

Stereotactic radiosurgery in intraocular malignant melanoma – retrospective study

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Abstract

OBJECTIVES: One day session linear accelerator based stereotactic radiosurgery of intraocular malignant melanoma is a method of “conservative” attitude to treat posterior uveal melanoma. **MATERIAL & METHODS:** Retrospective clinic-based study of patients with posterior uveal melanoma in stage T2/T3 who underwent stereotactic radiosurgery at linear accelerator in period 2001–2011. Immobilization of the affected eye was achieved by mechanical fixation to the stereotactic Leibinger frame. The stereotactic treatment planning after fusion of computed tomography and magnetic resonance imaging was optimized according to the critical structures (lenses, optic nerves, chiasm). **RESULTS:** In group of 96 patients with posterior uveal melanoma treated with one day session stereotactic radiosurgery, patient age ranged from 25 to 80 years with a median of 54 years. Median tumor volume at baseline was 0.6 cm³ (with range from 0.2 to 1.0 cm³). Median maximal dose applied was 49.0 Gy (range from 37.0 to 52.0 Gy). Secondary enucleation was necessary in 11 patients (11.5%) due to complications like irradiation neuropathy and secondary glaucoma. Tumor local control was successful in 95% of patients in 3 years interval after stereotactic radiosurgery and in 85% of patients in 5 years interval after stereotactic radiosurgery. **CONCLUSION:** One step LINAC based stereotactic radiosurgery with a single dose 35.0 Gy is one of treatment options to treat T2 or T3 stage posterior uveal melanoma.

INTRODUCTION

The incidence of intraocular tumors varies from 0.2 to 1.0. Uveal melanoma is the most common and most aggressive type of intraocular tumor in adults. Over 50% of patients die within 15 years after enucleation, or other therapeutical methods (Singh *et al.* 2001). This type of melanoma is rare

but sight or life-threatening malignancy. Age and volume (size) of the tumor have been shown to be prognostic indicators following therapy for posterior uveal melanoma (Seregard *et al.* 1995; Shields *et al.* 2000).

In less populated countries like Slovakia, where the whole population is slightly above 5.5 million inhabitants, the number of new cases

diagnosed per year varies from 10 to 25 uveal melanoma. According to the Slovak National Cancer Registry the incidence in Slovakia is 0.2 to 0.6/100 000 inhabitants (Ondrusova *et al.* 2008). The recorded data from Slovak regions correspond with the data reported from other countries and regions of Europe.

According to the report published by the Collaborative Ocular Melanoma Study group (COMS), the clinical diagnosis of choroidal melanomas corresponds in 99% with histopathological findings. Modern diagnostic tools, ophthalmological examination, computed tomography and magnetic resonance have led to significant advances in the ability to diagnose primary uveal melanoma.

Over the past three decades diagnostic methods have improved and radiotherapy (external beam, charged particle or brachytherapy) has become the preferred treatment for most patients with uveal melanoma. The desire to improve survival and preserve vision in patients with uveal melanoma has stimulated the devel-

opment of alternative therapies. Different radiation modalities are currently in use in treatment of posterior uveal melanoma. One of the methods of “conservative” approach is the stereotactic radiosurgery (SRS) by linear accelerator.

Radiotherapy acts by inducing DNA damage, resulting in tumor-cell death and proliferation arrest of remaining surviving cells. For the treatment of uveal melanoma, radiation may be delivered using a variety of different methods, including plaque brachytherapy, charged-particle therapy (CPT), gamma-knife and LINAC stereotactic delivery systems. Stereotactic radiation therapy and gamma-knife radiosurgery also provide good local control, with survival rates comparable with other treatments. Furthermore the current experience is limited, with relatively short follow-up periods and a lack of comparison with brachytherapy and CPT.

The single irradiation of the tumor itself is a new approach – it has been shown to achieve ultrasonic tumor regression in a similar fashion to brachytherapy. SRS of extracerebral lesions like uveal melanoma has been invented in the last two decades and is an alternative treatment for middle and large posterior choroidal melanoma. With plaque radiotherapy, eye salvage is achieved, and, particularly for cases in which the tumor is located away from the optic disc or macula, useful vision can be retained after treatment (Shields *et al.* 2000).

In this study we assess the treatment of posterior uveal melanoma by one-day session of LINAC based stereotactic radiosurgery.

METHODS

A retrospective analysis was undertaken for patients with posterior uveal melanoma (tumor arising from ciliary body or choroid) in stage T2 resp. T3 who underwent stereotactic radiosurgery at C LINAC in period

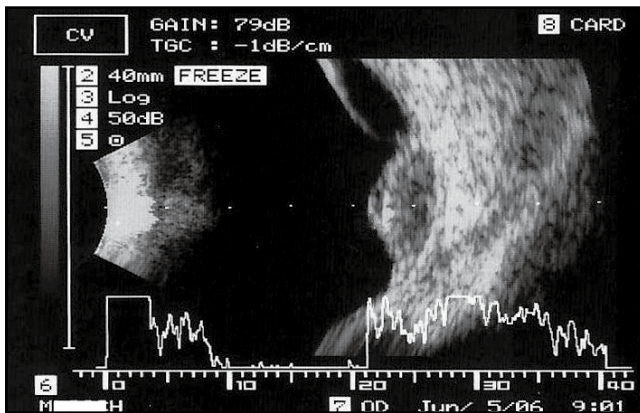


Fig. 1. Ultrasound findings on the posterior pole of the eye – small choroidal melanoma.



Fig. 2. Patient with stereotactic frame, the right eye is immobilized through stitches to the frame.

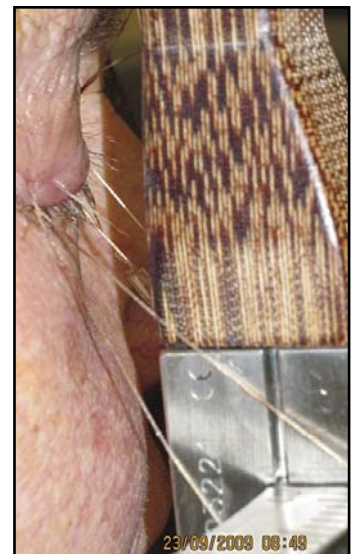


Fig. 3. Detail of fixed eye through 4 stitches to the frame.

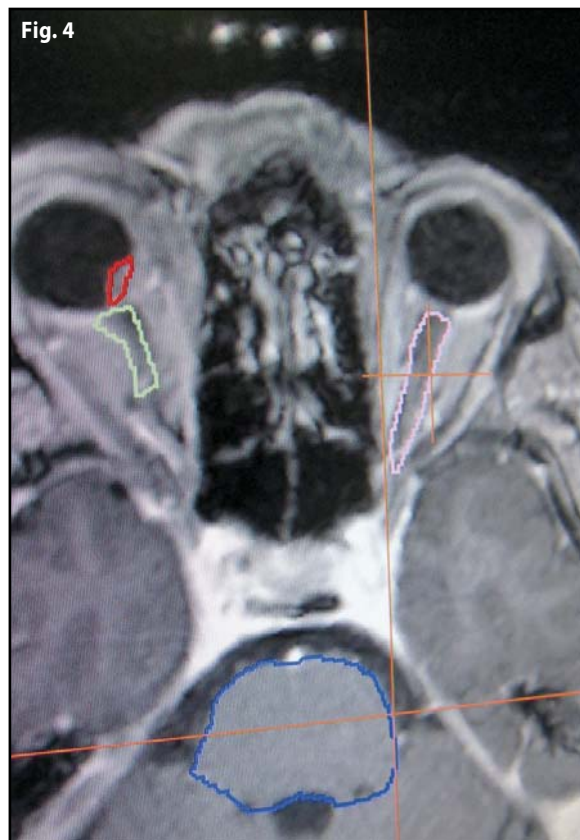


Fig. 4. Small choroidal melanoma of the right eye (CT / MR fusion).

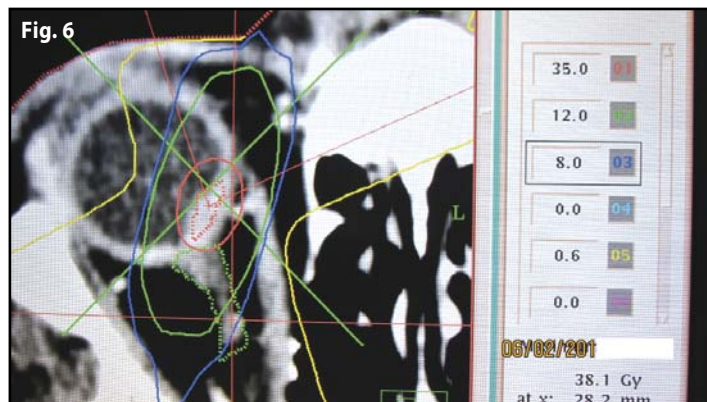
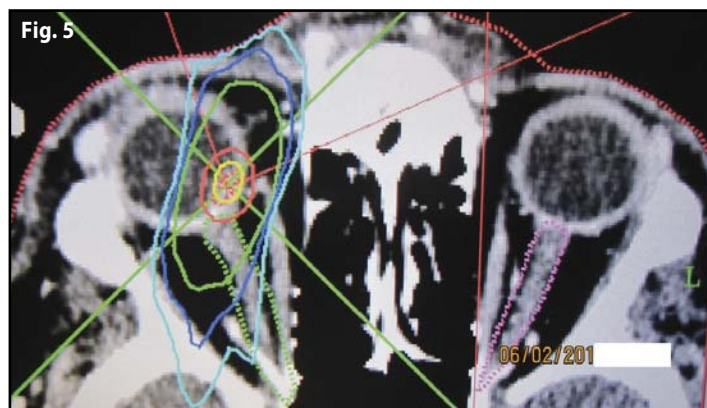


Fig. 5. Stereotactic planning scheme of the tumor (see Fig. 4).
Fig. 6. Isodose planning of the small choroidal melanoma in Fig. 4 (TD 35.0 Gy).

2001–2011. Patients were not randomized either to radical (enucleation) or to “conservative” procedure, but the treatment was determined exclusively on a case-by-case basis. Tumor stage, volume, maximum elevation, localization presence of secondary retinal detachment, general status, age, gender, the functional tests (visual acuity, perimeter, ultrasound) were taken into consideration (Figure 1). The patient was actively involved in the decision on the therapeutic procedure after explaining possible postoperative complications.

Before stereotactic irradiation immobilization of the affected eye was achieved by mechanical fixation to the

stereotactic Leibinger frame. Sutures were placed under 4 direct extraocular muscles through conjunctiva and through the lids. The stereotactic frame was fixed to the head and the sutures were tied to the stereotactic frame (Figures 2 and 3). The patient underwent CT and MRI examination with the fixed eye to the frame (Figure 4). The stereotactic treatment planning after fusion of CT and MRI was optimized according to the critical structures – lens, optic nerve, also lens and optic nerve at the contralateral side, chiasm (Figure 5). The best plan was applied for therapy at linear accelerator. Tumor volume calculation was based on the ROI (region of interest) of

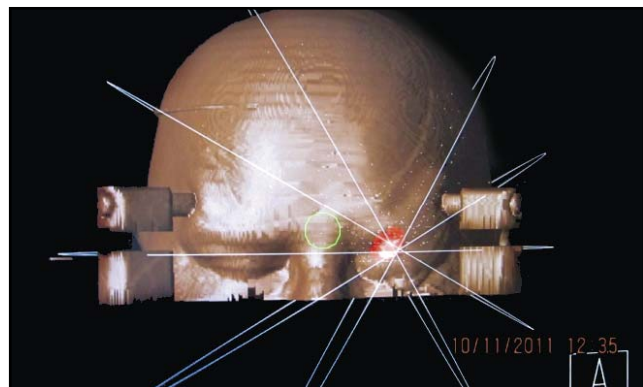


Fig. 7. 3D reconstruction of the head of the patient with uveal melanoma.

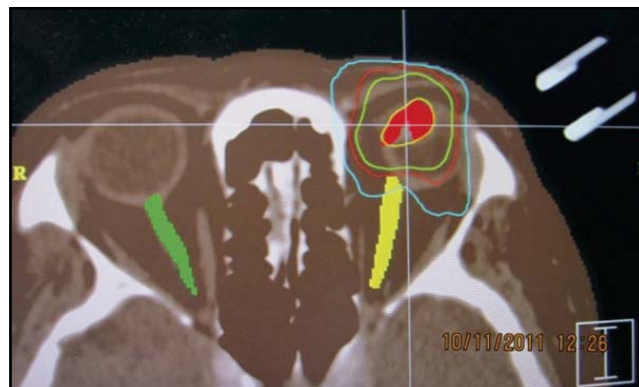


Fig. 8. Isodose planning of the tumor.

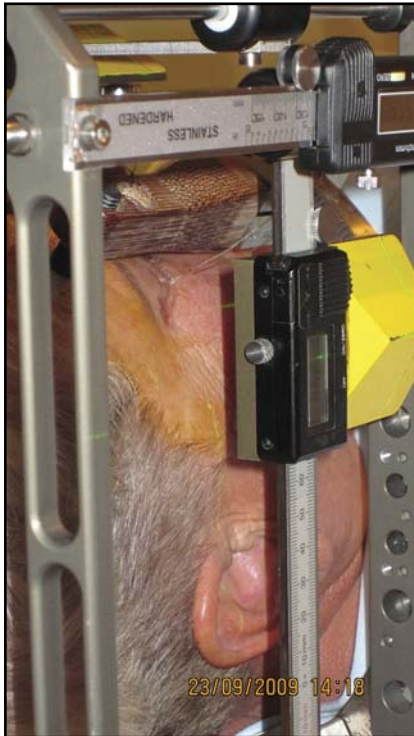


Fig. 9. Patient by stereotactic radiosurgery irradiation at linear accelerator.



Fig. 10. Detail of the patient's position by stereotactic radiosurgery irradiation at linear accelerator.



Fig. 11. Patient at the linear accelerator preparing his position of head.

the tumor and 3D reconstruction was done (Figure 6). The planned therapeutic dose was 35.0 Gy by 99% of DVH (dose volume histogram). Model LINAC C 600 C/D Varian with 6 MeV X was used.

The stereotactic treatment planning after fusion of CT and MRI was optimized according to the critical structures (lens, optic nerve, and also lens and optic nerve at the contralateral side, chiasm). The best plan was applied for therapy at C LINAC accelerator (Figures 7 and 8). In the afternoon the patient underwent irradiation at linear accelerator (Figures 9–11). Sutures and frame were removed. The next morning the patient underwent the slit lamp examination, ophthalmoscopy, intraocular pressure measuring and was released for home treatment with local therapy (eye drops – antibiotics, corticosteroids, lubricant).

The planned therapeutic dose in SRS was 35.0 Gy, TD_{min}. dose to the margin of the lesion varied from 35.0 to 38.0 Gy, TD_{max} 37.0–50.0 Gy. We used PTV (planning treatment volume) 95% isodose planning. The doses to the critical structures were below 8.0 Gy for the optic nerve and the optic disc and 10.0 Gy to the anterior segment of the eye. Patients with melanocytoma or patients with juxtapapillary melanomas were excluded from the study.

The record for each patient included the age at treatment, tumor size, tumor volume, the maximum height of the tumor by A, B scan ultrasound, the presence and the extent of secondary retinal detachment, and

the signs of extrascleral extension. Tumor volume was calculated in each SRS group patient directly by computer after CT and MRI examination as the step of SRS procedure and was involved to the stereotactic planning scheme.

Tumors were divided into 3 groups as follows: small – up to 5 mm of maximal elevation, middle – up to 8 mm, and large – over 8 mm. The elevation of the tumor was observed in 6 months interval by Bscan ultrasound by one ophthalmologist. We compared tumor regression by measuring the maximum elevation by Bscan ultrasound in the group of patients with single irradiation in interval 3, 6, 12 and 24 months after the therapy, or, in individual cases, every month, but 2 years after stereotactic radiosurgery patients were asked for examination at least 2 times per year.

Patients were recommended regularly in six month interval to their oncologist to a liver ultrasound, abdominal ultrasound, liver's function test; once per year chest X-ray to confirm or exclude the presence of metastases. In individual cases they were recommended to brain CT or PET (positron emission tomography).

RESULTS

In a group of 96 patients with posterior uveal melanoma treated with one day session stereotactic radiosurgery, patient's age ranged from 25 to 80 years with a median of 54 years. Median tumor volume at baseline

was 0.6 cm³ (with a range from 0.2 to 1.0 cm³). Median of the maximal dose applied was 49.0 Gy (ranged from 37.0 to 52.0 Gy). A secondary enucleation was necessary in 11 patients (11.5%) due to complications (e.g. secondary glaucoma).

The simple linear regression for patients' group (40 patients) followed in the period 2001 to 2008 showed that the correlation coefficient was not significantly different from zero, and the age was not significant factor that could determine any significant dependence on the size of the tumor. Age and volume were found as the main independent (Figure 12) predictors of survival outcome and therefore, they were included in the Cox model – a type of multivariable analysis.

Such adjustment is necessary, since performing the survival analysis without above mentioned covariates yielded a seemingly significant difference ($p=0.0498$) between the treatment groups favourizing the patients treated with SRS. Group of patients after stereotactic radiosurgery had a lower risk of death, respectively higher chance of survival. However, this analysis ignored other factors that affect survival and minimum age and tumor volume, which significantly affect survival independently of the chosen treatment modality. The adjustment for age and tumor volume removed confounding caused by these covariates and showed that there was no significant difference between the treatment modalities under comparison. Tumor local control was successful in 95% of patients in 3 years interval after stereotactic radiosurgery and in 80% of patients in 5 years interval after stereotactic radiosurgery.

Visual acuity outcome results in subgroup of patients treated in 2011

In the group of 19 patients (9 men and 10 women) with uveal melanoma, who were operated on linear accelerator in 2011, median of age was 57 years (from 31 to 73 years). Number of irradiated eyeballs was 7 right eyeballs and 12 left eyeballs.

Best corrected visual acuity (BCVA) on Snellen chart was converted to decimal values. Central visual acuity after irradiation was influenced by the size of dose irradiation of risk structures – the lens and the optic nerve of the affected eye (Figure 13, Table 1).

The average volume of the tumor was 0.6 cm³ (0.2–1.0 cm³), the average of maximal dose of radiation was 38.5 Gy (36.7–44.7 Gy), therapeutic dose of tumor was 35.0 Gy. The rate of age collocation raised up to $p=0.22$

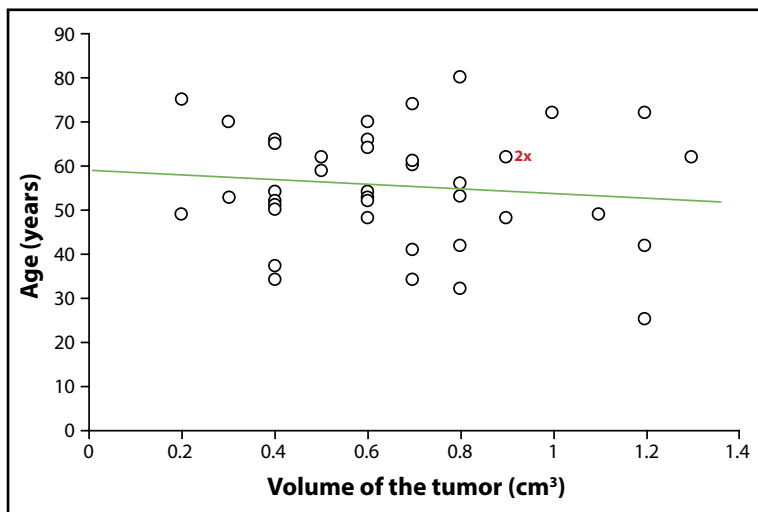


Fig. 12. Simple linear regression in the group of patients after stereotactic radiosurgery in 2001-2008 did not show presence of collinearity. Since the groups of patients differed with respect to age and tumor volume ($p=0.0007$ and $p<0.0001$, respectively), these covariates were incorporated in the complex regression model.

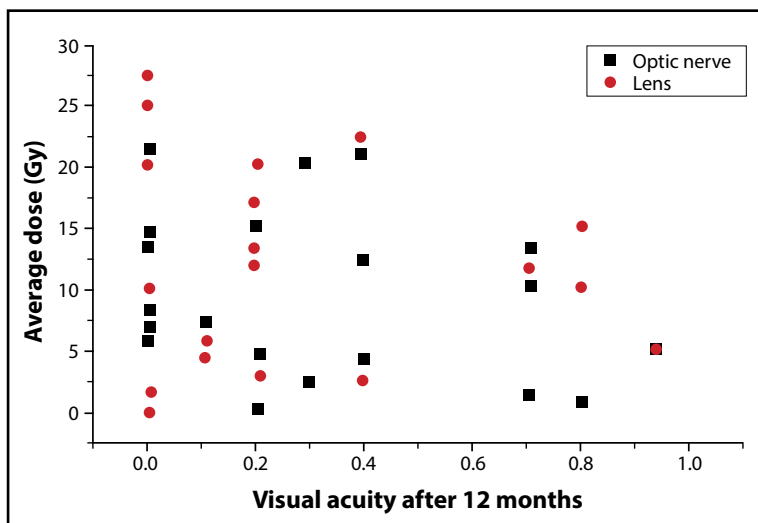


Fig. 13. Best corrected visual acuity in 12 month interval after stereotactic radiosurgery correlated with radiation dose (Gy) to the optic nerve and lens (in patients treated in 2011).

Tab. 1. Best corrected visual acuity (BCVA) in patients treated in 2011 before therapy and in interval 6 and 12 months after the therapy.

BCVA values	N° of patients (percentage)	BCVA (feet)	Snellen chart (decimal)
before therapy	3 (16 %)	$\geq 20/40$	≥ 0.5
	11 (58 %)	$<20/40$ & $\geq 20/200$	<0.5 & ≥ 0.1
6 months after SRS	5 (26 %)	$<20/200$	<0.1
	3 (16 %)	$\geq 20/40$	≥ 0.5
	10 (53 %)	$<20/40$ & $\geq 20/200$	<0.5 & ≥ 0.1
12 months after SRS	6 (31 %)	$<20/200$	<0.1
	2 (11 %)	$\geq 20/40$	≥ 0.5
	9 (47 %)	$<20/40$ & $\geq 20/200$	<0.5 & ≥ 0.1
	8 (42 %)	$<20/200$	<0.1

what shows no proofs of any abnormalities. We did not notice any dependence with incidence of tumors between age and gender ($p=0.34$). In this group there it was not significant difference in the size of tumor depending on gender ($p=0.84$).

Our description of dependence of central visual acuity on dose of radiation verified the hypothesis, that irradiated risk structures are not connected with volume of melanoma ($p=0.94$). Also we did not notice any correlation between changes of central visual acuity and volume of melanoma ($p=0.58$) or age ($p=0.72$). By simple linear regression we verified also relation between standard dose in lens and changes of central visual acuity ($p=0.98$) where we did not find any correlation. Accordingly, by assumption, that changes of central visual acuity after stereotactic radiosurgery does not influence only radiation load factor to lens, but to the optic nerve too, we tested this dependence by repeated linear regression, where we did not find correlation ($p=0.71$). Central visual acuity after the procedure is not affected by the size of the radiation dose to the lens and optic nerve of the eye operated as predictors.

Tumor regression in patients by Bscan ultrasound findings

Patients operated for uveal melanoma with single irradiation by SRS between 2001–2008 were divided into 3 subgroups according to the maximum elevation before irradiation: small – 4 to 5 mm high = 4 cases (16%), middle – up to 8 mm high = 15 cases (60%), large – over 8 mm = 6 cases (24%). Tumor regression after the treatment in 6 months interval 12 months after the therapy showed, that in the group of small tumors in all of the patients there was no presence of increase of the elevation, but in 24 months interval there was sign of tumor regression in 3 cases (75%). In the middle stage group in 12 months interval after the therapy there was no sign of tumor elevation regression, but in the 24 months interval after the therapy tumor regression more than 1mm of the maximum pre-treatment elevation was found in 4 cases (27%). In the third subgroup of large tumors there was no sign of tumor regression according to ultrasound results in the 12 months or in the 24 months interval after the therapy.

Secondary enucleation after stereotactic radiosurgery

Secondary enucleation after stereotactic radiosurgery due to irradiation neuropathy and secondary glaucoma was necessary in 11 patients (11.5%) in 3 to 5 year interval after irradiation. In all of the cases the tumors had pre-treatment maximum elevation 10 mm and more; the tumor volume was up to 0.7 mm³ (average 0.9 mm³). In 3 patients the tumor was arising from the ciliary body. Histopathological findings showed in 3 patients the spindle cell melanoma and in 2 patients the mixed cell melanoma. There was no presence of optic nerve infiltration in all of the enucleated eye-globes.

DISCUSSION

One-fraction LINAC radiotherapy/radiosurgery is an unusual approach to treatment of choroidal melanoma. Hypofractionation with a broad shoulder in linear-quadratic model is still in discussion for radioresistant tumors like choroidal melanoma. In this study we evaluated local failure leading to enucleation as an end point in patients treated by SRS with long-term follow-up having accrued at the time of analysis.

Image fusion of a contrast-enhanced magnetic resonance imaging (MRI) and computed tomography (CT) is used for treatment planning co-ordinates. Some authors prefer irradiation before enucleation for large uveal melanoma. This treatment is used in a way of SRS with a single fraction administered with a precious spatial accuracy using a collimating system (COMS Group 2001a; b).

No survival difference attributable to stereotactic irradiation or combined and surgical attitude – enucleation of uveal melanoma has been demonstrated in the retrospective study in Slovak Republic. Enucleation after SRS in 7 patients was in interval 6 to 24 months after SRS. A small difference is possible, but a clinically meaningful difference in mortality rates, whether from all causes or from metastatic melanoma, is unlikely (Furdova *et al.* 2010).

High rates of local control can be achieved with 5-year control rates exceeding 95% in patients treated with charged particles. Proton beam radiotherapy with a 62 MeV cyclotron achieves high rates of local tumor control and ocular conservation, with visual outcome depending on tumor size and location (Damato *et al.* 2005).

Large, prospective, randomized trials were designed to compare mortality figures for medium-sized melanomas treated by brachytherapy or enucleation (Cohen *et al.* 2003; Singh *et al.* 2001). The results were not able to show the difference in mortality rates between the two treatment groups after a maximum of 12 years of follow-up (COMS Group 2001b).

In the last three decades, the management of patients with uveal melanoma has changed towards globe sparing techniques. Alternatives to the radical enucleation vary from observation to transpupillary thermotherapy, block-excision, endoresection with pars plana vitrectomy, brachytherapy using a variety of radioisotopes, external beam radiotherapy, charged particles and stereotactic radiosurgery, or the methods can be combined. SRS has recently been proposed as an alternative treatment for posterior uveal melanoma.

The therapy for each patient should be chosen in accordance with the general status of the patient and with the local findings, stage and character of the tumor (Shields *et al.* 2000). The Collaborative Ocular Melanoma Study (COMS), a multi-center national trial, is intended to provide long-term data on the natural history as well as therapeutic intervention. This large, prospective, randomized trial was designed to compare

mortality figures for medium-sized melanomas treated by brachytherapy or enucleation (COMS Group 2001a; Melia *et al.* 2001). The results were not able to show the difference in mortality rates between the two treatment groups after a maximum of 12 years of follow-up (COMS Group 2001b). The study was set up in 1985 before introducing the stereotactic radiosurgery in the treatment of uveal melanoma.

Stereotactic photon beam irradiation has been under clinical investigation for the treatment of uveal melanoma for over 15 years. Single-fraction stereotactic radiosurgery (SRS) is usually done with a gamma knife as well as more recently with a cyberknife. The therapeutic single dose has been reduced to as low as 35.0 Gy over the past few years without reduction in tumor control. Doses of 40.0 Gy delivered at the 50% isodose result in good local tumor control and acceptable toxicity. Since radiobiological studies indicate a possible advantage of hypofractionated treatment over a single very large fraction to sterilize uveal melanoma cell lines, fractionated stereotactic radiotherapy (SRT) has gained additional interest. Besides increased tumor control, toxicity should theoretically be reduced by fractionation. Linear accelerators (LINAC) have the advantage of a feasible fractionation. Most LINAC studies employ a hypofractionated scheme of 4–5 fractions and total doses between 50.0 and 70.0 Gy. The efficacy of SRT for uveal melanoma has been proven in different studies with local tumor control rates reported over 90%, 5 and 10 years after treatment. Radiogenic side effects after SRT are reported similarly to other forms of radiotherapy, with cataract development, radiation retinopathy, opticopathy and neovascular glaucoma being responsible for the majority of secondary vision losses and secondary enucleations. Overall, stereotactic photon beam radiotherapies (SRS and SRT) are considered effective treatment modalities for uveal melanoma, with promising late tumor control and toxicity rates. SRS is a relatively new method, so there is a need for multi-center trial to compare the outcomes following stereotactic radiosurgery with other methods. However, until now, no study has been performed in this topic. Studies comparing survival rates following enucleation versus newer treatment modalities, including SRS, suggested similar rates for comparable lesions and because reported local tumor control rate following SRS appear comparable, we offer SRS to patients who would otherwise require enucleation (Cohen *et al.* 2003, Furdova *et al.* 2010, Gragoudas *et al.* 2002, Zehetmeyer *et al.* 2012).

Stereotactic photon therapy of uveal melanoma, based on CT and MRI images, is a safe and precise treatment option. Local control was found to be excellent. Because of selection criteria, the number of patients in the study with reduced visual acuity will probably increase in the future (Dieckmann *et al.* 2006).

Local control over 95% appears in some studies: in the study of Dieckmann *et al.* 2006 local control is 98%

after a median observation time 33 months follow up. The observation time is still too short to allow definitive conclusions, but their results are comparable with the 82–98% local control rate reported by other groups after a median observation time of up to 15 years.

Seddon *et al.* 1987 described visual loss after proton beam irradiation of 33 to 47% after 1 and 2 years, respectively, for tumors located near the optic disc and fovea.

Meyer *et al.* 2000 reported in a retrospective study that irradiation of 30.0 Gy of more than 2 mm of the optic nerve head initiated an optic neuropathy.

In the study of Dieckmann *et al.* 2003 due to unfavorable tumor size and location in the vicinity of critical structures, e.g. optic nerve and macula, visual reduction was noticed in a high number of the patients. After an observation time of more than 6 months visual acuity could be evaluated in 79 patients. In the group of 77 patients 85.5% presented with visual acuity of 0.1 or better prior to radiotherapy. 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.

The tumor localization is important to achieve good visual acuity result. Brachytherapy Ru¹⁰⁶ of posterior choroidal melanoma achieves good conservation of vision if the tumor does not extend close to the optic nerve or fovea (Damato *et al.* 2005).

It is important to realize that the power of a test to compare survival in two or more groups is related not to the total sample size but to the number of events of interest (such as deaths in this case). In other words, the survival tests perform better when the censoring is not too heavy, and, in particular, when the pattern of censoring is similar across the different groups. High number of right-censored data (from those patients who still were alive at the end of observation, or dropped out of the study for various reasons other than death prior to its termination) could affect the reliability of the results. Thus, the heavy censoring might complicate the estimation of the survival model, because it decreases the equivalent number of subjects exposed (at risk) at later times, reducing the effective sample sizes. Moreover, small sample sizes may further increase the effect of the assumption violation. It is not reasonable, however, to drop the selected explanatory variable(s) from the model, since there are “real world” reasons why these particular variables should remain in the final model (Augsburger *et al.* 1999; Li *et al.* 2000).

There has been performed no multi-center trial to assess dosimetry, safety and efficacy of SRS, or to evaluate outcomes of gamma knife radiosurgery for melanoma yet, but data from several reported case series suggest that SRS can have similar local tumor control rate, metastasis rate, mortality rate and complications rate when compared to brachytherapy (De Potter *et al.* 1994; Marchini *et al.* 1996; Rennie *et al.* 1996). 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 (Langmann *et al.* 2000, Mueller *et al.* 2000, Zehetmayer *et al.* 2000). The findings in the series suggest a role of SRS in the treatment of selected cases of uveal melanoma.

Complications after certain procedures can lead to secondary neovascular glaucoma and may result to the enucleation, that's why the eye retention is one of the main goals of the conservative treatment (Ghazi *et al.* 2008; Krema *et al.* 2009).

A multivariate data analysis by employing the supervised learning techniques, in particular the algorithm known as Regularized Least Squares (RLS) was used in study of Mosci *et al.* 2009. Their study was the largest one in Italy and they demonstrated the excellent local tumor control, survival and eye retention rate after the proton beam irradiation therapy. According to their results future refinements in treatment planning, dosing and delivery could be necessary to determine visual results and complications after proton beam therapy in ocular melanoma (Gragoudas *et al.* 2000).

The main issues with the single-session radiotherapy are the effects of distribution and hypofractionation of the dose. Tumor size and location, e.g. closer than 2 mm to the optic disc are the most important factors to assess clinical evaluation of visual acuity outcome.

Identification of risk factors may reduce the rates of recurrence and lead to fewer complications, preservation of the eye, improved visual function and, potentially, better survival outcome. The recurrence of optic neuropathy after stereotactic radiosurgery is a problem not only by intraocular tumors but also e.g. by perichiasmatic tumors stereotactic irradiation. Although rare, optic neuropathy may follow radiosurgery to lesions near the visual pathways. Careful dose planning guided by MRI with restriction of the maximal dose to the visual pathways to less than 8.0 Gy will likely reduce the incidence of this complication (Girkin *et al.* 1997; Mosci *et al.* 2009).

The same problems with visual acuity loss as in stereotactic radiosurgery are found in patients after other radiotherapy procedures, e.g. brachytherapy. In the consecutive series of patients after Ru¹⁰⁶ brachytherapy, patients retained some useful vision in the first post-operative years and a few even got better visual acuity, however, the long-term visual outcome is poor with a continuing visual acuity loss over time. A large number of patients became blind or lost reading ability after 5 years, either because of radiation complications or secondary enucleation (Isager *et al.* 2006).

According to our results tumor regression after the single SRS treatment in 6 months interval in first year after the therapy showed, that in the group of small tumors in all of the cases there was no presence of increase of the elevation, but in 24 months interval there was sign of tumor regression in 3 cases (75%). In the middle stage group in one year interval after the

therapy there was no sign of tumor elevation regression, but in the 2 year interval after the therapy tumor regression was found in 4 cases (27%), in the subgroup of large tumors there was no sign of tumor regression nor in the 12 or 24 months interval after the therapy. Probably in interval more than 5 years this numbers would be changed.

Stereotactic radiosurgery and fractionated stereotactic radiotherapy have emerged as promising, non-invasive treatments for uveal melanoma (Henderson *et al.* 2006). Although, historically, melanoma has been considered a relatively radioresistant tumor, newer data have challenged this viewpoint, and radiation therapy is now considered to be a useful component of the therapeutic armamentarium for malignant melanoma. According to our results a single one-day sessions SRS with 35.0 Gy is sufficient to treat small and middle stage melanoma (Furdova *et al.* 2012).

CONCLUSIONS

One step LINAC based stereotactic radiosurgery with a single dose 35.0 Gy in conjunction with a mechanical immobilization system with four sutures according to our study is a highly effective method to treat middle stage uveal melanoma and to preserve the eye globe with a sufficient visual acuity. SRS is a non-invasive alternative to enucleation in the treatment of uveal melanoma with a high tumor control.

The observed after-treatment decline in BCVA was not positively associated with higher prevalence of better BCVA before SRS, but the anatomical result after the treatment was at least anatomically preserved eye globe.

Encouraging our results justify further studies to evaluate one day session procedure and its efficacy as an alternative to other irradiation therapeutic approaches. If we used single SRS therapy only, in patients with tumor volume over 0.6 cm³ the risk of relapse was very high, over 50% and additional therapy was necessary. According to our experience the dose of 35.0 Gy is not sufficient irradiation and may cause relapse only in patients with high volume tumors, over 0.6 cm³. By analyzing individual patient's results of this study we conclude that this therapy is sufficient for small and intermediate tumors with the elevation not over 6 mm, resp. volume up to 0.4 cm³ according to individual stereotactic planning scheme of each patient as a single therapy procedure. Secondary enucleation after stereotactic radiosurgery due to irradiation neuropathy and secondary glaucoma was necessary only in 11.5% in 3 to 5 year interval after irradiation. Tumor local control in our study was successful in 95% of patients in 3 years interval after stereotactic radiosurgery and in 85% of patients in 5 years interval after stereotactic radiosurgery.

According to our results one-day session SRS with 35.0 Gy is sufficient to treat small and middle stage melanoma.

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