ORIGINAL ARTICLE

Choroidal Melanoma Stage T1 – Comparison of the Planning Protocol for Stereotactic Radiosurgery and Proton Beam Irradiation

[1]Furdová A., [2]Ružička J, [3]Šramka M., [3]Králik G., [3]Chorvát M., [1]Kusenda P.

[1]Ophthalmic Clinic of Medical Faculty, Komenius University and University Hospital, Hospital Ružinov, Bratislava, Head of the Clinic: V.Krásnik
[2]Department of Nuclear Physics, Biophysics, Faculty of Mathematic, Physics and Informatics of Komenius University, Bratislava, Head of Department: K. Holý
[3]Clinic of Stereotactic Radiosurgery OÚSA and College of health care and social work sv.Alžběty, Bratislava, Head: M. Šramka

SUMMARY

Choroidal Melanoma Stage T1 – Comparison of the Planning Protocol for Stereotactic Radiosurgery and Proton Beam Irradiation

Objective: Comparison of two methods of irradiation of patients with malignant choroidal melanoma – stereotactic radiosurgery and proton beam irradiation. External (non-contact) applied irradiation is used as a source of accelerated protons, respectively helium ions. This method allows applications of ionizing irradiation also despite the low radiosensitivity of cells of malignant melanoma of the uvea (MMU). External source of ionizing radiation is modulated current energy electrons, protons or neutrons, accelerated in linear accelerators. From the external medium voltages resources (4-16 MeV) are irradiated tissues with target dose of 5.0–24.0 Gy. Volume protons permeate straight the structures of the eye to a certain distance. The use of proton radiation density of ionized protons increases in the vicinity of the impact due to energy losses for electrons interacting with the environment. At the end of the track there is a huge increase in the ionization dose ("Bragg spike"). Therefore, the structures surrounding the eye at the point of entry and little affected and increasing the dose at the end of the proton beam is ideal for the desired therapeutic effect. Fractionated application is also possible.
Case report: In December 2011 we performed stereotactic radiosurgery to treat female patient (born 1939) with malignant melanoma of the choroid stage T1 N0 M0. Plan has been drawn up for stereotactic irradiation – model for linear accelerator Clinac, Corvus planning system ver. 6.2, verification and OmniPro IMRT planning system Liebinger ver. 4.3. Patient characteristics were compared with the virtual plan for proton radiation therapy, and we used the scheme in Physical parameters FIAN-technical center in the Russian Federation. We compared both planning protocols and assess in particular the extent of radiation surrounding non-tumor tissue.
Results: When comparing the two planning schemes irradiation levels of surrounding tissues and risk structures (lens, optic nerve, chiasm) in both methods were corresponding to the required standard.
Conclusion: Treatment of uveal melanoma through proton beam irradiation in Slovakia is not available yet, although it has several advantages, such as fractionation and the possibility of achieving a higher dose of irradiation to deposit (more than 50.0 Gy). The fundamental difference between the two methods for an eye is particularly the possibility of proton beam irradiation exposure of tumor of iris and ciliary body, which can not be solved through stereotactic radiosurgery. The dose to the tumor during irradiation can be optimized. The model device allowed us to make OPTMI – Therapy (Proton Treatment with Optimized Modulated Intensity).

Key words: malignant melanoma of the choroid, stereotactic radiosurgery for uveal melanoma, proton beam irradiation

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First author:
Assoc. Prof. MUDr. Alena Furdová, PhD., MPH
Ophthalmic Clinic of Medical Faculty, Komenius University and University Hospital, Hospital Ružinov
Ružinovská 6, 826 06 Bratislava
e-mail: afrf@mail.t-com.sk, alikafurdova@gmail.com

INTRODUCTION

The first reports on the results of effective therapeutic application of ionizing radiation of uveal melanomas began to be presented in the 1980s and 1990s. External noncontact application of ionizing radiation is used as a source of accelerated protons. This method of application enables the use of ionizing radiation even despite the low radiosensitivity of cells of malignant melanoma of the uvea (MMU). Radiotherapy by proton beam in MMU is indicated in processes where other procedures cannot be applied due to the dimension (volume) of the MMU, or in the case that it concerns the only eye, and is therefore an alternative to enucleation of the eye (4, 5).
With regard to the need for a high degree of precision upon applicati-

on of the proton beam, it is essential to use the latest diagnostic and planning techniques by computer. Upon application of proton radiation, the treatment is implemented over the course of five sessions – visits at an interval of 8-10 days, however treatment by protons is performed in only a few large centres in Europe. During radiation a system of fixing the irradiated eye with the help of "eye tracking" is used, by placing a mask (5).
The source of external ionizing radiation is a flow of modulated energy of electrons, protons or neutrons, accelerated in linear accelerators, in which the target structures are irradiated from external high-voltage (4-16 MeV) sources with a dose of 5.0-24.0 Gy. The density of the ionized protons increases in the vicinity of the point of impact due to energy losses for interaction with electrons within the environment. At the end of their course there is an enormous increase in the dose of ionization ("Bragg spike"). As a result, the surrounding structures of the eye at the point of entry are affected to only a small extent, and an increase of the dose at the end of the proton beam is ideal for the required therapeutic effect. Fractionated application is also possible here. From the perspective of the therapeutic efficacy, up to 97% destruction of the tumour is stated. The sources of external radiation upon Leksell gamma knife require specific systems of fixation of the irradiated eye (5). At present the stereotactic radiosurgical method is used in the treatment of MMU as a modification of Leksell gamma knife. The principle is analogous to the procedure upon targeted application of ionozing radiation by an external source as in treatment of brain tumours (3, 7).
Stereotactic radiosurgery (SRS) is defined as irradiation of intracranial lesions or other localisations with the use of one fraction of focused rays of ionizing radiation (X-rays), which eliminates the need for conventional invasive surgery. It is used especially in the treatment of tumours in the region of the head and neck. In ophthalmology MMUs localised in the posterior pole, which are unsuitable for brachytherapy or microsurgical procedures in other sections of the uvea, tumours with elevation up to 7 mm are an indication for primary stereotactic radiosurgical therapy. It is indicated palliatively for tumours with a larger elevation and in cases where the patient refused enucleation. It isused as the first step in combined processes (after stereotaxy is performed, endo-resection, block-excision and possible brachytherapy are planned). It requires co-operation of the radiosurgeon, radiotherapist, radiation physicist and ophthalmologist during the actual procedure. The calculation for directing the rays and the calculation of co-ordinates is enabled by the mounting of a special stereotactic frame before the actual focusing and calculation of the dose.
Various fixation procedures are used for immobilisation of the eye.
Melanomas of the uvea differ from melanomas of the skin not only in their radiosensitivity, but also in their biological characteristics. The required high doses of radiation, with reference to the high radiosensibility of the structures of the eye, lead to complications from radiation, in particular the vascular system of the retina, choroid and disc of the optic nerve, as well as the cornea and lens. Later complications following radiation treatment are described upon the application of brachytherapy, Leksell gamma knife, upon Cyberknife technique, stereotactic radiosurgery and upon proton radiation (6, 14).
External (noncontact) application of ionizing radiation uses accelerated protons or ions (helium, carbon) as a source. The method of application enables the use of ionizing radiation also in the case of low radiosensitivity of cells of malignant melanoma of the uvea (MMU). The target structures are irradiated remotely from external high-voltage (4-16 MeV) sources by a dose of 5.0-24.0 Gy, the required does in proton plans of treatment is up to 60.0 Gy. The proton beam penetrates the structures of the eye to a certain depth according to its energy, approximately rectilinearly.
Upon use of proton radiation, the density of ionization by protons is increased in the vicinity of the point of deceleration of the protons as a result of the energy loss for interaction with electrons in the environment, at the end of their course there is a considerable increase in the dose of ionization ("Bragg spike"). As a consequence of the "Bragg spike" the surrounding structures of the eye at the point of entry are affected to only a small extent, and an increase of the dose at the end of the course of the proton beam is ideal for the required therapeutic effect.
Proton therapy is considered an exceptionally beneficial modality of the treatment of tumours, and as a result several countries worldwide are attempting (regardless of the high investment costs) to construct their own proton centre (or further proton centres if they already operate such a centre).
Proton therapy enables better monitoring of the therapeutic dose of radiation to which the patient is exposed. Irradiation of the tumour by protons enables the destruction of more cancer cells and at the same time minimisation of the damage to the healthy tissue.
At present there are 39 centres in operation worldwide where it is possible to implement proton therapy. We are building a proton therapy complex with new, highly sophisticated equipment in Slovakia, in the Central Military Hospital in Ružomberok. The project is in the final phase of its realisation.
Conventional treatment by X-rays requires the application of a dose of approximately 60.0-70.0 Gy to the tumour, on average within approximately 30 fractions interspersed over the course of 6 weeks. Treatment by means of proton therapy ordinarily requires less than 20 fractions of radiation, in which it also enables the application of higher doses into the body of the tumour. It is necessary to note that treatment with higher doses is more effective, since even a small increase in the dose applied to the body of the tumour leads to a considerable increase in the probability of local control of the tumour. For example, transition in treatment from 60.0 Gy to 66.0 Gy (increase of 10%) increases the probability of local control of the tumour from 50 to 60% (i.e. by 20%), which is s substantial amount. This fact, which is independent of the method of implementing treatment, represents a strong argument in favour of proton therapy.
Protons and electrons (or gamma rays) have approximately the same biological effect on the irradiated cells. Better spatial distribution of

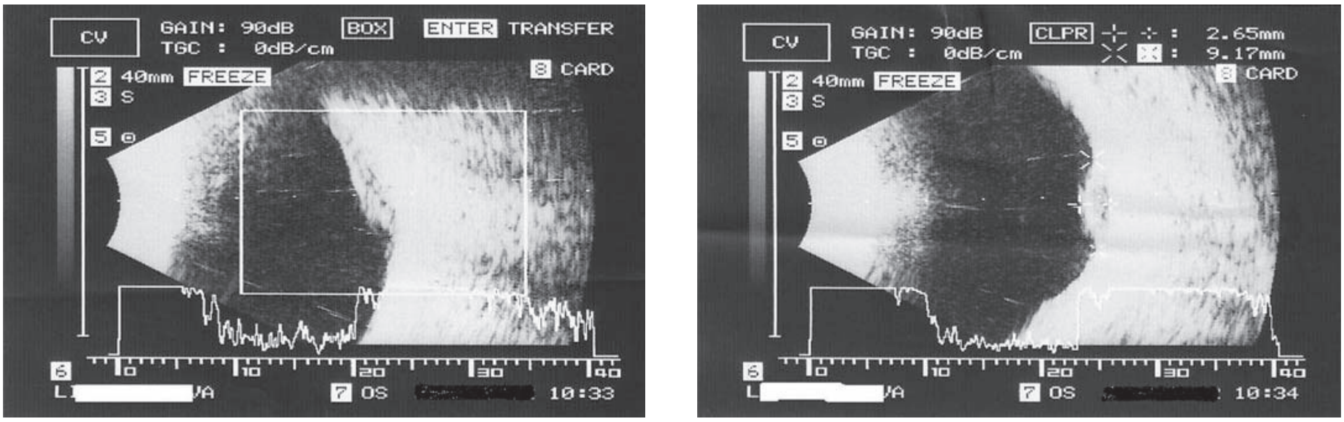

Fig. 1a, b Ultrasound image of deposit (December 2011)

the dose in the case of protons however necessarily leads either to a reduction in the side effects or an increase in the probability of control of the tumour.

Particularly good results were achieved in proton treatment of melanoma of the eye. For example, the result of the effectiveness of treatment of melanoma of the eye in 2069 patients in MGH Massachusetts in the United States of America (local control after 15 years) was on the level of 95% (8). Egger et al published the results of proton treatment of melanoma of the eye on 2435 patients in the Paul Scherrer Institute, Switzerland. The effectiveness of local control (after 10 years) in this case reached the level of 94.8% (2).

Five years ago there were 22 centres operating worldwide where proton therapy could be implemented, and approximately 37 000 patients had undergone this treatment. According to current statistics published towards the end of 2011, 83 667 patients had undergone proton therapy, i.e. their number had more than doubled. In 2012 39 centres were operating worldwide for proton (or ion) therapy and the construction of a further 24 is planned in the next 3 years (11).

At present a number of commercial firms offer various versions of proton therapeutic complexes on the market in the form of "key ready" supplies. The above facts merely confirm reports that there is currently a worldwide boom in proton therapy.

CASE REPORT

The patient, born in 1939, was observed for 3 years for a pigmented deposit on the posterior pole of the left eye, with clinical progression in the centre, indicated stereotactic radiosurgery in a dose of 35.0 Gy.

At the time of irradiation, the value of central visual acuity in December 2011 was bilaterally 6/12 (20/40 or LogMAR 0.3) without correction, not improving with correction, normal intraocular pressure, on the perimeter scotoma to an extent of up to 40 degrees, corresponding to the deposit. Optical Coherent Tomography – OCT examination: 367 ± 17

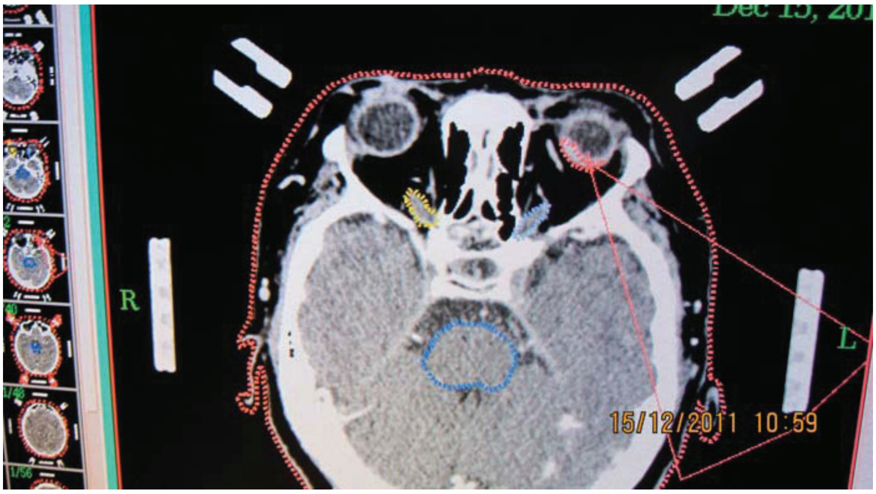

Fig 2 CT image of patient with mounted stereotactic frame – tumour deposit indicated in red

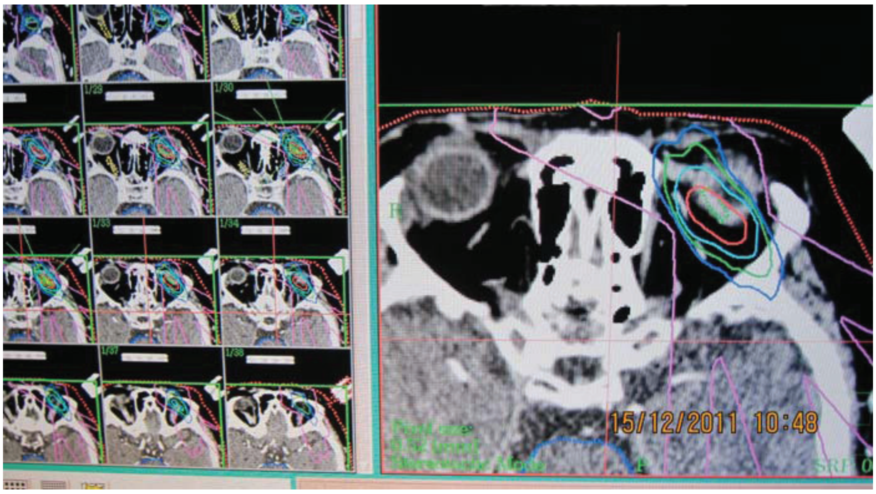

Fig 3 Isodose plan of patient for stereotactic radiosurgery in TD 35.0 Gy. Scheme of irradiation in stereotactic radiosurgery: indicated tumour deposit with TD – therapeutic dose of radiation 35.0 Gy in red, scope of irradiation of surrounding structures by dose of 15.0 Gy in green, 10.0 Gy in blue, 2.0 Gy in purple

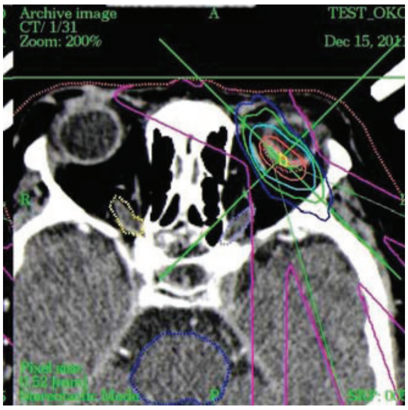

Fig. 4 Detail of CT image – dose field in irradiation of tumour in eye by photons, Tdmax – upper limit of dose 37.5 Gy, therapeutic dose TD 35.0 Gy

(7.99), foveolar depression cleared, epiretinal membrane with traction, diffuse intraretinal edema.

Deposit of the character of malignant melanoma localised in the upper nasal area between the upper nasal and temporal arcade, large greyish-white, irregularly pigmented deposit, size 4x5PD.

Ultrasound examination: elevation 2.65 mm, base 9.17 mm (fig. 1a, b). CT and MRI examination confirmed the size of the deposit (fig. 2).

We compiled an irradiation plan for stereotactic radiosurgical treatment for the Clinac model of linear acceleration, the planning system Covrus ver. 6.2, verification IMRT OmniPro and planning system Liebinger ver. 4.3 (fig. 3, 4).

We compared the patient's parameter with the virtual plan for treatment by proton radiation, in which we used a scheme according to the parameters of the Physical-Technical Centre FIAN, Protvino, Russian Federation (fig. 5, 6).

We compared both planning protocols and evaluated in particular the scope of irradiation of the surrounding, non-tumorous issue. Upon a comparison of both planning schemas, the levels of irradiation of the structures of the surrounding tissues and risk structures (lens, optic nerve) in both cases corresponded to the required norm.

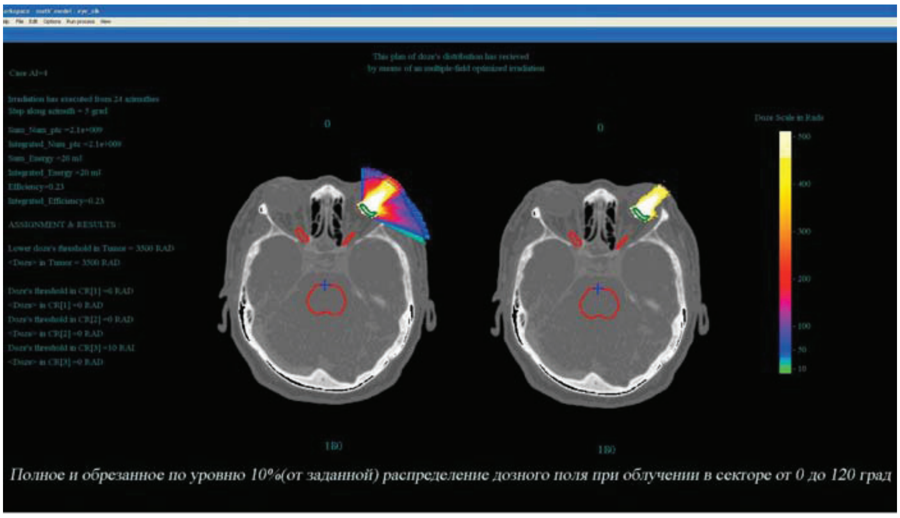

Fig. 5 Scheme of irradiation of the same patient within the framework of model planning upon irradiation of melanoma of the choroidea by protons. On the image on the left is overall distribution of the dose in the sector from 0° to 120° at the required level in the tumour of 35.0 Gy; on the right is distribution of the dose on the level of ≤ 10% (3.5 Gy)

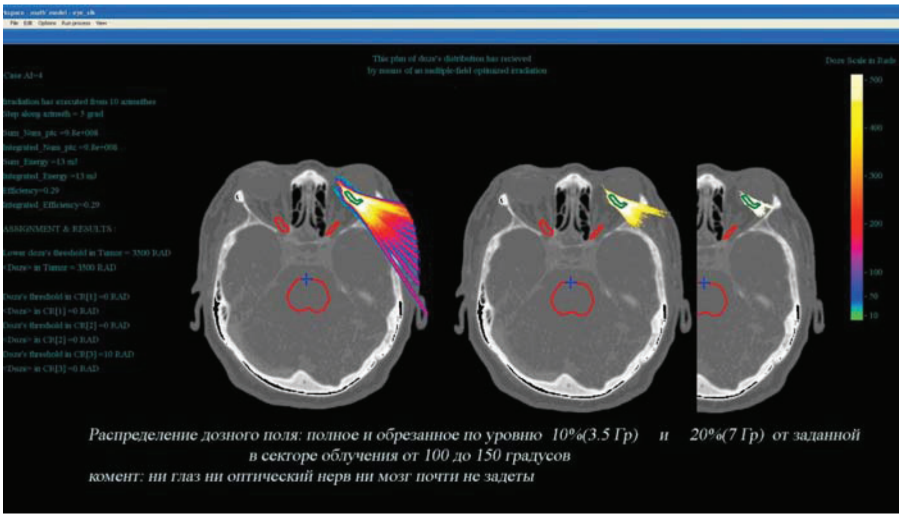

Fig. 6 Dose field of protons in sector 100-150°. On the left overall maximum 35.0 Gy, in the centre ≤ 10% (3.5 Gy), on the right ≤ 20%. It is visible that both the brain and the optic nerve are practically unaffected

DISCUSSION

In the study by Weber et al, the plans for proton and photon therapy of uveal melanomas were compared using planning systems of the Paul Scherrer Institute and Braniscan, version 5.2 (Brain-LAB, Heimstetten, Germany). Results: show target coverage of all simulated uveal melanomas and also conformed in photon and proton method of irradiation. The central CI (95%) value was 1.74, 1.86 and 1.83 for the static, dynamic and IMSRT plans or proton planning, central CI (95%) was 1.88 for OPTIS and was substantially improved by IMPT (Intensity Modulated Particle Therapy) in certain cases (median CI, 95%, 1.29). The homogeneity of the dose in the tumour in the proton plans was however always better than stereotactic planning of irradiation by photons (median heterogeneity coefficient 0.1 and 0.15 versus 0.46, 0.41 and 0.23 for OPTIS and IMPT versus static, dynamic and IMSRT plan, in that order). In comparison with the plans for treatment by photons, the use of protons did not lead to a substantial reduction of homolaterality in the total integrated dose. These results indicated that the use of SRT photon techniques, in comparison with protons, may result in similar levels of the dose conformity. IMPT does not increase the degree of conformity for small tumours. However, heterogeneity of the does in the tumour always increases upon photon planning. The dose for all contralateral tissues was however completely eliminated using the planning method for proton irradiation (12).

Despite the indisputable advantages of proton therapy, the number of centres equipped with proton accelerators worldwide (where it is possible to conduct treatment of oncological disorders by direct irradiation of tumours by accelerated proton beams) is very small in comparison with the number of linear electron accelerators designated for classic radiotherapy (8 000 – 9 000). This is a consequence of the very high initial investments required for the construction of a proton therapeutic centre (more than 100 million USD) and also the operating costs (13).
However, proton therapy is considered to be an exceptionally beneficial modality of the treatment of tumours, and as a result several countries worldwide are attempting, regardless of the high investment and operating costs, to construct their own proton centre (or further proton centres if they already operate such a centre).
For several years Japan has been conducting its National Programme, the aim of which is to equip the main and also prefecture hospitals with equipment for conducting proton (ion) therapy (9). The result of this programme today is that Japan now operates 9 centres (6 proton and 3 ion). In total Japan is planning to construct 22 centres (of which 5 are to be ion centres).
There are currently 10 proton centres in operation in the USA, whilst their number is due to more than double over the next 3 years, since a further 14 are under construction. It is estimated that a further 30-40 new proton complexes shall be built in the USA.
There are currently 10 proton and 2 ion centres in operation in EU states, and a further 12 proton (ion) centres are under construction; in Switzerland – 1, in the Czech Republic – 1, Austria – 1, Italy – 1, Germany – 2, Slovakia – 2, Sweden – 1, Poland – 1, Hungary – 1 and in England – 1 (11).
In Slovakia we are building a Proton Therapeutic Complex at the Cyclotron Centre of the Slovak Republic in the Central Military Hospital in Ružomberok, and proton therapy of the eye is planned also in the Cyclotron Centre of the Slovak Republic in Bratislava. The complex in the CMH in Ružomberok shall be equipped principally with new technology for conducting proton therapy. This highly sophisticated technology is so far only little known worldwide. It was developed at the FIAN Physical-Technical Centre in the Russian Federation, for the purpose of ensuring the wide availability of proton therapy. It is expected that the new technology, with respect to the low investment and operating costs, shall enable wide availability of proton therapy also in smaller countries. After the Russian Federation and the USA, Slovakia is the third country where this technology is being planned for initial launch into clinical operation. The responsibility for distributing this technology on the international market was undertaken by the Russian company ZAO PROTOM, with its headquarters in the city of Protvino, approx. 100 km to the south of Moscow (13).
A great advantage of the Proton Therapeutic Complex is the fact that it may be located within the premises of any larger hospital, or even in some larger already existing premises constructed for the location and operation of a linear radiotherapeutic electron accelerator. The system at the CMH in Ružomberok enables the operation of proton radiotherapy within a wide scope of energies, from 70 MeV to 250 MeV, i.e. not only proton therapy of melanomas of the eye (as is planned in the Cyclotron Centre of the Slovak Republic in Bratislava) is possible, but also full-scale deep proton therapy. The system utilises the method of 3D tumour scanning with a narrow proton beam and enables intensity modulated proton therapy (IMPT). The Proton Therapeutic Complex enables the performance of highly conforming proton therapy.
Of the 15 older member states of the European Union, Germany has the most experience with proton or ion therapy (10). At present IMRT (Intensity Modulated Radiotherapy) and IMPT (Intensity Modulated Proton Therapy) are considered the most state-of-the-art strategies for radiation therapy, and clinical use of these strategies has now commenced. Problems ensuing from the movement of the internal organs or problems arising as a consequence of anatomical change however persist. At present attempts are being made to resolve these issues by the introduction into practice of the new modality of radiation therapy IGRT (Image Gated Radiotherapy – radiotherapy controlled by an image, using a display via CT). A further improvement of this modality of therapy is expected by means of an incorporation into the process of functional display, i.e. the use of information from positron emission tomography (PET), or tomography on the principle of magnetic resonance with functional display (fMRT). Proton therapy in combination with IGRT, sometimes referred to as multi-dimensional radiotherapy, represents the future of radiation therapy over the next decade.
According to estimates of the Proton Therapy Global Management company, it is necessary to have at least one proton centre for approximately 1-2 million persons. In the long term it is expected that proton therapy shall replace current photon therapy in future.

CONCLUSION

Treatment of uveal melanomas by proton radiation is not yet available in Slovakia, although it has several advantages, such as the possibility of fractionation and thus attaining a higher dose of radiation into the deposit (more than 50.0 Gy).
The fundamental difference between stereotactic radiosurgery and proton therapy for ophthalmologists resides especially in the possibility of irradiation by proton radiation of tumours of the iris and corpus ciliare, which in the majority of cases cannot be resolved by stereotactic radiosurgery. Within the framework of proton therapy, it is possible to optimise the dose into the tumour during the course of irradiation.
Upon a comparison of both planning schemas of our patient (schema of the plan for photon irradiation in stereotactic radiosurgery on a linear accelerator and the schema of radiation for proton radiation), the levels of irradiation of the structures of the surrounding tissues (lens, optic nerve) in both cases corresponded to the required norm.
The equipment for proton treatment however enables the performance of “OPTMI therapy” (Optimised Proton Therapy with Modulated Intensity).

LITERATURE

1. **Damato, B., Kacperek, A., Chopra, M., et al.:** Proton beam radiotherapy of choroidal melanoma: the Liverpool-Clatterbridge experience, Int J Radiat Oncol Biol Phys, 2005; 1: 62, 5, 1405–11.
2. **Egger E. et al:** Maximizing local tumor control and survival after proton beam radiotherapy of uveal melanoma, Int J Radiat Oncol Biol Phys, 2001; 51: 1348–47.
3. **Furdová, A., Chorváth, M., Waczulíková, I., et al.:** No differences in outcome between radical surgical treatment (enucleation) and stereotactic radiosurgery in patients with posterior uveal melanoma, Neoplasma, 2010; 57 (4): 377–381.
4. **Furdová, A., Oláh, Z.:** Malígny melanóm v uveálnom trakte, Asklepios, Bratislava, 2002, 175 s.
5. **Furdová, A., Oláh, Z.:** Nádory oka a okolitých štruktúr, CERM, Brno, 2010, 151s.
6. **Furdova, A., Strmen, P., Sramka, M.:** Complications in patients with uveal melanoma after stereotactic radiosurgery and brachytherapy, Bratislava Medical Journal – BLL, 2005; 106 (12): 401–406.
7. **Furdova, A., Strmen, P., Waczulikova, I., et al.:** One-day session LINAC-based stereotactic radiosurgery of posterior uveal melanoma, Eur J Ophthalmol, 2012, Mar, 22 (2): 226–35.
8. **Gragoudas E. et al.:** Evidence-based estimates of outcom in patients irradiated for intraocular melanoma, Arch Ophtalmol, 2002; 120: 1665–71.
9. **Monzulj, G.D., Gladilina, I.A.:** Radiacionnaja biologija. Radioekologija, 2005, 6, p. 670–674.
10. **Oelfke, U.:** Intensity modulated radiotherapy with highenergy photon and hadron beams. Dostupné na internete: http://www.scribd.com/doc/95017648/Intensity- Modulated-Radiotherapy--With-High
11. PTCOG: Particle Therapy Co.Operative Group, Hadron Therapy Patient Statistics PTCOG50 Dostupné na internete: http://ptcog.web.psi.ch).
12. **Weber, D.C., Bogner, J., Verwey, J., et al.:** Proton beam radiotherapy versus fractionated stereotactic radiotherapy for uveal melanomas: A comparative study. Int J Radiat Oncol Biol Phys, 2005; 1, 63, 2: 373–84.
13. ZAO PROTOM, Dostupné na internete: www.protom.ru
14. **Zytkovicz, A., Daftari, I., Phillips, T.L. et al.:** Peripheral dose in ocular treatment with Cyberknife and Gamma Knife radiosurgery compared to proton radiotherapy, Phys Med Biol, 2007; 52: 5957–5971.