Stereotactic Radiosurgery in Uveal Melanoma

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Published Date: December 16, 2015

ABSTRACT

Uveal melanoma is the most common primary intraocular malignant tumor. Radiation therapy has now replaced enucleation as the treatment of choice, with radioactive eye plaques and proton therapy being the two most studied radio therapeutic modalities. More recently, stereotactic radiosurgery and fractionated stereotactic radiotherapy have emerged as promising, non-invasive treatments for uveal melanoma.

Stereotactic radiosurgery is a method, which may be considered like a not true surgery "because no incisions are involved." Instead, it is an advanced method of radiation therapy that delivers high doses of radiation to very small areas and volumes.

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

The publication presents the results of long-term cooperation of the authors from the Department of Ophthalmology, Comenius University, Faculty of Medicine in Bratislava and the Department of Stereotactic Radiosurgery of St. Elisabeth Oncology Institute in Bratislava.

Keywords: Intraocular Malignant Melanoma; Stereotactic Radiosurgery; Linear Accelerator

INTRODUCTION

Melanoma of the uveal tract (iris, ciliary body, and choroid), is the most common primary intraocular malignancy in adults. Uveal Melanoma **(UM)** is diagnosed mostly in older age, with a progressively rising age-specific incidence rate that peaks near the age of seventy. Ocular melanoma is likely to metastasize in other regions of the body such as liver, breast, lung, and kidney. Factors associated with the development of this tumor include genetic factors, race, color of the eyes, fair coloring of the skin and the ability to tan. Many observational studies have attempted to explore the relationship between exposure to the sunlight and risk of uveal melanoma.

The comparatively low incidence of iris melanomas has been attributed to the characteristic features of these tumors. Usually, uveal melanomas are in early stages of their development completely asymptomatic. Iris melanomas rarely metastasize. Choroidal melanoma is the most common ocular melanoma – comprising over 75 % of all intraocular melanomas. Posterior uveal melanomas are cytologically more malignant, and metastasize more frequently than iris melanomas. Typically, choroidal melanoma is a brown, elevated mass, and the degree of its pigmentation ranges from dark brown to totally amelanotic. Usually, uveal melanomas are in early stages of their development completely asymptomatic.

In advanced stages the symptoms are dependent on tumor location. The most important test to establish the presence of intraocular melanoma is the examination by an experienced clinician. Diagnostic testing can be extremely valuable in establishing and confirming the diagnosis. Prognosis can be influenced by number of factors. The most important are the type of cells, the size of tumor, the margins location of the tumor, karyo type and its extraocular extension. Cell type, however, remains the most often used predictor of outcome. The treatment depends on the site of origin (choroid, ciliary body or iris), the size and location of the lesion, the age of the patient and whether extraocular invasion, recurrence or metastasis has occurred. Extraocular extension, recurrence, and metastasis are associated with an extremely poor prognosis and long-term survival cannot be expected [1,2].

LINAC-based stereotactic radiosurgery of posterior uveal melanoma is a conservative method of treating uveal melanoma. The LINAC-based SRS treatment is a method to treat middle stage posterior uveal melanoma while preserving the eyeball (Figure 1).

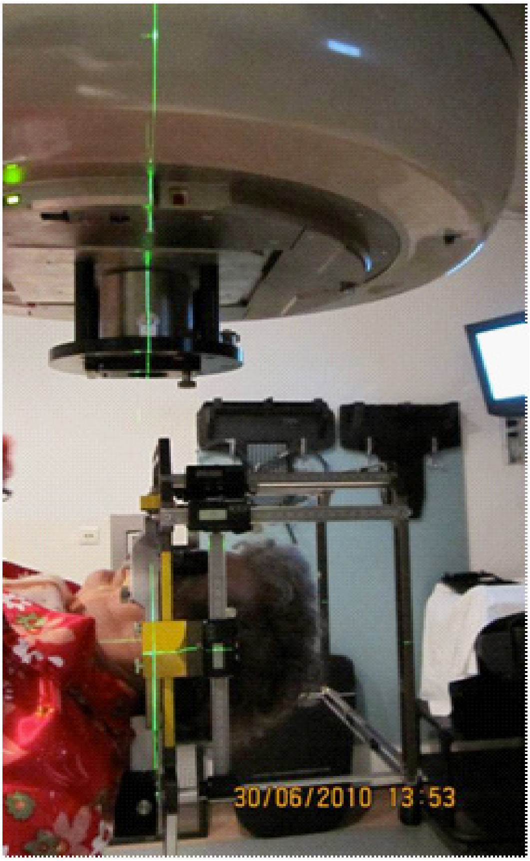

Figure 1: Position of the patient by stereotactic radiosurgery at linear accelerator.

The stereotactic method has continued to evolve, and employs an elaborate mixture of image-guided surgery that uses computed tomography, magnetic resonance imaging and stereotactic localization, at present. Stereotactic irradiation has during the past 15 years developed into a mainstream radiotherapeutic technique practiced in most major radiotherapy centers around the world.

The stereotactic frame is also used for patient set-up on the treatment machine and for patient immobilization during the actual treatment procedure (Figure 2).

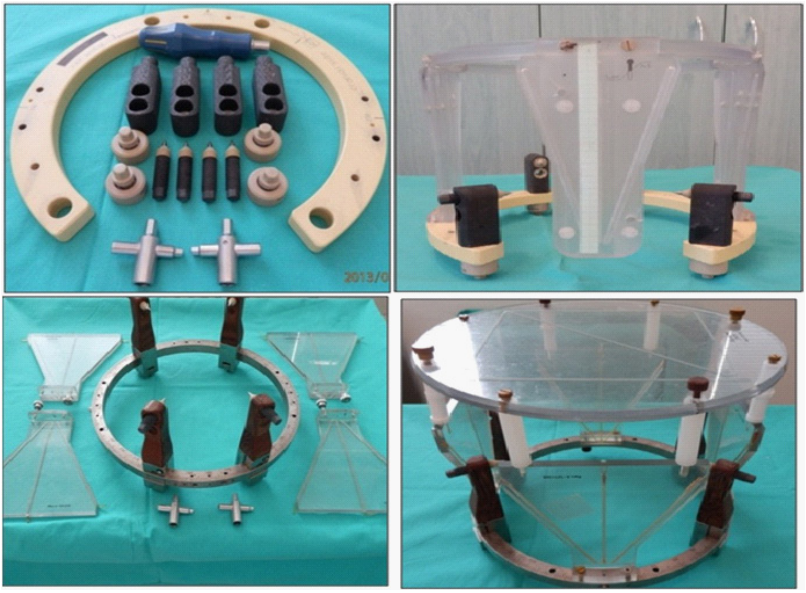

Figure 2: Stereotactic frame equipment.

The record for each patient includes 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 is calculated in each patient directly by computer after CT and MRI examination as the step of SRS procedure and is involved to the stereotactic planning scheme.

Before stereotactic irradiation immobilization of the affected eye is achieved by mechanical fixation to the stereotactic Leibinger frame. Sutures are placed under 4 direct extraocular muscles through conjunctiva and through the lids. The stereotactic frame is fixed to the head and the sutures are tied to the stereotactic frame (Figure. 3).

Figure 3: Immobilization of the eye by sutures before stereotactic radiosurgery.

With loaded stereotactic ring in which aiming device is mounted, the patient underwent CT examination with the eye fixed to the frame, the patient is transported to the workplace of Computer Tomography **(CT)**. After fixation in the holder of CT table and after administration drug contrasting substance, examination is made in one-millimeter slices.

After the CT examination the patient is transferred to the workplace of MRI. The patient undergoes MRI examination with the eye fixed to the frame. After placing to the MRI table and after administration of drug contrasting substance. MRI imaging records acquired from the CT are sent to the console of computer in computer room.

When the examinations listed above were carried out, the patient is transported to the resting room of Department of radiotherapy of St. Elizabeth Oncological Institute, where he is waiting for exposure in the linear accelerator.

When the targeted volume and risk structures are imaged, the neurosurgeon is plotting the target volume and risk structures in one millimeter slices to a CT record and consults it with ophthalmologist and radiologist. 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 contra lateral side, chiasm (Figure. 4).

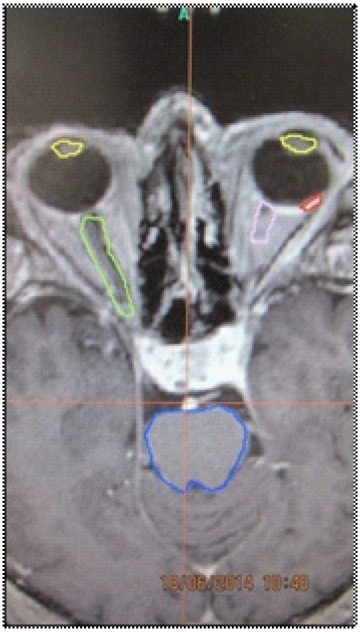

Figure 4: Uveal melanoma and critical structures - lens, optic nerve, also lens and optic nerve at the contralateral side, chiasm.

The stereotactic treatment planning after fusion of CT and MRI is optimized according to the critical structures - lens, optic nerve, lens and optic nerve at the contralateral side, chiasm (Figure 4). The best plan is applied for therapy at linear accelerator. Tumor volume calculation is based on the ROI (region of interest) of the tumor and 3D reconstruction is done. The planned therapeutic dose is 35.0 Gy by 99 % of DVH (dose volume histogram). Model LINAC C 600 C/D Varian with 6 MeV X is used.

The stereotactic treatment planning after fusion of CT and MRI images is optimized according to the critical structures - lens, optic nerve, and also lens and optic nerve at the contra lateral side, chiasm (Figure 5, 6).

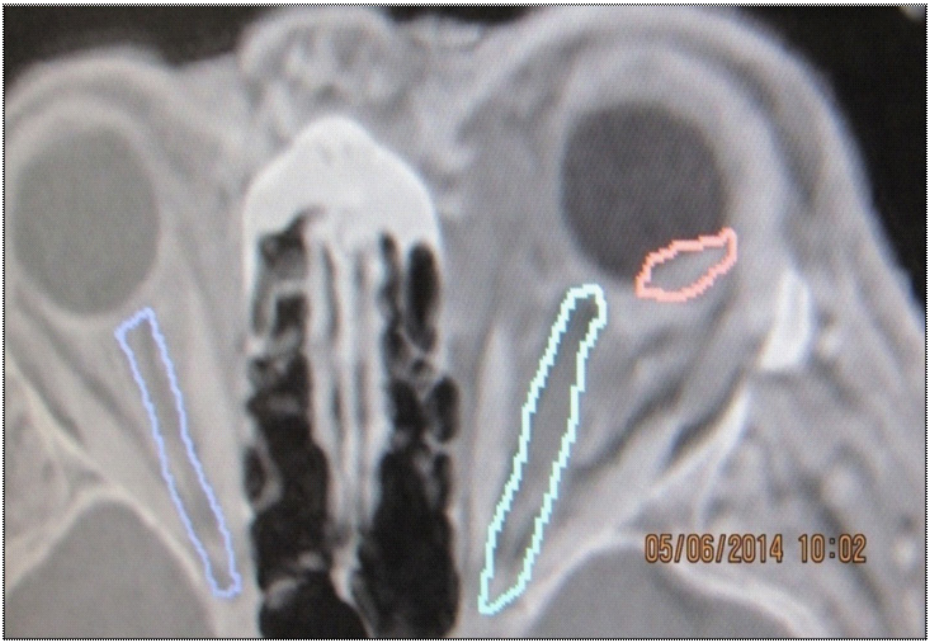

Figure 5: Uveal melanoma (red color, arrow) and optic nerves (blue color).

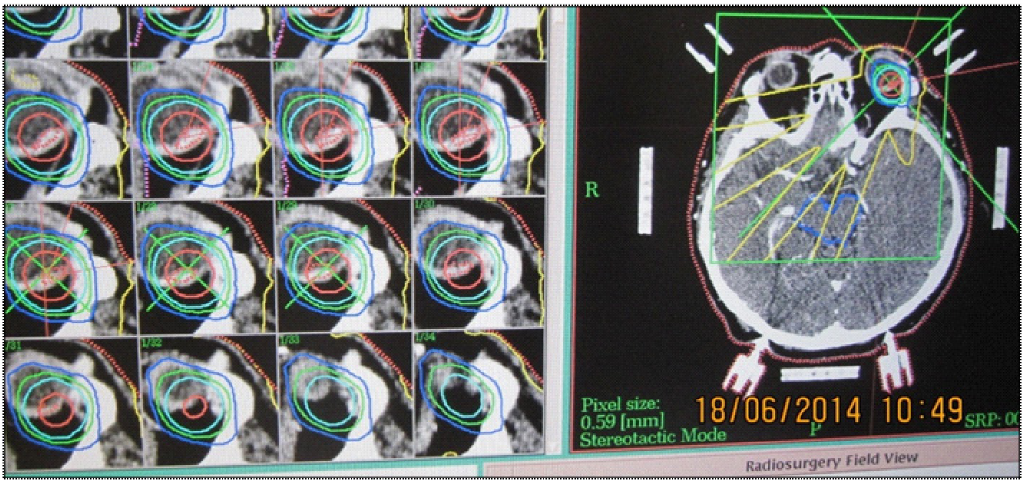

Figure 6: Planning scheme of small posterior uveal melanoma.

The best plan is applied for therapy at C LINAC accelerator (Figure. 7).

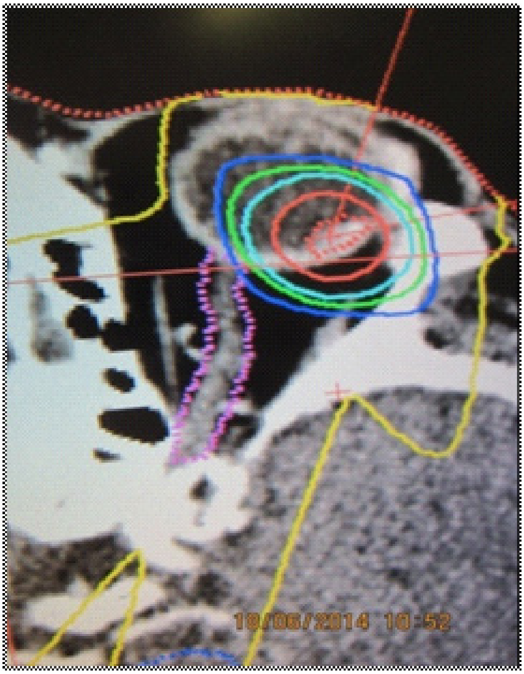

Figure 7: Stereotactic planning scheme.

The planned therapeutic dose in SRS is 35.0 Gy, TD min. dose to the margin of the lesion varies from 35.0 to 38.0 Gy, TDmax 37.0 - 50.0 Gy. We use PTV (planning treatment volume) at least 95 % isodose planning. The doses to the critical structures are below 8.0 Gy for the optic nerve and the optic disc and 10.0 Gy to the anterior segment of the eye.

After the printing of the irradiation parameters and documentation records, the clinical physicist inserts the plan into the verification system.

The same day after in the afternoon the patient undergoes irradiation at linear accelerator.

Figure 8: Stereotactic frame by stereotactic radiosurgery for uveal melanoma.

Fixation in a special holder of individual investigational modalities ensures that the head is in the examination and in treatment in the same position. Along with the merger of images it is ensured the accuracy of the method in the order of tenths of a millimeter. After completion of exposure the patient is unfixed from the operating table and transported into the operating room and the procedure lasts according to volume and collimators from 15 minutes to 50 minutes [3-5].

MATERIAL AND METHODS

In this study we assess the treatment of posterior uveal melanoma by one-day session of LINAC stereotactic radiosurgery [1,3-5].

The aim of our study was to assess after treatment BCVA decline in patients with posterior uveal melanoma treated with SRS in 6 months interval 24 months after SRS. Patients under went monitoring of the tumor regression by measuring the maximum elevation by Bscan ultrasound in the group of patients with Single Irradiation **(SRS)** in interval 12 and 24 months after the therapy.

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 2009 - 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, maximal elevation, localization presence of secondary retinal detachment, general status, age, gender, the functional tests (visual acuity, perimeter, ultrasound) were taken into consideration. The patient was actively involved in the decision on the therapeutic procedure after explaining possible postoperative complications. The record for each patient included the age at treatment, tumor size, tumor volume, the maximal 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 maximal 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

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.

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 increased up to p = 0.22 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.

Group of patients after stereotactic radiosurgery had a lower risk of death, respectively higher chance of survival. 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 preferring the patients treated with SRS. 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.

Results of patients with posterior uveal melanoma treated in period 2009 – 2011 at the Department of Ophthalmology, Comenius University Bratislava.

The average age of the group of 40 patients with malignant melanoma of the uvea operated on a linear accelerator in r. 2009 - 2011 was 55.13 ± 11.11 years. Irradiated were 17 right and 23 of the left eye. Average maximum of radiation dose was 39.0 Gy, the therapeutic dose administered directly into the tumor bed was 35.0 Gy. Average maximum of radiation dose to sensitive structures was the target of the optic nerve and 12.0 Gy to 10.0 Gy ciliary body. Enucleating had to be performed in 7 cases and with an average interval of 14 months after surgery.

The age group was normally distributed (p = 0.06); the youngest patient was 31years old and the oldest 75 years old. We analyzed data of 18 men and 22 women, the distribution of the proportions of men and women were uniform (p = 0.43). Between men and women, we confirmed the difference in age (p = 0.64). Analysis in our group confirmed that the prevalence of tumor does not depend on sex; increases with age, with most patients are diagnosed between 60 and 70 years of age.

Analysis of the difference in Intraocular Pressure **(IOP)** before surgery showed no significant difference between the group of men and women (p = 0.54). Using simple linear regression, we confirmed the assumption preoperative IOP values correlated with age (r = - 0.09, p = 0.65). Multiple linear regressions, we evaluated the relationship between predictors (dose on the risk structure - lens and optic nerve) and the change in value from the initial IOP / preoperative status at each time interval.

We compared the IOP values and we obtained at different time periods between the monitored group and the patients after enucleating the data can be shown in graph of box type (min. values, inter quartile range 25 - 75%). Differences between groups were evaluated using two-factor analysis of variance ANOVA. The analysis pointed to significant differences in averages between the groups - monitored and after enucleation (p < 0.0001), in average values of IOP at different time periods of recording (p = 0.0005). It is also significant interaction between the two factors - time and inclusion into group (p = 0.0118).

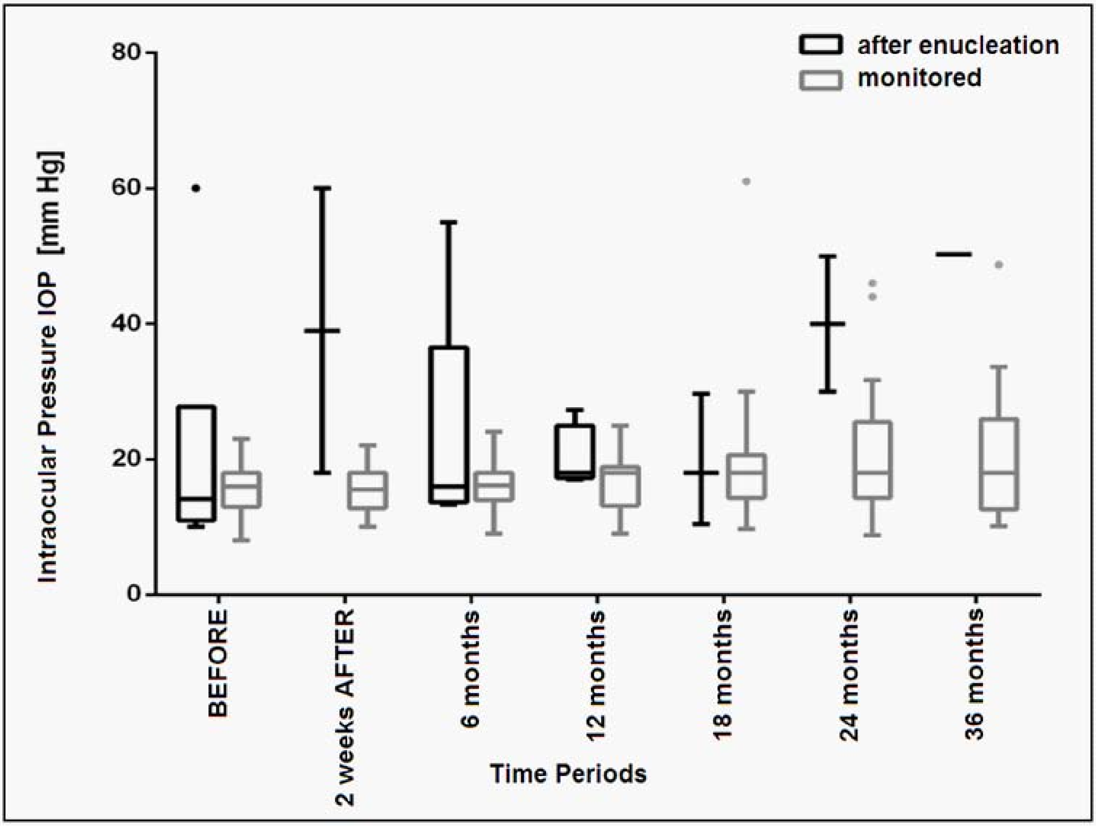

Figure 9: Patients with uveal melanoma after stereotactic radiosurgery - graphical display of IOP values obtained at different time periods between the group of patients after enucleation and monitored groups in the time evolution (Department of Ophthalmology, Comenius University, Bratislava, 2009 – 2011).

To detect time differences between the two groups we used the method of multiple comparisons. The significant difference between the groups, monitored and after enucleation, is considered the difference in the time period of two weeks ($p = 0.004$), 24 months ($p = 0.03$) and 36 months ($p = 0.009$) after the intervention.

Patients are 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 are recommended to brain CT or PET (positron emission tomography).

DISCUSSION

Current methods of radiotherapy allow for effective local tumor control with eyeball conservation, but visual morbidity is still high. 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.

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 [6-8].

Due to our results 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 eyeball.

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 [4].

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 [3].

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 [9].

In the last three decades, the management of patients with uveal melanoma has changed towards eyeball 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.

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 Cyber Knife. 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 hypo fractionated 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 hypo fractionated 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 [3,10-14].

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. Local control over 95 % appears in some studies: In the study of Dieckmann 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 [7].

Up today 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. 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 [15-18].

Stereotactic radiosurgery and fractionated stereotactic radiotherapy have emerged as promising, non-invasive treatments for uveal melanoma [13]. 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. There is a need for multi-center trials to compare the outcomes following stereotactic radiosurgery in treatment of uveal melanoma [19, 20, 21].

No survival difference attributable to stereotactic irradiation or radical surgical attitude - enucleation of uveal melanoma has been demonstrated in this retrospective study. A small difference is possible, but a clinically meaningful difference in mortality rates, whether from all causes or from metastatic melanoma, is unlikely [3]. SRS is a non-invasive alternative to enucleation in the treatment of uveal melanoma with a high tumor control.

SUMMARY

According to the authors experience based on results of their research results of the effectiveness of LINAC-based Stereotactic Radiosurgery **(SRS)** or the SRS treatment plus combined methods in patients with posterior uveal melanoma in stage T2/T3, the stereotactic radiosurgery is an effective method to treat intermediate stage of uveal melanoma. Finally, one-step LINAC-based SRS with a single dose 35.0 Gy can treat patients with middle-posterior uveal melanoma and preserve the eyeball or be the first step of combined methods: irradiation before endoresection or cyclectomy. According to our clinical experience one step LINAC based stereotactic radiosurgery with a single dose 35.0 Gy in conjunction with a mechanical immobilization system with four sutures is a highly effective method to treat middle stage uveal melanoma and to preserve the eyeball with a sufficient visual acuity and is a non-invasive alternative to enucleation or other irradiation techniques in the treatment of uveal melanoma with a high tumor control.

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