doi:10.4149/neo_2010_04_377

No differences in outcome between radical surgical treatment (enucleation) and stereotactic radiosurgery in patients with posterior uveal melanoma

A. FURDOVA[1], P. SLEZAK[4], M. CHORVATH[5], I. WACZULIKOVA[3], M. SRAMKA[2], G. KRALIK[2]

[1]Dpt. of Ophthalmology, Med. School, Comenius University, Bratislava, Ruzinovska 6, Bratislava, Slovak Republic, e-mail: afrf@mail.t-com.sk; [2]Dpt. of Stereotactic Radiosurgery, St. Elisabeth Cancer Inst., Bratislava; [3]Division of Biomedical Physics Fac. of Math., Phys. and Inform., Comenius University, Bratislava; [4]Institute of Normal and Pathological Physiology, Slovak Academy of Science, Bratislava; [5]Radiotherapy Dpt, St. Elisabeth Cancer Inst., Bratislava, Slovak Republic

Received September 22, 2009

To report the treatment outcome and possible survival difference between radical surgical treatment (enucleation) or stereotactic radiosurgery (SRS). LINAC stereotactic radiosurgery is an alternative treatment for posterior uveal melanoma used in Slovakia since 1999.

The study analyzed patients treated for posterior uveal melanoma in the period 2001-2008. The aim of the study was to compare the relapse-free survival in the cohort of patients primarily treated with surgery (enucleation) or SRS. A total number of 84 patients were included, treatment was determined on a case-by-case basis.

We reviewed the records of patients with ciliary body or choroidal melanoma treated by enucleation – 44 patients (52%) and SRS – 40 patients (48%). The therapeutic attitude was established on the basis of ophthalmoscopy, ultrasound (A, B mode), other ophthalmological findings, visual acuity, and general status of each patient. Volume of the tumor was calculated using the formula: "π/6 x length x width x height" for each patient. All of the patients before decision to "conservative" attitude therapy underwent MRI examination.

The therapeutic dose in SRS patients group was 35.0-38.0Gy.

The data were analyzed using Kaplan – Meier survival method for the differences in survival rates between the treatment groups, and afterwards by Cox ´s proportional hazard method with predictors involved.

Among the baseline covariates evaluated, only age affected the prognosis for survival to a statistically important, however not significant degree. The risk of death among patients treated with enucleation relative to those treated with stereotaxy after adjustment for baseline characteristics of patients, age, and tumor volumes was not significant [1.82] (95% CI, 0.46 to 7.30; P = 0.396). The overall five-year survival rate for patients with posterior uveal melanoma was 72%.

Treatment by either primary enucleation or SRS according to our results does not appear to influence the development of metastases in patients with uveal melanoma; the survival prognosis is essentially determined by the stage and character of the tumor. No survival difference attributable to stereotactic irradiation 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.

Treatment by either radical surgical attitude (enucleation) or "conservative" LINAC- SRS does not appear to influence the survival rate in patients with uveal melanoma

Key words. uveal melanoma, stereotactic radiosurgery, enucleation, relapse-free survival, overall survival

Malignant uveal melanoma is the most common intraocular tumor in adults, the incidence is 0.6, approximately 50% of the patients die within 15 years after enucleation. Uveal melanoma shows a peak incidence at age over 60, and there are many differences between cutaneous and uveal melanoma. The mortality rate of cutaneous melanomas has been rising in recent decades, whereas the mortality rate from uveal melanoma has remained steady over the same period [1, 2].

In the last decade diagnostic methods have improved, although clinical diagnosis remains to be the standard in eyes with clear media. Ultrasound is the most important technique before treatment planning. While enucleation has been the basic of therapeutic intervention for a long time, in the last three decades different types of irradiation techniques give hope for tumor control and functional preservation of the eye globe. The new trend in the management of choroidal melanoma is a retreat

from radical surgical removal of the whole eye-globe (enucleation) for the globe sparing treatments started by introducing brachytherapy into the treatment of intraocular tumors. Alternatives to enucleation in middle and large tumors include also local resection with adjuvant brachytherapy or lasertherapy or external beam radiotherapy. The single irradiation of the tumor itself is a new approach – it has been shown to achieve ultrasonic tumor regression in a similar fashion to brachytherapy and stereotactic radiosurgery (SRS). SRS of extracerebral lesions like uveal melanoma was invented in the last two decades of the 20th century and is an alternative treatment for middle and large posterior choroidal melanoma. Some authors prefer irradiation by SRS before enucleation for large uveal melanoma [3, 4, 5].

SRS is single fraction of a single high-dose irradiation administered with a precious spatial accuracy using a collimating system. Image fusion of a contrast--enhanced magnetic resonance imaging (MRI) and computed tomography (CT) is used for planning co-ordinates. SRS in treatment of uveal melanoma in Slovakia was introduced in 1999 at the St. Elisabeth Oncology Inst. SRS is performed on linear accelerator (LINAC) with 6 MV X. Rigid immobilization with the aim of Liebinger frame is used – the eye globe is fixed by stitches through four extraocular muscles to the stereotactic frame. Patients with intraocular melanoma are precisely diagnosed and the therapy is a result of all tests and complete examination of the patient due to his/her local findings and general status.

The Collaborative Ocular Melanoma Study (COMS), a multicentre national trial, is intended to provide long-term data on the natural history as well as therapeutic intervention. This large, prospective, randomized trial was designed to compare mortality figures for medium-sized melanomas treated by brachytherapy or enucleation [3]. The results were not able to show the difference in mortality rates between the two treatment groups after a maximum of 12 years of follow-up (COMS 2001a). The study was set up in 1985 before introducing the stereotactic radiosurgery in the treatment of uveal melanoma. There is a need for multicentre trials to compare the outcomes following stereotactic radiosurgery with enucleation, however, until now, no study has been performed in this topic.

Patients and methods

A retrospective survival analysis was undertaken for all patients with uveal posterior melanoma treated at the Dpt. Ophthalmology, Med. School, Comenius Univ., during the years 2001-2008. Patients were treated by either primary radical enucleation or SRS. The diagnosis was established on the basis of ophthalmological examination, ultrasound, CT or MRI examination. All patients with small intraocular melanoma treated only by transpupillary thermotherapy were excluded from the analysis and also patients with evidence of disease at the time of therapy. Metastatic intraocular tumors were not included to the analyzed cohort.

Patients were not randomized either to radical or to "conservative" procedure, but the treatment was determined exclusively on a case-by-case basis. General status, age, gender, the functional tests – visual acuity, perimeter, the visual acuity of the other eye, all were taken into consideration. The patient was actively involved in the decision on the therapeutic procedure after explaining possible postoperative complications.

The therapeutic dose in SRS TD min. varied from 35.0 to 38.0 Gy, TDmax 42.0-52.0 Gy. The doses to the critical structures were below 8.0 Gy for the optic nerve and the optic disc and 10.0Gy to the anterior segment of the eye.

The record for each patient included the age at treatment, tumor size, tumor volume, the maximum height of the tumor by A,B scan ultrasound, the presence and the extent of secondary retinal detachment, and the signs of extrascleral extension. The tumor volume was calculated in the group of stereotactic patients based on an individual stereotactic planning. In the patients who underwent enucleation and in whom MRI examination was not performed, the volume was calculated using the formula: volume=Pi/6 x length x width x height. Tumors were divided into three groups as follows: small – less than 4mm of max. elevation, middle – 4-8 mm, and large – over 8mm.

The disease-free interval was defined as the period from treatment (either enucleation or SRS) until the development of metastasis, or the death of the patient. The patients after enucleation were examined by ophthalmologist every six months, with a monthly interval in the first six months, dependent on problems with using individual prosthesis. The patients after stereotaxy were examined by an ophthalmologist every three months: visual acuity, biomicroscopy, intraocular pressure, ultrasound in A and B mode, fundus photography and since the year 2007 also OCT (optical coherence tomography) was routinely done. Postradiation complications and tumor dimension and extent of secondary retinal detachment were observed.

The disease free interval was defined as the time from treatment until the development of metastases. Patients were seen in three month interval in the first year after the SRS, later in six month interval following SRS. Patients in both groups were regularly in six month interval recommended to their oncologist to a liver ultrasound, abdominal ultrasound, liver function test, brain CT, 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).

The patients were observed in the period from 2001 (01/01) to 2008 (31/12) and the data were analyzed as indicated below.

Statistical analysis. Data that were confirmed to be non-normally distributed parameters (according to Shapiro-Wilk's test), are presented as median and a (quartile 1 – quartile 3) range.

Survival rates in both investigated groups (enucleated patients and those who underwent stereotactic surgery) were estimated with unconditional Kaplan-Meier survival method. Continuous baseline characteristics, which were assumed to influence survival, were tested for differences between the groups with unpaired t-test. The association of selected explanatory variables with the endpoint (death) was assessed

using logistic regression. The relationship between survival and selected predictors was afterwards examined by Cox's regression model with included baseline covariates.

Our statistical significance reporting criterion for differences between relevant data sets was $p < 0.05$.

Results are presented as respective survival plots with estimated survival probability and/or the relative hazard with 95% confidence intervals. (A note: The treatment groups could not be characterized by median survival times due to the low frequencies /insufficient number of endpoints/events.)

All statistical analyses were performed with StatsDirect 2.7.6 software (StatsDirect Ltd., Cheshire, UK).

Results

In the period 2001 – 2008 a total number of 84 patients with intermediate or large uveal melanoma were treated with either radical surgical removal of the whole eye-globe (enucleation), or SRS. In a group of 40 patients who underwent SRS there were 22 male and 18 female – the total median age was 55 years; the median age of female was 54 years and 58 years of male. In a group of 44 patients with enucleated eyes the median age was 68,5. In the group there were 21 male (median age 64), and 23 female (median age 73). The median tumor volume in group of stereotactic patients was 0,65 cm^3 (0,4-0,8), in group of enucleated patients 1,1 cm^3 (0,8-1,25).

Five patients treated in the first step with SRS required subsequent enucleation due to the complications – secondary neovascular glaucoma. Three patients of this subgroup underwent pars plana vitrectomy with endoresection of the tumors plus silicon oil, but the enucleation was necessary due to the complication – relapse of the tumor.

Histopathologically in the group of enucleated eyes after SRS due to complications in four patients malignant melanoma of the mixed cell type, in two cases an epitheloid type, and in one case a spindle-cell type A was confirmed.

In the group of primary enucleated eyes, there were four findings of an epitheloid-cell type, one case of a nodular type, as well as 10 cases of both, a mixed-cell type and 29 cases of a spindle-cell type (A or B) melanoma.

One patient with other distant metastasis (skin type in one case) was assigned to systemic therapy.

The period of follow-up ranged from 1 month to 7 years with medians 34 months in the stereotactic group and 29 months in the group of primarily enucleated patients.

Results on the differences between unconditional survival rates (not shown) in both investigated groups showed a significantly increased mortality in the group of enucleated patients (P=0.0498; generalized Wilcoxon test). However, the Kaplan-Meier survival distribution estimator is not appropriate descriptive device for this study, since it involves non-homogeneous populations of patients with respect to age and stage of the disease expressed as tumor volume ($P = 0.0007$ and $P < 0.0001$, respectively). The age and tumor volume are important explanatory variables (termed covariates)

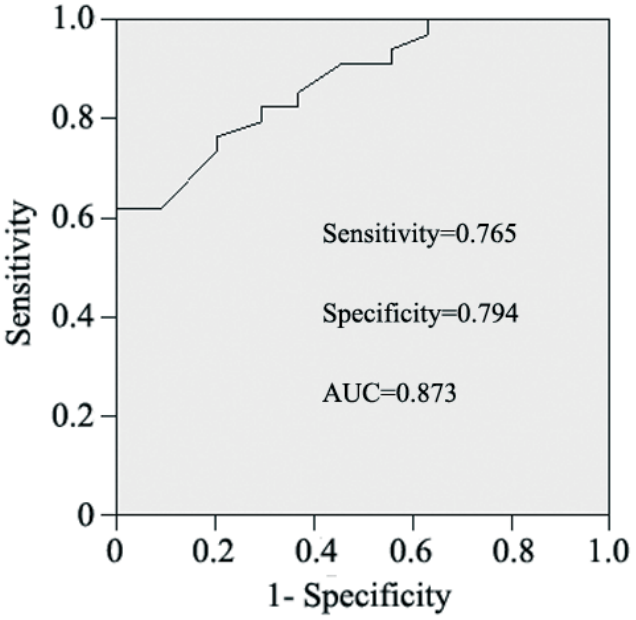

Fig.1. Estimated survival curves for patients treated with enucleation (identifier 2) or stereotactic surgery (identifier 1) based on the Cox model in Table 1. Censorship is marked with vertical tics and observed event times with circles for enucleation and squares for stereotaxy groups.

that are assumed to be associated with survival and need to be incorporated in the model (5). Results on logistic regression confirmed significance of the model with the predictors age and tumor volume ($P = 0.01$). The tumor volume was a significant unique predictor ($P = 0.035$); age with its borderline probability value of 0.1 could be assumed as possibly associated with the outcome. The estimator of survival rates adjusted for these predictors was constructed based on Cox's regression model which examines the relationship between survival and both predictors (Fig. 1). Multicolinearity of the predictors was not confirmed. Proportionality assumption was tested by the Kaplan-Meier plot of the survival functions for each group (Log survival probability-log survival time plot), which has demonstrated that they were approximately parallel (they did not cross each other).

From the Cox's regression (Tab. 1) it follows that the risk of death among patients treated with enucleation relative to those treated with stereotaxy after adjustment for baseline characteristics of patients, age, and tumor volumes was not

Table 1: Cox (proportional hazards) regression

Variable	Coefficient (β)	Standard Error	P Value	Risk Ratio	95% CI
Age	0.273	0.025	0.724	1.040	0.991 to 1.092
Volume	0.039	0.773	0.113	1.314	0.289 to 5.979

Deviance (likelihood ratio) chi-square = 2.808; df = 2; P = 0.246

significant [1.82] (95% CI, 0.46 to 7.30; P = 0.396). Estimated overall five-year overall survival rate (S) for patients with posterior uveal melanoma 72% (SE(S) = 0.08).

A test of the overall statistical significance of the model adjusted for age and tumor volume is given by the likelihood chi-square statistic and yields a P value of P = 0.140.

Among the baseline covariates evaluated, only age affected the prognosis for survival to a statistically important, however not significant degree (P = 0.095).

Discussion

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

The therapy for each patient should be chosen in accordance with the general status of the patient and with the local findings, stage and character of the tumor [2]. The Collaborative Ocular Melanoma Study (COMS), a multicentre national trial, is intended to provide long- term data on the natural history as well as therapeutic intervention. This large, prospective, randomized trial was designed to compare mortality figures for medium-sized melanomas treated by brachytherapy or enucleation [3]. The results were not able to show the difference in mortality rates between the two treatment groups after a maximum of 12 years of follow-up (COMS 2001a). The study was set up in 1985 before introducing the stereotactic radiosurgery in the treatment of uveal melanoma.

The first survival analysis comparing enucleation with stereotactic radiosurgery was published in 2003 [6]. According to this study treatment by either enucleation or SRS does not appear to influence the development of metastases in patients with uveal melanoma. Our results are similar to the outcome of previously published choroidal melanoma survival studies.

SRS is a relatively new method, so there is a need for multicentre trials to compare the outcomes following stereotactic radiosurgery with enucleation. 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 [6, 9] and because reported local tumor control rate following SRS appear comparable, we offer SRS to patients who would otherwise require enucleation.

It is important to realize that the power of a test to compare survival in two or more groups is related not to the total sample size but to the number of events of interest (such as deaths in this case). In other words, the survival tests perform better when the censoring is not too heavy, and, in particular, when the pattern of censoring is similar across the different groups. High number of right-censored data (from those patients who still were alive at the end of observation, or dropped out of the study for various reasons other than death prior to its termination) could affect the reliability of the results. Thus, the heavy censoring might complicate the estimation of the survival model, because it decreases the equivalent number of subjects exposed (at risk) at later times, reducing the effective sample sizes. Moreover, small sample sizes may further increase the effect of the assumption violation. It is not reasonable, however, to drop the selected explanatory variable(s) from the model, since there are "real world" reasons why these particular variables should remain in the final model [6, 7].

The incidence of intraocular tumors varies from 0.2 to 1.0. The recorded data from Slovak regions correspond to the values reported from other regions [8]. Malignant uveal melanoma is the most common intraocular tumor in adults; over 95 per cent of all intraocular tumors. In the countries like Slovakia, where the whole population is slightly above 5.5 million inhabitants, the number of new cases diagnosed per year varies from 10 to 25 uveal melanoma as issued by the National Oncology Register, that is the reason why the number of cases in our cohort, which included all the diagnosed melanoma in the period under study, is not sufficient and has an impact on the reliability of the result.

In the study by Cohen et al [6], the 5-year cumulative metastasis-free survival rate was 51% in the enucleation-treatment group compared to 74% in the group treated with stereotaxy. However, in the multivariate analysis there was found no statistical difference in the survival rates between the two treatment groups. The only variables that influenced survival rates were tumor location (p=0.002), ciliary body tumors with the worst prognosis, and tumor volume (p=0.001).

In our groups investigated, survival analysis adjusted for predictors showed that the group of patients after stereotactic radiosurgery had the same outcome as the group of patients treated with radical surgery. Based on our analysis, we assume that the survival prognosis is essentially determined by the character of the tumor in association to the status of the patient. Clinically, the most important factors that affect the metastatic process are the localization and size (volume) of the lesion.

There has been performed no multicentre 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 [13, 14, 15, 16, 17, 18]. 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 [19, 20, 21]. The findings in the series suggest a role of SRS in the treatment of selected cases of uveal melanoma.

In conclusion, treatment by either primary enucleation or SRS according to our results does not appear to influence the

development of metastases in patients with uveal melanoma; the survival prognosis is essentially determined by the stage and character of the tumor.

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.

SRS is a non-invasive alternative to enucleation in the treatment of uveal melanoma with a high tumor control.

References

[1] ONDRUSOVA M, PLESKO I, SAFEI-DIBA Ch, OBSITNIKOVA A, STEFANAKOVA D et al.: Complex analysis of cancer incidence and cancer mortality in Slovak Republic [online]. Bratislava, National Cancer Registry of SR, NCZI, 2007 [cit. 13.9.2009]. http://www.nor-sk.org/. ISBN 978-80-89292-05-9.

[2] MORAVCOVA A, OLAH Z, PLESKO I Concerning the problem of incidence and recording of malignant intraocular tumours in Slovakia over the years 1968-1985. Brat. lek. listy (Bratislava Medical Journal) 1990;7: 685–663

[3] Collaborative Ocular Melanoma Study Group (2001b): Assessment of metastatic disease status at deth in 435 patients with large choroidal melanoma in the Collaborative Ocular Melanoma Study. COMS Report No.15.Arch Ophthalmol 119: 670–676

[4] Collaborative Ocular Melanoma Study Group (2001a): The COMS Randomized Trial of Iodine 125 Brachytherapy for Choroidal melanomas III. Initial Mortality Findings. COMS Report No. 18. Arch Ophthalmol 119: 969–981.

[4] ZEHETMAYER M, KITZ K, MENAPACE R, ERTL A, HEINZ H et al.: Local tumour control and morbidity after one to three fractions of stereotactic external beam irradiation for uveal melanoma. Radiother Oncol . 2000;:55: 134–144 doi:10.1016/S0167-8140(00)00164-X

[5] ZIMMERMAN LE, MCLEAN IW, WALTER DF Does enucleation of the eye containing malignant melanoma prevent or accelerate the dissemination of tumour cells Br J Ophthalmol 1978; 62: 420–425 doi:10.1136/bjo.62.6.420

[6] COHEN V. M. L; CARTER M. J; KEMENY A; RADATZ A, RENNIE IG Metastasis-free survival following treatment for uveal melanoma with either stereotactic radiosurgery or enucleation, Acta Ophthalmologica Scandinavica 2003; 6: 383–388 doi:10.1034/j.1600-0420.2003.00101.x

[7] MCLEAN IW, SARAIVA VS, BURNIER MN Jr.Pathological and prognostic features of uveal melanomas. Can J Ophthalmol. 2004 Jun;39(4):343–50.

[8] SINGH AD, SHIELDS CL, SHIELDS JA. Prognostic factors in uveal melanoma. Melanoma Res. 2001 Jun;11(3):255–63 doi:10.1097/00008390-200106000-00007

[9] AUGSBURGER JJ, SCHNEIDER S, FREIRE J, BRADY L Survival following enucleation versus plaque radiotherapy in statistically matched subgroups of patients with choroidal melanomas: results in patients treated between 1980 and 1987. Graefes Arch Clin Exp Ophthalmol 1999;237: 558–567. doi:10.1007/s004170050279

[10] Collaborative Ocular Melanoma Study Group (2001a): The COMS Randomized Trial of Iodine 125 Brachytherapy for Choroidal melanomas III. Initial Mortality Findings. COMS Report No. 18. Arch Ophthalmol 119: 969–981.

[11] Collaborative Ocular Melanoma Study Group(2001b): Assessment of metastastic disease status at death in 435 patients with large choroidal melanoma in the Collaborative Ocular Melanoma Study. COMS Report No. 15. Arch Ophthalmol 119: 670–676.

[12] DE POTTER P, SHIELDS CL, SHIELDS JA, CATER JR, TARDIO DJ Impact of enucleation versus plaque radiotherapy in the management of juxtapapillary choroidal melanoma on patient survival. Br J Ophthalmol 1994;78:109–114. doi:10.1136/bjo.78.2.109

[13] LANGMANN G, PENDL G, MULLNER K, PAPAEFTHYMIOU G, GUSS H Gamma knife radiosurgery for uveal melanomas: an 8-year experience. J Neurosurg 2000; 93: 184–188.

[14] MARCHINI G, GEROSA M, PIOVAN E, PASOLI A, BABIGHIAN S et al.: Gamma knife stereotactic radiosurgery for uveal melanoma: clinical results after 2 years. Stereotactic Funct Neurosurg 1996;66: 208–213. doi:10.1159/000099812

[15] MUELLER AJ, TALIES S, SCHALLER UC, HORSTMANN G, WOWRA B et al.: Stereotactic radiosurgery of large uveal melanomas with the gamma knife. Ophthalmology 2000;107: 1381–1387. doi:10.1016/S0161-6420(00)00150-0

[16] RENNIE IG, FORSTER D, KEMENY A, WALTON L, KUNKLER I The use of single fraction Leksell stereotactic radiosurgery in the treatment of uveal melanoma. Acta Ophthalmol Scand 1996;74: 558–562. doi:10.1111/j.1600-0420.1996.tb00734.x

[17] SEDDON JM, GRAGOUDAS ES, EGAN KM, GLYNN RJ, HOWARD S et al.: Relative survival rates after alternative therapies for uveal melanoma. Ophthalmology 1990;97: 769–777.

[18] SEREGARD S, KOCK E Prognostic indicators following enucleation for posterior uveal melanoma. A multivariate analysis of longterm survival with minimized loss to follow-up. Acta Ophthalmol Scand 1995;73: 340–344. doi:10.1111/j.1600-0420.1995.tb00039.x

[19] ZIMMERMAN LE, MCLEAN IW, WALTER DF Does enucleation of the eye containing malignant melanoma prevent or accelerate the dissemination of tumour cells. Br J Ophthalmol 1978;62: 420–425. doi:10.1136/bjo.62.6.420

[20] GHAZI NG, KETSCHERIDE CS, SHEEHAN J, CONWAY BP Gamma knife radiosurgery for uveal melanoma ineligible for brachytherapy by the Collaborative Ocular Melanoma Study criteria. Open Access Surgery 2008;1: 21–24

[21] KREMA H, SOMANI S, SAHGAL A, XU W, HEYDARIAN M et al.: Stereotactic radiotherapy for treatment of juxtapapillary choroidal melanoma: 3-year follow-up. Br J Ophthalmol 2009; 93: 1172–1176 doi:10.1136/bjo.2008.153429