https://doi.org/10.31288/oftalmolzh202532530

Ultrasound features of epibulbar malignancies of various histogenesis (melanoma and carcinoma)

Safronenkova I. O., Buiko O. S., Yelagina V. A.

SI «The Filatov Institute of Eye Diseases and Tissue Therapy of the National Academy of Medical Sciences of Ukraine»

Odesa (Ukraine)

Purpose. *To assess the ultrasound features of epibulbar malignancies of various histogenesis (melanoma and carcinoma), including the thickness of adjacent sclera and the sonographic density and dimensions of the neoplasm before and at various time points after radiation therapy plus cryosurgery.*

Material and Methods: *Ultrasound (US) examination was performed in 75 patients with conjunctival melanoma (CM) or conjunctival carcinoma (CC) who underwent treatment at SI "The Filatov Institute of Eye Diseases and Tissue Therapy of the NAMS of Ukraine" in 2004-2021. Of these, 58 (77.3%) had CM, and 17 (24%) had CC. Of the patients with CM, 30 (51.7%) were men aged 18 to 88 years (median, 51.3 years), and 28 (48.3%) were women aged 26 to 87 years (median, 57.3 years). Of the patients with CC, 12 (70.6%) were men aged 28 to 82 years (median, 66.3 years), and 5 (29.4 %) were women aged 35 to 74 years (median, 57.0 years). US biomicroscopy images were obtained using the 50-MHz Aviso Ultrasound Platform. Dimensions and sonographic density of the tumor, thickness of the sclera underlying the tumor and scleral thickness on the opposite side were assessed at baseline and each 3 months over a one-year follow-up. All patients received radiation therapy (RT) plus cryosurgery (alias, cryodestruction of the tumor).*

Results: *For the total study sample, the thickness of the sclera beneath the tumor was, on average, 1.9 times thinner compared to scleral thickness on the opposite side, and this difference was significant ($p < 0.01$). Eyes with partial resorption of CM exhibited a thickness of the underlying sclera (0.42 mm) that was 1.3 times and 1.2 times thinner compared to eyes with complete resorption of CM ($\chi 2 = 3.13$, $p = 0.006$) and eyes with partial resorption of CC ($\chi 2 = 4.31$, $p = 0.01$), respectively. A middle sonographic density was the most common category of sonographic density for CM as well as CC ($\chi 2 = 3.1$, $p = 0.004$; $\chi 2 = 4.3$, $p = 0.006$, respectively). There was a conjugation between the category of sonographic density and the presence of tumor recurrence in patients with CM or CC. Recurrence of CM or CC was observed only in tumors with a middle sonographic density ($\chi 2 = 6.01$, $p = 0.004$). A thickness of the sclera underlying the tumor not exceeding 0.30 mm may be considered as a risk factor for the development of scleromalacia (odds ratio (OR) = 7.7, 95% confidence interval (CI) 3.2-53.8) (Copyright Registration Certificate for a Work No. 134003 issued on March 3, 2025).*

Conclusion: *The thickness of the sclera beneath the tumor as assessed by US was thinner compared to scleral thickness on the opposite side. A middle sonographic density was the most common category of sonographic density for CM. There was a conjugation between the category of sonographic density and the presence of tumor recurrence in patients with CM and those with CC. Recurrence of CM or CC was observed only in tumors with a middle sonographic density. A thickness of the sclera underlying the tumor not exceeding 0.30 mm may be considered as a risk factor for the development of scleromalacia (OR = 7.7, 95% CI 3.2-53.8).*

Key words:

ocular oncology, conjunctival melanoma, conjunctival carcinoma, ultrasound examination, radiation therapy, cryodestruction, radiation therapy plus cryosurgery, sclera, epibulbar neoplasm

Introduction

Scleroconjunctival melanoma and carcinoma are aggressive and invasive ocular malignancies [1] which, if late detected and/or inadequately treated, can result in loss of ocular function, loss of the eye or even death [2-4]. The outcome of treatment for epibulbar malignancy depends on the combination of risk factors like tumor dimensions, thickness and histology. Tumors with a thickness < 2 mm have the best prognosis, whereas those with a thickness ≥ 2 mm are associated with an increased risk of regional and distant metastases [1, 6-10]. Therefore, objective assessment of tumor dimensions and detection of lesions of ocular coats are important.

Publications on ultrasound (US)-based diagnostic assessment of epibulbar tumors are few in number. Ultra-

sound biomicroscopy with a high frequency (20-50 MHz) transducer has been reported for this purpose. Buchwald and colleagues [6] assessed the value of US biomicroscopy in the diagnosis of conjunctival and eyelid lesions. With optic coherence tomography and with US, in patients with compound nevus very small cystic structures were seen. The authors concluded that US biomicroscopy can be used as an auxiliary diagnostic tool for the assessment of the margins of the tumors. Finger and colleagues [7] evaluated the high-frequency B-scan US characteristics of squamous conjunctival neoplasia. Results of US examinations showed that the superficial aspect of the smaller limbal tumors appeared as fusiform thickening of the conjunctiva. In all patients, the tumor surface was highly reflective in contrast to the characteristically low reflectivity seen within the tumor stroma. Intraocular tumor extension was variably reflective, but evidenced by blunting of the anterior chamber angle and thickening of the uvea. High-frequency US was useful in determining tumor thickness, shape, and internal reflectivity, and especially in revealing tumor extension into the sclera, eye, and orbit [6, 7].

Therefore, in the opinion of the majority of ocular oncologists dealing with conjunctival malignancies, although these tumors can be early detected and examined, many aspects of this group of disorders are still poorly understood and require further research and practical studies on the diagnostic assessment, treatment and follow-up of patients.

The purpose of the study was to assess the ultrasound features of epibulbar malignancies of various histogenesis (melanoma and carcinoma), including the thickness of adjacent sclera and the sonographic density and dimensions of the neoplasm before and at various time points after radiation therapy plus cryosurgery.

Material and Methods

Seventy-five patients with scleroconjunctival malignancies underwent US examination of the eye. Of these, 58 (77.3 %) had conjunctival melanoma (CM), and 17 (24 %) had conjunctival carcinoma (CC). Of the patients with CM, 30 (51.7%) were men aged 18 to 88 years (median, 51.3 years), and 28 (48.3 %) were women aged 26 to 87 years (median, 57.3 years). Of the patients with CC, 12 (70.6%) were men aged 28 to 82 years (median age, 66.3 years), and 5 (29.4 %) were women aged 35 to 74 years (median age, 57.0 years). All patients had been under no treatment before admission to the institute.

US biomicroscopy images were obtained using the 50-MHz Aviso Ultrasound Platform (Quantel Medical, Clermont-Ferrand, France). Dimensions and sonographic density of the tumor, thickness of the sclera underlying the tumor and scleral thickness on the opposite side were assessed at baseline and each 3 months over a one-year follow-up.

All patients received radiation therapy (RT) plus cryosurgery (alias, cryodestruction of the tumor).

Histomorphological studies of tumor biopsies were performed at the pathomorphology laboratory of the institute.

A microcryogenic cylinder-and-throttle system capable of producing low temperatures within the range of -120…-90 °C was used to perform the destruction. The duration of cryogenic exposure depended on the amount and location of tumor tissue, dimensions of cryogenic tip, and cryogen pressure, and was determined by the use of specially designed nomograms. RT consisted of brachytherapy with a strontium-90/yttrium-90 (90Sr/90Y) beta-radiation source, a single local dose of 40 Gy and a mean total equivalent dose of 380 ± 54.0 Gy.

Patients were followed up at 3 to 6 months (early follow-up visits) and 3 to 6 years (late follow-up visits).

An MS Access database was generated to store, organize and retrieve the data associated with the results of examination and treatment of patients with CM or CC. Numerical parameters were entered as numerical data, and clinical characteristics as ordinal data. Mean and standard deviation (SD) were calculated for quantitative data. Pearson's chi-square test was used to compare nominal data, and Student's t-test was used to compare quantitative data. P values ≤ 0.05 were considered significant. Med Calc 9 (Demo) software was used for receiver operating characteristic (ROC) analysis. The contingency-table Pearson chi-square test was employed for group comparison for categorical variables. Power analysis was performed using G*Power 3.1 software [11].

This paper is part of the research project "Pathogenetic Mechanisms of the Clinical Effect of New Combination Treatment Modalities for Uveal Melanoma (Iridocyclectomy, Transpupillary Thermotherapy, Brachytherapy and Immunotherapy) and Epibulbar Conjunctival Malignancies (Cryotherapy and Radiation Plus Cryotherapy)" (state registration number, 0119U101013).

This study involved human subjects and followed ethical standards as outlined in the Declaration of Helsinki of the World Medical Association and the European Convention on Human Rights and Biomedicine, and relevant laws of Ukraine. 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 May 14, 2018). Informed consent was obtained from all study subjects.

Results

Results of US examinations showed that CM and CC appeared as fusiform thickening of the conjunctiva (Fig. 1-3). Blunting of the anterior chamber angle was sometimes seen in limbal tumors (Figs. 1c and 3c). There was no evidence of intraocular tumor growth or orbital seeding of the tumor in the study sample.

Table 1 presents the dimensions of epubulbar tumors (tumor height above the sclera; tumor length; tumor width; thickness of the underlying sclera; and scleral thickness on the opposite side) at baseline as assessed by ultrasound.

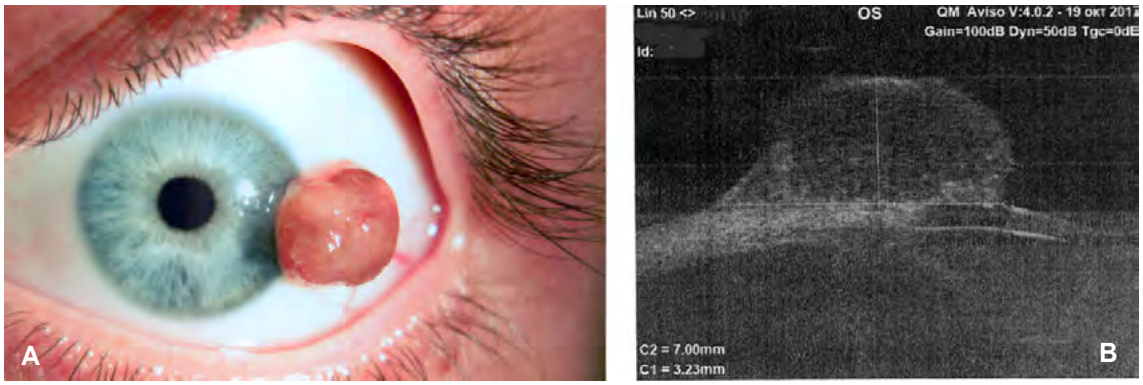

Fig. 1. Melanoma of the conjunctiva of sclera and cornea (A) and sonogram of the melanoma (B)

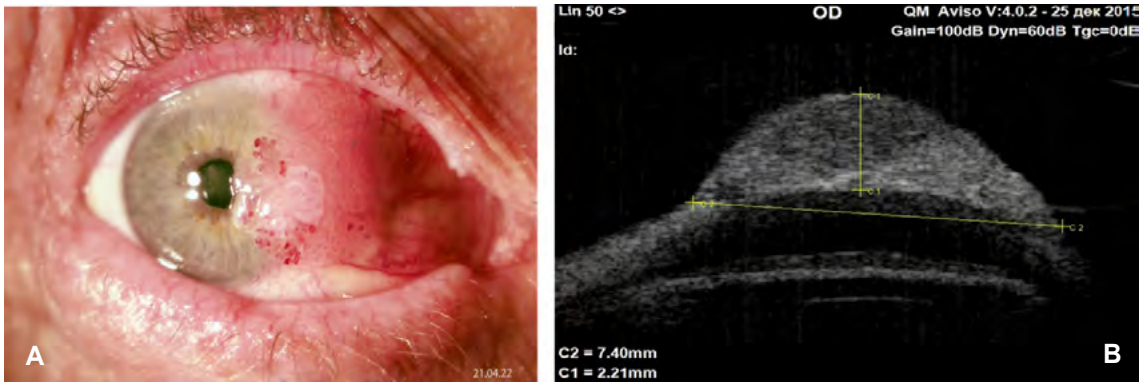

Fig. 2. Carcinoma of the conjunctiva of sclera and cornea (A) and sonogram of the carcinoma (B)

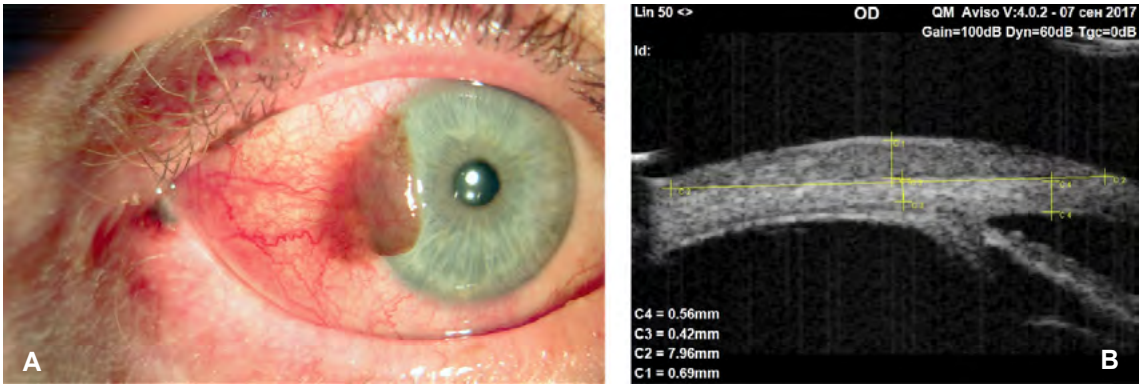

Fig. 3. Melanoma of the conjunctiva of sclera and cornea (A) and sonogram of the melanoma (B)

There was no significant difference between CM and CC in terms of tumor width, length or height, or thickness of the underlying sclera (Table 1).

The ratio of the thickness of the sclera beneath the tumor to the scleral thickness on the opposite side averaged 1.9 for the total sample of tumors, and 1.2 and 1.3 for CM and CC, respectively (χ^2 = 3.9, p = 0.004 and χ^2 = 4.1, p = 0.003, respectively) (Fig. 4). There was, however, no significant difference in the scleral thickness beneath the tumor between CM and CC.

Table 2 presents categories of sonographic density for CM versus CC. A middle sonographic density was significantly more common than other categories of sonographic density for CM as well as CC (χ^2 = 3.1, p = 0.004; χ^2 = 4.3, p = 0.006, respectively). Thus, a middle sonographic density was 24 times more common than a low sonographic density and 6 times more common than a low-middle sonographic density for CM. Additionally, a middle sonographic density was 13 times more common than a low sonographic density and 1.3 times more common than a low-middle sonographic density for CC. We found no significant difference in the category of sonographic density between CM and CC (χ^2 = 12.6, p = 0.12; χ^2 = 9.1 and p = 0.09; χ^2 = 9.3, p = 0.07, respectively).

We examined associations between the thickness of the sclera beneath the tumor and early treatment outcomes (partial or complete tumor resorption 3 to 6 months after RT plus cryosurgery). Eyes with partial resorption of CM

exhibited a thickness of the underlying sclera (0.42 mm) that was 1.3 times thinner compared to eyes with complete resorption of CM (0.53 mm) (χ^2 = 3.13, p = 0.006) and 1.2 times thinner compared to eyes with partial resorption of CC (0.52 mm) (χ^2 = 4.31, p = 0.01) (Table 3).

Table 4 presents the categories of sonographic density as assessed by ultrasonography for CM and CC exhibiting versus not exhibiting recurrence.

There was a conjugation between the category of sonographic density and the presence of tumor recurrence in patients with CM and those with CC. Recurrence of CM or CC was observed only in tumors exhibiting a middle sonographic density.

Scleromalacia developed in 6 (5.9%) patients with CM 6 months to 5 years (median, 9 months) after RT combined with cryosurgery. At 6 months of the follow-up, the thickness of the sclera underlying the tumor did not exceed 0.30 mm in 5 of 6 (83.3%) CM patients who developed scleromalacia (Table 5).

A thickness of the sclera underlying the tumor not exceeding 0.30 mm may be considered as a risk factor for the development of scleromalacia, with the odds ratio (OR) of this factor showing that an eye was 7.7 times more likely to develop scleromalacia if it had a thickness of the sclera underlying the tumor not exceeding 0.30 mm (OR = 7.7, 95% CI 3.2-53.8) (Copyright Registration Certificate for a Work No. 134003 issued on March 3, 2025).

Therefore, results of US examinations showed that, for all histological types of epibulbar neoplasms, the thickness of the sclera beneath the tumor was, on average, 1.9 times thinner compared to scleral thickness on the opposite side, and this difference was significant (p < 0.01). Eyes with partial resorption of CM exhibited a thickness of the underlying sclera (0.42 mm) that was 1.3 times thinner compared to eyes with complete resorption of CM (0.53 mm) (χ^2 = 3.13, p = 0.006) and 1.2 times thinner compared to eyes with partial resorption of CC (0.52 mm) (χ^2 = 4.31, p = 0.01). A middle sonographic density was significantly more common than a low or high sonographic density for CM as well as CC (χ^2 = 3.1, p = 0.004; χ^2 = 4.3, p = 0.006, respectively). There was a conjugation between the category of sonographic density and the presence of tumor recurrence in patients with CM and those with CC. Recurrence of CM or CC was observed only in tumors with a middle sonographic density (χ^2 = 6.01, p = 0.004). A thickness of the sclera underlying the tumor not exceeding 0.30 mm may be considered as a risk factor for the development of scleromalacia (OR = 7.7, 95% CI 3.2-53.8) (Copyright Registration Certificate for a Work No. 134003 issued on March 3, 2025).

Table 1. Parameters of epibulbar malignancies of various histogenesis (conjunctival melanoma and conjunctival carcinoma) as assessed by ultrasound

Tumor parameters	Histological type of the tumor		P value
	CM (n = 58)	CC (n = 17)	
	1	2	
Width	7.5 ± 3.24	8.85 ± 4.76	0.14
Length	7.4 ± 2.46	8.97 ± 3.56	0.15
Height	2.7 ± 1.81	3.93 ± 3.57	0.12
Thickness of the sclera beneath the tumor	0.45 ± 0.09	0.46 ± 0.08	0.37
Scleral thickness on the opposite side	0.56 ± 0.05	0.61 ± 0.11	0.35

Note: n, number of patients; CC, conjunctival carcinoma; CM, conjunctival melanoma; P value, P value assessed by Student's test

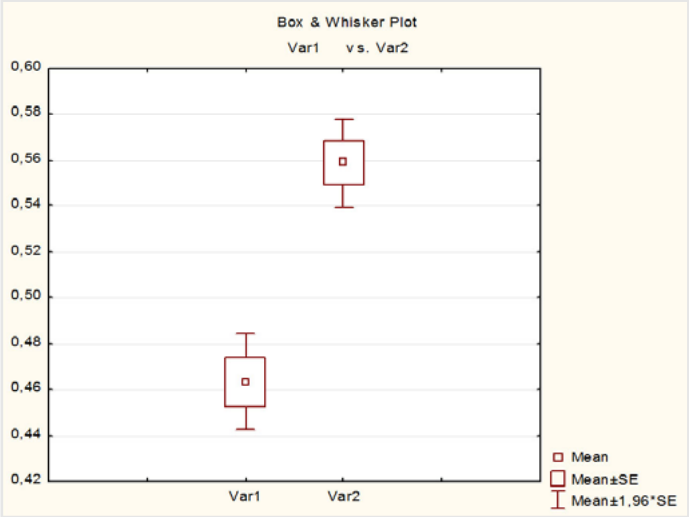

Fig. 4. Box-and-whisker plot for thickness of the sclera beneath the tumor (Var 1) and scleral thickness on the opposite side (Var 2) as assessed by ultrasound. The ordinate displays the thicknesses in mm. The whiskers mark the minimum and the maximum.

Table 2. Distribution of patients with conjunctival melanoma versus patients with conjunctival carcinoma among categories of sonographic density for tumors as assessed by ultrasound

Category of sonographic density for tumors	Histological type of the tumor		Total
	Melanoma	Carcinoma	
Low	2 (3.4 %)	1 (5.9 %)	3 (4 %)
Low-middle	8 (13.8 %)	3 (17.6 %)	11 (14.7 %)
Middle	48 (82.8 %)	13 (76.5%)	61 (81.3 %)
Total	58	17	75

Table 3. Ultrasonographic thickness of the sclera beneath the tumor after radiation therapy plus cryosurgery for melanoma versus carcinoma

	Histological type of the tumor and presence of complete or partial resorption of the tumor				p
	CM (n = 58)		CC (n = 17)		
	Complete resorption (n = 45)	Partial resorption (n = 13)	Complete resorption (n = 13)	Partial resorption (n = 4)	
	1	2	3	4	
Ultrasonographic thickness of the sclera beneath the tumor after radiation therapy plus cryosurgery	0.53±0.06	0.42±0.09	0.56±0.08	0.52±0.12	P_{1-2}=0.006 P_{1-3} = 0.37 P_{3-4} = 0.12 P_{2-4} = 0.04

Note: n, number of patients; CC, conjunctival carcinoma; CM, conjunctival melanoma; P value, P value assessed by Student's test

Table 4. Distribution of patients with conjunctival tumors of various histogenesis among categories of sonographic density as assessed by ultrasonography for conjunctival melanoma versus conjunctival carcinoma exhibiting and not exhibiting recurrence

Sonographic density	Histological type of the tumor and presence or absence of recurrence				Total
	Melanoma		Carcinoma		
	No recurrence	Recurrence	No recurrence	Recurrence	
Low	2	-	1	-	3
Low-middle	8	-	3	-	11
Middle	38	10 (16.4%)	4	9 (14.8 %)	61
Total	48	10	8	9	75

Table 5. Thickness of the sclera beneath the tumor (mm) at baseline and 3 and 6 months after radiation therapy plus cryosurgery in patients with scleromalacia

Patients	Timepoints		
	Baseline	3 months	6 months
L-ov	0.51	0.51	0.30
G-k	0.52	0.52	0.34
P-na	0.50	0.45	0.31
N-ko	0.31	0.31	0.17
R-k	0.45	0.35	0.20
Ch-r	0.41	0.41	0.30

Discussion

Given the aggressiveness of treatments used in ocular oncology, underestimation of their effects on the globe is dangerous and may lead to the development of severe complications. Therefore, US evaluation of the thickness of ocular coats over time after treatment is important for early detection of their thinning and taking measures to meet a threat of sclerocorneomalacia [7-10].

Our US studies found that the scleral thickness beneath the tumor was less than the scleral thickness on the opposite side (1.2 times and 1.3 times thinner for CM and CC, respectively). Scleral thinning beneath the epubulbar carcinoma was also reported by other researchers [6, 7].

We found that malignant epibulbar tumors most commonly exhibited a middle sonographic density (24 times more commonly than a low sonographic density for CM and 6 times more commonly than a low sonographic density for CC). This is comparable with the findings of other studies [6, 7, 12, 13].

There was a conjugation between the category of sonographic density and the presence of tumor recurrence in patients with CM and those with CC. In the current study, recurrence of CM or CC was observed only in tumors exhibiting a middle sonographic density. To the best of our knowledge, this has not been reported by other authors.

Additionally, we have established that a scleral thickness beneath the tumor not exceeding 0.30 mm may be considered as a risk factor for the development of scleromalacia (OR = 7.7, 95% CI 3.2-53.8) (Copyright Registration Certificate for a Work No. 134003 issued on March 3, 2025). We have failed to find any reports on similar findings in the literature.

In sum, it should be noted that conjunctival malignancies, melanoma and carcinoma, are rare tumors posing a threat to the eye and life. Although these tumors can be early detected and examined, many aspects of this group of disorders are still poorly understood and require further research and practical studies. Ultrasound scanning is an

objective diagnostic and follow-up tool for patients with CM and CC, and requires further improvement.

Conclusion

Our US studies found that the scleral thickness beneath the tumor was less than the scleral thickness on the opposite side (1.2 times and 1.3 times thinner for CM and CC, respectively). CM and CC most commonly exhibited a middle sonographic density. Additionally, there was a conjugation between the category of sonographic density and the presence of tumor recurrence in patients with CM and those with CC. Recurrence of CM or CC was observed only in tumors exhibiting a middle sonographic density. A thickness of the sclera underlying the tumor not exceeding 0.30 mm may be considered as a risk factor for the development of scleromalacia (OR = 7.7, 95% CI 3.2-53.8) (Copyright Registration Certificate for a Work No. 134003 issued on March 3, 2025).

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Disclosures

Received: 28.02.2025

Accepted: 14.05.2025

Corresponding author: Iryna Safronenkova - safronenkova@ukr.net

Author contributions. *Safronenkova I.O. - concept and design of the study, data collection and creation of the electronic database, interpretation of results, preparation and writing of the manuscript, review and revision; Buiko O.S. - creation of the electronic database, statistical processing, review; Elagina V.A. - conceptualization and collection of data, design, formal analysis. All authors have read and approved the final version of the manuscript.*

Statement of ethical standards. *The study was conducted with human subjects. The study was approved by the Ethics Committee of the State Institution "Filatov Institute of Eye Diseases and Tissue Therapy of the National Academy of Medical Sciences of Ukraine" (Protocol No. 2, dated 04/21/2025). Measures were taken to comply with the main provisions of the Council of Europe Convention on Human Rights and Biomedicine, the World Medical Association Declaration of Helsinki on the Ethical Principles for Scientific Medical Research Involving Human Subjects and were in line with the current legislation of Ukraine.*

Disclaimer. *The views expressed in this article are those of the authors and do not reflect the official position of the institution.*

Sources of support: *none.*

Funding. *The article is part of the research work on the topic "Pathogenetic mechanisms of realization of the clinical effect of new combined methods of treatment of melanomas of the uveal tract (iridocyclectomy, transpupillary thermotherapy, brachytherapy, immunotherapy) and malignant epibulbar tumors of the conjunctiva (cryo- and radio-cryotherapy)", state registration No. 0119U101013.*

Conflict of interest. *The authors declare that they have no conflict of interest that may have influenced their opinions regarding the subject matter or materials described and discussed in this manuscript.*

Informed consent. *Informed consent was obtained from all participants included in the study.*

Data availability statement. *All data obtained or analyzed during this study are included in this publication.*

Abbreviations: *MC - conjunctival melanoma, CC - conjunctival carcinoma, RT - radiation therapy, CD - cryodestruction, RC - radio cryosurgery, ultrasound - ultrasound.*