

OCULAR RETENTION IN PATIENTS WITH UVEAL MELANOMA MANAGED BY A MULTIMODALITY APPROACH

ESTUDIO DE LA CONSERVACIÓN DEL GLOBO OCULAR CON UN ABORDAJE MULTITERAPÉUTICO EN EL MELANOMA UVEAL

GARCÍA-ÁLVAREZ C¹, MUIÑOS Y¹, SAORNIL MA², ALMARAZ A², LÓPEZ-LARA F², FRUTOS JM³, MUÑOZ MF⁴

ABSTRACT

Objective: to analyze ocular survival in eyes with uveal melanoma treated with conservative therapies, in a centre that applies all treatment modalities.

Methods: Patients diagnosed with uveal melanoma and treated between September 1990 and April 2007 were included in an historical cohorts study. Results: 273 patients were included. 193 were treated with conservative treatments (70.69%) and 80 were enucleated as primary treatment. 14 patients were enucleated after conservative treatment (7.2%). Kaplan-Meier survival analysis showed an 88% survival probability of the eye in the first 5 years after conservative treatment and 83% at 10 years.

Conclusions: Conservative treatments for uveal melanoma, especially brachitherapy, are safe and effective in relation to tumor control and rate of secondary effects (*Arch Soc Esp Oftalmol* 2009; 84: 145-150).

Key words: Intraocular tumors, uveal melanoma, episcleral brachitherapy, enucleation.

RESUMEN

Objetivo: Analizar la supervivencia de los globos oculares afectados de melanoma uveal sometidos a tratamiento conservador, en un centro que aplica todas las modalidades de tratamiento.

Métodos: Se han incluido en el estudio los pacientes diagnosticados de melanoma de úvea tratados entre septiembre de 1990 y abril de 2007 en la unidad de Oncología Ocular del Hospital Clínico Universitario de Valladolid realizándose un estudio de cohortes histórico.

Resultados: De los 273 pacientes incluidos en el estudio, se trataron 193 pacientes con terapias conservadoras (70,69%), mientras que se enuclearon de forma primaria 80 (29,30%). Se enuclearon de forma secundaria 14 de los sometidos a tratamiento conservador (7,2%) El análisis de supervivencia de Kaplan-Meier reveló que tras la aplicación de un tratamiento conservador, la probabilidad de conservación del globo ocular a los 5 años es del 88% y a los 10 años es del 83%.

Conclusiones: El presente estudio pone de manifiesto la seguridad de los tratamientos conservado-

Received: 25/6/08. Accepted: 23/3/09.

Adult Intra-Ocular Tumor Unit. CSUR of SNS. Radiotherapy, ophthalmology and Research Unit. Clinical University Hospital. Valladolid. Spain.

¹ Graduate in Medicine.

² Ph.D. in Medicine.

³ Graduate in Physics.

⁴ Graduate in Statistics.

Correspondence:

Ciro García-Álvarez
Hospital Clínico Universitario
Ramón y Cajal
47003 Valladolid
Spain
E-mail: cigore@yahoo.es

res en el melanoma uveal, especialmente de la braquiterapia episcleral, en cuanto a control local de la enfermedad y a tasa de efectos secundarios.

Palabras clave: Tumores intraoculares, melanoma uveal, braquiterapia episcleral, enucleación.

INTRODUCTION

Uveal melanoma is the most common primary ocular neoplasia among adults, with an estimated incidence in the United States of approximately 5 cases per million inhabitants per year (1), and unknown in our environment.

For a long time, the disease treatment was based on enucleation. However, in the last decades of the 20th century, conservative techniques were developed which proved to be as efficient as enucleation as far as local control of tumors with certain characteristics (2). Local treatments, besides from being less mutilating, allow for preserving the eye globe and retaining visual function (3-8). As for the systemic control of the disease, conservative therapies and enucleation have not proven successful in reducing the incidence of metastasis during patient follow-up (9).

These conserving techniques are episcleral brachytherapy with different isotopes (the most widely used being Ruthenium-106 and Iodine-125); external radiotherapy with protons; transpupillary thermotherapy (although nowadays discarded as exclusive treatment and used in combination with other treatments) (10); and surgical endo- and exoresection of tumors. Failure to control the disease (appearance of recurrences) or the presence of side effects once these treatments have been applied will sometimes require secondary enucleation of previously treated eyes.

The purpose of the present study is to analyze survival rates for eye globes affected by uveal melanoma and subjected to conservative treatment at a healthcare center which provides all types of treatment.

SUBJECTS, MATERIAL AND METHODOLOGY

The prospective, consecutive study included patients diagnosed with choroidal melanoma bet-

ween September 1990 and April 2007 in the Ocular Oncology Unit at Valladolid's Clinical University Hospital.

All patients underwent full ocular exploration, including determination of best visual acuity (VA) with optical correction; biomicroscopy of the anterior pole; eye fundus examination with retinography and ultrasonography B-mode with vector A; and measurements of the tumor. Other imaging techniques such as magnetic resonance (MR) and/or computerized axial tomography (CAT) were used in the case of media opacities and/or extensive retinal detachment which hindered adequate assessment of the tumor size, and also to confirm the existence of extraocular extension. In order to assess systemic extension, hepatic ultrasonographies and hepatic profiles of blood were performed.

The criterion used to diagnose melanomas is based on observation of ophthalmoscopic lesions and echographic characteristics compatible with heights over 3 mm or bases larger than 5 mm. Based on the criteria published by the «Collaborative Ocular Melanoma Study» (5,7), small-sized melanomas were defined as tumors with height less than or equal to 3.1 mm and base between 5 and 10 mm; medium-sized melanomas were 3.1-10 mm in height, the base being less than or equal to 16 mm; large-sized melanomas were over 10.1 mm high, the base exceeding 16 mm. Signs of activity were based on those described by Shields (10), i.e., the presence of orange pigment, subretinal fluid (associated retinal detachment), mushroom shape or documented growth (5), whereas the presence of druses was considered to be a sign of no activity.

The following patient-related data were registered: filiation; general background; ophthalmologic history; clinical data (date of symptoms onset, date of diagnosis and reason for diagnosis); exploration (laterality, visual acuity, intraocular pressure, iris color, invasion of the iris, rubeosis iridis, lens involvement, hemovitreous and invasion of angle structures, among others); location and size of tumors

(maximum base, base at 90 degrees, maximum height, distance from the optic nerve, distance to the fovea, location of the anterior rim, location of the posterior rim, anterior or posterior location, temporal or nasal location, number of affected quadrants, macular involvement and shape of tumors: flat, nodular or mushroom); signs of activity; causes for decreased visual acuity due to melanoma (cataract, glaucoma, hemovitreal, retinal detachment, subretinal hemorrhage, macular edema or macular tumor); extraocular extension tests; systemic extension tests; melanoma classification; treatments; and the presence of metastasis.

Questionnaires were filled based on questions posed to patients, exploration and additional tests performed. The person responsible for collecting the data from the questionnaires was an ophthalmologist (assistant, resident or master student) from the unit. Once each questionnaire was completed, it was codified in a Microsoft® Access® database designed after obtaining the patient's informed consent. The person in charge of codifying the data was also an ophthalmologist (resident, master student or assistant) from the unit.

Treatment Protocol

Brachytherapy was prescribed for medium-sized or small-sized tumors whose growth had been documented. It was also indicated for patients with large tumors who rejected enucleation or in those cases where only one eye was affected.

Tumors classified as small-sized presented no signs of activity.

External radiotherapy with protons was indicated for tumors whose proximity to the optic nerve advised against the use of episcleral radiotherapy and for large-sized tumors (height > 10 mm and/or base > 16 mm) which had received conservative therapy.

Transpupillary thermotherapy was used only as adjuvant treatment of the above.

Surgical excision was indicated in patients with medium-sized pre-equatorial tumors not susceptible of treatment with brachytherapy.

Patients presenting large tumors, unrecoverable visual function, invasion of the optic nerve, extraocular extension, diffuse flat infiltrative tumors or patients who for psychological reasons rejected conservative treatment were subjected to enucleation.

Assessment of Results and Follow-Up

Patients were checked at the Ocular Oncology Unit every 6 months for the next 5 years and subsequently underwent annual check-ups aimed at assessing the appearance of complications and confirming treatment efficacy. Check-ups included visual acuity, biomicroscopy of the anterior pole, intraocular pressure, eye fundus and ultrasound exploration. Treatment was deemed successful when tumors ceased to grow or had decreased in size in subsequent ultrasound controls (11). During check-ups, hepatic ultrasonographies and hepatic profiles were requested in order to discard systemic extension of the disease.

Statistical Treatment

The data obtained from the historical cohort study are shown in the frequencies tables. Survival rate for eye globes was estimated using the Kaplan-Meier survival analysis. Values where $p < 0.05$ were considered statistically significant. SPSS™ Version 12.0 (SPSS Inc, Chicago, Illinois, USA) statistical software was used to perform the statistical analysis.

RESULTS

Epidemiological and Tumor Profile of Patients included in the Study

The study included 273 patients diagnosed with uveal melanoma and treated or observed between January 1990 and April 2007.

Mean age was 61.48 years (standard deviation: 14.64; minimum: 16; maximum 93). No differences were observed in terms of gender and laterality (table I). Mean follow-up time was 53.46 months (standard deviation: 37.73; minimum: 27; maximum 117).

Primary Treatment

193 patients were treated with conservative therapies (70.69%), while 80 underwent primary enucleation (29.30%). Table II shows the above data broken down according to the treatment prescribed.

Table I.

	n	%
Gender		
Male	127	46.52
Female	146	53.47
Laterality		
RE	150	54.94
LE	122	44.65

Table II.

Treatment	N
Enucleation	80
Surgery	4
TTT	14
RT with protons	11
Brachytherapy	121
Observation	43
Total	273

Secondary Enucleation

Patients whose treatment had failed or suffered side effects which did not respond to any kind of treatment were subjected to secondary enucleation. Out of 193 treated patients, 14 (7.2%) underwent secondary enucleation. Table III shows the percentage of secondary enucleations based on treatment (table III).

The Kaplan-Meier survival analysis (Fig. 1) revealed that once conservative treatments were applied, the rate of eye globe conservation was 88% at 5 years and 83% at 10.

DISCUSSION

In the series under study, out of 273 patients diagnosed with uveal melanoma, 80 (29.3%)

Table III.

Treatment	n	Secondary enucleation (%)
Surgery	4	1 (25%)
TTT	14	1 (7.1%)
RT with protons	11	6 (54.5%)
Brachytherapy	121	6 (4.9%)
Observation	43	0
Total	193	14 (7.2%)

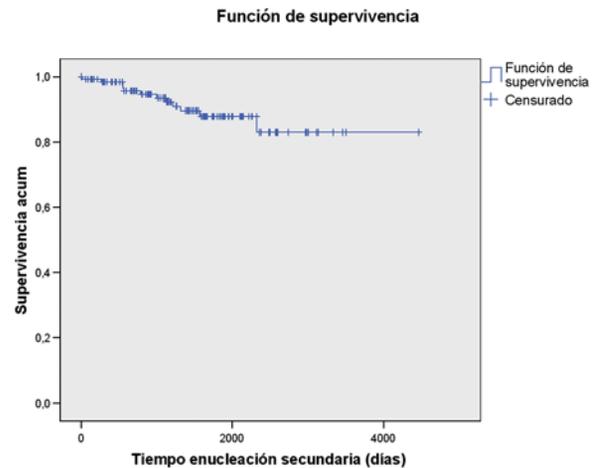


Fig. 1.

(table I) required enucleation at first, in most cases due to the presence of large tumors. Early diagnosis of this disease is of crucial importance, since it allows for the use of conservative therapies. Such conservative treatments have proven to be as efficient as enucleation as far as locally controlling the disease, while being less mutilating and capable of preserving visual function in many cases.

As for eyes treated with conservative procedures, out of 193 it was necessary to perform secondary enucleation on 14 (7.2%). The most widely used conservative treatment was episcleral brachytherapy, which in addition yielded the best results, so that out of 121 patients treated this way, only 6 (4.9%) required secondary enucleation. At this point, it should be mentioned that today the use of TTT in isolation for the treatment of choroidal melanoma is highly controversial and its use in combination with brachytherapy is advised (11).

The survival analysis revealed that survival rates for eye globes treated with conservative therapy is 88% at 5 years and 83% at 10 years, these results improving when applied only to those treated with brachytherapy.

The results of the present study may be compared with those published by the Collaborative Ocular Melanoma Study Group and Damato (12,13) as far as the percentage of secondary enucleations and rate of eye globe conservation at 5 years (Table IV).

The present study highlights the safety of conservative treatments for uveal melanoma, especially that of episcleral brachytherapy, in terms of local control of the disease and side effects. The main

Tabla IV.

Study	N	Conservative treatments %	Secondary enucleations %	Estimated rate of eye globe conservation at 5 years
Damat et al	1,632	65%	8.15%	89%
COMS report 19	638	100%	10.81%	87.5%
García-Álvarez	273	70.69	7.25%	88%

limitation is tumor size, since large tumors inevitably require enucleation, thus the crucial importance of early diagnosis.

REFERENCES

1. Singh A, Topham A. Incidence of uveal melanoma in the United States: 1973-1997. *Ophthalmology* 2003; 110: 956-961.
2. Bell JB, Wilson MD. Choroidal Melanoma: Natural History and management options. *Cancer Control* 2004; 11: 296-303.
3. Diener-West M, Earle JD, Fine SL, Hawkins BS, Moy CS, Reynolds SM, et al. Collaborative Ocular Melanoma Study Group. The COMS randomized trial of iodine 125 brachytherapy for choroidal melanoma: initial mortality findings. COMS Report No. 18. *Arch Ophthalmol* 2001; 119: 969-982.
4. Seddon JM, Gragoudas ES, Egan KM, Glynn RJ, Howard S, Fante RG, et al. Relative survival rates after alternative therapies for uveal melanoma. *Ophthalmology* 1990; 97: 769-777.
5. Augsburger JJ, Schneider S, Freyre J, Brady LW. 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.
6. Damato B. Developments in the management of uveal melanoma. *Clin Exp Ophthalmol* 2004; 32: 639-647.
7. Margo CE. The collaborative ocular melanoma study: an overview. *Cancer Control* 2004; 11: 304-309.
8. The collaborative Ocular Melanoma Study (COMS) randomized trial of pre-enucleation radiation of large choroidal melanoma: initial mortality findings. COMS report no. 10. *Am J Ophthalmol* 1998; 125: 779-796.
9. Singh AD, Rennie IG, Kivela T, Seregard S, Grossniklaus H. The Zimmerman-McLean-Foster hypothesis: 25 years later. *Br J Ophthalmol* 2004; 88: 962-967.
10. Shields CL, Cater J, Shields JA, Singh AD, Santos MC, Carvalho C. Combination of clinical factors predictive of growth of small choroidal melanocytic tumors. *Arch Ophthalmol* 2000; 118: 360-364.
11. Win PH, Robertson DM, Buettner H, McCannel CA, Bennett SR. Extended follow-up of small melanocytic choroidal tumors treated with transpupillary thermotherapy. *Arch Ophthalmol* 2006; 124: 503-506.
12. Damato B, Lecuona K. Conservation of eyes with choroidal melanoma by a multimodality approach to treatment. *Ophthalmology* 2004; 111: 977-983.
13. Jampol LM, Moy CS, Murray TG, Reynolds SM, Albert DM, Schachat AP, et al. The COMS Randomized Trial of Iodine 125 brachytherapy for Choroidal Melanoma. Local Treatment Failure and Enucleation in the First 5 Years after Brachytherapy. COMS Report No. 19. *Ophthalmology* 2002; 109: 2197-2206.