ELSEVIER

BRACHYTHERAPY

Brachytherapy xxx (xxxx) xxx

Original Article

Ruthenium-106 (^{106}Ru) plaque brachytherapy as salvage treatment for retinoblastoma following intravenous chemotherapy

Vijay Anand Reddy Palkonda[1,2], Aiswarya Ramachandran[1], Bolajoko Abidemi Adewara[1], Ritesh Verma[1], Vishal Raval[1,*], Swathi Kaliki[1,#]

[1] *The Operation Eyesight Universal Institute for Eye Cancer, L V Prasad Eye Institute, Road no 2, Banjara Hills, Hyderabad, 500034 India*
[2] *Department of Radiation Oncology, Apollo Cancer Hospital, Hyderabad, India*

ABSTRACT

PURPOSE: To describe the clinical presentation and treatment outcomes of patients undergoing Ruthenium-106 (^{106}Ru) plaque brachytherapy as salvage treatment for retinoblastoma (RB) following intravenous chemotherapy (IVC).

METHODS: Retrospective chart review of 44 eyes of 42 patients. The indications for plaque brachytherapy included solid tumor recurrence (n=20; 45%), solid tumor residual (n=16; 36%), new subretinal seeds (n=5; 12%), and new solid tumor (n=3; 7%).

RESULTS: The median age at the presentation was 12 months (range, 3–72 months). Based on ICRB classification, 8 (18%), 8 (18%), 16 (36%), and 5 (12%) tumors belonged to Groups B, C, D, and E, respectively. A median interval of 5 months (range 3–21 months) was noted between the last IVC cycle and plaque brachytherapy. The mean tumor height was four mm (range, 1.5–6 mm). All patients were treated with ^{106}Ru plaque (round or notch) with a median total dose of 45 Gy (range, 40–55 Gy) delivered to the tumor apex. At a mean post plaque follow-up period of 28 months (median, 23 months; range, 3–132 months), tumor completely regressed in 25 eyes (56%). Tumor recurrence within the plaque site was noted in eight eyes (18%) associated with a type 2 regression pattern (75%). At the last follow-up, the globe salvage rate was 24 eyes (55%), while 2 patients (5%) died due to metastasis.

CONCLUSION: ^{106}RU plaque brachytherapy can be a useful salvage treatment for focal tumors (new or recurrent) following systemic IVC.

Keywords: Eye; Tumor; Retinoblastoma; Plaque brachytherapy; Ruthenium-106; Salvage treatment

Introduction

Retinoblastoma (RB) is the most common intraocular cancer of childhood, accounting for approximately 11% of cancers occurring in the first year of life, with 95% diagnosed before 5 years of age (1). In developed countries, the goal of treatment has shifted from globe salvage to vision preservation; whereas in developing and underdeveloped countries, which account for more than 90% of RB children, the intraocular tumor often goes undiagnosed and presents as advanced disease threatening globe salvage (2). Enucleation remains the definitive treatment in case of advanced unilateral intraocular retinoblastoma, particularly group E RB. Globe salvage treatment modalities include chemotherapy either delivered through the intravenous route (IVC) or intra-arterial route (IAC) along with local ocular delivery of melphalan or topotecan injection directly into vitreous cavity (iVitC) or using periocular subconjunctival carboplatin injection.

With the advancements in treatment of RB, the reported globe salvage outcomes for advanced intraocular RB (group D and E eyes) have significantly improved with IAC ranging from 36% to 100% for group D eyes and 17 to 87% for group E eyes (3–5). However, the rates of new tumor development (6%–45%) (6,7) and rate of tumor

Received 25 April 2024; received in revised form 26 June 2024; accepted 27 June 2024; Available online xxx

Disclosures: No conflicting relationship exists for any author. The Operation Eyesight Universal Institute for Eye Cancer (VR, SK) and Hyderabad Eye Research Foundation (VR, SK), Hyderabad, India. The funders had no role in the preparation, review, or approval of the manuscript.

* Corresponding author. The Operation Eyesight Universal Institute for Eye Cancer, L V Prasad Eye Institute, Hyderabad 500034 India.
E-mail address: drvishalraval@gmail.com (V. Raval).
# Equal contribution.

1538-4721/$ - see front matter
https://doi.org/10.1016/j.brachy.2024.06.008

recurrence following IVC (35% to 45%) and IAC (0%–23%) remains a concern (7–9). Ruthenium-106 plaque radiotherapy for RB has been used for many years both as a primary treatment or as a salvage treatment for incomplete tumor regression and/or focal retinal tumor recurrences after chemoreduction in RB (10–16). Reported studies have shown excellent outcomes in terms of local tumor control (60%–90%) and globe salvage rates with use of Ruthenium-106 (^{106}Ru) and Iodine-125 (^{125}I) isotopes (11,14–26). From the Asian Indian context, Khetan et al. have reported the use of ^{125}Iisotope as a salvage treatment for recurrent RB with good tumor control and eye salvage rates (83%) (27). In this study, we will analyze our center's experience with use of ^{106}Ruisotope for the treatment of recurrent RB who have received initial systemic IVC. This study will highlight patient demographics, indications, and treatment outcomes such as local tumor control and globe salvage rates following the use of ^{106}Ru isotope for the treatment of recurrent RB in an Asian Indian setting at a tertiary eye care institute.

Methods

This was a retrospective study conducted at a tertiary eye care institute with an approval obtained from the institutional review board. The study adhered to the tenets of the Declaration of Helsinki. Medical records of all patients who underwent ^{106}Ru plaque brachytherapy as a salvage treatment for RB following systemic IVC from 2002 to 2022 were reviewed. All patients who underwent secondary plaque radiotherapy and had a minimum follow-up of three months post-treatment were included in the study. Patients with incomplete relevant data, extraocular RB, or orbital RB at the first visit, and those with a follow-up period of less than three months after ^{106}Ru plaque were excluded from the study.

Patients' demographic details such as age, gender, family history of RB, presenting signs, symptoms, and tumor laterality were recorded. Photographic documentation was performed in all cases using a RetCam 2 wide field imaging system at all EUA visits, and all tumors were appropriately documented with fundus drawings. Fundus drawings and RetCam images were reviewed for accurate tumor details such as location, size, number, distance from the optic nerve and fovea, presence of SRF, and associated features such as vitreous seeding, vitreous hemorrhage, and retinal detachment. All eyes with intraocular tumors were classified based on the International Classification of Intraocular Retinoblastoma (ICRB) (28).

The details of primary treatment (transpupillary thermotherapy (TTT), cryotherapy, IVC, IAC, intravitreal chemotherapy (iVitC), external beam radiotherapy) were recorded. As per the institute protocol, all bilateral cases were treated with a standard intravenous chemotherapeutic regimen consisting of six cycles of vincristine, etoposide, and carboplatin, administered every 3 weeks. All unilateral cases were offered both options for IVC and IAC, and the treatment was planned based on the parents' choice of treatment. Recurrences in the form of solid retinal tumor, subretinal, or vitreous seeding were recorded. Postchemotherapy, all patients with focal solid tumor recurrence, solid tumor residual following incomplete response to IVC or an isolated new tumor or new subretinal seeds were treated with a ^{106}Ru plaque. All episcleral ^{106}Ru plaque applicators were inserted under general anesthesia. Before the operation, tumor location and height were assessed by clinical examination and confirmed using ultrasonography and an appropriate plaque (round; 16 mm or notch; 20 mm) was selected. ^{106}Ru plaques were supplied by BEBIG Isotopen und Medizintechnik GmbH, Berlin, Germany (till 2020) and later supplied by Bhabha Atomic Research Centre (BARC), Mumbai. The dose was prescribed to the tumor apex, representing the minimal dose applied to the tumor. All cases were planned one dimensionally based on the dose distribution along plaque central axis. Since May 2002, BEBIG has delivered its ^{106}Ru eye plaques with new protocols of radioactivity measurements in accordance with the National Institute of Standards and Technology calibration (NIST) system. This recalculation of the radiation dose values according to the NIST calibration standard was based on the conversion tables originally provided by the manufacturer (BEBIG) and verified in our Department of Radiotherapy.

As per recommendations of the American Brachytherapy Society (ABS) a minimum treatment dose rates of 0.6–1.05 Gy/hr, with a prescription dose of 40–46 Gy was delivered in three-seven consecutive days (10). The reference depth was the height of tumor plus sclera thickness (1 mm) with a safety margin of 1 mm. Lateral tumor margin was set to 2–3 mm as suggested by the ABS recommendations (10). Focal consolidation therapies, such as cryotherapy, TTT, and iVitC, were not used in conjunction with plaque treatment; if needed, they were used after an interval of 6 weeks postplaque. Post-treatment, all patients were followed up at three monthly intervals to determine the response to radiation, regression pattern, and any complications during the postoperative period. The regression patterns were classified as type 0 (no visible residua), type I (fully calcified tumor), type II (fleshy tissue with without any calcification), type III (mixed calcific and fleshy tumor), or type IV (atrophic chorioretinal scar) (29). A solid tumor residual was defined as an incomplete response to IVC with persistent active tumor within or adjacent to regressed tumor. Tumor recurrence was defined as any new tumor or reactivation of a previous tumor in the form of subretinal seeds, vitreous seeds, or a solid tumor after complete regression of tumor with primary treatment or ^{106}Ru plaque brachytherapy. Post plaque brachytherapy tumor regression was categorized as complete or partial regression. Complete regression was defined as complete inactivity of the tumor, and partial regression defined as small residual active tumor or seeds adjacent to solid tumor area. Last,

Please cite this article as: V.A.R. Palkonda *et al.*, Ruthenium-106 (106Ru) plaque brachytherapy as salvage treatment for retinoblastoma following intravenous chemotherapy, Brachytherapy, https://doi.org/10.1016/j.brachy.2024.06.008

Table 1
Demographic features of retinoblastoma patients treated with ^{106}Ru plaque.

Features	n = 42 patients (44 eyes) n (%)
Age at presentation (months) median (range) months	12 (3–72)
Gender	
Male	22 (53)
Female	20 (47)
Family history of retinoblastoma	3 (7)
Presenting complaints[a]	
Leukocoria	30 (68)
Strabismus	11 (26)
Proptosis	2 (5)
Redness	1 (3)
Duration of presenting complaints (months) median (range)	2 (<1–36)
Laterality of retinoblastoma	
Bilateral	25 (60)
Unilateral	17 (40)

[a] Two patients had more than one presenting complaint.

follow up persistent tumor regression was defined as no evidence of disease activity within the eye. Eyes with massive tumor recurrence involving more than two quadrants, presence of diffuse subretinal seeds, vitreous hemorrhage and total retinal detachment were absolute contraindications for plaque brachytherapy.

The main outcome measures were tumor regression, globe salvage, metastasis, and overall survival. For time to enucleation, the association with potential risk factors was analyzed using the Cox proportional hazard regression model. SPSS ver. 17.0 (SPSS Inc., Chicago, IL, USA) was used for all statistical analyses. The cumulative incidence providing an estimate of the risk (probability) of the enucleation and death were calculated using a cumulative incidence graph. Similarly, the 2-years and 4-years incidence rate for enucleation were calculated using Fine-Gray model. Statistical significance was set at $p \leq 0.05$.

Results

A total of 44 eyes of 42 patients with a male: female ratio of 1.1:1 were included (Table 1). Three patients had a family history of RB in one parent. Bilateral RB was seen in 25 patients (60%). Unfortunately, genetic testing for *RB1* mutation was not performed due to financial constraints. The median age at the presentation was 12 months (range, 3–72 months). The most common presenting complaint was leukocoria (n = 30, 68%) followed by strabismus (n = 11, 26%) with a mean duration of symptoms of 5 months (median, 2 months; range, 1–36 months). Based on ICRB, eight eyes (18%) belonged to Group B, eight (18%) to Group C, sixteen (36%) to Group D, and five (12%) to Group E. Seven eyes (16%) could not be classified as they were referred cases with a history of prior treatment.

All patients were treated with six cycles of primary systemic IVC along with adjuvant focal treatment (laser/cryotherapy) at 3-week intervals (Table 2). At a median interval of 5 months (range, 3–21 months) following IVC, solid tumor recurrence (n = 20; 45%), solid tumor residual (n = 16; 36%), new subretinal seeds (n = 5; 12%), and new solid tumor (n= 3; 7%) were noted. The most common regression patterns associated with tumor recurrences following IVC were type 3 (28 eyes, 64%) and type 1 (7 eyes, 16%). Prior to ^{106}Ru plaque application, the mean largest basal diameter was six mm (median, 6.5 mm; range, 3–12 mm) and the mean tumor height was four mm (median, 4.5 mm; range, 1.5–6 mm). Most tumors were located posterior to the equator (75%) and involved the inferotemporal (27%) and temporal quadrants (23%). Patients were treated with ^{106}Ru plaque with a median total dose of 45 Gy (range, 40 to 55 Gy) delivered to the tumor apex over a median time of 42.5 hours (range 14–113 hours). A round plaque design (16 mm) was used in 28 (64%) eyes, and a notch plaque (20 mm) was used in the remaining 16 (36%) eyes. Associated additional focal small tumors (<2 mm) and subretinal seeding were treated with TTT and/or cryotherapy (29 eyes), while vitreous seeding was treated with intravitreal topotecan injection (five eyes).

Post ^{106}Ru plaque brachytherapy, at 3 months follow-up, the tumor completely regressed in 36 eyes (82%), and partially regressed in eight eyes (18%) (Table 3). The most common regression patterns observed following plaque were type 3 (36%) and type 4 (32%). However, at a median interval of 5 months (4-7 months), nineteen eyes (43%) had tumor recurrence; eight (18%) at the original site of plaque, and eleven (26%) at other areas in the retina. At a mean follow-up period of 28 months (median, 23 months; range, 3–132 months), the tumor completely regressed in 25 eyes (56%). Of the five eyes that received intravitreal topotecan injection for vitreous seeds following plaque treatment, globe was salvaged in three eyes. Of the 24 eyes with visual acuity details, six (25%) eyes had a final visual acuity of ≥20/200 and only two (8%) eyes had a visual acuity of 20/60 at the last follow-up. Complica-

Please cite this article as: V.A.R. Palkonda *et al.*, Ruthenium-106 (106Ru) plaque brachytherapy as salvage treatment for retinoblastoma following intravenous chemotherapy, Brachytherapy, https://doi.org/10.1016/j.brachy.2024.06.008

Table 2
Clinical features at presentation and preplaque brachytherapy treatment details.

Clinical features	n = 44 eyes n (%)
Intraocular pressure (mm Hg) mean (median; range)	10 (10; 6–17)
Number of tumors	
Single	31(70)
Multiple	13 (30)
Basal diameter of largest tumor in the eye (mm) mean (median; range)	14 (14; 4–24)
Thickness of largest tumor in the eye (mm) mean (median; range)	12 (12; 4–20)
Associated features[a]	
Subretinal seeds	17 (44)
Vitreous seeds	11 (28)
Retinal detachment	23 (59)
ICRB Classification of retinoblastoma	
Group B	8 (18)
Group C	8 (18)
Group D	16 (36)
Group E	5 (12)
Not applicable[b]	7 (16)
TNM classification of retinoblastoma	
cT1b	9 (20)
cT1c	2 (5)
cT2	26 (59)
Not applicable[b]	7 (16)
Primary treatment	
IVC	44 (100)
Total number of IVC courses before plaque radiotherapy[c] mean (median; range)	9 (8; 6–18)
Adjuvant treatment	
TTT[d]	n = 29 tumors
mean (median; range)	5 (4; 1–15)
Cryotherapy[d]	n = 19 tumors
mean (median; range)	5 (4; 1–16)
Intravitreal chemotherapy	n = 5 eyes
mean (median; range)	5 (6; 2–6)
Periocular chemotherapy	n = 4 eyes
mean (median; range)	4 (4; 2 to 8)

[a] Multiple associated features were observed in a few eyes; ICRB = International Classification of Intraocular Retinoblastoma.
[b] Not classified since patients had already received treatment elsewhere before presenting to us; AJCC= American Joint Committee on Cancer; IVC=intravenous chemotherapy.
[c] All patients received 6 cycles of IVC as primary treatment. Few patients received additional cycles of IVC as secondary treatment for persistent or recurrent tumor after primary IVC; TTT=transpupillary thermotherapy.
[d] Adjuvant treatments to only the tumor that underwent plaque radiotherapy.

tions noted in the early postoperative period included vitreous hemorrhage in four (9%) eyes, retinal detachment in two (5%) eyes, and cataract in one (2%) eye, whereas late radiation-related retinopathy was seen in one (2%) eye at a mean interval of 30 months. At the last follow-up, globe salvage was achieved in 24 (55%) eyes, while secondary enucleation was performed due to tumor recurrence at the plaque site (n= 4), tumor recurrence elsewhere in the eye (n = 11) and complications such as vitreous hemorrhage obscuring the tumor details (n = 4). The estimated cumulative incidence (probability) for enucleation at 2 years was 0.25 (95% CI: 0.12–0.41) and 4 years was 0.58 (95% CI: 0.37–0.75). Similarly, the estimated probability of death at 2 years was 0.02 (95% CI: 0.002–0.105) and remained around 0.06 from 4 to 10 years (Fig. 1). Using the Fine-Gray model, the incidence rate of enucleation was 47% (95% CI: 24%–68%) at 2 years and 84% (95% CI: 53%–95%) at 4 years, showing an increasing enucleation risk over time ($p < 0.001$). The median time interval between plaque radiotherapy and enucleation was 8 months (range, 2–28 months). At the last follow-up, 2 patients (5%) died due to metastasis, one was secondary to advanced RB in the contralateral eye and the other was due to a progressive tumor in the ipsilateral eye. Cox proportional hazards regression analysis showed that patients with tumor regression type 2 (HR, 7.33; $p = 0.04$) and the presence of vitreous seeds (HR, 8.95; $p = 0.007$) had an increased risk of enucleation (Table 4). Illustrative case examples highlight-

Please cite this article as: V.A.R. Palkonda *et al.*, Ruthenium-106 (106Ru) plaque brachytherapy as salvage treatment for retinoblastoma following intravenous chemotherapy, Brachytherapy, https://doi.org/10.1016/j.brachy.2024.06.008

Table 3
Episcleral plaque brachytherapy parameters and treatment outcomes.

Features	n = 44 eyes n (%)
Tumor laterality	
Right eye	22 (50)
Left eye	22 (50)
Indication	
Solid tumor recurrence	20 (45)
Tumor residue[a]	16 (36)
New subretinal seeds	5 (12)
New solid tumor	3 (7)
Post IVC regression pattern	
Type 1	7 (16)
Type 2	4 (9)
Type 3	28 (64)
Type 4	5 (11)
Type of tumor treated with plaque	
Solid retinal tumor alone	36 (82)
Subretinal seeds alone	6 (15)
Solid retinal tumor + subretinal seeds	2 (3)
Quadrant involved	
Inferotemporal	12 (27)
Temporal	10 (23)
Inferior	8 (18)
Inferonasal	5 (11)
Others	9 (21)
Tumor location	
Posterior pole	14 (32)
Equator	5 (11)
Periphery	24 (55)
Ora	1 (2)
Tumor basal dimension (mm)	6 (6, 3–12)
mean (median; range)	
Tumor height (mm)	4 (4, 1.5–6)
Mean (median, range)	
Ruthenium-106 plaque design	
Round	28 (64)
Notch	16 (36)
Median tumor apex dose (range) (Gy)	45 Gy (40–55 Gy)
Tumor treated with 4600 Gy	21 (48)
Tumor treated with 4000 Gy	14 (32)
Initial tumor response to plaque radiotherapy	
Complete tumor regression	36 (82)
Partial tumor regression	8 (18)
Regression pattern	
Type 1	3 (7)
Type 2	11 (25)
Type 3	16 (36)
Type 4	14 (32)
Tumor response over follow-up period[b]	
Persistent tumor regression	25 (56)
Tumor recurrence in area of plaque	8 (18)
Tumor recurrence elsewhere	11 (26)
Post plaque regression type associated with recurrence	
Type 2	6 (75)
Type 3	1 (12.5)
Type 4	1 (12.5)
Visual outcomes (n = 24)	
≥20/200	6 (35)
<20/200	18 (65)
Complications	
Vitreous haemorrhage	4 (9)
Retinal detachment	2 (5)
Cataract	1 (2)
Radiation retinopathy	1 (2)

(*continued on next page*)

Please cite this article as: V.A.R. Palkonda *et al.*, Ruthenium-106 (106Ru) plaque brachytherapy as salvage treatment for retinoblastoma following intravenous chemotherapy, Brachytherapy, https://doi.org/10.1016/j.brachy.2024.06.008

Table 3 (*continued*)

Features	n = 44 eyes n (%)
Final outcome at last follow-up	
Globe salvage	24 (55)
Enucleation	19 (43)
Metastasis and death	2 (5)
Follow up postplaque radiotherapy (months) mean (median, range)	28 (23, 3–132)

[a] Includes 12 solid tumor residues and 2 subretinal seed residues.
[b] Includes only the tumor treated with plaque radiotherapy and the eyes which showed complete tumor regression initially.

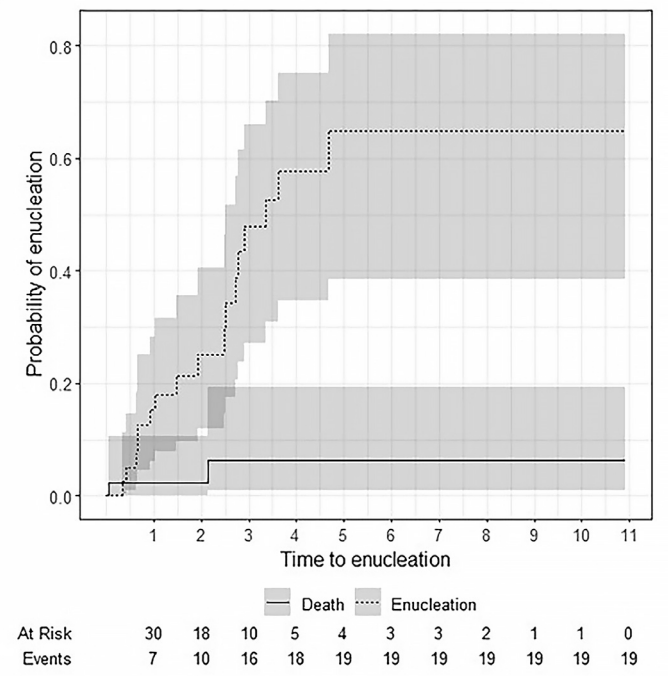

Fig. 1. Cumulative incidence graph of probability of enucleation and death overtime of follow-up.

ing salvage treatment with plaque brachytherapy after IVC are shown in Fig. 2.

Discussion

Despite recent advances such as IAC and iVitC in the last decade, tumor recurrence in form of solid tumor, vitreous seeding, subretinal seeding or aqueous seeding or the development of new retinal tumors in the immediate post-treatment follow-up period remains a concern. Studies have reported development of new tumors or recurrence ranging from 24% to 73% majority within the first year following systemic IVC (7,30–32). Focal treatment such as plaque radiotherapy has been used either as a primary or as a salvage therapy following systemic IVC or IAC for focal new or recurrent tumors as well as following failure of intravitreal or periocular chemotherapy (10,13,15,16,18,27). Alternative treatment options in centers with unavailability of plaque include a repeat cycle of systemic IVC or IAC along with focal treatments. In our in-house study, a globe salvage rate of 54% was observed in patients with refractory/recurrent RB who received secondary salvage IVC with appropriate focal treatment (33). Similarly, Kumari et al. showed that 54% of eyes could be salvaged after a secondary IAC for refractory/recurrent RB following primary IVC (34). This study reviewed our experience of using ^{106}Ru plaque as a salvage treatment for new or recurrent retinal tumor following systemic IVC.

In our previous study of all RB cases, the median age at presentation was 24 months (35), suggesting that younger median age at presentation of 12 months in the current study had an increased risk of tumor recurrence thereby necessitating need for other treatment modalities such as plaque brachytherapy, repeated chemotherapy (IVC or IAC) and enucleation. The mean time to tumor recurrence following systemic IVC as reported in previous studies ranged from 3 to 6 months (7,32,36). while in our series, retinal tumor recurrence or new solid tumor was

Please cite this article as: V.A.R. Palkonda *et al.*, Ruthenium-106 (106Ru) plaque brachytherapy as salvage treatment for retinoblastoma following intravenous chemotherapy, Brachytherapy, https://doi.org/10.1016/j.brachy.2024.06.008

Table 4
Cox proportional hazard regression model to determine risk factors predictive of enucleation in patients with retinoblastoma.

	p-value	Hazard Ratio (HR)	95% CI of HR		*p*-value	Hazard Ratio (HR)	95% CI of HR	
			Lower	Upper			Lower	Upper
Recurrence in what type of regression (compared to Type 4)	0.94							
• Type 1	0.59	0.61	0.10	3.68				
• Type 2	0.98	0	0					
• Type 3	0.88	0.89	0.20	3.94				
Tumor regression	0.349	0.589	0.194	1.786				
Regression post Plaque (Compared to Type 4)	0.01				0.05			
• Type 1	0.99	0	0		0.99	1.27	0	7.21E+04
• Type 2	**0.003**	10.231	2.207	47.430	**0.04**	7.33	1.51	46.73
• Type 3	0.16	3.10	0.64	14.96	0.59	1.74	0.24	12.67
Type of Plaque (Round vs Notch)	0.59	1.29	0.51	3.3				
cTNM staging (compared to cT2)	0.23				0.98			
• cT1b	0.09	0.02	0	1.87	0.86	0	0	1.72E+34
• cT1c	0.75	0.03	0	63246581.9	0.99	0	0	-
Vitreous seeding	0.052	2.537	0.993	6.479	**0.007**	8.95	1.81	44.38
Subretinal seeding	0.249	1.700	0.690	4.188	0.22	2.55	0.58	11.23
Retinal detachment	0.253	1.760	0.668	4.641	0.49	0.63	0.17	2.37
Gender	0.480	0.743	0.327	1.692				
Tumor location (compared to location at ora serrata)	0.91							
• Posterior pole	0.95	1294.8	0	5.52E+109				
• Equator	0.95	1566.3	0	6.70E+109				
• Periphery	0.95	987.2	0	4.21E+109				
Plaque dose	0.420	1.000	0.999	1.001				
Plaque duration (hrs)	0.558	1.006	0.987	1.025				
Base diameter (mm)	0.688	0.943	0.707	1.257				
Thickness (mm)	0.654	0.902	0.575	1.415				
Age	0.599	0.993	0.966	1.020				
ICRB classification (compared to stage E)	0.34				0.26			
• Stage B	0.95	0	0	7.96E+184	0.99	1.17	0	1.98E+04
• Stage C	0.07	0.21	0.04	1.16	0.08	0.09	0.006	1.35
• Stage D	0.57	0.72	0.23	2.28	0.06	0.42	0.05	1.08

Bold values signify P value < 0.05.

noted at a median interval of 5 months. The delayed presentation in our series can be explained as the previously reported series included all types of recurrences such as retinal tumors, subretinal, or vitreous seeding. Of the 44 eyes treated with systemic IVC, solid tumor recurrence was noted in 20 eyes, whereas the solid tumor residual was noted in 16 eyes.

Episcleral plaque brachytherapy using ^{106}Ru or ^{125}I isotopes has been the treatment of choice for focal new or recurrent retinal tumors located either anterior or posterior to the equator with tumor height of more than 3 mm. The reported local tumor control rates following use of ^{106}Ru or ^{125}I isotopes range from 60% to 90% (10,11,14–18). However, in our institute due to unavailability of ^{125}I, ^{106}Ru was the preferred isotope, being amenable for tumor height more than three mm and less than six mm. In our series, the mean tumor height was four mm, which was amenable to be treated with ^{106}Ru isotope. Compared with previous studies, the dose delivered to the tumor apex varied from 40 Gy to 67 Gy considering that the isotope is manufactured by different companies all around the world. (11,14,17,24) The initial tumor control rate achieved in our series was 82% (36 eyes) in the immediate treatment period, while the long-term tumor control rate reduced to 56% (25 eyes). This finding varied from reports from other centers (11,15–18,24). However, direct study comparison is difficult due to the different study populations and factors such as the use of varied or multiple radiation isotopes, varied stage of disease at presentation and at the time of plaque brachytherapy, the use of different primary treatments before plaque radiotherapy, and different follow-up durations. Consequently, the data from this study is unique in that it clearly describes the local tumor control and subsequent globe salvage outcomes following use of ^{106}Ru plaque as a salvage treatment for RB following IVC, which is the most common treatment modality across the globe.

Post plaque treatment, 19 eyes showed retinal tumor recurrence either in the same location where radiation was given (n = 8) or in the adjoining quadrant (n = 11). Studies have identified various factors predictive for local recurrence after plaque brachytherapy, such as older age, lack

Please cite this article as: V.A.R. Palkonda *et al.*, Ruthenium-106 (106Ru) plaque brachytherapy as salvage treatment for retinoblastoma following intravenous chemotherapy, Brachytherapy, https://doi.org/10.1016/j.brachy.2024.06.008

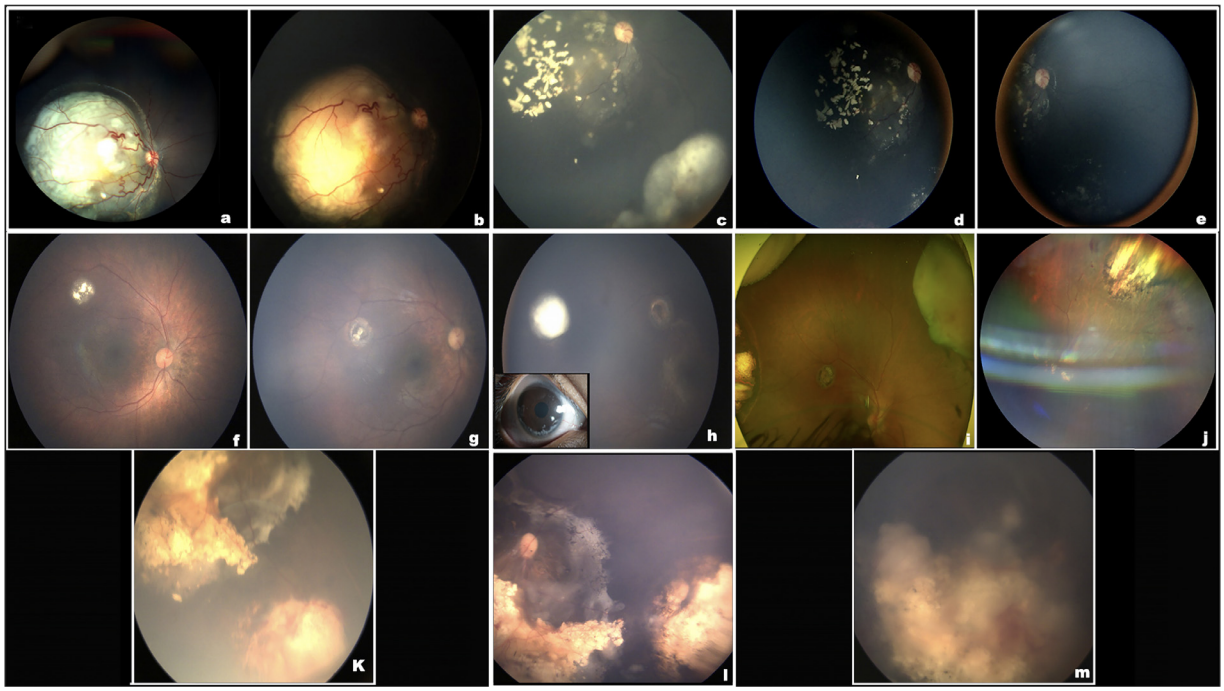

Fig. 2. Episcleral plaque radiotherapy as salvage treatment for retinoblastoma. (a–e): A 2-year-old girl diagnosed with Group C Rb in the right eye (a). She underwent six cycles of intravenous chemotherapy following which the tumor regressed (b). A new solid tumor noted 8 months later in the inferonasal quadrant (c), which was treated with Ru-106 plaque brachytherapy. At the last follow-up, the tumor regressed (d–j). (f–j): A 4-month-old boy diagnosed with bilateral Rb with Group B in the right eye (f). Following six cycles of IVC, the tumor regressed (g). At 5 months, a small new retinal tumor was noted in the inferotemporal quadrant, which was managed with cryotherapy (h). At 15 months, a solitary new tumor was noted in the nasal quadrant along with anterior chamber seeds (i). Plaque brachytherapy was performed using Ru-106 (46 Gy) delivered to tumor apex, following which the tumor regressed (j). (k–m): A 5-month-old boy presented with bilateral Rb having Group E in the right eye. He underwent six cycles of IVC. At 9 months post IVC, tumor recurrence was noted for which plaque brachytherapy was performed (l). Despite initial success, a massive tumor recurrence was noted from the same area (m), and the eye was ultimately enucleated.

of previous focal laser therapy, advanced tumors of more than 5-disc diameter, presence of vitreous seeds, partial or total fish-flesh tumor regression, and prior EBRT treatment (12,14,16,18,24). These necessitate frequent and long-term follow-up to detect recurrence at an early stage. However, in our series, patients with vitreous seeds at presentation and tumor regression type 2 were the only factors predictive of higher risk of enucleation on Cox proportional hazard regression analysis. We also noted that tumor control was maintained over a mean follow-up period of about two and a half years. However, about a third of the tumors developed recurrences after initial tumor control. The mean interval between EPR and tumor recurrence in the area of plaque was 7 months, suggesting that follow-up to assess for recurrences following plaque is crucial in the first 7 months and patients should be counseled accordingly. This may also indicate a delay in tumor recurrence when compared to a previous study by Shields et al., (25) where the mean time to recurrence was 3 months following secondary plaque treatment.

Our visual outcome results were comparable to previous studies using either ^{106}Ru or ^{125}I plaque either as primary or as a salvage treatment following IVC or IAC (17). The final visual acuity in our series was ≥20/200 in only six eyes, which might be explained by posterior location of tumors (75%) and shorter time interval between IVC and plaque treatment (median, 5 months). A study by Francis et al. (37) showed that shorter the time interval between IAC and plaque treatment (2.5 months), higher were the complication rates when compared to an interval of more than 6.6 months which results in no complications.

Long-term radiation-related complications such as retinopathy, optic neuropathy, and cataract have been reported following the use of ^{106}Ru with a mean dose of 138 Gy (SD, 67 Gy) at the tumor apex (24). Previous studies have reported that the dose delivered to the tumor apex varies from 40 Gy to 67 Gy depending upon the surgeon's choice and different companies manufacturing Ru-106 plaques all around the world (11,14,17,38). In our series, a mean dose of 45 Gy was delivered to the tumor apex achieving tumor control rate of 56% and a globe salvage rate of 55%. In our study, all patients received IVC. The most common complications noted in our series were vitreous hemorrhage (four eyes) and retinal detachment (two eyes). Various studies have shown variable results with a slight increase in maculopathy rates compared to other complications, particularly using plaque as a primary treatment versus as a salvage therapy (15,16,18,19,27,37). This

Please cite this article as: V.A.R. Palkonda *et al.*, Ruthenium-106 (106Ru) plaque brachytherapy as salvage treatment for retinoblastoma following intravenous chemotherapy, Brachytherapy, https://doi.org/10.1016/j.brachy.2024.06.008

is explained by the larger size of tumors in the primary group receiving the cumulative increased dose compared with the salvage treatment group. The lower rate of complications in our study might be attributed to use of ^{106}Ru as a salvage treatment with cumulative total dose quite less as compared to use of plaque brachytherapy as a primary treatment.

This study has some inherent drawbacks because of its retrospective nature. Some patients were excluded because of a shorter follow-up period, whereas some patients were lost to follow-up after plaque brachytherapy. However, this study has been able to provide valuable information that can enhance practice by reporting the local tumor control and globe salvage outcomes of ^{106}Ru following IVC.

Conclusion

^{106}Ru can be a useful salvage treatment for focal tumors (new or recurrent) following systemic IVC. After treatment, patients must be monitored closely for radiation-related complications and tumor recurrences. Future research is of great value to analyze and compare the results of plaque brachytherapy as a primary treatment versus as a salvage treatment post IVC or IAC.

Data sharing statement

All data generated and analyzed during this study are included in this manuscript.

Acknowledgments

None.

References

[1] Broaddus E, Topham A, Singh AD. Incidence of retinoblastoma in the USA: 1975-2004. *Bri J Ophthalmol* 2009;93:21–23.
[2] Rodriguez-Galindo C, Wilson MW, Chantada G, et al. Retinoblastoma: one world, one vision. *Pediatrics* 2008;122:e763–e770.
[3] Suzuki S, Yamane T, Mohri M, et al. Selective ophthalmic arterial injection therapy for intraocular retinoblastoma: the long-term prognosis. *Ophthalmology* 2011;118:2081–2087.
[4] Abramson DH, Marr BP, Brodie SE, et al. Ophthalmic artery chemosurgery for less advanced intraocular retinoblastoma: five year review. *PloS one* 2012;7:e34120.
[5] Manjandavida FP, Stathopoulos C, Zhang J, et al. Intra-arterial chemotherapy in retinoblastoma—a paradigm change. *Indian J Ophthalmol* 2019;67:740–754.
[6] Shields CL, Honavar SG, Meadows AT, et al. Chemoreduction plus focal therapy for retinoblastoma: factors predictive of need for treatment with external beam radiotherapy or enucleation. *Am J Ophthalmol* 2002;133:657–664.
[7] Dalvin LA, Bas Z, Tadepalli S, et al. Risk factors for tumor recurrence following primary intravenous chemotherapy (chemoreduction) for retinoblastoma in 869 eyes of 551 patients. *J Pediatr Ophthalmol Strabismus* 2020;57:224–234.
[8] Shields CL, Dockery PW, Yaghy A, et al. Intra-arterial chemotherapy for retinoblastoma in 341 consecutive eyes (1,292 infusions): comparative analysis of outcomes based on patient age, race, and sex. *J AAPOS* 2021;25:150.e1–150.e9.
[9] Berry JL, Kogachi K, Murphree AL, et al. A review of recurrent retinoblastoma: children's hospital Los Angeles classification and treatment guidelines. *Int Ophthalmol Clin* 2019;59:65–75.
[10] The american brachytherapy society consensus guidelines for plaque brachytherapy of uveal melanoma and retinoblastoma. *Brachytherapy* 2014;13:1–14.
[11] Abouzeid H, Moeckli R, Gaillard MC, et al. (106)ruthenium brachytherapy for retinoblastoma. *Int J Radiat Oncol Biol Phys* 2008;71:821–828.
[12] Lucas JT, McGee R, Billups CA, et al. Prior non-irradiative focal therapies do not compromise the efficacy of delayed episcleral plaque brachytherapy in retinoblastoma. *Bri J Ophthalmol* 2019;103:699–703.
[13] Merchant TE, Gould CJ, Wilson MW, et al. Episcleral plaque brachytherapy for retinoblastoma. *Pediatr Blood Cancer* 2004;43:134–139.
[14] Murakami N, Suzuki S, Ito Y, et al. ^{106}ruthenium plaque therapy (rpt) for retinoblastoma. Int J Radiat Oncol *Biol Phys* 2012;84:59–65.
[15] Sarıcı AM, Celkan TT, Oto BB, et al. Episcleral iodine-125 radioactive plaque brachytherapy as a salvage treatment for retinoblastoma in the era of intraarterial chemotherapy. *Turk J Pediatr* 2022;64:285–292.
[16] Shields CL, Shields JA, Cater J, et al. Plaque radiotherapy for retinoblastoma: long-term tumor control and treatment complications in 208 tumors. *Ophthalmology* 2001;108:2116–2121.
[17] Negretti GS, Quhill H, Duncan C, et al. Ruthenium plaque radiotherapy in the current era of retinoblastoma treatment. *Ophthalmic Genet* 2022;43:756–761.
[18] Echegaray JJ, Al-Zahrani YA, Singh A. Episcleral brachytherapy for retinoblastoma. *Bri J Ophthalmol* 2020;104:208.
[19] Shields CL, Mashayekhi A, Sun H, et al. Iodine 125 plaque radiotherapy as salvage treatment for retinoblastoma recurrence after chemoreduction in 84 tumors. *Ophthalmology* 2006;113:2087–2092.
[20] Amendola BE, Markoe AM, Augsburger JJ, et al. Analysis of treatment results in 36 children with retinoblastoma treated by scleral plaque irradiation. Int J Radiat Oncol *Biol Phys* 1989;17:63–70.
[21] Echegaray JJ, Al-Zahrani YA, Singh A. *Episcleral brachytherapy for retinoblastoma* 2020;104:208–213.
[22] Gündüz K, Günalp I, Yalçindağ N, et al. Causes of chemoreduction failure in retinoblastoma and analysis of associated factors leading to eventual treatment with external beam radiotherapy and enucleation. *Ophthalmology* 2004;111:1917–1924.
[23] Nakamura S, Murakami N, Suzuki S, et al. Monte carlo simulation of tilted contact plaque brachytherapy placement for juxtapapillary retinoblastoma. *Radiat Oncol (London, England)* 2022;17:16.
[24] Schueler AO, Flühs D, Anastassiou G, et al. Beta-ray brachytherapy with ^{106}ru plaques for retinoblastoma. *Int J Radiat Oncol Biol Phys* 2006;65:1212–1221.
[25] Shields CL, Shields JA, De Potter P, et al. Plaque radiotherapy in the management of retinoblastoma. Use as a primary and secondary treatment. *Ophthalmology* 1993;100:216–224.
[26] Shields JA, Giblin ME, Shields CL, et al. Episcleral plaque radiotherapy for retinoblastoma. *Ophthalmology* 1989;96:530–537.
[27] Khetan V, Gopal L, Shanmugam MP, et al. Brachytherapy of intra ocular tumors using 'barc i-125 ocu-prosta seeds': an Indian experience. *Indian J Ophthalmol* 2014;62:158–162.
[28] Shields CL, Mashayekhi A, Au AK, et al. The international classification of retinoblastoma predicts chemoreduction success. *Ophthalmology* 2006;113:2276–2280.
[29] Singh AD, Garway-Heath D, Love S, et al. Relationship of regression pattern to recurrence in retinoblastoma. *Bri J Ophthalmol* 1993;77:12–16.

Please cite this article as: V.A.R. Palkonda *et al.*, Ruthenium-106 (106Ru) plaque brachytherapy as salvage treatment for retinoblastoma following intravenous chemotherapy, Brachytherapy, https://doi.org/10.1016/j.brachy.2024.06.008

[30] Gündüz AK, Mirzayev I, Dinçaslan H, et al. Recurrence and new tumor development after frontline intravenous chemotherapy for retinoblastoma: risk factors and treatment results. *Eur J Ophthalmol* 2022;32:1795–1803.

[31] Shields CL, Shelil A, Cater J, et al. Development of new retinoblastomas after 6 cycles of chemoreduction for retinoblastoma in 162 eyes of 106 consecutive patients. *Arch Ophthalmol (Chicago, Ill : 1960)* 2003;121:1571–1576.

[32] Kaliki S, Vempuluru VS, Priya Y, et al. Risk factors for recurrent retinoblastoma after intravenous chemotherapy. *Int Ophthalmol* 2021;41:2033–2039.

[33] Kaliki S, Gavara S, Patil G, et al. Secondary salvage intravenous chemotherapy for refractory/recurrent retinoblastoma: a study of 41 eyes. *Retina (Philadelphia, Pa)* 2024;44:144–150.

[34] Kumari N, Jain N, Saboo S, et al. Intra-arterial chemotherapy in refractory and advanced intraocular retinoblastoma. *Indian J Ophthalmol* 2023;71:436–443.

[35] Kaliki S, Patel A, Iram S, et al. Retinoblastoma in india: Clinical presentation and outcome in 1,457 patients (2,074 eyes). *Retina (Philadelphia, Pa)* 2019;39:379–391.

[36] Berry JL, Jubran R, Kim JW, et al. Long-term outcomes of group d eyes in bilateral retinoblastoma patients treated with chemoreduction and low-dose imrt salvage. *Pediatr Blood Cancer* 2013;60:688–693.

[37] Francis JH, Barker CA, Wolden SL, et al. Salvage/adjuvant brachytherapy after ophthalmic artery chemosurgery for intraocular retinoblastoma. *Int J Radiat Oncol Biol Phys* 2013;87:517–523.

[38] Schlüter S, Bornfeld N, Valiyev E, et al. Combination of brachytherapy and intravitreal chemotherapy in the treatment of retinoblastoma with vitreous seeding. *Ocular Oncol Pathol* 2022;8:64–70.

Please cite this article as: V.A.R. Palkonda *et al.*, Ruthenium-106 (106Ru) plaque brachytherapy as salvage treatment for retinoblastoma following intravenous chemotherapy, Brachytherapy, https://doi.org/10.1016/j.brachy.2024.06.008