PHOTODYNAMIC THERAPY OF PRIMARY AND RECURRENT FORMS OF WEAKLY PIGMENT CHOROIDAL MELANOMA

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Abstract

Treatment of poorly-pigmented tumors of small sizes can be carried out using photodynamic therapy (PDT). The material for the analysis was data on 112 patients. We used data from the Belarusian Cancer Registry, medical records of patients with clinically diagnosed choroid melanoma (C69.3 according to ICD-10) for the period 2013–2021. The size and level of blood flow in the tumors were assessed using an ultrasound machine with a doppler attachment. PDT was carried out using a «UPL PDT» semiconductor laser (Lemt, Republic of Belarus, λ=661 nm) with a light spot diameter of 1 to 3 mm for 60 s per field with a light dose of 50 J/cm^2. The entire surface of the tumor was exposed to the action, with the fields "tiled", from the periphery to the top of the tumor, with overlapping fields. Tumor pigmentation was assessed visually. To evaluate the treatment outcome, the general group of patients was divided into three subgroups according to thickness and basal diameter. Group I – 40 (35.7%) patients, with an average tumor thickness of 1.4±0.2 mm, basal diameter – 5.8±1.5 mm. II – 51 (45.5%) patients, with an average tumor thickness of 2.3 ± 0.3 mm, basal diameter – 7.9 ± 1.5 mm. III – 21 (18.8%) patients. The mean value of the tumor thickness was 3.8±0.4 mm, the basal diameter was 9.8±1.4 mm. After PDT in the general group (n=112), 29 (25.9%) patients had complete tumor resorption, and 83 (74.1%) patients had stabilization. The eyeball was saved in 107 (95.5%) patients. Continued growth and relapse were recorded in 34 patients: 25 (22.3%) and 9 (8.0%), respectively. In 29 (85.3%) patients, the eyeball was preserved after treatment of relapse and continued growth. 5 (4.5%) enucleations were performed. Adjusted one-year cumulative survival was 100%, 3-year and 5-year 95.8±2.4%, 93.7±3.1%, respectively.

Key words: choroid melanoma, poorly pigmented tumor, photodynamic therapy, laser transpupillar thermotherapy, brachytherapy, recurrence.

For citations: Zhyliayeva K.P., Demeshko P.D., Navumenka L.V., Krasny S.A., Tzerkovsky D.A., Zherko I.Yu. Photodynamic therapy of primary and recurrent forms of weakly pigment choroidal melanoma, *Biomedical Photonics*, 2022, vol. 11, no. 3, pp. 17–23. doi: 10.24931/2413–9432–2022–11-3-17–23.

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ФОТОДИНАМИЧЕСКАЯ ТЕРАПИЯ ПЕРВИЧНЫХ И РЕЦИДИВНЫХ СЛАБОПИГМЕНТНЫХ ФОРМ МЕЛАНОМЫ СОСУДИСТОЙ ОБОЛОЧКИ ГЛАЗА

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Резюме

Лечение слабопигментных опухолей малых размеров может проводиться с применением фотодинамической терапии (ФДТ). Материалом для анализа послужили полученные из Белорусского канцер-регистра данные медицинской документации 112 пациентов с клинически установленным диагнозом меланомы сосудистой оболочки глаза (С69.3 по МКБ-10) за период 2013–2021 гг. Оценку размеров и уровня кровотока в опухолях осуществляли с использованием УЗИ аппарата с приставкой допплер. ФДТ проводили с использованием полупроводникового лазера «УПЛ ФДТ» (Lemt, Республика Беларусь, λ=661 нм) с диаметром светового пятна от 1 до 3 мм в течение 60 с на одно поле со световой дозой 50 Дж/см^2. Воздействию подвергали всю поверхность опухоли, располагая поля «черепицеобразно», от периферии к вершине опухоли, с перекрытием полей. Пигментацию опухоли оценивали визуально. Для оценки результата лечения общая группа пациентов была разделена на три подгруппы по толщине и базальному диаметру опухоли. I группа – 40 (35,7%) пациентов со средним значением толщины опухоли 1,4±0,2 мм и базальным диаметром 5,8±1,5 мм. II – 51 (45,5%) пациент со средним значением толщины опухоли 2,3±0,3 мм и базальным диаметром 7,9±1,5 мм. III группа – 21 (18,8%) пациент со средним значением толщины опухоли 3,8±0,4 мм и базальным диаметром 9,8±1,4 мм. После ФДТ в общей группе (n=112) у 29 (25,9%) зарегистрирована полная резорбция опухоли, у 83 (74,1%) стабилизация. Сохранить глазное яблоко удалось у 107 (95,5%) пациентов. Продолженный рост и рецидив регистрировался у 34 пациентов: 25 (22,3%) и 9 (8,0%), соответственно. У 29 (85,3%) пациентов сохранено глазное яблоко после лечения рецидива и продолженного роста. Произведено 5 (4,5%) энуклеаций Скорректированная одногодичная кумулятивная (СКВ) выживаемость составила 100%, 3-летняя и 5-летняя – 95,8±2,4%, 93,7±3,1%, соответственно.

Ключевые слова: меланома хориоидеи, слабопигментная опухоль, фотодинамическая терапия, лазерная транспупиллярная термотерапия, брахитерапия, рецидив, продолженный рост.

Для цитирования: Жиляева Е.П., Науменко Л.В., Красный С.А., Демешко П.Д. Церковский Д.А. Жерко И.Ю. Фотодинамическая терапия первичных и рецидивных слабопигментных форм меланомы сосудистой оболочки глаза // Biomedical Photonics. – 2022. – Т. 11, № 3. – С. 17–23. doi: 10.24931/2413–9432–2022–11-3-17–23.

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Introduction

Melanoma of the vascular membrane of the eye (choroidal melanoma, CM) is a tumor that develops from a clone of cells of the second pigment system (neural crest) which has a malignant potential. The average age of the patients is 64.0±10.0 years [1]. In the Republic of Belarus, the peak of morbidity has shifted to older age groups recently [2]. Almost half of the patients who seek help have large tumors and cannot be cured by organ-preserving treatments. Minimally invasive methods with preservation of the functions of the eyeball are preferable for the treatment of small tumors. Patients are cured with good results using laser techniques such as laser transpupillary thermotherapy (TTT), photodynamic therapy (PDT). In recent years, PDT has been actively developed [3] and has proven itself well in the treatment of CM and other malignant lesions of the membranes of the eyes, including osteomas and metastatic lesions [4]. According to some authors, PDT can be used before a biopsy to reduce the risk of bleeding from a tumor during an invasive method [5]. PDT gives encouraging results related to visual acuity compared with radiation therapy in the treatment of severe oncopathology of the eye membranes [4, 6, 7, 8]. CM develops from melanocytes and belongs to one of the most resistant tumors to all known methods of treatment. Studies conducted all over the world show encouraging results of the use of PDT in CM treatment [9].

Materials and methods

Database from the Belarusian Cancer Registry and case histories of patients with a clinically established diagnosis of CM (C 69.3 according to ICD-10) for the period of 2013-2021 are used in the study.

The research includes the study of 112 patients with weakly pigmented CM. 37 (33.0%) of the patients are men and the remaining are women75 (67.0%). Tumor pigmentation was assessed visually. All patients received PDT. The minimum age was 22 years, the maximum was 85 years, the median was 64.5±9.0 years. The average values of tumor thickness were 2.3±0.7 mm, basal diameter – 7.4±1.9 mm. 84 (75.0%) patients were diagnosed with a tumor with a prevalence of cT1N0M0, 28 (25.0%) – cT2N0M0. One course of PDT was used to treat 80 (71.4%) patients, 2 courses for 21 (18.8%) patients, 3 courses for 10 (8.9%) patients, and 1 (0.9%) patient underwent 4 courses of PDT. There were 93 (83.0%) patients with a single diagnosed CM. Synchronous and metachronous cancer was registered in the case of 19 (17.0%) patients.

For a detailed assessment of the results of the conducted treatment, the patients were divided into three groups depending on the thickness and basal diameter of the tumor.

Group I included 40 (35.7%) patients, with the number of 12 (30.0%) men and 28 (70.0%) women. The minimum age was 22 years, the maximum was 81 years, the median was 65.5±8.1 years. In the case of 38 (95.0%) patients, the prevalence of shingles was cT1N0M0, in 2 (5.0%) cases – cT2N0M0. The minimum thickness of pubescence is 0.8 mm, the maximum is 1.7 mm, the average value is 1.4 ± 0.2 mm. The minimum basal pubescence diameter is 1.2 mm, the maximum is 10.3 mm, the average value is 5.8 ± 1.5 mm. One course of PDT was applied to 34 (85.0%) patients, 2 courses – 5 (12.5%), 3 courses – 1 (2.5%). Synchronous and metachronous cancer was registered in the case of 5 (12.5%) patients.

Group II included 51 (45.5%) patients with the number of men – 16 (31.4%), women-35 (68.6%). The minimum age was 30 years, the maximum was 85 years, the median was 62.5±9.0 years. 42 patients (82.4%) were diagnosed with cT1N0M0 tumor, 9 patients (17.6%) – cT2N0M0. The minimum thickness of the tumor was 1.8 mm, the maximum was 3.0 mm, the average values were 2.3± 0.3 mm, the minimum size of the basal diameter of the tumor was 3.0 mm, the maximum was 11.9 mm, the average value was 7.9±1.5 mm. Synchronous and metachronous cancer was registered in the case of 7 (13.7%) patients. One course of PDT was applied to 31 (60.8%) patients, 2 courses – 13 (25.5%), 3 courses – 6 (11.8%), 4 courses – 1 (1.9%).

Group III included 21 (18.8%) patients with the number of men – 9 (42.9%), women – 12 (57.1%). The minimum age was 31 years, the maximum was 83 years, the median was 63.0±9.1 years. 4 (19.0%) patients were diagnosed with cT1N0M0 tumor, 17 (81.0%) – cT2N0M0. The minimum thickness of the tumor is 3.1 mm, the maximum is 5.2 mm, the average values were 3.8± 0.4 mm, the minimum size of the basal diameter of the tumor was 7.0 mm, the maximum was 13.5 mm, the average

value was 9.8±1.4 mm. One course of PDT was applied to 15 (71.4%) patients, 2 courses – 3 (14.3%), 3 courses – 3 (14.3%). Synchronous and metachronous cancer was registered in 7 (33.3%).

The size and level of blood flow in the tumors were evaluated using ultrasound with the Doppler prefix. Photolon (RUE "Belmedpreparaty", the Republic of Belarus) was used as a photosensitizer, which was administered intravenously for 30 minutes at a dose of 2.0–2.5 mg/kg of the patient's body weight in a darkened room 3 hours before PDT. A semiconductor laser "UPL PDT" (Lemt, Republic of Belarus, λ=661 nm) with a light spot diameter from 1 to 3 mm was used for 60 seconds per field with a light dose of 50 J/cm2. The entire surface of the tumor was exposed, placing the fields "tile-like", from the periphery to the top of the tumor, with overlapping fields.

Table 1 shows the distribution of tumor in groups depending on the localization on the fundus.

The immediate result of treatment was evaluated according to the WHO recommendation for solid tumors. Complete resorption of the tumor was characterized by the formation of a full-fledged focus of atrophy in the area of the former occurrence of the tumor, however, possible dispersion or a slight accumulation of pigment was allowed. The decrease in the size of the tumor, the absence of size changes in the case of the pronounced pigmentation and the absence of blood flow were considered to be the main criteria for stabilizing the tumor process. The ineffectiveness of the treatment consisted in the absence of tumor changes or the increase in its size with the preservation or enhancement of blood flow in it. The positive result of treatment was considered complete resorption or stabilization of the tumor process.

During dynamic observation of patients with stabilization of the tumor process, a case when, amid the stabilization, an increase in size of the tumor and the appearance of a vascular network was referred to as the continued growth of the tumor in the eye membranes. The case when tumor growth was recorded amid an atrophic chorioretinal focus (complete regression) was considered a relapse. The appearance of distant metastases in other organs was considered as the progression of the disease.

The SLE indicator was used to calculate the survival rate.

Таблица 1
Распределение опухолей в группах с учетом локализации опухоли на глазном дне
Table 1
The distribution of tumors in groups, taking into account the localization of the tumor in the fundus

Локализация Localization	Группа I Group I n=40		Группа II Group II n=51		Группа III Group III n=21	
	Абсолютное число Absolute number	%	Абсолютное число Absolute number	%	Абсолютное число Absolute number	%
Прилежит к диску зрительного нерва Adjacent to the optic nerve	3	7,5	2	3,9	1	4,8
Менее 3 мм (задний полюс) к диску зрительного нерва Less than 3 mm (posterior pole) to the optic disc	18	45,0	28	54,9	16	76,2
Более 3 мм от диска зрительного нерва More than 3 mm from the optic disc	5	12,5	5	9,8	2	9,5
Прилежит к макуле менее 3 мм Adjacent to the macula less than 3 mm	10	25,0	9	17,6	2	9,5
Отстоит от макулы более 3 мм More than 3 mm away from the macula	2	5,0	2	3,9	0	0
Периферия Periphery	2	5,0	5	9,8	0	0

Results

After PDT in the general group (n=112), complete tumor resorption was registered in the case of 29 (25.9%) patients, and stabilization of the tumor process was registered in the case of 83 (74.1%) patients with follow-up periods from 2.5 months to 3 years. Continued growth and relapses amid the stabilization and continued tumor growth were registered in the case of 34 patients: 25 (22.3%) men and 9 (8.0%) women, respectively. 5 (4.5%) enucleations were carried out to treat patients with continued tumor growth and recurrence. The eyeball was preserved after treatment of relapses and continued growth in the case of 29 (85.3%) patients. It was possible to preserve the eyeball in the general group of 107 (95.5%) patients. SLE constituted 100%, 3-year and 5-year 95,8±2,4%, 93,7±3,1%, accordingly.

In group I, 10 (25.0%) complete tumor resorption with the formation of a chorioretinal atrophic focus and 30 (75.0%) stabilization of the tumor process were registered. During the dynamic observation, continued growth amid recorded stabilization was detected in the case of 1 (2.5%) patient 5 months after treatment, the patient underwent brachytherapy (BT). 2 (5.0%) relapses were detected after 1 year and 1.5 years, patients underwent BT. In the case of 5 (12.5%) patients with synchronous and metachronous disease, there was no continued growth and recurrence of the tumor. All patients are alive. Complications and progression of the disease have not been established.

In group II, 15 (29.4%) patients had complete tumor resorption, 36 (70.6%) had stabilization of the tumor process. Continued growth amid recorded stabilization was noted in the case of 14 (27.5%) patients during the dynamic follow-up period from 2 to 8 months. 11 (21.6%) of these patients underwent BT, 1 (2.0%) patient underwent combined laser treatment, including PDT and TTT courses. 2 (4.0%) patients underwent enucleation. Relapse was registered in the case of 7 (13.7%) patients during the follow-up period from 8 months up to 2 years. Five (9.8%) patients were cured by PDT courses, and 2 (4.0%) patients underwent combined laser treatment using PDT and TTT. No complications of treatment have been registered. Among 7 (13.7%) patients with synchronous and metachronous disease, 4 patients had continued growth (3 patients) of the tumor and one patient had relapse of the disease. 2 patients were diagnosed with the progressed disease in the liver (the patient died) and bones (the patient is alive) in the first and second year after diagnosis and treatment.

In group III, 4 (19.0%) patients were diagnosed with complete tumor resorption, 17 (81.0%) – with stabilization of the tumor process. Continued growth amid recorded stabilization was registered in the case of 10 (46.7%) patients during dynamic follow-up period from 3 months up to 1.2 years. 8 of these patients underwent combined treatment, including TTT and BT courses. 2 patients underwent laser therapy courses, including TTT and PDT. Subsequently, 2 patients underwent enucleation. 3 (14.3%) patients had developed complications: secondary retinal detachment, hemorrhage into the eye membranes, opticoretinopathy after 11 months of continued growth and the second course of BT. 2 patients from 7 (33.3%) with synchronous and metachronous disease had continued growth. One patient died from the progression of the disease in the liver two years after the registration of continued tumor growth in the membranes of the eye.

Tumor resorption is slow during dynamic observation after PDT, so the proportion of stabilization of the tumor process is 3 times higher than full tumor resorption ($p<0.05$). The localization of the tumor in the vascular membrane of the eye (central zone, equator, periphery) does not affect the result of PDT ($p>0.05$).

Table 2 shows the indicators of SLE by study groups.

Таблица 2
Показатели скорректированной кумулятивной выживаемости по группам исследования
Table 2
Indicators of adjusted cumulative survival by study groups

Скорректированная кумулятивная выживаемость Adjusted cumulative survival	Группа I Group I	Группа II Group II	Группа III Group III
1-летняя (%) 1-year old (%)	100,0	100,0	100,0
3-летняя (%) 3-year old (%)	100,0	94,9±3,6	93,3±5,4
5-летняя (%) 5-year old (%)	100,0	93,3±6,4	93,3±5,4

The result of the antitumor efficacy of PDT did not depend on the localization of the tumor ($p>0.05$).

Cumulative indicators of 1-year SLE in the general group were 100%. 5-year SLE in the first group consisted 100%. In the second group, where tumors were larger, 3-year and 5-year survival was 94.9±3.6% and 93.3±6.4%, respectively. 3-year and 5-year SLE was 93.3±5.4% in the group where the observed tumors after PDT were the largest.

Discussion

The mechanism of PDT action is based on the selective accumulation of photosensitizing medicaments inserted into the body in cells with increased mitotic activity (in tumor cells, endothelium of newly formed vessels, etc.). Subsequent irradiation of a weakly pigmented tumor with light with a wavelength corresponding to the maximum of the absorption band of the injected photosensitizer induces photochemical reactions in sensitized cells and tissues with the release of singlet oxygen and free radicals – highly active biological oxidants, which leads to phototoxic damage to pathologically altered cells [10, 11]. The selectivity of the action determines the undoubted advantages of PDT for use in ophthalmology. This mechanism of action on a weakly pigmented tumor amid antitumor exposure allows to obtain the least destructive effect on adjacent structures, which is attractive for achieving the preservation of visual acuity associated with the absence of the development of vasculitis and subsequent opticoretinopathy.

However, sporadic studies describing the results of treatment of small tumors are devoted to the use of PDT in CM [12, 13]. One of the main reasons hindering the development of this direction in the world is the lack of photosensitizers with the necessary photophysical and pharmacokinetic properties. The production of photolon in the Republic of Belarus, which has high photodynamic activity with low skin phototoxicity and rapid elimination from the body, as well as the improvement of laser technology, bring new perspectives for a wider integration of the PDT method into ophthalmological practice.

Reviewing scientific and medical literature sources, the use of verteporphyrin and an insignificant number of patients in groups (from 8 patients in the smallest group up to 38 patients in the largest one) attracts attention [4-23]. It indicates a small world experience of PDT use in the treatment of CM. Short follow–up periods after the treatment are presented: the shortest ones are 15, 27 and 31 months, respectively, and the longest follow–up period is 3.5 and 5 years in one observation. The sizes of tumors that can be overthrown by PDT vary greatly, according to the data presented by the authors. This is due to the used PDT protocols (from 1 to many sessions before the expected result is obtained). According to some publications, PDT is most effective in melanomas with a tumor thickness of <4 mm [4], in other publications, the average thickness of the tumor subjected to PDT was 2.7 mm [25]. Some authors conduct PDT in tumors reaching a height of up to 4.4 mm [25] and even up to 5.7 mm [23]. In all unsuccessful cases, the tumors were 100% pigmented, there was a de novo CM, not transformed nevi, the radial nature of tumor growth, and not an increase in its thickness [21].

Tumor pigmentation plays a significant role in obtaining a positive result from PDT. It is known that the pigment shields the cells and vessels of the tumor. Hence, highly pigmented tumors do not react well to PDT. We do not use PDT for pigmented tumors in our treatment experience. However, some authors, on the contrary, note a positive effect in the treatment of pigmented CM [19, 20, 21]. One publication clearly shows that it was the well-pigmented part of the tumor that did not respond to PDT in the case of a mixed form of pigmentation [23]. The PDT method is most effective in low-pigmented forms of CM. The advantage of the PDT method is a decrease in the level of subretinal fluid after treatment, the presence of only isolated cases of fluid increase are recorded [19, 21, 22]. The amount of subretinal fluid decreased after treatment ($p<0.001$), vision did not deteriorate ($p=0.11$) and even improved in the case of the patients with a subfoveal tumor location ($p=0.018$) [21]. It has also been shown that photodynamic therapy does not significantly affect visual acuity [22, 23, 25].

According to literature data, 73.4% of patients recovered 1 month after PDT [8], 80% of cured patients 15 months after PDT [20], 62% of cured patients 27 months later [19], 80% of cured patients 31 months later [4], after PDT performed using the verteporfin photosensitizer, with a follow–up period of 5 years of cured patients – 67% [22]. All authors claim that PDT does not cause serious complications that cause visual acuity decreases. Some authors describe cases when the amount of subretinal fluid decreases up to complete resorption after the use of PDT [19, 21, 22]. Among the described complications, the authors note local atrophy of the retinal pigment epithelium at the treatment site in 25% of the eyes without affecting the function of the macular or optic nerve [22]. The cases of 2 patients with developed scleritis requiring a short course of systemic steroids were described [25].

Conclusion

The main criterion for choosing the method concerning the treatment of patients with weakly pigmented forms of melanoma of the vascular membrane of the eye is the size of the tumor. The best results were

obtained with a tumor thickness of up to 1.7 mm and a basal diameter of 10.3 mm, (25.0% complete tumor resorption and 75.0% stabilization of the tumor process with an adjusted 5-year survival rate of 100%). Photodynamic therapy shows high rates of adjusted 1-year cumulative survival – 100%, 3-year and 5-year – 95.8± 2.4% and 93.7± 3.1%, respectively. Photodynamic therapy being one of the methods of laser therapy can be used to preserve the eyeball and visual functions in the treatment of patients with relapse and continued growth of low-pigmented forms of melanoma of the vascular membrane of the eye.

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