CLINICAL STUDY

Complications in patients with uveal melanoma after stereotactic radiosurgery and brachytherapy

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Abstract

Malignant uveal melanoma is the most common intraocular tumour with the incidence about 0.7–1.0 in 100.000 inhabitants. Enucleation is still a standard treatment method for posterior uveal melanoma, but conservative methods are an adequate alternative. Brachytherapy has been used more than 20 years in our Department, stereotactic radiosurgery was introduced in 1999. In years 1991–2004, 145 patients with uveal melanoma were treated at the Department of Ophthalmology, Comenius University, Bratislava. Conservative treatment/brachytherapy is indicated in tumours staged T1–T3. Survival is comparable for all conservative methods. After stereotactic radiosurgery (Linac), the necessity of enucleation because of complications (e.g. secondary glaucoma), after brachytherapy (Ru^{106} plaques), it was 5 %. Conservative methods and combined techniques are effective methods for the therapy of uveal melanomas *(Fig. 5, Tab. 1, Ref. 6)*.

Key words: malignant choroidal, uveal melanoma, brachytherapy Ru^{106} plaques, enucleation, stereotactic radiosurgery (Linac).

Primary tumors of the eye are rare but important malignant lesions. They represent less than 0.2 % of all cancers. Primary malignant uveal melanoma is the most common primary tumor of the eye- it constitutes more than 80 % of primary eye tumors. This tumor is seen in older patients, with nearly equal frequency in males and females. As expected, nearly all (more than 90 %) tumors origin in the choroid.

Enucleation, as a standard method for the therapy of posterior uveal melanoma, has been questioned more than 30 years, so called „conservative" methods have been used with some success, destroying the tumor and preserving vision.

After experiments have shown it is possible to destroy intraocular tumors by ß-irradiation, this new procedure was introduced. Today, brachytherapy is a successful method in the therapy of choroidal melanoma. Radiation therapy with preservation of the eye using primary radiotherapy with external charged particle beams or with surface applicators has been increasingly used in recent years in patients with uveal melanoma. Conservative treatment using radiation therapy can arrest and reverse tumor growth in a high percentage of cases. Unfortunately, the most serious late complication – rubeosis iridis with neovascular glaucoma and cataract develop in about 15–30 % of patient after external beam irradiation.

Radiogenic tissue damage must be considered when dealing with the radiosensitive structures of the eye, even after local ß-irradiation. Exudative reactions occurring several days after irradiation, such as chemosis, choroidal detachment and transient retinal detachment, should not be considered as serious complications due to good prognosis.

Radiogenic side effects must be taken into consideration in all radiation techniques, but using X-rays they can be limited. Severe radiogenic chororetinopathy was seen in some eyes. Most of patients with a tumor located 1–2 PD from the posterior pole show destruction of the macula due to scarring process. When biopsy is absent, it is possible that some small tumors responding favorably to brachytherapy may be benign lesions, thereby improving the results. To overcome this uncertaintly some ophthalmologists recommend that the morphology of intraocular

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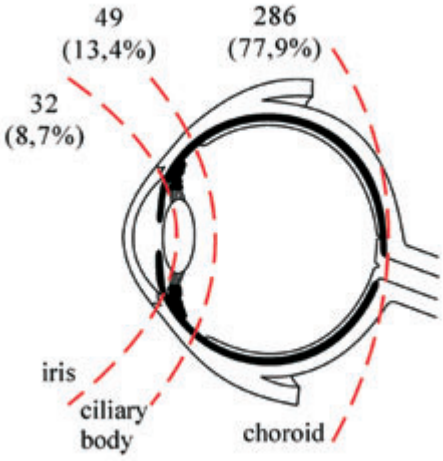


Fig. 1. Localization of the uveal melanoma at the Dpt. Ophthalmol Comenius Univ. Bratislava in the period 1968-2004 (No = 367)

tumors can be established using a transvitreal retinochoroidal biopsy.

Material and methods

Clinical data of 145 patients, hospitalized with posterior uveal melanoma at the Department of Ophthalmology, Faculty Hospital, Comenius University, Bratislava in period 1991–2004 were evaluated. A review of the clinical features, management, histopathologic analysis and prognosis was performed. Uveal melanoma patients were treated by radical surgical methods (enucleation) and conservative methods using brachytherapy (plaques Ru^{106}/Rh^{106}) or stereotactic radiosurgery (since 1999) or with combined methods. The treatment method was carefully selected to meet the principal goals (COMS study group). We have compared group of patients treated with conservative therapy to group of patients treated with radical surgery. Clinical findings were recorded for each patient (age, sex, visual acuity, tumor category, FAG, ultrasound). In the group of stereotactic radiosurgery, CT and MRI were compared before operation and in 3-month interval after the intervention. Applicators Ru^{106} were removed after 100Gy had been delivered to the apex of the tumor. Patients were followed in a 3-month interval, after a tumor regression every 6 months, after 5 years once per year. Patients indicated to stereotactic radiosurgery underwent intervention using local immobilisation of the eye globe applied to a stereotactic frame, and after CT and MRI examination a total 35 Gy dose was applied to the apex of the tumor. The average residual dose for the lens was less than 10 Gy, the optic disc irradiation due to the height of the tumor was less than 8 Gy. The development of secondary cataract was (since 2000) followed by retroillumination (EAS-system). The percentage of complications – radiogenic side effects, percentage of enucleation after Ru^{106}/Rh^{106} plaque irradiation and stereotactic radiosurgery, survival interval after brachytherapy and stereotaxy due to complications like secondary neovascular glaucoma.

Results

In the group of 145 patients, applicators were used in 33 patients (23 %), in 87 patients (60 %) enucleation was necessary, in 2 % enucleation after brachytherapy was necessary due to tumor re-growth or other complications. 25 patients (17 %) were treated with fotocoagulation or combined techniques, 5 % were treated with block-excision and other techniques (transpupillar thermotherapy). A second treatment-reimplantation of the plaque was performed in 5 patients because the melanoma

Tab. 1. TNM classification of intraocular melanoma treated with brachytheraphy (No = 33)

T-primary tumour*	Nº of patients	%
T1 – tumour 10 mm or less in greatest dimension with an elevation 3 mm or less	**18**	**55**
T1a – tumour 7 mm or less in greatest dimension with an elevation 2 mm or less	10	30
T1b – tumour more than 7 mm but not more than 10 mm in greatest dimension with an elevation more than 2 mm but not more than 3 mm	8	24
T2 – tumour more than 10 mm but not more than 15 mm in greatest dimension with an elevation more than 3 mm but not more than 5 mm	**12**	**36**
T3 – tumour more than 15 mm in greatest dimension or with an elevation more than 5 mm	**3**	**9**

Notes: * Tumour base was estimated in optic disc diameters and the elevation in dioptres
* In everz patient other categories were defined as: NX – regional lymph nodes weren't assessed
MX – distant metastasis weren't assessed
VX – venous invasion wasn't assessed
SX – scleral invasion wasn't assessed

* G-histopathological grading was assessed in 7 cases (21%) – after blockexcision or enucleation

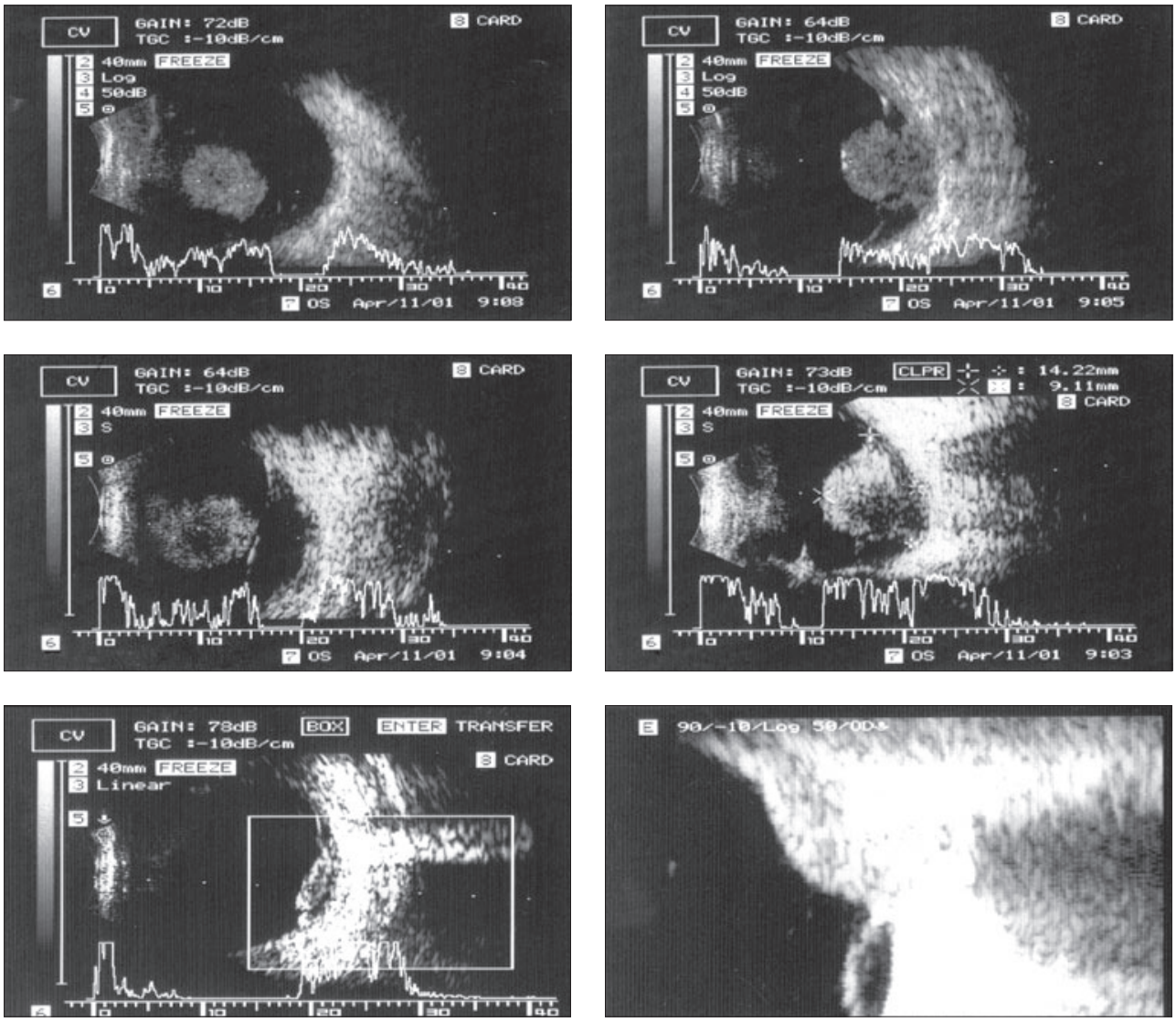


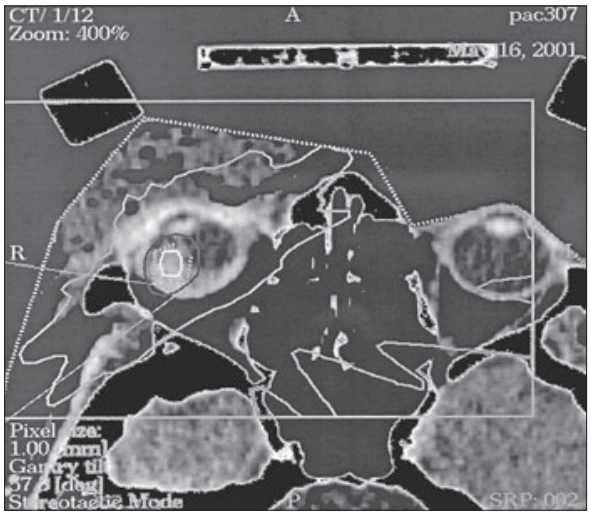
Fig. 2. Ultrasound examination in A, B mode is important (size, localization of the tumor, secondary retinal detachment, exsudative retinal detachment)

showed an insufficient regression after the first irradiation. In patients treated with plaque therapy (N^0=35) in 9 cases (30.5 %) secondary neovascular glaucoma was present, in 4 cases (1.4 %) enucleation of the eye was indicated (Figs 1, 2, 3).

Visual acuity between 6/9–6/18 retained in 22 patients; others developed loss of vision due to postradiation chororetinopathy and macular destruction due to scarring around the tumor margin, which developed up to 1 year after irradiation. The following late complications led to deterioration of visual acuity and were observed 3 to 5 years after brachytherapy: macular destruction due to scarring round the tumor (4 patients), macular oedema in 1 patient, optic nerve atrophy in 1 patient, retinopathy in 18 cases, partial lens opacity in 8 cases, total cataract in 8 cases, vitreous haemorhage in 4 cases, secondary glaucoma in 3 cases, trombosis of the central retinal vein in 2 cases; no case of scleral necrosis was observed.

Histopathological findings in all enucleated eyes of 90 patients are shown in figure bellow. In 6 patients enucleation after brachytherapy was necessary; in 4 patients histologic examination showed persistent melanoma cells without certain damage of the tumor tissue besides necrotic areas – it was G1/a spindle cell melanoma type A, in other 2 cases it was G3/a mixed cell melanoma.

A survival after brachytherapy was compared with a survival after enucleation (in time intervals) up to 10 years – there was no sign of increasing mortality rate after enucleation in 5 to 10 interval. The data of dead patients haven't indicated a metastasis, we have only recorded other oncological (mostly carcinomatous) conditions. The survival in patients with small tumors (T1a and T1b) was the best (we didn't mention death due to metastases of the primary intraocular tumor); the survival interval for the medium stage (T2 and T3) was from 5 to 7 years in 10 %.



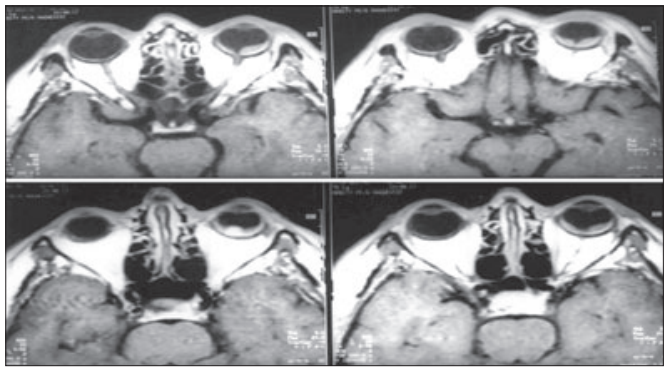


Fig. 3. Pre-treatment 3-D planning by computer (superposition of CT and MRI in the basis for planning a dose rate for irradiation by stereotactic radisurgery)

Survival after ß-irradiation and enucleation of the eye-globe is similar. Brachytherapy with Ru^{106} plaques is effective in small tumors (T1a and T1b), which have developed a complete regression.

In patients treated with stereotactic radiosurgery (N^0=8) the tumor height was 3–12 mm – average 6 mm. In 3 cases (38 %), a secondary neovascular glaucoma with cataract was a reason for the enucleation of the eye.

Complications after stereotactic radiosurgery

This method for the irradiation of a tumor allows a very precise determination of the target volume and a sharp fall off in dose outside thereby reducing unwanted irradiation of surrounding healthy tissues to a minimum. Despite this advantages, some complications occur, mainly due to the fact that about 50 % of the treated tumors are located close to he fovea or the optic disc and about 50 % are more than 5 mm in height.

A cataract has developed in 3 patients (36 %). Significant predictors of the appearance of lens opacities were: age, tumor height, location of the anterior tumor margin and irradiation of the lens periphery.

The cataract has developed in patients in whom the periphery of the lens was not irradiated. In these cases we can presume that other predictors, especially age, were the cause. We investigated the influence of irradiation upon lens opacity by dividing the patients in two groups: 1st group where less than 30 % of the lens periphery was irradiated and 2nd group where more than 30 % of the lens was irradiated.

Glaucoma was the most important reason for enucleation after stereotactic irradiation in our group of patients: 38 % developed glaucoma. Glaucoma free survival probability is shown here:

Multifactorial analysis indicates tumor height (P=0,00), age (p=0.0542) and irradiation of the optic disc (p=0.0721) as factors leading to the development of glaucoma. Large tumors and older patients were particularly affected by glaucoma when the optic disc had to be irradiated due to tumor size or location.

Rubeosis iridis developed in all patients, who later developed a secondary glaucoma. The contributors to rubeosis were tumor height (p=0.00), irradiation of the optic disc (p=0.00), the largest tumor diameter (p=0.01) and the extension of retinal detachment (p=0.024).

Patients with large tumors near the optic disc and a large retinal detachment were more pronounced to develop rubeosis.

Discussion

The management of choroidal melanoma will probably remain controversial. Recently, new irradiation techniques has become the therapy of choice in almost all melanomas, except for very large tumors (T3, T4), filling more than half of the globe, where the enucleation is indicated. Stereotactic radiotherapy is indicated in small tumors (T1–T2) located far away from the optic disc, macula and the lens, where therapy with episcleral

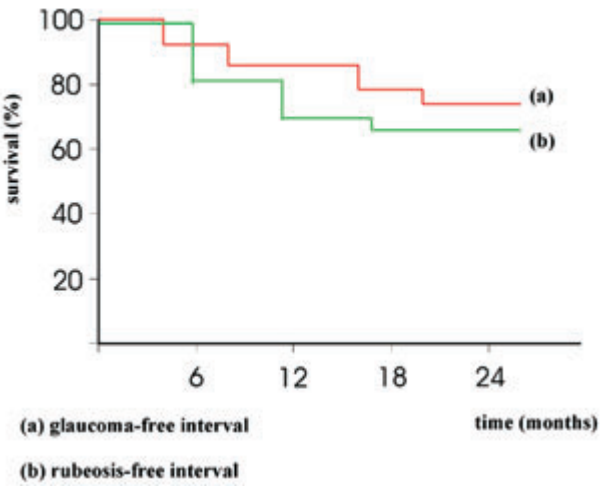


Fig. 4. Glaucoma/rubeosis free interval in patients in melanoma after irradiation (No = 8)

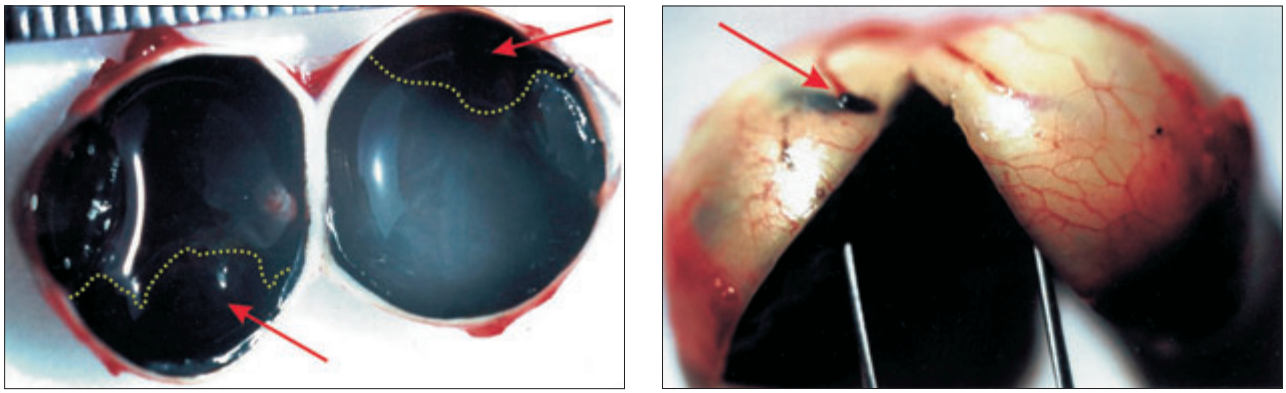


Fig. 5. Enucleated eye - tumor mass infiltration into the angle, filling more than 1/3 of the vitreous body space (12 months after insufficient stereotaxy)

plaques is still indicated. The efficiency of external irradiation of the eye-globe using stereotactic radiosurgery has been demonstrated. Our first results show, that survival is comparable for all conservative treatments, despite the fact, that the tumors irradiated by protons are larger than those treated by radioactive applicators, and that's why the complications in group of patients undergoing stereotactic radiosurgery is up to 38 %.

Brachytherapy with Ru^{106} plaques is effective in small tumors (stage T1a and T1b), which had developed a complete regression. In our group of patients (stage T2a and T3b), treated with stereotactic radiosurgery, 38 % of secondary complications like secondary glaucoma and cataract were indication to enucleation.

The fundamental objective of radioactive therapy is to control malignancy while maintaining useful vision. Present techniques result in a high incidence of tumor control for intermediate and small lesions (<8 mm in height). Tumor control is not optimal in large lesions; there is a higher incidence of late complications resulting in impaired vision. It is likely that the reduction of radiation dose to the uninvolved part of the eye will reduce the incidence of late complications while maintaining a high incidence of tumor control for smaller tumors.

It is expected that major benefit regarding the treatment optimization and lower incidence of late complications will be obtained using a 3-D radiation dosimetry. The 3-D system permits precise pre-treatment planning and modifications of the plan at short notice, in the case of new intraoperative findings. There is overwhelming evidence that malignant melanoma of the uveal tract can be treated safely with radioactive plaques with long-term survival rates equal to those of enucleation. We suspect, that the vessels around the optic disc are damaged by a full dose irradiation, leading to retinal ischemia, which favors the development of neovascular glaucoma. Preservation of the eye function is expected in majority of radioactive-plaque treated patients. Application of low energy isotopes, collimation of individual seeds, and routine use of 3-D imaging and 3-D dosimetry should help to further optimize episcleral plaque therapy. In literature, the incidence of post-radiotherapy enucleation from all causes is about 20 %. The decrease of the incidence of complications like cataract, radiation papillitis, radiation maculopathy, and secondary glaucoma is because of very strict indications for posterior uveal melanoma. Now, no randomized prospective study of the effect of the alternative conservative treatments for choroidal melanoma on visual outcome have been performed.

Conclusion

Our results have shown the enucleation rate due to complications after stereotactic radiosurgery to be 38 %, after simple or combined brachytherapy less than 5 %. In our group of patients after Ru^{106}/Rh^{106} plaque therapy the following late complications have led to deterioration of visual acuity and were observed at the last follow-up: macular destruction due to scarring round the tumor, optic nerve atrophy, macular degeneration, retinopathy, partial lens opacity, total cataract, vitreous hemorrhage, secondary glaucoma, thrombosis of the central retinal vein.

We can conclude that if more than 30 % of the lens periphery is irradiated, the patient is likely to develop a radiation cataract. In the cases where tumor height is large, invasion of the iris is present, or the anterior margin of the tumor is very close to the equator, the lens may be more sensitive to the irradiation and the cataract can develop even if less than 30 % of its periphery is irradiated. Age is a well-known indicator of cataract development.

The main contributors to visual loss are the height of the tumor and irradiation of the fovea and the optic disc. Unfortunately, in our clinical study only the worst cases (with tumor height exceeding 8 mm or a location close to the optic disc or fovea) are referred to combined or stereotactic radiotherapy. We can assume, there are no negative consequences for survival, but the visual outcome is not the best because irradiation of the tumor without irradiation of the fovea or the optic disc is not possible in many cases. Stereotaxy is a useful alternative to brachytherapy or a first step to combined micro-surgical methods.

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