Review paper

Personalized re-treatment strategy for uveal melanoma local recurrences after interventional radiotherapy (brachytherapy): single institution experience and systematic literature review

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Abstract

Purpose: To report the results of a patient's tailored therapeutic approach using a second course of interventional radiotherapy (brachytherapy) in patients with locally recurrent uveal melanoma.

Material and methods: Patients who had already undergone ocular brachytherapy treated at our IOC (Interventional Oncology Center) were considered. Five patients who has received a second course of treatment with a plaque after local recurrences were included in our study. Re-irradiation was performed with Ruthenium-106 (prescribed dose to the apex 100 Gy) or with Iodine-125 plaques (prescribed dose to the apex 85 Gy). Moreover, a systematic literature search was conducted through three electronic databases, including Medline/PubMed, Scopus, and Embase.

Results: All patients were initially treated with Ruthenium-106 plaque; the re-irradiation was performed with Ruthenium-106 plaque in three cases and with Iodine in two cases. Mean time between the first and the second plaque was 56.8 months (range, 25-93 months). Local tumor control rate was 100%, no patient underwent secondary enucleation owing to re-treatment failure. Distant metastasis occurred in 1 patient after 6 months from re-treatment. After a median follow-up of 44.2 months (range, 26-65 months) from re-treatment, all patients experienced worsening of the visual acuity (median visual acuity was 0.42 at time of recurrence and decline to 0.24 at the most recent follow-up); cataract occurred in two cases, no patient developed scleral necrosis. We considered 2 papers for a systematic review.

Conclusions: In selected cases, especially in presence of marginal local recurrence, a personalized re-treatment strategy with a plaque may offer high probability of tumor control and organ preservation but worsening of visual acuity.

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Key words: uveal melanoma, brachytherapy, re-treatment, re-irradiation.

Purpose

Episcleral plaque radiotherapy is an effective method of controlling uveal melanoma locally as confirmed by long-term results [1]. Unfortunately, failure of the radioactive plaque to control tumor growth is occasionally observed [2]. Data published in a review by Chang presents local failure rates following various forms of conservative treatments for uveal melanoma [3]: among 49 identified studies, the local treatment failure rate ranged from 0% to 55.6%. The two most widely used forms of interventional radiation therapy, Iodine-125 and Ruthenium-106

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brachytherapy, were associated with a weighted average of local recurrence rate of 9.6%. Furthermore, proton beams resulted in 4.2%, while transpupillary thermotherapy had the largest reported variation of local treatment failure from 0% to 55.6%, with a weighted average of 20.8%. It is possible to observe different kinds of recurrences and a specific dependence from their growth patterns; they may take the form of marginal, central, diffuse, distant, or extrascleral extensions. Marginal recurrences might be related to an insufficient radiation dose to the tumor border following an underdosage to the tumor's edge mainly due to the microscopic disease spread or displacement of the plaque.

Distant recurrences are rare, and they might be caused by melanoma cell spreading throughout the anterior chamber or by the extension of the tumor along the ciliary body. As suggested by some authors, they may be present due to the migration of tumor cells into the exudative retinal detachment [4]. The work of Caujolle *et al*. analyzed the prognosis of different types of uveal melanoma recurrences and reported superior survival rate of marginal recurrence compared to other recurrences in patients treated with proton beams [5].

Usually, the treatment approach for a local recurrence is an enucleation, resulting in several side effects, including poor esthetic results and visual loss [6], which has been investigated and related to tumor localization and dose to the fovea [7]. The main aim of this work is to evaluate outcomes of recurrence re-treatment using eye plaque interventional radiotherapy by analyzing the institutional experience and performing a systematic review of the literature.

Material and methods

The records of patients treated between December 2006 and December 2014 at our institutional IOC [8] (Interventional Oncology Center) [9] for primary uveal melanoma were retrospectively reviewed [10]. All patients have been treated with Ruthenium-106 plaques or Iodine-125 seeds, and the tumor's apex prescription dose was 100 Gy and 85 Gy, respectively. For the treatment, the adequate size and shape of the episcleral plaque has been selected to provide a 1 mm margin in all directions of the base of the tumor. The dose prescription and the CTV definition have been the same for the first course and for the re-treatment. After analyzing all recurrences, patients with marginal recurrences located at the equator, re-treated with the use of interventional radiotherapy were selected for the study.

The exclusion criteria were posterior location of the recurrence and diffuse or global recurrence.

A systematic literature search was conducted through three electronic databases from their inception until February 2018, including Medline/Pubmed, Scopus, and Embase. The following medical subject heading (MeSH) terms were used: "uveal melanoma", "recurrence", "brachytherapy" ("uveal melanoma" [supplementary concept] or "uveal melanoma" [all fields], and ("recurrence" [MeSH terms] or "recurrence" [all fields]), and ("brachytherapy" [MeSH terms] or "brachytherapy" [all

Table 1. Tumor and treatment characteristics of re-treated group of patients (n = 5)

	First treatment radionuclide	Tumor location	First clinical thickness (mm)	Kind of recurrence	First treatment scleral dose (Gy)	Treatment duration (hours)	Time to local recurrence (months)	Second treatment radionuclide	Recurrence thickness (mm)	Second treatment scleral dose (Gy)	Retreatment duration (hours)
1	Ru-106	Equatorial	3.33	Marginal	254.2	41	35	Ru-106	2.17	167.3	31
2	Ru-106	Equatorial	3.70	Marginal	415.5	88	43	I-125	5.80	375.1	73
3	Ru-106	Equatorial	3.46	Marginal	215.5	45	93	I-125	2.17	93.6	74
4	Ru-106	Equatorial	3.18	Marginal	296.9	63	50	Ru-106	2.00	174.8	29
5	Ru-106	Equatorial	3.02	Marginal	263.8	44	63	Ru-106	2.91	219.3	34
Mean			3.33		340.01	56	56.8		3.01	206.02	48

fields]). Two independent authors (BF, MGS) screened citations at the title and abstract level to identify potentially relevant studies without any duplication. Eligible citations were retrieved for full text review, and any uncertainty was resolved by 2 other radiation oncologist experts from ocular interventional radiotherapy (LT, RA) and 2 ophthalmologist experts of the same field (MMP, AS) from the same institution. An independent review of the data was performed by 4 radiation oncologists (VL, GK, RM, SC) from 4 different radiotherapy centers (Perugia, Lubeck, Navarra, Bologna) and by a medical physicist (LA). The senior members of the Gemelli Ocular Melanoma team dedicated to clinical decision-making in ocular cancer, reviewed the paper and gave the final approval to the manuscript (MAG, VV, MAB).

Results

From our database [11], 23 patients affected by recurrence were considered in this analysis. Among these cases of local recurrences, 14 were treated with enucleation, 1 with trans scleral resection, 3 with proton beam, and 5 were selected to undergo a second cycle of brachytherapy. The characteristics of this radioactive plaque re-treated group of five patients with locally recurrent uveal melanomas are reported in Table 1. The median apex height was 3.33 mm at the time of initial diagnosis and 3.01 at the time of recurrence. The mean time between the first and the second plaque was 56.8 months. All patients were initially treated with Ruthenium-106 plaque. The re-irradiation was performed with Ruthenium-106 plaque in three cases and with Iodine-125 seeds in two cases, and the mean dose delivered to the sclera was 340 Gy in the first treatment and 206 Gy in the second plaque. The choice of the kind of radionuclide was based on the final dose to the sclera. The mean total dose delivered to the sclera was 495 Gy. No patients developed scleral necrosis. After a mean follow-up of 44.2 months, the local tumor control rate was 100%, no patient underwent secondary enucleation owing to re-treatment failure. Distant metastasis occurred in 1 patient after 6 months from re-treatment (Table 2).

All patients experienced worsening of the visual acuity. The median visual acuity at time of local recurrence was 0.42, after a median follow-up of 44.2 months (range, 26-65 months). From the time of re-treatment, all patients evolved, as expected, towards a worsening of the visual acuity, with a median decline to 0.24 at the most recent follow-up. No patient developed scleral necrosis [12]. After the re-treatment, cataract occurred in two cases (Table 3).

Figure 1 presents visible tumor's regression after treatment of a patient included in the study. In Figure 2, the visual acuity before and after re-treatment at the last follow-up of all patients included in the study are presented. Regarding the systematic review, 103 papers were identified and carefully evaluated, out of which 72 papers were excluded because BT re-irradiation was not the primary topic of the paper, 24 papers were excluded because BT was used as the first line treatment and not in the setting of a recurrence, 4 papers were excluded because authors reported a mixed cases of patients with recurrent disease treated using several modalities, includ-

Table 2. Follow-up outcomes of the patients

	Follow-up from re-treatment (months)	Total dose to sclera (Gy)	Scleral necrosis	Enucleation	Thickness reduction	Metastasis
1	65	421.5	0	0	54.9%	M0
2	38	790.6	0	0	11%	M0
3	50	309.1	0	0	53.7%	M0
4	42	471.7	0	0	37.10%	M0
5	26	483.1	0	0	22.84%	M1
Mean	44.2	495.20	0	0	35.9%	1/5 (20%)

Table 3. Visual acuity troughout follow-up

	Radionuclide	Visual acuity at time of recurrence	Follow-up from re-treatment (months)	Radionuclide	Visual acuity at last follow-up after re-treatment	Cataract
1	Ru-106	20/20	65	Ru-106	20/40	1
2	Ru-106	20/400	38	I-125	Counting finger	0
3	Ru-106	20/40	50	I-125	20/80	0
4	Ru-106	20/80	42	Ru-106	20/160	1
5	Ru-106	20/32	26	Ru-106	20/40	0
Mean		20/50	44.2		20/80	

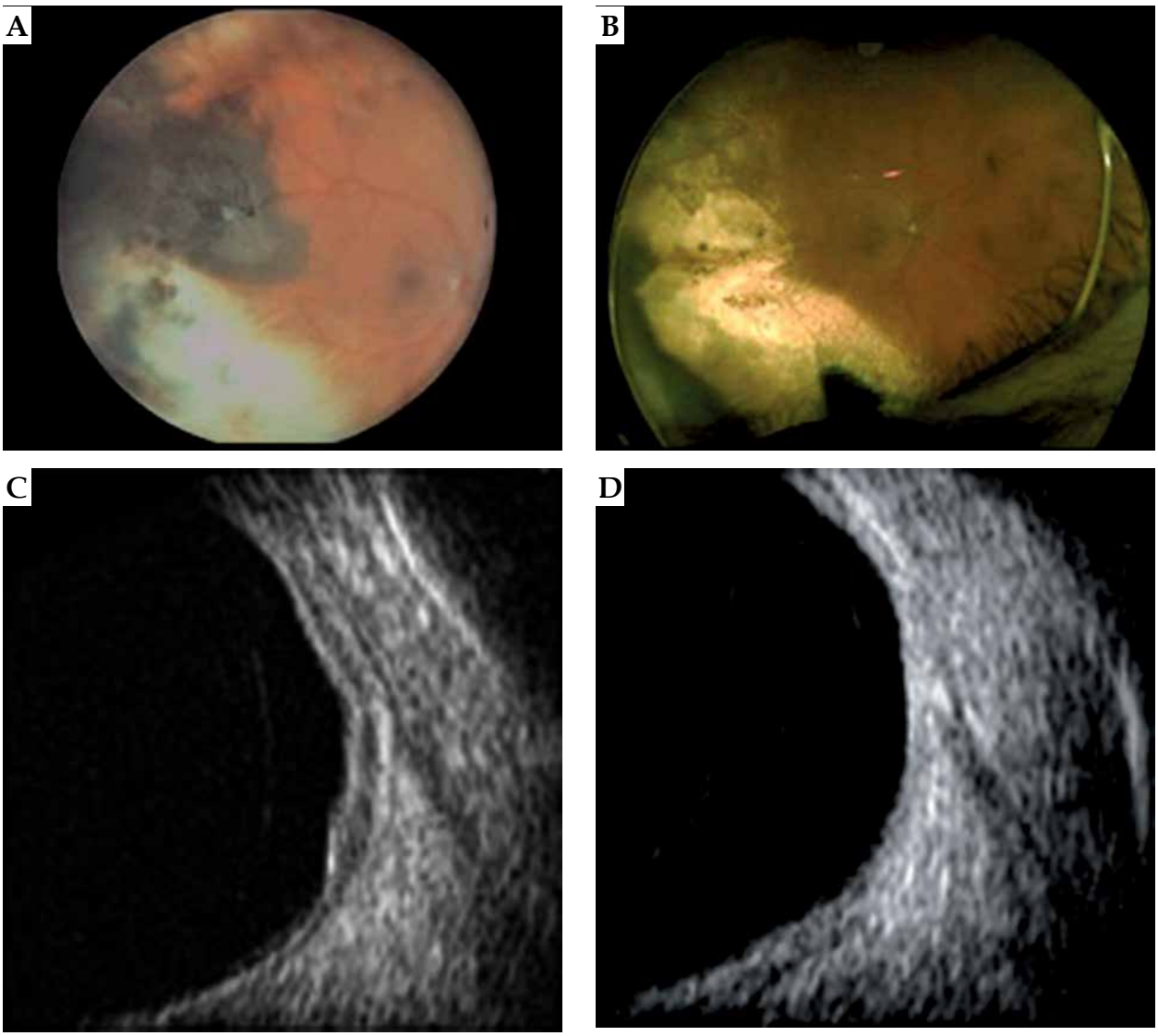

Fig. 1. A, B) Choroidal melanoma before and after treatment, showing the appearance of an extensive scar area; **C, D**) Ultrasonography (USG) shows tumor's regression after treatment

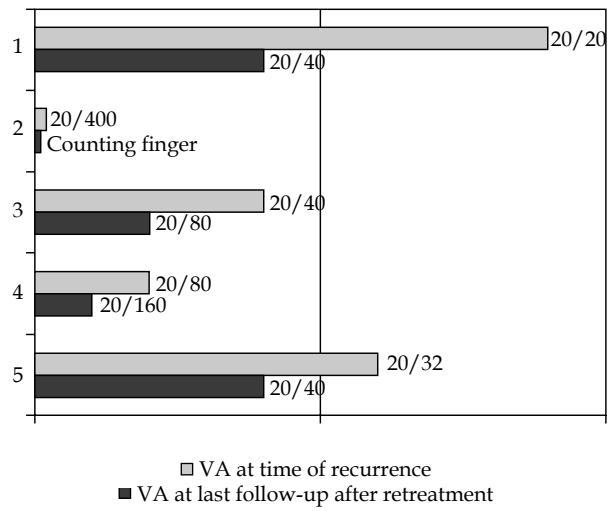

Fig. 2. Differences in visual acuity at the time of recurrence and after retreatment

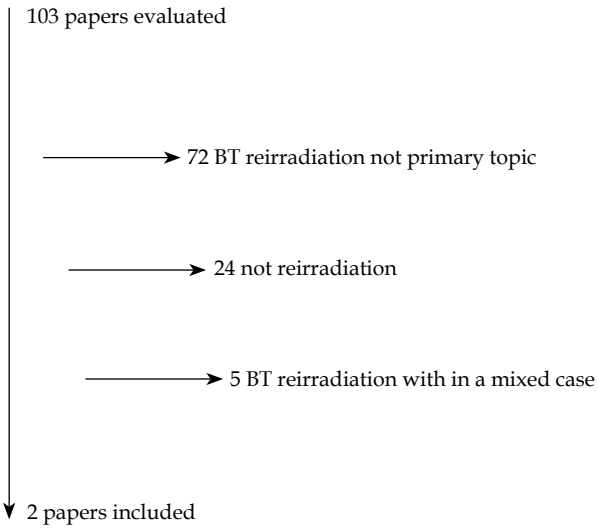

Fig. 3. Search results of literature

ing BT with Ru-106, but with no chance to extrapolate the specific data. Eventually, only two papers dealing with the specific topic of our review were found (Figure 3).

Discussion

Local tumor control is a critical goal in patients' management of the entire head and neck region [13], especially in case of choroidal melanoma, since patients with local treatment failure are prone to an increased risk of metastasis and an increased morbidity of an eye and vision [14].

As there is no established management for cases of local treatment failure, the therapeutic approach depends on the extent and the location of the recurrence and remains a case-by-case decision; even though enucleation is still the most used procedure for recurrent melanoma [15].

Important tumor and treatment features [16,17] as well as the total dose of treatment may influence the outcomes (as reported in literature) of both Iodine-125 [18] and Ruthenium-106 [19,20]. That is why there is an increasing evidence in literature towards supporting a personalized approach for shaping target-specific dose distributions [21].

In this study, we report our single institution experience about the use of a second course of brachytherapy for the re-treatment of patients with choroidal melanoma recurrences. The enrolled patients were selected according the following criteria: the presence of a marginal recurrence and a non-posterior localization of the tumor.

Patients with a diffuse or global recurrence were not considered eligible for re-treatment with plaque, since these types of recurrences are not easily covered by a plaque and might cause tumor re-growth.

Patients with posterior tumor recurrence can be elected for proton beam re-treatment or enucleation, since more posterior or close to the optic disc tumor locations are more challenging; plaques cannot be placed accurately to cover the tumors [22]. Moreover, during brachytherapy treatment for posterior uveal melanomas, Almony *et al*. [23] reported that posterior tilting of a plaque is an important factor contributing to local failure. The tilting and the consequent higher failure rate for posterior tumors could be explained by the difficult surgical access and visualization caused by the orbital anatomy. Furthermore, the optic nerve sheath caused by the obstruction as well the compression of the inferior oblique muscle, the posterior ciliary vessels, and nerves can impede to achieve a close plaque placement to the sclera [24].

In our opinion, in the cases of a re-treatment with plaques, there is an increased risk of posterior tumors tilting, although, in our practice, we use intraoperative ultrasonography for optimal plaque placement [25].

Additionally, epibulbar tissue and inferior oblique muscle fibrosis caused by the first irradiation may create problems to achieve a close apposition of the plaque to the sclera during a second treatment procedure. For these reasons, we excluded the posterior uveal melanoma recurrence from the second course of brachytherapy treatment. In patients with marginal recurrences, the failure of the first brachytherapy might be due to an insufficient radiation dose to the tumor border following errors in treatment planning or in the irradiation delivery, as mentioned by Desjardins *et al*. [26]. Moreover, as suggested by Caujolle *et al*. [5], very large or thin melanomas are more likely to reappear, because of the difficulty to properly definie the lateral tumor limits by an ultrasound. In an analysis of prognosis of different types of uveal melanoma recurrences, the same authors reported superior survival rate of marginal recurrences compared to that of the other recurrences in patients treated with proton beams. Marucci *et al*. [27] supposed that the marginal recurrences represent a less aggressive subtype or phenotype than the other recurrences, as they found lower mortality rate in patients with marginal recurrences treated with a second course of proton beam than in recurrences treated with enucleation. We found only two papers dealing with the specific topic of our review (Figure 2). Gaspar de Souza Neves *et al*. [28] report seven patients who underwent re-irradiation with Ru-106 plaque for uveal melanoma recurrences. The median time between the first treatment and re-irradiation was 24 months and after a median follow-up of 30 months, they found 87.5% of 2-year local control and 60% of progression-free survival. In terms of side effects, the authors specified that all patients evolved with worsening of the visual acuity and cataract; other observed complications were maculopathy and glaucoma. In another study by King *et al*. [29] included twenty-seven patients who were re-irradiated with I-125, the median follow-up from initial treatment was 100 months, with a median time to local recurrence of 43 months. The median follow-up after re-treatment was 47 months and the reported 5-year local control was 77.2%. Furthermore, the authors reported that the visual acuity was 20/70 (20/20 to counting fingers at 1 foot) at the time of recurrence and declined to count fingers (20/25 to hand motion) at their most recent follow-up examination. A comprehensive view of these data is shown in Table 4. In his study, Gaspar de Souza Neves *et al*. [28] did not specify the kind of recurrence, while 44.4% of patients re-treated with plaque studied by King *et al*. [29] were diagnosed with marginal recurrences and 55% by diffuse recurrence. No differenc-

Table 4. Studies available in literature about uveal melanoma retreated with brachytherapy

Author	Year	No. of patients	Radionuclide used for re-irradiation	FU	Local control
Tagliaferri *et al*.	2019	5	Ru-106 or I-125	44.2 months	100% at 3 years
King *et al*. [29]	2017	27	I-125	47 months	87.5% at 2 years
Gaspar de Souza Neves *et al*. [28]	2014	7	Ru-106 or I-125	30 months	77.2% at 5 years

es were reported from the latter author among the local control in the two groups. In the light of the above considerations, marginal recurrences appear to be the most adequate indications for re-treatments with plaques [30]. Supported by our experience, we suggest that clinical implementation of validated nomograms [31] based on large patient cohorts may contribute to a better patient selection [32]. There are existing experiences in the literature regarding similar approaches for data collection and sharing [33], especially in the head and neck region [34].

In the presented study, local tumor control after a mean follow-up of 44.2 months was 100% and no patients underwent a secondary enucleation due to re-treatment failure. Distant metastasis occurred in 1 patient after six months. As reported by Marucci *et al*. [27], the survival in the re-irradiated patients was not compromised by a second course of irradiation. In our study, all patients were initially treated with Ruthenium plaques, and were re-irradiated with Ruthenium-106 plaque in three cases and with Iodine-125 in two cases. In second procedure, the mean total dose delivered to the sclera was 495 Gy. The therapeutic approach was personalized in order to obtain the best functional and local control outcomes [35]. No patients developed scleral necrosis during follow-up. Scleral necrosis is an uncommon complication of radiation therapy because of the radioresistant nature of this avascular, hypocellular, and relatively inactive tissue [36]. It has been reported as a side effect of brachytherapy, with an incidence of up to 14% [37]. After Iodine-125 plaque radiotherapy of melanomas, Shields *et al*. [2] found 1% of cases with scleral melting, all included cases of ciliochoroidal melanomas, two of which had a temporarily rectus muscle disinsertion. Although second course of brachytherapy allows the preservation of an eyeball, the procedure may increase ocular morbidity and the risk of vision-threating ocular side effects. In our patient cohort, cataract occurred in two patients after re-treatment. After a median follow-up of 44.2 (range, 26-65) from re-treatment, all patients evolved with worsening of the visual acuity: median visual acuity was 0.42 at the time of recurrence and declined to 0.24 at the most recent follow-up.

Conclusions

In summary, our experience and the systematic review suggest that, in selected cases (especially in the presence of marginal local recurrences), a personalized re-treatment approach with plaques may offer high probability of tumor control and eye preservation, but a worsening of the visual function may occur.

Disclosure

Authors report no conflict of interest.

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