Polskie Towarzystwo Okulistyczne
www.pto.com.pl
KLINIKA OCZNA 2022, 124, 4: 211-215
Received: 5.07.2021 Accepted: 29.09.2021

ORIGINAL ARTICLE

Access this article online
Website: www.klinikaoczna.pl
DOI: https://doi.org/10.5114/ko.2021.111473

Episcleral brachytherapy for intraocular retinoblastoma with ^{106}ruthenium plaque: analysis of 13 procedures

Krzysztof Cieślik[1], Anna Rogowska[1], Małgorzata Danowska[1], Karolina Trocka[1], Olga Rutynowska[2], Bożenna Dembowska-Bagińska[2], Agnieszka Kołodziejczyk-Gietka[2], Ingeborga Charzyńska[3], Wojciech Hautz[1]

[1]Department of Ophthalmology, Children's Memorial Health Institute in Warsaw, Poland
[2]Department of Oncology, Children's Memorial Health Institute in Warsaw, Poland
[3]Department of Nuclear Medicine, Children's Memorial Health Institute in Warsaw, Poland

ABSTRACT

Aim of the study: To evaluate the efficacy of ^{106}Ru episcleral brachytherapy for the treatment of retinoblastoma.

Material and methods: Retrospective series of all 13 children with retinoblastoma treated with ^{106}Ru plaques at the Department of Ophthalmology of the Children's Memorial Health Institute in Warsaw between 01.01.2015 and 31.12.2020.

Results: A total of 13 tumors were treated with ^{106}Ru brachytherapy. In all cases it was a salvage treatment for tumors resistant to other treatment modalities, after a mean of 3.15 relapses. Overall tumor control was achieved in 12 cases (92.3%). Tumor recurrence was observed in 1 case (7.7%) which led to enucleation. Radiation complications included persistent hemorrhages from neovascularization in 4 cases (30.8%).

Conclusions: ^{106}Ru brachytherapy can be an effective salvage treatment for retinoblastoma.

KEY WORDS: episcleral brachytherapy, plaque radiotherapy, retinoblastoma, ruthenium.

INTRODUCTION

Brachytherapy (plaque radiotherapy) is a method of treatment that involves delivering radiation directly to lesions, by placing a source of radiation in a tumor (or other lesion) or in its immediate proximity. It enables the irradiation of the tumor with minimum damage to the surrounding healthy tissues. In ophthalmology, brachytherapy is most often used for intraocular tumors such as choroidal melanoma in adults and retinoblastoma in children [1].

Brachytherapy, in contrast to external beam radiation therapy (EBRT), due to the possibility of more precise and local irradiation of the tumor, does not induce orbital bone deformities in infants and carries much smaller risk of induction of second cancers in the treated orbit. Moreover, brachytherapy is in selected cases more effective in treatment of retinoblastoma than EBRT [2].

The use of brachytherapy to treat intraocular tumors was introduced by Moore at the beginning of the 20th century and then modified and further popularized in retinoblastoma treatment by Stallard [3, 4]. In the 1970s, Lommatzsch utilized the β-emitting isotope ^{106}Ru in a shell-shaped applicator with silver casing which provided effective protection of nearby tissues [5].

In Poland, the pioneer of brachytherapy (cobalt-60 – ^{60}Co) in the 1960s in the treatment of eye tumors was Professor Helena Żygulska-Mach in Cracow. The Department of Ophthalmology in Kraków was among the first centers in the world to use brachytherapy to treat ocular tumors [6]. Brachytherapy in the treatment of children with retinoblastoma has been used in the Department of Ophthalmology of the University Hospital in Kraków since 1968, initially with the use of Co-60 applicators, and since 1995 with Ru-106 applicators, while very large tumors are irradiated with I-125. Both methods of brachytherapy are still used today in the treatment of retinoblastoma [7]. At present, ruthenium-106 (^{106}Ru) is the most popular isotope used in Europe, while iodine-125 (^{125}I) is preferred in the USA [8, 9].

^{106}Ru emits β-particles with penetration of 10% of the surface dose to 5–6 mm through water or tissue. ^{106}Ru plaques are suitable for tumors up to 6 mm thick, because of the steep dose gradient in tissue [10]. Applicators with ^{125}I can be used for larger tumors, with a greater radiation range (also use-

CORRESPONDING AUTHOR
Krzysztof Cieślik, MD, Department of Ophthalmology of the Children's Memorial Health Institute, Al. Dzieci Polskich 20, 04-730 Warsaw, Poland, e-mail: okoioczko@gmail.com

This is an Open Access journal, all articles are distributed under the terms of the Creative Commons Attribution-Noncommercial-ShareAlike 4.0 International (CC BY-NC-SA 4.0). License (https://creativecommons.org/licenses/by-nc-sa/4.0/).

ful in cases of tumor dissemination into the vitreous), which allows the eyeball to be preserved, often with useful vision [7]. Treatment with ^{106}Ru plaques, compared with ^{125}I ones, reduces the radiation dose delivered to sensitive structures of the eye: lens, macula and optic disc. Major adverse effects such as cataract formation or optic nerve atrophy are less common after ^{106}Ru brachytherapy in comparison with ^{125}I [10, 11]. Another advantage of ^{106}Ru brachytherapy over ^{125}I is smaller thickness of the former (1 mm vs. 3 mm), which has great importance particularly in infants [12].

In Poland, the total number of children undergoing chemotherapy combined with focal treatment (brachytherapy, cryotherapy, transpupillary thermotherapy (TTT)) increased significantly from 2010 to 2017. In the same period, the number of enucleations and external beam radiotherapies decreased [13].

Brachytherapy with ^{106}Ru has been used in the treatment of retinoblastoma in the Department of Ophthalmology of the Children's Memorial Health Institute in Warsaw, Poland for more than 15 years.

AIM OF THE STUDY

The purpose of this study is to evaluate the efficacy of ^{106}Ru brachytherapy for the treatment of retinoblastoma, in the era of modern treatment modalities: intra-arterial and intravitreal chemotherapy.

MATERIAL AND METHODS

Patients

This study included 13 eyes of 13 patients (9 male, 4 female) – all patients treated with ^{106}Ru brachytherapy in the Department of Ophthalmology of the Children's Memorial Health Institute in Warsaw, Poland from 01.01.2015 to 1.11.2020. The mean time between the initial diagnosis of retinoblastoma and brachytherapy was 19.92 months (median 19; range 10-41). The mean follow-up time from brachytherapy to the last visit was 24.33 months (median 22; range 7-54).

Inclusion criteria

Tumors qualified for brachytherapy were active, repeatedly recurring, not amenable to other methods of local treatment such as cryotherapy, transpupillary thermotherapy (TTT) or indocyanine green enhanced transpupillary thermotherapy (ICG-TTT). Tumors qualified for treatment were less than 6 mm in height, located at a distance not smaller than 2 DD from the optic disc or fovea.

Tumor classification

Bilateral retinoblastoma was diagnosed in 7 patients (53.85%), unilateral in 6 (46.15%). During the initial examination of the child, at the time of retinoblastoma diagnosis, tumors in eyes, that were later treated with brachytherapy, were classified according to the International Classification of Retinoblastoma (ICRB) [14] (Table I).

Three tumors were classified as group A (23.08%), two tumors as group B (15.38%), three tumors as group C (23.08%), one tumor as group D (7.69%) and four tumors as group E (30.77%). The mean tumor height (with sclera) immediately before brachytherapy was 3.7 mm (median 3.74; range 2.66-4.87). Immediately before brachytherapy, tumors were located on white scar in 12 cases (92.3%) and on calcification in one case (7.7%).

Table I. International classification of retinoblastoma [12]

Group	Quick reference	Specific features
A	Small tumor	Retinoblastoma ≤ 3 mm in size*
B	Larger tumor Macula Juxtapapillary Subretinal fluid	Retinoblastoma >3 mm in size* or Macular retinoblastoma location (≤ 3 mm to foveola) Juxtapapillary retinoblastoma location (≤ 1.5 mm to disc) Clear subretinal fluid ≤ 3 mm from margin
C	Focal seeds	Retinoblastoma with Subretinal seeds ≤ 3 mm from retinoblastoma Vitreous seeds ≤ 3 mm from retinoblastoma Both subretinal and vitreous seeds ≤ 3 mm from retinoblastoma
D	Diffuse seeds	Retinoblastoma with Subretinal seeds > 3 mm from retinoblastoma Vitreous seeds > 3 mm from retinoblastoma Both subretinal and vitreous seeds > 3 mm from retinoblastoma
E	Extensive retinoblastoma	Extensive retinoblastoma occupying >50% globe or Neovascular glaucoma Opaque media from hemorrhage in anterior chamber, vitreous, or subretinal space Invasion of postlaminar optic nerve, choroid (> 2 mm), sclera, orbit, anterior chamber

** Refers to 3 mm in basal dimension or thickness*

Previous treatment

In all cases brachytherapy was used as salvage therapy on the active tumor, after inefficacy of other treatment modalities. The mean number of tumor recurrences before brachytherapy was 3.15 (median 3; range 2-7).

All eyes received systemic or intra-arterial chemotherapy before the final relapse which was the indication for brachytherapy. Every tumor before brachytherapy had already received in the past other forms of local treatment (Table II).

Plaque

^{106}Ru plaque, made by Eckert & Ziegler BEBIG GmbH, model CCA 15.3 mm diameter, was used. The plaque was round, shaped correspondingly to the globe curvature, designated for tumors not adjacent to the optic nerve or cornea.

Table II. Systemic and focal treatment of tumors before brachytherapy

Patient number	Systemic chemotherapy – number of cycles	Intra-arterial chemotherapy – number of cycles	TTT of the tumor – number of procedures	ICG-TTT of the tumor – number of procedures	Cryotherapy of the tumor – number of procedures	IVIM of the tumor – number of procedures
1	0	3	0	0	2	0
2	6	0	0	0	3	0
3	6	7	1	0	5	3
4	8	0	1	1	0	0
5	0	3	0	0	1	4
6	6	1	1	0	0	0
7	6	0	0	0	2	0
8	6	2	0	0	4	3
9	6	0	1	0	1	0
10	6	0	1	0	1	0
11	6	1	1	1	2	0
12	2	3	1	0	2	0
13	4	2	0	1	0	3
Mean	**4.77**	**1.69**	**0.54**	**0.23**	**1.77**	**1.00**
Median	**6.00**	**1.00**	**1.00**	**0.00**	**2.00**	**0.00**
Range	**0-8**	**0-7**	**0-1**	**0-1**	**0-5**	**0-4**

Dosimetry

The aimed prescription dose at the tumor apex was 40 Gy. Tumor apex dose calculation was based on the one-dimensional depth dose curve given by the manufacturer on fact sheets for each individual plaque.

Surgical procedure

The episcleral plaques were inserted under general anesthesia after precise tumor localization using indirect ophthalmoscopy and scleral depression. A temporary disinsertion of one extraocular muscle was performed if required. Plaques were affixed to the globe with nonabsorbable sutures. We did not use additional mattress suture to prevent the plaque from possibly tilting away from the globe. Plaques were removed under general anesthesia, after the calculated treatment time corresponding to the delivery of the prescribed radiation dose.

RESULTS

Brachytherapy as the only treatment on active recurrence of retinoblastoma was effective in 12 cases (92.3%). Tumor relapse occurred in one case (7.7%) – 8 months after brachytherapy. Initially, the tumor in this eye was classified as group E. Prior to brachytherapy this eye received: 6 cycles of systemic chemotherapy, 7 cycles of intra-arterial chemotherapy, 5 cryotherapy procedures, 1 TTT procedure, and 3 intravitreal injections of melphalan. The tumor was located on white scar and its height before brachytherapy was 4.13 mm with sclera. In this case, enucleation was suggested to parents at an earlier stage before brachytherapy, but the parents did not give their consent.

In two cases, after brachytherapy, an additional method of treatment was applied, which could have an influence also on the tumor treated with brachytherapy. In both cases, intravitreal injections of melphalan were administered. In the first case, adjuvant treatment was planned at the moment of qualification for brachytherapy. In the second case, it became necessary to treat recurrence in the vitreous 7 months after brachytherapy (recurrence in another part of the vitreous, probably not related to the tumor treated with brachytherapy). In both cases, all intraocular tumors remained in regression.

Ocular survival

Enucleation was performed in one case (7.7%) out of all 13 brachytherapy procedures.

Overall survival

None of the patients died from retinoblastoma. There were no metastases or second cancers in any patient.

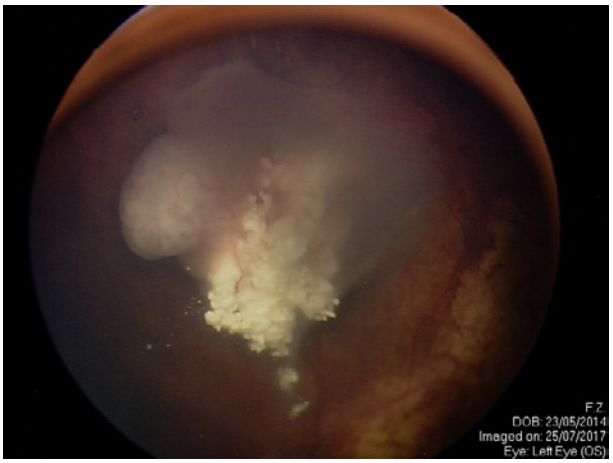

Figure 1. Active tumor (recurrence on calcification) on the day of qualification for brachytherapy

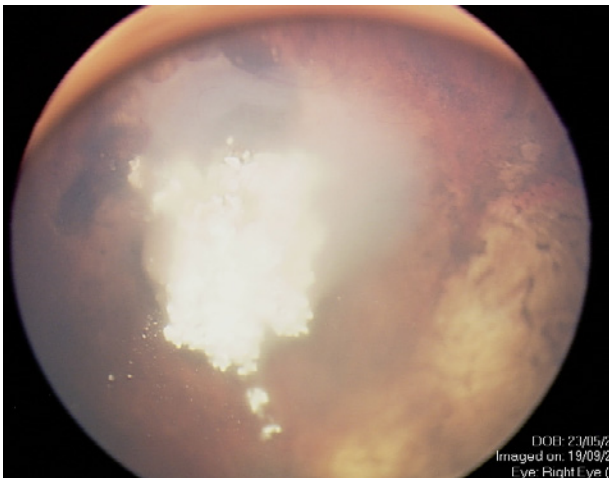

Figure 2. Regressed tumor one month after brachytherapy.

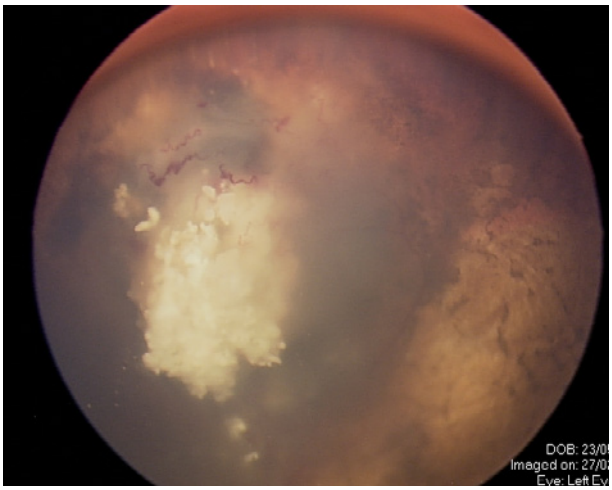

Figure 3. Tumor 6 months after brachytherapy. Abnormal blood vessels visible

Complications

Neovascularisation that caused recurrent retinal and preretinal hemorrhages was found in 4 eyes (30.8%). Abnormal blood vessels were usually located on the tumor apex. Recurrent vitreous hemorrhages from these blood vessels occurred at the mean time of 7.75 months after brachytherapy (median 8.5; range 3-11). Exudate in the area of the tumor was found in 1 eye (7.69%). No cases of optic neuropathy or cataract were observed.

DISCUSSION

In the literature, there is a very limited number of publications concerning the efficacy of brachytherapy for the treatment of retinoblastoma (particularly using ^{106}Ru) after the introduction of both important modern chemotherapy techniques: OAC (ophthalmic artery chemosurgery) and IVIM. In 2013, Francis *et al.* assessed the efficacy of ^{125}I brachytherapy after OAC (only in one case ^{106}Ru plaque). At that time, administering IVIM was not yet widespread [15]. Introduction of IVIM in treatment of retinoblastoma has a major impact on the brachytherapy regimen. At present it is not necessary to consider the vitreous seeds, during treatment field planning, which are often present near the main mass of the treated tumor. Therefore, IVIM administration enables, in selected cases, significant reduction of the radiation dose – which has an influence on reducing the number of complications, particularly involving sensitive structures such as lens and optic nerve. On the other hand, introduction of OAC significantly reduces the risk of subretinal recurrence.

In our work, in all cases, we used brachytherapy for treatment of active tumors. We do not use brachytherapy as consolidation treatment, because after OAC usually there is no need for consolidation, and brachytherapy is associated with complications (recurrent vitreal hemorrhages in 30.8% of patients in our study) too serious to use it as a method to prevent possible recurrences.

In our material, we used brachytherapy as a treatment to save the eye – salvage therapy. Tumors had already received comprehensive systemic and local treatment. All tumors had multiple recurrences before brachytherapy (mean: over 3 recurrences). Almost all tumors were located on white scar, except for one tumor located on calcification (Figures 1-3). At this location of the tumor other local treatment modalities are usually ineffective [16]. Despite these conditions, very high efficacy of brachytherapy draws attention in our data (92.3%).

In our study, the aimed prescription dose at the tumor apex was 40 Gy. Using 106Ru plaque, different centers calculate different doses at the tumor apex: 40 Gy, 55 Gy, 88 Gy [9, 11, 15]. In our study, the dose at the tumor apex of 40 Gy seems to be sufficient. We also did not apply an additional safety margin during dose calculation, adding e.g. 1 mm to the height of the tumor [12].

Notably, there is a small number of complications in our study. Particularly, we did not observe any case of cataract or optic neuropathy. The cause of a small percentage of radiation-related complications might be the use of plaques, in

which the source of radiation is the ^{106}Ru isotope. It emits β-radiation of a very short range (penetration of 10% of the surface dose to 5–6 mm through water or tissue) [10, 11]. Other reasons for the small number of complications in our study are: margin of 2 DD from plaque to optic disc or fovea, no cases of double use of plaque in the same eye, not using EBRT in treatment of intraocular retinoblastoma (method not used for 15 years in our center), average dose of 40 Gy at the tumor apex. The mean follow-up time in our study was 24.33 months (median 22; range 7-54), and occurrence of late complications cannot be excluded [17]. It is worth emphasizing that apart from the greater safety for patient, ^{106}Ru plaque, because of the shorter range of β-radiation, is safer than ^{125}I plaque for medical staff in the operating room and for parents (who could have a mutation of the Rb1 gene) who stay with the child in close proximity in the postoperative period [10, 18, 19].

CONCLUSIONS

^{106}Ru plaque brachytherapy is a highly effective method of treatment for retinoblastoma recurrence even in patients with relapses after OAC. Brachytherapy is associated with adverse effects which have to be taken into account, but are acceptable considering the alternative of enucleation in patients with recurrence after previous treatment.

DISCLOSURE

The authors declare no conflict of interest.

References

1. 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.
2. 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.
3. Moore RF. Choroidal sarcoma treated by the intraocular insertion of radon seeds. Br J Ophthalmol 1930; 14: 145-152.
4. Stallard HB. Radiotherapy of malignant intra-ocular neoplasms. Br J Ophthalmol 1948; 32: 618-639.
5. Lommatzsch PK. Results after beta-irradiation (106Ru/106Rh) of choroidal melanomas: 20 years' experience. Br J Ophthalmol 1986; 70: 844-851.
6. Zygulska-Mach H, Maciejewski Z. Traitement du rétinoblastome par cobalt radioactif et photocoagulation au xénon [Treatment of retinoblastoma by radioactive cobalt and xenon photocoagulation]. Mod Probl Ophthalmol 1977; 18: 118-123.
7. Romanowska-Dixon B, Jakubowska B. History of ocular tumors radiotherapy in Krakow. In: Ocular Oncology. Romanowska-Dixon B, Jager M, Coupland SE (eds.). Wyd. Lek. PZWL, Warszawa 2020; 1-10
8. Echegaray JJ, Al-Zahrani YA, Singh A. Episcleral brachytherapy for retinoblastoma. Br J Ophthalmol 2020; 104: 208-213.
9. Abouzeid H, Moeckli R, Gaillard MC, et al. (106)Ruthenium brachytherapy for retinoblastoma. Int J Radiat Oncol Biol Phys 2008; 71: 821-828.
10. Schueler AO, Flühs D, Anastassiou G, et al. Beta-ray brachytherapy with 106Ru plaques for retinoblastoma. Int J Radiat Oncol Biol Phys 2006; 65: 1212-1221.
11. Schueler AO, Flühs D, Anastassiou G, et al. Beta-ray brachytherapy of retinoblastoma: feasibility of a new small-sized ruthenium-106 plaque. Ophthalmic Res 2006; 38: 8-12.
12. 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.
13. Nowak MS, Romanowska-Dixon B, Grabska-Liberek I, Żurek M. Incidence and Characteristics of Retinoblastoma in Poland: The First Nationwide Study 2010-2017. Int J Environ Res Public Health 2021; 18: 6539.
14. Shields CL, Mashayekhi A, Au AK, et al. The International Classification of Retinoblastoma predicts chemoreduction success. Ophthalmology 2006; 113: 2276-2280.
15. 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.
16. 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. Br J Ophthalmol 2018; 28:bjophthalmol-2018-311923.
17. Bellerive C, Singh AD. Radiation Retinopathy 47 Years following Brachytherapy for Retinoblastoma. Ocul Oncol Pathol 2018; 4: 157-160.
18. Merchant TE, Gould CJ, Wilson MW, et al. Episcleral plaque brachytherapy for retinoblastoma. Pediatr Blood Cancer 2004; 43: 134-139.
19. American Brachytherapy Society - Ophthalmic Oncology Task Force. Electronic address: paulfinger@eyecancer.com; ABS – OOTF Committee. The American Brachytherapy Society consensus guidelines for plaque brachytherapy of uveal melanoma and retinoblastoma. Brachytherapy 2014; 13: 1-14.