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Salvage/Adjuvant Brachytherapy After Ophthalmic Artery Chemosurgery for Intraocular Retinoblastoma

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Summary

The efficacy and toxicity of brachytherapy following ophthalmic artery chemo-surgery for retinoblastoma was investigated in 15 eyes of 15 patients. This combination was effective, even in eyes with vitreous seeding, and the toxicity appeared to be no worse than reported with other radiation/chemotherapy treatments for retinoblastoma. Brachytherapy represents a potentially valuable salvage treatment for patients with recurrent retinoblastoma following ophthalmic artery chemosurgery treatment.

Purpose—To evaluate the efficacy and toxicity of brachytherapy after ophthalmic artery chemo-surgery (OAC) for retinoblastoma.

Methods and Materials—This was a single-arm, retrospective study of 15 eyes in 15 patients treated with OAC followed by brachytherapy at (blinded institution) between May 1, 2006, and December 31, 2012, with a median 19 months' follow-up from plaque insertion. Outcome measurements included patient and ocular survival, visual function, and retinal toxicity measured by electroretinogram (ERG).

Results—Brachytherapy was used as adjuvant treatment in 2 eyes and as salvage therapy in 13 eyes of which 12 had localized vitreous seeding. No patients developed metastasis or died of retinoblastoma. The Kaplan-Meier estimate of ocular survival was 79.4% (95% confidence interval 48.7%-92.8%) at 18 months. Three eyes were enucleated, and an additional 6 eyes developed out-of-target volume recurrences, which were controlled with additional treatments. Patients with an ocular complication had a mean interval between last OAC and plaque of 2.5 months (SD 2.3 months), which was statistically less ($P=.045$) than patients without ocular complication who had a mean interval between last OAC and plaque of 6.5 months (SD 4.4 months). ERG responses from pre- versus postplaque were unchanged or improved in more than half the eyes.

Conclusions—Brachytherapy following OAC is effective, even in the presence of vitreous seeding; the majority of eyes maintained stable or improved retinal function following treatment, as assessed by ERG.

Introduction

Brachytherapy has been used successfully as primary and salvage treatment for unilateral and bilateral retinoblastoma worldwide for 80 years, but there are no reports of its use following modern-day ophthalmic artery chemosurgery (OAC). Moore (1) first described brachytherapy for retinoblastoma through the interstitial placement of radon seeds. Stallard later fashioned a curved disc applicator loaded with ^{60}Co ; similar applicators (commonly called plaques) are currently used with a lower energy isotope (^{106}Ru ^{125}I or ^{103}Pd) (1-3). Brachytherapy was originally used as primary treatment of small discrete tumors (4, 5), but later its use was expanded to adjuvant and salvage therapy (6). Radioactive plaques were placed on eyes that progressed despite mainstay treatment with external beam radiation, and when this modality was replaced by systemic chemotherapy (because of concerns over radiation-induced second cancers), plaques were also used to treat these eyes.

We have entered a new era when, at our center and others worldwide, systemic chemotherapy is being replaced by ophthalmic artery chemosurgery (OAC) as the standard of care. This novel technique was introduced by our group and built on the work of Kaneko and colleagues (7, 8). It involves passing a catheter through the femoral artery and guiding it to the ostium of the ophthalmic artery, where chemotherapy is injected. It provides a high, localized concentration to the eye (using a porcine model, it is calculated to be 14-fold higher local drug concentration compared with intravenous chemotherapy) (9), while limiting systemic exposure to cytotoxic drugs and their short-term (infections, cytopenia, etc) and long-term (ototoxicity, second malignancies, etc) repercussions. This technique is highly effective in treating tumors and saving eyes otherwise destined for enucleation, and, like other treatment modalities and can benefit from supplemental focal treatments such as cryotherapy, laser, and brachytherapy. Of the many articles in the literature describing brachytherapy treatment of retinoblastoma, none addresses the efficacy or toxicity of brachytherapy in retinoblastoma eyes previously treated with OAC. There is some concern regarding retinopathy when radioactive plaques are used early following systemic chemotherapy, and it is of interest to determine whether this is also true of intraarterial chemotherapy. Here we present our findings of brachytherapy in OAC-treated eyes since we started OAC in June 2006.

Methods and Materials

This retrospective, single-institution, institutional review board-approved study included all eyes of retinoblastoma patients meeting the inclusion criteria treated at (blinded institution) from May 30, 2006, to December 31, 2012. Inclusion criteria consisted of those patients previously treated with OAC who received brachytherapy as adjuvant or salvage therapy. Brachytherapy was used to treat localized disease not amenable to transpupillary thermotherapy (TTT) or cryotherapy: for example, tumors or vitreous seeds too large, too high, too posterior for cryotherapy or too anterior for TTT. Patient data included age, sex,

laterality, weight, treatment status (naive or no treatment before OAC vs previous treatment involving systemic chemotherapy or radiation therapy), age at brachytherapy, follow-up time. Tumor data included Reese-Ellsworth classification, International Classification, treatment before and after brachytherapy, and response to treatment.

Eyes were initially examined under anesthesia at 3- to 4-week intervals. Evaluation consisted of visual assessment, motility and pupillary responses, indirect ophthalmoscopy, fundus photography with RetCam (Massie Industries, Dublin, CA), ophthalmic ultrasonography (OTI Ophthalmic Technologies, Toronto, Canada), and electroretinography (Espion ColorBurst, Diagnosys, Lowell, MA). OAC was performed every 3 or 4 weeks in a manner that has previously been described in detail (10, 11). Focal treatment (TTT or cryotherapy) was performed if indicated for out-of-target volume disease, or to the target disease, either to supplement the brachytherapy or to treat disease uncontrolled by the plaque. Baseline, preplaque electroretinogram (ERG) measurements were compared with recordings obtained at most recent follow-up. Reported here are the response amplitudes to 30-Hz photopic flicker stimulation, which are representative of the full ERG protocol. As previously described (12), ERG amplitudes were classified according to the following scale: 0: undetectable; 0.1 to 25 μ V: poor; 25.1 to 50 μ V: fair; 50.1 to 75 μ V: good; 75.1 to 100 μ V: very good; >100 μ V: excellent.

An individualized brachytherapy plan was generated for each patient using an in-house planning system that complies with the American Association of Physicists in Medicine Task Group Report 43 and the Collaborative Ocular Melanoma Study dosimetry protocols (13). Maximum tumor and/or vitreous seed diameter at and distance from the inner sclera were used for treatment planning. The prescription dose was 40 to 45 Gy to the prescription point, defined as the tumor and/or vitreous seed distance from the inner sclera, plus 1 mm to account for scleral thickness. The mean dose rate was 60.3 cGy per hour, and the mean duration of brachytherapy was 72.7 hours. If vitreous seeds were targeted, an additional 1 mm was included to determine the prescription point. The plaque diameter was chosen based on the largest diameter of the tumor and/or vitreous seed at the inner sclera and included a lateral margin of 2 mm around the target. All episcleral plaques were inserted under general anesthesia following careful tumor localization and temporary disinsertion of extraocular muscles if required. Plaques were temporarily affixed to the globe with nonabsorbable sutures and removed under general anesthesia after delivery of the prescribed radiation dose based on calculated treatment time. ^{125}I sources (GE Healthcare, Arlington Heights, IL) were loaded in Collaborative Ocular Melanoma Study type plaques (Trachsel Dental Studio, Rochester, MN) and used for brachytherapy in all patients except for 1 who received treatment with a ^{106}Ru source (Eckert & Ziegler BEBIG, Berlin, Germany).

Statistical analysis was performed using Prism (GraphPad Software, La Jolla, CA). Kaplan-Meier survival data with log-rank test was used to evaluate ocular, recurrence-free, and overall survival following plaque placement. Comparison of the interval from last OAC to plaque insertion between eyes with complication and those without complication was performed with the Student *t* test. Comparison of cumulative drug doses between complicated and uncomplicated eyes were also evaluated by Student *t* test.

At the time of this study, our cohort consisted of 158 patients with 205 eyes receiving 746 OAC infusions. Fifteen of these eyes underwent plaque brachytherapy, meaning 7.3 % of eyes had brachytherapy following OAC (and 5.9% as salvage brachytherapy). All patients included in this study received OAC at our institution. One patient had additional OAC before treatment at our institution.

Results

Fifteen eyes of 15 patients were included, having received OAC followed by brachytherapy as a secondary or salvage treatment. Patients had a median of 5 OAC infusions per patient and received a median cumulative drug dose of 19 mg, 1.5 mg, and 40 mg for melphalan, topotecan, or carboplatin, respectively. The median follow-up since plaque placement was 19 months (range 5-72 months), and the mean age at the time of brachytherapy was 46 months. Patient and eye demographics are shown in Table 1. Two-thirds of patients were naive to radiation therapy or systemic chemotherapy before OAC treatment, and all eyes received OAC before brachytherapy (Table 1). Two patients received plaques as adjuvant treatment, which was part of the initial OAC protocol that called for adjuvant radiation even in eyes with a favorable OAC treatment response. After these initial patients, it was determined that adjuvant radiation was no longer required for all patients after OAC.

Brachytherapy characteristics are depicted in Table 2. All but 1 patient was treated with an ^{125}I source. The mean prescription and delivered dose were 4200 and 4209 Gy, respectively, over a mean duration of 73 hours. The mean prescription point was 6.9 mm. A plaque as salvage therapy was received by 86.7% of patients, and all but 1 eye (93%) contained active vitreous seeds at the time of brachytherapy. Ten (66%) eyes had a plaque placed in the inferior hemisphere of the eye, 4 patients had plaques at the horizontal meridian (9 or 3 o'clock), and 1 eye had a plaque placed in the superior hemisphere at 10 o'clock.

There were no deaths or metastatic disease in any patient. The Kaplan-Meier estimate of 18-month ocular survival was 79.4% (95% confidence interval [CI] 48.7%-92.8%) and is shown in Figure 1. Excluding the eyes treated adjuvantly yielded an 18-month Kaplan-Meier ocular survival estimate of 71.6% (95% CI 35%-89.9%). The 18-month Kaplan-Meier estimate of recurrence-free survival was 100% for in-volume target and 47.7% (95% CI 19.7%-71.4%) for out-of-target volume, as shown in Figure 2. Additional outcome characteristics are shown in Table 3.

Three eyes were enucleated following out-of-target volume recurrence of disease at a mean of 4 months after brachytherapy. An additional 6 eyes developed out-of-target-volume recurrences, which were successfully controlled with additional treatment (see Table 3), and 2 eye was given an additional cryotherapy application to further extirpate already regressing vitreous seeds. Four eyes retained useful (better than 20/150) vision. Excluding 1 eye that began and ended with an "extinguished" ERG, ERG responses were stable in 36%, improved in 14%, reduced to "good" or "very good" range in 36%, and reduced to "fair" or worse in 14% of eyes. Complications are listed in Table 3: 3 eyes (Eyes 3, 4, and 15) developed cataracts, 5 developed vitreoretin-opathy (Eyes 2, 4, 5, 6, 15), and 3 (Eyes 5, 7,

14) had evidence of radiation optic neuropathy with severely compromised vision. Complications occurred following brachytherapy at a mean of 42 months (SD 0.6 months) for cataracts, 7.7 months (SD 7.4 months) for optic neuropathy, and 4.2 months (SD 3.1 months) for vitreoretinopathy. Patients with an ocular complication had a mean interval between last OAC and plaque of 2.5 months (SD 2.3 months), which was statistically less ($P = .045$) than patients without ocular complication who had a mean interval between last OAC and plaque of 6.5 months (SD 4.4 months). The individual cumulative drug doses between complicated and uncomplicated eyes were not significantly different ($P = .95, .54, .45$ for cumulative melphalan, topotecan, and carboplatin, respectively).

Discussion

In 1903, Hilgartner first demonstrated the radiosensitivity of retinoblastoma to external beam radiation therapy (EBRT), thereby offering an alternative treatment to enucleation or exenteration. In the 1930s, investigators explored delivering radiation via localized applicators with radon as their source (14). However, Stallard raised concerns that, due to the cylindrical nature of the seeds, the distribution of the radiation was nonuniform (15). This led him to create curved disc applicators to fit the radius of curvature of the sclera, allowing for a more even distribution of radiation (4). They were originally loaded with radon, but this practice was subsequently abandoned and was replaced with ^{60}Co . In contrast to the relatively uniform, homogenous dose delivered by EBRT, brachytherapy provides a treatment dose to the apex of the tumors and a higher dose at the base. By histopathologic examination, Stallard determined 3500 rads to the apex was an effective dose with tolerable toxicity (4), and clinical experience has supported doses of 3500 to 4500 cGy for retinoblastoma (16-31).

In the 1970s, Lommatzsch pioneered use of the beta-emitting isotope ^{106}Ru using a shell-shaped applicator with silver casing that provided effective shielding, sparing the surrounding tissues (2). ^{125}I is both a beta- and gamma-emitting source, which emerged around the same time for retinoblastoma (3). These low-energy isotopes became the preferred sources for brachytherapy because of their improved patient and personnel radiation safety profile.

In the early days, brachytherapy was used mainly as primary treatment, predominantly in those eyes with smaller, discrete tumors. Stallard treated 69 eyes with his ^{60}Co applicator and saved >95% of eyes (32). As plaques were used more widely, indications for its use were further refined (32, 33). Before long, plaques were used for secondary and salvage therapy, and many groups have published their results. One of the earliest and most extensive investigations reports saving 62% of 71 eyes from enucleation, 67 of which had failed before EBRT (6). Similar ocular survival rates were confirmed by the same physicians, and other groups subsequently quoted ocular survival percentages for eyes treated previously with EBRT ranging from 52% to 89% (17, 19-22, 24). As treatment trends shifted, plaques were also used to secondarily treat or to salvage eyes that had failed systemic chemotherapy. Many reports give survival rates for previously treated eyes, and in those in which eyes predominantly received previous chemotherapy, the ocular survival percentages or rates are remarkably similar to those failing EBRT, ranging from 52% to 95%

(29-31, 34, 35); this latter figure is from an article that excluded eyes with seeds (29). It appeared that the nature of the previous treatment, whether EBRT or intravenous chemotherapy, had little influence on the success of the brachytherapy-treated eyes. Consistent with this, our 18-month ocular survival for brachytherapy following OAC is within the range just described. Groups searched for other determinants of treatment response or failure with some reporting statistically significant factors and others groups finding none (23, 30, 31).

At our center, OAC has supplanted EBRT and systemic chemotherapy and constitutes first-line treatment in nearly all cases. We use OAC as treatment to both naive and previously treated eyes, and as with EBRT and systemic chemotherapy, we often rely on supplemental focal treatments for success. Here we report on 15 eyes that received brachytherapy following OAC, the majority as salvage treatment (representing 5.9% of our entire OAC cohort). With an 18-month ocular survival rate of 79.4%, we demonstrate brachytherapy can successfully treat retinoblastoma eyes following incomplete success or recurrence of OAC and can be particularly useful for localized vitreous or subretinal seeding.

Vitreous seeds remain a challenge in the treatment of intraocular retinoblastoma, and eyes without vitreous seeds treated with brachytherapy have historically had better outcomes than eyes with seeds (26). Vitreous seeds lack a blood supply, have low mitotic activity, and are notoriously resistant to treatment. All but 1 of the eyes in our series contained localized vitreous seeds and we demonstrate efficacy despite this. Others have reported successful treatment of vitreous seeds with brachytherapy (23, 24), and given the inherent nature of these seeds, it is puzzling to observe such an impressive response. Because of their low mitotic activity, seeds may respond slower to radiation and making us more inclined to observe these eyes for longer periods in case of a delayed response.

Complications included cataracts in 20%, optic neuropathy in 20%, and vitreoretinopathy in 33% of eyes. These rates are within the ranges reported in the literature which range up to 43%, 26%, and 57% of eyes for cataracts, optic neuropathy and vitreoretinopathy, respectively, in eyes that had not received previous OAC (see Table 4). This suggests that the toxicity incurred from treating brachytherapy in combination with OAC is no worse than that seen after combining it with other treatment modalities. However, in our cohort, for eyes receiving OAC without brachytherapy, the rates of retinopathy and cataract were both 3.4%, and there were no cases of optic neuropathy (10). This demonstrates that brachytherapy following OAC greatly increases the risk for ocular complications compared with eyes receiving OAC without brachytherapy.

Toxicity can be dose-dependent, meaning cumulative methods of treatment (particularly combining radiation with chemotherapy) or shorter interval between modalities can heighten the risk of ocular toxicity. We did not show any significance of previous cumulative intraarterial drug dose on risk of complication. However, eyes with an ocular complication had a statistically significant shorter interval between last OAC and plaque compared with eyes with no complication (2.5 vs 6.5 months). Furthermore, 4 of the 5 eyes that required additional OAC following brachytherapy developed a complication. Although these factors may well reflect a selection bias, it is important for parents to be aware of this relationship

particularly if it would help guide their treatment decision. In terms of retina-specific toxicity, we found that retinal function (as measured by ERG) remained stable or improved in the majority of eyes, and only 13% of eyes had responses that decreased to levels of “fair” or below (the equivalent of 50 μ V or lower).

Nine eyes had progressive disease despite salvage brachy-therapy: all of these occurred out of the radiation target volume. The rate of out-of-target volume recurrence was higher in those eyes receiving plaques along the horizontal meridian (3 or 9 o'clock) or in the superior hemisphere, compared with those in the inferior hemisphere (80% of eyes recurred compared with 50% of eyes, respectively). Vitreous seeds typically gravitate to the inferior meridians of the eye and can be ophthalmoscopically invisible. Brachytherapy to the inferior hemisphere may treat these ophthalmoscopically invisible vitreous seeds, thereby reducing the risk of recurrence that may originate from them.

In conclusion, we found that brachytherapy following OAC is effective in saving lives, eyes, and vision, even in the presence of vitreous seeding, and that the toxicity appears to be no worse than that reported with brachytherapy combined with other treatments. There appears to be a trend toward fewer complications if the interval between OAC and plaque insertion is prolonged (6.5 months), although this is not always clinically indicated and may reflect a selection bias. These encouraging results suggest OAC is another therapeutic modality that can be combined with brachytherapy.

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Fig. 1.
Kaplan-Meier ocular event-free survival curve of all eyes.

Fig. 2.
Kaplan-Meier recurrence-free survival curve.

Table 1

Characteristics of patients, eyes, and previous treatment

Patient	Sex	Laterality	RE	ICRB	Age at plaque (mo)	Previous treatment	Previous OAC (Mcum, Tcum, Ccum)
1	F	U	Vb	D	25	Naïve	OAC × 5 (M15.5 mg, T0.3 mg)
2	F	B	Vb	E	41	IVC; VEC × 5	OAC × 7 (M35 mg, T2.8 mg, C70 mg)
3	F	U	Vb	D	50	Naïve	OAC × 6 (M17 mg, T2.2 mg, C60 mg)
4	M	U	Vb	D	8	Naïve	OAC × 2 (M6 mg)
5	F	U	Va	D	16	Naïve	OAC × 2 (M10 mg)
6	F	B	Vb	D	23	IVC; VEC × 9	OAC × 4 (M9.5 mg, C30 mg)
7	M	B	Vb	E	46	Naïve	OAC × 6 (M37.5 mg, T3.0 mg, C250 mg)
8	F	U	Vb	E	70	Naïve	OAC × 6 (M32.5 mg, T2.5 mg, C200 mg)
9	M	U	Vb	D	61	OAC × 2	OAC × 4 (M27.5 mg, T1.7 mg, C150 mg)
10	F	B	Vb	D	31	IVC; VC × 3	OAC × 6 (M18.5, T1.5 mg, C40 mg)
11	F	U	Vb	D	119	Naïve	OAC × 3 (M16 mg, T1.1 mg, C60 mg)
12	M	U	Vb	D	41	Naïve	OAC × 5 (M20.5 mg, T1.1 mg, C40 mg)
13	F	U	Vb	D	19	IVC; VEC × 6	OAC × 5 (M20 mg, T1.5 mg, C120 mg)
14	F	U	Vb	D	80	Naïve	OAC × 7 (M41 mg, T2.3 mg, C60 mg)
15	F	U	Vb	D	60	Naïve	OAC × 4 (M19 mg, T4 mg.)

Abbreviations: B = bilateral; C = carboplatin; Ccum = carboplatin cumulative over all OAC cycles; cryo = cryotherapy; E = etoposide; ICRB = international classification of retinoblastoma; intravit = intravitreal melphalan 30 mcg weekly; IVC = intravenous chemotherapy; Mcum = melphalan cumulative over all OAC cycles; naïve = no previous radiation or systemic chemotherapy; OAC = ophthalmic artery chemosurgery; RE = Reese-Ellsworth classification; Tcum = topotecan cumulative over all OAC cycles; TTT = transpupillary thermotherapy; U = unilateral; V = vincristine.

Table 2
Indication and characterization of plaque and brachytherapy treatment ^{125}I

Patient	Source	Plaque diameter (mm)	Duration of brachy (hrs)	Air kerma strength (U)	Rx depth (mm)	Rx dose (cGy)	Rx depth delivered dose (cGy)	Rx depth dose rate (cGy/h)	Sclera surface delivered dose (cGy)	Indication	Clock hour/treated
1	^{125}I	12.0	70.98	55.3	8	4000	4086	57.6	50,799	Salvage: tumor, vit seeds	0300
2	^{125}I	16.0	74.42	43.2	6.4	4250	4265	57.3	21,546	Salvage: tumor, vit seeds	0600
3	^{125}I	16.0	76.43	36.1	6	4000	4075	53.3	22,107	Salvage: vit seeds	0700
4	^{125}I	16.0	51.33	56.0	6	4200	4138	80.6	19,360	Secondary: tumor	0600
5	^{125}I	20.0	54.52	60.7	6	4200	4200	77.0	12,236	Secondary: tumor, vit seeds	0900
6	^{125}I	16.0	95.95	19.7	4	4100	4100	42.7	12,700	Salvage: tumor, implanted seeds	0700
7	^{125}I	12.0	73.52	36.8	8	4250	4328	58.9	41,203	Salvage: vit seeds	0900
8	^{125}I	18.0	97.43	38.0	7	4250	4217	43.3	24,379	Salvage: vit seeds	0430
9	^{125}I	18.0	69.03	75.8	9	4250	4252	61.6	34,716	Salvage: vit seeds	0600
10	^{125}I	16.0	71.37	43.1	6	4250	4415	61.9	20,652	Salvage: tumor, vit seeds	0800
11	^{125}I	20.0	46.93	92.7	8	4250	4096	87.3	25,029	Salvage: vit seeds	0600
12	^{125}I	16.0	69.80	46.9	7	4000	3888	55.7	22,035	Salvage: vit seeds	0600
13	^{125}I	18.0	68.27	37.7	5	4250	4187	61.3	15,694	Salvage: vit seeds	1000
14	^{125}I	16.0	74.35	59.0	8	4250	4389	59.0	33,480	Salvage: vit seeds	0500
15	^{106}Ru	15.3	96.42	NA	5	4500	4500	46.7	21,440	Salvage: vit seeds	0900

Abbreviations: I-125 = iodine-125; NA = not applicable; NR = not recorded; Ru-106 = ruthenium-106; Rx = prescription; vit = vitreous.

Table 3
Outcome following brachytherapy: Additional treatment, Visual, and ERG findings

Patient	Outcome	Additional treatment	Vision		ERG response		Complications
			Before	After	Before	After	
1	OOT recurrence at 2 mo	Enucleated	No F&F	Enucleated 3 mo	Poor	Poor	
2	OOT recurrence, diffuse seeds at 5 mo	TTT × 1, Cryo × 1, intravit × 4, ruthenium plaque	F&F	20/40	Very good	Fair	Intraretinal hemorrhage
3	Controlled	None	F&F	HM	Fair	Good	Cataract
4	Controlled	None	F&F	LP	Fair	Fair	Intraretinal hemorrhage, chorioretinal atrophy, cataract
5	Controlled	None	NoF&F	NoF&F	Undetectable	Undetectable	Radiation papillotomy, rubeosis, intraretinal hemorrhage, phthisis
6	OOT recurrent at 1 mo	OAC × 9 (M31.5 mg, T2.2 mg, C120 mg), TTT × 2, cryo × 2	F&F	F&F	Very good	Fair	Intraretinal hemorrhage
7	OOT recurrence at 6 mo	OAC × 1 (M7.5 mg, 0.5 mg, C50 mg), TTT × 3, Cryo × 5, intravit × 8	F&F	NLP	Excellent	Very good	Radiation optic neuropathy
8	Controlled	None	CF	CF	Very good	Very good	
9	Controlled	None	20/60	20/60	Excellent	Very good	
10	OOT recurrence 14 mo	OAC × 2 (M12 mg, T2 mg, C100 mg), TTT × 1	F&F	F&F	Poor	Poor	
11	Controlled	Cryo × 1	20/40	20/150	Excellent	Good	
12	OOT recurrence at 5 mo	Enucleated	F&F	Enucleated 5 mo	Fair	Fair	
13	OOT recurrence at 5 mo	TTT × 3, enucleated	F&F	Enucleated 5 mo	Very good	Good	
14	OOT recurrence at 6 mo/15 mo	OAC × 2 (M13.5 mg, T2.5 mg, C90 mg), TTT × 5, Cryo × 3	20/50	NLP	Fair	Poor	Papilloedema
15	OOT recurrence at 8 mo/40 mo	OAC × 3 (M18 mg, T1.0 mg, C100 mg), TTT × 2, Cryo × 2	CF	20/100	Fair	Fair	Vitreoretinopathy, subretinal fibrosis, cataract

Abbreviations: CF = count fingers; F&F = fix and follow; HM = hand motion; intravit = intravitreal melphalan; LP = light perception; NLP = no light perception; OOT = out-of-target volume.

Number in front of OAC signifies the number of cycles.

Table 4
Previous published literature on brachytherapy for retinoblastoma

Author	Year	No. pts	No. eyes	Radioactive source	% pts receiving previous treatment	% of eyes with seeds	Pt survival (%)	Eye survival (%)	Complications
Stallard	1966	69	69	Co60	PT (3%); EBR (3%)		99%	96%	
Paterson	1965	8	9	Radon	PT (22%); EBR (22%)		88%	67%	
Abramson et al	1983	64	71	Co60	PT (94%); EBR (94%)		88%	62%	Scleral necrosis (1%)
Kock et al	1986	33	33	Co60	PT (15%); EBR (15%)		100%	82%	Cat (6%)
Stannard et al	1987	14	14	Ir192	PT (50%); EBR 50%		93%	PT (57%)	Vit heme: naive (29%), PT (57%)
Shields et al	1989	50	51	Ir125, Co60, Ir192, Ru106	PT (63%); EBR (55%)	Vit (96%)	96%	PT (72%)	
Amendola et al	1989	36	36	Ir125, Co60, Ir192, Ru106	PT (56%); EBR (56%)	PT: RE V (100%)	97%	PT (80%)	PT: cat (15%), retinopathy (10%), papillopathy (10%), vit hem (10%)
Amendola et al	1990	51	54	Ir125, Co60, Ir192, Ru106	PT (54%); EBR (54%)	PT: RE V (97%)	97%	PT (52%)	PT: cat (31%), vit hem (14%)
Fass et al	1991	72	75	60 Co	PT (100%); EBR (100%)		90%	60%	
Desjardins et al	1993	26	34	Co60, Ir125	PT (100%); EBR (100%)	RE V (27%)	100%	62%	Vit heme (9%), papillopathy (3%), cat (3%)
Shields et al	1993	103	103	Ir125, Co60, Ir192, Ru106	PT (70%); EBR (50%)	Vit (49%)	99%	PT (88%)	
Shields et al	1994	91	91	Ir125, Co60, Ir192, Ru106	PT (100%); EBR (69%), plaque (10%)	Vit (48%)	100%	89%	Retinopathy (3%)
Stannard et al	2001	22	24	Ir125 ("claws")	PT (25%); chemo (17%), plaque (8%)	RE V (75%)	68%	RE V (33%)	Vit heme (8%), cat (17%)
Shields et al	2001	141	147	Ir125, Co60, Ir192, Ru106	PT (71%); chemo (14%), EBR (31%), chemo+EBR (13%)	Vit (7%), subretinal (4%)	99%	94%	Retinopathy (42%), papillopathy (26%), cat (3%)
Merchant et al	2004	21	25	Ir125	PT (100%); EBR (76%), chemo (71%)		95%	60%	Vit heme (4%)
Schueler et al	2005	13	13	Ru106	PT (54%); chemo (23%)		100%	100%	Retinal hemorrhage (8%)
Sohajda et al	2006	13	13	Ru106	PT (85%); chemo (85%)		92%	92%	

Author	Year	No. pts	No. eyes	Radioactive source	% pts receiving previous treatment	% of eyes with seeds	Pt survival (%)	Eye survival (%)	Complications
Schueler et al	2006	134	140	Ru106	PT (68%); EBR (28%), chemo (32%)	Vit/subretinal (21%)	KM 5 yr 96.4%	87% KM 5 yr	Vit heme (45%), retinopathy (20.7%)
Shields et al	2006	64	71	I125	PT (100%); chemo (71%), chemo+EBR (27%)	Eyes with seeds excluded	100%	95% KM 5 yr	Vit heme (59%), vit heme (54%), cat (43%)
Abouzeid et al	2008	39	41	Ru106	PT (92%); chemo (51%), chemo+EBR (41%)	Vit (33%)	97%	76%	Retinopathy (2.4%), retinal detachment (17.1%), cat (9.7%), vit heme (1.6%)
Murakami et al	2012	85	90	Ru106	PT (96%); EBR (32%)	Vit (41%), subretinal (37%)	KM 3 yr 97.3%	52% KM 4 yr	Vitreoretinopathy (51.2%) cat (25.6%)

Abbreviations: cat = cataract; chemo = chemotherapy; Co60Z cobalt-60; EBR = external beam radiation; heme = hemorrhage; I125 = iodine-125; Ir = iridium-192; KM = Kaplan-Meier; PT = previously treated; pts = patients; RE = Reese-Ellsworth classification; Ru106 = ruthenium-106; vit = vitreous.