Ocular Oncology and Pathology

Research Article

Ocul Oncol Pathol 2024;10:65–71
DOI: 10.1159/000537795

Received: September 10, 2023
Accepted: February 5, 2024
Published online: February 17, 2024

Dose-Related Visual Outcomes in the Treatment of Choroidal Melanoma with Stereotactic Radiotherapy

Eugene Michael[a] Reid A. Ferguson[a] Peter W. Hadden[a, b]

[a]Department of Ophthalmology, Greenlane Clinical Centre, Auckland, New Zealand; [b]Department of Ophthalmology, University of Auckland, Auckland, New Zealand

Keywords
Choroidal melanoma · Prognosis · Stereotactic radiotherapy

Abstract
Introduction: Stereotactic radiotherapy (SRT) in the treatment of choroidal melanoma (CM) may be indicated if the tumour is located close to the optic nerve or is unsuitable for a radiotherapeutic plaque. It is thought that the rate of visual decline and ocular sequelae with SRT is influenced by dose and location of radiation in relation to important visual structures. This study therefore aimed to look at these prognoses with respect to localisation and dose of radiation when treatment of CM with SRT occurs. ***Methods:*** A retrospective data analysis was conducted on all patients at Dunedin Hospital (DH) from August 2001 to May 2017 who were followed up for 4 years. SRT consisted of 50 Gy divided into five fractions over 5 days to tumours, with 2-mm treatment margins. The primary outcome measure was retention of functional vision – better than hand movements (HMs) within the treated eye. Secondary outcome measures included time to non-functional vision (HM or less) in relation to location, dose and tumour thickness, the presence of radiation retinopathy, local and metastatic tumour progression, enucleation, and disease-specific mortality. ***Results:*** Seventy-five patients were identified in this study. Follow-up was incomplete in 10 patients, and 4 patients became deceased within the 4-year study period. Twenty-nine patients (48%) retained visual acuity (VA) better than HMs in the treated eye at 4 years, and thirty-two (52%) of patients did not. Calculated dose to the optic nerve and macula and proximity of the tumour to the optic nerve and macula were not statistically determinative of vision outcomes, although presenting VA was. Fifty-six per cent of patients developed radiation retinopathy involving the macula. The local progression, metastatic progression and enucleation rates were 4.6%, 6%, and 12.3%, representing 3, 4, and 8 patients, respectively. ***Conclusion:*** This study demonstrates that approximately half of patients treated with SRT can expect to maintain functional vision better than HM at 4 years. The rate of visual decline and final vision outcome are independent of location of the tumour in relation to the optic nerve and macula. While it affirms that SRT achieves high rates of local tumour control and eye retention, preservation of functional VA remains an unpredictable endpoint for individual cases and highlights the therapeutic challenge of this treatment modality.

Introduction

Choroidal melanoma (CM) is the most common primary ocular malignancy in adults with a histologically confirmed annual incidence of 7.58 ± 1.34 cases per

karger@karger.com
www.karger.com/oop

Correspondence to:
Peter W. Hadden, peter.h211@gmail.com

million population per year in New Zealand [1]. Untreated CM can infiltrate intra-ocularly, affecting visual structures, and extra-ocularly, which may have fatal consequences if tumour cells migrate to other regions in the body. Metastatic CM preponderantly disseminates to the liver [2]. Early detection and treatment are therefore imperative, as hepatic spread is reported to have a 1-year survival rate of 10% despite aggressive treatment [3]. This emphasises the importance of prompt intervention and local control, noting that stereotactic radiotherapy (SRT) is an established intervention in the treatment of CM [4].

Vision loss is a well-documented complication of SRT, and it has been shown in other studies that 33% of patients will retain Snellen acuity of 6/60 or better [5]. To the best of our knowledge, no study has analysed the time at which patients lose functional vision, defined in this study as better than hand movement (HM) vision, or determined whether the dose and localisation in relation to the posterior pole anatomy affect the vision outcome.

The most common treatment options for CM are brachytherapy and enucleation, with other interventions including radiation therapy, tumour resection, exenteration and laser modalities such as trans-pupillary thermotherapy [6]. Radiation therapy incorporates the aforementioned SRT and plaque brachytherapy, as well as proton beam radiotherapy (PBT) [6]. SRT may be indicated if the tumour is large, posteriorly located close to the optic nerve, or unsuitable for a plaque brachytherapy [5, 7]. In New Zealand, SRT is the treatment of choice for focussed external beam radiotherapy as there is currently no facility for PBT.

Radiation-induced pathology of the posterior pole is a known complication impacting vision outcomes. SRT-induced radiation optic neuropathy may be as high as 77.8% when the dose is 15 Gy or more and 26.7% when the dose is between 10 and 15 Gy [8]. SRT-induced radiation retinopathy (RR) affects approximately 71–88% of patients ≥5 years post-treatment [9, 10]. RR can be identified by the presence of clinical or angiographic evidence of propagating retinal ischaemic vasculopathy, 2 mm or more away from the treated tumour margin, with or without macular involvement. This can be characterised by retinal haemorrhage, exudation, infarction, oedema, or neovascularisation [11]. There is, however, some difficulty distinguishing RR from toxic tumour syndrome (TTS). For the purposes of this study, both conditions were combined under the umbrella term of RR. In TTS, tumour necrosis and intra-tumoural radiation vasculopathy lead to oedema, exudation, serous retinal detachments, and neovascularisation within 2 mm of the tumour margin [12]. TTS tends to have a more sudden onset than RR, which typically manifests between 6 months and 3 years post-treatment [13], although it has been reported anywhere from 1 month [14] to 15 years [15]. One explanation for this difference in time course is thought to be due to average lifespan of vascular endothelial cells being >1 year [16], accounting for the signs of ischaemia in RR typically peaking at 2 years on average [13]. This may also partially explain the variable effectiveness of prophylactic intravitreal bevacizumab (Avastin; Genentech, San Francisco, CA, USA) [4], given that the elimination half-life of the medication has been calculated at 6.86 days, albeit in animal models [17]. Bevacizumab is a monoclonal antibody used to inhibit vascular endothelial growth factor, with vascular endothelial growth factor being a driver of retinal neovascularisation and vascular leakage, especially from compromised blood vessels [18].

In this study, the aim was to review all uveal melanoma treated with SRT in New Zealand with a minimum follow-up period of 4 years. The final visual acuity (VA) results were examined, and further analysis was conducted to look for a correlation between presenting VA, radiation dose (to optic nerve and macula), tumour thickness, and location. Such information could therefore help clinicians to estimate and advise patients of the likely visual outcomes when undergoing SRT and the potential rate of visual decline.

Methods

A retrospective analysis was performed on all patients undergoing SRT for CM at Dunedin Hospital (DH), over the period of August 2001 to May 2017 at DH in New Zealand. The study was conducted in accordance with the tenets of the Declaration of Helsinki and the National Ethics Advisory Committee guidelines and met the criteria for exemption from formal review by the New Zealand Health and Disability Ethics Committee in accordance with national guidelines.

Patients were excluded from the study if the choroidal lesion was not conclusive for CM or if there were incomplete follow-up details. Data were collected from the patients' electronic health records (iSOFT, MOSAIQ, and XKnife) and ophthalmic clinical notes. Baseline characteristics obtained were age, gender, ethnicity, eye involved, referring district health board, ocular and medical comorbidities, and smoking history. Other data collected included best-corrected VA (BCVA) in the affected eye (pre-radiation and final follow-up), incidence of post-radiation ocular complications, enucleation, incidence of metastasis, and duration of follow-up.

Twenty MHz ultrasonography was performed by the Dunedin Hospital Radiology Department for staging of the CM lesion as per American Joint Committee on Cancer (AJCC) and Collaborative Ocular Melanoma Study (COMS) staging system. Lesion characteristics were also gathered from ultrasonography including distance of nearest margin to optic nerve and location of the

Table 1. Baseline characteristics of the study demographic

Patients, *n*	75
Mean age, years	64
Female	51%
Ethnicity	New Zealand European or other European: 74 Maori: 1
Laterality	Left eye: 35 Right eye: 40
Domiciled in Southern District Health Board	55%
Documented comorbidities	Cancer Hypertension Diabetes mellitus
Smoking history	20%

Table 2. Characteristics of CM

Eye, *n*	
Left eye	35
Right eye	40
Location, *n*	
Juxta and parapapillary	34
Post-equatorial	17
Pre-equatorial	10
Equatorial	14
Morphology, *n*	
Lentiform	58
Pedunculated	2
Sessile	3
Bilobed	5
Collar stud	7
AJCC stage, *n*	
T1	28
T2	28
T3	16
T4	3
COMS size, *n*	
Large	20
Medium	34
Small	21

tumour relative to the macula, echogenicity, presence of subretinal fluid, iris and ciliary body involvement.

Treatment planning, tumour, and ocular anatomy localisation measurements utilised Radionics knife RT2 software (Integra Radionics, Burlington, MA, USA) and application of a pre-treatment computed tomography head scan. The gross tumour volume was outlined and compared with the ultrasound representation. Tumour margins were expanded by 1 mm to form the clinical target volume and then by another 2 mm to form the planning target volume. Radiation doses to the optic nerve head and macula were estimated by calculating the dose at the centre of the intraocular portion of the optic nerve and the posterior pole, respectively.

Patients were positioned supine with the head immobilised by a Gill-Thomas-Cosman frame. Each frame had an individualised bite piece and occipital headrest. Eye positioning was aligned with an external light-emitting diode attached to the Gill-Thomas-Cosman frame and observed by a camera linked to the control room. SRT was administered at a dose of 50 Gy (at the 80% line) divided into five fractions (10 Gy each day) each day for 5 days. Radiation was delivered with constant eye camera guidance in multiple non-coplanar arcs. Pupil and eye movement tolerance margins were maintained during radiation administration.

Fifty-seven patients had prophylactic intravitreal bevacizumab after completing the 5th dose of radiotherapy at a posology of 1.25 mg. The primary outcome measure was duration of functional vision (HM or better) in relation to radiation dose and location. Secondary outcome measures included the timepoint of non-functional vision (HMs or less), local and metastatic tumour progression, the presence of RR, enucleation, and disease-specific mortality.

Juxta and parapapillary lesions were defined as tumours that are at some point adjacent to the optic disc and pre-equatorial lesions as those lesions that did not extend posterior to the equator (a circumferential demarcation connecting the ampullae of the vortex veins). R statistical software environment was used for statistical analysis [19].

Statistical Analysis

The variables "dose to optic nerve," "dose to macula," and "presenting VA" were tested against whether or not the patient progressed to HM vision, first by using Levene's test for equality of variances. This was then analysed with a one-sided *t* test for equality of means as we assumed that those patients with a lower dose of radiation would be very unlikely to suffer more RR. The variables "distance to nerve" and "distance to macula" had data that were irregular and not normally distributed and were therefore divided into three groups: those immediately adjacent to the anatomical structure concerned, those not adjacent but within 5 mm, and those more than 5 mm from the structure. These were then compared using the Fisher's exact test.

Results

Seventy-five CMs in 75 patients were treated with SRT over the study period. Four-year follow-up was incomplete in 10 patients, and 4 became deceased before 4 years (3 from uveal melanoma metastases and 1 from lung cancer). These patients were excluded from further evaluation. Patient and tumour characteristics were recorded (Tables 1, 2).

Twenty-nine of the remaining 61 patients (48%) retained BCVA in the treated eye of better than HM at 4 years, and 32 (52%) were HM or worse. Three of these patients had BCVA worse than HM pre-treatment and were therefore excluded from further analysis regarding

Fig. 1. Calculated dose to the optic nerve, distance from tumour margin to nerve, calculated dose to the macula, distance to macula, and presenting VA of the treated eye, in relation to functional VA (HM) at 4 years.

vision loss. The only variable of statistical significance associated with visual deterioration to HM or worse was poorer presenting VA in the treatment eye: $p = 0.0023$, equal variances not assumed (shown in Fig. 1; Table 3). Tumour thickness did not have a statistically significant effect on post-treatment VA.

There was no statistically significant association between distance to the optic nerve and progression to HM when distance to nerve was analysed as 3 categories (0 mm, >0 to ≤5 mm, and >5 mm) or 2 categories (≤5 mm and >5 mm). Fisher's exact test p values were 0.28 and 0.13, respectively. Similarly, there was no statistically significant association between distance to macula and HM when distance to macula was analysed as 3 categories (0 mm, >0 to ≤5 mm, and >5 mm) or 2 categories (≤5 mm and >5 mm). Fisher's exact test p values were 0.76 and 0.61, respectively.

The local progression, metastatic progression and enucleation rates were 4.6%, 6.2%, and 12.3%, representing a total of 3, 4, and 8 patients, respectively. There

Table 3. Tumour treatment for each patient, by nerve dose, macular dose, distance to macula, and presenting VA, separated by whether the vision was better than HMs at 4 years or HM or worse at 4 years

	VA better than HM at 4 years	VA equal or worse than HM at 4 years	Significance
Distance to nerve, mm	5.13	4.93	0.28[a]
Distance to macula, mm	3.55	4.39	0.76[a]
Nerve dose, Gy	33.15	37.22	0.442[b]
Macula dose, Gy	37.41	35.83	0.431[b]
Tumour thickness, mm	3.5	4.7	0.064[b]
Presenting VA, logMAR	0.13	0.46	0.0023[c]

[a]Fisher's exact test, analysed as three categories (adjacent to nerve/macula, less than 5 mm from nerve/macula, and 5 mm or more from nerve/macula). [b]One-sided *t* test, equal variances assumed (Levene's test for equality of variances not significant, $p > 0.05$). [c]One-sided *t* test, equal variances not assumed (Levene's test for equality of variances not significant, $p < 0.05$).

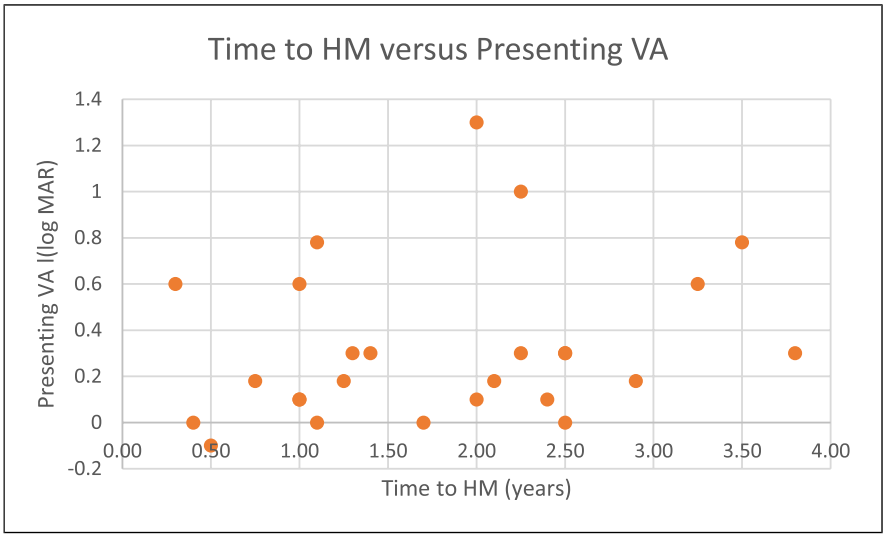

Fig. 2. Time to reach HM and presenting VA in patients whose vision was HM or worse at 4 years.

was no correlation between the variables: distance to nerve, distance to macula, macula and optic nerve dose, thickness of the tumour, and time to loss of vision to HM or worse (all Pearson correlations <0.3 and *p* values >0.1). Figure 2 demonstrates variability in time to visual decline to HM when compared with presenting VA.

Discussion

This study demonstrates that approximately half of all patients treated with SRT for CM can expect to maintain visual function of HM or better at 4 years. This level of acuity has implications for the perception of movement, particularly in monocular patients and those reliant on peripheral vision and dynamic visual cues.

There was no statistically significant correlation between the likelihood of vision loss and the calculated dose to the optic nerve and macula, or the distance of tumour to the macula or papillary region. We posit that, in this context, there is no feasible sub-threshold dosage that predictably avoids radiation-induced ocular sequelae to these structures. SRT dosage protocols are standardised at DH, and unlike PBT, SRT's dispersive field of radiation means that collateral damage beyond the propinquity of the tumour location may explain the discrepancy of outcomes between these treatment modalities.

Conversely, patients with a presenting VA of greater than logMAR 0.3 (Snellen acuity of 6/12) were statistically

less likely to progress to HM vision. This correlation may reflect the observation that patients with better presenting VA have greater "vision reserve" before reaching HM compared to those with poorer VA at baseline.

Literature suggests that PBT is superior to SRT with regard to retention of vision but similar with regard to local tumour recurrence, ocular conservation, and survival [5]. In a study by Sikuade et al. [5], 91% of juxta- and circum-papillary tumours of cases treated with SRT had a VA of 6/60 or less compared to 73% of those treated with PBT at 36–39 months. However, the study notes that the SRT group had tumours closer to the optic nerve and occupying a greater proportion of the disc margin, thereby confounding results. The current study did not find the same association.

Historically, non-invasive SRT treatment protocols had a practical advantage over PBT in that SRT does not require the insertion of tantalum rings or general anaesthesia [20]. Metastasis-related mortality and ocular conservation are similar between SRT and PBT. Retention rates of functional vision in PBT are higher compared to SRT and should also be considered given that availability and cost of PBT remain barriers to its use.

Another option for dealing with peripapillary tumours is the use of notched plaque brachytherapy, which has been shown to retain VA of 6/60 or better in 62.5% of individuals [21]. However, a common concern with these devices is it requires an experienced operator to avoid inadvertent damage to the optic nerve during placement and imprecise appositional contact increases the risk of tumour recurrence [11].

Dosimetry protocol modification can also be considered to limit collateral damage to ocular structures – it is thought that limiting doses to 12 Gy to the optic nerve as a single fraction of SRT lowers the risk of radiation-induced optic neuropathy [22]. In cumulative treatment protocols, the anterior visual pathway is said to tolerate a total irradiation dose of 50 Gy, when given in fractions of less than 2 Gy [23]. Krema et al. [11] showed that at 3 years, juxta-papillary tumours treated with SRT at a cumulative dose of 70 Gy fractionated over 5 days had optic neuropathy rates of 64%. This study did not exceed 50 Gy as a total cumulative dosage.

Limitations of this study include bias inherent in a retrospective data analysis, despite patient recruitment being prospective. It is also acknowledged that there was heterogeneity in follow-up times due to the data collection retrieval – part of this is due to a high number of patients from regions in New Zealand where DH is not their usual referral centre (45% were domiciled outside of the DH eye department catchment area). No differentiation was made between tumours at the macula and those involving the fovea at the time of treatment.

In conclusion, approximately half of patients treated with SRT can expect to maintain Snellen VA of HM or better at 4 years, independent of the dose given or the distance of the tumour to the macula and disc. Treatment hierarchy is an incontrovertible paradigm: patient survival, followed by ocular conservation and then retaining the best possible vision outcomes. Prognostic information can guide patient expectations as they transition to greater monocular reliance, particularly if the unaffected eye has other ocular disease. In centres that utilise SRT as part of their treatment armamentarium, informing patients of expected vision outcomes should be emphasised even when treatment of peripheral tumours at a distance from the optic nerve and macula is part of the dosage protocol.

Statement of Ethics

This was conducted in accordance with the tenets of the Declaration of Helsinki and the National Ethics Advisory Committee guidelines and met the criteria for exemption from formal review by the New Zealand Health and Disability Ethics Committee in accordance with national guidelines.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

The authors have not declared a specific grant for this research from any funding agency in the public, commercial, or not-for-profit sectors.

Author Contributions

Study conception and design, and analysis and interpretation of results: Dr. Eugene Michael, Dr. Reid Alexander Ferguson, and Dr. Peter William Hadden. Data collection: Dr. Reid Alexander Ferguson. Draft manuscript preparation: Dr. Eugene Michael.

Data Availability Statement

Further enquiries can be directed to the corresponding author. The data that support the findings of this study are not publicly available due to privacy reasons but are available from the corresponding author upon reasonable request.

References

1 Lim JZ, Gokul A, Misra SL, Hadden PW, Cavadino A, McGhee CNJ. The burden of histologically confirmed uveal melanoma in Aoteoroa: New Zealand – a 21-year review of the National Cancer Registry. Asia Pac J Ophthalmol. 2023;12(4):384–391.
2 Damato BE, Coupland SE. Ocular melanoma. Saudi J Ophthalmol. 2012;26(2):137–44.
3 Jovanovic P, Mihajlovic M, Djordjevic-Jocic J, Vlajkovic S, Cekic S, Stefanovic V. Ocular melanoma: an overview of the current status. Int J Clin Exp Pathol. 2013;6(7):1230–44.
4 Haji Mohd Yasin NAB, Gray AR, Bevin TH, Kelly LE, Molteno AC. Choroidal melanoma treated with stereotactic fractionated radiotherapy and prophylactic intravitreal bevacizumab: the Dunedin Hospital Experience. J Med Imaging Radiat Oncol. 2016;60(6):756–63.
5 Sikuade MJ, Salvi S, Rundle PA, Errington DG, Kacperek A, Rennie IG. Outcomes of treatment with stereotactic radiosurgery or proton beam therapy for choroidal melanoma. Eye. 2015;29(9):1194–8.
6 Singh P, Singh A. Choroidal melanoma. Oman J Ophthalmol. 2012;5(1):3–9.
7 Damato BE, Kacperek A, Chopra M, Campbell IR, Errington RD. Proton beam radiotherapy of choroidal melanoma: the Liverpool-Clatterbridge experience. Int J Radiat Oncol Biol Phys. 2005;62(5):1405–11.
8 Leber KA, Bergloff J, Pendl G. Dose-response tolerance of the visual pathways and cranial nerves of the cavernous sinus to stereotactic radiosurgery. J Neurosurg. 1998;88(1):43–50.
9 Al-Wassia R, Dal Pra A, Shun K, Shaban A, Corriveau C, Edelstein C, et al. Stereotactic fractionated radiotherapy in the treatment of juxtapapillary choroidal melanoma: the McGill University experience. Int J Radiat Oncol Biol Phys. 2011;81(4):e455–62.
10 Dunavoelgyi R, Georg D, Zehetmayer M, Schmidt-Erfurth U, Potter R, Dorr W, et al. Dose-response of critical structures in the posterior eye segment to hypofractioned stereotactic photon radiotherapy of choroidal melanoma. Radiother Oncol. 2013;108(2):348–53.
11 Krema H, Heydarian M, Beiki-Ardakani A, Weisbrod D, Xu W, Laperriere NJ, et al. Dosimetric and late radiation toxicity comparison between iodine-125 brachytherapy and stereotactic radiation therapy for juxtapapillary choroidal melanoma. Int J Radiat Oncol Biol Phys. 2013;86(3):510–5.
12 Kubicka-Trzaska A, Morawski K, Markiewicz A, Romanowska-Dixon B. Prevention and treatment of the toxic tumour syndrome following primary proton beam therapy of choroidal melanomas. Arch Med Sci Civil Dis. 2020;5(1):22–8.
13 Durkin SR, Roos D, Higgs B, Casson RJ, Selva D. Ophthalmic and adnexal complications of radiotherapy. Acta Ophthalmol Scand. 2007;85(3):240–50.
14 Char DH, Lonn LI, Margolis LW. Complications of cobalt plaque therapy of choroidal malanomas. Am J Ophthalmol. 1977;84(4):536–41.
15 Stallard HB. Radiotherapy for malignant melanoma of the choroid. Br J Ophthalmol. 1966;50(3):147–55.
16 Montezano AC, Neves KB, Lopes RAM, Rios F. Isolation and culture of endothelial cells from large vessels. Methods Mol Biol. 2017;1527:345–8.
17 Bakri SJ, Snyder MR, Reid JM, Pulido JS, Singh RJ. Pharmacokinetics of intravitreal bevacizumab (avastin). Ophthalmol. 2007;114(5):855–9.
18 Bakri SJ, Larson TA. The variable efficacy of intravitreal bevacizumab and triamcinolone acetonide for cystoid macular edema due to radiation retinopathy. Semin Ophthalmol. 2015;30(4):276–80.
19 R Core Team. R: a language and environment for statistical computing [Internet]. Vienna, Austria: R Foundation for Statistical Computing; 2017. [cited 2022 Nov 4]. Available from: https://www.R-project.org/.
20 Gragoudas ES, Seddon JM, Egan K, Glynn R, Munzenrider J, Austin-Seymour M, et al. Long-term results of proton beam irradiated uveal melanomas. Ophthalmology. 1987;94(4):349–53.
21 Sobti MM, Edington M, Connolly J, McLernon DJ, Schipani S, Ritchie D, et al. Outcomes following notched Ruthenium-106 plaque brachytherapy for juxtapapillary choroidal melanomas. Ocul Oncol Pathol. 2021;7(6):411–7.
22 Pollock BE, Link MJ, Leavitt JA, Stafford SL. Dose-volume analysis of radiation-induced optic neuropathy after single-fraction stereotactic radiosurgery. Neurosurgery. 2014;75(4):456–60.
23 Ferguson I, Huecker J, Huang J, McClelland C, Van Stavern G. Risk factors for radiation-induced optic neuropathy: a case-control study. Clin Exp Ophthalmol. 2017;45(6):592–7.