Original paper

A study comparing baseline and best-corrected visual acuity after iodine-125 episcleral brachytherapy in uveal melanoma

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Abstract

Purpose: The aim of this study was to analyze the course of visual acuity (VA) in visual outcomes of patients treated with iodine-125 (^{125}I) brachytherapy in our center, based on original VA before treatment.

Material and methods: Visual acuity was prospectively assessed using a case series of 305 patients treated with ^{125}I between 1996 and 2022. To examine how VA behaves over time, we divided patient sample into 4 groups: (1) Patients with visual acuity of less than V ≤ 0.1 at baseline; (2) Patients with low to moderate VA, ranging 0.1 < V < 0.4; (3) Patients with moderate-high VA, ranging 0.4 < V < 0.8; (4) Patients with very high VA of V > 0.8. Each of the four groups was studied separately over a 60-month period to determine the percentage of patients with VA improvement, worsening, or with the same VA status. Finally, visual outcomes over time were estimated with 95% confidence interval (CI) using Kaplan-Meier analysis, and VA maintenance rates were reported at 1, 3, 5, 10, 15, and 20 years of follow-up.

Results: The median follow-up time was 78.2 months (range, 6-254 months). The cumulative probabilities of survival analysis at 1, 3, 5, and 10 years were 16%, 3%, 2%, and none for the first sub-group; 46%, 20%, 17%, and 14% for the second; 65%, 53%, 29%, and 15% for the third; and 86%, 56%, 48%, and 41% for the fourth sub-group. The median survival in years was 0.30, 0.80, 3.10, and 4.40 for each sub-cohort, respectively.

Conclusions: The decrease and maintenance of VA depends on the initial VA of patients. Most patients experience a marked worsening of their VA, regardless of their VA status before treatment with episcleral brachytherapy. Patients with a higher baseline VA retain VA best over time.

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Key words: uveal melanoma, outcomes, visual acuity.

Purpose

Uveal melanoma is the most common primary malignant intraocular tumor in adults, with an annual age-adjusted incidence of 5.1 per million cases [1]. It used to be treated by enucleation, but since the Collaborative Ocular Melanoma Study (COMS) publication, plaque brachytherapy is assumed to play an important role in the treatment of posterior uveal melanoma [2, 3]. According to the COMS classification system, brachytherapy was indicated in the following three conditions: small melanomas, with a documented tendency to grow or with clear signs of activity; all medium-sized melanomas; and some large melanomas, with a reasonable potential for preserving vision upon patient consent [4, 5]. Although this procedure is effective, it can lead to various ocular complications [6-8], and often results in significant loss of visual acuity (VA) because of high radiation dose. There are several reasons for this, but the main side effects include retinopathy, maculopathy, cataract, neovascular glaucoma, and nerve atrophy. The severity depends primarily on the amount of incidental irradiation to various tissues and ocular structures that are radiosensitive [9].

Duration of treatment does not seem to be particularly important in the occurrence of late toxicity related to radiobiological dose [10, 11]. However, in a recent study by Miguel *et al*., statistically significant variables for visual loss were found in a multivariate model, such as apical height, plaque size, juxtapapillary location, and dose to foveola [12]. Multivariate studies conducted by various authors revealed significant values in many different characteristics depending on variables analyzed, including larger size [13, 14], lesser distance to fovea or macula [13, 15], lesser distance to optic nerve [6, 16], dose

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to optic nerve [14, 17], dose to sclera [14], dose to macula [14], high macular dose rates [18], older age [13], younger age [17], initial VA [17], retinal invasion before treatment [19], tumor shape [20], plaque shape [20], diabetes mellitus [21], and serous macular detachment [22]. Numerous studies have shown that lower irradiation doses were correlated with lower rates of visual loss [23].

The aim of the present study was to analyze the course of VA in patients treated with ^{125}I brachytherapy based on pre-treatment VA evaluation.

Material and methods

Patients diagnosis, treatment, workflow, and treatment features

Patients prospectively and consecutively treated with ^{125}I (ROPES [24] and COMS [25]) plaques for uveal melanoma in the Intraocular Tumors Unit of Intraocular Tumors Unit Intraocular Tumors Unit, Valladolid University Hospital, Valladolid, Spain from January 1, 1996, to May 1, 2022 were included in this study. Patients treated with transpupillary thermotherapy before brachytherapy were excluded.

All patients were initially examined by an ophthalmologist experienced in ocular oncology, and diagnosed with choroidal melanoma. Brachytherapy was performed according to standard protocol of the American Brachytherapy Society (ABS) guidelines [26-28]. The ophthalmologist and oncologist outlined the target, and plaque size was chosen to include the basal margin. The radiation oncologist defined clinical target volume (CTV) considering tumor thickness from B-scan sonography images and safety margin extension of 1-2 mm in all directions. Planning target volume (PTV) could be added by the radiation oncologist in case of a doubt regarding plaque localization or tumor delineation [29].

Applicators were sutured to the sclera and removed after an appropriate time. Tumors were located by transillumination and indirect ophthalmoscopy. Prescribed dose to the tumor apex was 85 Gy in all cases. Plaque heterogeneity correction functions were incorporated in treatment planning. Moreover, collimation of dose through the lip on the gold alloy base and global attenuation factor accounting for the effect of plaque seed in the eye were applied. All patients signed an informed consent form, after being duly informed about possible side effects. Before treatment, the following information were obtained: treatment duration, plaque size, number of seeds (in case of iodine plaques), total activity, and distribution of ^{125}I seeds required to apply the prescribed dose to target volume.

Regular follow-up visits were performed at 1, 3, 6, and 12 months, every 6 months from 1 to 5 years after therapy, and annually thereafter, if local control had been achieved. In practice, the number of revisions may be higher in many patients during the first 5 years, mainly because of special surveillance, and follow-up times may also vary because of hospital stay scheduling. All patients underwent a complete ophthalmologic examination, including Snellen VA measurements.

Visual acuity definition and study groups

Visual acuity is defined as a reciprocal of ratio between the letter size a patient can evaluate and the size a standard eye can recognize. Pre-operatively and post-operatively, VA was recorded in decimal logarithmic scale (V). Linear scales are not meant for clinical records, but they are required for statistical purposes They convert the progression of V values into a linear one, based on Weber-Fechner law stating that proportional increases in stimulus lead to linear increases in perception. One of the most used scales is a VA score (VAS) that relates to V as follows [30]: VAS = 100 + 50 log V. This score is more intuitive because it indicates higher values. On this scale, the value of 100 (V = 1) corresponds to normal vision, while the value of 50 (V = 0.1) represents the limit of legal blindness in our country.

To determine how VA changes over time as a function of pre-treatment VA, the total cohort was divided into 4 groups: (1) Patients who previously had an initial VA of $V \leq 0.1$ (VAS ≤ 50); (2) Patients who could see but had a low to moderate VA, ranging $0.1 < V \leq 0.4$ ($50 < VAS \leq 80.1$); (3) Patients with medium-high VA, ranging $0.4 < V \leq 0.8$ ($80.1 < VAS \leq 95$); and (4) Patients with a very high VA that in this study was considered as $V > 0.8$ (VAS > 95).

Each of the four groups was studied separately over a 60-month period time to determine the percentage of patients with VA improvement, worsening, or remaining the same VA status. Each semester, in which VA was monitored, was compared with baseline VA values before brachytherapy. Based on our internal standards, patients were classified as having experienced VA improvement when their visual analog scale (VAS) score increased by 10%. Patients were categorized as having suffered a loss of visual acuity when their VA decreased by 10%. If a patient had more than two follow-up visits in the same semester, VA was set as a geometric mean of individual corrections in the linear scale for that semester. For enucleated patients, VA was classified as no light perception at the time of enucleation. Finally, visual outcomes over time were estimated with 95% confidence interval (CI) using Kaplan-Meier analysis, and VA maintenance rates were reported at 3, 5, 10, 15, and 20 years of follow-up. Kaplan-Meier analysis and estimation of differences with log-rank test were performed for the four groups to determine statistically significantly differences.

Statistics analysis

All analyses were performed with SPSS version 24.0 (IBM, Somers, NY, USA) and XLSTAT version 2016.02.28451 (Addinsoft). Statistical significance level was set at 0.05.

Results

Patients

From 1996 to June 2022, 305 cases of choroidal melanoma were treated with ophthalmic brachytherapy. A total of 3,618 post-treatment visual follow-up measurements were used in this study, with a median follow-up of

78.2 months (range, 6-254 months) and loss of follow-up of less than 1%. Thirty-one patients underwent an enucleation after brachytherapy. Tables 1 and 2 display baseline patient demographics, tumor characteristics, and doses to the tumor apex for each sub-cohort.

Sub-cohort 1. Initially blind patients, V ≤ 0.1. Blind

Sixty-one of the 305 patients were included in this sub-group (20% of the total cohort). The preservation of the organ was achieved in majority of patients (82%), and 11 of 61 patients were enucleated. Figure 1 shows how the percentage of patients with lost VA was greater than those whose VA maintained or even improved. A small number of patients gained VA after the intervention. However, this fact did not mean the recovery of vision even in those with a VA close to the limit. In 3 of 57 patients, the vision recovered but after one year, only one patient remained vision with V > 0.1; the rest remained blind. Despite this, a small number of patients reduced over time have gained VA, with values below the limit of 0.1.

Actuarial Kaplan-Meier curves are described in Figure 2. Visual acuity preservation rates at 1, 3, and 5 years

Table 1. Patient and tumor summary statistics for 305 eligible cases. Quantitative variables

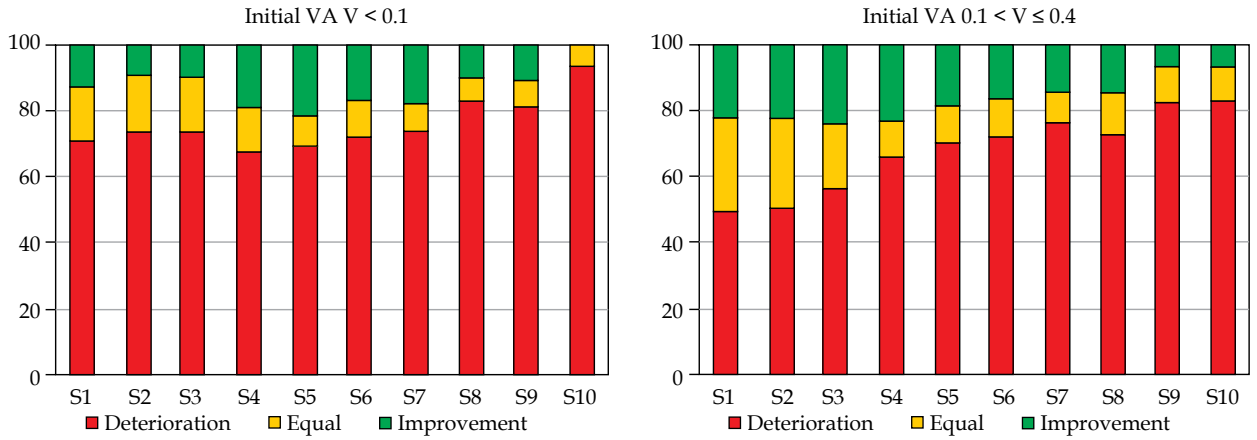
Variable		Blind		Low-medium		Medium-high		Very high	
		n	%	*n*	%	*n*	%	*n*	%
Gender	Female	25	42.6	36	49.3	52	61.2	49	57.0
	Male	34	57.4	37	50.7	33	38.8	37	43.0
Laterality	Right eye	26	44.3	43	58.9	44	51.8	45	52.3
	Left eye	35	55.7	30	41.1	41	48.2	41	47.7
Length	Nasal	13	23.0	13	17.8	21	24.7	29	33.7
	Temporal	48	77.0	60	82.2	64	75.3	56	65.1
Latitude	Inferior	27	45.9	23	31.5	33	38.8	42	48.8
	Superior	32	54.1	50	68.5	52	61.2	43	50.0
Location of anterior tumor border	Ciliary body	6	9.8	1	1.4	8	9.4	11	12.8
	Equator to ora serrata	22	37.7	25	34.2	28	32.9	33	38.4
	Posterior to equator	31	52.5	47	64.4	49	57.6	42	48.8
Location of posterior border	< 1 mm OD	8	13.1	8	11.0	7	8.2	10	11.6
	> 1 mm OD	49	83.6	65	89.0	74	87.1	69	80.2
	Ciliary body	1	1.6	0	0.0	1	1.2	0	0.0
	Equator to ora serrata	1	1.6	0	0.0	3	3.5	7	8.1
Tumor shape	Mushroom	26	44.3	16	21.9	14	16.5	15	17.4
	Diffuse	0	0.0	3	4.1	2	2.4	1	1.2
	Nodular	33	55.7	54	74.0	69	81.2	70	81.4
Juxtapapillary localization	No	49	82.0	60	82.2	77	90.6	74	86.0
	Yes	12	18.0	13	17.8	8	9.4	12	14.0
COMS	Large	7	11.5	4	5.5	3	3.5	3	3.5
	Medium	48	82.0	63	86.3	75	88.2	76	88.4
	Small	4	6.6	6	8.2	7	8.2	7	8.1
Type of plaque	COMS	44	76.7	57	78.1	73	85.9	70	81.4
	ROPES	14	23.3	16	21.9	12	14.1	16	18.6
Shape plaque	Notched	9	15.0	11	15.1	11	12.9	13	15.1
	Not notched	49	85.0	62	84.9	74	87.1	73	84.9

Juxtapapillary choroidal melanoma is considered with a posterior margin within 1 mm of the optic disc (OD)

Table 2. Patient and tumor summary statistics for 305 eligible cases. Qualitative variables

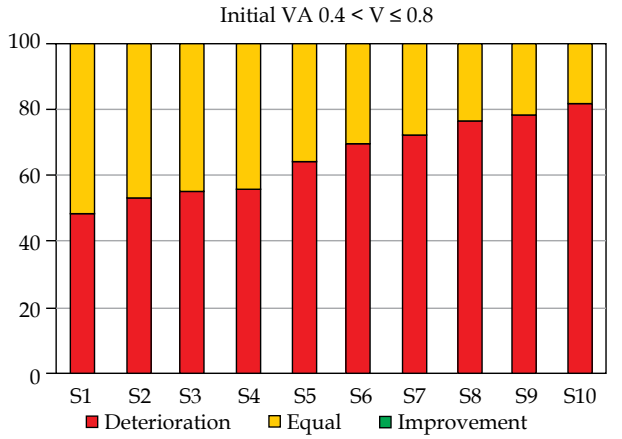
Variable	Blind		Low-medium		Medium-high		Very high	
	Median	SD	Median	SD	Median	SD	Median	SD
Age (years)	62.0 (18-91)	15.5	60.2 (16- 91)	15.7	64.2 (20-88)	13.0	56.7 (23-82)	12.9
Tumor apical height (mm)	6.4 (1.2-11.5)	2.7	5.6 (1.8-10.7)	2.4	5.0 (1-12.1)	2.16	4.7 (1.5-10.6)	2.2
Longest basal dimension (mm)	12.2 (5-17.4)	2.6	11.9 (6.1-20.5)	2.8	10.8 (5.0-16.3)	2.4	10.9 (4.5-18.1)	2.7
Apex dose (Gy)	85.8 (68.8-95.7)	4.2	85.5 (74.7-93.3)	3.6	85.6 (75.4-127.2)	7.0	85.6 (76.8-109.8)	4.2

SD – standard deviation

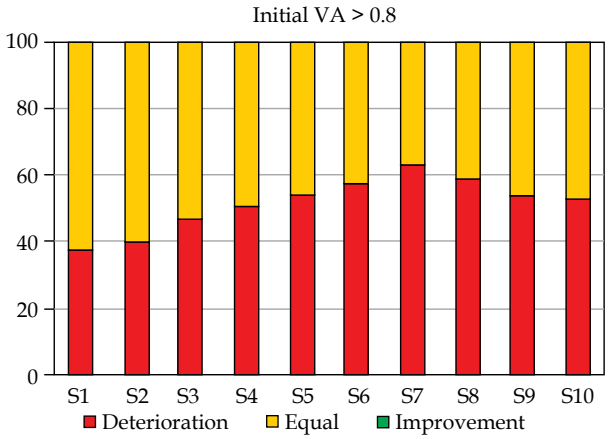


	S1	S2	S3	S4	S5	S6	S7	S8	S9	S10
MV	1	4	7	14	15	21	23	27	30	41
Det. (%)	71.4	73.6	74.0	67.4	69.1	72.2	73.5	83.3	81.5	93.8
Equal (%)	16.1	17.0	16.0	14.0	9.5	11.1	8.8	6.7	7.4	6.3
Impr. (%)	12.5	9.4	10.0	18.6	21.4	16.7	17.7	10.0	11.1	0.0

	S1	S2	S3	S4	S5	S6	S7	S8	S9	S10
MV	0	6	11	12	19	23	28	32	34	45
Det. (%)	49.3	50.8	56.5	65.6	70.4	72.0	76.0	73.2	82.1	83.1
Equal (%)	28.8	26.9	19.4	11.5	11.1	12.0	10.0	12.2	11.1	10.7
Impr. (%)	21.9	22.4	24.2	23.0	18.5	16.0	14.0	14.6	6.8	6.2



	S1	S2	S3	S4	S5	S6	S7	S8	S9	S10
MV	1	4	14	20	24	30	39	43	48	58
Det. (%)	47.6	52.6	54.3	55.4	63.9	69.1	71.7	76.2	77.7	81.5
Equal (%)	52.4	47.4	45.7	44.6	36.1	30.9	28.3	23.8	22.3	18.5
Impr. (%)	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0



	S1	S2	S3	S4	S5	S6	S7	S8	S9	S10
MV	0	3	9	14	19	23	26	32	38	54
Det. (%)	37.2	39.8	46.8	50.0	53.7	57.1	63.3	59.3	54.2	53.1
Equal (%)	62.8	60.2	53.3	50.0	46.3	42.9	36.7	40.7	45.8	46.9
Impr. (%)	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0

Fig. 1. Progression of visual acuity in patients as a function of their initial visual acuity. S1-S10 are the semesters after brachytherapy, and MV show the missing value

were 16% (95% CI: 7-25%), 3% (95% CI: 0-11%), and 2% (95% CI: 0-5%), respectively. The median survival time (Table 3) was 0.3 years (95% CI: 0.2-0.4%).

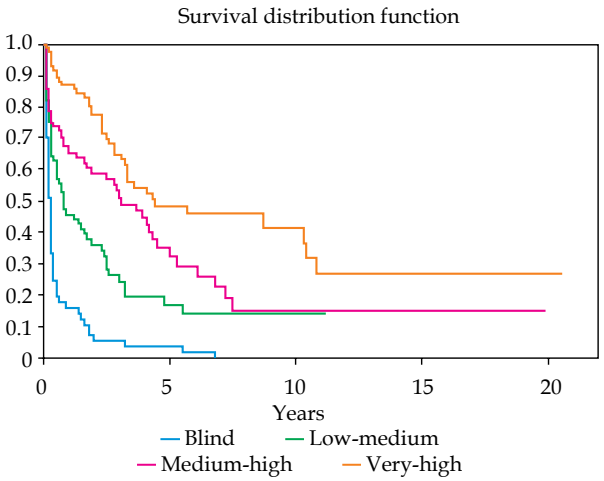
Sub-cohort 2. Patients with 0.1 < V ≤ 0.4 before brachytherapy. Low-medium

Seventy-three of the 305 patients were included in this sub-group (24% of the total cohort). The preservation of the organ was achieved in majority of patients (87%), and 10 of 73 patients were eventually enucleated. Figure 1 shows the percentage of patients who gained VA was higher than in a previous case. A significant number of patients gained VA after being subjected to the procedure, but VA deteriorated over time.

Actuarial Kaplan-Meier curves are described in Figure 2. Visual acuity preservation rates at 1, 3, 5, and 10 years were 46% (95% CI: 36-56%), 20% (95% CI: 10-30%), 17% (95% CI: 7-27%), and 14% (95% CI: 4-24%), respectively. The median survival time (Table 3) was 0.8 years (95% CI: 0.5-1.7%).

Sub-cohort 3. Patients with 0.4 < V ≤ 0.8 before brachytherapy. Medium-high

Eighty-five of the 305 patients were included in this sub-group (28% of the total cohort). For patients with baseline medium-high VA (0.4 < V ≤ 0.8), the preservation of the organ was achieved in majority of patients (95%), and 4 of 85 patients were enucleated.



Survival probability in % of function depending on different initial visual acuity

	1 year	3 years	5 years	10 years	15 years	20 years
Blind	16	3	2	–	–	–
Low-medium	46	20	17	14	–	–
Medium-high	65	53	29	15	15	15
Very-high	87	56	48	41	27	27

Fig. 2. Actuarial Kaplan-Meier for VAS ≤ 50 in patients depending on different initial visual acuity

Table 3. Median survival time (years) of patients with different baseline conditions of visual acuity

	Median survival time (years)	Lower bound (95%)	Upper bound (95%)
Blind	0.30	0.20	0.40
Low-medium	0.80	0.50	1.70
Medium-high	3.10	1.70	4.50
Very high	4.40	3.20	10.40

Figure 2 shows that in this sub-group on average, the loss of VA was greater and the number increased with time. No patient gained VA.

Actuarial Kaplan-Meier curves are described in Figure 2. Visual acuity preservation rates at 1, 3, 5, and 10 years were 65% (95% CI: 56-74%), 53% (95% CI: 45-61%), 29% (95% CI: 15-42%), and 15% (95% CI: 3-27%), respectively. The median survival time (Table 3) was 3.1 years (95% CI: 1.7-4.5%).

Patients with V > 0.8 before brachytherapy. Very high

Eighty-six of the 305 patients were included in this sub-group (28% of the total cohort). For patients with high initial VA (V > 0.8), the preservation of the organ was achieved in majority of patients (93%), and 6 of 86 patients were enucleated. Tables 1 and 2 display baseline patient demographics, tumor characteristics, and doses to the tumor apex for the study population.

Figure 1 presents the loss of VA as the most numerous events. No patient improved his VA during follow-up visits. Most patients maintained their initial VA values but with time, these values were reduced till half. As in the previous cohort, no patient gained VA.

Actuarial Kaplan-Meier curves are described in Figure 2. VA preservation rates at 1, 3, 5, 10, and 15 years were 86% (95% CI: 80-92%), 56% (95% CI: 46-66%), 48% (95% CI: 35-61%), 41% (95% CI: 26-56%), and 27% (95% CI: 10-43%), respectively. The median survival time (Table 3) was 4.4 years (95% CI: 3.2-10.4%).

Log-rank test

Figure 2 shows survival curves for the relevant variables of multivariate analysis, where the curves are separated according to their initial VA. All four groups analyzed with log-rank test reported $p < 0.05$, so the survival curves differed significantly. Figure 2 demonstrates the median survival time for each sub-group and survival rates for 1, 3, 5 10, 15, and 20 years.

Discussion

In this report, we present our experience with VA outcomes after plaque brachytherapy in a large series of patients from a single center. The results accurately reflect the outcomes in this center, and provide a useful internal audit. A multicenter study with a larger patient population could confirm or refute the results. Visual acuity measurement can be challenging, because there are no specific standards for the type of use, for which the test is designed [31]. This highlights difficulties in comparing studies from different institutions and various patient populations. Although the organ was preserved in the majority of patients (95%), a significant number of cases experienced a decline in VA as a result of therapy. The actuarial five-year eye preservation rate was 90%. The COMS Report 18 [32] provides enucleation results of 12.5% at 5 years. The decrease and maintenance of VA, as shown in this study, depend on the initial VA of patients. In this way, patients with a low to medium VA seem to benefit the most from brachytherapy. However, on average, VA worsens over time after treatment. Patients with good baseline VA have, on average, more time remaining vision with a VAS > 50 than those with a lower baseline VA. Some of the blind or moderately sighted patients gain VA from treatment, improving their initial examination score. Therefore, VA will almost inevitably decrease after treatment, although less rapidly if the initial acuity is higher.

In cases experiencing a decline in visual acuity following cataract treatment, whether due to radiation or other factors, surgery may offer the opportunity to recover a significant portion of lost visual acuity. However, the visual outcomes of patients in our series were comparable with results of other reported studies [13, 14, 33], and the outcome of VA test was worse on average over time.

Char *et al.* [34] reported that the risk of vision loss was greatest immediately after treatment and decreased over time. After 3 years, 36% of the eyes had 6/12 (> 0.5) or better VA score in a retrospective analysis of 230 patients treated with brachytherapy. The COMS 18 Report 18 [32] found that 50.1% of COMS participants still had usable

vision at 36 months. The results of the current study provide significantly lower values for all sub-groups investigated.

Study limitations

Uveal melanomas are linked with two primary factors contributing to vision loss, which are somewhat intertwined with exudative retinal detachment and radiation exposure. As a result, it can be challenging to attribute vision impairment solely to brachytherapy. Furthermore, anterior uveal and large posterior melanomas commonly lead to cataracts, resulting in temporary vision loss that can impact outcomes.

Our retrospective study reports the outcomes of treatment of patients with choroidal melanoma in Spain from 1996 to 2022. However, this study has several limitations. The most important is that the initial visual acuity and even the final visual outcomes, depend on several factors. For example, low initial visual acuity may depend on a small tumor near the macula with serous detachment of the fovea, or a large tumor with extensive detachment and hemorrhage. Although both patients may have the same vision at baseline, their outcomes are likely to be different. Conversely, a large tumor in the anterior segment of the eye may not interfere with central vision more than a small tumor in the mid-periphery, but again, outcomes will be different. The present study makes no attempt to account for these variables; it considers only pre-treatment vision as an explanatory variable. Second, the outcome depends on how actively and by what method unavoidable side effects of irradiation are treated, e.g., enucleation vs. anti-VEGF with cyclophotocoagulation for neovascular glaucoma, different intravitreal injections for radiation maculopathy and radiation optic neuropathy, etc. These complications and their treatment strategies (which are likely to evolve during the study period) are not described and analyzed in the manuscript.

Another limitation is that Kaplan-Meier curves behave poorly in tails, and the reliability of estimates is intuitively poor with less than 10% of patients remaining in the cohort. The second limitation is the amount of lost data in the last tracking intervals. Despite these limitations, this review provides truly valuable information on treatment outcomes in VAS after episcleral brachytherapy.

Conclusions

Most patients experience a marked worsening of their VA regardless of their VA prior to treatment with episcleral brachytherapy. Patients with a higher baseline VA best maintain VA over time. Episcleral brachytherapy cannot prevent the loss of visual acuity, especially in advanced cases, or when the tumor caused significant damage before treatment. Blindness is virtually irreversible, even when the disease is controlled locally.

Disclosure

The authors report no conflict of interest.

References

1. Singh AD, Turell ME, Topham AK. Uveal melanoma: trends in incidence, treatment, and survival. *Ophthalmology* 2011; 118: 1881-1885.
2. Margo CE. The Collaborative Ocular Melanoma Study: an overview. *Cancer Control* 2004; 11: 304-309.
3. Rao YJ, Sein J, Badiyan S et al. Patterns of care and survival outcomes after treatment for uveal melanoma in the post-coms era (2004-2013): a surveillance, epidemiology, and end results analysis. *J Contemp Brachytherapy* 2017; 9: 453-465.
4. Singh AD, Kivelä T. The collaborative ocular melanoma study. *Ophthalmol Clin North Am* 2005; 18: 129-142.
5. Markiewicz A, Skórkiewicz K, Bogdał A et al. Ophthalmic applicator displacement as a method of treating large diffuse uveal melanomas. *J Contemp Brachytherapy* 2023; 15: 184-190.
6. Jensen AW, Petersen IA, Kline RW et al. Radiation complications and tumor control after 125I plaque brachytherapy for ocular melanoma. *Int J Radiat Oncol Biol Phys* 2005; 63: 101-108.
7. Fionda B, Pagliara MM, Lancellotta V et al. Radiological and clinical findings in uveal melanoma treated by plaque interventional radiotherapy (brachytherapy): Visual atlas and literature review on response assessment. *J Contemp Brachytherapy* 2022; 14: 96-106.
8. Wong AJ, Teh BS, Nguyen BT et al. Three-year outcomes of uveal melanoma treated with intra-operative ultrasound-guided iodine-125 brachytherapy using custom-built eye plaques. *J Contemp Brachytherapy* 2022; 14: 130-139.
9. Parsons JT, Bova FJ, Mendenhall WM et al. Response of the normal eye to high dose radiotherapy. *Oncology* 1996; 10: 837-847.
10. Miguel D, de Frutos-Baraja JM, López-Lara F et al. Radiobiological doses , tumor , and treatment features influence on local control, enucleation rates, and survival after episcleral brachytherapy. A 20-year retrospective analysis from a single-institution: part I. *J Contemp Brachytherapy* 2018; 10: 337-346.
11. Miguel D, de Frutos-Baraja JM, López-Lara F et al. Radiobiological doses , tumor , and treatment features influence on outcomes after episcleral brachytherapy. A 20-year retrospective analysis from a single-institution: part II. *J Contemp Brachytherapy* 2018; 10: 347-359.
12. Miguel D, Frutos-Baraja JM de, López-Lara F et al. Visual outcome after posterior uveal melanoma episcleral brachytherapy including radiobiological doses. *J Contemp Brachytherapy* 2018; 10: 123-131.
13. Khan N, Khan MK, Bena J et al. Plaque brachytherapy for uveal melanoma: a vision prognostication model. *Int J Radiat Oncol Biol Phys* 2012; 84: 285-290.
14. Wagner A, Chen A, Cook T et al. Outcomes and control rates for I-125 plaque brachytherapy for uveal melanoma: A community-based institutional experience. *ISRN Ophthalmol* 2014; 2014: 1-7.
15. Belaïd A, Nasr C, Jmour O et al. Brachytherapy of uveal melanomas with ruthenium-106 plaques. *Asian Pac J Cancer Prev* 2016; 17: 6181-6185.
16. Naseripour M, Aghaei H, Sedaghat A et al. Corneal patch graft: A new approach for scleral necrosis secondary to plaque radiotherapy. *Cornea* 2016; 35: 565-568.
17. Aziz HA, Singh N, Bena J et al. Vision loss following episcleral brachytherapy for uveal melanoma. *JAMA Ophthalmol* 2016; 134: 615-620.
18. Jones R, Gore E, Mieler W et al. Posttreatment visual acuity in patients treated with episcleral plaque therapy for choroidal melanomas: dose and dose rate effects. *Int J Radiat Oncol Biol Phys* 2002; 52: 989-995.

19. Shields CL, Naseripour M, Cater J et al. Plaque radiotherapy for large posterior uveal melanomas (>8-mm thick) in 354 consecutive patients. *Ophthalmology* 2002; 109: 1838-1849.
20. Naseripour M, Jaberi R, Sedaghat A et al. Ruthenium-106 brachytherapy for thick uveal melanoma: reappraisal of apex and base dose radiation and dose rate. *J Contemp Brachytherapy* 2016; 8: 66-73.
21. Packer S, Rotman M. Radiotherapy of choroidal melanoma with iodine-125. *Ophthalmology* 1980; 87: 582-590.
22. Lumbroso-Le Rouic L, Charif Chefchaouni M, Levy C et al. 125I plaque brachytherapy for anterior uveal melanomas. *Eye* 2004; 18: 911-916.
23. Perez BA, Mettu P, Vajzovic L et al. Uveal melanoma treated with iodine-125 episcleral plaque: An analysis of dose on disease control and visual outcomes. *Int J Radiat Oncol Biol Phys* 2014; 89: 127-136.
24. Granero D, Pérez-Calatayud J, Ballester F et al. Dosimetric study of the 15 mm ROPES eye plaque. *Med Phys* 2004; 31: 3330-3336.
25. Chiu-Tsao ST, Astrahan MA, Finger PT et al. Dosimetry of (125)I and (103)Pd COMS eye plaques for intraocular tumors: report of Task Group 129 by the AAPM and ABS. *Med Phys* 2012; 39: 6161-6184.
26. Nag S, Quivey JM, Earle JD et al. The American Brachytherapy Society recommendations for brachytherapy of uveal melanomas. *Int J Radiat Oncol Biol Phys* 2003; 56: 544-555.
27. Simpson ER, Gallie B, Laperrierre N et al. The American Brachytherapy Society consensus guidelines for plaque brachytherapy of uveal melanoma and retinoblastoma. *Brachytherapy* 2014; 13: 1-14.
28. Chevli N, Zuhour RJ, Messer JA et al. Contemporary trends in management of uveal melanoma. *J Contemp Brachytherapy* 2022; 14: 123-129.
29. Gagne NL, Rivard MJ. Quantifying the dosimetric influences of radiation coverage and brachytherapy implant placement uncertainty on eye plaque size selection. *Brachytherapy* 2013; 12: 508-520.
30. Masin SC, Zudini V, Antonelli M. Early alternative derivations of Fechner's law. *J Hist Behav Sci* 2009; 45: 56-65.
31. Ferris FL, Bailey I. Standardizing the measurement of visual acuity for clinical research studies: Guidelines from the Eye Care Technology Forum. *Ophthalmology* 1996; 103: 181-182.
32. Jampol LM, Moy CS, Murray TG et al. The COMS randomized trial of iodine 125 brachytherapy for choroidal melanoma: IV. Local treatment failure and enucleation in the first 5 years after brachytherapy. COMS report no. 19. *Ophthalmology* 2002; 109: 2197-2206.
33. Melia BM, Abramson DH, Albert DM et al. Collaborative ocular melanoma study (COMS) randomized trial of I-125 brachytherapy for medium choroidal melanoma. I. Visual acuity after 3 years COMS report no. 16. *Ophthalmology* 2001; 108: 348-366.
34. Char DH, Kroll S, Quivey JM et al. Long term visual outcome of radiated uveal melanomas in eyes eligible for randomisation to enucleation versus brachytherapy. *Br J Ophthalmol* 1996; 80: 117-124.