doi: 10.17116/engoftalma20161322-1

Size-based classification of choroidal melanoma and its role in treatment decision-making

A.F. BROVKINA[1], A.S. STOYUKHINA[2], I.P. CHESALIN[1]

[1]Russian Medical Academy of Postgraduate Education, Ministry of Health of the Russian Federation, 2/1 Barrikadnaya St., Moscow, Russian Federation, 123995; [2]Research Institute of Eye Diseases, 11 A, B, Rossolimo St., Moscow, Russian Federation, 119021

Aim— to specify indications for brachytherapy (BT) in large choroidal melanoma (CM) so that tumor size and vital prognosis were considered. **Material and methods**. We retrospectively analyzed data from 161 CM patients who were treated with BT and followed up at either the Ophthalmological Clinical Hospital or some other Moscow medical facility and also registered by the City Cancer Registry. **Results**. Patient age at the time of starting the treatment lied within the range of 17 to 84 years and averaged 56.89±1.93 years. During the follow-up period (12-275 months, 95.65±8.4 months on average) hematogenous metastases were found in 23 (14.29%) patients. Liver involvement was diagnosed in 8 patients within the average of 23.13 months after treatment. Their average survival time was 11 months. A total of 142 patients were followed up for more than 36 months (104.87 months on average). Of them, 15 patients were diagnosed with metastatic CM within 37-167 months after BT (80.27 months on average). Despite metastatic disease they generally survived 2.8 times longer than the aforementioned patients (30.8 months). The cases were then divided into 3 groups according to J. Shields classification of CM. Small melanoma patients did not develop metastases within 99.96±12.47 months of follow-up. In medium melanomas, as many as 13.35% of cases were metastatic (with the average survival time of 20.66 months); in large melanomas— 19.51% (with the average survival time of 13.5 months). **Conclusion**. Treatment modality and follow-up periods being the same (7-8 years after BT), larger choroidal melanomas has been shown to be associated with higher risk of hematogenous metastases. For local treatment to be successive, the maximal diameter of the tumor should not exceed 10 mm. Every fifth patient of those with CM larger than 15 mm will develop hematogenous metastases. The results obtained indicate the necessity of decreasing the size thresholds for choroidal melanomas, small and medium in the first place.

Keywords: *choroidal melanoma, brachytherapy, classification of choroidal melanoma, metastatic choroidal melanoma.*

Vestnik_Oftalmologii_2016-2_4EN

Despite the almost 5-century-old doctrine of choroidal melanoma (CM), its first size-based classification suitable for determining indications for local tumor destruction, brachytherapy (BT) in particular, has only emerged in the early 1980s [1]. All the CMs were clearly divided into early (small), medium, and large lesions **(Table 1)**. The two latter forms are diagnosed most often, regardless of predominantly postequatorial (accessible for visual examination) location of the tumors. Thus, in England an average CM prominence at first presentation can reach 4.9 mm [2], in Finland — 6.3 mm [3], and in Korea — 7.8 mm [4]. In France, medium and large lesions together account for 82% of all primarily diagnosed CM cases [5], while in Russia — for 76% [6]. Solving this problem is crucial for improving the treatment of CM. Ten years after the original Shield's classification, a modified version was suggested as a result of Collaborative Ocular Melanoma Study (COMS) conducted in USA (**see Table 1**) [7, 8].

The possibility of successful local treatment of small and medium CMs has not been doubted for many years now. However, the statistically significant risk factors for hematogenous metastases are being widely discussed. These currently include not only the thickness of the tumor [4, 9], but also its maximum diameter [10, 11]. Shifting thresholds for small and medium lesions toward larger diameters by COMS has confused the limits of tumor metrical types. Thus, to estimate the related mortality, an early (small) choroidal melanoma is defined as a 2 (or 3)×10 (or 11) mm lesion; a medium CM — as a 3—8 (or 10!)×15 (or 16) mm lesion, while everything above 10 and 15 mm, correspondingly, is considered large [12—14]. Using the mentioned values for tumor prominence (3, 8, or even 10) one comes across significant variations in its thickness. Not only the two classifications differ in numbers, but also contradict each other in terms of vital prognosis. As shown by E. Kujala et al. in their long-term study of 289 CM patients, the CM-related mortality rate greatly depends on the tumor basal diameter [10]. It has been proved that early (small) CM is associated with a 16% 5-year mortality rate, while medium and large CM (tumor diameter of more than 15-16 mm) — with 32—35% [15, 10]. Moreover, the risk of metastases is 5.6 times higher for every 5-mm increase in tumor basal diameter [16]. Available data evokes contradictory attitudes toward the existing classification of choroidal melanomas at the

For correspondence:
Stoyukhina Alevtina Sergeevna – MD, PhD, senior research associate of the Department of Clinical Studies in Ophthalmology
e-mail: Alevtinast@gmail.com

Table 1. **Size-based classification of CM**

Tumor metrical type	Prominence, mm		Maximum diameter, мм	
	J.A. Shields	COMS	J.A. Shields	COMS
Small	<3	3	<10	5-16
Medium	3.1–5	3–8	10.1–15	⩽16
Large	>5	8	>15	>16

Table 2. **Patient distribution according to J. Schield's classification of CM**

Tumor metrical type	Thickness, mm	Diameter, mm	Number of patients
Small	<3	<10	27
Medium	3.1—5	10.1—15	52
Large	⩾5.1	>15	82

stage of considering local treatment in a particular patient.

This study aimed to specify indications for brachytherapy (BT) in large choroidal melanoma with tumor size and vital prognosis taken into account.

Material and methods

We retrospectively analyzed data from 161 CM patients who were treated with BT and followed up at either the Ophthalmological Clinical Hospital or some other Moscow medical facility and also registered by the City Cancer Registry. At the beginning of treatment the mean patient age was 56.89**±1.93** years (17-84 years).

All patients were re-examined (including ophthalmoscopy and ultrasound examination of the irradiated zone) every 3 months during the first two years after treatment and every 6 months thereafter. Moreover, every 6 months they underwent liver ultrasound scan and once a year — chest X-ray.

The cases were divided into 3 groups according to the J. Schield's classification of CM (**Table 2**).

Results and discussion

During 12—275 months (95.65±8.4 months on average) of follow-up of CM patients treated with BT, hematogenous metastases were found in 23 cases (14.29%) at very different terms. For example, 8 patients developed liver metastases at the average of 23.13 months after treatment and survived for about 11 months (1-30 months). A total of 142 patients were followed up for more than 36 months (104.87 months on average). Of them, 15 patients appeared to have metastases at some point between 37 and 167 months after BT (80.27 months on average) and showed a 2.8 times longer survival than the previous group (30.8 months). Contradictory opinions exist as to the speed at which choroidal melanoma metastasizes. It is believed that 80% of patients die within the first year and 92% — within the first two years after being diagnosed with metastatic CM [17]. However, according to some authors [4], it is only about 4.8 months (1—15 months) between discovering the first metastasis and metastatic death of the patient. At the same time, computed tomography reveals latent liver metastases in 1.98-4% of patients at first presentation [18, 19]. Thus, early metastasizing in CM and fulminant course of metastatic disease can be explained by clinically latent metastases that are already present at the time of brachytherapy. Proof of this are not only our data but also the results of other authors that show longer survival of metastatic CM patients in case of late metastases (up to 35.2 months) [20, 21].

It is generally accepted that the risk of metastases is higher in larger tumor sizes. As to our study, the frequency of metastases depending on the tumor size and duration of follow-up is presented in **Table 3**.

Four patients with early (small) CMs were followed up for the average of 26.75 months, the remaining 23 patients — for 36-263 months (99.96±12.47 on average).

Table 3. **Frequency of metastases depending on tumor size and duration of follow-up**

Tumor metrical type	Number of patients	Duration of follow-up			Total number (followed up patients)	Mean age, years
		<35 months	36—90 months	>91 months		
Small	27	None	None	None	None	63.37±4.25
Medium	52	1	4	2	7	60.40±3.14
Large	82	3	13	None	16	52.52±2.64

None of the patients developed metastases within the specified time period (see Table 3). According to the literature, it usually takes 7 years between the beginning of treatment of a small CM and liver metastases [20]. In our experience, this period was more than 8 years.

Patients with medium CMs (52 patients) were followed up for the average of 100.88±14.28 months after treatment (14-167 months). Of them, 13.45% developed liver metastases. In 6 patients the metastasis-free period was 37—167 months (69.8 months on average), the median survival — 18.5 months (average — 20.66 months).

Patients with large CMs were followed up for 14—261 months after BT (94.79±12.21 months on average). In this group, metastatic cases were 19.51%. Within the first 35 months, metastases were found in only two patients (at 24 and 27 months). The most 'vulnerable' period for tumor metastases was from month 37 to month 85. The two patients with early metastases survived 4 and 8 months, while in those who developed metastases between 37 and 85 months, the median survival was 13.5 months. There is just one female patient who underwent sectoral hepatic resection for metastatic CM and is alive at 172 months. Thus, the risk of metastases in large choroidal melanomas is 20 times as high as that in small CMs (15 times, if medium) and, naturally, the patient lifespan shortens. Literature data confirm these results. As a small CM (<10 mm at baseline) grows, the risk of metastases increases by 18%. In medium CMs (10—15 mm at baseline), the increase can be by up to 52%, in large CMs (⩾16 mm at baseline) — by 59% [22]. As mentioned above, elderly age and large basal tumor diameter are considered the main risk factors for metastatic death [11]. Recently, data has emerged on the role of cytogenetic abnormalities in the development of metastatic CM, particularly, monosomy 3 and class II mutations that are found in 30—40% of medium CM patients, 50—60% of large CM patients, and only 10% of small CM patients [23, 24]. In other words, cytogenetic changes in some melanomas also point out the significance of tumor size for the development of metastatic disease. If so, should we really increase thresholds for 'small' and 'medium' CM metrical types? Or should we set the limits for local treatment of large CMs?

Conclusion

Periods of follow-up after BT being the same (more than 7—8 years in our case), the frequency of hematogenous metastases is higher in larger CMs. For successful local treatment, the maximum allowable diameter of the tumor is 10 mm. Every fifth case of choroidal melanoma that is more than 15 mm in diameter ends up with hematogenous metastases. The results obtained prove the expediency of decreasing metrical limits for different types of choroidal melanomas, small and medium in the first place.

Author contributions:
Study conception and design — A.B, A.S.
Acquisition and handling of data — A.S., I.Ch.
Statistical analysis of data — A.S, I.Ch.
Drafting of manuscript — A.B, A.S.
Critical revision — A.B.

The authors declare no conflict of interests.

REFERENCES

1. Shields J.A. Diagnosis and management of intraocular tumors– St. Louis: The C.V. Mosby Company; 1983.
2. Domato B. Detection of uveal melanoma by optometrists in the United Kingdom. Ophthalmic Physiol Opt. 2001; 21(4):268-271.
3. Eskelin S, Kivela T. Mode of presentation and time to treatment of uveal melanoma in Finland. Br J Ophthalmol. 2002;86(3):333–338.
4. Kwon HJ, Ko JS, Kim M, Lee CS, Lee SC. Prognosis of choroidal melanoma and the result of ruthenium brachytherapy combined with transpupillary thermotherapy in Korean patients. Br J Ophthalmol. 2013; 97(5):653-658 doi:10.1136/bjophthalmol-2012-302584
5. Vidal JL, Bacin F, Albuisson E, Rozan R, Desjardins L, D'Hermies F, Grange JD, Chauvel P, Caujolle JP, Sahel J, et al. "Melanoma 92". epidemiological study of uveal melanoma in France. J Fr Ophtalmol. 1995;18(8-9):520-528.
6. Panova I.E., Pilat A.V., Bukhtiyarova N.V., Semenova L.E., Vazhenina D.A., Ushenina L.A. Multimodal treatment of uveal melanomas. Ophthalmokhirurgiya. 2007; (2):24-27. (In Russ.).
7. Collaborative Ocular Melanoma Study Group: Design and methods of a clinical trial for a rare condition: The Collaborative Ocular Melanoma Study: COMS Report No3. Controlled Clin Trials 1993; 14(4):362-391.
8. Factors predictive of growth and treatment of small choroidal melanoma: COMS Report No5. Collaborative Ocular Melanoma Study Group. Arch Ophthalmol 1997; 115(12):1537-1544.
9. Shields CL , Furuta M, Thangappan A, Nagori S, Mashayekhi A, Lally DR, Kelly CC, Rudich DS, Nagori AV, Wakade OA, Mehta S, Forte L, Long A, Dellacava EF, Kaplan B, Shields JA. Metastasis of uveal melanoma millimeter-by-millimeter in 8033 consecutive eyes. Arch Ophthalmol. 2009;127(8):989-98. doi: 10.1001/archophthalmol.2009.208.
10. Kujala E, Makitie T., Kivela Very long-term prognosis of patients with malignant uveal melanoma. Invest. Ophthalmol.Vis Sci. 2003;44(11),4651-4659
11. Collaborative Ocular Melanoma Study Group. The COMS randomized trial of iodine 125 brachytherapy for choroidal melanoma: V. Twelve-year mortality rates and prognostic factors: COMS report No. 28. Arch Ophthalmol. 2006;124(12):1684-1693
12. Mäkitie T, Summanen P, Tarkkanen A, Kivelä T. Microvascular loops and networks as prognostic indicators in choroidal and ciliary body melanomas. J Natl Cancer Inst. 1999; 91(4):359-67.
13. Diener-West M, Reynolds SM, Agugliaro DJ, Caldwell R, Cumming K, Earle JD, Green DL, Hawkins BS, Hayman J, Jaiyesimi I, Kirkwood JM, Koh WJ,Robertson DM, Shaw JM, Thoma J; Screening for metastasis from choroidal melanoma: the Collaborative Ocular Melanoma Study Group Report 23. J Clin Oncol. 2004;22(12):2438-44.
15. Curtis E. Margo The Collaborative Ocular Melanoma Study:An Overview. Cancer Control. 2004; 11 (5): 304-309
16. Diener-West M, Earle JD, Fine SL, Hawkins BS, Moy CS, Reynolds SM, Schachat AP, Straatsma BR; Collaborative Ocular Melanoma Study Group. The COMS randomized trial of iodine 125 brachytherapy for choroidal melanoma, II: characteristics of patients enrolled and not enrolled. COMS report no. 17. Arch Ophthalmol 2001; 119(7): 951–965
17. Damato B., Couplands SE A reappraisal of the significance of largest basal diameter of posterior uveal melanoma. Eye (Lond) 2009; 23(12):2152-2160 quiz 2161-2. doi: 10.1038/eye.2009.235-cme.

18. Diener-West M., Reynolds SM, Aquqliaro DJ, Caldwell R., Cumming K., Earle JD. Hawkins BS., Hayman JA., Jaiyesimi I., Jampol LM, Kirkwood JM, Koh WJ., Robertson DM, Shaw JM, Straatsma BR, Thoma J., Collaborative Ocular Melanoma Study Group. Development of metastatic disease after enrollment in the COMS trials for treatment of choroidal melanoma: Collaborative Ocular Melanoma Study Group Report No26. Arch. ophthalmol.2005; 123(12):1639-1643.

19. Brovkina AF, Val'skiy VV, Zarubey GD. [Metastatic involvement of liver in patients with uveal melanoma]. Vestnik Oftal'mologii. 1998;114(1):21-23. (In Russ.).

20. Finger PT,Kurli M.,Reddy S.,Tena LB, Pavlick AC. Whole body PET/CT for initial staging of choroidal melanoma. Br.J Ophthalmol. 2005; 89(10): 1270-1274

21. Malclès A, Kivelä T, Svetlosakova Z, Jean-Louis B, Nguyen AM, Sallit R, Négrier S, Pommier P, Rivoire M, Chauvel P, Mammar H, Devouassoux-Shisheboran M, Kodjikian L, Denis P, Grange JD. Small metastasizing choroidal melanomas. Acta Ophthalmol. 2015; 93(2): 160-166. doi: 10.1111/aos.12523.

22. Albert DM, Niffennegger AS, Willson JK. Treatment of metastatic uveal melanoma: review and recommendations. Surv Ophthalmol. 1992; 36(6):429-438.

23. Kaliki S., Shieds CL., Shields JA. Uveal melanoma: Estimating prognosis. Indian J. Ophthalmol. 2015; 63(2): 93-102. doi: 10.4103/0301-4738.154367.

24. Augsburger J, Correa Z., Trichopoulos N. An alternative hipothesis for observed mortality rates due to matastasis after treatment of choroidal melanomas of different sizes. Trans AM ophthalmol Soc. 2007; 105: 54-60

25. Ossowski L., Aquirre-Ghiso J.A. Dormancy of metastatic melanoma. Pigment Cell Melanoma Res. 2010; 23(1):41-56. doi: 10.1111/j.1755-148X.2009.00647.x.

Received 25.05.2015