STEREOTACTIC REDIOSURGERY FOR UVEAL MELANOMA; POSTRADIATION COMPLICATIONS

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SUMMARY
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Objective: The authors evaluate a group of patients with malignant uveal melanoma treated with stereotactic radiosurgery in the year. 2009–2011 on a linear accelerator LINAC.
Material and methods: In 2009–2011 were followed 40 patients with malignant melanoma of the uvea in stage T2 and T3 treated with stereotactic radiosurgery (LINAC), the therapeutic dose of 35,0 Gy TD, TD max 42,0 Gy. We evaluated the influence of factors (age, exposure risk structures, time) to intraocular pressure (IOP) and temporal changes in intraocular pressure after surgery between the control group and the group of patients who underwent enucleation.
The normality of data distribution was tested Shapiro-Wilk W test and graphically. The relations between the parameters were tested using simple and multiple linear regression (correlation coefficient r, the significance level p).
Results: The mean age of the group of 40 patients with malignant melanoma of the uvea treated by one day session stereotactic radiosurgery on a linear accelerator in the year. 2009–2011 was 55.13 ± 11.11 years. Average maximum radiation dose to sensitive structures has been the target of 12,0 Gy to the optic nerve and the ciliary 10,0 Gy.
The analysis in our group confirmed that the prevalence of the tumor independent of sex, increasing 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 assumptions, related to IOP before stereotactic radiosurgery with age (r = -0.09, p = 0.65). Multiple linear regression, we evaluated the relationship between predictors (dose at-risk structures – lens and optic nerve) and the change in IOP from the value before stereotactic radiosurgery at each time interval. Relations between predictors (Dose aperture – L, the dose of the optic nerve – O) and IOP of the file being described partial correlation coefficients after 2 weeks. For the relationship is significant correlation between the dose and the IOP in the lens at the time of 1 year, 1.5 years, and 2 years after the stereotactic radiosurgery.
Conclusion: A single stereotactic radiosurgery on a linear accelerator LINAC is possible at a dose of 35,0 to 38,0 Gy in intraocular melanomas in stage T1 to T3. According to our results, this is a highly effective method of treatment of uveal melanomas elevation to 6 mm and a capacity of up to 0,4 cm^3. Secondary glaucoma is one of the most serious causes of enucleation after one day session stereotactic radiosurgery at linear accelerator (LINAC) for uveal melanoma. The percentage of enucleation in our investigated group (17.5%) for secondary glaucoma is about the same as in other studies.
Key words: intraocular tumors, malignant melanoma of the uvea, stereotactic radiosurgery, linear accelerator

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INTRODUCTION

Malignant melanoma is the most commonly occurring intraocular tumour in adulthood, and to the present day its diagnosis continues to come up against several uncertainties. Therapy depends on the stage in which the process was diagnosed, and upon the overall condition of the patient. In the past, the determination of a diagnosis of intraocular melanoma meant a radical surgical procedure – enucleation of the eyeball or exenteration of the orbit. In recent years there has been a shift away from primary radical treatment, and procedures which preserve the visual organ are coming to the forefront.

Malignant melanoma of the uvea (MMU), in 75-85% of cases localised in the choroidea, is the most common primary intraocular tumour in adulthood. One of the options for treatment is the use of ionising radiation in stereotactic radiosurgery from an external source of radiation, with the help of a linear accelerator (LINAC). The aim of treatment is targeted irradiation of the tumour by means of a therapeutic dose of 35.0 Gy, whilst at the same time minimising the harmful impact of radiation on the sensitive structures of the eye such as the vascular system of the retina, the disc of the optic nerve and the corpus ciliare (14, 25, 36).

Despite the maximum endeavour to avoid damage to radiosensitive structures, complete elimination of this risk is impossible. The main reason is the frequent occurrence of the tumour in the region of the fovea or the disc of the optic nerve. The most common and also most serious postradiation complication is secondary glaucoma. The incidence of secondary glaucoma is preceded by the development of rube-

osis iridis on a basis of neovascularisation. It is assumed that irradiation of the blood vessels leads to ischemia, which subsequently supports the new formation of blood vessels and the development of secondary glaucoma, which in some cases may constitute a reason for enucleation of the eyeball. In the case of ischemia there is an increased formation of factors such as VEGF (vascular endothelial growth factor), dinitrogen dioxide, inflammatory cytokines, free radicals and increased accumulation of intracellular glutamate. The most important is VEGF, which triggers the formation of blood vessels of the iris and fibrovascular tissue, the formation of synechias and closure of the angle, which mechanically prevents the drainage of the intraocular fluid and leads to an increase of intraocular pressure. With the increase in intraocular pressure there is a decrease of perfusion pressure, which deteriorates the ischemic condition of the optic nerve and cells of the retina, causing damage thereto, which results in a constriction of the visual field, blindness or the necessity of performing enucleation of the eyeball (32).

AIM OF STUDY

Observation of a group of patients with malignant melanoma of the uvea treated by stereotactic radiosurgery in the period 2009-2011 on a LINAC linear accelerator, observation of postradiation complications.

METHOD

We observed 40 patients with malignant melanoma of the uvea in stages T2 and T3, who were treated by stereotactic radiosurgery (LINAC) during the period from 2009 to 2011. The therapeutic dose into the tumour was TD 35.0 Gy, maximum TD max. 42.0 Gy (fig. 1, 2, 3, 4, 5).

We evaluated the influence of factors (age, irradiation of risk structures, time) on the value of intraocular pressure (IOP) and temporal changes of intraocular pressure following the procedure between a control group and the group of patients who had undergone enucleation.

We tested the normality of data distribution by means of a Shapiro-Wilk W test and graphically. The relationships between the parameters were tested using simple and multiple linear regression (correlation coefficients r, level of significance p). We performed an evaluation of the differences between the groups over time using a two factor analysis of variance (ANOVA). We conducted all the tests on the level of significance alfa 5% ($\alpha = 0.05$). The results were statistically processed and evaluated using the program StatsDirect® 2.7.8 software (StatsDirect Ltd., Cheshire, UK), GraphPad Prism 6.01 (GraphPad Software Inc.) and Microsoft Office Excel 2007.

RESULTS

The average age in the group of the 40 patients with malignant melanoma of the uvea who were indicated for stereotactic radiosurgery on a linear accelerator in the period from 2009 to 2011 was 55.13 ± 11.11 years. The average maximum dose of radiation for the sensitive structures was 12.0 Gy for the disc of the optic nerve and 10.0 Gy for the corpus ciliare. It was necessary to perform enucleation in 7 cases, with an average time interval of 14 months following the stereotactic radiosurgical procedure.

The analysis in our group confirms that the prevalence of tumours is not dependent on sex, increases with age, in which the largest number of patients are diagnosed between the ages of 60 and 70.

An analysis of the difference in intraocular pressure (IOP) before the procedure did not demonstrate a significant difference between the group of men and women ($p = 0.54$). Using simple linear regression we did not confirm the assumption of a dependency of the IOP value before stereotaxy upon age ($r = 0.09$, $p = 0.65$). We evaluated the relationship between predictors (dose on risk structures – lens and optic nerve) and the change of the IOP value from the value before stereotaxy at a time interval using multiple linear regression. The relationships between predictors (dose on lens – L, dose on optic nerve – O) and the IOP values in the entire cohort are described by partial correlation coefficients after 2 weeks. We consider the correlation between the dose on the lens and IOP at the time of 1 year, 1.5 years, 2 and 4 years after the procedure to be significant relationships.

Upon a comparison of the IOP values obtained in various time periods between the control group and the enucleated patients we presented the data in a box-type graph (distant values, min. interquartile range 25-75%, max. abstract values). The differences between the groups were evaluated using a two-factor analysis of variance ANOVA (graph 1). The analysis indicated significant differences in the averages between the groups – the control group and the group after enucleation ($p < 0.0001$), in the average IOP values at various times of recording ($p = 0.0005$). At the same time the interaction between both factors – time and inclusion in the group – is significant ($p = 0.0118$).

In order to determine the differences between the two groups over time we used the method of multiple comparison. The difference at the time of 2 weeks ($p = 0.004$), 24 months ($p = 0.03$) and 36 months ($p = 0.009$) after the procedure is considered to be a significant difference between the groups (graph 1).

Fig. 1 Indication of intrabulbar tumour (red colour) and risk structures (lenses, optic nerves, stem) before the creation of a stereotactic radiosurgical plan for the patient with malignant melanoma of the choroidea

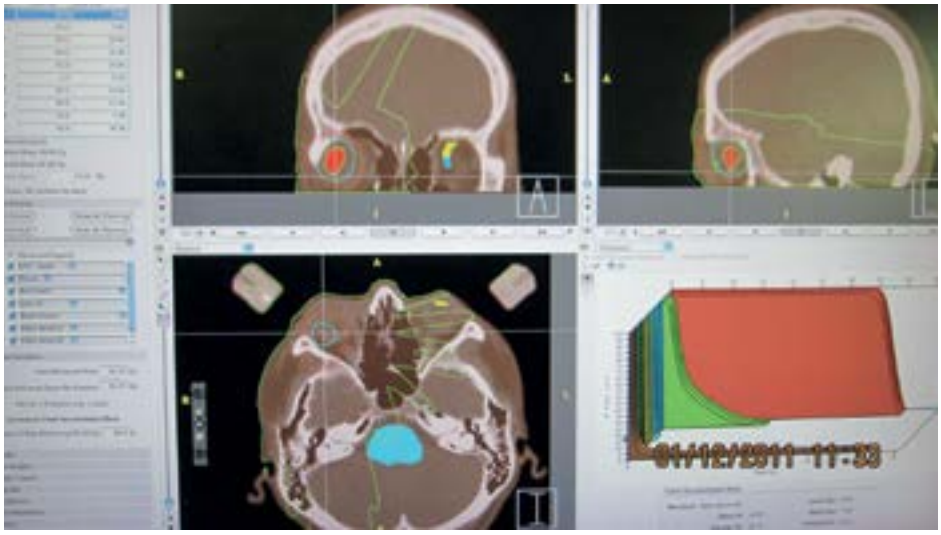


Fig. 2 Stereotactic radiosurgical plan for patient with malignant melanoma of the choroidea, graphic illustration of DVH (Dose Volume Histogram)

Fig. 3 Position of patient with placed stereotactic ring and immobilised eyeball before irradiation

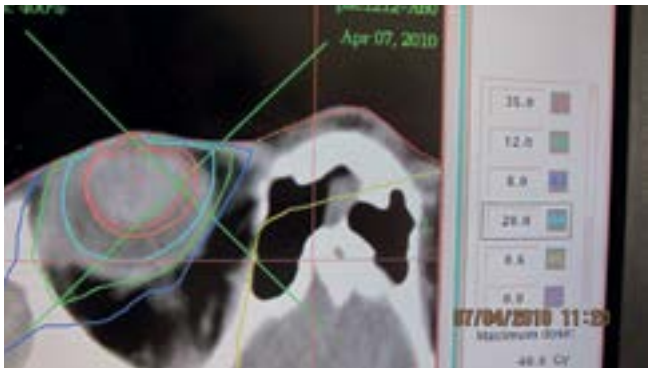


Fig. 4 Stereotactic radiosugical plan for patient with large intraocular melanoma – volume 1.0 cm3 (April 2010)

Fig. 5 Position of patient during irradiation on linear accelerator (April 2010)

Postradiation complications following stereotactic radiosurgery

Transitional difficulties immediately following stereotactic radiosurgery (erosion of the cornea following removal of the sutures) were resolved for all patients using lubrications and antibiotic drops, we did not record any later complication of a corneal defect, which would be an indication for

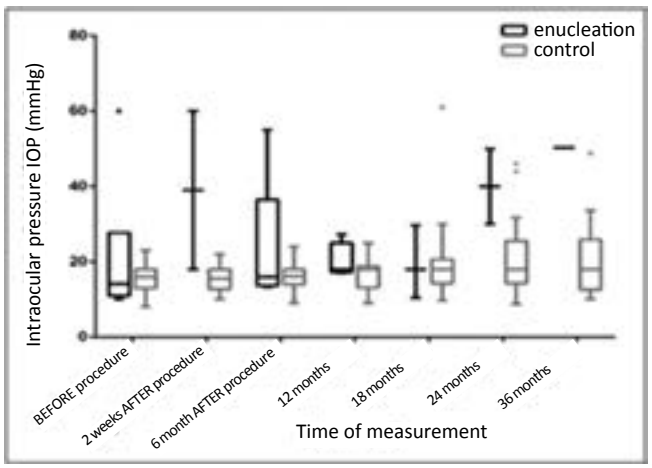
example for suturing of the amniotic membrane.
We did not record early or later postradiation complications on the skin around the eye, in 2 patients we recorded madarosis – at an interval of more than 12 months after irradiation on the side on which the tumour in the eyeball was irradiated, but without cosmetic problems.
Of later complications following a single radiosurgical procedure, in 3 patients we recorded keratopathy more than 2 years after irradiation (this concerned lesions in the region of the corpus ciliare, and the dose on the region of the chamber angle and the cornea was more than 10.0 Gy). These were not indications for enucleation.
In 2 patients following combined radiosurgery and subsequent incomplete endoresection, the eyeball progressively passed from a glaucoma stage during the course of the next year to atrophy also with a finding on the cornea, and enucleation was indicated.
Complications in patients following isolated stereotactic radiosurgery, which led to secondary enucleation in 5 patients, were connected in all patients with the presence of a residual tumour or progression of the primary tumour. For each patient the basic indication for enucleation was secondary glaucoma with an IOP value above 55 Torr, which could not be managed by means of a conservative procedure. Haemophthalmos was present in these patients – the fourth stage of classification according to Finger – and we also determined the presence of haemorrhage into the anterior chamber.

Postradiation cataract

Cataract surgery with implantation of an artificial intraocular lens on the irradiated eyeball was indicated for 5 patients. We did not record any later complications on the lens of the contralateral eye in any case.

In the case of patients in whom cataract surgery was performed with implantation of an artificial intraocular lens (AIOL) at an interval from 2 to 5 years following stereotactic radiosurgery (SRS) and for whom we did not have data available about the opalescence of the posterior capsule at a time interval, we did not evaluate these changes.

We recorded a stabilised finding more than 2 years after irradiation of the eyeball in 15 patients, regardless of the progression of a senile cataract or the finding on the lens before the SRS procedure on linear acceleration. The development of a postradiation cataract at a time interval of more than 2 years after stereotaxy was only gradual (fig. 6, 7).



Graph 1 Graphic illustration of IOP values in the group of patients following enucleation and the control group in temporal development

Postradiation optic neuropathy

Postradiation optic neuropathy was recorded in 8 patients at an interval of 12 and 24 months following stereotactic radiosurgery. In these cases this concerned a tumour at a distance of less than 2 PD from the disc. In 4 patients in whom the dose of irradiation was more than 12.0 Gy on the region of the boundary of the disc of the optic nerve, postradiation neuropathy and ischemic changes of the retina developed in the period from 12 to 24 months after the procedure, and this progressively led to an incidence of secondary glaucoma. Secondary glaucoma occurred in one patient with a peripapillary tumour with an elevation of up to 4 mm at an interval of 24 months after radiosurgery, IOP values are more than 55 Torr over the long term and the eyeball is progressively passing into the stage of atrophy; the patient refused enucleation and we are clinically observing him; the original tumour has been reduced to a maximum elevation of 1 mm.

In patients in whom the borderline dose of radiation on the region of the disc of the optic nerve did not exceed 8.0 Gy, and in whom the tumour was marginalised over the course of more than 2 years, we recorded optic neuropathy.

Postradiation maculopathy

Postradiation maculopathy in the case of tumours in the vicinity of the macula or up to a distance of 1 PD from the macula developed in 9 patients within 24 months of irradiation. Macular edema was also present as another reason for the deterioration of central visual acuity. We send the patients for examination by optical coherence tomography (OCT) at 6-month intervals and evaluate the volume of the macula and progression of the edema.

In the cases of patients in whom we were unable to record changes on the ocular fundus by a camera or by OCT examination due to the opacity of the optic media, we recorded progression of the development of secondary amotio, the height of the elevation in the region of the macula only by ultrasound. We observed elevation of the tumour by US B system examination, in which we always evaluated the maximum elevation in the central part of the macula in the case of opaque optic media. In some patients, changes in the macula or on the posterior pole such as neovascularisation were connected also with haemorrhage into the vitreous body.

We indicated an MRI examination at 6-monthly intervals for all patients, but for technical and other reasons many did not attend examination by magnetic resonance. From the MRI finding we always accepted the value of maximum elevation of the tumour in the description, and we determined the range of secondary amotio by our ultrasound examination of the posterior pole or the region of the macula.

Clinical observation of patients following isolated SRS with a height of maximum elevation of tumour from 5

Fig. 6 Finding on anterior segment of patient in April 2013

Fig. 7 Finding on anterior segment of patient in February 2014

to 7 mm before irradiation

At present there is an endeavour for patients who have undergone radiosurgical therapy to undergo the first MRI examination 3 months following the treatment at the St. Elizabeth Oncological Institute, and later at intervals according to the character of the tumour and the clinical course at the same workplace, in order to ensure that it is possible to compare the findings.

Since this concerns a very small cohort of patients and the tumours were not in the corresponding areas in all the patients, we were unable to process the data statistically. However, from our perspective this concerns the significant fact that it is possible to stabilise a tumour of malignant choroidal melanoma with a maximum elevation from 5 to 7 mm by means of the stereotactic radiosurgical method in a dose of 35.0 Gy, and we also recorded regression at an interval of 24 months following treatment.

DISCUSSION

The question as to whether irradiation alone is sufficient therapy in the case of uveal melanoma, and as to what the dose of radiation should be, has been discussed since the 1980s (26). New approaches to the management of treatment of uveal melanoma came into being at the beginning of the 1980s (33, 34).

On the basis of 20-year observation of a cohort of 309 patients following episcleral application of β irradiators, 61.5% is stated, surviving on average 6.7 years after irradiation, or 12.9% of those enucleated due to metastases in the same period (24). According to the data of this study, 52.8% of successfully treated patients have a flat scar following irradiation. At present a slight growth is stated (by 2.7%) between the 2nd and 3rd years following the original reduction of the tumour. Previously Shields determined, in a cohort of 500 patients treated by episcleral irradiators with 60Co, that the prognosis at an interval of 5 years is good if not better than after enucleation for MMU of equal dimensions (33, 34). Analogous conclusions were reached by Augsburger et al. on the basis of an evaluation of a group of 237 patients, of whom 140 were treated by enucleation and 97 by an episclerally fixed irradiator 60Co, over the course of 15-year dispensary observation (1). On the basis of the above-stated retrospective study they demonstrated that there is a relatively small difference in the survival of patients with primary malignant melanoma of the choroidea and corpus ciliare treated by local brachytherapy 60Co and by enucleation. The results of the patients treated by brachytherapy are better only by approximately 10%.

It is very important to take into consideration the fact that upon therapeutic procedures for MMU without enucleation of the eyeball in destroyed, necrotic and subsequently scarrily transformed material of the tumour, groups of tumour cells without cytolisis may remain, which form a basis for local recurrence and metastasis. This was negatively reflected in the prognosis (1, 7, 12, 15).

Damato et al. point to risk factors increasing the possibility of metastasis following transscleral local excision of MMU, supplemented by subsequent brachytherapy 106Ru (5). In this they evaluated a group of 332 patients with MMU with a diameter of 13.1 mm and an elevation of 7.5 mm, histologically predominantly from the epitheloid cells. They determined 52 deaths from metastases and state the following as significant risk factors:

1. age (above 60 years);
2. cell types mixed and epitheloid;
3. localisation (in anterior and upper sections);
4. diameter of tumour 16 mm and more;
5. supplementary brachytherapy not performed;
6. secondary enucleation due to residual/recurring tumour;
7. secondary enucleation due to residual or recurring tumour outside of eye.

Mortality was not significantly altered after enucleation following incomplete removal of a tumour or in the case of small residual or recurring tumours. Survival falls to 30% over the course of three and a half years if more than 3 risk factors are determined in the patient. In a parallel study Damato et al. evaluated a group of 286 patients, in whom in 57 cases (6%) they determined recurrence of MMU following local transscleral resection (6). In the group in question there was no connection with the stated risk factors in 57% of cases.

From the perspective of the prognosis of MMU, it is further necessary to emphasise the necessity of enucleation of atrophic eyeballs, inasmuch as it is possible upon a histological examination to determine the presence of an uveal melanoma which was not clinically determined, or also that the

finding was equivocal upon examination for example by ultrasound before enucleation of the eyeball. In approximately 10% of eyeballs following enucleation due to other causes, MMU was determined histopathologically (35). The most common cause of errors is the opacity of the optic media of the eye. Upon clear determination of enucleated eyeballs at our clinic in the period from 2001 to 2008, all the eyeballs sent for a histopathological examination which had a clinically determined diagnosis of MM were also confirmed by a pathologist. In all the other eyeballs enucleated due to other causes (atrophic, amaurotic eyeballs), there was no diagnosis of intrabulbar melanoma in any case (16).

From the perspective of clinical-pathological correlation of MMU, one of the options for diagnosis is also cytodiagnosis via a transscleral approach. This represents a sample for determining the presence of cells in the subretinal fluid, or direct puncture of the tumour is possible, currently also in the case of PPV. However, the procedure is linked to problems of distinguishing isolated groups of cells, especially upon differentiating cells of malignant melanoma and histiocytes. It is also necessary to reckon with an increased risk of inoculation of MMU cells into the para- and retrobulbar tissue structures during sampling, and thus also a more rapid or early/earlier metastasis (35). In our cohort we did not perform direct puncture of the tumour by a transscleral approach in any case.

Evaluation of the clinical-pathological correlation is also a basis for the decision-making process for the selection of the therapeutic procedure in the sense of microsurgery (iridocyclectomy or en bloc excision, brachytherapy or a combination of both with laser therapy), or in the sense of enucleation of the eyeball. An analysis of the mutual relationship of the clinical finding and the pathohistological structure of the tumour and the surrounding structures enables also an assessment of the effectiveness of the selected therapeutic procedure, or an assessment of the healing process and at the same time the possibility of immediate therapeutic reaction to any applicable later determined changes.

Stereotactic radiosurgery is a “conservative” and non-invasive alternative to enucleation of the eyeball in the treatment of malignant melanomas of the uveal tract. It enables us to achieve a regression of the tumour without the necessity of opening of the eyeball by means of targeted irradiation of the tumour. A number of characteristics are observed in order to evaluate the success of intervention procedures. An increase of IOP following a radiosurgical procedure is a later but serious complication, which in some cases may lead to the enucleation of the irradiated eye, even when regression of the tumour process is demonstrated by clinical observation. In our group of 40 patients with malignant melanoma of the uvea we did not determine any difference in the IOP value before the procedure between the group of men and women. We did not confirm any significant relationship between age and IOP value. Our aim was to evaluate the influence of the dose on the risk structures and temporal changes of the IOP value following irradiation. We assumed a connection between the size of the dose on the risk structures and IOP values over time, with regard to the known delay in the manifestation of a number of postradiation complications. We found significant relationships in all time periods, where the size of the dose on the lens correlated with the IOP value. Further data gathering is necessary in order to confirm the hypothesis of determination of the dose on the lens as a predictor for IOP with regard to the incidence of temporal data where the relationship was not confirmed.

Secondary difficulties leading to enucleation are present in approximately 16.3% of cases (10).

In our cohort of patients we recorded 7 secondarily enucleated eyes in the patients (17.5%).

Radiosurgical methods of treatment began to develop in the 1980s. A group of doctors from Vienna observed a total of 90 patients with MMU treated by stereotactic radiotherapy on a linear accelerator from 1997 to 2001. Irradiation was performed in 5 fractions in a total dose of 60.0 Gy. Immobilisation of the eye was secured by an optical fixation system. The volume of the tumours was 70-1430 mm3 and the height of elevation was 2.7-15.9 mm. A reduction of the tumour was achieved in 98% of the patients, secondary enucleation was realised in 7 patients (8).

The dose of radiation in the centre of the tumour, but not on its edges, is still continually discussed. The first study comparing irradiation of an uveal melanoma on its edge by gamma knife and proton radiation was not published until 2007. In the planning system there are precise criteria for irradiation of the individual parts of the lesion (39). Different workplaces apply different doses of radiation into the tumour, depending on technical possibilities. In our cohort we determined that regression or stabilisation of the primary melanoma tumour with a maximum elevation from 5 mm to 7 mm can be achieved using the radiosurgical method in a dose of 35.0 Gy.

Workplaces use various systems of fixation of the eyeball during irradiation; mechanical, as we use up to now in Slovakia, or non-invasive – external fixation systems which do not require direct implementation of sutures before the procedure (21). Some authors prefer fractionated stereotactic radiosurgery in the treatment of uveal melanomas (37).

Authors from Munich observed a group of 100 with MMU treated by gamma knife over the course of 3 years (28). These were patients with large tumours localised on the posterior pole. Recurrence occurred in 2 patients. Before irradiation the maximum apical height of the tumour was 7.8 mm, one year after irradiation this height was 5.7 mm, after 2 years 4.3 mm and after 3 years 4.6 mm. During the course of the first year after irradiation, enucleation was performed on 7 patients due to secondary glaucoma, during the second year on a further 2 patients and during the third year on one more patient. The tumour was reduced in size in 98% of patients (28).

Doctors at a workplace in Prague treated 11 patients with MMU by Leksell gamma knife from November 1995 to December 1996. The tumours had a prominence above 8 mm and parapapillary or macular localisation. The average observation period was 6 months. Visual acuity decreased in 5 patients. Reduction of the tumour was achieved in 10 patients. Enucleation was realised on one patient due to growth of the tumour (30).

An advantage of cyclotron is homogeneous dosing and the possibility of fractionation. A disadvantage is the fact that cyclotron can be applied only in certain areas under precisely defined conditions. Therapy requires demanding and precise

localisation of the tumour, determination of the volume, edge and position of the tumour, stipulation of the scope of the finding in 3D imaging, stipulation of a protective margin of minimally 2.5 mm. The first studies appeared at the end of the 1990s. Egger et al. published a cohort of 2 465 patients with MMU treated by proton and hadron radiotherapy from 1984 to 1999 (9). The average observation period was 44 months. Preservation of the eye over the course of 5, 10 and 15 years was achieved in 88%, 86% and 83% of cases respectively. 218 eyes were enucleated. Upon optimisation of the therapeutic technique, preservation of the eye after 5 years was increased from 97% to 100% for small tumours, from 86% to 99% for medium sized tumours and from 71% to 89% for large tumours. In large groups of MMU treated by proton radiation, recurrence of the original tumour and progression of growth are stated as the most common causes of enucleation (20).

A multimodal approach to the treatment of uveal melanomas is also accentuated by Damato (4). Long term results with the application of treatment of uveal melanoma by gamma knife have been presented by Ghazi (18). A study by Gragoudas et al. processed 2 069 patients with MMU treated by proton and hadron radiotherapy (20). As many as 95% of patients were observed over the course of 15 years. Repeated growth occurred in 60 patients. The treated eye was preserved over the course of 15 years in 84% of patients (20). In another study, Gragoudas et al. published the results of therapy on 1 922 patients treated by means of teletherapy at the Harvard cyclotron laboratory from 1975 to 1996 (19). The average observation period was 5.2 years. Local recurrence was documented in 45 patients, in a further 17 patients the eye was enucleated due to growth of the tumour. Recurrence was recorded from 2 months to 11 years after irradiation of the tumour. Another study documented a cohort of 39 patients with MMU treated by proton radiotherapy, on whom fluorescence angiography and angiography with indocyanine green was performed in the period from 1998 to 2001 (22). The tumours had an average elevation of 3. 65 mm and had parapapillary or paramacular localisation. Angiography was performed before irradiation and subsequently after 3 months, 6 months and 1 year. The blood vessels in the tumour were displayed in 89% of all tumours upon the use of indocyanine green, but only in 33% upon the use of fluorescence angiography. No changes were found after 3 months, and after 6 months large scale seepage was detected from the blood vessels in the region of the tumour with the help of indocyanine green. After 1 year this seepage became more pronounced and was also visible upon fluorescence angiography.

Following teletherapy of intraocular melanomas it is also necessary to reckon with complications after a certain time interval, in the case of lesions with the presence of secondary amotio it is necessary also to reckon with a higher percentage of complications such as rubeosis iridis, secondary glaucoma to total retinal detachment. This is the most common cause and reason for subsequent enucleation (11). Changes of choroidal circulation are a consequence of irradiation (27).

In our cohort we have recorded one patient with a juxtapapillary melanoma, in whom there was a radical deterioration of visual function following treatment, but the eyeball is anatomically preserved. Juxtapapillary melanomas can be resolved by radiosurgery, but the risk of neuropathy is practically unavoidable (23).

Reduction of postradiation complications is the goal of ophthalmo-onocological centres. In 2010 a study was published which demonstrated a substantial reduction of postradiation damage to the macula upon irradiation of malignant melanoma, in which silicone oil implanted into the vitreous cavity absorbed up to 50% of the dose of radiation (29).

Previous irradiation by gamma knife before resection and endoresection was performed by Bornfeld et al. (2). They performed endoresection of MMU on 29 patients, the volume of the tumours was within the range of 0.2 to 1.4 cm3. In 17 patients they performed additional irradiation of the tumour using a ruthenium irradiator. Enucleation was later necessary only for 5 patients (2).

The dose of radiation before endoresection is different in every ophthalmo-oncological centre, in our conditions it was 35.0-38.0 Gy in one sitting (13, 14). Upon irradiation by gamma knife in a single sitting it is possible to apply a higher dose of radiation. Immobilisation of the eyeball is possible also by a non-mechanical method (28). Upon fractionated therapy by stereotactic radiosurgery using an external optical fixation system in Vienna, doctors do not apply a mechanical method but rather optical fixation of the eyeball, which enables fractionation and thus also an increase of the total dose of radiation (38). In our conditions it is not currently possible to perform fractionation for technical reasons, and we continue to perform stereotactic radiosurgical procedures by means of mechanical fixation of the eyeball (immobilisation via the direct extraocular muscles) and fixation is subsequently performed by means of sutures on a stereotactic ring.

In a retrospective study in the period 1990-2000, Cohen et al. analysed 198 patients with choroidal melanoma who were treated by stereotactic radiosurgery – 78 patients, or by enucleation – 118 patients (3). In all the patients with confirmed metastases during the observation interval from therapy, metastases of the liver were confirmed sonographically or by CT examination – 53 patients (27%). Enucleation was necessary in the case of 8 patients following treatment by stereotactic radiosurgery. The length of observation was from 1 month to 10 years, 7 patients dropped out of the observed cohort in the group of enucleated patients, none of the patients from the group following stereotaxy dropped out of observation. This study was the first analysis of patient survival following enucleation and following stereotactic radiosurgery. No significant influence on the interval without the presence of metastases following treatment was demonstrated depending on age, sex, presence of extrascleral extension or secondary amotio (3). This study confirmed that the largest dimensions of the tumour and localisation of the tumour are independent prognostic factors upon patient survival (31).

CONCLUSION

Single application of stereotactic radiosurgery on a LINAC linear accelerator is possible in a dose of 35.0-38.0 Gy for intra-

ocular melanomas in stages T1 to T3. According to our results this represents a highly effective method of treatment of uveal melanomas with an elevation of up to 6 mm and volume of up to 0.4 cm3. In patients with a melanoma with a volume of more than 0.8 cm3 it is necessary to embark upon a combined surgical procedure. At present stereotactic radiosurgery is the only possible method of treatment of uveal melanomas using ionising radiation in Slovakia, and requires sophisticated co-operation of a number of fields of medicine (17).

Secondary glaucoma is one of the most serious causes of enucleation in patients with uveal melanoma for whom stereotactic radiosurgery on a linear accelerator (LINAC) has been indicated; the percentage of enucleations in our observed group (17.5%) for secondary glaucoma is approximately equal to that in other studies. The envisaged correlation between the size of the dose on the risk structure and the value of intraocular pressure was also manifested in our cohort.

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