Gamma Knife Radiosurgery for Uveal Melanoma: A Retrospective Review of Clinical Complications in a Tertiary Referral Center

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Keywords

Choroidal melanoma · Gamma knife radiosurgery · Ultra-widefield imaging · Radiation retinopathy

Abstract

Introduction: Gamma knife radiosurgery (GKR) has shown promising results in the treatment of intraocular uveal melanoma (UM) in terms of local tumor control. However, GKR is not free from potentially sight-threatening side effects, including cataract, dry eye disease, vitreous hemorrhage, radiation retinopathy (RR), radiation maculopathy (RM), optic neuropathy, and neovascular glaucoma. The aim of this paper is to report our 20-year experience in UM management with GKR focusing on the rate of clinical treatment-induced complications. **Methods:** Single-center, retrospective, observational study, including all patients with UM treated at the Ocular Oncology and Uveitis Service, in the Department of Ophthalmology of the San Raffaele Scientific Institute, Milan from September 1993 to September 2018. Clinical charts comprised complete ophthalmological examination with measurement of best-corrected visual acuity, slit-lamp biomicroscopy, intraocular pressure measurement, gonioscopy,

and indirect ophthalmoscopy at each visit. B-scan ultrasound (Aviso S, 10 MHz probe; Paris, France), optical coherence tomography (Heidelberg Spectralis; Heidelberg Engineering, Heidelberg, Germany), retinography, and fundus fluorescein angiography (standard or ultra-widefield [UWF; California, Optos, Dunfermline, Scotland, UK]) were performed aiding in the diagnosis of complications. **Results:** Overall, 194 patients (100 males, 51.6%) were reviewed. The median age at the time of the treatment was 65 years (range 27–89) and all participants were Caucasian. In 185 eyes (95.4%), the tumor was primarily located at the choroid. The median follow-up was 57.6 months; radiation-induced complications were found in 145 eyes (74.7%). Radiation-induced cataract and RR were the most frequent events, with a relative incidence of 41.2 and 34.5%, respectively, followed by neovascular glaucoma (27.3%), optic neuropathy (18.6%), RM (11.4%), vitreous hemorrhage (14.4%), phthisis bulbi (7.7%), hyphema (0.5%), and corneal melting (0.5%). The shorter onset of side effects involved the optic nerve (median 14.9 months) and the macula (median 13.7 months). **Conclusion:** Despite modern and ad-

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vanced strategies introduced to limit GKR side effects, cataract and RR still represent a serious limitation of this treatment. Incidence of RR was higher in our cohort compared to other reports, probably due to increased diagnosis rate permitted by UWF retinal imaging.

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Introduction

Uveal melanoma (UM) is the most commonly diagnosed primary intraocular malignancy in adults, with an annual incidence of about 2–11 per 1,000,000 persons in the USA and in Europe [1–4]. Despite recent advances in diagnosis and treatment, UM remains life-threatening, with an overall mortality rate of 40–50% in 15 years, mainly due to liver metastasis [5].

Since the Collaborative Ocular Melanoma Treatment Study (COMS) revealed that conservative treatments had the same survival outcome as mutilating surgical treatment as enucleation, many sight- and/or globe-sparing strategies have been proposed [6, 7]. At present, several options are available, including transpupillary thermotherapy, plaque brachytherapy (iodine-125 or ruthenium-106) [8], proton beam radiotherapy [9], stereotactic radiotherapy [10], and stereotactic radiosurgery [11, 12]. The selected approach depends on different clinical factors, namely the tumor size, location (choroid, ciliary body, or iris) and the extension of the tumor, as well as the status of the fellow eye, the age, the general health, and the psychological status of the patient.

Gamma knife radiosurgery (GKR), initially developed for the treatment of intracranial lesions, has shown promising results in the treatment of orbital and intraocular UM in terms of local tumor control [13]. The primary advantage of GKR is preservation of the globe, with complete or relative sparing of the visual function [14]. GKR also represents a precious resource in cases where brachytherapy is contraindicated, as large tumors (greater than 15 mm in diameter or 10 mm in height) or lesions within 2 mm from the optic disc [15]. However, GKR is not free from the risk of damage to the healthy adjacent eye structures [13], leading to potentially sight-threatening side effects, including cataract, dry eye disease, vitreous hemorrhage, radiation retinopathy (RR), radiation maculopathy (RM), optic neuropathy, and neovascular glaucoma [14]. The optic nerve pathway, as well as the lacrimal glands, have been shown to be particularly radiosensitive, and damage of these structures often leads to irreversible visual impairment which significantly reduces the quality of life [16, 17].

Adequate selection of the patient, record of the baseline characteristics, and regular follow-up are crucial for early identification of GKR-related side effects. Moreover, modern imaging techniques, including ultra-wide-field (UWF) imaging instruments, capturing up to 200° of the retina in a single shot, aid in the recognition of these complications and serve as a guide for the treatment of each condition. The aim of the paper is to report our 20-year experience in UM management with GKR focusing on the rate of clinical treatment-induced complications.

Material and Methods

The present study was a single-center, retrospective, observational study, including all patients with UM consecutively treated at the Ocular Oncology and Uveitis Service, in the Department of Ophthalmology of the San Raffaele Scientific Institute, Milan from September 1993 to September 2018. Each subject signed a written consent to participate in observational studies, which gained the approval of the Ethics Committee of San Raffaele Hospital. This study adhered to the tenets of the Declaration of Helsinki for research involving human subjects.

Inclusion criteria were: diagnosis of UM based on clinical evaluation by a retina specialist (i.e., biopsy was not required); age older than 18 years; treatment with GKR; charts and imaging studies available at our Department. Technical details of the GKR treatment have been published elsewhere [11]. Exclusion criteria were: inability to obtain the informed consent; other ocular tumors different from UM (namely, choroidal metastasis, choroidal hemangioma, optic nerve glioma, etc.); treatment with other modalities other than or in concomitance with GKR (transpupillary thermotherapy, brachytherapy, proton beam radiotherapy, etc.).

We reviewed charts and imaging studies of each patient up to April 2019. Clinical charts comprised a complete ophthalmological examination with measurement of best-corrected visual acuity (BCVA, measured in Snellen units), color vision, pupillary reaction to light, slit-lamp biomicroscopy and photography, intraocular pressure measurement, gonioscopy, and indirect ophthalmoscopy at each visit. Accurate drawings and/or fundus photography were used to catalogue location (choroid, ciliary body, cilio-choroidal), position (macular, peripapillary, mid- or far-periphery), and quadrant (superior, inferior, nasal, temporal or diffuse). For all patients, diagnostic investigations available at the time of each visit were revised, including ophthalmic B-scan ultrasound (Aviso S, 10 MHz probe; Paris, France), optical coherence tomography (Heidelberg Spectralis; Heidelberg Engineering, Heidelberg, Germany), and standard (Topcon Trc-50Dx Retinal Camera) or UWF retinography (California; Optos, Dunfermline, Scotland, UK). Diagnosis of RR or RM was made from ancillary fundus fluorescein angiography (FFA, standard or UWF, if available). FFA was performed at the first detection of signs of RR to quantify the extent of peripheral capillary nonperfusion and to distinguish between the proliferative and nonproliferative form of the disease. Suggestive angiographic features were peripheral capillary dropout, choroidopathy, ischemic maculopathy, epiretinal neovascularization, retinal branch occlusion, and rupture of the blood-retinal barrier.

Parameters included in the analysis were patients' gender, age at the time of the treatment, ethnicity, mean follow-up, rate of both anterior and posterior segment complications, interval between GKR and each event, and specific treatment. Quantitative variables were expressed as mean $\pm$ SD, median and/or range; absolute frequencies were expressed as absolute values and percentage. GraphPad Prism 6.0 (GraphPad software, Inc., San Diego, CA, USA) was used for statistical analysis.

Results

Clinical records of 194 patients (100 males, 51.6%) were reviewed. The median age at the time of the treatment was 65 years (range 27–89) and all participants were Caucasian. All cases were unilateral. Overall, in 185 eyes (95.4%), the tumor was primarily located at the choroidal level, in 3 eyes (1.5%) at the ciliary body level, and in 6 eyes (3.1%) the tumor involved both the choroid and the ciliary body. Ophthalmoscopy revealed that the majority of tumors were pigmented, and only 14 eyes featured an amelanotic UM (7.2%). UWF fundus photography, allowing a 3-dimensional virtual reconstruction of the globe, helped to realistically replicate the clinical features of the tumor, revealing as an ancillary technique to B-scan ultrasound in assessing the exact position of the lesion.

Patients were treated with a single-fraction marginal dose of 35.8 ± 4.7 Gy at the 50% isodose line with a maximum dose of 63.5 ± 9.1 Gy. The median lesion volume was 475 ± 428 mm³.

The median follow-up was 57.6 months (range 2–296); in 168 eyes (93.3%), local control of the tumor was achieved, while in 12 eyes (6.2%) a recurrence was noted, after a median time of 29.43 months (range 7.1–74.7). Nine patients were enucleated (75%), 1 eye with a small tumor underwent transpupillary thermotherapy (8.3%), 1 proton beam radiotherapy (8.3%), and 1 refused any treatment (8.3%). Enucleation was performed in 18 eyes (9.3%), including all 9 eyes with recurrence, plus 1 eye which developed an extraocular extension despite treatment, and 8 blind eyes which experienced phthisis bulbi and/or untreatable pain.

During the follow-up, radiation-induced complications were found in 145 eyes (74.7%; Table 1).

Anterior segment complications included a new-onset cataract or a significant worsening of previously known lens opacification in 80 eyes (41.2%), of which 26 eyes (32.5%) were treated with phacoemulsification (Fig. 1a–c). Neovascular glaucoma was documented in 53 eyes (27.3%; Fig. 1d); it was managed with simple observation in 1 eye (1.9%), topical medications in 38 eyes (71.7%),

Table 1. Rate and interval of the different clinical complications of gamma knife radiosurgery in 194 patients with uveal melanoma

Complication	n (rate, %)	Interval, months
Cataract	80 (41.2)	18 (median) 23.4 $\pm$ 22.5 (mean $\pm$ SD) 2.7–143.8 (range) 18.4–28.4 (95% CI)
NVG	53 (27.3)	28.4 (median) 30.7 $\pm$ 22.3 (mean $\pm$ SD) 1–113.1 (range) 24.6–36.9 (95% CI)
Radiation retinopathy	67 (34.5)	23.9 (median) 25.2 $\pm$ 16.3 (mean $\pm$ SD) 3–78.9 (range) 21.2–29.2 (95% CI)
Optic neuropathy	36 (18.6)	14.9 (median) 21.7 $\pm$ 14.7 (mean $\pm$ SD) 3–58.4 (range) 16.5–26.9 (95% CI)
Radiation maculopathy	23 (11.4)	13.7 (median) 24.2 $\pm$ 23.2 (mean $\pm$ SD) 1.4–87.5 (range) 13.9–34.5 (95% CI)
Vitreous hemorrhage	28 (14.4)	26.8 (median) 29.5 $\pm$ 26.5 (mean $\pm$ SD) 1.1–113.1 (range) 19–40 (95% CI)
Phthisis bulbi	15 (7.7)	53.3 (median) 66.3 $\pm$ 39.9 (mean $\pm$ SD) 18.2–150.2 (range) 43.3–89.3 (95% CI)
Hyphema	1 (0.5)	43.1
Melting	1 (0.5)	52.1
NVG, neovascular glaucoma.		

retinal laser photocoagulation in 2 eyes (3.8%), intravitreal injections of anti-vascular endothelial growth factors (anti-VEGF) in 2 (3.8%), combination of the 2 in 8 (13.2%), cyclophotocoagulation in 1 (1.9%), and enucleation in 2 eye (3.8%). One eye (0.5%) developed complete corneal pannus and then corneal melting (Fig. 1e), while 1 eye (0.5%) presented with complete hyphema (Fig. 1f).

The most frequent posterior segment complication was radiation retinopathy, documented in 67 eyes (34.5%) and presenting as peripheral capillary nonperfusion, epiretinal neovascularization or vascular occlusion (Fig. 2a–e); 3 eyes featured epiretinal neovascularization (4.5%). This condition was treated with observa-

Fig. 1. Spectrum of anterior segment complications of gamma knife radiosurgery. **a–c** Cataract, recognizable as a whitish hue of the lens behind the iris. **d** Neovascular glaucoma, defined as the

presence of abnormal blood vessel along the pupillary border. **e** Corneal pannus, with complete loss of corneal transparency. **f** Blood in the anterior chamber and in the vitreous cavity.

tion in 28 eyes (41.8%), retinal laser photocoagulation in 13 eyes (19.4%), intravitreal anti-VEGF in 8 eyes (11.9%), or combination of both in 9 eyes (13.4%). The remaining cases were treated with local steroids plus laser (8 eyes, 11.9%) or transconjunctival anterior cryotherapy (1 eye, 1.5%). Radiation maculopathy, featuring either macular ischemia/atrophy or intraretinal edema and exudation, was observed in 23 eyes (11.4%), of which 5 eyes presented without any sign of RR. This condition was managed with intravitreal anti-VEGF in 9 eyes (40.9%), local steroids in 4 eyes (18.2%), or combination of both in 1 eye (4.5%); the rest of the cases were observed.

Optic neuropathy was diagnosed in 36 eyes (18.6%), ranging from acute papillopathy with disc edema and hemorrhages to pale optic disc atrophy (Fig. 2a, d). Vitreous hemorrhage took place in 28 eyes (14.4%) and was treated with observation in 22 eyes (78.6%), vitrectomy plus endolaser in 4 eyes (14.3%), or only laser photocoagulation in 2 eyes (7.1%; Fig. 2c, d). At the end of follow-up, 15 eyes experienced phthisis bulbi (7.7%), managed with globe removal in 7 eyes (46.7%).

Discussion/Conclusion

In essentially every patient with UM treated with radiotherapy, normal cells neighboring tumors inevitably receive a considerable dose of ionizing radiation, causing damage to healthy tissues, which may appear immediately or years after the initial treatment. As the number of GKR treatments have been increasing in the past decades for both intracranial and intraocular or orbital lesions [18, 19], the adverse effects related to local irradiation should elicit serious concern.

We found that radiation-induced cataract and RR were the most frequent events, with a relative incidence of 41.2 and 34.5%, respectively. Conversely, the shorter onset of side effects involved the optic nerve (median onset of 14.9 months) and the macula (median onset of 13.7 months). This shorter interval might be related to the timely detection of symptoms (such as vision loss and metamorphopsia) connected to alteration to the normal function of these 2 ocular structures, or to an earlier occurrence of these complications with respect to RR [20].

Fig. 2. Spectrum of posterior segment complications of gamma knife radiosurgery. **a** Fundus photograph of the posterior pole, revealing exudates around the optic nerve head and cotton-wool spots. **b** Fluorescein angiography showing temporal capillary nonperfusion. **c** Fundus photograph showing hemorrhages in the superior retina, an indirect sign of branch retinal vein occlusion.

In the periphery, laser treatment is noticeable. **d, e** Radiation maculopathy, with extensive exudation involving the macula (yellow halo around the pigmented lesion) and leakage of fluorescein. **f, g** Optical coherence tomography revealing retinal thinning, atrophy of the external retinal layers, and intraretinal edema and exudates.

The response of normal tissue to radiation is complex and involves different molecular pathways, including DNA damage repair, cell death, inflammation, angiogenesis, and matrix remodeling, depending on the dose and time course of the exposure [21]. The lens is thought to be one of the most sensitive organs to radiation injuries, because of its superficial location and direct contact with the radiation beam during therapy for intraocular tumors. The first dose-effect quantification of the relationship between cataract formation and cumulative doses of ionizing radiation was documented in epidemiologic studies from atomic bomb survivors in Japan [22]. Recently, the occurrence of cataract was specifically linked to GKR [23] as an independent risk factor, with a global hazard ratio of 1.5; this risk was even higher in subjects between 30 and 50 years old (up to a hazard ratio of 3.5).

Although specific data on the outcome of phacoemulsification surgery after GKR are missing, several studies

have shown that cataract extraction with or without intraocular lens placement in patients who have previously received radiation treatment is generally safe and well-tolerated [24]. When intraocular malignancy is present, the surgery has not been associated with tumor recurrence or spread [25, 26]. On the other hand, the functional outcome of cataract extraction might be severely limited by ocular posterior segment complications of GKR.

RR and optic nerve disease are the major causes of irreversible vision loss in irradiated patients. RR comprises a wide spectrum of retinal manifestations secondary to radiation-induced damage [27]. One of the first clinical signs of the disease is capillary nonperfusion, which leads to retinal ischemia, upregulation of the VEGF, and formation of epiretinal neovascularization and macular edema, that is an additional cause of vision loss in these patients [28]. Macular involvement can present even independently from RR, as our series demonstrated.

Table 2. Relative prevalence of radiation retinopathy in the published literature

Author	Year	Dose of radiation, Gy	Isodose, %	Follow-up, months	<i>n</i>	Incidence of relative risk, %
Marchini et al. [29]	1996	55 (surface)	60–90	6 (median)	36	8.3
Mueller et al. [30]	2000	25 (average)	50	12 (median)	35	2.9
Haas et al. [31]	2002	50 (marginal)	50	38 (mean)	32	84
Modorati et al. [11]	2009	35 (marginal)	50	31.3 (median)	78	13.5
Schirmer et al. [32]	2009	22.2 (marginal)	50	20.9 (median)	14	14
Chan et al. [33]	2011	25 (marginal)	50	24 (median)	6	16.7
Kang et al. [13]	2012	45.6 (marginal)	50	67 (median)	22	22.7
Dinca et al. [34]	2012	35–70 (marginal)	50	63.5 (median)	170	25.8–41.7
Sarici and Pazarli [35]	2013	30 (marginal)	50	40 (median)	30	24
Joye et al. [36]	2014	21.7 (average)	50	41.5 (median)	23	8.7
Reynolds et al. [37]	2017	25 (marginal)	50	19.74 (median)	12	18.2
Modorati et al.	Present study	35.8 (marginal)	50	57.6 (median)	194	34.5

The relative prevalence of RR in our cohort seems to be slightly higher compared with the previously published literature (Table 2). This could be related to the longer follow-up of our study, a higher rate of diagnosis, or the tendency of underreporting of clinically insignificant RR (i.e., exam changes without a decline in best-corrected visual acuity or constriction of the visual field). While slit-lamp examination and indirect ophthalmoscopy have been the standard of care for many years, these methods require cooperation (many patients might be limited by intense photophobia) and adequate pupil dilation to explore the retinal periphery (response to mydriatic drops might be suboptimal, especially if laser or intraocular surgery have been performed). FFA was particularly useful in eyes with media opacity, such as cataract or vitreous hemorrhage, increasing the detection rate of peripheral changes with respect to indirect ophthalmoscopy or fundus photography. UWF-FFA was of undeniable aid in the clinical practice; while traditional fundus imaging devices only include 45–50° of the posterior pole, which is optimal for imaging the optic nerve and of the macula, they are inadequate for the visualization of the medium-far and of the very-far retinal periphery. On the contrary, UWF allows to photograph very peripheral retina and to identify early signs of RR in patients who are otherwise judged healthy by traditional methods; consequently, the rate of RR incidence invariably surges.

Another explanation for the higher rate of RR in our cohort could be related to a higher marginal dose with respect to other series. Although the comparison could be affected by the heterogeneity in dose reporting (Table 2), a higher dosage of radiation is associated with a greater rate of cataract and ischemic complications [31, 32, 34,

38]. A median marginal dose as low as 22 Gy has been proven to provide a favorable local tumor control (93%) with a lower rate of RR (50%) and neovascular glaucoma (7%), compared with previous series using higher doses. Similarly, a dramatic decrease in blindness and posttraumatic enucleation has been described shifting from 45 to 35 Gy marginal dose [34]. However, the threshold for radiation retinopathy depends on other factors as well, as the fractionation scheme, the radiation delivery system, the dose received by 1% of the optic nerve, and the presence of systemic risk factors like diabetes mellitus [14].

Diverse studies have highlighted the importance of preoperative planning of the radiation, especially for critical structures, such as the optic nerve and the lacrimal gland. One of the first strategies that have been successfully introduced to limit GKR side effects relied either on fractionation [39] or on reduction of the global dose of irradiation [14]. According to Schirmer et al. [32], a marginal tumor dose of <25 Gy resulted in excellent local tumor control with limited local and regional damage. Recently, de-escalation strategies have been applied also with brachytherapy, showing a significant reduction in the dose-dependent ocular radiotoxicity and rate of side effects [40].

Modern imaging techniques, along with traditional ones (namely ultrasound, computed tomography, and magnetic resonance imaging) may play a pivotal role in increasing the safety and the tolerability of the treatment. Integrated data from all the aforementioned imaging techniques can aid in the accurate delineation of the tumor and healthy anatomical structures, which can help further spare critical normal tissue (i.e., optic nerve and

chiasma, brain stem, lacrimal gland, and lens). We have started to routinely use UWF imaging system in patients with UM who underwent GKR, finding relevant support in their management [Cicinelli et al. 3D Wrap™ ultra-widefield reconstruction in stereotactic radiosurgery for choroidal melanoma. *Ocul Oncol Pathol.*, in press]. The device gives a consistent appreciation of the location and size of the lesion and the pseudo-color retinography acquired pre-treatment works well as baseline documentation for comparing reference during the follow-up [41]. Recently, new grading systems for RR with UWF have also been proposed [42].

Reviewing the classification proposed by McCannel et al. [42], 4 degrees of RR have been described: grade 1, identified by late foveal leakage; grade 2, peripheral vascular leakage in addition to foveal leakage; grade 3, associated with nonperfusion, peripheral and foveal leakage; and grade 4, demonstrating retinal neovascularization. In our series, RM, angiographically corresponding to McCannel's grade 1, was observed in 23 eyes (11.4%); 5 eyes out of 23 presented without any sign of RR, while in the remaining cases maculopathy was associated with retinopathy. Of the 67 eyes diagnosed with RR, the great majority was distributed between grades 2 and 3. Only 3 eyes featured epiretinal neovascularization, corresponding to grade 4. However, a coded treatment scheme has not been proposed yet for the different stages of the disease; further studies are needed to clarify the therapeutic management.

In conclusion, this paper represents one of the largest experiences with GKR for UM with long-term follow-up assessing the rate of complications found in an Italian tertiary referral center. Despite modern and advanced strat-

egies introduced to limit GKR side effects, cataract and RR still represent a serious limitation of this treatment. Nevertheless, we remain hopeful that continued advancement in imaging and radiation delivery techniques combined with refined dose/fractionation schemes will provide valuable advantages regarding the management of patients undergoing GKR.

Statement of Ethics

The research complied with the guidelines for human studies and the research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. Patients gave their written consent to participate in the study.

Disclosure Statement

The authors have no competing interest in publishing the present work.

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Author Contributions

All the authors contributed to the conception or design of the work, the acquisition, analysis and interpretation of data, drafting the work, revising it critically for important intellectual content and gave final approval of the version to be published.

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