary, vitreous hemorrhage noted 46 months after irradiation was successfully controlled by laser tumor-demarcation. With 19-years follow up, there has been no clinical scleropathy, or local tumor recurrence. The eye yields 20/20 vision and there has been no systemic metastasis.

Conclusion and importance: Palladium-103 plaque brachytherapy successfully controlled retinoblastoma, while preserving the globe, vision, and life.

1. Introduction

Retinoblastoma (RB) represents 3% of all childhood cancers and is the most common intraocular malignancy of childhood.¹ The mean age at diagnosis is 9 months (bilateral) and 23 months (unilateral).^{1–3} The primary goals of management of retinoblastoma are to save life, preserve the eye, and vision.

Intravenous chemotherapy is used most widely in treatment of primary treatment for retinoblastoma.⁴ Alternatively, the American Brachytherapy Society (ABS) together with the American Association of Physicists in Medicine (AAPM) consensus guidelines suggest plaque brachytherapy is typically used for smaller, anterior, solitary tumors.⁵ In addition, plaque has been used for select tumors, specifically for eye salvage threatened by residual or recurrent tumors.⁶ It is generally believed that plaque brachytherapy is more localized and thus less likely to induce second non-ocular cancers compared to external beam techniques.⁷

Plaque modalities that have been previously described in literature include: cobalt-60 (⁶⁰Co), iodine-125 (¹²⁵I), iridium-192 (¹⁹²Ir) and ruthenium-106 (¹⁰⁶Ru).^{6,8–10} Typical radioactive plaque treatment for RB as described the ABS-AAPM consensus guidelines as well as by

Munier and colleagues involves its placement onto the eye (sclera) as to cover the base of the tumor plus a margin of safety; then continuous dose in a range of 40–50 Gray (Gy) is given over 3–5 days.^{5,11,12} In a literature review utilizing the keywords retinoblastoma, palladium-103, iodine-125, ruthenium-106, plaque, brachytherapy, visual acuity, and survival; we could find no prior reported cases of RB treated with palladium-103 (¹⁰³Pd) plaque brachytherapy. Herein, we present our experience treating a select, unifocal, anterior RB utilizing ¹⁰³Pd plaque brachytherapy.

2. Case presentation

An 8-year-old girl was referred to The New York Eye Cancer Center for evaluation of a white retinal tumor discovered during fundus examination of an asymptomatic right eye. An only daughter of RB negative patients, her first cousin was noted to have bilateral RB. She was evaluated by clinical examination, ophthalmic imaging (photography, angiography, optical coherence tomography and ultrasound). Though available in 2004, germline RB1 mutation testing was not routinely covered and too expensive for our patient.

Ophthalmic oncology examination revealed a best corrected visual

Abbreviations: RB, retinoblastoma; ¹⁰³Pd, palladium-103; Gy, Gray; ABS, American Brachytherapy Society; AAPM, American Society of Physicists in Medicine; ¹⁹²Ir, iridium-192; ¹⁰⁶Ru, ruthenium-106; ⁶⁰Co, cobalt-60; OCT, optical coherence tomography; TTT, transpupillary thermotherapy; EBRT, external beam radiation therapy.

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acuity of 20/20 in both eyes. Her anterior segment, pupillary reactions and extraocular muscle movements were normal. Intraocular pressures were 20 and 17-mm Hg, respectively. There was no iris neovascularization or anterior segment manifestation of tumor. Indirect ophthalmoscopy revealed and fundus photography documented a white, fungating, irregular tumor in the supero-temporal quadrant measuring 8.5×8 mm in basal diameter (Fig. 1). Its posterior margin was measured to be 13 mm away from the edge of the optic disc and 14 mm from the center of the fovea. The vitreous was clear and without tumor seeding.

Fluorescein angiography showed a well-defined pattern of retinal capillaries that filled during the arterial phase and became diffusely hyperfluorescent in the later phases (Fig. 2). Optical coherence tomography revealed subretinal fluid over the surface of the tumor, less than 5 mm from the edge of the tumor and not in the macula. High-resolution 20MHz B-scan ultrasound imaging revealed a dome-shaped tumor with highly reflective intrastromal masses yielding variable acoustic reflectivity and orbital shadowing. No evidence of extraocular extension was noted. The tumors maximal thickness of was 2.8 mm (Fig. 3).

According to the most current, “8th edition” American Joint Committee on Cancer staging system for retinoblastoma the tumor would be classified a T1aN0M0 (Stage I).¹ In consideration of our patient’s family history, MRI was the preferred method for screening our patient, but the patient and her family refused MRI in favor of computed radiographic tomography of her orbit and brain, which were negative for extraocular RB. Then informed consent led to shared decision. Her parents chose local plaque treatment to avoid side effects of systemic chemotherapy.

At treatment, a 14-mm gold plaque therapy contained 12 ¹⁰³Pd seeds (Theragenics, Buford, Georgia, USA) at 1.47 mCi/seed for a total 19.3 mCi. With prescription point at 2.8 axial mm from the inner scleral surface, the plaque duration was 5 days for a total dose of 47.4 Gy. Calculated doses (in Gy) to normal ocular structures when utilizing the ¹⁰³Pd plaque were lens center (5.4), optic disc (5.3), central fovea (4.2), opposite retina (1.4) and inner sclera (128.5), respectively (Table 1). As the dosimetry of only ¹⁰³Pd was available for review, we requested medical physics to calculate comparative dosimetry of ¹²⁵I versus ¹⁰³Pd. As Principal Investigator for the Collaborative Ocular Melanoma Study Protocol, Dr. Finger notes that doses to opposite retina, optic disc and fovea were all collected as important parameters to assess the effect of ocular irradiation, and were later found to be prognostic for secondary ischemic radiation oculopathy.¹³⁻¹⁷ The results are summarized in Table 1.

Intraoperatively, scleral transillumination was used to place episcleral markings at the tumor base and 2–3 mm safety margin.^{5,18} The plaque was affixed to the eye wall over the targeted zone using interrupted 5-0 absorbable sutures (Fig. 4). Intraoperative ultrasound imaging was used to confirm proper plaque placement. The patient received continuous radiation over 5 days, after which the radioactive plaque was surgically removed.⁵

After 46 months the tumor began to bleed into the vitreous without growth. There was no tumor growth (Fig. 5). In an effort to contain the hemorrhage, the retina posterior to the tumor residua was treated with transpupillary thermotherapy (TTT), 3 mm spot size, laser



Fig. 2. Left, fluorescein angiographic image of the hyperfluorescent retinoblastoma before ¹⁰³Pd plaque radiation therapy. Right, 19-years after palladium-103 ophthalmic plaque radiation therapy. Note the resolution of the retinoblastoma and reduction in intrinsic vascularity.

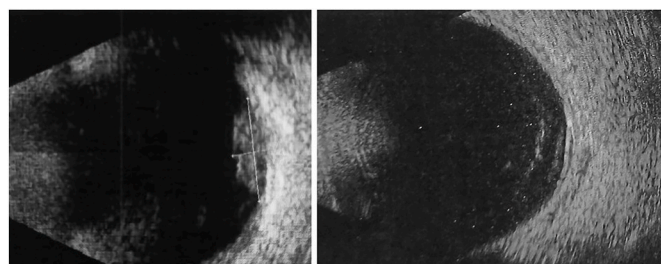


Fig. 3. Left, B-scan ultrasound imaging reveals a variably reflective retinoblastoma prior to palladium-103 plaque therapy. Right, The tumor is flattened to scar with some overlying vitreal debris.

Table 1
Comparative plaque dosimetry of ¹⁰³Pd and ¹²⁵I.

Ocular Structure	¹⁰³ Pd Dose (Gy)	¹²⁵ I Dose (Gy)	Increase in Dose If Using ¹²⁵ I
Lens center	5.4	7.2	+33.5%
Optic disc	5.3	8.5	+60.4%
Fovea	4.2	6.8	+62.8%
Opposite retina	1.4	2.79	+99.6%
Inner sclera	128.5	125	-2.7%
Apex of tumor	47.4	47.4	Equal

1 Gray = 100 cGy, ¹⁰³Pd = palladium-103, ¹²⁵I = iodine-125.

photocoagulation at 1000 mW and 900 msec durations. The strategy was to cut off the tumor circulation, then directly treat the tumor residua and any surrounding radiation-related retinal microangiopathy.

Post-treatment periodic ophthalmic examinations included: clinical examination, fundus photography, ultrasound imaging and optical coherence tomography (OCT). Fluorescein angiography was performed every 6-months to monitor radiation related vasculopathy as well as monitor tumor regression.^{19,20}

Her most recent examination was 19-years after ¹⁰³Pd plaque

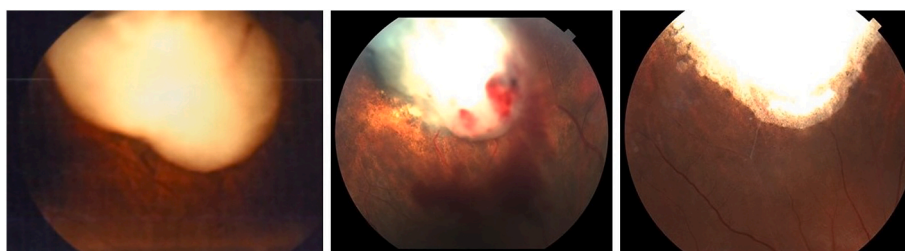


Fig. 1. Left, fundus photograph of retinoblastoma prior to treatment. Center, Note the hemorrhage on the tumor surface and vitreous that occurred 46 months after treatment. Right, Note that the residual tumor and vitreous hemorrhage resolved after 3 sessions of TTT laser. Image taken 19-years after ¹⁰³Pd plaque brachytherapy.

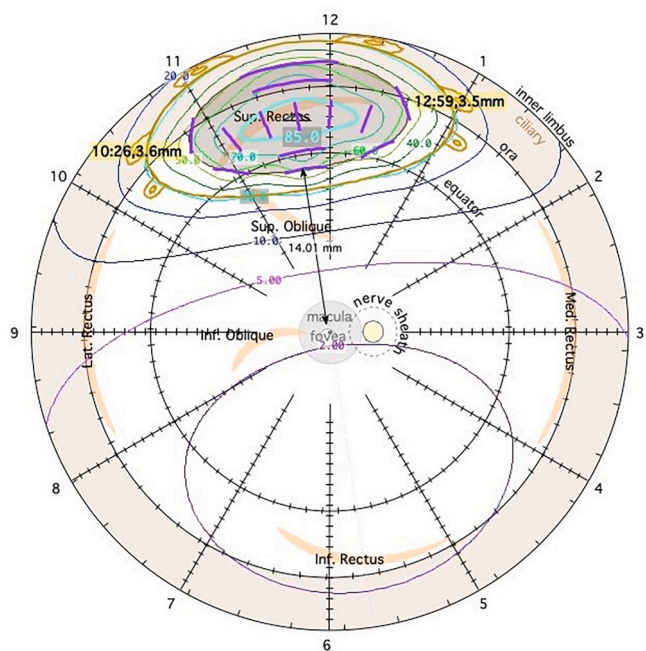


Fig. 4. Graphic rendering of the radiation dose distribution when a palladium-103 plaque is centered over the retinoblastoma. The isodose lines indicate a distribution of radiation around the tumor, with little reaching the macula or optic disc. Image created on Eye Physics Software, Los Alamitos, California, USA.

brachytherapy. The original tumor location is an atrophic flat white scar with well-defined margins (Fig. 1). At her last ultrasound imaging measurement, there was a documented reduction of tumor thickness from the original 2.8 to 0.9 mm (a 68% decrease). There is evidence of relatively static, Finger Stage-I radiation retinopathy without maculopathy or optic neuropathy as well as 20/20 vision in the affected eye.²¹ There has been no scleropathy or metastatic disease.

3. Discussion

Each case of RB is unique; therefore, treatment regimens must be customized to maximize outcomes for varying disease presentations. In this case we chose ¹⁰³Pd plaque brachytherapy as primary treatment for

retinoblastoma. Irradiation caused a reduction in tumor thickness and resolution of subretinal fluid with Shield’s Type 4 regression, which is the most common regression pattern in retinoblastoma.^{22–24} Treatment resulted in local cancer control, vision retention and lack of metastatic disease. Tumor control was related to the use of treatment margins, lack of vitreous seeding, and the small American Joint Committee on Cancer (AJCC) tumor stage 1 (T1aN0M0).¹ In that this retinoblastoma presented in an older child, the differential diagnosis included solitary astrocytoma (without tuberos sclerotic) and retinocytoma. This prompted a literature search where we found no cases of solitary astrocytoma in this age group.^{25–27} Retinocytomas are on a spectrum with retinoblastoma and are treated when active.

Retinoblastoma has been treated with ¹²⁵I and ¹⁰⁶Ru eye plaques.^{6,11,28} Kiratli et al. used ¹²⁵I as a primary procedure in 5 patients and noted no tumor recurrence or complications.²⁸ Shields et al. reported using a variety of radionuclides: ⁶⁰Co, ¹²⁵I, ¹⁹²Ir and ¹⁰⁶Ru as primary treatment for 31 cases and noted local recurrences in 16% at a follow up of 3.5 years.⁶ In a later study, they reported on 60 tumors treated with ¹²⁵I plaque radiotherapy, yielding a recurrence rate of 12% at 1 year.¹¹ Similarly, Abouzeid et al. noted a tumor recurrence in 12.5% tumors at 1 year, when ¹⁰⁶Ru plaque brachytherapy was used as a first- or second-line treatment.⁸ Lastly, Amendola et al. also used various plaques ⁶⁰Co, ¹²⁵I, ¹⁹²Ir and ¹⁰⁶Ru with a recurrence in 17% at 2 years.¹⁰

Clearly, local plaque therapy can avoid exposure to and potential complications from common systemic chemotherapy treatments that include 6-cycles (1 month apart) of carboplatin 500 mg/m² on day 1, vincristine 1.50 mg/m² on day 1 and etoposide 150 mg/m² on day 1 and 2.⁴ However, due to variable and specifically multifocal presentations of RB, plaque use has been limited.

Current indications for the use of plaque therapy in cases of retinoblastoma include solitary RB where plaque treatment offers less side effects and an improved prognosis for vision.⁵ Other common plaque brachytherapy indications include: globe salvage due to a recurrent tumor following EBRT, secondary treatment for medium sized chemotherapy-resistant tumors (<16 mm diameter and 3–9 mm thickness) with or without localized vitreous or sub retinal seeding, and following recurrence after IVC or IAC.^{4,23,29,30}

Though, retinoblastoma tends to be radiation sensitive, RB in late childhood can be quite different in presentation and resistant to focal therapy (compared to RB in children less than 5-years of age).³¹ The strengths of this unique ¹⁰³Pd plaque study include the use of a radiation source that (for an equivalent dose to the tumor’s apex), delivered a greater dose to the tumors base and thereby increased the amount of

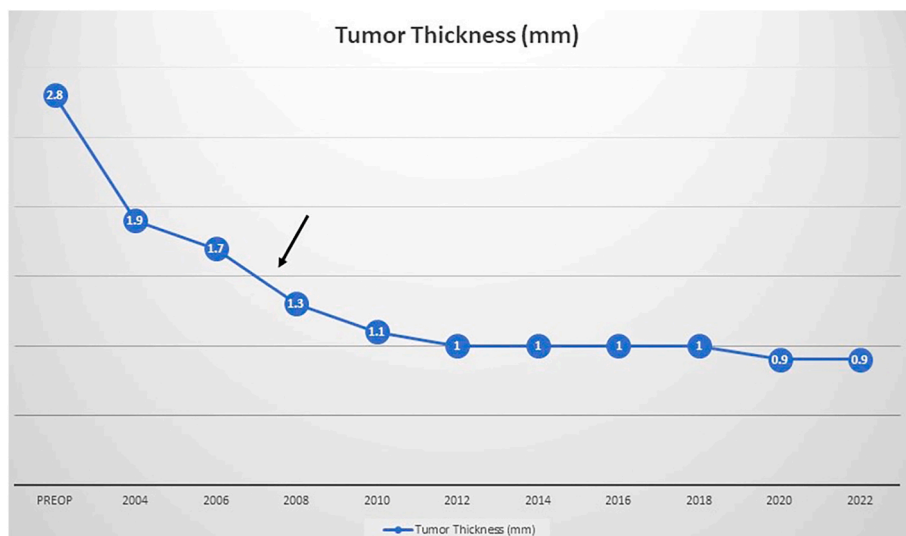


Fig. 5. Ultrasonographic measurements reveals progressive reductions of tumor thickness over 19-years follow up. Timing of TTT-laser shown at black arrow.

radiation delivered within the retinoblastoma. At the same time, due to the relatively rapid absorption of ^{103}Pd radiation within the vitreous, less radiation reached the visually important fovea and optic nerve compared to the more commonly used ^{125}I (Table 1).¹⁷ Though these actual doses to these vision critical structures may have been low in this case, the option to use ^{103}Pd and pre-operative comparative dosimetry offers a potential method to improve outcomes. In this case, when comparing ^{103}Pd vs ^{125}I , the higher measured dose to the tumor cannot be correlated to improved local control, nor can the reductions in fovea and optic disc to vision retention without a case-matched control. However, these differences need be reported for later study.

While posterior segment complications were not expected at the calculated doses, cataract was anticipated due to the anterior location of the tumor and corresponding radiation dose to the natural lens. Other than the transient vitreous hemorrhage which resolved after laser demarcation of the tumor. There were no visually significant radiation side effects. Lastly, this report uniquely includes a rare 19-year post-plaque follow up experience.

In conclusion, this report suggests that RB may be successfully treated with ^{103}Pd plaque brachytherapy yielding tumor control, with preservation of both life and vision.

Patient consent

The patient consented to publication of the case in writing. This report does not contain any personal information that could lead to the identification of the patient. Therefore, the case conforms to the Tenet's of Declaration of Helsinki and the Health Insurance Privacy and Portability Act. It has been approved for publication by The New York Eye Cancer Center's IRB and Ethics committee.

Intellectual property

We confirm that we have given due consideration to the protection of intellectual property associated with this work and that there are no impediments to publication, including the timing of publication with respect to intellectual property. In doing so we confirm that we followed the regulations of our institutions concerning intellectual property.

Research ethics

We further confirm that any aspects of the work covered in this manuscript that has involved human patients has been conducted with the ethical approval of all relevant bodies and that such approvals are acknowledged within the manuscript.

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Declaration of competing interest

Dr. Finger is the Chief Executive Officer of LV Liberty Vision Corporation <https://libertyvision.com>.

Authorship

All authors attest that they meet the current ICMJE criteria for authorship.

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