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Clinical characteristics of medium and large T1-T4 choroidal melanomas in Ukraine

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Purpose. *To evaluate the clinical characteristics of medium to large T1-T4 choroidal melanomas (CM) in patients treated at SI "The Filatov Institute of Eye Diseases and Tissue Therapy of the NAMS of Ukraine".*

Material and Methods. *We retrospectively reviewed the medical records of 283 patients treated for medium to large CM at SI "The Filatov Institute of Eye Diseases and Tissue Therapy of the NAMS of Ukraine" in 2007-2024. The study sample consisted of 125 men (44.2%) and 158 women (55.8%), with a mean age (standard deviation (SD)) of 54.2 (12.4) years. Patients underwent standard ophthalmological examination. Additionally, they received ocular ultrasonography using a Cinescan ultrasound system, OCT examination using a Stratus OCT 300 system and fluorescein angiography. No metastasis was detected in any patient at presentation and the start of treatment.*

Results. *The case distribution included stage T1 in 15 patients (5.3%), stage T2 in 132 patients (46.64%), stage T3 in 115 patients (40.64%), and stage T4 in 21 patients (7.42%). Paramacular and peripheral locations of CM were more common in the total sample (88.4%) ($p < 0.05$), and stages T2 (59 [44.7%] and 53 [40.15%], respectively) and T3 (60 [52.17%] and 50 [43.48%], respectively), and were the only two locations seen in stage T4 (10 [47.62%] and 11 [52.38%], respectively). Parafoveal and juxtapapillary tumor locations were seen in stages T1 to T3 (10 [3.53%] and 23 [8.13%], respectively, of the 283 patients), and were more common in stage T2 (6 [60.0%] and 14 [60.87%], respectively). Heterogeneously pigmented CM were most common (132 [46.64%]), followed by mildly pigmented (104 [36.75%]), pigmented (41 [14.49%]) and amelanotic (6 [2.12%]). There were no amelanotic cases in stages T1 and T4. Mildly pigmented CM were present among tumors of any stage, and were most common in stage T2 (60 [21.2%]). Heterogeneously pigmented and pigmented CM were present among tumors of any stage, and were more common in stages T3 (62 [53.91%]) and T2 (54 [40.91%]). T4 tumors were predominantly heterogeneously pigmented and pigmented (13 [61.9%] and 5 [23.81%], respectively) ($p < 0.05$). Among 283 cases of CM, 147 (147 (51.9%) were dome-shaped, 73 (25.8%) were mushroom-shaped, 54 (19.1%) were finger-shaped and 9 (3.2%) were multilobulated. All patients had diffuse tumors without distinct borders, with a secondary retinal detachment above and around the tumor.*

Conclusion. *We examined the clinical signs depending on the stage of CM. These signs have a prognostic value for the efficacy of treatment, which will be reported subsequently.*

Key words:

ophthalmic oncology, choroidal melanoma, tumor stage, retina, choroid, transpupillary therapy, ionizing radiation

Introduction

Melanoma is one of the most aggressive tumors in humans; it is a tumor of melanocytic origin that is most commonly cutaneous. In analyses of the United States National Cancer Data Base (NCDB) performed on cases diagnosed between 1985 through 1994, a total of 84,836 cases comprised of cutaneous and noncutaneous melanomas were evaluated, and the percentage of melanomas that were ocular was 5.2% [1].

Approximately 90% of uveal melanomas (UM) develop in the choroid, 7% in the ciliary body and 3% in the iris [2-8].

Recently, the incidence per 100,000 for UM has tended to increase, ranging from 0.6 to 2.2. Additionally, the diagnosis is made in increasingly younger individuals, about 1 case per million occurs in the less than 20 years age group, the incidence increases more than seven-fold after the age of 30, the average patient age ranges from 50.9 to 62.5 years, and most patients are men [1, 3, 9-14].

An analysis of the Surveillance, Epidemiology, and End Results (SEER) database from 1992 to 2000 reported

that the majority (98.0%) of cases of UM occurred in the White population. Intrinsic host factors that predispose Caucasians to uveal melanoma include ancestry from northern latitudes, fair skin color, light eye color, and propensity to sunburn. Moreover, the analysis reported that the annual age-adjusted incidence per million for UM was 0.31 in Blacks, 0.38 in Asian and Pacific Islanders, 1.67 in Hispanics, and 6.02 in non-Hispanic Whites [15].

The incidence per million for UM in Ukraine has been reported to range from 8 cases to 10 cases, with a steady increase in the incidence [16].

The outcome of treatment for UM depends mostly on its clinical signs, including primary size (especially tumor base), pigmentation, location, presence of extension into the ciliary body or extrascleral extension, cellular tumor type, tumor vascularization, and genetic and molecular changes (a high mytosis rate, loss of chromosomes 3 and 1p and/or gain of chromosomes 6p and 8q) [17-20].

Because the eye-preserving treatment for UM is undoubtedly feasible, it is important to determine which clinical characteristics of the tumor should be taken into account while selecting the strategy of treatment in an effort to improve local control, visual outcome, patient survival and quality of life.

The purpose of the study was to evaluate the clinical characteristics of patients that were treated for medium to large T1-T4 choroidal melanoma (CM) at SI "The Filatov Institute of Eye Diseases and Tissue Therapy of the National Academy of Medical Sciences of Ukraine".

Material and Methods

We retrospectively reviewed the medical records of 283 patients that received an eye-sparing treatment (transpupillary thermotherapy (TTT) combined with strontium-90 (Sr90)/ yttrium-90 (Yt90) brachytherapy (BT)) for medium to large T1 to T4 UM at SI "The Filatov Institute of Eye Diseases and Tissue Therapy of the National Academy of Medical Sciences of Ukraine" in 2007-2024.

The study sample consisted of 125 men (44.2%) and 158 women (55.8%), with a mean age (standard deviation (SD)) of 54.2 (12.4) years and the age ranging from 20 to 86 years. The right eye was affected in 148 patients (52.3%), and the left eye in 135 patients (47.7%).

Tumor stage was determined using the 2018 American Joint Commission on Cancer Tumor, Node and Metastases (TNM) classification scheme (Table 1) [21].

Patients underwent standard ophthalmological examination including visual acuity measurement, tonometry, refractometry, visual fields, biomicros-copy and ophthalmoscopy. Additionally, they received ocular ultrasonography using a Cinescan (Quantel Medical, Clermont-Ferrand, France) ultrasound system, OCT examination using a Stratus OCT 300 system (Carl Zeiss Medi-tec, Dublin, CA) and fluorescein angiography.

Moreover, patients underwent ultrasonography or magnetic resonance imaging of the liver, fluorography, and X-ray or computed tomography of the lung for detection of potential metastasis. No metastasis was detected in any patient at presentation and the start of treatment.

An MS Access database was developed to store, organize and retrieve the data associated with the results of examination and treatment of patients with CM. Numerical parameters were entered as numerical data, and clinical characteristics as ordinal data. Data were analyzed using JASP (JASP Team (2024). JASP (Version 0.95.0) Computer software, Amsterdam, the Netherlands). Mean and standard deviation (SD) were calculated for quantitative data.

For comparisons involving quantitative parameters in more than two groups, one-way analysis of variance (ANOVA) was used. When ANOVA demonstrated significant differences among the groups, pair-wise comparisons were tested by Fisher or Newman-Keuls post-hoc tests [22]. Student t-test was also used to assess differences in quantitative parameters. P values ≤ 0.05 were considered significant.

Results

Ocular complaints at presentation included flashes of light or lightning-like streaks (250 patients [88.3%]), decreased vision (165 patients [58.3%]), and a dark spot in front of the eye (10 patients [3.5%]). In 60 patients (21.2%), the tumor was detected by chance.

Patients were assigned to one of the four visual acuity categories: 0 (total blindness), 1 (light perception to 0.1),

Table 1. Tumor stage according to the Tumor Nodule Metastasis (TNM) classification system in tumors with different thicknesses and diameters

Tumor thickness, mm	Tumor stage (T)						
>15.0	–	–	–	–	4	4	4
12.1-15.0	–	–	–	3	3	4	4
9.1-12.0	–	3	3	3	3	3	4
6.1-9.0	2	2	2	2	3	3	4
3.1-6.0	1	1	1	2	2	3	4
≤3.0	1	1	1	1	2	2	4
Tumor diameter, mm	≤3.0	3.1-6.0	6.1-9.0	9.1-12.0	12.1-15.0	15.1-18.0	>18.0

Table 2. Distribution of patients with choroidal melanoma among categories of visual acuity

Number of patients (%)	Category of visual acuity					Total
	0 (zero)	1 (≤ 0.1)	2 (0.12-0.25)	3 (0.3-0.6)	4 (0.7-1.0)	
n (%)	1 (0.4%)	117 (41.3%)	55 (19.4)	66 (23.3)	44 (15.6)	283 (100%)

2 (0.12-0.25), 3 (0.3-0.6), or 4 (0.7-1.0). Table 2 shows the distribution of patients into these visual acuity categories.

At baseline, low visual acuity (light perception to 0.1) was most common (117 patients [41.3%]), 44 patients (15.6%) had high visual acuity (0.7-1.0), and one patient (0.4%) was totally blind (Table 2).

Maklakoff intraocular pressure (IOP) readings were normal, ranging from 18.0 to 20 mmHg. Of the 283 patients, 253 (89.40%) had visual field loss and 29 (10.25%) had no visual field loss. In one patient, visual field measure-ments could not be established due to the absence of vision.

Additionally, of the 283 patients, 90 (31.8%) had no lens opacities, 75 (26.5%) had phacosclerosis, 116 (40.99%) had lens opacities, and 2 (0.71%) had an artiphakic eye.

The case distribution included stage T1 (3.1-6.0 mm in thickness and 3.1-9.0 mm in largest base diameter) in 15 patients (5.3%), stage T2 (3.1-6.0 mm in thickness and 9.1-15.0 mm in largest base diameter; 6.1-9.0 mm in thickness and 3.1-12.0 mm in largest base diameter) in 132 patients (46.64%), stage T3 (3.1-6.0 mm in thickness and 15.1-18.0 mm in largest base diameter; 6.1-9.0 mm in thickness and 12.1-18.0 mm in largest base diameter; 9.1-12.0 mm in thickness and 3.1-18.0 mm in largest base diameter; 12.1-15.0 mm in thickness and 9.1-15.0 mm in largest base diameter) in 115 patients (40.64%), and stage T4 (3.1-12.0 mm in thickness and >18.0 mm in largest base diame-ter; 12.1-15.0 mm in thickness and 15.1->18 mm in largest base diameter) in 21 patients (7.42%).

Therefore, the majority (87.2%) of patients had T2 or T3 tumors ($p < 0.05$).

Tumors were classified into four categories based on their location with respect to the fundus: parafoveal (with the tumor margin not reaching the fovea), juxtapapillary (with the tumor intimately attached to, or located < 1 mm from the optic disc), paramacular (with one tumor margin not reaching the macula, and the peripheral tumor margin not approaching the equator), and peripheral (with the tumor located preequatorially. [23]. Fig. 1 shows the distribution of tumor locations among patients with CM T1 to T4, and Fig. 2 shows distributions of tumor location among patients with CM T1 versus T2 versus T3 versus T4.

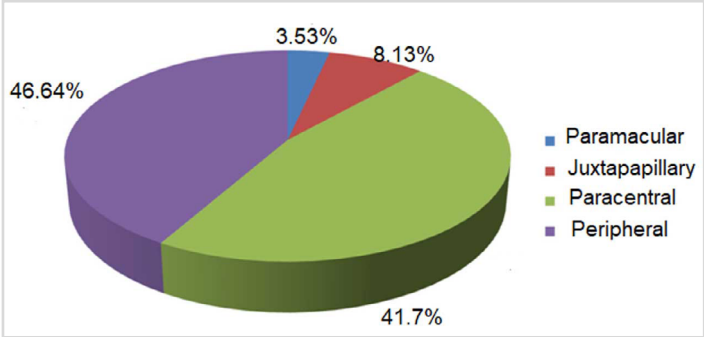

Fig. 1. Pie chart showing the distribution of location of choroidal melanomas among the total sample of patients with T1 to T4 choroidal melanoma

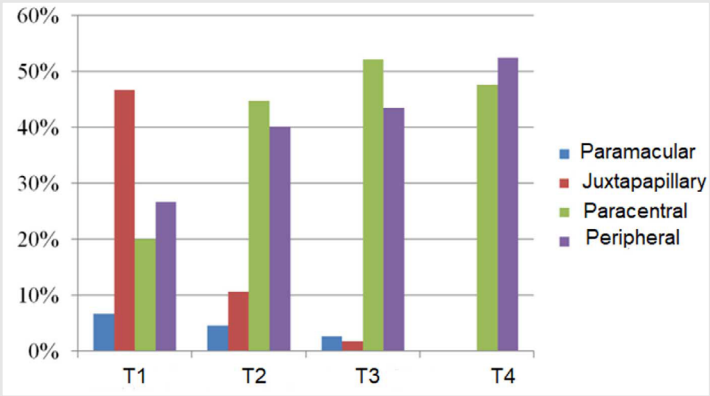

Fig. 2. Bar graphs showing distributions of tumor location among patients with T1 versus T2 versus T3 versus T4 choroidal melanoma

The majority (88.4%) of patients of the total study sample had tumors located paramacularly or peripherally. Paramacular and juxtapapillary tumor locations were seen in patients with T1 to T3 tumors (10 [3.53%] and 23 [8.13%], respectively, of the 283 patients), and were more common among pa-tients with T2 CM (6 [60.0%] and 14 [60.87%], respectively, of the 283 patients). Paramacular and peripheral tumor locations were seen in any stage of the tumor, and were more common among patients with T2 CM (59 [44.7%] and 53 [40.15%], respectively). However, only a paramacular and peripheral locations (10 [47.62%] and 11 [52.38%], respectively) were seen among pa-tients with T4 CM ($p < 0.05$).

Heterogeneously pigmented CM were most common (132 [46.64%]), fol-lowed by mildly pigmented (104 [36.75%]), pigmented (41 [14.49%]) and amelanotic (6 [2.12%]) (Fig. 3).

Amelanotic choroidal melanomas were equally common among T2 tu-mors and T3 tumors, but were not seen among T1 tumors and T4 tumors (Fig-ure 4). Mildly pigmented choroidal melanomas were present among tumors of any stage, and were more common among T2 tumors (60 [45.54%]) and T3 tumors (31 [26.96%]).

Heterogeneously pigmented and pigmented melanomas were also present among tumors of any stage, and were more common among T3 tumors (62 [53.91%]) and T2 tumors (54 [40.91%]). T4 tumors were pre-dominantly heterogeneously pigmented and pigmented melanomas t (13 [61.9%] and 5 [23.81%], respectively) ($p < 0.05$).

Among 283 cases of CM, 147 (147 (51.9%) were dome-shaped, 73 (25.8%) were mushroom-shaped, 54 (19.1%) were finger-shaped and 9 (3.2%) were multilobulated. All patients had diffuse tumors without distinct borders, with a secondary retinal detachment above and around the tumor.

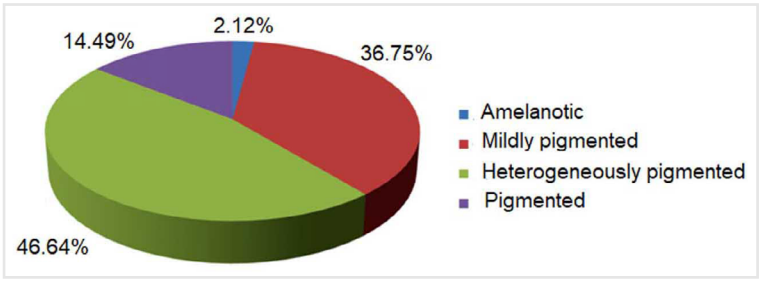

Fig. 3. Pie chart showing the distribution of types of pigmentation of choroidal melanomas among the total sample of patients with T1 to T4 choroidal melanoma

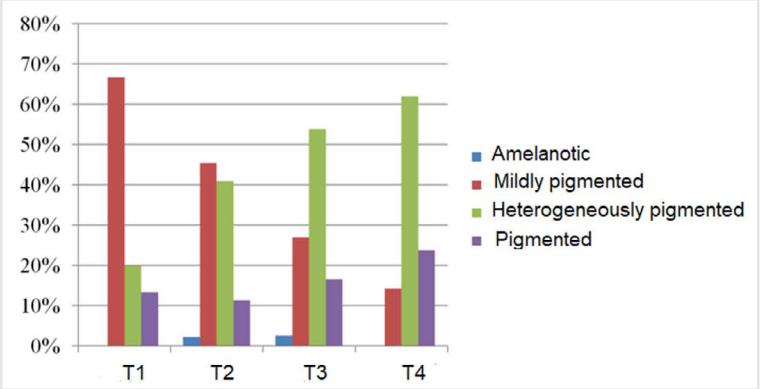

Fig. 4. Bar graphs showing distributions of types of pigmentation of choroidal melanomas among patients with T1 versus T2 versus T3 versus T4 choroidal melanoma

Discussion

In the sample of patients that received eye-saving treatment for CM, the majority (87.2%) had T2 or T3 tumors. To the best of our knowledge, most studies on the efficacy of eye-saving treatment for CM did not note the stage of the tumor, but paid attention only to the size, noting that the efficacy depended more on the largest base diameter than the amount of tumor extension into the vitreous [14, 16, 19].

Our findings are in agreement with the literature that CM more common-ly affects individuals of 50 to 60 years of age [1, 3, 9-14]. The mean age (SD) of our study sample was 54.2 (12.4) years. For the 283 patients in our sample, the mean age (SD) was 54.2 (12.4) years, with most patients being females (55.8% versus 44.2%), although the difference was not statistically significant. Left eye was affected more frequently than the right eye (52.3% versus 47.7%), but the difference was also not statistically significant ($p > 0.05$). These find-ings are in agreement with the literature [15].

In the current study, the majority (88.4%) of patients had tumors located paramacularly or peripherally ($p < 0.05$). Additionally, paramacular and peripheral tumors accounted for the majority of T2 tumors (59 [44.7%] and 53 [40.15%], respectively) and T3 tumors (60 [52.17%] and 50 [43.48%], respectively) and only paracentral and peripheral tumors were seen among T4 tu-mors (10 [47.62%] and 11 [52.38%], respectively). Parafoveal and juxtapapillary tumor locations were seen in patients with T1 to T3 tumors (10 [3.53%] and 23 [8.13%], respectively), and were more common in patients with T2 tumors (6 [60.0%] and 14 [60.87%], respectively).

To the best of our knowledge, there have been no reports on the tumor location in the fundus for different stages of CM. Shields and colleagues [24, 25] reported that small tumors are commonly macular, paramacular or juxtapapillary tumors, whereas large tumors are commonly peripheral tumors. This could be explained by the likelihood that posterior pole tumors are diag-nosed earlier than peripheral tumors [24, 25].

We did not observe amelanotic melanomas among T1 and T4 tumors. Heterogeneously pigmented tumors were most common (132 [46.64%]), fol-lowed by mildly pigmented (104 [36.75%]) and pigmented (41 [14.49%]). Mildly pigmented tumors were found in any tumor stage, and were more com-mon in T2 tumors (60 [21.2%]) than in T1, T3 or T4 tumors. Heterogeneously pigmented and pigmented tumors were also found in any tumor stage, and were more common in T3 tumors (62 [53.91%]) and T2 tumors (54 [40.91%]). Only heterogeneously pigmented and pigmented melanomas were present among T4 tumors (13 [61.9%] and 5 [23.81%], respectively). Clinical pigmentation of the tumor is an important prognostic factor of the efficacy of treat-ment for CM. Mixed/epithelial-cell melanoma is relatively rare among amelanotic and mildly pigmented melanomas and has a higher mortality rate than spindle cell melanoma [26-29].

Conclusion

We studied the clinical characteristics of medium and large T1-T4 choroidal melanomas in patients treated at the ST "The Filatov Institute of Eye Diseases and Tissue Therapy of the National Academy of Medical Sciences of Ukraine". These characteristics generally coincide with the literature data and will be used to study the efficacy of eye-sparing treatment for CM using our methodology.

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Disclosures

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Reviewing and editing the manuscript. All authors have read and approved the final version of the manuscript.

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The study was approved by the bioethics committee of SI "The Filatov Institute of Eye Diseases and Tissue Therapy of the National Academy of Medical Sciences of Ukraine" (committee minutes dated April 12, 2021), and informed consent was obtained from subjects.

Data Availability Declaration: *All the data obtained or examined during this study has been incorporated into this published article.*

Abbreviations: *UM, uveal melanoma; CM, choroidal melanoma*