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CLINICAL STUDY

Secondary glaucoma in small versus large uveal melanoma patients treated with stereotactic radiosurgery on linear accelerator

Sekac J[1], Ferkova SL[1], Kollarova A[1], Kusenda P[1], Furda R[2], Gregus M[2]

Department of Ophthalmology, Faculty of Medicine, Comenius University in Bratislava and University Hospital Ruzinov, Bratislava, Slovakia. **afrf@mail.t-com.sk**

ABSTRACT

AIM: Secondary radiation-related side effects like secondary glaucoma (SG) of different modalities of treatment in uveal melanoma patients can appear in certain interval after therapy. This study describes the incidence of SG in patients after stereotactic radiosurgery (SRS).

METHOD: The data of 230 patients treated by SRS were reviewed for SG. Group of 83 patients who were observed 5 years after treatment in one center with follow-up regularly at least 4 times per year were analyzed.

RESULTS: In group of 83 patients with the median age 59 years, the median tumor volume at baseline was 0.41 cm^3. The survival without SG after single dose SRS was 94 % in 1.5 year, 77 % in 2 years, 57 % in 3 years, 43 % in 3.5 years, and 18 % in 4.5 year after irradiation. In 6 patients (7.2 %) secondary enucleation was necessary due to SG. Both predictors (tumor volume and age of patient) at the time of SRS were not statistically significant by Cox proportional-hazards regression.

CONCLUSIONS: Complications like SG in 5 year interval after irradiation can lead to secondary enucleation of the eye globe *(Fig. 3, Ref. 44)*. Text in PDF *www.elis.sk.*

KEY WORDS: secondary glaucoma, stereotactic radiosurgery, melanoma.

Introduction

The most common and most aggressive primary intraocular tumor in adults is uveal melanoma. The incidence of uveal melanoma varies from 0.2 to 1.0 / 100 000 inhabitants and the predilection site of uveal melanoma is the choroid (90 %). On a smaller scale, they are found in the iris (4 %) or the ciliary body (6 %) (1, 2). We know two basic components of the metastatic process so called Zimmermann effect, that can lead to metastasis, these are properties of the primary uveal melanoma and host mechanisms involved with controlling pre-existent metastatic diseas (3). In last century enucleation was the standard treatment method for posterior uveal melanoma wit aim to prevent metastatic process. A suitable and increasingly preferred alternative has been to use conservative methods (4). Currently, first-line treatment for this malignancy is currently resection, radiation therapy, and enucleation. Radiotherapy can be performed as plaque brachytherapy and teletherapy, in which a proton beam, helium ion, or SRS can be used using a cyber knife, a gamma knife, or a linear accelerator (LINAC) (2). Despite any attempt to minimize adverse effects, there is a development of therapeutic complications.

Large choroidal melanoma or iridociliary melanoma can rarely present primary with the features of nevascuilar glaucoma (5). Secondary glaucomas are a heterogeneous of conditions in which elevated intraocular pressure is the leading pathological factor causing glaucomatous optic neuropathy (6). There are many causes of SG. It may also arise as a result of treatment that appears to be effective (6). SG may occur despite effective treatment of uveal melanoma (7). It has been described as the second most common complication of radiation therapy, leading to the need for enucleation. Furdova et al have analyzed the association between secondary enucleation and the presence of SG or haemophthalmus and radiation-induced optical neuropathy after SRS. Enucleation as a result of SG was found in 16.7 % of patients while optical neuropathy was significantly associated with a higher dose in SRS. Overall survival of patients undergoing secondary enucleation did not differ from patient survival without enucleation (8).

Secondary post-irradiation glaucoma may be treated with any group of antiglaucomatic drugs, taking into account the specific drug or its active agent conitraindications (9). Depending on the intraocular pressure value, we treat it as a first-choice method for monotherapy or combination therapy. Most publications recommend treatment with β receptor blockers, α-2 receptor agonists, and carbonic anhydrase inhibitors (10). Prostaglandin-like drugs

[1]Department of Ophthalmology, Faculty of Medicine, Comenius University in Bratislava and University Hospital Ruzinov, Bratislava, Slovakia, and [2]Department of Information Systems, Faculty of Management, Comenius University, Bratislava, Bratislava, Slovakia

Address for correspondence: J. Sekac, MD, Department of Ophthalmology, Faculty of Medicine, Comenius University, Pazitkova 4, SK-821 03 Bratislava, Slovakia.
Phone: +421.2.48234777

increase the activity of matrix metalloproteinases and reduce the resistance of aqueous fluid discharge through the uveal scleral pathway, thus potentially increasing the risk of tumor dissemination. When drugs are ineffective and do not reach the target IOP, glaucoma surgery is an option. Conventional glaucoma operations, including filtration operations such as basal iridectomy trabeculectomy, drainage implants, and the like, may be used (11,12). Lee et al however, it states that surgery alone can speed up tumor spread (12). Piirtola et al in their work, the use of transcleral photocoagulation therapy as a possibility to reduce IOP in patients with SG has been reported because ciliary body photocoagulation or cryotherapy can cause regional death of tumor cells and thereby alleviate high intraocular pressure (13).

Cyclocryopexia can be used to treat or ameliorate SG. The action of cryosondy at the site of the ciliary body causes destruction of its cells and consequent reduction of aquous humor production as well as regional cell death, thus relieving high eye pressure. Finger in his work also mentions another possibility of using cryosons in the treatment of melanoma, for eye traction during enucleation. Cryoprobe was used to induce proptosis during optic nerve transsection. The surface of the probe creates corneal adhesion and lifts the eye. This simplifies access to the optic nerve. The aim of our work is to describe the incidence and prevalence of SG as a complication of SRS on LINAC depending on individual types of uveal melanoma. In this study we assess the treatment of posterior uveal melanoma by one-day session LINAC based SRS and risk for SG.

Methods

The data of all 230 patients treated by LINAC based therapy for uveal melanoma (ciliary body and choroid) were reviewed. Patients with follow-up less than 36 months were excluded. Data of 83 patients who were observed 5 years after treatment with follow-up regularly at least 4 times per year were analyzed.

Medical records were screened for neovascularization of the iris, increased intraocular pressure (IOP) > 23 mmHg and antiglaucomatous therapy of IOP lowering medication was analyzed in the interval after irradiation on LINAC. Ophthalmological examinations were scheduled after 3, 6, 12, 18, and annually after treatment. Follow-up care by an oncologist included ultrasound of liver, CT or 18FDG PET/CT in some patients, if needed.

Ultrasound and magnetic resonance findings were basic to indicate patient for LINAC therapy. After stereotactic frame fixed to the head and the sutures from extraocular direct muscles were tied to the stereotactic Leibinger frame patient underwent CT and MRI examination. The individual plan for SRS was optimized according to the critical structures - lenses, optic discs, optic nerves and chiasm. The planned therapeutic dose into the tumor mass was 35.0 Gy. The doses to the critical structures for the optic nerve and the optic disc were 8.0 Gy and 10.0 Gy to the anterior segment of the eye and lens.

The regular follow-up examination included slit lamp examination, ophthalmoscopy, intraocular pressure measuring, ultrasound, optical coherence tomography and photodocumentation.

Results

The group of 83 patients after applied exclusion criteria was identified from 230 patients treated on LINAC. The therapeutic dose for irradiation was 35.0 Gy (Fig. 1).

Age of patients ranged from 24 to 82 years with the median 59 years. The number of male was 36 (43.4 %) and number of female 47 (56.6 %). The median tumor volume at baseline was 0.41 cm^3 (with range from 0.11 to 0.95 cm^3). The survival without SG after single dose SRS was 94 % in one and half year, 77 % in two years, 57 % in three years, 43 % in three and half years, and 18 % in four and half year after irradiation. In 6 patients (7.2 %) secondary enucleation was necessary due to complications – SG (Fig. 2). Enucleation free interval ranged from one and half year to three years.

We calculated one Cox proportional-hazards regression (Fig. 3). Two predictors were taken into account: tumor volume and age of patient at the time of SRS. The calculation results confirmed that no one predictor, age of patient ($p = 0.51$ with Risk Ratio 1.0159) or tumor volume ($p = 0.24$ with Risk Ratio 9.5257), was significant prognostic factors in this Cox proportional-hazards regression for survival without SG analysis. The results of this analysis indicate that both predictors are not statistically significant.

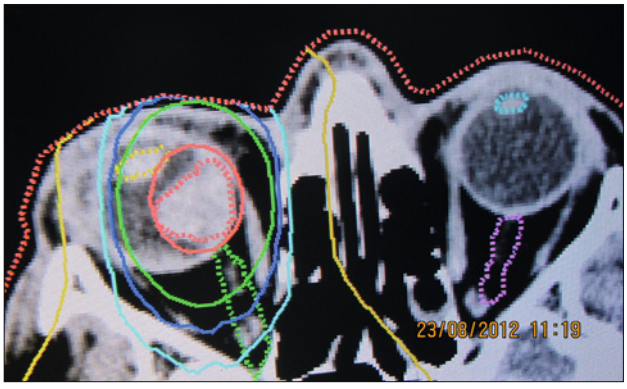

Fig. 1. Stereotactic planning scheme for patient with large uveal melanoma (tumor volume 1.0 cm^3).

Fig. 2. Macrophotograph of the same patient's anterior segment 1.5 years after SRS with developed secondary neovascular glaucoma and complicated cataract.

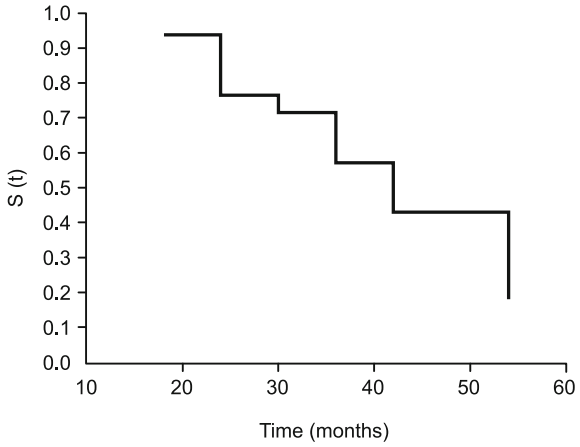

Fig. 3. The survival without SG after single dose of SRS.

Discussion

Photon beam irradiation has been under clinical investigation for the treatment of uveal melanoma over 20 years. The therapeutic single dose has been reduced to as low as 35.0 Gy over the past few years (14, 15). This dose is used in our study. Doses of 40.0 Gy delivered at the 50 % isodose result in good local tumor control and acceptable toxicity. Linear accelerators have the advantage of a feasible fractionation. A hypofractionated scheme of 4–5 fractions in different studies for uveal melanoma has been reported over 90 %, 5 and 10 years after treatment good local tumor control rates (16, 17).

High rates of local control can be achieved with 5-year control rates exceeding 95 % in patients treated with charged particles, while visual acuity is depending on tumor stage – tumor size and location (1, 18).

Recent studies have suggested that gamma knife radiosurgery and SRS may be an appropriate alternative for treating uveal melanoma in those patients, in whom lesions are ineligible for conventional brachytherapy. The findings in the series suggest a role of SRS in the treatment of selected cases of uveal melanoma (15,19).

Radiogenic side effects after stereotactic radiotherapy are cataract, radiation retinopathy development, opticopathy and neovascular glaucoma. They result to secondary visual acuity losses and in some cases it is necessary to perform secondary enucleation. An important cause of visual morbidity can be secondary glaucoma. To prevent irreversible visual acuity reduction is necessary to start treatment as soon as possible (20). Overall, stereotactic photon beam radiotherapies are considered effective treatment modalities for uveal melanoma, with promising late tumor control and toxicity rates. Stereotactic irradiation of uveal melanoma is safe and precise treatment option. Local control was found to be excellent. LINAC based stereotactic irradiation for uveal melanoma is feasible and well tolerated and can be offered to patients with medium sized and unfavorably located uveal melanoma who are searching for an eye-preserving treatment (21).

A retrospective study of Meyer et al pointed out that irradiation of 30.0 Gy of more than 2 mm of the optic nerve head initiated an optic neuropathy (22).

Recent studies have suggested that gamma knife radiosurgery and SRS may be an appropriate alternative for treating uveal melanoma in those patients in whom lesions are ineligible for conventional brachytherapy (23). The findings in the series suggest a role of SRS in the treatment of selected cases of uveal melanoma.

The eye retention is one of the main goals of the conservative treatment but in some cases enucleation can be indicated due to complications after therapy, e.g. secondary neovascular glaucoma (24, 25).

Fractionated stereotactic radiotherapy and one day session SRS have emerged as promising, non-invasive treatments for uveal melanoma (26). According to our results a single one-day sessions SRS with 35.0 Gy is sufficient to treat small and middle stage melanoma (27).

Secondary complications after brachytherapy is most frequently SG (28–30) but only few studies concerning CyberKnife irradiation are available (31, 32). These studies use different criteria of SG (in some of them increase intraocular pressure over 23 mmHg, in others over 25 mmHg). In our study elevated IOP was measured by non-contact tonometry and patients with primary open angle glaucoma before stereotactic irradiation were excluded from our study.

Siedlecki et al diagnosed 96 % of patients with SG they had therapy by eye drops, and some of them needed secondary enucleation due to blind amaurotic eye (7). In this study they compared SG in group of patients treated with brachytherapy and patients with robotic CyberKnife radiosurgery and SG was significantly more frequent after robotic radiosurgery than brachytherapy with Ru-106 plaques. In that study the incidence of SG at 5 years interval was 46.7 %. Comparable results, 33 %, can be found in study of Klingenstein et al (33).

Shields et al assumed that higher tumor thickness may be associated with increased incidence of SG (34). Tumor thickness is a very important risk factor for SG (35–37).

In brachytherapy the elevation of the tumor in maximum is mostly 6 mm, by external radiotherapy we can irradiate tumor above 6 mm and also in close proximity to the macula or optic nerve head. But patients with a tumor thickness less than 6 mm are eligible for both BT and external radiotherapy. CyberKnife/RRS irradiation represents one of the most advanced forms of radiosurgery nowadays (38). No difference in severity of SG was found between RRS and BT (7). This is important, because about 50 % of patients with SG in that study needed IOP/lowering medication and need of surgery and especially of enucleation, which was necessary in every fourth patient with SG.

The most important radiation/related risk factors for SG are localization of the tumor in the ciliary body and near the posterior pole (36, 39, 40).

In our study first signs of SG were observed after a median of 24 months, in studies of Mueller et al and Muacevic et al it was 10-21 months (23, 31).

In other studies they compared RRS to BT. They realized a comparable safety profile in terms of incidence of SG to both radiation modalities. Irradiation techniques have a great importance for eye retention, but SG with tumor recurrence make up 82–90 % of reasons for secondary enucleation (37, 41, 42).

Long term follow-up screening for late complications after stereotactic irradiation like SG is necessary. In patients after irradiation techniques in treatment of secondary glaucoma medical therapy, transscleral cyclophtotocagulation, laser iridotomy or minimally invasive glaucoma surgery can be applied for eyes with regressed posterior segment melanoma in patients with no iridociliary involvement, but in some conditions also enucleation is necessary (43). In study of Fatehi (44) they reported patients safety and IOP control after placement of a glaucoma drainage device in eyes treated for uveal melanoma. Due to their results they suggest that glaucoma filtration surgery can be effective in patients with uveal melanoma with secondary glaucoma development , but local tumor control is basic to decide in that treatment modality. In our study we did not apply filtration surgery in patienst with secondary glaucoma.

Conclusions

Secondary complications after stereotactic one day session LINAC based radiosurgery with a single dose 35.0 Gy is one of treatment options in uveal melanoma. According to our results one-day session SRS with 35.0 Gy is sufficient to treat small and middle stage choroidal melanoma. SG in 5 year interval after irradiation can lead to secondary enucleation of the eye globe.

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