Incidence and Predictors of Radiation Retinopathy after I^{125} Plaque Brachytherapy for the Treatment of Choroidal Melanoma

Incidência e Preditores de Retinopatia da Radiação Após Braquiterapia em Placa com I^{125} para o Tratamento do Melanoma da Coróide

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ABSTRACT

INTRODUCTION: Plaque brachytherapy is an established modality for the treatment of eligible choroidal melanomas. Radiation retinopathy (RR) is a known complication of brachytherapy, responsible in part for the loss of vision after treatment. We aim to present the first report on the incidence and the predictors of radiation retinopathy after the treatment of choroidal melanomas in the Portuguese Ocular Oncology Reference Centre.

METHODS: Retrospective case series of eligible choroidal melanoma patients submitted to plaque brachytherapy with I^{125} in the Ocular Oncology Unit of the Coimbra University and Hospital Centre (CHUC) between 2013-2021. Clinical, tumor and treatment variables were collected. Primary endpoints were defined as the cumulative incidence and the incidence rate of RR. Secondary endpoints were the clinical predictors of RR as obtained through multivariable logistic regression. Candidate variables were determined through univariate logistic regression, based on clinical and an α level of 0.15. Using these variables, we built a stepwise multivariable logistic regression model, for which we considered an α level of 0.05.

RESULTS: We included 150 eyes of 150 patients, mean aged 61.1±13.3 years and a median follow-up time of 33.5 months (15-52). Incidence rate of RR was 2.14/100 person-years, and the cumulative incidence of radiation retinopathy was 44.7% (67/150). Median time to RR development was 13 (7-18) months. Multivariable logistic regression revealed increased odds of RR with higher baseline tumor thickness (OR 1.39; 1.17-1.65; p<0.01), decreased odds of RR with pre-equator location of the tumor (OR 0.32; 0.11-0.95; p=0.04), and a trend towards decreased odds of RR with increasing age (OR 0.97; 0.95-1.00; p=0.07).

CONCLUSION: The incidence of radiation retinopathy in our cohort agrees with results of published landmark trials in plaque brachytherapy. Increased baseline tumor thickness increased the odds of RR, while pre-equatorial location protected against RR and increased age showed a trend towards a protective effect.

KEYWORDS: Brachytherapy/adverse effects; Choroid Neoplasms/radiotherapy; Iodine Radioisotopes/adverse effects; Melanoma/radiotherapy; Retina/radiation effects.

RESUMO

INTRODUÇÃO: A braquiterapia episcleral é uma opção terapêutica estabelecida no tratamento de melanomas da coroideia. Uma complicação conhecida da braquiterapia, a retinopatia da radiação (RR) é parcialmente responsável pela perda de visão após o tratamento. O nosso objetivo é apresentar o primeiro relato da incidência e respetivos fatores preditores de RR após tratamento do melanoma da coroideia no Centro de Referência em Onco-Oftalmologia.

MÉTODOS: Série retrospetiva de casos de melanoma da coroideia submetidos a tratamento com braquiterapia episcleral com I^{125} no Centro de Referência de Onco-Oftalmologia do Centro Hospitalar e Universitário de Coimbra (CHUC), entre 2013-2021. Foram recolhidas variáveis demográficas, relativas ao tumor e ao protocolo de tratamento. Os desfechos primários foram definidos como a incidência cumulativa e taxa de incidência de RR. Os desfechos secundários foram definidos como os preditores de RR obtidos através de regressão logística multivariada. As variáveis selecionadas para a construção do modelo final multivariado foram selecionadas por via de regressão logística univariada, com base no seu potencial interesse clínico-patológico e/ou um valor de p<0,15. Com base nestas variáveis, foi construído um modelo multivariado *stepwise*, no qual foram incluídas variáveis com interesse clínico-patológico e/ou um valor de p<0,05.

RESULTADOS: Foram incluídos 150 olhos de 150 doentes, com idade média de 61,1±13,3 anos e um tempo mediano de seguimento de 33,5 meses (15-52). A taxa de incidência de RR foi 2,14/100 pessoas-ano e a incidência cumulativa de RR foi de 44,7% (67/150). O tempo mediano para o desenvolvimento de RR foi de 13 (7-18) meses. O modelo multivariado revelou uma maior probabilidade de RR na presença de maior espessura inicial do tumor (OR 1,9; 1,17-1,65; p<0,01) e menor probabilidade de RR com localização tumoral anterior ao equador (OR 0,32; 0,11-0,95; p=0,04). O mesmo modelo multivariado revelou uma tendência para menor probabilidade de RR com o aumento da idade do doente (OR 0,97; 0,95-1,00; p=0,07).

CONCLUSÃO: A incidência de RR na população deste estudo é concordante com os resultados de ensaios clínicos em braquiterapia episcleral. A maior espessura tumoral associou-se a maior probabilidade de RR, enquanto a localização anterior ao equador pareceu protetora quanto ao desenvolvimento de RR. Da mesma forma, a idade avançada do doente apresentou uma tendência, ainda que não significativa, para menor desenvolvimento de RR.

PALAVRAS-CHAVE: Braquiterapia/efeitos adversos; Neoplasias da Coroide/radioterapia; Melanoma/radioterapia; Radioisótopos do Iodo/efeitos adversos; Retina/efeitos da radiação.

INTRODUCTION

Uveal melanoma (UM) is the most common ocular cancer in adults.1 With an average incidence of 6 cases per million population per year in Europe,[1] we estimate there are around 60-70 new cases of uveal melanoma per year in Portugal. Most of these tumors are choroidal melanomas (CM).

The Collaborative Ocular Melanoma Study (COMS) was a landmark randomized clinical trial which showed that for medium-sized CM (2.5-10 mm in thickness and 5-16 mm in basal diameter) local episcleral radiotherapy treatment (i.e., plaque brachytherapy) was comparable to globe enucleation in terms of mortality, an effect lasting over a decade after treatment.[2,3] Until then, there was no consensus as to what the best therapy to offer a patient diagnosed with CM. This signaled a shift in practice to more widespread adoption of globe and vision-preserving strategies. The Ocular Oncology Unit of the Coimbra University and Hospital Centre started offering plaque brachytherapy with radioactive iodine (I^{125}) and subsequent follow-up of patients in the year 2013, in a national effort to develop quality and dignified care for CM patients and filling a gap which by that time had been unaddressed in Portugal.

The increasing use of ionizing radiation for the treatment of CM also meant that clinicians were to deal more frequently with the direct ocular complications of radiation. One such complication is radiation retinopathy (RR). In terms of pathophysiology, RR is suggested to start with endothelial cell loss, subsequent capillary closure and dropout, which ultimately produce retinal ischemia.[4] The

appearance of microaneurysms and cotton-wool spots are common initial signs. Ischemia, in turn, leads to a cycle of malfunctioning of the blood-retinal barrier, with ensuing macular edema, exudation and further ischemia, which, left untreated, sets the stage for a proliferative retinopathy. This process, on a faster timescale, resembles what happens in diabetic retinopathy (DR).[5] Radiation retinopathy is one of the culprits for vision loss after the treatment for uveal melanoma. According to an analysis of COMS trial data, poor vision (defined as <20/200) affected up to 43% of patients 3 years after brachytherapy.[6] Other studies reported up to 68% of patients with poor vision at the 10-year mark.[7] Specifically, RR is reported to occur in up to 43% of patients treated with plaque brachytherapy[8] and it usually begins within 6 months to 3 years after treatment,[5] although longer interval times were reported, especially in what concerns proliferative radiation retinopathy (PRR) stage.[9]

Research on RR has identified several risk factors for its development. Diabetes mellitus (DM) is unsurprisingly linked to the risk of developing RR, especially in its proliferative form.[4,5,9] Other vascular diseases, such as hypertension have also been suggested to play a role.[5] Tumor and eye-related risk factors vary in terms of definition and methodology employed in different research studies, but there seems to be some strength concerning the association of metrics reflecting tumor size, distance to the optic disc and macula, radiation received by the retina and the dose of radiation employed and the subsequent development of clinical manifestations of radiation retinopathy.[5,7,9,10]

With the goal of maintaining visual acuity in treated patients, strategies have been employed to treat RR. The pathophysiological resemblance with DR translates in a similarity of treatment agents, such as panretinal photocoagulation (in the case of PRR), antagonists of the vascular endothelial growth factor (anti-VEGF) and corticosteroids.[5] Anti-VEGF agents, although on an off-label basis, have shown efficacy in preserving vision in treated patients.[11] However, it is important to state that there are currently no established guidelines for the treatment of radiation retinopathy.[5]

The main aim of this study is to determine the incidence of radiation retinopathy and study the predictors of its development in a group of patients diagnosed with choroidal melanoma submitted to episcleral brachytherapy with I^{125} in the Ocular Oncology Unit of the Coimbra University Hospital Centre.

MATERIAL AND METHODS

STUDY DESIGN

Retrospective case series of patients diagnosed with CM referred to the Ocular Oncology Unit of the Coimbra University Hospital Centre (CHUC), Coimbra, Portugal, for treatment with I^{125} plaque brachytherapy between November 2013 and June 2021. Patients with less than 3 months of follow-up after treatment were excluded.

DATA COLLECTION

Electronic and archival print health records were used for the collection of patient demographics, clinical, treatment, and tumor variables.

Patient baseline variables were *gender*, *age*, *diabetes mellitus*, and *best-corrected visual acuity* (BCVA) (natural log of the minimum angle of resolution – logMAR – scale), and laterality of affected eye. In cases of low-vision, semi-quantitative metrics of BCVA such as *counting fingers*, *hand motion*, *light perception*, and *absence of light perception* were converted to 2.0, 2.3, 2.8, and 3.2 logMAR units, respectively, based on previous research in low-vision settings[12,13] BCVA at the date of RR diagnosis was also collected.

Tumor variables were *location* (based on its epicenter as macular, macula to equator, equator to ora serrata, and peripapillary); *initial dimensions* (diameter and thickness). Treatment variables were *total radiation duration* (hours), *radiation dose* (Gy) and *rate* (Gy/h) to the tumor apex, sclera, optic nerve, lens, macula, and opposite retina. A diagnosis of *radiation retinopathy* (RR) was made when there was evidence of one of the following: *microaneurysms*, *hard exudates*, *cotton-wool spots*, *iris* and/or *retinal neovascularization*, and optical coherence tomography (OCT)-evidence of *cystoid macular edema* (CME), after brachytherapy.

BRACHYTHERAPY PROCEDURE

Patients with a confirmed diagnosis of ocular melanoma fitting the Collaborative Ocular Melanoma Study (COMS) trial[14] criteria for brachytherapy were submitted to the attachment of a radioactive plaque to the sclera in an operating room, under general anesthesia. Plaque position was confirmed with intraoperative ocular ultrasound. The treatment duration was calculated with the aim of providing a target delivery dose of 85Gy to the apex of the tumor or at a thickness of 5-mm in the case of melanomas with <5 mm in thickness, at a planned rate non-inferior to 0.6Gy/hour. After completion of the treatment, the plaques were extracted and taken to a laboratory for recycling of the radioactive seeds.

STUDY ENDPOINTS

The *incidence rate and cumulative incidence of radiation retinopathy* after plaque brachytherapy was defined as primary endpoints. As secondary endpoints, we defined the predictors of radiation retinopathy.

STATISTICAL ANALYSIS

Normal continuous variables were expressed as mean ± standard deviation and skewed continuous variables as median and interquartile range (IQR). Categorical variables were expressed as percentages (%).

We performed a time-to-event analysis to determine the incidence rate of radiation retinopathy in the study population and to develop a Kaplan-Meier survival curve of the

outcome radiation retinopathy. We used Logistic regression to perform exploratory analysis of predictors of radiation retinopathy, first through univariate analysis with selection of clinically and statistically significant (at an α level of 0.15) variables for inclusion in a final stepwise multivariable model for the prediction of RR. For the final model, an α level of 0.05 was considered. Furthermore, variables deemed as clinically relevant and capable of strengthening the model were also considered for inclusion in the multivariable stepwise process. The evaluation of model fit was carried out using the Hosmer & Lemeshow's goodness-of-fit test.

The statistical analysis was carried out using STATA® (version 14.0, StataCorp LLC, College Station, TX, USA). An alpha level of 0.05 was chosen as statistically significant.

ETHICS

This study received approval by the local Ethics Committee of the Coimbra University and Hospital Centre and followed the tenets of the Declaration of Helsinki for biomedical research.

RESULTS

BASELINE CHARACTERISTICS

Overall, we included 150 eyes of 150 patients, with and average age of 61.1±13.3 years and a median follow-up time of 33.5 months (15-52). For more detailed demographics, treatment and tumor variables refer to Tables 1 and 2.

Table 1. Demographics of the study population.

Demographic feature	
BCVA (logMAR)	
Baseline	0.5 (0.2-2)
At time of RR diagnosis	2 (1-2.3)
Affected eye (%)	
Right eye	56
Left eye	44
Gender (%)	
Male	44
Female	56
Diabetes (%)	
Yes	11.3
No	62.7
Missing	26

BCVA – best-corrected visual acuity; logMAR – logarithm of the minimum angle of resolution.

STUDY ENDPOINTS

With 67 patients developing radiation retinopathy over 3123 follow-up months, the incidence rate of radiation retinopathy in our sample was 2.14/100 person-years. The cumulative incidence of radiation retinopathy in our study population was 44.7% (67/150 patients). The median time if took for the development of RR was 13 (7-18) months. The Kaplan-Meier survival function curve for the outcome RR is shown on Fig. 1. From its observation, it is apparent that most failures (development of RR) take place before the 3-year mark.

Table 2. Tumor and treatment variables.

Tumor	
Location (%)	
Macular	33.3
Equator to macula	42.7
Equator to ora serrata	14.0
Peripapillary	10.0
Thickness (mm)	6.1 ± 2.2
Diameter (mm)	11.6 ± 2.7
Treatment	
Duration (hours)	120 (120-168)
Radiation dose (Gy)	
Apex	87.1 (85.3-100.6)
Sclera	301.4 (220.0-441.8)
Optic nerve	50.2 (35.2-69.0)
Macula	74.6 (42.3-130.7)
Opposite retina	9.9 (7.9-13.0)
Crystalline lens	20.1 (14.0-26.5)
Radiation rate (cGy/h)	
Apex	71.2 (51.5-89.9)
Sclera	274.4 (190.1-361.8)
Optic Nerve	41.4 (28.3-62.5)
Macula	63.5 (33.6-122.2)
Opposite retina	8.7 (7.0-11.1)
Crystalline lens	17.3 (12.1-23.2)

Gy – gray.

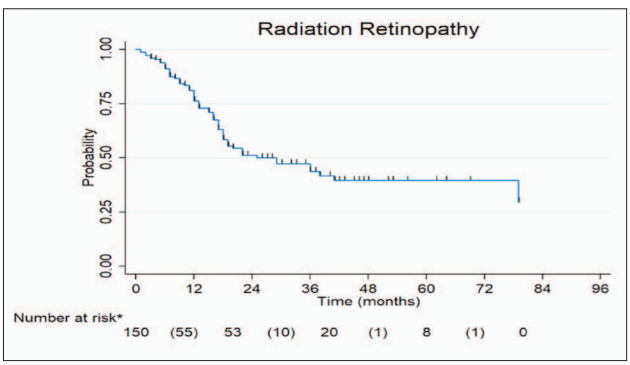

Figure 1. Kaplan-Meier survival function curve of the outcome radiation retinopathy.

The number of individuals at risk is stated at the beginning of every 12-month period, while the number of events during that period is stated within parenthesis.

UNIVARIATE REGRESSION ANALYSIS

On univariate logistic regression analysis baseline tumor thickness (OR 1.34; 1.14-1.57; p<0.01), tumor diameter >10 mm (OR 2.04; 1.01-4.12; p=0.04), both the dose (0.96; 0.94-0.99; p<0.01) and rate (OR 0.98; 0.96-0.99; p<0.01) of radiation to the apex, the dose (OR 1.002; 1.000-1.004; p<0.01) and rate of radiation to the sclera (OR 1.003; 1.000-1.005; p<0.01), and the dose (OR 1.11; 1.02-1.21; p<0.01) and rate (OR 1.12; 1.01-1.25; p=0.03) of radiation to the retina opposite the tumor were significantly associated with RR. The remainder of univariate logistic regression analyses are displayed on Table 3.

MULTIVARIABLE REGRESSION ANALYSIS

After stepwise selection of univariate predictors for the building of the multivariable model, the baseline tumor thickness (OR 1.39; 1.17-1.65; p<0.01) and pre-equator location of the tumor (OR 0.32; 0.11-0.95; p=0.04) were significantly associated with the outcome radiation retinopathy. Furthermore, despite not being a statistically significant predictor in conjunction with the other two variables, age (OR 0.97; 0.95-1.00; p=0.07) was deemed as a potentially clinically interesting variable whose inclusion also strengthened the model performance, so we chose to add it. The Hosmer & Lemeshow's goodness-of-fit test yielded a high p-value of 0.78, indicating good fit.

DISCUSSION

Plaque brachytherapy is a globe-preserving therapy widely established for the treatment of choroidal melanoma.[15] Nevertheless, the complications of radiation are recognized as further threats to the maintenance of vision - when there is such a chance -, but also as an important focus of attention during the follow-up period to the brachytherapy procedure. With this work, we presented the first report on the occurrence of radiation retinopathy in the Ocular Oncology Unit of the Coimbra University Hospital Center, the Portuguese Reference Centre for Ocular Oncology.

After almost a decade of treatment with I^{125} plaque brachytherapy, the cumulative incidence of RR in our cohort was 44.7% and the incidence rate of RR was 2.14/100 person-years. Furthermore, most of our cases of RR happened before the 3 year-mark. These results are in overall agreement with results of landmark studies and well-established Ocular Oncology centers.[6,7]

Table 3. Univariate logistic regression analysis for predictors of the outcome radiation retinopathy

Predictor variable	Odds Ratio	Lower 95%	Upper 95%	*p* value
Age	0.98	0.96	1.00	0.12*
Diabetes	0.85	0.30	2.39	0.76
Male sex	0.95	0.49	1.82	0.87
Macular location	1.08	0.55	2.14	0.82
Pre-equator location	0.45	0.16	1.22	0.11*
Post-equator location	1.04	0.55	2.00	0.89
Peripapillary location	1.99	0.67	5.91	0.22
Treatment duration	0.99	0.99	1.00	0.98
Diameter	1.09	0.96	1.22	0.17
Diameter >10 mm	2.04	1.01	4.12	**0.04**
Thickness	1.34	1.14	1.57	**<0.01**
Apex dose	0.96	0.94	0.99	**<0.01**
Apex rate	0.98	0.96	0.99	**<0.01**
Sclera dose	1.002	1.000	1.004	**<0.01**
Sclera rate	1.003	1.000	1.005	**<0.01**
Nerve dose	1.004	0.99	1.01	0.29
Nerve rate	1.01	0.99	1.01	0.31
Opposite retina dose	1.11	1.02	1.21	**<0.01**
Opposite retina rate	1.12	1.01	1.25	**0.03**
Lens dose	1.02	0.99	1.05	0.17
Lens rate	1.02	0.98	1.06	0.26
Macula dose	1.003	0.99	1.01	0.14*
Macula rate	1.002	0.99	1.01	0.27

* Variables chosen for further testing on a stepwise multivariable model based on both clinical significance and a p value <0.15.

With respect to predictors of radiation retinopathy, univariate logistic regression revealed several significant predictors. With respect to clinical variables and perhaps to some surprise, patient history of diabetes mellitus was not associated with the outcome radiation retinopathy. This risk factor has been demonstrated in several previous studies and the absence of a significant positive association with RR might be explained by the retrospective collection of patient data, in which diabetes status might have been missing. On the other hand, it could be the case that our diabetic patients showed a higher prevalence of laser photocoagulation thereby distorting the association between diabetes and RR. Nonetheless, we are not able to go beyond speculation as we did not include such laser status in this study.

As expected, tumor size variables were associated with the development of radiation retinopathy, especially the baseline tumor thickness, which held its significance both in the univariate and multivariable models and tumor diameter >10 mm. Once again, this result are in agreement with well-established studies.[7,8,16] The likely explanation for this effect is the need for increased radiation penetration deeper within the eye with subsequent collateral damage to ocular structures. Treatment variables also showed, to some extent, expected results on univariate logistic regression, except the parameters related to dose and rate of radiation to the apex which showed a significant negative association with radiation retinopathy. Nevertheless, radiation variables' associations did not hold after stepwise multivariable regression analysis.

As stated, on multivariable regression analysis, higher baseline tumor thickness was associated with an increased odd of RR. On the other hand, according to our data, a choroidal tumor located between the equator and the ora serrata was less likely to be associated with RR. This supports a previously suggested lower susceptibility of the peripheral retina to the effects of radiation.[8]

Age was included in our model because we wanted to study whether a patients age could be important to his/her likelihood of developing RR. Although the association was not statistically significant, there was nearly significant trend towards a lower likelihood of radiation retinopathy with increasing age. One possible explanation we suggest for this is the fact that an older retina with less functional reserve, in the same way that a laser treated retina protects from further proliferative retinopathy, could have less tissue available for damage, hence lowering its likelihood of developing the RR cascade.

The research for an optimal regimen for prevention/treatment of radiation retinopathy is the subject of intense efforts in the ocular oncology community. Nevertheless, we have not yet reached a consensus on such a regimen. In our centre, patients start treatment with bevacizumab in response to signs of developing RR. Other groups have actively studied and implemented the use of prophylactic bevacizumab, with good results.[11] One interesting avenue of research could be the development and validation of risk score models for the outcome of radiation retinopathy based on patient, tumor, and treatment variables, to allow for tailored pre- and perioperative planning. To the extent of our knowledge, such a tool is not available for widespread use in the ocular oncology community.

This study has some limitations. First, and despite extensive and organized records of patient data, its retrospective nature hampers the full collection of clinical data. Second, our data are relative to the clinical experience of a single center with less than a decade in practice when there are centers with over 3 decades of expertise in brachytherapy. Nevertheless, this represents the first ever report on the incidence of radiation retinopathy and its predictors among our patients. As such, it is a valuable tool to gauge our practice and a chance to reflect on possible ways to further improve patient treatment and follow-up.

In summary, brachytherapy is a consensual treatment modality for eligible choroidal melanoma patients. Nevertheless, it is essential to actively search and recognize its complications during follow-up. Our results show that, among our patients, radiation retinopathy happens in a little over 40% of them, mostly within the first 3 years after treatment. Increased baseline tumor thickness is associated with higher chances of RR, while increased age and a pre-equator tumor location might be protective of RR.

CONTRIBUTORSHIPS TATEMENT / DECLARAÇÃO DE CONTRIBUIÇÃO:

ERN, CF: Study design

ERN, JC and CF: Data collection

ERN and CF: Statistical analysis and interpretation of results

ERN and JC: Writing of the manuscript

All authors critical appraisal and approval of the final version

RESPONSABILIDADES ÉTICAS

Conflitos de Interesse: Os autores declaram a inexistência de conflitos de interesse na realização do presente trabalho.

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Confidentiality of Data: The authors declare that they have followed the protocols of their work center on the publication of data from patients.

Protection of Human and Animal Subjects: The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki as revised in 2013).

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