Title:

Ruthenium Plaque Radiotherapy in the Current Era of Retinoblastoma Treatment

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Abstract

Background

Two major treatment modalities for retinoblastoma, intraarterial chemotherapy (IAC) and intravitreal chemotherapy (IVitC), have superseded external beam radiotherapy for eye salvage. In this new setting our objectives were to evaluate the indications for plaque radiotherapy, complications, and recurrence rates.

Methods

Retrospective detailed review of patient's charts was performed for all subjects treated with plaque radiotherapy for retinoblastoma between January 2015 and December 2020.

Results

A total of 12 eyes of 12 patients were included. Mean age at plaque insertion was 45 months (median 29, range 17-150). The treatment dose was 40 Gy to the tumour apex. The indication for plaque radiotherapy was salvage therapy in 11 eyes (92%) and primary treatment in one eye (8%). At last follow-up from plaque insertion (mean 36 months, range 3-67), four (33%) patients had visual acuity better than 0.5 LogMAR and four (33%) had visual acuity worse than 1.0 LogMAR. Radiation-related complications were: one (8%) vitreous haemorrhage, two (16%) non-proliferative radiation retinopathy and one (8%) cataract. Recurrence was detected in four (33%) patients at a mean of 7.8 months (median 5, range 1-20) post-plaque. Globe salvage rate was 75%, as three eyes required enucleation, one to treat recurrence of the tumour treated with plaque and two to treat recurrence of other tumours.

Conclusions

In the current era of retinoblastoma management, a role for plaque radiotherapy remains for salvage or primary treatment in eyes with localised active tumour, providing tumour control in 66%. Close observation is recommended to both detect recurrence and radiation-related complications.

Keywords

Retinoblastoma

Plaque radiotherapy

Ruthenium

Oncology

Retina

Introduction

Ocular brachytherapy, using radon seeds, was first used to treat retinoblastoma in the 1930s.[1] Now, in Europe, ruthenium-106 is commonly used for plaque radiotherapy. In the United States, iodine-125 is the preferred radioactive source. The radioactive plaque is sutured onto the sclera over the tumour and a dose of 40-45 Gray at a dose rate of 1000 CGy per day is typically prescribed.[2] Plaque radiotherapy is generally used to treat smaller solitary tumors (AJCC group cT1 and cT2) that have only very localized seeding that can be incorporated into the radiation field or for ocular salvage for the treatment of residual or recurrent tumors.[3,4]

Reported rates of 5-year overall tumour control following plaque radiotherapy as both a primary treatment and a salvage treatment range from 79% to 94.4%.[3,4] Although the dose of radiation used for the treatment of retinoblastoma is significantly less than that used in uveal melanoma, radiation-related complications have been observed. Schueler *et al*., delivered a mean radiation dose of 138 Gy to the tumor apex and demonstrated 22% rate of retinopathy, 21% rate of optic neuropathy and 17% rate of cataract at five years follow-up.[4] Abouzeid *et al.* used a lower dose of radiation (50Gy to the apex) and observed 2% rate of radiation retinopathy and 73% rate of tumour control at one year follow-up.[5] Murphree *et al.*, delivered 40Gy to the tumor apex, in patients previously treated with platinum-based chemotherapy and demonstrated 100% risk of radiation retinopathy.[6] The radiation dose rate administered per day is a function of isotope activity and depends on the age of plaque used in each individual case in these previous studies.[3-6]

Intraarterial chemotherapy (IAC) treatment was first started in Japan in 2004 and then developed and popularized in New York in 2008.[7,8] The safety-enhanced technique of intravitreal chemotherapy (IVitC) was described in 2012.[9] These two treatment options were therefore not in use when previous studies looking at plaque radiotherapy were performed and many of the patients in these previous studies had undergone external beam radiotherapy.[3-6,10] The aim of our study was to investigate the current use of ruthenium-106 plaque radiotherapy, with an apex dose of 40Gy, in the modern era of retinoblastoma treatment. In this new setting our objectives were to find out what the indications for plaque radiotherapy are, and what complication and recurrence rates are.

Material and Methods

The medical records of the London Retinoblastoma service were retrospectively reviewed from January 2015 to December 2021 to select patients treated with plaque radiotherapy for retinoblastoma. This study was approved as an audit by the Institutional Review Board of Barts Health NHS Trust (Number 12436) and adhered to the tenets of the Declaration of Helsinki.

The diagnosis of retinoblastoma was made by a retinoblastoma specialist using examination under anaesthesia (EUA) with indirect ophthalmoscopy, and multimodal imaging including ultrasonography and fluorescein angiography. All eyes with retinoblastoma were graded according to the International Intraocular Retinoblastoma Classification (IIRC) and American Joint Committee on Cancer Staging (AJCC) at diagnosis.[11,12] Decisions to treat with plaque radiotherapy were made by a multi-disciplinary team including ocular oncologists and paediatric oncologists.

Plaque radiotherapy was performed using a 12mm, 15mm or 20mm circular Ruthenium-106 plaque by a single surgeon (MSS). Plaque size was chosen based on allowing at least 2mm of safety margin around the tumour. Plaques were secured to the sclera with 5-0 non-absorbable polyester sutures. Extraocular muscles were temporarily removed if needed to ensure correct plaque placement and haemostasis was ensured to prevent plaque lifting. If there was concern of possible lifting of the plaque a mattress suture could be placed over the body of the plaque. Vitreous seeds were incorporated into the radiation field of the plaque if localised close to the tumor and if radiation planning allowed. Patients were examined under anaesthesia 3-4 weeks following plaque radiotherapy and subsequent follow up intervals were chosen based on tumour response and the status of other tumours in the same and fellow eye.

Visual acuities (VA) were tested before every EUA using Cardiff Cards (fixed choice preferential looking (FCPL)), Keeler Cards (FCPL), Kays picture tests (optotype) and crowded LogMAR, depending on the age of the child. If quantitative assessment was not possible, qualitative methods were used; fixing and following a target, fixation preference or objection to occlusion of the fellow eye.

Data was collected from each patient chart regarding patient demographics, all treatment modalities previously employed, clinical features of the patient and tumours, details of the plaque used and outcomes. Outcome data included data from date last seen including VA, radiation-related complications, tumour recurrence and retinoblastoma-related metastasis/death. Data on any further treatments used was also collected.

Results

There were a total of 12 eyes from 12 patients who underwent plaque radiotherapy for the treatment of retinoblastoma during the study period. Patient demographics including AJCC grade of the plaque-treated eye are shown in table 1. The mean patient age at the time of plaque insertion was 45 months (median 29, range 17-150). The mean time between diagnosis and plaque insertion was 29 months (median 23, range 1-79). Bilateral retinoblastoma was seen in eight (66%) patients and unilateral in four (33%). None of the unilateral retinoblastoma

cases had genetic retinoblastoma. In the eight patients with bilateral retinoblastoma, the AJCC grades of their fellow eyes at presentation were: cT1a (n=1, 13%), cT1b (n=1, 13%), cT2a (n=1, 13%), cT2b (n=3, 38%) and cT3c (n=2, 25%).

Clinical and tumour features are shown in table 2. Plaque radiotherapy was used as a primary treatment in one patient (8%). This patient had a long-standing retinoma that converted to retinoblastoma after 4 years of follow up. All the other patients in the study (n=11, 92%) had plaque radiotherapy performed as salvage therapy to treat retinoblastoma relapses that were resistant to other forms of treatment.

Outcomes are shown in table 3. At final review, in those patients with globe salvage, four had VA better than 0.5 LogMar (20/60 Snellen) and four had VA worse than 1.0 LogMar (20/200 Snellen) in their plaqued eye. Following treatment, 11 (91%) patients were judged to have a complete response to the plaque radiotherapy. Figure 1 illustrates the rapid initial response to treatment three weeks following plaque radiotherapy. The mean time from plaque treatment to maximum response was 2.3 months (median 1.5, range 1-4). Radiation related complications were observed in four (33%) patients: non-proliferative radiation retinopathy (n=2, 16%), vitreous hemorrhage (n=1, 18%) and cataract (n=1, 8%). The patient who developed vitreous haemorrhage had previously been treated with IAC. The two patients with non-proliferative retinopathy had previously received systemic chemotherapy. Recurrence was detected in four patients (33%) at a mean of 7.8 months (median 5, range 1-20) post-plaque (figure 2). Of the four patients with recurrence, one patient had an enucleation four months following plaque radiotherapy, the others had further salvage therapy with either transpupillary thermotherapy laser or intravitreal chemotherapy. The patient requiring intravitreal chemotherapy required no further treatment to the primary tumor following three injections of 20 micrograms of intravitreal melphalan one week apart. Two of the patients had further relapses of other tumours in same eye, eventually requiring enucleation (at 13 months and 22 months following plaque radiotherapy). One (8%) of these patients had trilateral retinoblastoma and developed disseminated central nervous system metastatic disease from which they died at 5 years of age, this was the same patient that developed vitreous haemorrhage post-plaque. Of the four patients with relapse, 3 patients had tumors located posterior to the equator but not involving the posterior pole and one had a tumor anterior to the equator. The patient who developed a cataract did not undergo surgical removal of the cataract as it was not precluding tumor monitoring and it was felt that surgery would not give significant visual improvement.

Discussion

Approximately one child is diagnosed with retinoblastoma per week in the UK.[13] In the London Retinoblastoma service, approximately 25 new cases of retinoblastoma are seen per year. Over the past 7 years only 12 plaques have been inserted. Plaque radiotherapy is therefore not commonly performed, however, in the context of modern treatment modalities for retinoblastoma it remains an important option. We have shown that plaque radiotherapy is used mainly in the salvage of localised relapse that is refractory to other treatment. Eleven (92%) patients in this study had plaque radiotherapy as salvage therapy following multiple other treatments. Only one (8%) patient had the procedure done as a primary treatment and this was for an isolated peripheral tumour. Radiation-related complications were seen in four (33%) patients. Tumour control rate at one year was 75%, and after a mean follow-up of three years was 66%. One patient died from metastatic trilateral retinoblastoma.

The main strength of this study is that it is the first to be carried out looking at ruthenium-106 plaque radiotherapy for the treatment of retinoblastoma in the current era of intraarterial and intravitreal chemotherapy. Patients in this study had a full orthoptic assessment with age-appropriate visual acuity testing at every visit. Previous studies have tended not to report visual acuity outcomes. The main weakness is the low number of patients included in the study. This is due to the low numbers of children diagnosed with retinoblastoma and the infrequency with which radioactive plaques are used.

Our relapse rate of 33% following plaque radiotherapy sits in the middle of figures reported by previous studies which range from 5.6% to 66.3%.[4,10] It is however difficult to make direct comparisons. For instance, Shields *et al.* found a 21% recurrence rate at 5 years, however in 29% of their cases, plaque radiotherapy was used as primary treatment rather than salvage treatment, they also used several different radioisotopes including cobalt-60, ruthenium-106 and iodine-125.[3] Schueler *et al.* had a 5.6% recurrence rate at 5 years.[4] They used significantly higher radiation doses with an average dose of 138 Gy delivered to the tumour apex with ruthenium-106. They had a 29.1% incidence of intraocular haemorrhage following plaque radiotherapy with half of these patients developing vitreous haemorrhage. Abouzeid *et al.* is the most comparable to our study in that they used Ruthenium-106 at a dose of 50 Gy to the apex and 4.8% of their patients were being treated as primary treatments.[5] They report a 27% recurrence rate, but with only one year of follow up, which is similar to our 1-year recurrence rate of 25%.[5] Recurrence following plaque radiotherapy may be secondary to radiation-resistant retinoblastoma cells or due to insufficient radiation dose to the edge or apex of the tumor. Meticulous planning of the plaque procedure by a trained ocular oncologist in conjunction with a radiation physicist experienced in plaque radiotherapy together with careful attention to plaque positioning to avoid plaque mispositioning or lifting are important in preventing recurrence.[2]

Our radiation-related complication rates lie in the middle of figures reported by previous studies but again it is difficult to compare studies because of the multiple differing variables, particularly the fact that many of the patients included in previous studies were exposed to external beam radiotherapy as well as plaque radiotherapy. We report a 24% risk of retinopathy and an 8% risk of cataract. Murphree *et al.*, using Iodine-125 at a dose of 40Gy to the tumour apex, in patients previously treated with platinum-based chemotherapy, demonstrated a 100% risk of radiation retinopathy.[6] Shields *et al.* reported retinopathy in 27%, papillopathy in 26%, cataract in 31% and glaucoma in 11%.[3] Schueler *et al.* reported retinopathy in 22%, papillopathy in 21% and cataract in 17%.[4] Abouzeid *et al.* reported retinopathy in 2.4%, radiation-related retinal detachment in 17.1% and cataract in 9.7%.[5] The high rate of papillopathy in many of these older studies may be due to the use of external beam radiotherapy.

This study is important as it benchmarks outcomes of Ruthenium-106 plaque radiotherapy with an apex dose of 40 Gy, the most frequently prescribed dose, in the current era of retinoblastoma treatment.[2] The recurrence rate, visual acuity figures and complication rates will be helpful to patients and their physicians when deciding about the risks and benefits of plaque radiotherapy versus other options. The recurrence rate of 33% and the retinopathy rate of 24% emphasises the importance of regular follow up and vigilance when assessing patients treated with plaque radiotherapy for retinoblastoma. Even though tumours may initially show complete responses, as 91% did in this study, they can reactivate later. We had only one case of vitreous haemorrhage which was when plaque radiotherapy and IAC were used in the same patient. We first reported this risk in 2012 when all 3 children developed vitreous haemorrhages when IAC was used following relapse after radiotherapy.[12]

Further studies should examine why plaque radiotherapy is being used less frequently than before as a primary treatment. Shields *et al* used plaque radiotherapy as a primary treatment in 29% of cases and had a 12% recurrence rate at 1 year.[3] We used it as a primary treatment in one patient (8%) and no recurrence has developed after 3 years of follow up. Further research also needs to examine larger numbers of retinoblastomas treated with plaque radiotherapy in the current era so that statistical analysis can be done to determine risk factors for failure of plaque radiotherapy and radiation-related complications.

In conclusion, plaque radiotherapy offers a way of delivering localized radiation to retinoblastoma tumours whilst avoiding the wide-spread side-effects associated with external beam radiotherapy. At our institution where multiple other treatment modalities are available, it is rarely used. When it is used, it is predominantly a salvage treatment. Recurrence rate after plaque radiotherapy with a 40Gy apex dose is 33% at a

mean of 3 years. Radiation-related complications are not uncommon and we report a 24% risk of retinopathy and an 8% risk of cataract

Declaration of Interest Statement

The authors report there are no competing interests to declare.

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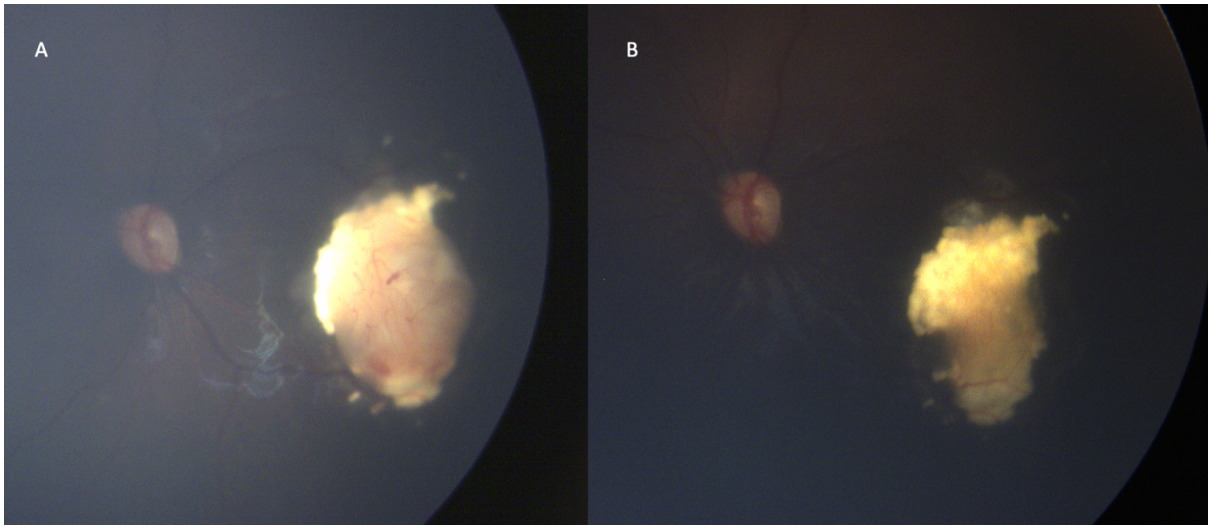
Figures

Figure 1:

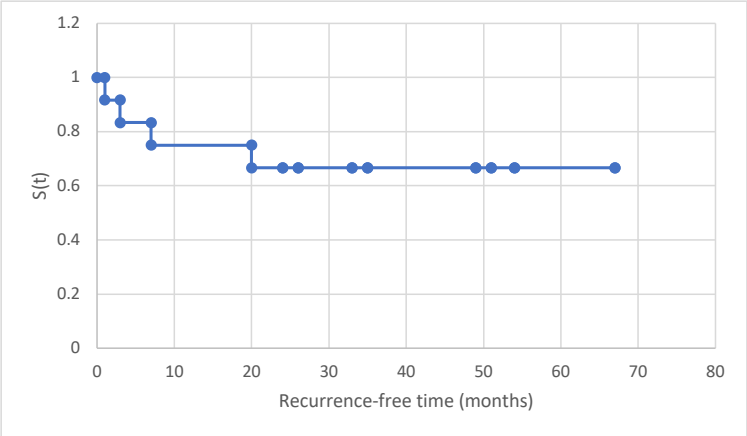
An example of a retinoblastoma tumor responding to ruthenium-106 plaque radiotherapy. A, pre-treatment; B, Three weeks post treatment, showing a rapid early response.



279 **Figure 2:**

280 Kaplan Meier survival curve of tumor recurrence following plaque radiotherapy.

Figure 2



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283 **Table 1:** Ruthenium plaque radiotherapy for the treatment of retinoblastoma in 12 consecutive patients. Patient
284 demographics and clinical features at presentation of the eye that eventually had plaque radiotherapy.
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Demographics	**Number (%), n=12**
Age at presentation (months) mean (median, [range])	18 (6, [0-149]
Sex	
Male	4 (33%)
Female	8 (66%)
Genetic status	
Somatic retinoblastoma	4 (33%)
Genetic retinoblastoma	8 (66%)
Eye	
Left	6 (50%)
Right	6 (50%)
Visual acuity (logMAR)	
-0.18	1 (8%)
0.2	1 (8%)
0.5	2 (16%)
Fixes and follows	3 (25%)
Objects to occlusion	1 (16%)
Reacts to light	1 (8%)
No objection to occlusion	1 (8%)
Unable to measure	2 (16%)
AJCC grade	
cT1a	1 (8%)
cT1b	1 (8%)
cT2a	1 (8%)
cT2b	9 (75%)

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Table 2: Ruthenium plaque radiotherapy for the treatment of retinoblastoma in 12 consecutive patients. Clinical and plaqued tumour features.

Clinical and tumour features	Number (%), n=12
Age at plaque treatment (months) mean (median, [range])	45 (29, [17-150])
Time between diagnosis and plaque (months) mean (median, [range])	27 (21, [1-79])
Indication for plaque	
Primary treatment	1 (8%)
Salvage treatment	11 (92%)
Visual acuity immediately pre-plaque (logMAR)	
-0.2	1 (8%)
0.0	1 (8%)
0.1	1 (8%)
0.2	2 (17%)
1.0	2 (17%)
1.6	1 (8%)
Fixing and following	3 (25%)
No light perception	1 (8%)
Sectoral location of tumour	
Inferotemporal	7 (58%)
Inferonasal	2 (17%)
Superotemporal	2 (17%)
Superonasal	1 (8%)
Anteroposterior location of tumour	
Anterior to equator	6 (50%)
Equator	2 (17%)
Posterior to equator	3 (25%)
Posterior pole	1 (8%)
Size of tumour (mm) mean (median, [range])	
Transverse diameter	5.3 (4.7, [3.8-9.1])
Longitudinal diameter	5.2 (5.1, [2.8-6.8])
Elevation (not including sclera)	3 (2.9, [0.7-7.4])
Radiation dose prescribed to tumour apex	
40 Gy	12 (100%)
Plaque diameter (mm)*	
12	10
15	1
20	1
Treatments received prior to plaque	
None	1 (8%)
IVC and Focal	5 (42%)
IVC, IAC and Focal	4 (33%)
IVC, IVitC and Focal	1 (8%)
IVC, IAC, IVitC and Focal	1 (8%)

IVC = intravenous chemotherapy; IAC = intraarterial chemotherapy; IVitC = intravitreal chemotherapy; Focal = cryotherapy or transpupillary thermotherapy laser. *all patients had circular (non-notched) plaques.

295 **Table 3:** Ruthenium plaque radiotherapy for the treatment of retinoblastoma in 12 consecutive patients.
296 Outcomes.
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Outcomes	Number (%), n=12
Follow-up (months) mean (median, [range])	36 (34, [3-67])
Visual acuity at date last seen (LogMAR)	
-0.3	1 (8%)
0.0	1 (8%)
0.1	2 (16%)
0.7	1 (8%)
1.1	1 (8%)
1.2	2 (16%)
1.3	1 (8%)
Enucleation	3 (25%)
Tumour regression patterns (type)	
1	4 (33%)
2	1 (8%)
3	2 (16%)
4	5 (42%)
Radiation-related complications	
Non-proliferative radiation retinopathy	2 (16%)
Vitreous hemorrhage	1 (8%)
Cataract	1 (8%)
Tumour recurrence following plaque	
Within 1 year	3 (25%)
Within 2 years	4 (33%)
Treatment of recurrence	
Enucleation	1 (8%)
TTT laser followed by Enucleation	2 (16%)
Intravitreal chemotherapy	1 (8%)
Death from metastatic retinoblastoma	1 (8%)

298 TTT=transpupillary thermotherapy
299